Protocol I3O-MC-JSBF(a)

Randomized, Double-Blind, Phase 2 Study of Ramucirumab or Merestinib or Placebo plus Cisplatin and Gemcitabine as First-Line Treatment in Patients with Advanced or Metastatic Biliary Tract Cancer

NCT02711553

Approval Date: 30-Mar-2016

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Randomized, Double-Blind, Phase 2 Study of Ramucirumab or Merestinib or Placebo plus Cisplatin and Gemcitabine as First-Line Treatment in Patients with Advanced or Metastatic Biliary Tract Cancer

Merestinib (LY2801653) and Ramucirumab (LY3009806)

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Protocol Electronically Signed and Approved by Lilly: 09-Dec 2015.
Amendment (a) Electronically Signed and Approved by Lilly on on approval date provided below.

Approval Date: 30-Mar-2016 GMT

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1. Synopsis

Protocol Title:

Randomized, Double-Blind, Phase 2 Study of Ramucirumab or Merestinib or Placebo plus Cisplatin and Gemcitabine as First-Line Treatment in Patients with Advanced or Metastatic Biliary Tract Cancer

Rationale:

This Phase 2, multicenter, double-blinded study is designed to evaluate the efficacy and safety of 2 new combinations for the treatment of first-line advanced or metastatic biliary tract cancer (BTC):

1. Arm A: ramucirumab (LY3009806, intravenous [IV]) in combination with cisplatin and gemcitabine (Arm A1) versus placebo (IV) plus cisplatin and gemcitabine (Arm A2)

2. Arm B: merestinib (LY2801653, oral) in combination with cisplatin and gemcitabine (Arm B1) versus placebo (oral) plus cisplatin and gemcitabine (Arm B2)

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Evaluate the efficacy, in terms of PFS, in patients with advanced or metastatic BTC, for • ramucirumab (8 mg/kg, IV) versus placebo, in combination with cisplatin (25 mg/m^2, IV) and gemcitabine (1000 mg/m^2, IV), on Days 1 and 8 of a 21-day cycle. • merestinib (80 mg, oral each day) versus placebo, in combination with cisplatin (25 mg/m^2, IV) and gemcitabine (1000 mg/m^2 IV), on Days 1 and 8 of a 21-day cycle.	PFS (objective progression or death), as determined by investigator assessment per RECIST 1.1
Secondary	
Evaluate the efficacy, in combination with cisplatin and gemcitabine, in terms of OS, for ramucirumab versus placebo and merestinib versus placebo.	OS
Evaluate the efficacy, in combination with cisplatin and gemcitabine, in terms of ORR and DCR for ramucirumab versus placebo and merestinib versus placebo.	ORR and DCR
• Safety profile of merestinib • Safety profile of ramucirumab	The safety endpoints evaluated will include but are not limited to the following: • TEAEs, AESIs, SAEs, and hospitalizations • Clinical laboratory tests, vital signs, and physical examinations
• PK of ramucirumab • PK of merestinib	• Minimum ramucirumab concentration in serum • Postdose merestinib concentration in plasma
Immunogenicity of ramucirumab	Blood samples for immunogenicity testing will be collected to determine antibody production against ramucirumab.
Evaluate PRO measures of disease-specific symptoms, in combination with cisplatin and gemcitabine, for ramucirumab versus placebo and merestinib versus placebo.	Functional Assessment of Cancer Therapy Hepatobiliary Questionnaire (FACT-Hep) EuroQol 5-Dimension 5-Level (EQ-5D-5L)

Abbreviations: AESIs = adverse events of special interest; BTC = biliary tract cancer; DCR = disease control rate; IV = intravenous; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria In Solid Tumors; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

Overall Design:

Study I3O-MC-JSBF is a global, multicenter, randomized, double-blind, Phase 2 study in patients with advanced or metastatic BTC who have had no prior therapy for advanced or metastatic BTC.

Number of Patients:

The study will screen approximately 364 patients, and will randomize approximately 300 patients such that patients in each of the IV cohorts and the oral cohorts will be allocated to receive investigational treatment or control in a 2:1 fashion.

Treatment with all study drugs will be given in an outpatient setting. Treatment will continue until there is evidence of disease progression or any other discontinuation criteria are met. Treatment with cisplatin and gemcitabine will be capped at a maximum of 8 cycles. Treatment with the randomly assigned study therapy of ramucirumab, merestinib, or placebo will not be capped at a maximum number of cycles and should be continued until there is evidence of disease progression or any other discontinuation criteria are met. During the planned treatment period, if one or more therapeutic agent is permanently discontinued for a reason other than progressive disease, then treatment with the other study agent(s) should continue and the patient should remain on study with full adherence to all protocol-related requirements.

Crossover between arms is not permitted.

Treatment Arms and Duration:

	Dose and Schedule (q 21 Days)		
Arm A	**Ramucirumab/Placebo (IV) D1 and D8**	**Cisplatin (IV) D1 and D8**	**Gemcitabine (IV) D1 and D8**
A1	8 mg/kg	25 mg/m^2	1000 mg/m^2
A2	equivalent volume	25 mg/m^2	1000 mg/m^2
Arm B	**Merestinib/Placebo (oral with food) Each Day**	**Cisplatin (IV) D1 and D8**	**Gemcitabine (IV) D1 and D8**
B1	80 mg	25 mg/m^2	1000 mg/m^2
B2	Similar appearing placebo tablet(s)	25 mg/m^2	1000 mg/m^2

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

2. Schedule of Activities

Table JSBF.1. Schedule of Screening Activities I3O-MC-JSBF

			Baseline			
		Cycle	BL			
		Visit	0			
		Relative Day Prior to Cycle 1 Day 1	**≤28**	**≤14**	**≤7**	**Notes**
Procedure Category	**Prot. Ref.**	**Procedure**				
Study Entry/ Enrollment	6.1, 6.4, Appendix 2	Informed consent form signed	X			ICF must be signed prior to performance of any protocol-specific tests/procedures. If the ICF is revised during the course of the study, re-consenting of patients may be required if deemed necessary by Lilly or the IRB/ERB.
	6.1, 6.2, 7.2	Inclusion/exclusion evaluation	X			Randomization by IWRS to be done once all the screening (baseline) assessments are completed. Patients will be randomized to treatment within 24 to 72 hours prior to Visit 1 (Day 1, Cycle 1). Every attempt should be made to randomize the patient as close as possible to Day 1 of Cycle 1 and not more than 72 hours prior to Day 1.
Medical History	9.4	Medical History		X		Including preexisting conditions, historical illnesses, prior treatment and any alcohol/tobacco habits.
Physical Exam		Height		X		Height measurement to be performed at baseline only.
	7.2.1	Weight		X		Include an estimation of the amount of weight loss that has occurred over the prior 1-month and 6-month periods.
	9.4.1	Physical Exam/Vital Signs		X		Including temperature, blood pressure, pulse rate, respiration rate. Physical exam to include a screening neuromuscular exam with focus on monitoring for tremors.
	6.1, Appendix 7	ECOG PS		X		
Patient-Reported Outcomes	9.1.3.1	FACT-Hep questionnaire		X		The instruments should be completed before any extensive contact and consultation, which may bias patient responses. It is recommended that the instruments be administered together, with the FACT-Hep completed first, followed by the EQ-5D-5L.
	9.1.3.2	EQ-5D-5L questionnaire		X		
Concomitant Medications	7.7	Concomitant Medications	X			Concomitant medications (including over the counter medications and supplements) will be recorded, including any taken within 30 days prior to randomization.

Schedule of Screening Activities I3O-MC-JSBF

			Baseline			
		Cycle	BL			
		Visit	0			
		Relative Day Prior to Cycle 1 Day 1	**≤28**	**≤14**	**≤7**	**Notes**
Procedure Category	**Prot. Ref.**	**Procedure**				
Adverse Events	9.2	AE collection and CTCAE v4.0 grading (Preexisting conditions)		X		To be reported only after study eligibility is confirmed
Laboratory/ Diagnostic Tests	6.1, Appendix 3	Hematology profile		X		
	6.1, Appendix 3	Serum Chemistry profile		X		Two measurements are required that are separated by at least 5 days. Serum chemistry to include TSH, free thyroxine (T4), and free triiodothyronine (T3).
	6.1, Appendix 3	Coagulation Profile		X		
	6.1, Appendix 3	Urinalysis		X		Routine dipstick measurements, and if clinically indicated, microscopic analysis. If urine dipstick or routine analysis indicates proteinuria ≥2+ at evaluations, a 24-hour urine collection (to assess protein) must be obtained.
	6.1, Appendix 3	Pregnancy Test			X	Required for women of child-bearing potential. A serum β-HCG test (minimum sensitivity 25 IU/L or equivalent units of β-hCG) must be done within 7 days prior to Day 1 of Cycle 1. If required per local regulations and/or institutional guidelines, pregnancy testing can also be performed at other times during the study treatment period, the post discontinuation follow up period and the continued access period.
	6.1, Appendix 6	Glomerular Filtration Rate		X		GFR of ≥ 50 ml/min/1.73 m^2. GFR should be calculated by the CKD-EPI equation, or GFR may also be measured using 24 hour urine collection or clearance of exogenous filtration markers (such as iothalamate or 51-CrEDTA or Tc99m-DTPA).
	9.4.1	ECG	X			

Schedule of Screening Activities I3O-MC-JSBF

			Baseline			
		Cycle	BL			
		Visit	0			
		Relative Day Prior to Cycle 1 Day 1	**≤28**	**≤14**	**≤7**	**Notes**
Procedure Category	**Prot. Ref.**	**Procedure**				
Efficacy Assessments	9.1.1, Appendix 8	Radiological Tumor Assessment (according to RECIST v1.1)	X			To be performed ≤ 28 days prior to Cycle 1 Day 1. These scans can be assessed locally.
Sample Collection	9.7.1, Appendix 4	DNA Genotyping Blood Sample (stored)	Refer to Appendix 4, Table APP.4.1			Can be collected any time after eligibility has been confirmed throughout the trial.
	9.8.1. Appendix 4	Whole blood, plasma, and serum samples for biomarkers	Refer to Appendix 4, Table APP.4.1			Should only be taken after study eligibility is confirmed.
	6.1, 9.8.2, Appendix 4	Tumor biopsy (new specimen or recent archived specimen, see Section 9.8.2)	X			Where possible review of medical records and routine labs should be performed to aid eligibility assessment before biopsy in order to minimize unnecessary procedures.

Abbreviations: β-HCG = beta human chorionic gonadotropin; AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; BL = baseline; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EQ-5D-5L = EuroQol 5-Dimension 5 Level; FACT-HEP = The Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) questionnaire consisting of the 27-item FACT-General (FACT-G) and the disease-specific 18-item Hepatobiliary Subscale (HepCS-18); GFR = glomerular filtration rate; ICF = informed consent form; IRB/ERB = institutional review board/ethical review board; IWRS = interactive web-response system; RECIST = Response Evaluation Criteria In Solid Tumors; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; v = version.

Table JSBF.2. Treatment Period, I3O-MC-JSBF

After Cycle 1, a treatment delay at the start of a cycle (Day 1) of ±7 days, because of holidays, weekends, inclement weather, or other justifiable events, will be permitted and not counted as a protocol violation. 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.

			Treatment Period								
		Study Period									**Notes**
		Cycle (21-day cycle)	**1-8**				**9+**				
		Relative Day within Cycle)	**1**	**2-7**	**8**	**9-21**	**1**	**2-7**	**8[a]**	**9-21**	
Procedure Category	**Protocol Section**	**Procedure**									
Physical Examination	9, 9.4.1	Physical Exam	X				X				Predose. Physical exam to include visible or palpable tumor measurements and screening neuromuscular exam with focus on monitoring for tremors.
	7.2.1	Weight, BSA	X				X				Predose. Weight and BSA are to be determined, as needed at each cycle until discontinuation of all IV study treatment(s). If the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior dose, then the dose of IV study treatment will not need to be recalculated.
	Appendix 7	ECOG PS	X				X				Predose. For ECOG PS, a time window of -3 days is permitted for the Cycle 1 Day 1 assessment.
	9.4.1	Vital Signs	X		X		X		X		Predose. Include temperature, blood pressure, pulse rate, respiration rate. For the patient's first 2 doses of ramucirumab/placebo, measure all vital signs 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 postinfusion observation period. For all infusions of gemcitabine, cisplatin and all subsequent infusions of ramucirumab/placebo, measure blood pressure and pulse prior to the infusion and measure other vital signs as clinically indicated.

Treatment Period, I3O-MC-JSBF

			Treatment Period								
		Study Period									**Notes**
		Cycle (21-day cycle)	**1-8**				**9+**				
		Relative Day within Cycle)	**1**	**2-7**	**8**	**9-21**	**1**	**2-7**	**8[a]**	**9-21**	
Procedure Category	**Protocol Section**	**Procedure**									
Patient-Reported Outcomes	9.1.3.1	FACT-Hep questionnaire	X		X*		X				To be performed on Days 1 and 8 for Cycles 1 through 3 and on Day 1 for Cycle 4 onward. May be completed up to 3 days prior to start of each cycle, prior to any infusion. The instruments should be completed before any extensive contact and consultation, which may bias patient responses. It is recommended that the instruments be administered together, with the FACT-Hep completed first, followed by the EQ-5D-5L.
	9.1.3.2	EQ-5D-5L questionnaire	X		X*		X				
Efficacy Assessment	9.1.1, 7.7.4, Appendix 8	Radiologic imaging (according to RECIST 1.1) and tumor measurement	X*								*To be performed, by the same method used at baseline, every 6 weeks (±7 days) after randomization (regardless of treatment delays) during the Study Treatment Period, until disease progression OR study completion or 14 months after randomization, whichever occurs first. Refer to footnote b for any patient whose disease has not progressed by 14 months after randomization. A confirmatory radiological scan is required after documented progression has occurred in the previous 4 to 6 weeks.
Adverse Events	9.2	AE collection and CTCAE v4.0 grading	X		X		X		X		Throughout the cycle as needed. Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.
Concomitant Medications	7.7	Concomitant medication notation	X				X				Concomitant medications (including over the counter medications and supplements) will be recorded throughout the cycle as needed.

Treatment Period, I3O-MC-JSBF

			Treatment Period								
		Study Period									**Notes**
		Cycle (21-day cycle)	**1-8**				**9+**				
		Relative Day within Cycle)	**1**	**2-7**	**8**	**9-21**	**1**	**2-7**	**8[a]**	**9-21**	
Procedure Category	**Protocol Section**	**Procedure**									
Laboratory/ Diagnostic Tests	Appendix 3	Hematology Profile	X		X		X				Assessments performed within 3 days prior to each infusion may be used for treatment decisions, if the results are deemed still clinically valid by the treating investigator.
	Appendix 3	Full chemistry profile	X		X		X				Assessments performed within 3 days prior to Day 1 of the cycle may be used for treatment decisions, if the results are deemed still clinically valid by the treating investigator. Day 8 chemistry to be collected during Cycles 1 through 8. Thereafter, Day 8 collections will be optional as clinically indicated at the discretion of the treating investigator. In Cycle 8, serum chemistry on any day in the cycle to include TSH, free thyroxine (T4), and free triiodothyronine (T3).
	Appendix 3	Coagulation Profile	X								Baseline assessments may be used for treatment decisions for Cycle 1 D 1 if the baseline assessments were performed within 7 days prior to Cycle 1 D1 and the results are deemed still clinically valid by the treating investigator. Thereafter, perform within 3 days prior to D1 of every odd-numbered cycle.
	Appendix 3	Urinalysis	X				X				For Arm A only: Perform dipstick or routine urinalysis within 3 days prior to D1 of each cycle. Baseline assessments may be used for treatment decisions for Cycle 1 D1 if the baseline assessments were performed within 7 days prior to Cycle 1 D1 and the results are deemed still clinically valid by the treating investigator. If baseline urine protein ≥2+ on dipstick or routine urinalysis, 24-hour urine protein results must be obtained prior to the first infusion. See Table JSBF.11 for information about dose modifications required for proteinuria
	Appendix 3	Pregnancy Test	X*				X*				* Required for women of child-bearing potential (WOCBP). Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of β-hCG) to be performed in WOCBP every second cycle or per institutional guidelines, whichever is shorter. Pregnancy test results will not be collected on the CRF.
	Appendix 3	CA19-9, CEA, CA 125	X				X				Predose; Refer to Appendix 3.

Treatment Period, I3O-MC-JSBF

			Treatment Period								
		Study Period									**Notes**
		Cycle (21-day cycle)	**1-8**				**9+**				
		Relative Day within Cycle)	**1**	**2-7**	**8**	**9-21**	**1**	**2-7**	**8[a]**	**9-21**	
Procedure Category	**Protocol Section**	**Procedure**									
Sample Collection	9.5, Appendix 4	PK	Refer to Appendix 4, Table APP.4.2 (Arm A), Table APP.4.3 (Arm B) and Table APP.4.4 (Arms A and B).								For Arm A: If a patient experiences an IRR to ramucirumab/placebo, blood samples for both immunogenicity and PK analysis should be drawn, with no more than 15 minutes' time difference. 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.
	9.8.3, Appendix 4, Table APP.4.2	Immunogenicity: Anti-ramucirumab antibodies	(For Arm A only) Refer to Appendix 4, Table APP.4.2								
	9.8.2, Appendix 4	Tumor tissue	Refer to Appendix 4								At any time during the study, if tumor tissue becomes available, a sample should be provided.
	9.8, Appendix 4	Whole blood, plasma, and serum samples for biomarkers	Refer to Appendix 4								During screening, on C1D1 (before dosing and at the end of study day), on C1D8, and then to coincide within 7 days of the Radiological Tumor Assessment at 6 and 12 weeks, and then every 12 weeks thereafter.
Premedication	7.2.1.1.1 7.2.1.1.2	Premedication notation	X		X		X		X		Ramucirumab/Placebo: Refer to Section 7.2.1.1.1. Cisplatin and Gemcitabine: Refer to Section 7.2.1.1.2.
Study Drug	7.2.1.2	Ramucirumab/Placebo	X		X		X		X		For Arm A only.
	7.2.1.3	Merestinib/Placebo	X	X	X	X	X	X	X	X	For Arm B only.
	7.2.1.4	Cisplatin	X		X						For Arm A and B.
	7.2.1.5	Gemcitabine	X		X						For Arm A and B.

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; ASCO = American Society of Clinical Oncology; BSA = body surface area; CRF = case report form; CRP = (Lilly) clinical research physician; CRS = (Lilly) clinical research scientist; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECOG PS = Eastern Cooperative Oncology Group performance status; EQ-5D-5L = EuroQol 5-Dimension 5 Level; FACT-HEP = The Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) questionnaire consisting of the 27-item FACT-General (FACT-G) and the disease-specific 18-item Hepatobiliary Subscale (HepCS-18); IRR = infusion-related reaction; IV = intravenous; MRI = magnetic resonance imaging; PK = pharmacokinetic(s); RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = serious adverse event; TSH = thyroid-stimulating hormone; v = version; WOCBP = women of childbearing potential.

a Patients who have completed treatment with cisplatin and gemcitabine and are no longer receiving IV treatment on Day 8 are not required to return to the clinic on Day 8 of subsequent cycles

b Any patient whose disease has not progressed by 14 months after randomization (note that the patient may or may not still be on study treatment) will be evaluated for response every 12 weeks (±7 days) from 14 months after randomization, until disease progression OR study completion OR 3 years after randomization, whichever occurs first; then as per standard clinical practice after that.

Table JSBF.3. Postdiscontinuation Follow-Up Schedule, I3O-MC-JSBF

			Postdiscontinuation Follow-up		
		Cycle	**Short-term Follow-up**	**Long-term Follow-up**	**Notes**
		Visit	801	802-8XX	
		Duration	Refer to footnote for duration	Refer to footnote for duration	
Procedure Category	**Protocol Reference**	**Procedure**			
Physical Examination	7.2.1	Weight	X		
	9.4.1	Vital Signs	X		Include temperature, blood pressure, pulse rate, respiration rate.
	6.1, Appendix 7	ECOG performance status	X		
Patient-Reported Outcomes	9.1.3.1	FACT-Hep questionnaire	X		The instruments should be completed before any extensive contact and consultation, which may bias patient responses. It is recommended that the instruments be administered together, with the FACT-Hep completed first, followed by the EQ-5D-5L.
	9.1.3.2	EQ-5D-5L questionnaire	X		
Efficacy Assessment	9.1.2, 7.7.4, Appendix 8	Radiologic imaging (according to RECIST 1.1) and tumor measurement	X	X	Patients who discontinue study treatment for any reason other than disease progression will continue to undergo radiographic tumor assessments, by the same method used at baseline and throughout the study, every 6 weeks (±7 days) after randomization until disease progression OR study completion OR 14 months after randomization, whichever occurs first. Refer to footnote a for any patient whose disease has not progressed by 14 months after randomization. A confirmatory radiological scan is required after documented progression has occurred in the previous 4 to 6 weeks. Thereafter, radiologic tests are no longer required and the patient will be followed for survival.
Survival information	9.1.2	Collection of survival information	X	X	Collection of survival data every 3 months (±7 days) until the patient's death or study completion, whichever occurs first. Whenever possible, survival follow-up is conducted in person. If an in-person visit is not possible, the site may confirm survival by contacting the patient directly via telephone.
Adverse Events	9.2	AE collection and CTCAE v4.0 grading	X	X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System. During Postdiscontinuation Long-term Follow-up, only SAEs that are related to protocol procedures or study treatment will be collected.
Concomitant Medications	7.7	Concomitant medication notation	X		Concomitant medications (including over the counter medications and supplements) will be recorded.

Postdiscontinuation Follow-Up Schedule, I3O-MC-JSBF

			Postdiscontinuation Follow-up		
		Cycle	**Short-term Follow-up**	**Long-term Follow-up**	**Notes**
		Visit	801	802-8XX	
		Duration	Refer to footnote for duration	Refer to footnote for duration	
Procedure Category	**Protocol Reference**	**Procedure**			
Laboratory/ Diagnostic Tests	Appendix 3	Hematology	X		
	Appendix 3	Chemistry	X		Serum chemistry to include TSH, free thyroxine (T4), and free triiodothyronine (T3).
	Appendix 3	Coagulation	X		
	Appendix 3	Urinalysis	X		Routine dipstick measurements, and if clinically indicated, microscopic analysis. If urine dipstick or routine analysis indicates proteinuria ≥2+ at evaluations, a 24-hour urine collection (to assess protein) must be obtained.
Sample Collection	9.5, Appendix 4	PK	Refer to Appendix 4, Table APP.4.2 (Arm A).		For Arm A: If a patient experiences an IRR to ramucirumab, blood samples for both immunogenicity and PK analysis should be drawn, with no more than 15 minutes' time difference. 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.
	9.8.3, Appendix 4, Table APP.4.2	Immunogenicity: Anti-ramucirumab antibodies	(For Arm A only) Refer to Appendix 4, Table APP.4.2.		
	9.8, Appendix 4	Whole blood, plasma, and serum samples for biomarkers	Refer to Appendix 4		
Other	10.3.4.5	Collection of postdiscontinuation anticancer therapy	X	X	

Postdiscontinuation Follow-Up Schedule, I3O-MC-JSBF (concluded)

Abbreviations: AE = adverse event; CRP = (Lilly) clinical research physician; CRS = (Lilly) clinical research scientist; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQol 5-Dimension 5 Level; FACT-HEP = The Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) questionnaire consisting of the 27-item FACT-General (FACT-G) and the disease-specific 18-item Hepatobiliary Subscale (HepCS-18); OS = overall survival; PK = pharmacokinetic(s); RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAEs = serious adverse events; TSH = thyroid-stimulating hormone.

Note: No follow-up procedures will be performed for patients who withdraw informed consent unless he or she has explicitly provided permission and consent.

Short-term Follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.

Long-term Follow-up begins the day after Short-term Follow-up is completed and continues until the patient's death or study completion. Patients who discontinue study treatment for reasons other than disease progression will continue to undergo radiographic tumor assessments according to the timing stated in Section 9.1.2, by the same method used at baseline and throughout the study, until the patient has radiographic documentation of disease progression as defined by RECIST 1.1 or until study completion (that is, the final analysis of OS), whichever occurs first. Patients will be followed for survival every 3 months (±7 days) until the patient's death or study completion, whichever occurs first.

a Any patient whose disease has not progressed by 14 months after randomization (note that the patient may or may not still be on study treatment) will be evaluated for response every 12 weeks (±7 days) from 14 months after randomization, until disease progression OR study completion OR 3 years after randomization, whichever occurs first; then as per standard clinical practice after that.

Table JSBF.4. Continued Access Schedule of Activities

			Continued Access Period		Notes
			Treatment Period	Continued Access Follow-up	
		Cycle	X-Y	Follow-up	
		Visit	501-5XX	901	
		Relative day within a cycle	1		
Procedure Category	**Protocol Section or Attachment**	**Procedure**			
Physical Examination	7.2.1	Weight	X		BSA to be calculated at each cycle until cisplatin and gemcitabine are discontinued.
Adverse Events	9.2	AE collection and CTCAE grading	X	X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.
Sample Collection	9.5, Appendix 4	PK	Refer to Appendix 4, Table APP.4.2 (Arm A).		For Arm A: If a patient experiences an IRR to ramucirumab, blood samples for both immunogenicity and PK analysis should be drawn, with no more than 15 minutes' time difference. 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.
	9.8.3, Appendix 4, Table APP.4.2	Immunogenicity: Anti-ramucirumab antibodies	(For Arm A only) Refer to Appendix 4, Table APP.4.2.		
Premedication	7.2.1.1.1 7.2.1.1.2	Premedication notation	X		Ramucirumab/Placebo: Refer to Section 7.2.1.1.1. Cisplatin and Gemcitabine: Refer to Section 7.2.1.1.2.
Study Drug	7.2.1.2	Ramucirumab	X		After study completion, all patients who are on study treatment and who are eligible for continued access will be unblinded. Patients receiving study treatment and experiencing ongoing clinical benefit and no undue risks may continue to receive study treatment in the Continued Access Period until one of the criteria for discontinuation is met (Section 8). During the Continued Access Period, placebo will no longer be administered.
	7.2.1.3	Merestinib	X		
	7.2.1.4	Gemcitabine	X		
	7.2.1.5	Cisplatin	X		

Abbreviations: AE = adverse event; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction; IV = intravenous; PK = pharmacokinetics; SAE = serious adverse event.

Note: No follow-up procedures will be performed for patients who withdraw informed consent unless he or she has explicitly provided permission and consent.

Continued Access Period begins after study completion and ends at the end of trial. During the Continued Access Period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met. The Continued Access Period includes Continued Access Follow-up. During the Continued Access Period, required evaluations are shown in the table. Investigators will perform any other standard procedures and tests needed to treat and evaluate patients and to confirm patient eligibility to continue on treatment; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

Continued Access Follow-up begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the Continued Access Period and lasts approximately 30 days.

Note: Efficacy assessments will be done at the investigator's discretion based on the standard of care.

3. Introduction

3.1. Study Rationale

This Phase 2, multicenter, double-blinded study is designed to evaluate the efficacy and safety of 2 new combinations for the treatment of first-line advanced or metastatic biliary tract cancer (BTC):

1. Arm A: ramucirumab (LY3009806, intravenous [IV]) in combination with cisplatin and gemcitabine (Arm A1) versus placebo (IV) plus cisplatin and gemcitabine (Arm A2)
2. Arm B: merestinib (LY2801653, oral) in combination with cisplatin and gemcitabine (Arm B1) versus placebo (oral) plus cisplatin and gemcitabine (Arm B2)

3.1.1. Biliary Tract Cancers

Biliary tract cancers (BTC) include a spectrum of invasive adenocarcinomas encompassing cancer of the gallbladder, intra- and extra-hepatic biliary ducts, and Ampulla of Vater (Hezel and Zhu 2008, Castro et al. 2013). Globally, there are more than 178,000 new gall bladder cases, alone, diagnosed annually (Ferlay et al. 2013). The incidence and mortality of some forms of BTC are rising, especially in the United States and in some European countries (Chang et al. 2009; Castro et al. 2013), and is the 7th leading cause of cancer mortality in Japan (Ferlay et al. 2013). However, the majority of patients do not present at an early stage, and only about 10% of patients are surgical candidates (Hezel and Zhu 2008).

In 2010, the Phase 3 randomized ABC-02 trial established gemcitabine plus cisplatin as the global standard of care in the first-line setting. This study demonstrated an advantage in overall survival (OS) and progression-free survival (PFS) in favor of the cisplatin / gemcitabine doublet versus gemcitabine (11.7 vs. 8.1 months; $p<0.001$ and 8.0 vs. 5.0 months; $p<0.001$, respectively) (Valle et al. 2010). While the results of the ABC-02 study established the combination of cisplatin and gemcitabine as a reference standard in this disease, improvements in treatment options are still required as demonstrated by the fact that half of patients still succumb to the disease at 1 year.

3.1.1.1. Rationale for Exploration of Ramucirumab Combination Therapy in BTC

Vascular endothelial growth factor (VEGF), one of the main growth factors regulating angiogenesis, is overexpressed in 40% to 75% of BTC, especially at the invasive edge of the tumor (Giatromanolaki et al. 2003; Tang et al. 2006; Möbius et al. 2007; Yoshikawa et al 2008). VEGFR1 and VEGFR2 are also overexpressed in the adjacent endothelial cells (Benckert et al. 2003). Clinically, VEGF expression is also associated with the presence of metastases in intrahepatic cholangiocarcinoma (Yoshikawa et al. 2008); adverse prognosis in extrahepatic cholangiocarcinoma (Hida et al. 1999), and increased microvascular density (MVD) in both cholangiocarcinoma and gallbladder cancer (Giatromanolaki et al. 2003; Tang et al. 2006). High MVD is an independent adverse prognostic factor for disease-free survival after resection of extrahepatic cholangiocarcinoma and for OS in lymph node-negative intrahepatic cholangiocarcinoma and gallbladder cancer (Giatromanolaki et al. 2003; Shirabe et al. 2004; Möbius et al. 2007).

Targeted therapies have enhanced outcomes in combination with systemic chemotherapy in other malignancies (that is, colorectal, breast, and lung cancer) and are thought to be the future of systemic treatment for BTC, and studies with agents targeting angiogenesis have suggested targeting this pathway may provide benefit in treating BTC. A Phase 2 trial of gemcitabine, oxaliplatin, and bevacizumab enrolled 35 patients with biliary cancers and resulted in a response rate of 40%, a PFS of 7.0 months and an OS of 12.7 months, which compared favorably with historic controls (Zhu et al. 2010). Lubner and colleagues reported a multicenter Phase 2 trial of bevacizumab and erlotinib in patients with unresectable biliary cancer. The confirmed partial response rate in this study was 12%, median OS was 9.9 months, and time to progression (TTP) was 4.4 months, suggesting a regimen including an antiangiogenic agent has activity in this disease (Lubner et al 2010). Modest anti-tumor efficacy against biliary cancers was also demonstrated with multitargeted anti-angiogenic tyrosine kinase inhibitors, including sorafenib and sunitinib (Bengala et al. 2010; Yi et al. 2012; Lee et al. 2013).

ABC-03, a double-blind placebo-controlled Phase 2 study of the pan-VEGF receptor tyrosine kinase inhibitor cediranib in combination with gemcitabine/cisplatin versus placebo with gemcitabine/cisplatin, demonstrated an improved radiological response rate (44% vs. 19%, p=0.0036), a 10% improvement in 6-month PFS survival (71% vs. 61%), and a 10% difference in 1-year survival (58 vs. 48%). Toxicity of the cediranib/chemotherapy combination led to relatively early discontinuation of study drug (median 4.6 months), and an apparent early PFS benefit diminished soon after, suggesting that treatment with a well-tolerated anti-VEGFR therapy could result in greater benefit in combination with gemcitabine/cisplatin (Valle et al. 2015).

Ramucirumab, is a recombinant human monoclonal antibody (mAb) of the immunoglobulin G, subclass 1 (IgG1) that specifically binds to the extracellular domain of VEGF Receptor 2 with high affinity, thus blocking VEGF binding and inhibiting angiogenesis. Ramucirumab has demonstrated benefit across multiple tumor types, both as single agent or in combination with cytotoxic chemotherapy, and has been well tolerated. Despite preliminary evidence of activity for antiangiogenic agents in BTC, no targeted agent has been approved in this setting, and there remains a high unmet need for new treatment options for this disease.

3.1.1.2. Rationale for Exploration of Merestinib Combination Therapy in BTC

The tyrosine kinase receptor MET has been linked to the promotion of a metastatic and invasive tumor phenotype (Maulik et al. 2002). Aberrant MET signaling, whether due to genetic lesions, transcriptional upregulation, or ligand-dependent autocrine or paracrine mechanisms, plays a key role in tumorigenesis and angiogenesis (Migliore and Giordano 2008). Studies demonstrate that many types of human cancers, including gastric, colorectal, renal, breast, pancreatic, lung, cholangiocarcinoma, and hepatocellular carcinoma, have upregulated MET and/or elevated hepatocyte growth factor (HGF) expression. In many cases, this aberrant expression correlates with a poor prognosis (reviewed in Birchmeier et al 2003; Comoglio et al. 2008). Amplification of MET has also been demonstrated in tumor cells that have acquired resistance to treatments targeting other tyrosine kinase receptors, such as erlotinib and gefitinib (Bean et al. 2007; Engelman et al. 2007).

MET receptor expression is a common feature of BTC with 50% to 60% of cholangiocarcinoma cases demonstrating high expression of MET by immunohistochemistry (IHC) and only about 10% of cases demonstrating poor or no staining (Miyamoto et al. 2011; Thobe et al. 2013). The frequency of MET expression does not appear to differ significantly between Asian and Non-Asian cases and appears to occur at a stable rate, regardless of mutation rates for KRAS or IDH1/2. In addition to supporting tumor biology, high MET expression may contribute to resistance to first-line therapy (Engelman 2007; Bean 2007; Dulak et al. 2011; Casado et al. 2012). Data from other tumor types suggest that cisplatin therapy results in selection of MET expressing cells and that cells with MET expression are resistant to cisplatin therapy (Sun and Wang 2011). Improvements in response to cisplatin have been seen in combination with merestinib in cholangiocarcinoma models (Investigator's Brochure [IB] for merestinib). In cholangiocarcinoma cell line-derived xenograft models (EGI-1, SNU869 and SNU1196) and in patient-derived cholangiocarcinoma xenograft tumor models [BIL001 (also known as CTG-0011] and CTG-0399), concurrent treatment with merestinib and cisplatin resulted in enhanced suppression of tumor growth compared to that seen with cisplatin alone.

In addition to expressing MET, BTC tumors have been shown to have activation of AXL, activation of eIF4E, and activating ROS kinase fusion proteins (Gu et al. 2011; Yan et al. 2014; Fujimori et al. 2015). Merestinib (LY2801653) is a potent and selective type II MET kinase inhibitor and has also been shown to be capable of inhibiting 13 MET mutations/variants and is an inhibitor of several other oncokinases including AXL, ROS, and eIF4E (Yan et al. 2013; Table JSBF.5). Similar to high MET expression, high AXL expression may contribute to resistance to cisplatin (Hong et al. 2013). In the cholangiocarcinoma cell line-derived xenograft model SNU1196, AXL is very highly expressed. In this model, concurrent treatment with merestinib and cisplatin resulted in enhanced suppression of tumor growth compared to that seen with cisplatin alone (merestinib IB). Preclinical testing suggests that increased antitumor activity could be achieved with the addition of merestinib to the combination of cisplatin and gemcitabine (merestinib Investigator Brochure).

Given the dysregulation of the MET, AXL, eIF4E, and ROS kinase pathways in BTCs, and based on the hypothesis that inhibition of MET or AXL could be used to sensitize tumors to cisplatin therapy or prevent resistance to cisplatin, Phase 1 testing of merestinib (Study I3O-MC-JSBA [JSBA]) included testing in BTC as a single agent in refractory and advanced or metastatic patients, in combination with cisplatin after first-line therapy, and in combination with cisplatin and gemcitabine in first-line advanced or metastatic patients. While enrollment to these cohorts has completed, final results are not yet available and testing is ongoing. Among the BTC cohort receiving second-line treatment with merestinib and cisplatin, 1 patient has had a confirmed complete response (CR) and median PFS for the cohort has not yet been reached. Among 6 first-line CCA evaluable patients, 1 partial response (PR) and 2 stable disease (SD) have been reported. In Study JSBA, treatment with merestinib alone or in combination has demonstrated a clinically acceptable safety profile. Additional details are available in the merestinib IB.

3.2. Background

3.2.1. Ramucirumab

Ramucirumab (LY3009806) is a recombinant human monoclonal antibody (mAb) of the immunoglobulin G, subclass 1 (IgG1) that specifically binds to the extracellular domain of VEGF Receptor 2 with high affinity. This antibody potently blocks the binding of the VEGF ligand to VEGF Receptor 2, inhibits VEGF-stimulated activation of both VEGF Receptor 2 and p44/p42 MAP kinases, and neutralizes VEGF-induced mitogenesis of human endothelial cells.

Ramucirumab has been shown to block the interaction of VEGF and VEGF Receptor 2 (with a concentration that inhibits binding by 50% of approximately 1 nM), and to inhibit VEGF-stimulated proliferation of endothelial cells and VEGF-induced migration of human leukemia cells. The results of these preclinical pharmacodynamic studies supported the initial investigation of ramucirumab in the treatment of solid tumors.

Clinical investigations with ramucirumab in solid tumors have resulted in 4 positive Phase 3 trials, with 2 in gastric cancer (REGARD and RAINBOW), 1 in non-small cell lung cancer (NSCLC; REVEL), and 1 in metastatic colorectal cancer (CRC; RAISE). Ramucirumab (Cyramza®) is approved in the United States, as a single agent or in combination with paclitaxel, as a treatment for people with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose cancer has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy, in combination with docetaxel as a treatment for people with metastatic NSCLC whose cancer has progressed on or after platinum-based chemotherapy and in combination with FOLFIRI for the treatment of metastatic CRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. In addition, the European Commission approved ramucirumab (Cyramza) in combination with paclitaxel and as a single agent when combination therapy is not appropriate, for people with advanced gastric cancer after prior chemotherapy.

3.2.2. Merestinib

Merestinib (LY2801653) is a type II ATP competitive, slow-off inhibitor that was designed in an effort to target MET and RON kinase. Preclinical testing has demonstrated anti-proliferative and anti-angiogenic activity of this compound. Broad kinase screening against 400 kinases demonstrated potent restricted inhibition of a select group of oncokinases (Table JSBF.5 and Figure JSBF.1) (Yan et al. 2013). Merestinib inhibits MET phosphorylation in HGF-stimulated H460 cells with an inhibitory concentration (IC_{50}) of 35 nM (Yan et al. 2013). It also inhibits MET phosphorylation in autocrine S114 cells and is active against 13 different activating mutant forms of MET with similar potency. Merestinib inhibits macrophage-stimulating protein (MSP) induced RON (MST1R) phosphorylation in NIH3T3-RON cells with an IC_{50} of 11 nM. In vitro, merestinib is also a potent inhibitor of the migration of human umbilical vein endothelial cells (HUVEC) and angiogenic cord formation in ASC1/EPC-D2 co-culture assays. Merestinib inhibits the phosphorylation of ROS1, an oncogenic tyrosine kinase closely related to the

MET/RON family; in U118MG cells harboring the FIG-ROS1 translocation, merestinib inhibits phosphorylation of constitutively activated FIG-ROS1 fusion protein with an IC_{50} of 23 nM.

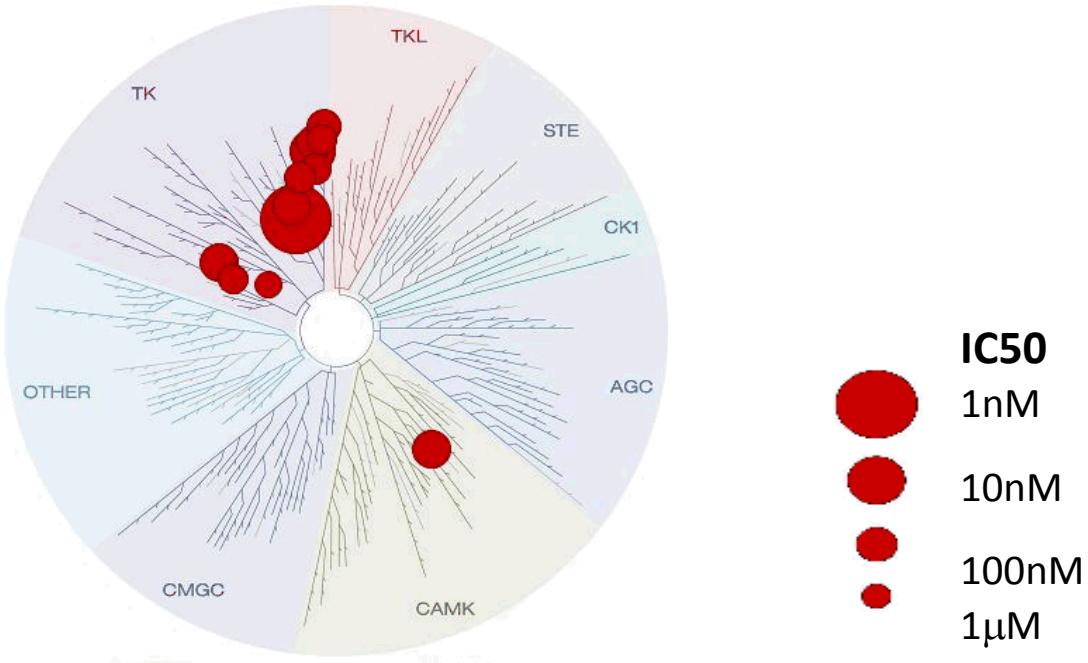
Table JSBF.5. In Vitro Inhibitory Activity of Merestinib against MET and Other Kinases

Kinase	Biochemical Activity IC_{50} or Kd (nM)	Cell-Based Activity[a] IC_{50} (nM)
MET	4.7	35 – 52
MST1R (aka RON)	12	11
AXL	11	2
ROS1	43	23 – 170
MKNK1/2	130 / 109	7
PDGFRA	620	41
FLT3	31	7
MERTK	0.8	10
TYRO3	1210	28
TEK (aka Tie2)	4	63
DDR1	0.95	0.1
DDR2	41	7
CSFR1	32	300
FLT1	76	>1000
FLT4	23	>316
TIE1	0.9.	>1000
KDR	53	347
RET	590	2000

Abbreviations; IC_{50} = concentration producing 50% inhibition; Kd = dissociation constant.

a Cell-based activity was cell proliferation or target inhibition.

Source: Yan et al. 2013



Abbreviation: IC_{50} = half maximal inhibitory concentration.
Source: Yan et al. 2013

Figure JSBF.1. Dendrogram of the in vitro cell-based activity of merestinib with IC_{50} less than 200 nM.

Table JSBF.6. Merestinib In Vitro Inhibitory Activity Against *MET*-Activating Mutations in BaF3 Cells Cultured Without IL-3

MET mutation	IC_{50} (nM)
TPR-MET wild type	42
Y1230C	54
D1228N	111
V1092I	12
M1250T	119
V1188L	23
L1195V	248
K1244R	77
M1131T	208
V1220I	18
S1040P	53
H1106D	33
G1119V	62
H1094Y	25

Abbreviations: IC_{50} = half maximal inhibitory concentration; IL-3 = interleukin 3.
Source: Yan et al. 2013

Dose-dependent antitumor activities (measured by tumor volume reduction) of merestinib have been demonstrated in a number of human tumor xenograft models (Wu et al. 2013; Yan et al.

2013; Kawada et al. 2014). These included models that are MET, AXL, and or RON driven models.

In addition to reducing tumor growth in multiple tumor xenograft models (MET autocrine U87MG glioblastoma model, *MET* amplified MKN45 gastric tumor model, and AXL over-expression SNU-1196 cholangiocarcinoma model), merestinib treatment also resulted in a dramatic modulation of many angiogenesis parameters indicating a normalization of tumor vessels (a decrease in GLUT1 expression, an increase in pericyte coverage of vessels, decrease levels of hypoxia) (Yan et al. 2013; Yan et al. 2014).

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of merestinib and ramucirumab are to be found in the IB for merestinib (LY2801653) and ramucirumab (LY3009806), respectively.

4. Objectives and Endpoints

Table JSBF.7 shows the objectives and endpoints of the study.

Table JSBF.7. Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluate the efficacy, in terms of PFS, in patients with advanced or metastatic BTC, for • ramucirumab (8 mg/kg, IV) versus placebo, in combination with cisplatin (25 mg/m^2, IV) and gemcitabine (1000 mg/m^2, IV), on Days 1 and 8 of a 21-day cycle. • merestinib (80 mg, oral each day) versus placebo, in combination with cisplatin (25 mg/m^2, IV) and gemcitabine (1000 mg/m^2, IV), on Days 1 and 8 of a 21-day cycle.	PFS (objective progression or death), as determined by investigator assessment per RECIST 1.1.
Secondary	
Evaluate the efficacy, in combination with cisplatin and gemcitabine, in terms of OS, for ramucirumab versus placebo and merestinib versus placebo.	OS
Evaluate the efficacy, in combination with cisplatin and gemcitabine, in terms of ORR and DCR for ramucirumab versus placebo and merestinib versus placebo.	ORR and DCR
• Safety profile of ramucirumab • Safety profile of merestinib	The safety endpoints evaluated will include but are not limited to the following: • TEAEs, AESIs, SAEs, and hospitalizations • Clinical laboratory tests, vital signs, and physical examinations
• PK of ramucirumab • PK of merestinib	• Minimum ramucirumab concentration in serum • Postdose merestinib concentration in plasma
Immunogenicity of ramucirumab	Blood samples for immunogenicity testing will be collected to determine antibody production against ramucirumab.
Evaluate PRO measures of disease-specific symptoms, in combination with cisplatin and gemcitabine, for ramucirumab versus placebo and merestinib versus placebo.	Functional Assessment of Cancer Therapy Hepatobiliary Questionnaire (FACT-Hep) EuroQol 5-Dimension 5-Level (EQ-5D-5L)
Tertiary/Exploratory	
• To explore biomarkers relevant to ramucirumab or merestinib, angiogenesis, immune function, and the disease state, and to correlate these markers to clinical outcome. • Explore the relationship of pretreatment weight loss with primary and secondary treatment response outcomes.	• Biomarker research may be assessed from tissue, whole blood, serum, and plasma samples, unless precluded by local regulations.

Abbreviations: AESIs = adverse events of special interest; BTC = biliary tract cancer; DCR = disease control rate; IV = intravenous; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PRO = patient-reported outcomes; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

5. Study Design

5.1. Overall Design

Study I3O-MC-JSBF (JSBF) is a global, multicenter, randomized, double-blind, Phase 2 study in patients with advanced or metastatic BTC who have had no prior therapy for advanced or metastatic BTC.

The primary objective is to compare the PFS in BTC patients treated with ramucirumab plus cisplatin and gemcitabine versus placebo plus cisplatin and gemcitabine and merestinib plus cisplatin and gemcitabine versus placebo plus cisplatin and gemcitabine. To assess the primary objective, approximately 300 patients will be randomized, such that patients in each cohort (IV and oral) will be allocated to receive investigational treatment or control in a 2:1 fashion:

Intravenous Treatment:

- Arm A1: ramucirumab 8 mg/kg plus cisplatin (25 mg/m^2) and gemcitabine (1000 mg/m^2) intravenously on Days 1 and 8, every 21 days

or

- Arm A2: placebo plus cisplatin (25 mg/m^2) and gemcitabine (1000 mg/m^2) intravenously on Days 1 and 8, every 21 days

Oral Treatment:

- Arm B1: merestinib 80 mg orally each day, plus cisplatin (25 mg/m^2, IV) and gemcitabine (1000 mg/m^2, IV) on Days 1 and 8, every 21 days

or

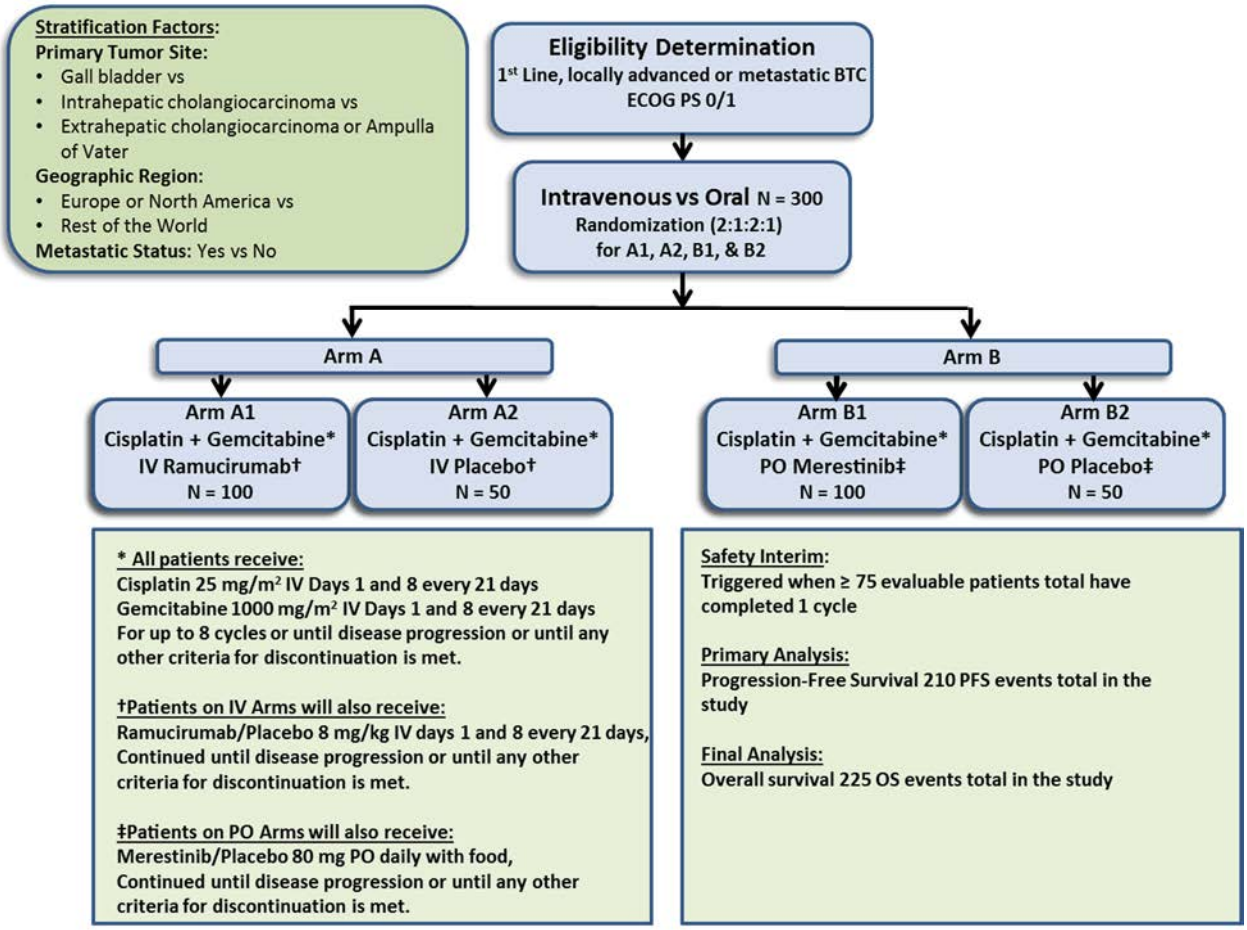
- Arm B2: placebo orally each day, plus cisplatin (25 mg/m^2, IV) and gemcitabine (1000 mg/m^2, IV) intravenously on Days 1 and 8, every 21 days

A cycle is defined as an interval of 21 days. Treatment with all study drugs will be given in an outpatient setting. Treatment will continue until there is evidence of disease progression or any other discontinuation criteria are met (Section 8). Treatment with cisplatin and gemcitabine will be capped at a maximum of 8 cycles. Treatment with the randomly assigned study therapy of ramucirumab, merestinib, or placebo will not be capped at a maximum number of cycles and should be continued until there is evidence of disease progression or any other discontinuation criteria are met. During the planned treatment period, if one or more therapeutic agent is permanently discontinued for a reason other than progressive disease, then treatment with the other study agent(s) should continue and the patient should remain on study with full adherence to all protocol-related requirements.

Crossover between arms is not permitted.

All patients will be offered best supportive care, as determined appropriate by the investigator and as not otherwise limited specifically within the protocol.

Figure JSBF.2 illustrates the study design.



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IV = intravenous; OS = overall survival; PFS = progression-free survival; PO = oral.

Figure JSBF.2. Illustration of study design.

5.2. Number of Patients

The study will randomize approximately 300 patients such that patients in each of the IV cohorts and the oral cohorts will be allocated to receive investigational treatment versus control in a 2:1 fashion, as described in Section 5.1.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure for the last patient. The end of study occurs after study completion and after the last patient has discontinued study treatment and completed the final follow-up visit (including the final follow-up visit for the continued access period, if applicable) or has been declared lost to follow-up.

5.4. Scientific Rationale for Study Design

Study JSBF is designed as a randomized, double-blinded study to evaluate the safety and efficacy of 2 new potential treatments when each is individually combined with the current first-

line standard of care for the treatment of advanced or metastatic BTC. The study uses a standardized eligibility criteria and stratification to facilitate consistency of sample populations. The patients will be randomized such that patients in each of the IV cohorts and the oral cohorts will be allocated to receive investigational treatment or control in a 2:1 fashion.

5.5. Justification for Dose

5.5.1. Cisplatin and Gemcitabine

All randomized patients on this study will receive treatment with cisplatin and gemcitabine according to the regimen that was used in the ABC-02 trial, which consisted of repeating cycles of cisplatin (25 mg/m^2) followed by gemcitabine (1000 mg/m^2) with each drug administered on Days 1 and 8 every 21 days for a maximum of 8 cycles (Valle et al. 2010).

5.5.2. Merestinib

The recommended dose of merestinib identified in Study JSBA for patients with BTC who received concurrent cisplatin and gemcitabine was 80 mg when given by mouth with food daily. Merestinib 80 mg daily in combination with cisplatin and gemcitabine has demonstrated a clinically acceptable safety profile in Study JSBA. Plasma exposure of merestinib after repeated administration at this dose level observed in patients exceeds the concentration shown to produce efficacy in preclinical in vitro and in vivo models. In individuals across tumor types who have not tolerated the 80-mg dose concurrent with other therapy, a reduced dose of 40 mg daily has been shown to be acceptable. Patients randomized to receive oral tablets will be randomized to receive merestinib or placebo at a starting dose of 80 mg daily.

5.5.3. Ramucirumab

Ramucirumab at a dose of 8 mg/kg on Day 1 and Day 8 on an every-21-day (3-week) schedule will be examined in this study. This dose of ramucirumab is different from the approved dose regimens: 8 mg/kg every-2-week (gastric cancer and CRC) and 10 mg/kg every-3-week (NSCLC). All approved indications are in second-line settings.

Dose selection for Study JSBF is based on information obtained from exposure-response (efficacy and safety) findings from 4 Phase 3 studies: REGARD (gastric cancer, monotherapy), RAINBOW (gastric cancer, in combination with paclitaxel), REVEL (NSCLC, in combination with docetaxel), and RAISE (CRC, in combination with FOLFIRI) and safety experience from Phase 1 multiple ascending dose (MAD) studies (I4T-IE-JVBM [JVBM] and I4T IE-JVBN [JVBN]) (Cohn et al. 2015; Smit et al. 2015; Tabernero et al. 2015).

Efficacy

Exposure-efficacy response analyses performed on data obtained from REGARD, RAINBOW, REVEL, and RAISE demonstrated that an increase in exposure is associated with improvement in efficacy in terms of both OS and PFS over the ranges of exposures achieved by a dose of 8 mg/kg every-2-week (REGARD, RAINBOW, and RAISE) or 10 mg/kg every-3-week (REVEL).

Safety

Weekly doses of ramucirumab ranging from 2 to 16 mg/kg were evaluated in the Phase 1 Study JVBM. An MTD was identified as 13 mg/kg/week. Every-2-week (6 to 10 mg/kg) and every-3-week (15 to 20 mg/kg) dose regimens were evaluated in an additional dose-ranging study (Study JVBN). All dose regimens in Study JVBN were well-tolerated and no MTD was identified in this study.

The ramucirumab dose regimen, 8 mg/kg every 2 weeks or 10 mg/kg every 3 weeks, demonstrated manageable safety profiles in all pivotal trials. Overall, the safety profiles of ramucirumab plus different combination therapies were largely consistent with the safety profiles of the individual treatment components and the combinations revealed no unexpected safety findings. Exposure-safety analyses indicated that an increasing ramucirumab exposure was correlated with increased incidence of Grade ≥3 hypertension in RAINBOW and REVEL, Grade ≥3 neutropenia in RAINBOW and RAISE, Grade ≥3 leukopenia in RAINBOW, and Grade ≥3 febrile neutropenia in REVEL. Of note, there were no Grade 4 or 5 hypertension events in RAINBOW or REVEL. Hypertension was managed primarily by the use of standard antihypertensive medication. Neutropenia and leukopenia are known risks with chemotherapies and are considered as clinically manageable. In addition, incidence of febrile neutropenia appeared to reach plateau at the third exposure quartile in REVEL.

These exposure-efficacy and exposure-safety data indicate that there may be an opportunity to further enhance efficacy of ramucirumab while maintaining an acceptable safety profile using a dose regimen which can generate exposure higher than 8 mg/kg every-2-weeks or 10 mg/kg every-3-weeks regimens. Based on pharmacokinetic (PK) simulation, a dose regimen of 8 mg/kg on Day 1 and Day 8 on an every-21-day (3-week) schedule was selected for Study JSBF for the following reasons:

1. This dose regimen may produce exposure that is approximately 33% higher than the 8 mg/kg every-2-weeks and approximately 60% higher than the 10 mg/kg every-3-weeks dose regimen and is therefore expected to produce better clinical efficacy outcomes relative to the either 8 mg/kg every-2-week or 10 mg/kg every-3-week regimen.
2. It is expected that ramucirumab-related adverse events (AEs) in the BTC indication may not be significantly increased using the selected ramucirumab dose of 8 mg/kg on Day 1 and Day 8 on an every-21-day (3-week) since the selected dose for Study JSBF is still approximately 60% lower than the maximum tolerated weekly dose identified in the Phase 1 dose-escalation study, Study JVBM (13 mg/kg weekly).
3. In addition, Study JVCX studied the safety and tolerability in Japanese patients of ramucirumab at an IV dose of 8 mg/kg given on Days 1 and 8 of a repeating 3-week regimen in 3 separate 3-drug combinations, one with capecitabine and cisplatin and the other with S-1 and oxaliplatin. Interim findings from the study supported the safety of this dose and schedule of ramucirumab administration.

In summary, the dosing regimen of ramucirumab 8 mg/kg on Day 1 and Day 8 every 21 days in combination with cisplatin and gemcitabine in Study JSBF is anticipated to produce a clinically acceptable benefit-risk profile in BTC patients.

6. Study Population

All patients meeting the eligibility requirements will be considered for enrollment regardless of race, religion, or gender. The investigator or the Sponsor will not grant exceptions to eligibility criteria.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

[1] Are of an acceptable age to provide informed consent according to the local regulations and are at least 18 years of age.

[2] Have an estimated life expectancy ≥3 months.

[3] Have an Eastern Cooperative Oncology Group performance status of 0 or 1 at the time of randomization (refer to Appendix 7).

[4] Have a histologically or cytologically confirmed diagnosis of non-resectable, recurrent, or metastatic biliary tract adenocarcinoma (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or Ampulla of Vater).

[5] Have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 on computed tomography (CT) or magnetic resonance imaging (MRI) assessments performed ≤ 28 days prior to Cycle 1 Day 1.

[6] Have resolution of all clinically significant toxic effects of prior therapy to Grade ≤1 by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0.

[7] Have adequate biliary drainage (per investigator's discretion), with no evidence of ongoing infection.

[8] Have adequate organ function as determined by:

a. Hepatic: Total bilirubin, aspartate transaminase (AST), and alanine transaminase (ALT) are all ≤ 3 times upper limit of institutional normal value (ULN) on 2 measurements separated by at least 5 days.

b. Renal:

i. Glomerular filtration rate (GFR) of ≥50 ml/min/1.73 m^2. GFR should be calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (refer to Appendix 6), or may be measured using 24 hour urine collection or clearance of exogenous filtration markers (such as iothalamate or 51-CrEDTA or Tc99m-DTPA).

ii. The patient's urinary protein is ≤1+ 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 to allow participation in the study.

c. Hematologic:

i. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L,

ii. hemoglobin ≥9 g/dL (5.58 mmol/L; packed red blood cell transfusions are not allowed within 1 week prior to baseline hematology profile), and

iii. platelets ≥ 100 x 10^9/L.

d. Coagulation: The patient must have adequate coagulation function as defined by International Normalized Ratio (INR) ≤1.5 and a partial thromboplastin time (PTT/aPTT) ≤5 seconds above the ULN. Patients receiving low-dose anticoagulant therapy at prophylactic doses (such as prophylaxis with low-molecular weight heparin) are eligible, provided that INR ≤1.5 and PTT/aPTT ≤5 seconds above the ULN. Treatment with acetylsalicylic acid (aspirin) at a daily dose of ≤325 mg is permitted.

[9] Males and females are sterile, postmenopausal, or compliant with a highly effective contraceptive method during study participation and for 3 months following the last dose of study drug.

[10] Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to first dose.

[11] The patient has provided signed informed consent and authorization for release of health information for research prior to any study-specific procedures and is amenable to compliance with protocol schedules and testing.

[12] Are willing to provide blood/serum/plasma and tumor tissue samples for research purposes. Submission of blood/serum/plasma and tumor tissue samples is mandatory for participation in this study, unless restricted per local regulations. Tumor tissue biopsies may be taken by either core needle or excisional biopsy.

In the event that the patient has available tumor tissue from a prior biopsy obtained within the preceding 28 days for which existing specimen is available and of sufficient amount, submission of this material may occur in lieu of a repeated biopsy.

In the event that available tumor tissue is limited to cytology from brushing, the patient may be considered to be eligible if approval is granted by the Lilly clinical research physician (CRP)/clinical research scientist (CRS) following discussion between the investigator and the CRP/CRS.

If a patient is being rescreened who has adequate tumor tissue that was already obtained in a prior screening window, approval may be granted by the Lilly CRP/CRS to excuse the patient from a repeated biopsy.

[13] Are able to swallow tablets. Patients who have a nontemporary gastric or enteral feeding tube may be permitted to participate in the study with prior approval from the Sponsor's CRP/CRS.

6.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[14] Previous systemic therapy for locally advanced or metastatic disease is not allowed. Transarterial chemoembolization (TACE) or radiotherapy, including use of radioactive beads, is not allowed unless otherwise addressed in the Exclusion Criterion 18. The following previous treatments are allowed:

- a non-curative operation (that is, R2 resection [with macroscopic residual disease] or palliative bypass surgery);
- curative surgery with evidence of non-resectable disease relapse requiring systemic chemotherapy for which study participation will represent first line of chemotherapy;
- adjuvant chemotherapy, provided neither gemcitabine nor cisplatin were used and the treatment was completed more than 6 months before trial entry. Patients who received adjuvant gemcitabine and/or cisplatin greater than 12 months before relapse and study entry will be permitted.
- photodynamic treatment, provided that there was clear evidence of disease progression at the local site or measurable and progressing disease is present at another site.

[15] Have a history of or have current hepatic encephalopathy of any grade, or ascites of Grade >1, or cirrhosis with Child-Pugh Stage B or higher.

[16] Have ongoing or recent (≤6 months) hepatorenal syndrome

[17] Have had a major surgical procedure or significant traumatic injury including non-healing wound, peptic ulcer, or bone fracture ≤28 days prior to randomization, or anticipate having a major surgical procedure during the course of the study. Randomization should only occur after complete wound healing. Subcutaneous venous access device placement should not be considered a significant surgery, but should be placed greater than 7 days prior to randomization.

[18] Have had radiation to any site (for example, bone) within 14 days prior to randomization. Palliative radiation to symptomatic metastatic sites (for example, bone) is permitted, provided it is performed >14 days prior to randomization. If any tumor lesion is administered radiotherapy, then it cannot be considered for response assessment.

[19] Has documented brain metastases, leptomeningeal disease, or uncontrolled spinal cord compression. Screening of asymptomatic patients without history of central nervous system (CNS) metastases is not required. However, patients with findings consistent with CNS malignancy or metastasis should be evaluated fully before study participation.

[20] Have had any previous systemic therapy with VEGF inhibitors or VEGF-Receptor inhibitors (including investigational agents).

[21] Are receiving therapeutic dose anticoagulation with warfarin, low-molecular-weight heparin, or similar agents (see also Inclusion Criterion 8d).

[22] Are receiving chronic therapy with nonsteroidal anti-inflammatory agents (NSAIDs: for example, indomethacin, ibuprofen, naproxen, or similar agents) or other anti-platelet agents (for example, clopidogrel, ticlopidine, dipyridamole, anagrelide). Aspirin use at doses up to 325 mg/day is permitted

[23] Symptomatic congestive heart failure (New York Heart Association III-IV are excluded, Class I and II are eligible), unstable angina pectoris, or symptomatic or poorly controlled cardiac arrhythmia.

[24] Within 6 months prior to randomization, have had any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack.

[25] Have an uncontrolled arterial hypertension with systolic blood pressure ≥150 or diastolic blood pressure ≥90 mm Hg despite standard medical management.

[26] Have a previous malignancy within 5 years of study entry or a concurrent malignancy. Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low, as judged by the Lilly CRP/CRS in consultation with the treating investigator, are eligible for this study. The approval by the CRP/CRS of such patients is required before these patients may be enrolled.

[27] The patient is currently enrolled in, or discontinued within the last 28 days from, a clinical trial involving an investigational product or non-approved use of a drug or device (other than the study drugs used in this study), or are currently enrolled in a clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study. Patients participating in surveys or observational studies are eligible to participate in this study.

[28] Have a history of gastrointestinal perforation and/or fistulae within 6 months prior to randomization.

[29] Have a known allergy or hypersensitivity reaction to any of the treatment components.

[30] Have a history of uncontrolled hereditary or acquired thrombotic disorder.

[31] Have uncontrolled metabolic disorders or other nonmalignant organ or systemic diseases or secondary effects of cancer that induce a high medical risk and/or make assessment of survival uncertain. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient ineligible for entry into this study.

[32] Have mixed hepatocellular biliary tract cancer histology.

[33] Females who are pregnant or lactating.

[34] Have a QTc interval >470 msec as calculated be the Fridericia equation.

[35] The patient experienced any bleeding episode considered life-threatening, or any Grade 3 or 4 gastrointestinal/variceal bleeding episode in the 3 months prior to randomization requiring transfusion or endoscopic or operative intervention

6.3. Lifestyle Restrictions

Not applicable.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened, only after discussion with and permission from the Lilly CRP/CRS or designee. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

Note that repeating laboratory tests during the screening period does not constitute re-screening. Screening laboratory tests may not be repeated more than twice in order to meet eligibility during the screening period. If a repeat screening laboratory value meets eligibility, it is recommended that the test is rechecked to confirm stability.

7. Treatments

7.1. Treatments Administered

Table JSBF.8 shows the treatment regimens.

Table JSBF.8. Treatment Regimens/Dosing Schedule

Arm	Study Drug[a,b]	Dose	Route	Day (21-day Cycle)	Infusion Duration
A1	Ramucirumab[c]	8 mg/kg	IV	Days 1 and 8	over approx. 60 minutes
	Cisplatin	25 mg/m^2	IV	Days 1 and 8	over approx. 60 minutes
	Gemcitabine	1000 mg/m^2	IV	Days 1 and 8	over approx. 30 minutes
A2	Placebo[c]	equivalent volume	IV	Days 1 and 8	over approx. 60 minutes
	Cisplatin	25 mg/m^2	IV	Days 1 and 8	over approx. 60 minutes
	Gemcitabine	1000 mg/m^2	IV	Days 1 and 8	over approx. 30 minutes
B1	Merestinib[d]	80 mg	PO with food	Each Day	N/A
	Cisplatin	25 mg/m^2	IV	Days 1 and 8	over approx. 60 minutes
	Gemcitabine	1000 mg/m^2	IV	Days 1 and 8	over approx. 30 minutes
B2	Placebo	Similar appearing tablet(s) for dose	PO with food	Each Day	N/A
	Cisplatin	25 mg/m^2	IV	Days 1 and 8	over approx. 60 minutes
	Gemcitabine	1000 mg/m^2	IV	Days 1 and 8	over approx. 30 minutes

Abbreviations: IRR = infusion-related reaction; IV = intravenous; N/A = not applicable; PO = oral.

a For Arm A administer ramucirumab/placebo (IV) before the administration of cisplatin. For Arms A and B administer cisplatin before the administration of gemcitabine.

b Treatment with all study drugs will be given in an outpatient setting. Treatment will continue until there is evidence of disease progression or any other discontinuation criteria are met (Section 8). Treatment with cisplatin and gemcitabine will be capped at a maximum of 8 cycles. Treatment with the randomly assigned study therapy of ramucirumab, merestinib, or placebo will not be capped at a maximum number of cycles and should be continued until there is evidence of disease progression or any other discontinuation criteria are met. During the planned treatment period, if one or more therapeutic agent is permanently discontinued for a reason other than progressive disease, then treatment with the other study agent(s) should continue and the patient should remain on study with full adherence to all protocol-related requirements.

c IRRs may occur during or following administration of ramucirumab (placebo). See Appendix 10 for a definition of IRRs. For the first and second infusions: IV administration of the next study drug should start only after at least a 1-hour observation period (after ramucirumab/placebo administration). If there is no evidence of an IRR during the initial 2 infusions of ramucirumab/placebo, then no observation period is required for subsequent (third and later) treatment cycles, and IV administration of the next study drug can begin immediately after the infusion of ramucirumab/placebo. In the event an IRR occurs thereafter, the 1-hour observation should be reinstituted.

d Merestinib should be administered in the morning for Cycle 1 Day 1. Thereafter, tablets should be taken at approximately the same time each day, where evening administration is preferred.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient/study site personnel/legal representative
- verifying that instructions are followed properly
- maintaining accurate records of study treatment dispensing and collection
- at the end of the study, returning all unused medication to Lilly, or its designee, unless Lilly and the investigator's site have agreed all unused medication is to be destroyed by the site, as allowed by local law

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

7.1.1. Packaging and Labelling

Ramucirumab/placebo (IV) and merestinib/placebo (oral) will be provided by Lilly.

Commercial cisplatin and gemcitabine will be used (see Sections 7.1.1.3 and 7.1.1.4).

7.1.1.1. Ramucirumab or Placebo (Intravenous)

Ramucirumab is a sterile, preservative-free solution for infusion of ramucirumab drug substance formulated in an aqueous solution at a concentration of 10 mg/mL (500 mg/50-mL vial). The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine, and 0.01% polysorbate 80. The pH is 6.0.

Placebo is a sterile, preservative-free solution for infusion containing histidine buffer in a 50-mL vial to mimic the ramucirumab container and closure. The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine, and 0.01% polysorbate 80. The pH is 6.0.

All excipients used for the manufacture of ramucirumab (and placebo) are of pharmacopeial grade. No animal-derived components are used in the manufacture of ramucirumab excipients.

7.1.1.2. Merestinib or Placebo (Oral)

Merestinib will be supplied as 40-mg tablets for oral administration. The tablets should be stored at room temperature according to the label and not crushed or dissolved. Investigators should instruct patients to store the tablets in the original package and in a location inaccessible to children.

The placebo is a light blue, nonagon tablet, which is identical in appearance to the 40-mg merestinib tablet.

7.1.1.3. Gemcitabine

Gemcitabine will be supplied in commercially available dosage forms and provided according to the country's regulatory requirements. Gemcitabine should be stored in accordance with the product information.

7.1.1.4. Cisplatin

Cisplatin will be supplied in commercially available dosage forms and provided according to the country's regulatory requirements. Cisplatin should be stored in accordance with the product information.

7.2. Method of Treatment Assignment

Approximately 300 patients will be randomly assigned. Patients who meet all criteria for enrollment will be randomly assigned such that patients in each of the IV cohorts and the oral cohorts will be allocated to receive investigational treatment or control in a 2:1 fashion within 24 to 72 hours prior to Visit 1 (Day 1, Cycle 1). Every attempt should be made to randomize the patient as close as possible to Day 1 of Cycle 1 and not more than 72 hours prior to Day 1. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive Web response system (IWRS).

Randomization will be stratified by the following factors:

- Primary Tumor Site (gall bladder versus intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma or Ampulla of Vater)
- Geographic regions (North America or Europe versus Rest of World)
- metastatic disease (yes versus no)

The chosen stratification factors have been identified as potentially important adverse prognostic factors or regional considerations in this disease. Randomization will be performed separately within each of the strata (or cells) defined by all combinations of these 3 variables.

7.2.1. Selection and Timing of Doses

A cycle is defined as an interval of 21 days. Treatment with all study drugs will be given in an outpatient setting. Treatment will continue until there is evidence of disease progression or any other discontinuation criteria are met (Section 8). Treatment with cisplatin and gemcitabine will be capped at a maximum of 8 cycles. Treatment with the randomly assigned study therapy of ramucirumab, merestinib, or placebo will not be capped at a maximum number of cycles and should be continued until there is evidence of disease progression or any other discontinuation criteria are met. During the planned treatment period, if one or more therapeutic agent is permanently discontinued for a reason other than progressive disease, then treatment with the other study agent(s) should continue and the patient should remain on study with full adherence to all protocol-related requirements.

After Cycle 1, a treatment delay at the start of a cycle (Day 1) of ±7 days, because of holidays, weekends, inclement weather, or other justifiable events, will be permitted and not counted as a protocol violation. 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.

7.2.1.1. Premedication

7.2.1.1.1. Premedication Prior to Administration of Ramucirumab/Placebo (Intravenous)

Prior to each infusion of ramucirumab/placebo (IV), premedicate all patients with a histamine H1 antagonist, such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at the investigator's discretion. All premedication administered must be adequately documented in the case report form (CRF).

See Table JSBF.11 for ramucirumab dose modifications and additional premedication requirements for patients who have experienced a prior ramucirumab infusion-related reaction (IRR).

7.2.1.1.2. Premedication Prior to Administration of Cisplatin and Gemcitabine

Sites should consult the most current manufacturer's instructions for cisplatin and gemcitabine for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures and local guidelines for the administration of each agent. Premedication with hydration and prophylactic use of antiemetics for cisplatin is recommended. Investigators should follow American Society of Clinical Oncology (ASCO) Guidelines for Antiemetics in Oncology or their local standards of care (Kris et al. 2006; Basch et al. 2011; Hesketh et al. 2015).

7.2.1.2. Administration of Ramucirumab/Placebo (Intravenous)

The patient's actual dose of ramucirumab/placebo (IV) will be determined by measuring the patient's weight at the beginning of each cycle. If the patient's weight fluctuates by more than ±10% from the weight used to calculate the prior dose, the ramucirumab/placebo dose must be recalculated. Recalculation of the ramucirumab/placebo (IV) dose for weight fluctuations of <10% is permitted but not required. A ±5% variance in the calculated total dose will be allowed for ease of dose administration.

For patients undergoing repeated palliative drainage procedures to remove pleural or peritoneal fluid, dry weight will be defined as weight obtained after the drainage procedure and before fluid reaccumulation. In such circumstances, dry weight will be used for dose calculation, if obtained ≤30 days prior to dose. If no recent dry weight is available, actual weight will be used.

A patient may continue to receive ramucirumab/placebo (IV) until a criterion for discontinuation is met (as described in Section 8.1).

7.2.1.2.1. Treatment Requirements for Ramucirumab/Placebo (Intravenous)

Prior to each infusion of ramucirumab/placebo (IV), the patient must meet the criteria shown in Table JSBF.9.

Table JSBF.9. Criteria to Be Met Prior to Each Ramucirumab Administration

Urine protein	• <2+ on dipstick or routine urinalysis for C1D1; ≤2+ on dipstick or routine urinalysis for subsequent infusions[a] -or- • <2 g on 24-hour urine collection
Hypertension	• Hypertension is controlled
Wound healing	• Any wound is fully healed
Ramucirumab-related toxicities and AEs (other than AESIs [see Section 7.4.1.2])	• CTCAE (Version 4.0) Grade <2 or the patient's baseline level, except for clinically insignificant AEs (such as alopecia), as determined by the investigator.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; C1D1 = Cycle 1 Day 1; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009).

[a] If urine protein =2+ on dipstick or routine urinalysis, refer to Table JSBF.11.

Ramucirumab infusions should be delivered in approximately 60 minutes. The infusion rate should not exceed 25 mg/min. Infusions >60 minutes are permitted in the following situations:

1. if needed in order to maintain an infusion rate ≤25 mg/min, or
2. if the patient previously experienced a ramucirumab IRR. See Section 9.2.1.1 for dose modifications and premedication requirements.

7.2.1.3. Administration of Merestinib/Placebo (Oral)

A flat dose of merestinib/placebo will be taken orally once daily in a 21-day cycle. Merestinib should be administered in the morning for Cycle 1 Day 1. Thereafter, tablets should be taken at approximately the same time each day, where evening administration is preferred. If the patient chooses to take their dose in the mornings, dosing should be withheld on days scheduled for PK sampling (Day 1 and Day 8 on Cycles 1, 2, 4, 6 and 8), and be administered after the PK sample has been drawn (Appendix 4, Table APP.4.3). The administration time and date of the dose preceding these PK sample draws should be captured by the clinic.

Tablets must be taken with a meal or within 1 hour after a meal and should be taken with at least 8 ounces (240 ml) of fluid. As an example, a meal should consist of approximately 500 calories or more for a patient whose standard diet consists of 1500 to 1800 calories per day.

A patient may continue to receive merestinib/placebo (oral) until a criterion for discontinuation is met (as described in Section 8).

7.2.1.4. Administration of Cisplatin

Administration of cisplatin chemotherapy has a high emetogenic potential. While this potential may be decreased when administering lower doses of cisplatin the use of prophylactic and continuing antiemetic medications is recommended in this study. Investigators should follow ASCO Guidelines for Antiemetics in Oncology or their local standards of care (Kris et al. 2006; Basch et al. 2011; Hesketh et al. 2015).

The cisplatin dose specified in this protocol should be administered according to local standard of care. Suggested administration is on an outpatient basis as a 1.5-hour IV infusion (1 liter of

0.9% saline including cisplatin, 20 mmol of potassium chloride, and 8 mmol of magnesium sulfate over 1 hour followed by 500 ml of 0.9% saline over 30 minutes). Cisplatin treatment should be administered on Days 1 and 8 and will repeat every 21 days. Treatment with cisplatin may continue for a planned maximum of 8 cycles, or until a criterion for discontinuation is met (as described in Section 8). The initial dose of cisplatin is 25 mg/m^2. This initial dose is to be followed as scheduled with recurring doses of cisplatin 25 mg/m^2 IV unless dose modification is required (see Section 7.4.2). The dose of cisplatin administered should be rounded to the nearest 1 mg.

As a routine precaution, patients enrolled in this study are to be observed closely by the medical staff for any potential AEs for the duration of the infusion, in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. A nurse must be present in the immediate treatment area throughout the infusion and observation period. A physician must be in close proximity to the patient treatment area.

7.2.1.5. Administration of Gemcitabine

Patients will receive 1000 mg/m2 gemcitabine administered over approximately 30 minutes on Days 1 and 8 of each 21-day treatment cycle. Treatment with gemcitabine may continue for a planned maximum of 8 cycles, or until a criterion for discontinuation is met (as described in Section 8). Investigators should consult the approved gemcitabine product information for complete packaging and labeling information.

7.3. Blinding

This is a double-blind study. To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is completed. Additionally, there are no anticipated or identified toxicities from ramucirumab or merestinib that would potentially result in unblinding to treatment assignment.

Unblinding of the study team will not occur until after the final analysis of the primary endpoint (PFS). Following final analysis of the primary endpoint (PFS), investigators and patients may be unblinded to study treatment assignment (see Section 7.8).

7.3.1. Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP/CRS prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

Emergency unblinding for AEs must be performed through the IWRS. All actions resulting in an unblinding event are recorded and reported by the IWRS.

7.3.2. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment, but the inadvertent unblinding of a patient may occur. If an investigator, site personnel, or patient is inadvertently unblinded, the unblinding will not be sufficient cause for the patient to be discontinued from study treatment or excluded from study analyses.

Additionally, there may be ethical reasons for the patient to remain on the study treatment. In the event of unblinding, the investigator must obtain specific approval from a Lilly CRP/CRS for the patient to continue in the study.

Unblinding of treatment to determine eligibility for a subsequent trial should not be deemed to constitute sufficient cause for emergency unblinding.

7.4. Dosage Modification

Treatment for the first cycle should commence only if all the inclusion and exclusion criteria are met. For subsequent cycles, dose delay/modification is permitted as described in sections specific for ramucirumab/placebo (Section 7.4.1), merestinib/placebo (Section 7.4.2), cisplatin and gemcitabine (Section 7.4.3). Ramucirumab/placebo dose modifications are permanent; no dose escalations are allowed after dose reduction.

In the event of observed toxicities that may be associated with more than one agent (for example, hepatic toxicity or unexpected hematologic toxicity) a temporal association should be evaluated to aid in assessment of drug relatedness and dose modification. Other potentially reversible risk factors for the AE should be identified and addressed as appropriate. For example, in the case of hepatic toxicity, patients should be evaluated for the need to undergo biliary drainage. In the absence of temporal association or other potentially reversible or modifiable risks factors for the AE, for overlapping toxicities, consideration should be given to first reduce the dose of the investigational drugs and try to maintain the dose of gemcitabine and cisplatin.

Therapy with ramucirumab/placebo or merestinib/placebo should continue as scheduled if there is a delay or discontinuation of gemcitabine or cisplatin. Likewise, if there is a delay or modification of ramucirumab/placebo or merestinib/placebo due to toxicity, treatment with cisplatin and gemcitabine can continue as scheduled. An attempt should be made to resynchronize administration with intravenous agents (that is, at Day 1 of the next normally scheduled cycle). If clinically appropriate, the investigator can delay intravenous treatment components up to a maximum of 7 days to allow synchronized administration of agents.

7.4.1. Ramucirumab/Placebo (IV) Dose Modifications

This section provides instructions for ramucirumab/placebo dose modifications applicable to treatment Arm A. The ramucirumab dose may need to be delayed and/or reduced if the patient experiences an AE, including adverse events of special interest (AESIs) and non-AESIs.

Table JSBF.10 presents the specific ramucirumab/placebo dose reductions.

Table JSBF.10. Ramucirumab/Placebo Dose Reductions[a]

Starting dose	8 mg/kg
First dose reduction	6 mg/kg
Second dose reduction	5 mg/kg

a Ramucirumab/Placebo dose reductions are allowed between cycles and within a given cycle.

Ramucirumab/placebo dose modifications are permanent; no dose escalations are allowed after dose reduction. Any patient who requires a ramucirumab/placebo dose reduction will continue to receive a reduced dose until discontinuation from ramucirumab/placebo or discontinuation from the study.

No dose reduction is required for the first instance of reversible, Grade 3 or 4 non-life-threatening toxicity that is considered at least possibly related to treatment, provided that the AE recovered to Grade ≤1 or pretreatment level within 21 days. However, if the event required treatment delay for greater than 21 days or in the event of a second instance of the event, upon recovery (Grade ≤1 or pretreatment level), the dose should be reduced by one level (Table JSBF.10). Dose reductions may be warranted if worsening of symptoms or laboratory values is clinically significant in the opinion of the investigator and after discussion and approval of the Lilly CRP/CRS or designee. At the discretion of the investigator, ramucirumab/placebo treatment may be delayed for up to 21 days for Grade 2 AEs that are reversible and not life-threatening (dose reduction is not required). Dose adjustments or delays are not required for Grade ≤2 alopecia, fatigue, or peripheral neuropathy.

If a toxicity related to ramucirumab/placebo does not resolve in the same treatment cycle, the administration of ramucirumab/placebo can be delayed for up to 42 days (2 cycles). If the toxicity does not resolve within 42 days, ramucirumab/placebo will be discontinued.

A total of up to 2 dose-level reductions are allowed during the study. Any patient who has had 2 ramucirumab/placebo dose reductions and who experiences an event that would cause a third dose reduction must be discontinued from ramucirumab/placebo.

7.4.1.1. Ramucirumab/Placebo Dose Modifications for AESIs

Table JSBF.11 presents the criteria for ramucirumab/placebo dose modifications applicable if the patient experiences an AESI. A list of the AESIs for ramucirumab is provided below:

- Infusion-related reactions (IRRs)
- Hypertension
- Proteinuria
- Arterial thromboembolic events (ATEs)
- Venous thromboembolic events (VTEs)
- Bleeding/hemorrhage
- Gastrointestinal perforation
- Congestive heart failure
- Wound healing complications
- Fistula
- Liver failure/liver injury
- Reversible posterior leukoencephalopathy syndrome (RPLS)

Table JSBF.11. Dose-Modifications for Ramucirumab/Placebo Adverse Events of Special Interest

Adverse Event of Special Interest		Dose Modification
1.	**Infusion-related reaction** (Section 9.2.1.1)	
1.a.	• Infusion-related reaction - Grade 1 or 2	Reduce the infusion rate by 50% for the duration of the infusion and for all future infusions. Prior to all future infusions of ramucirumab/placebo, premedicate with: • an intravenous histamine H1 antagonist, such as diphenhydramine hydrochloride, • dexamethasone or equivalent, and • acetaminophen
1.b.	• Infusion-related reaction - Grade 3 or 4	Discontinue ramucirumab/placebo.
2.	**Hypertension** (Section 9.2.1.2)	
2.a.	• Hypertension (non-life-threatening and associated with symptoms) - Grade 2 or 3	Delay ramucirumab/placebo until the hypertension is controlled with medication and is resolved to Grade <2. • If controlled with medication and resolved to Grade <2 within **14 days**, then resume ramucirumab/placebo at current dose. • If controlled with medication and resolved to Grade <2 within 28 days, then resume ramucirumab/placebo at a reduced dose as shown in Table JSBF.10. • If **not** controlled with medication and **not** resolved to Grade <2 within **28 days**, then discontinue ramucirumab/placebo. • Investigators have the discretion to consider the clinical circumstances of individual patients, especially involving borderline hypertension, and administer unchanged dose of ramucirumab/placebo for blood pressure up to systolic 160 mm Hg and diastolic 100 mm Hg, if clinically appropriate.
2.b.	• Uncontrolled hypertension, hypertensive crisis, or hypertensive encephalopathy - Grade 4	Discontinue ramucirumab/placebo.
3.	**Proteinuria** (Section 9.2.1.3)	
3.a.	• Proteinuria =2+ (dipstick or routine urinalysis)[a]	• Administer ramucirumab/placebo at the patient's current dose if clinically indicated. • Obtain 24-hour urine protein results within 3 days prior to the next ramucirumab/placebo dose. o If urine protein is <2 g/24 h, administer ramucirumab/placebo at the patient's current dose. o If urine protein is ≥2 g/24 h, modify the ramucirumab/placebo dose based on 24-hour collection. See *Proteinuria ≥2 g/24 h (24-hour urine collection)*, Line 3.c in this table.

Dose-Modifications for Ramucirumab/Placebo Adverse Events of Special Interest (concluded)

Adverse Event of Special Interest		Dose Modification
3.b.	• Proteinuria >2+ (dipstick or routine urinalysis)[a]	• Delay ramucirumab/placebo dose for up to 28 days. Obtain 24-hour urine protein results within 3 days prior to the next ramucirumab/placebo dose. If urine protein is <2 g/24 h, no further dose delay or dose reduction is required.
3.c.	• Proteinuria ≥2 g/24 h (24-hour urine collection)[a]	**First or second occurrence**: delay ramucirumab/placebo until urine protein returns to <2 g/24 h. Reduce ramucirumab/placebo dose, as shown in Table JSBF.10. If urine protein remains ≥2 g/24 h after holding ramucirumab/placebo for 28 days, discontinue ramucirumab/placebo. **Third occurrence**: discontinue ramucirumab/placebo.
3.d.	• Proteinuria >3 g/24 h **or** in the setting of nephrotic syndrome[a]	Discontinue ramucirumab/placebo.
4.	Arterial thromboembolic events, venous thromboembolic events (Section 9.2.1.4.1) - Grade 3 or 4	Discontinue ramucirumab/placebo.
5.	Bleeding/hemorrhage (Section 9.2.1.5) - Grade 3 or 4	Discontinue ramucirumab/placebo.
6.	Gastrointestinal perforation (Section 9.2.1.6)	Discontinue ramucirumab/placebo.
7.	Reversible posterior leukoencephalopathy syndrome (Section 9.2.1.7)	Discontinue ramucirumab/placebo.
8.	Congestive heart failure (Section 9.2.1.8) – Grade 3 or 4	Discontinue ramucirumab/placebo.
9.	Fistula formation (Section 9.2.1.9)	Discontinue ramucirumab/placebo.
10.	Impaired wound healing (Section 9.2.1.10)	
10.a.	• Prior to planned surgery	• Withhold ramucirumab/placebo.
10.b	• After surgery	• Resume ramucirumab/placebo based on clinical judgment (maximum delay is 28 days after the patient's previous dose).
10.c.	• Wound-healing complications developed during study treatment	• Delay ramucirumab/placebo dosing (for up to 28 days) until the wound is fully healed.
11.	Liver injury/liver failure (Section 9.2.1.11)	
11.a.	• Hepatic encephalopathy and/or hepatorenal syndrome	Discontinue ramucirumab/placebo.

a Perform dipstick or routine urinalysis within 3 days prior to each infusion of ramucirumab/placebo (see Table JSBF.9). If 24-hour urine collection is also performed, the results of 24-hour urine collection should be used for clinical decision-making.

Refer to Section 9.2.1 for detailed information about AESIs for ramucirumab.

7.4.1.2. Ramucirumab/Placebo Dose Modifications for Non-AESIs

The ramucirumab/placebo dose may be modified if the patient experiences a Grade 3 clinical AE that meets all of the following conditions:

- the AE is reversible and non-life-threatening
- the AE is not an AESI
- the AE is considered to be at least possibly related to ramucirumab
- the AE resolves to Grade ≤1 or to the patient's pretreatment baseline level within 28 days

If the patient experiences Grade 4 fever or a Grade 4 laboratory abnormality, ramucirumab/placebo may be continued at the discretion of the investigator if the fever or laboratory abnormality resolves to Grade ≤1 or to the patient's pretreatment baseline level within 28 days.

If a second instance of Grade 4 fever or Grade 4 laboratory abnormality occurs, resume ramucirumab/placebo at a lower dose, as shown in Table JSBF.10.

Patients who enter the study with symptoms or laboratory values equivalent to Grade 1 or 2 AEs should not have dose reductions related to the persistence or mild worsening of those symptoms or laboratory values; dose reductions may be warranted if worsening of symptoms or laboratory values is clinically significant in the opinion of the investigator. Asymptomatic laboratory abnormalities should not result in dose delays, modifications, or discontinuation of ramucirumab/placebo unless determined by the investigator to be clinically significant or life-threatening.

7.4.2. Gemcitabine and Cisplatin Dose Modifications

Treatment cycles will be repeated every 21 days. Patients will receive gemcitabine (with cisplatin) on Days 1 and 8 or unless treatment is delayed due to toxicity requiring dose adjustment. Gemcitabine and cisplatin dose adjustment for toxicity is summarized in Table JSBF.12.

Initiation of a new cycle with gemcitabine or cisplatin requires an absolute neutrophil count of at least 1000/µL, platelets of at least 100,000/µL, and resolution of nonhematologic toxicities to CTCAE v4.0 Grade 0, 1, or baseline (except alopecia and fatigue). If these parameters are not met, then defer by 1 week. If deferred by 2 consecutive weeks, then consider dose reduction.

Resolution of toxicity is required to occur within 3 weeks of the intended start of the cycle, otherwise gemcitabine and cisplatin therapy should be discontinued. Patients discontinuing gemcitabine and/or cisplatin therapy may be allowed to continue with the other study treatments if they are receiving clinical benefit.

Table JSBF.12. Gemcitabine and Cisplatin Dose Adjustment for Toxicity

	Event			Gemcitabine Dose	Cisplatin Dose
In previous Cycle*	Febrile Neutropenia or Grade 4 ANC ≥ 7 days			Dose at 75% of prior dose. Prior to treatment toxicity should have recovered to ≤ Grade 2 and ANC ≥1000/μL and Platelets ≥100,000/μL. Consider growth factor support per ASCO guidelines.	
Current or Prior Cycle	Cisplatin or Gemcitabine associated Grade 3-4 non-hematologic AE			Treatment with gemcitabine and/or cisplatin should be deferred until recovery, and then continued with an appropriate dose reduction, adjustment of mitigatable factors, or discontinued as clinically indicated.	
	Bilirubin > 1.6 mg/dL (>27 μmol/L)			Initiate gemcitabine dose at 800 mg/m^2. May reduce further for hematologic AEs as defined below	
	ANC (/μL)		**Platelets (/μL)**		
Day 8	> 1000	And	≥ 100,000	Dose at 100% of prior dose.	Dose at 100% of prior dose.
	500 to 1000	Or	50,000 to <100,000	Administer 75% of prior dose (25% dose reduction; if already receiving a 75% dose, reduce by a further 25%); continue this reduced dose in next cycle.	Give 100% of dose.
	<500	Or	<50,000	Hold for recovery. At next cycle, restart at 75% of prior dose.	Hold for recovery. At next cycle, restart at 75% of prior dose.

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology.
Source: Meyerhardt et al. 2008 and Valle et al. 2010.

If a dose reduction to 75% has been made for gemcitabine or cisplatin and cell counts return to within normal limits, then the dose may be increased to 100% on the subsequent doses.

7.4.3. Merestinib /Placebo (Oral) Dose Modifications

The merestinib/placebo dose may be modified if the patient experiences a Grade 3 clinical AE that meets all of the following conditions:

- the AE is reversible and non-life-threatening
- the AE is considered to be at least possibly related to merestinib
- the AE resolves to Grade ≤1 or to the patient's pretreatment baseline level within 28 days of merestinib/placebo treatment interruption

If the patient experiences Grade 4 fever or a Grade 4 hematologic laboratory abnormality, merestinib/placebo may be continued at the discretion of the investigator if the fever or laboratory abnormality resolves to Grade ≤1 or to the patient's pretreatment baseline level within 7 days.

Patients treated with merestinib/placebo, are permitted to continue dosing of merestinib/placebo without dose reductions or interruptions in merestinib/placebo if they maintain an ANC ≥500/μL

and a platelet count of ≥25,000/μL, provided that the suppression of ANC and/or platelet counts is deemed to be related to cisplatin or gemcitabine therapy.

In the event that a patient experiences a merestinib/placebo-related toxicity requiring treatment to be held (as above) that resolves with treatment interruption, treatment may be resumed at a reduced dose of 40 mg. No patient will have their merestinib/placebo dose reduced below 40 mg per day. At the start of the next cycle re-escalation to the original dose is acceptable in the absence of continuing toxicity. However, if subsequent dose reduction is again required, the patient must be maintained at the reduced dose level for all remaining cycles.

If a patient has recurrence of the same toxicity at the 40-mg dose in the absence of other identifiable risk factors, then he/she will be discontinued from treatment. In the presence of other identifiable risk factors attempts should be made to mitigate those risks, if possible, before making the determination to discontinue merestinib/placebo therapy.

7.5. Preparation/Handling/Storage/Accountability

Refer to the respective IBs for detailed information about preparation, handling, and storage of ramucirumab and merestinib. Additional information is provided in the study pharmacy manual.

Refer to the manufacturer's instructions for instructions on preparation, handling, and storage of cisplatin and gemcitabine. Additional information for dosing is provided in the study pharmacy manual.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

7.6. Treatment Compliance

Ramucirumab/placebo (IV), cisplatin and gemcitabine will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured.

Patient compliance with merestinib/placebo (oral) will be assessed at each visit by direct questioning and counting returned tablets. A patient dosing diary may also be used to assist in collection of administration data related to the PK analysis. Deviation(s) from the prescribed dosage regimen should be recorded on the CRF. The patient must take 80% of the intended dose to be deemed compliant with study drug administration. Similarly, a patient may be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP/CRS before making the final determination for discontinuation.

7.7. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications must be captured at each visit in the CRF. Concomitant medications (including over

the counter medications and supplements) and supportive care therapies must also be documented at the time of discontinuation and at the (30-day) Short-term Follow-up visit.

With the exceptions listed in the sections below, no other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications will be permitted while patients are on study treatment.

7.7.1. Supportive Care

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to all patients on this trial, with the intent to maximize quality of life. Patients will receive supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP/CRS or designee.

Details of interventions (for example, medications such as sedatives, antibiotics, analgesics, antihistamines, steroids, or erythropoietin), procedures (for example, paracentesis or thoracentesis), or blood products (for example, blood cells, platelets, or fresh frozen serum transfusions) must be recorded in the CRF.

Guidelines regarding the use of permitted supportive care agents (which include, but are not limited to, colony-stimulating factors (CSFs), erythropoiesis-stimulating agents, antidiarrheal agents, antiemetic agents, and analgesic agents) are presented in the following sections.

For Arm A, premedication and treatment of hypersensitivity (infusion-related) reactions is described in Section 9.2.1.1.

7.7.1.1. Colony-Stimulating Factors

The use of G-CSF is permitted at the discretion of the investigator, based on ASCO (Smith et al. 2015) and European Society for Medical Oncology (Crawford et al. 2010) guidelines. G-CSF or similar agents are strongly recommended following Grade 3 or 4 neutropenia of duration >5 days or following any incidence of febrile neutropenia (ANC $<1.0 \times 10^9$/L with a single temperature ≥38.5°C) or a sustained temperature (≥38.0°C for >1 hour).

In addition, the use of prophylactic antibiotics such as ciprofloxacin may be considered for patients who may be susceptible to neutropenia or infections. Ciprofloxacin 250 to 500 mg orally daily starting on Day 2 of a cycle for 7 to 10 days may be considered.

7.7.1.2. Erythropoiesis-Stimulating Agents

The use of erythropoiesis-stimulating factors (for example, erythropoietin) is permitted at the discretion of the investigator based on ASCO guidelines (Rizzo et al. 2010).

7.7.1.3. Antidiarrheal Agents

In the event of Grade 3 or 4 diarrhea, supportive measures may include hydration, loperamide, octreotide, and other antidiarrheals. If diarrhea is severe (that is, requires IV hydration) and associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics may be

prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be considered for hospitalization for IV hydration and correction of electrolyte imbalance.

7.7.1.4. Antiemetic Therapy

The routine use of standard antiemetics, including dexamethasone, 5-HT3 antagonists (such as granisetron or ondansetron), and NK1 antagonists as premedication and/or symptomatic management, should be administered as per the Multinational Association of Supportive Care in cancer and ASCO (Kris et al. 2006; Basch et al. 2011; Hesketh et al. 2015), or institutional guidelines.

7.7.1.5. Analgesic Agents

The use of analgesic agents is permitted at the discretion of the investigator. The chronic use of NSAIDs with a high risk of bleeding (for example, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged unless at the discretion and responsibility of the investigator after careful assessment of the individual bleeding risk of the patient. If required, the chronic use of analgesic agents with no or low bleeding risk (for example, paracetamol/acetaminophen, metamizole, dipyrone, or propyphenazone) is recommended.

7.7.2. Prohibited Medication

No other chemotherapy, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications will be permitted while patients are on study treatment.

Patients may not receive chronic antiplatelet therapy (for example, clopidogrel, ticlopidine, dipyridamole, and anagrelide). Aspirin is permitted as per Section 7.7.3.

7.7.3. Restricted Therapies

Aspirin is permitted at doses ≤325 mg once daily. Ongoing aspirin therapy at doses exceeding 325 mg/day is not permitted.

Patients who develop venous thromboembolism during study therapy may continue study therapy and receive anticoagulation. Patients who begin anticoagulation therapy during treatment on study must receive low-molecular-weight heparin (not oral anticoagulation).

Palliative radiation therapy is permitted after discussion with and agreement of the Lilly CRP/CRS or designee for irradiating small areas of painful metastases that cannot be managed adequately using systemic or local analgesics. Such areas must not be an identified target lesion and must not constitute progressive disease or meet RECIST criteria for progressive disease. Any symptomatic deterioration or clinical disease progression requiring, in the opinion of the investigator, other forms of specific antitumor systemic therapy, will be cause for discontinuation of study therapy.

Biliary stenting is permitted on study and should be recorded in the study CRF.

Use of photodynamic therapy to manage biliary obstruction is permitted after discussion with and agreement of the Lilly CRP/CRS or designee for management of biliary obstruction. Such areas must not be an identified target lesion and must not constitute progressive disease or meet RECIST criteria for progressive disease.

7.7.4. Other Study Conditions: Surgery (or Procedure) during Study Treatment Period

If any surgery should be required during the study (palliative surgery or medically indicated by the investigator), the patient should undergo radiologic evaluation before surgery for documentation of disease status. Elective, nonemergent surgery is strongly discouraged during study participation. The time of study treatment interruption before surgery should be at least 28 days following the last dose of ramucirumab/placebo or 4 days following the last dose of merestinib/placebo. Timing of surgery following gemcitabine or cisplatin should be based on local practice or guidelines. Patients may resume all study treatment no less than 28 days following surgery, provided there has been adequate recovery in the opinion of the investigator. Following surgery, radiological evaluation of disease is required prior to resumption of study treatment if treatment is not resumed within 3 weeks of treatment being held.

The additional radiologic evaluation before surgery should not reset the schedule of periodic radiographic evaluation for disease. Patients undergoing surgery before disease progression should continue to be followed by imaging on their prior schedule.

7.7.5. Merestinib / Placebo (Oral) – Drug-Drug Interactions

Based on the available nonclinical data, there is a possible risk of clinical drug-drug interaction (DDI) when merestinib is coadministered with substrates of CYP2C19, 2C8, and 2C9. In the absence of more data to refine the risk of interaction, caution is warranted in the concomitant use of LY2801653 with CYP2C19, 2C8, and 2C9 substrates known to have a narrow therapeutic range (CYP2C19: phenytoin, tricyclic antidepressants, tolbutamide; CYP2C8; CYP2C9: phenytoin). When, in the investigators opinion, concomitant use of phenytoin, tricyclic antidepressants, or tolbutamide is indicated, use of these agents should be carefully monitored.

7.8. Treatment after the End of the Study

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis for OS (approximately a total of 225 OS events in the study), as determined by Lilly.

Investigators will continue to follow Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

Refer to Section 7.3 for unblinding that occurs after the final analysis of the primary endpoint (PFS).

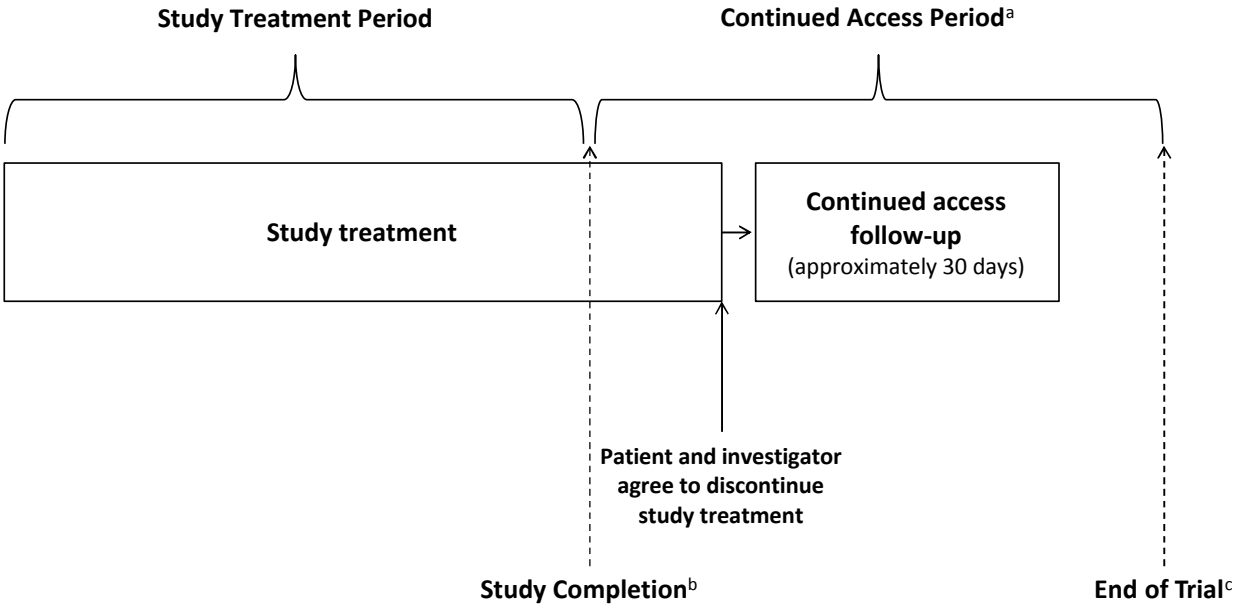
7.8.1. Continued Access

Patients who are still on study treatment at the time of study completion may continue to receive study treatment if they are experiencing clinical benefit and no undue risks. Placebo will no longer be administered, and crossover will not be permitted.

The continued access period will apply to this study only if at least 1 patient is still on study treatment when study completion occurs. Lilly will notify investigators when the continued access period begins.

Lilly may allow patients to enroll in a "rollover" protocol to provide long-term continued access for patients enrolled in this study. If a "rollover" protocol is used patients, must sign a new ICF before continued access is provided.

The patient's continued access to ramucirumab or merestinib will end when a criterion for discontinuation is met (Section 8). Continued access follow-up will begin the day after the patient and the investigator agree to discontinue study treatment and lasts approximately 30 (±7) days. Follow-up procedures will be performed as shown in the Continued Access Schedule of Activities (Table JSBF.4).



[a] Lilly will notify sites when the continued access period begins and ends.
[b] Final analysis of overall survival. Lilly will notify sites when study completion occurs.
[c] End of trial occurs at the last visit or last scheduled procedure for the last patient.

Figure JSBF.3. Continued access diagram.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Patients will be permanently discontinued from all study treatment in the following circumstances:

- the patient is enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- the patient becomes pregnant during the study
- the patient is significantly noncompliant with study procedures and/or treatment
- radiographic determination of disease progression
- unacceptable toxicity
- an intercurrent illness or change in the patient's condition that renders the patient unsuitable for further treatment in the opinion of the investigator
- the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study treatment will occur prior to introduction of the new agent
- the investigator decides that the patient should be discontinued from study treatment
- the patient requests to be discontinued from study treatment
- the patient's designee (for example, parents, legal guardian, or caregiver) requests that the patient be discontinued from study treatment;

Patients should be permanently discontinued from ramucirumab or placebo (IV) for any of the following circumstances:

- an unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient)
- the patient has had 2 dose reductions of ramucirumab/placebo and experiences an AE that would cause a third dose reduction
- a Grade 3 or 4 infusion-related reaction that is clearly attributed to ramucirumab.
- a Grade 3 or 4 arterial thrombotic event.
- a Grade 3 or 4 venous thrombotic event that is considered to be life-threatening in the opinion of the investigator, or that cannot be adequately treated with anticoagulant therapy
- any pulmonary embolism or deep vein thrombosis occurring or intensifying during anticoagulant therapy
- a Grade 3 or 4 bleeding or hemorrhagic event
- gastrointestinal perforation or fistulae
- any therapy-related event that is deemed life-threatening, regardless of NCI-CTCAE v 4.0 grade
- delay of ramucirumab/placebo >42 days (2 cycles) unless investigator considers continuation might be clinically beneficial for patient, is discussed with Sponsor physician and is appropriately documented

- new occurrence of hepatic encephalopathy and/or hepatorenal syndrome. In the event that study drug (ramucirumab or placebo) is not administered because of either of these 2 conditions, re-treatment with study drug will not be permitted.
- any Grade 3 or 4 events consistent with congestive heart failure (CHF)
- Impaired Wound Healing: Discontinue ramucirumab/placebo if wound is not fully healed within 42 days of withholding ramucirumab.
- Reversible Posterior Leukoencephalopathy Syndrome
- urine protein level of 3 g/24 hours or in the setting of nephrotic syndrome
- any Grade 4 (life-threatening) non-hematologic toxicity considered by the investigator to be possibly, probably, or definitely related to ramucirumab/placebo;

Patients should be permanently discontinued from merestinib or placebo (po) for any of the following circumstances:

- 1 dose reduction of merestinib/placebo and experiences an AE that would cause a second dose reduction
- an unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient)
- any toxicity considered clinically significant by the treating clinician that results in a delay of merestinib/placebo treatment >42 days (2 cycles), unless investigator considers continuation might be clinically beneficial for patient, is discussed with Sponsor physician and is appropriately documented
- any Grade 4 (life-threatening) non-hematologic toxicity considered by the investigator to be possibly, probably, or definitely related to merestinib/placebo;

Patients should be permanently discontinued from cisplatin and gemcitabine for any of the following circumstances:

- any event related to cisplatin and gemcitabine that is deemed life-threatening, regardless of NCI-CTCAE v. 4.0 grade
- any toxicity considered clinically significant by the treating clinician (for example, ANC <1.0 10^9/L or platelets <75 x 10^9/L, gastrointestinal toxicity ≥Grade 2, serious electrolyte imbalance, etc.) and showing no sign of recovery despite adequate clinical intervention for more than 42 days

Patients who are discontinued from study treatment will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP/CRS and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without study treatment.

8.2. Discontinuation from the Study

Patients will be discontinued from the study in the following circumstances:

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- the patient becomes pregnant during the study. See Section 9.2 regarding regulatory reporting requirements on fetal outcome and breast-feeding
- the investigator decides that the patient should be discontinued from the study
- the patient requests to be discontinued from the study
- the patient's designee (for example, parents, legal guardian, or caregiver) requests that the patient be discontinued from the study

Patients who discontinue from the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

Study site personnel, or an independent third party, will attempt to collect the survival status for all randomized patients who are lost to follow-up, including randomized patients who do not receive any dose of study treatment, within legal and ethical boundaries. Public sources may be searched for survival status information. If the patient's survival status is determined, the survival status will be documented, and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect survival status information.

9. Study Assessments and Procedures

Written informed consent must be obtained prior to any study-specific pretreatment evaluations.

Section 2 provides the Schedule of Activities for this study. Physical examinations and radiological assessments performed as part of routine clinical care may be used as baseline assessments if performed within the pre-treatment/pre-randomization windows specified in the schedule of events.

Appendix 3 provides a list of the laboratory tests that will be performed for this study.

Appendix 4 provides the schedule for collection of samples in this study.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

This study will be analyzed based on results of local (investigative site) radiologic assessments, including dates of progression and death. Since radiographic imaging scans may be needed for future regulatory purposes, or an independent review of all or a representative sample of scans may be considered following the completion of PFS analysis, copies of all scans will be collected throughout the study and stored centrally by a coordinating vendor designated by Lilly. Investigative sites will send radiologic images routinely to Lilly (or designee) based on the study-specified frequency. Lilly will collect and store tumor measurement images on all randomized patients.

Further details are provided in the manual of central radiology.

9.1.1. Efficacy Assessments at Baseline and During Study Treatment

Tumor assessments will be performed for each patient at the times shown in the *Schedule of Activities* (Section 2).

Within 28 days prior to Cycle 1 Day 1, baseline tumor measurements will be performed on each patient. Computed tomography (CT) scans, including spiral CT, and magnetic resonance imaging (MRI), are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm). Intravenous and oral contrast is required unless medically contraindicated.

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

All patients will be evaluated for response at these time points:

- at baseline
- every 6 weeks (±7 days) after randomization (regardless of treatment delays) during the Study Treatment Period, until disease progression OR study completion OR 14 months after randomization, whichever occurs first
- a confirmatory radiological scan is required after documented progression has occurred in the previous 4 to 6 weeks.

In addition, any patient whose disease has not progressed by 14 months after randomization (note that the patient may or may not still be on study treatment) will be evaluated for response at these time points:

- every 12 weeks (±7 days) from 14 months after randomization, until disease progression OR study completion OR 3 years after randomization, whichever occurs first; then as per standard clinical practice after that.

Except when deemed not feasible in the opinion of the investigator because of the patient's clinical status, imaging studies and tumor assessments will be performed as scheduled, even if therapy is delayed. In the event that a patient is discontinuing study treatment due to clinical progression, attempts should be made to re-evaluate response by imaging prior to discontinuation.

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiological scan of the thorax and abdomen is required. Imaging of the pelvis may also be considered depending on clinical presentation.

See Section 10.3.1 for definitions of the efficacy endpoints.

9.1.2. Efficacy Assessments During Postdiscontinuation Follow-Up

Postdiscontinuation follow-up will be conducted as described and shown in the Schedule of Activities (Section 2).

For patients who discontinue all study drugs without objectively measured progressive disease, continue to perform tumor assessment and imaging as follows:

- every 6 weeks (±7 days) after randomization until disease progression OR study completion OR 14 months after randomization, whichever occurs first.
- In addition, any patient whose disease has not progressed by 14 months after randomization will be evaluated for response every 12 weeks (±7 days) from 14 months after randomization, until disease progression OR study completion OR 3 years after randomization, whichever occurs first; then as per standard clinical practice after that.

After the patient has completed the confirmatory radiological scan, after documented radiographic disease progression, radiologic tests are no longer required, and the patient will be followed approximately every 3 months (±7 days) until patient's death, withdrawal of consent, or study completion (as defined in Section 7.8), whichever occurs first. Whenever possible, survival follow-up is conducted in person. If an in-person visit is not possible, the site may confirm survival by contacting the patient directly via telephone.

9.1.3. Health Outcome/Quality of Life Measures

The assessment of patient-reported outcomes, including disease-specific symptoms and health status, will be assessed using the Functional Assessment of Cancer Therapy Hepatobiliary Questionnaire (FACT-Hep) and the EuroQol 5-Dimension 5-Level (EQ-5D-5L). The instruments will be administered together with the FACT-Hep presented first, followed by presentation of the EQ-5D-5L. Patients will complete the instruments only if the instruments have been translated into a language in which the patient is fluent and the translation has been validated. Refer to the Study Schedule (Section 2) for the specific timing of these assessments.

9.1.3.1. Functional Assessment of Cancer Therapy Hepatobiliary (FACT-Hep) Questionnaire

The FACT-Hep, is a patient self-reported questionnaire consisting of 2 sub-questionnaires: 1) the FACT-G that includes 27 general items to evaluate physical, social, emotional, and functional well-being; and 2) the 18-item Hepatobiliary Subscale (HepCS-18) for assessing disease-specific issues (Heffernan et al. 2002).

9.1.3.2. EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire

The EQ-5D-5L is a nonspecific and standardized instrument for use as a measure of self-reported health status (EuroQol Group 1990; Herdman et al. 2011). Patients will complete the 5-level (no problems, slight problems, moderate problems, severe problems, and extreme problems), 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) questionnaire concerning their current health state. A unique EQ-5D-5L health state is defined by combining 1 level from each of the 5 dimensions. Additionally, patients will indicate their current health status by marking on a continuum ranging from 100 (best imaginable health state) to 0 (worst imaginable health state).

The EQ-5D-5L should be completed by the patient following completion of the FACT-Hep, before any extensive contact or consultation with study site personnel.

9.1.4. Appropriateness of Assessments

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional oncology trials.

9.2. Adverse Events

The investigator will use Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (NCI 2009) to assign AE terms and severity grades.

Investigators are responsible for:

- monitoring the safety of patients in this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient
- the appropriate medical care of patients during the study
- documenting their review of each laboratory safety report

- following through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue study treatment before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via CRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, study site personnel will record via CRF any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study procedure or study treatment via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatments, or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the study treatment and/or study procedure and the AE.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must report any dose modifications or treatment discontinuations that result from AEs to Lilly or its designee via CRF, clarifying, if possible, the circumstances leading to the dose modification or discontinuation of treatment.

9.2.1. Adverse Events of Special Interest for Ramucirumab

Table JSBF.11 presents the criteria for dose modifications applicable if the patient experiences an AESI. Contact the Lilly CRP/CRS if questions arise concerning AESIs.

9.2.1.1. Infusion-Related Reactions

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

A 1-hour observation period following the ramucirumab infusion is mandatory for the first 2 infusions. If the patient shows no evidence of an IRR with the first 2 infusions of ramucirumab, no observation period is required for subsequent infusions. In the event an IRR occurs thereafter, the 1-hour observation should be reinstituted.

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.

If the patient experiences a Grade 2 IRR, interrupt the infusion and treat the patient with anti-allergic medication. If symptoms resolve, resume the infusion at a reduced rate (50%).

In the event of an IRR, blood samples will be collected for both PK and immunogenicity 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.

9.2.1.1.1. Guidelines for Reporting IRRs

Any treatment-related IRRs are defined according to the CTCAE Version 4.0 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.

9.2.1.2. Hypertension

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

Monitoring of blood pressure is required during ramucirumab therapy. Every attempt should be made to control blood pressure to systolic <140 mm Hg and diastolic <90 mm Hg prior to starting treatment with ramucirumab. Routine clinical and laboratory monitoring is required in patients who again develop hypertension or experience a deterioration in previous hypertension.

9.2.1.3. Proteinuria

Proteinuria is an adverse effect for all therapies targeting the VEGF/VEGF Receptor 2 pathway, including ramucirumab. Proteinuria has been associated with ramucirumab in clinical studies. 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 or nephrotic syndrome.

9.2.1.4. Thromboembolic Events

9.2.1.4.1. Arterial Thromboembolic Events

Serious, sometimes fatal arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, have been reported in clinical trials.

9.2.1.4.2. Venous Thromboembolic Events

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

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

9.2.1.5. Bleeding/Hemorrhage

Ramucirumab is an antiangiogenic therapy and has the potential to increase the risk of severe bleeding. Severe gastrointestinal (GI) hemorrhages, including fatal events, have been reported in patients with gastric 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 (that is, variceal bleeding from portal hypertension in hepatocellular carcinoma, lower GI hemorrhage from bowel metastases in ovarian carcinoma), although the rate of these complications varies considerably. As detailed in the ramucirumab IB, the incidences of hemorrhagic events to date, significant background incidence of bleeding in some malignancies, and use of concomitant antiplatelet therapy in some of the reported cases preclude any definitive association between bleeding and ramucirumab, although ongoing surveillance and identification (and exclusion) of patients with high bleeding risk remain essential and are detailed in the inclusion/exclusion criteria.

9.2.1.6. Gastrointestinal Perforation

Patients with unresected (or recurrent) primary tumors or mesenteric or peritoneal disease who participate in this clinical study may be at increased risk for gastrointestinal perforation due to the nature of the disease.

An infrequent incidence of GI perforations has been associated with some antiangiogenic therapeutic agents, most specifically in the context of CRC (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.

9.2.1.7. Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS) is a clinical and radiologic syndrome typically consisting of reversible cortical neurological dysfunction and brain-imaging findings of subcortical edema involving the posterior circulation, particularly the occipital lobes (Hinchey et al. 1996). The symptoms of RPLS most often include generalized seizures, headache, delirium, and cortical blindness, although these may vary significantly and occasionally include focal neurological deficits (Hinchey et al. 1996; Garg 2001; Lee et al. 2008). MRI represents the most reliable method for diagnosis (Lee et al. 2008). Clinical symptoms and MRI abnormalities usually recover within days to weeks with proper management, although permanent neurologic dysfunction has been reported (Hinchey et al. 1996; Tajima et al. 1999; Garg 2001; Lee et al. 2008).

Across the ramucirumab clinical program, cases of RPLS have been reported. Refer to the IB for the most current information,

Reversible posterior leukoencephalopathy syndrome should be identified and treated promptly in order to minimize potential for permanent neurological damage. Treatment encompasses careful control of blood pressure, withdrawal of potentially causative medication, and administration of anticonvulsant agents to those experiencing seizures (Stott et al. 2005).

9.2.1.8. 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.

Treatment with ramucirumab has the potential to enhance cardiotoxicity of agents within the anthracycline/anthracenedione class of chemotherapy medications.

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.

9.2.1.9. 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).

9.2.1.10. 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.

9.2.1.11. 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.

9.2.2. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

Although all AEs after signing the ICF are recorded in the CRF, SAE reporting begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE but should be reported. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Planned hospitalizations or procedures for preexisting conditions that were recorded in the patient's medical history at the time of enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

9.2.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording

and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

9.2.4. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the product label or investigator brochure of the overdosed agent for the most current information related to management of an overdose.

9.4. Safety

9.4.1. Other Safety Measures

For each patient, ECGs, vital signs, laboratory tests, or other specified tests should be collected as shown in the Schedule of Activities (Section 2).

Any clinically significant findings that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via CRF.

9.4.2. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

If a patient experiences an elevated ALT ≥5x ULN and elevated total bilirubin ≥2x ULN, clinical and laboratory investigation should be initiated by the investigator for possible causes based on the Lilly Hepatic Algorithm for Oncology Studies (Appendix 11) and in consultation with the Lilly CRP/CRS. Concurrently, patients should be evaluated for the need to undergo biliary drainage by stent placement.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests. See Appendix 5.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring committee (DMC; an advisory group for this study formed to protect the integrity of data; refer to Section 10.3.6) can conduct additional analyses of the safety data.

During the study, Lilly will perform a blinded review of all reports of deaths and SAEs to ensure completeness and accuracy. If a death or other clinical AE is deemed serious, unexpected, and possibly related to study treatment, a limited number of Lilly Global Patient Safety representatives external to the study team will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this study and minimize any potential for bias, while providing for appropriate safety monitoring.

9.5. Pharmacokinetics

Pharmacokinetic (PK) samples will be collected as shown in Appendix 4.

Blood samples will be drawn for all subjects in Arm A for the assessment of concentration of ramucirumab in serum.

Blood samples will be drawn for all subjects in Arm B for the assessment of concentration of merestinib and its metabolites in plasma.

Blood samples will be drawn for all subjects in Arm A and Arm B for the assessment of plasma concentrations of total platinum derived from cisplatin and plasma concentrations of gemcitabine and its major metabolite.

A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon by the investigator and Lilly.

Drug concentration information that could unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

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

9.6. Pharmacodynamics

Please refer to Section 9.8 below.

9.7. Genetics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in Appendix 4, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research, either now or in the future. Samples will be used to investigate variable response to ramucirumab and/or merestinib and to investigate genetic variants thought to play a role in BTC. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by Lilly. This retention

period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of ramucirumab and/or merestinib.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies include whole genome and exome sequencing, genome-wide association studies, multiplex assays, candidate gene studies, and epigenetic analyses. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics (PD), mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules , including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

As part of Lilly's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to ramucirumab or merestinib, angiogenesis, immune function, and the disease state, and to correlate these markers to clinical outcome and/or for related research methods or validation of diagnostic tools or assays.

Required samples for biomarker research to be collected from all patients in this study are the following:

1. blood samples (see Section 9.8.1)
2. pretreatment tumor tissue (archived or newly biopsied) (see Section 9.8.2)

Samples for biomarker research will be collected as specified in Appendix 4, where local regulations allow. These samples are also described in the following sections.

It is possible that biomarker data for patients in the study has already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 9.8.1 and 9.8.2.

9.8.1. Samples for Nonpharmacogenetic Biomarker Research

Whole blood, serum, and EDTA plasma samples for nonpharmacogenetic biomarker research will be collected as specified in Appendix 4 where local regulations allow.

Samples will be examined for biomarkers related to BTC, variable response to ramucirumab or merestinib, the mechanism of action of ramucirumab or merestinib, immune function, and/or for research-related methods, or validating diagnostic tools or assays.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by Lilly. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of ramucirumab or merestinib or after ramucirumab or merestinib become commercially available.

9.8.2. Tissue Samples for Research

Tumor tissue will be examined for biomarkers related to ramucirumab or merestinib, angiogenesis, immune function, and the disease state, and to correlate these markers to clinical outcome and/or for related research methods or validation of diagnostic tools or assays.

Collection of the following tumor tissue sample is **required** for all patients in order to participate in this study:

- a newly obtained biopsy specimen during screening or an archived tumor sample obtained ≤28 days before screening

Patients may be asked to undergo collection of an additional (optional) biopsy specimen and blood sample after treatment with ramucirumab and merestinib has been initiated or after disease progression. If requested, this biopsy specimen and blood sample will be used to further investigate molecular features that may explain treatment response and resistance mechanisms.

Formalin-fixed paraffin-embedded tumor tissue obtained from the primary tumor or metastatic site should be provided as a block or unstained slides. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided. Pathology notes accompanying archival tissue may also be requested. The report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Archival blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by Lilly. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of ramucirumab and merestinib or after ramucirumab or merestinib become commercially available.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies, including mutation profiling, copy number variability, gene expression, multiplex assays, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations with these biomarkers and clinical outcomes.

9.8.3. Immunogenicity Assessments

For patients in Arm A, blood samples for immunogenicity testing will be collected as shown in Appendix 4 to determine antibody production against ramucirumab. 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.

Samples will be retained for a maximum of 15 years after last the patient visit for the study, or for a shorter period if regulations and ERBs/IRBs impose shorter time limits, at a facility selected by Lilly. The duration allows Lilly to respond to future regulatory requests related to ramucirumab.

9.9. Health Economics

Health Care Resource Use (HCRU) data collection will be scheduled on Day 1 of each 21-day cycle, beginning with Cycle 2 and covering the past 21 days. Data collection will be done through a standard, or a study-specific CRF. Resource use data collection will, at a minimum, include hospitalization episodes along with the corresponding lengths of stay, transfusions, concomitant medication, and any treatment-associated regimens, such as the administration of growth factors.

10. Statistical Considerations

10.1. Sample Size Determination

The study will randomize 300 patients such that patients in each of the IV cohorts and the oral cohorts will be allocated to receive investigational treatment or control in a 2:1 fashion. The primary analysis of PFS for the comparison of each investigational treatment to pooled control will be performed when a minimum of a total of 210 events in the study have been observed, assuming a 30% censoring rate in the study.

Assuming a PFS hazard ratio of 0.70, this sample size yields approximately 80% statistical power to detect superiority of each investigational treatment over the pooled control with the use of a log-rank test, and a 1-sided type I error of 0.10, taking into account of the worst case scenario that same numbers of events are observed in an investigational treatment and pooled control.

The analysis of OS for the comparison of each investigational treatment to pooled control will be performed when a minimum of a total of 225 events in the study have been observed. Assuming an OS hazard ratio of 0.75, this sample size yields approximately 68% statistical power to detect superiority of each investigational treatment over the pooled control with the use of a log-rank test and a 1-sided type I error rate of 0.10.

10.2. Populations for Analyses

The following populations will be defined for this study:

Intention-to-Treat (ITT) population: will include all randomized patients. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized and not by actual treatment received. This population will be used for all baseline, efficacy, and health economics analyses.

Per-protocol population: will include all randomized patients who receive at least 1 dose of study treatment and do not have any major protocol violations that could potentially affect the efficacy conclusions of the study. This population will be defined in detail in the Statistical Analysis Plan (SAP) prior to database lock.

Safety population: 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 population will be used for all dosing/exposure, safety, and resource utilization analyses.

Pharmacokinetic population: will include all treated patients who received at least 1 dose of study treatment and have at least 1 post baseline evaluable PK sample.

Biomarker population: will include the subset of patients from the randomized population from whom a valid assay result has been obtained.

10.3. Statistical Analyses

All tests of treatment effects will be conducted at a 1-sided alpha level of .1, unless otherwise stated. Unless otherwise stated, all confidence intervals (CIs) will be given at a 2-sided 95% level.

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.

10.3.1. Efficacy Analyses

Progression-free survival is defined as the time from randomization until the first radiographic documentation of progression 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 Table JSBF.13). Progression-free survival will be compared between each investigational treatment to pooled control using a log-rank test and 1-sided alpha level of 0.1. The same comparison will also be conducted using 1-sided alpha level of 0.025. The corresponding hazard ratio (HR) between treatment arms will be estimated using a Cox regression model (Cox 1972). Progression-free survival curves, median PFS, and PFS rates at various time points with 95% CI for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). Sensitivity analyses for PFS will be described in the SAP.

Overall survival is defined as the time from randomization until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. Overall survival will be compared between each investigational treatment to pooled control using a log-rank test. The corresponding HR between treatment arms will be estimated using a Cox regression model (Cox 1972). Overall survival curves, the median and survival rates at various time points with 95% CI, for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958).

Table JSBF.13. PFS Event/Censoring Scheme

Situation[a]	Event/Censor	Date of Event or Censor
Investigator assessed tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)[b]
Unless		
No baseline radiological tumor assessment available	Censored	Date of randomization
No adequate postbaseline radiological 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 radiological tumor assessment or randomization (whichever is later)[b,c]	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)[b]

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

a Symptomatic deterioration (that is, symptomatic progression that is not radiologically confirmed) will not be considered as tumor progression.

b Adequate radiological tumor assessment 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.

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). The confirmation of CR and PR is not required. The ORR, with 95% CI, will be summarized for each treatment arm and compared between each investigational treatment to pooled control using the Fisher's exact test.

Disease control rate (DCR) is defined as the number of patients who achieve a best overall response of CR, PR, or SD divided by the total number of patients randomized to the corresponding treatment arm (ITT population). The confirmation of CR and PR is not required. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks). The DCR, with 95% CI, will be summarized for each treatment arm and compared between each investigational treatment to pooled control using the Fisher's exact test.

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

10.3.2. Health Outcome/Quality of Life Analyses

The main analysis will be conducted in the ITT population as defined in Section 10.2. Exploratory analyses of patient-reported outcomes (PROs) may be performed on subpopulations as appropriate.

For each instrument, the compliance rate by treatment arm will be calculated as the number of completed assessments divided by the number of expected assessments (that is, patients still on study). Compliance rates, reasons for noncompliance, and data collected for each instrument will be summarized by treatment arm.

10.3.2.1. Functional Assessment of Cancer Therapy Hepatobiliary Questionnaire (FACT-Hep)

FACT-Hep scores and their change from baseline will be summarized descriptively at each assessment time point. The change from baseline in FACT-Hep scores will be evaluated to investigate statistically significant differences between ramucirumab and placebo and between merestinib and placebo.

A mixed model repeated measure analysis model will be applied to evaluate trajectories of pre-specified scores, domains, and items to investigate differences between ramucirumab and placebo and between merestinib and placebo; the model will include time, treatment, and the interaction of time and treatment. Time to deterioration (TtD) of selected scores, domains, and items will be characterized using the Kaplan-Meier method; between-treatment arm comparisons will be estimated using the Cox proportional hazards models (Cox 1972). Analysis details will be presented in the SAP.

10.3.2.2. EuroQol 5-Dimension 5-Level (EQ-5D-5L)

For the EQ-5D-5L patient responses, based on their experiences during that day, the first 5 EQ-5D items form a 5-digit code uniquely identifying 1 of the 3125 possible health states. These unique 5-digit health states serve only as an index, or locator, into a pre-selected, country-specific value set to assign a utility value to this particular EQ-5D descriptive profile. These utility values are applied to the OS estimate for the estimation of quality-adjusted-life-years (QALYs) that are used to inform economic evaluations of health care interventions. No inference on these descriptive measures was intended by the questionnaire developers. Nonetheless, descriptive presentation of these data will be provided, by visit and by treatment, and will include numbers and proportions of responders on each of the 5 dimensions across each of the 5-level categorical responses (that is, mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). The visual analogue scale (VAS) will be scored from 0 (worst imaginable health state) through 100 (best imaginable health state) to represent the patient's self-report concerning how bad or how good their health was during that day. For both, the VAS scores and the produced utility values descriptive statistics will include a measure of the central tendency and a measure of dispersion (that is, these can be mean values and standard deviations [or standard errors, or 95% CIs] or if the data are skewed, median values and the 25th and 75th percentiles). Completion compliance of the EQ-5D-5L questionnaires will be described by assessment time point (including baseline, on-study, and short-term follow-up) by the number

and percentage of patients who filled out a questionnaire (per patient, at least 1 question answered) over number of patients who are expected to complete the questionnaire at that time point. Reasons for noncompliance will be summarized.

10.3.3. Safety Analyses

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

The Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA Lower Level Term (LLT) will be used in the treatment-emergent computation. Treatment-emergent adverse events will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term (PT) within SOC.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- SAEs, including possible relationship to study drug
- AEs leading to dose adjustments
- discontinuations from study treatment due to AEs or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs

10.3.4. Other Analyses

10.3.4.1. Immunogenicity Analysis

The number and percentage of patients with positive anti-ramucirumab antibodies will be summarized. Any relationship with the occurrence of an IRR and positive anti-ramucirumab antibodies may be explored.

10.3.4.2. Patient Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients completing the study, as defined in the SAP, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

10.3.4.3. Patient Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population considered for regulatory approval.

A summary of baseline patient and disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported using descriptive statistics.

10.3.4.4. Concomitant Therapy

A summary of prior and concomitant medications by treatment arm will be reported.

10.3.4.5. Postdiscontinuation Anticancer Therapy

The numbers and percentages of patients receiving postdiscontinuation anticancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug class and/or name, overall and by line of therapy.

10.3.4.6. Treatment Compliance

The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by treatment arm.

For IV arm only, study treatment will be administered at the investigator site, therefore treatment compliance is assured.

For oral arm only, study treatment compliance will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. Study treatment taken will be derived from the difference between the total number of tablets dispensed and returned over the course of the patient's treatment.

10.3.4.7. Pharmacokinetics

Ramucirumab C_{min} and concentrations at 1 hour post end of infusion (approximately C_{max}) in serum will be summarized by descriptive statistics. Additional analysis utilizing the population PK approach may also be conducted if deemed appropriate.

Merestinib plasma concentrations will be summarized by descriptive statistics. Additional analysis utilizing the population PK approach may also be conducted if deemed appropriate.

The relationship between ramucirumab or merestinib exposure and selected efficacy and safety outcomes may be explored.

Plasma concentrations of total platinum derived from cisplatin and plasma concentrations of gemcitabine and its major metabolite will be summarized by descriptive statistics.

10.3.4.8. Healthcare Resource Utilization

Hospitalizations, transfusions, and emergency room visits, during the study and at the 30-day visit, will be summarized descriptively by treatment arm.

10.3.5. Subgroup Analyses

A prespecified list of subgroups will be identified in the SAP. 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.

10.3.6. Interim Analyses

One interim analysis of safety will be conducted after a total of at least 75 evaluable patients have completed Cycle 1. The interim analysis will be conducted to assess safety.

An assessment committee (AC) will be established to conduct safety reviews. The membership, roles, and responsibilities of the AC are defined in the AC Charter. Blinded Lilly study team

members will not be part of the AC. The AC members will review unblinded safety data at the prespecified time point to determine whether there are sufficient safety concerns to justify modifying the study or the termination of study treatment and/or enrollment. Only the AC and statistical analysis center are authorized to evaluate unblinded interim safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their patients.

Details of the unblinding plan will be described in the Assessment Committee Charter. Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

A limited number of preidentified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population PK/PD model development processes for interim or final analyses. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

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Appendix 1. Abbreviations and Definitions

Term	Definition
AC	assessment committee
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 events of special interest
ALT	alanine transaminase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
ATE	arterial thromboembolic event
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment. Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BTC	biliary tract cancer
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	central nervous system
collection database	a computer database where clinical trial data are entered and validated.
CR	complete response
CRC	colorectal cancer
CRF	case report form

CRP/CRS	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 [CRS], global safety physician, or other medical officer.
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-drug interaction
DMC	data monitoring committee
ECG	electrocardiogram
effective method of contraception	male condom with spermicide, female condom with spermicide, diaphragm with spermicide, cervical sponge, or cervical cap with spermicide. bilateral tubal ligation, male condom with spermicide, intrauterine device that has been in place for at least 3 months before the first dose of study treatment, or an oral contraceptive pill taken for at least 3 months before the first dose of study treatment. Also see the definition of highly effective method of contraception.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	EuroQol 5-Dimension 5 Level
end of study	End of study is the date of the last visit or last scheduled procedure for the last patient.
ERB/IRB	ethical review board/institutional review board: /A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
FACT	Functional Assessment of Cancer Therapy
FACT-Hep	FACT Hepatobiliary Questionnaire
GCP	good clinical practice
GFR	glomerular filtration rate
GI	gastrointestinal
HGF	hepatocyte growth factor
highly effective method of contraception	combined oral contraceptive pill and mini-pill, NuvaRing®, implantable contraceptives, injectable contraceptives (such as Depo-Provera®), intrauterine device (such as Mirena® and ParaGard®), contraceptive patch for women <90 Kg (<198 pounds), total abstinence, or vasectomy. Also see the definition of effective method of contraception.

IB	investigator's brochure
IC_{50}	inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG1	immunoglobulin G, subclass 1
INR	International Normalized Ratio
IV	intravenous
interim analysis	An interim analysis is an analysis of clinical trial data conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
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 (that is, 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
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epithelial transition factor
MVD	microvascular density
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival

PK	pharmacokinetic(s)
PO	oral
PR	partial response
PRO	patient-reported outcomes
PTT/aPTT	partial thromboplastin time /activated partial thromboplastin time
QTc	corrected QT interval
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.
re-screen	to screen a patient who was previously declared a screen failure for the same study
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SAP	Statistical Analysis Plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
Study completion	This study will be considered complete following the final analysis of overall survival is performed), as determined by Lilly.
SUSARs	suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event

Appendix 2. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in the study
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of study treatment.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

Ethical Review

Documentation of ERB/IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs/IRBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERBs/IRBs should be provided with the following:

- the current IB and updates during the course of the study
- the ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations.

Some obligations of Lilly may be assigned to a third-party organization.

Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

Protocol Signatures

Lilly's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The investigator will sign the final clinical study report for this study, indicating agreement, to the best of his or her knowledge, with the analyses, results, and conclusions of the report.

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most enrolled patients will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The Lilly responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs/IRBs with direct access to original source documents.

Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into Lilly provided electronic data capture system.

Electronic patient-reported outcome (ePRO) measures (for example, a rating scale) are entered into an ePRO instrument (for example, personal data assistant [PDA], or by means of IWRS) at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

If ePRO records are stored at a third-party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome (PRO) measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB/IRB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3. Clinical Laboratory Tests

Randomization and treatment decisions will be based on local laboratories. For each local chemistry blood draw, samples for central laboratory shipment should be collected as well.

Hematology[a]: (local laboratory only)

Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume (MCV)
Mean cell hemoglobin concentration (MCHC)
Leukocytes (WBC)
Neutrophils, segmented
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Urinalysis (Local)[a]:

Routine dipstick measurements, and if clinically indicated, microscopic analysis. If urine dipstick or routine analysis indicates proteinuria ≥2+ at evaluations, a 24-hour urine collection (to assess protein) must be obtained.

Exploratory Biomarkers/Other[b]: (central laboratory only)

Anti-ramucirumab antibody
Ramucirumab concentrations in serum

Clinical Chemistry[a,c]: (local and central laboratory)

Sodium
Potassium
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Blood urea nitrogen (BUN)
Creatinine
Magnesium
Calcium
Glucose, non-fasting
Albumin
LDH
Chloride

Serum Thyroid Function Tests (central)

TSH
Free thyroxine (T4)
Free triiodothyroxine (T3)

Tumor Markers (central)

Carbohydrate antigen 19-9 (CA19-9)
Carcinoembryonic antigen (CEA)
CA 125

Pregnancy Test: (local laboratory only)

(females only)[a,d]

Coagulation Tests: (local laboratory only)[a]:

Prothrombin time (PT or INR)
Partial thromboplastin time (PTT)

Abbreviations: β-hCG = beta human chorionic gonadotropin; RBC = red blood cells; TSH = thyroid-stimulating hormone; WBC = white blood cells; WOCBP = women of childbearing potential.

a Assayed by Investigator designated (local) laboratory. For Arms A and B, perform urinalysis at baseline and short-term follow-up visit. During the treatment period, perform urinalysis for Arm A.

b Assayed by Sponsor-designated (central) laboratory.

c Investigator-designated (local) laboratory results are to be used for on-study dosing decisions. Samples must also still be submitted for testing by the Sponsor-designated central laboratory but will not be used to make treatment decisions.

d Serum pregnancy test in WOCBP will be done at baseline; thereafter, serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of β-hCG) to be performed.

Appendix 4. Sampling Schedule for Genetics/ Biomarkers/Immunogenicity/Pharmacokinetics/ Pharmacodynamics

It is essential that the exact infusion start and stop times (actual clock readings), as well as infusion parameters (such as, type of infusion pump, flow rate settings) are recorded. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. It is essential that the pharmacokinetic blood samples not be withdrawn from the same site as the drug infusion.

Table APP.4.1. Sampling Schedule for Genetics/Biomarkers/Pharmacodynamics (Arms A and B)

	Screening	Cycle 1 Day 1		Cycle 1 Day 8	6 weeks post-treatment	12 weeks post-treatment	24-X weeks post-treatment	Short-Term Follow-Up
		Before dosing	End of study day					
Pharmacogenetics (PGx) sample[a]	X							
Mandatory tumor tissue[b]	X							
Whole blood[c]	X	X	X	X	X	X	X	X
Plasma[c]	X	X	X	X	X	X	X	X
Serum[c]	X	X	X	X	X	X	X	X

a A pretreatment blood sample is preferred; however, the whole blood sample for genetic analysis may be collected at a later time point if necessary.

b Collection of a fresh tumor biopsy tumor tissue during screening is required unless an archived tumor sample is available that was obtained ≤28 days prior to screening. 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.

c Whole blood, plasma, and serum samples for exploratory purposes should be obtained during screening, on Cycle 1 Day 1 (before dosing and at the end of study day), on Cycle 1 Day 8, and then to coincide within 7 days of the Radiological Tumor Assessment at 6 and 12 weeks, and then every 12 weeks thereafter.

Table APP.4.2. Pharmacokinetic and Immunogenicity, Schedule (Arm A)

Visit	Time Point[a]	Window	Ramucirumab	
			PK[b]	IK[b]
Cycle 1 Day 1	Prior to infusion	Within 7 days Prior to infusion	X	X
Cycle 1 Day 1	1 hr post end-of-infusion	1 to 1.5 hours after the end of the infusion	X	
Cycle 1 Day 8	Prior to infusion	Within 3 days prior to infusion	X	
Cycle 2 Day 1	Prior to infusion	Within 3 days prior to infusion	X	
Cycle 3 Day 1	Prior to infusion	Within 3 days prior to infusion	X	X
Cycle 3 Day 1	1 hr post end-of-infusion	1 to 1.5 hours after the end of the infusion	X	
Cycle 4 Day 1	Prior to infusion	Within 3 days prior to infusion	X	
Cycle 5 Day 1	Prior to infusion	Within 3 days prior to infusion	X	
Cycle 7 Day 1	Prior to infusion	Within 3 days prior to infusion	X	
Cycle 9 Day 1	Prior to infusion	Within 3 days prior to infusion	X	
Cycle 9 Day 1	1 hr post end-of-infusion	1 to 1.5 hours after the end of the infusion	X	
Cycle 13 Day 1	Prior to infusion	Within 3 days prior to infusion	X	
Short-term follow-up	Follow-up	Anytime during the follow-up visit	X	X

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

[a] Relative to ramucirumab or placebo infusion.

[b] In the event of an IRR, blood samples will be collected for both PK and IK analysis at the following time points: (i) as soon as possible after the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days following the IRR.

Table APP.4.3. Pharmacokinetic Schedule (Arm B)

Visit	Cycle/Day	Time	Merestinib PK (plasma concentration)
C1 D8[a]	C1 D8[a]	Morning	X
C2,4,6,8 D1[a]	C2,4,6,8 D1	Morning	X
C2,4,6,8 D8[a]	C2,4,6,8 D8	Morning	X

Abbreviations: C = cycle; D = day; PK = pharmacokinetic(s).

[a] If patient has not taken drug on the evening before a visit, it should be taken after the PK sample has been drawn.

Note: It is essential that the dosing dates, dosing times, draw dates and draw times are accurately recorded. Timing of outpatient doses administered on Day 7 and Day 21 of every cycle should be recorded by the clinic.

Table APP.4.4. Pharmacokinetic Schedule (Arm A + Arm B)

Visit	Time Point	Window	PK	
			Gemcitabine	Cisplatin
Cycle 3 Day 1	Prior to cisplatin infusion	Within 30 min prior to cisplatin infusion		X
	end-of-cisplatin-infusion	Within 10 min after the end of cisplatin infusion		X
	Prior to gemcitabine infusion	Within 30 min prior to gemcitabine infusion	X	
	end-of-gemcitabine-infusion	Within 10 min after the end of gemcitabine infusion	X	
Cycle 3 Day 8	Prior to cisplatin infusion	Within 30 min prior to cisplatin infusion		X
	end-of-cisplatin-infusion	Within 10 min after the end of cisplatin infusion		X
	Prior to gemcitabine infusion	Within 30 min prior to gemcitabine infusion	X	
	end-of-gemcitabine-infusion	Within 10 min after the end of gemcitabine infusion	X	

Abbreviation: PK = pharmacokinetics.

Note: It is essential that the dosing dates, dosing times, draw dates, and draw times are accurately recorded.

Appendix 5. 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 clinical research physician.

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 Lilly-designated 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.

Appendix 6. Creatinine Clearance Formula

The CKD-EPI Creatinine Equation (2009)

The CKD-EPI creatinine equation is based on the same 4 variables as the MDRD Study equation, but uses a 2-slope spline to model the relationship between estimated GFR and serum creatinine, and a different relationship for age, sex and race. The equation was reported to perform better and with less bias than the MDRD study equation, especially in patients with higher GFR. This results in reduced misclassification of CKD. As of November 2009, very few clinical laboratories report the estimated GFR using the CKD-EPI creatinine equation. In the future, other GFR estimating equations may outperform CKD-EPI.

The CKD-EPI creatinine equation is:

$$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$$

$\kappa = 0.7$ if female
$\kappa = 0.9$ if male

$\alpha = -0.329$ if female
$\alpha = -0.411$ if male

min = The minimum of Scr/κ or 1
max = The maximum of Scr/κ or 1

Scr = serum creatinine (mg/dL)

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-612.

Appendix 7. ECOG Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead.

Source: Oken et al. 1982.

CCI

[redacted]

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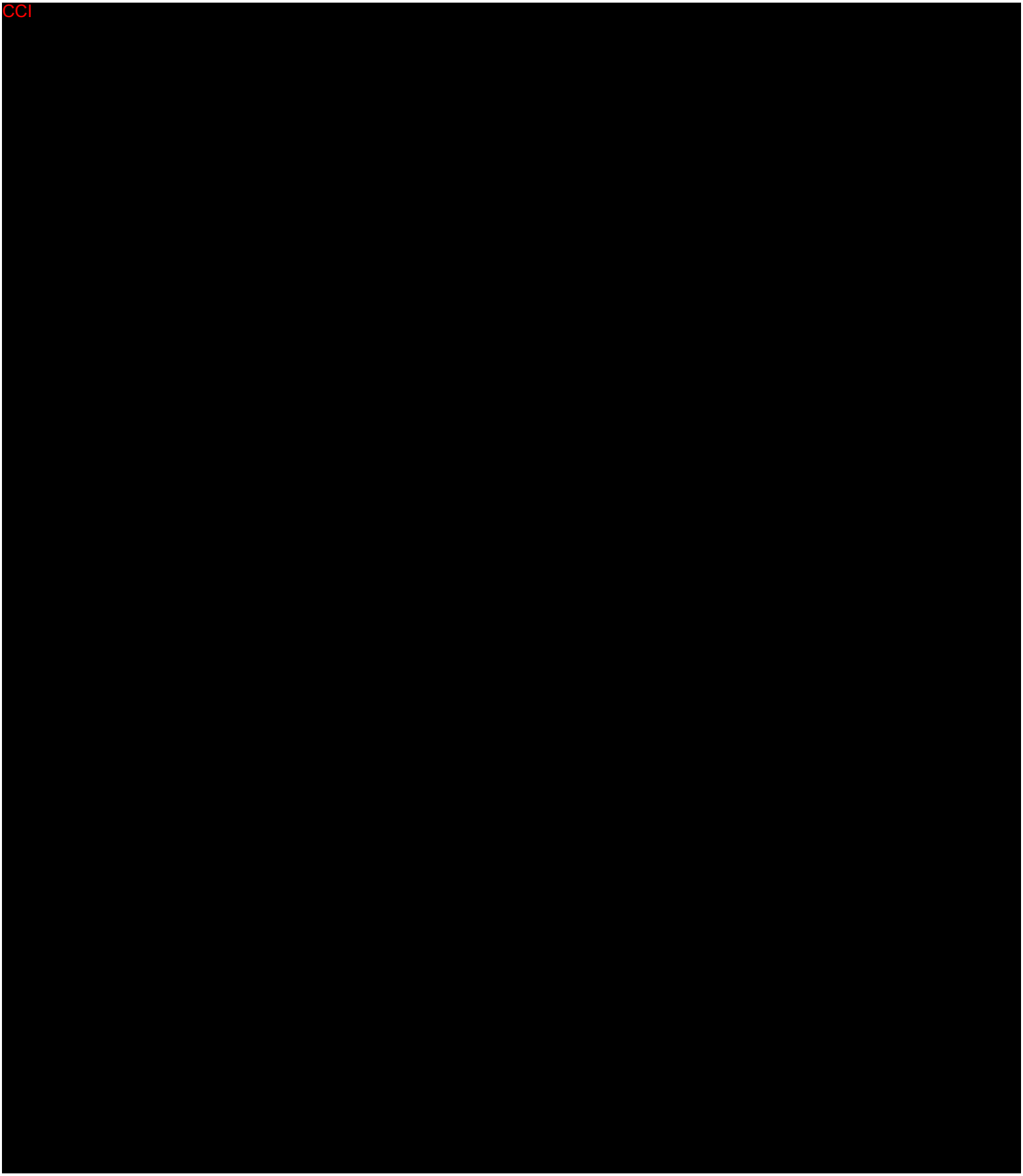

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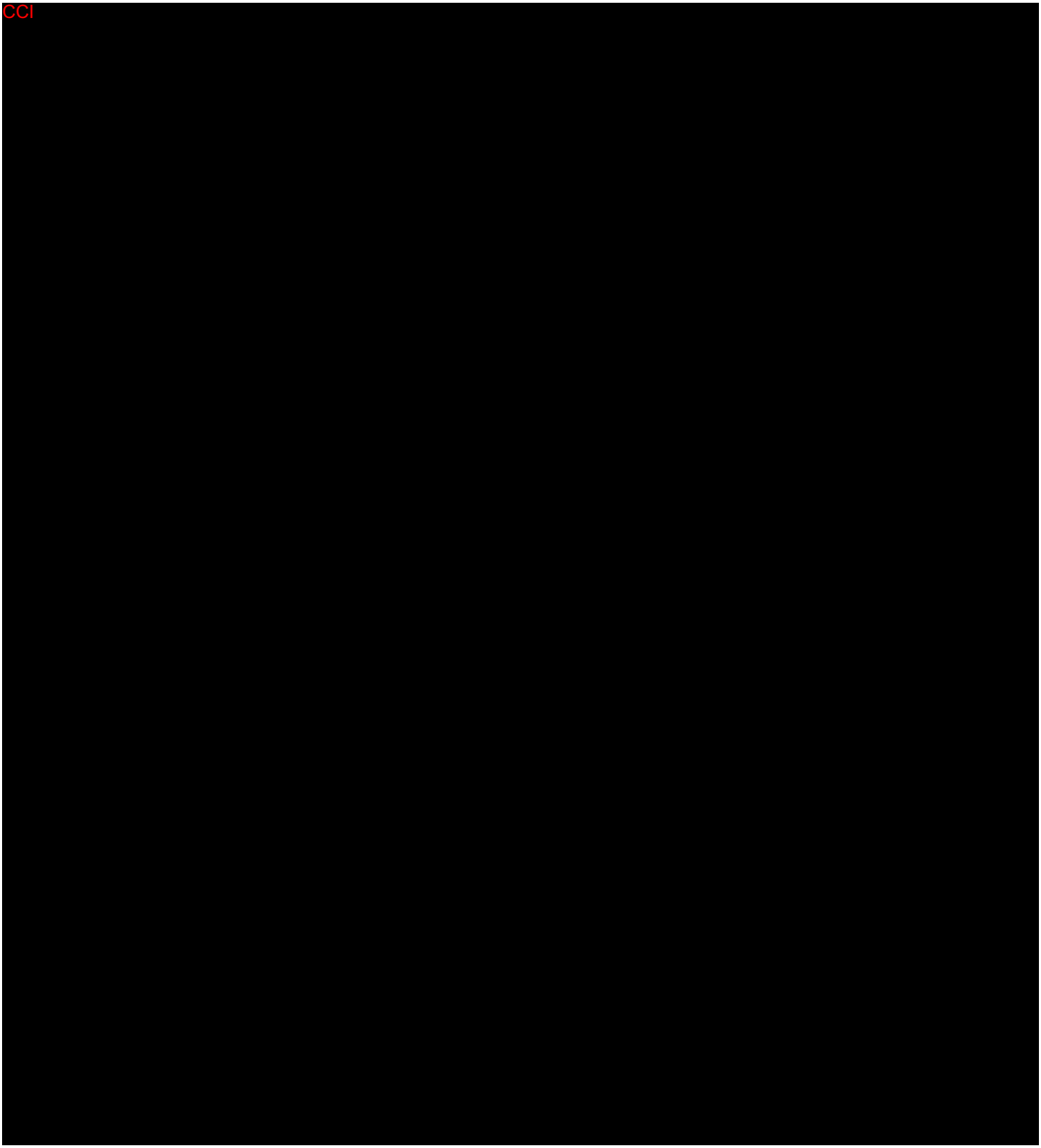

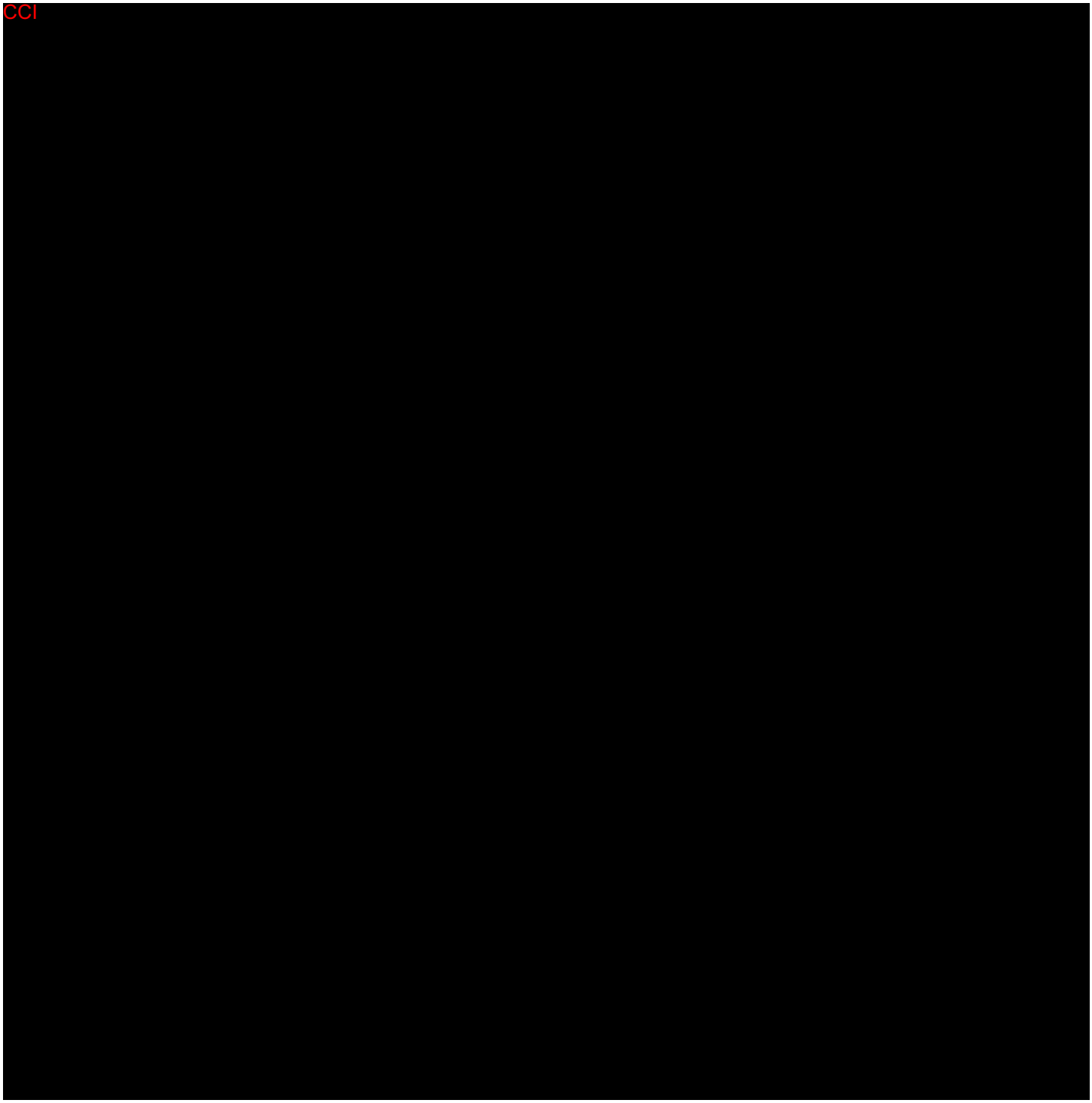
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Appendix 9. Permitted and Prohibited Concomitant Therapy (Arm A)

Below is a table of medications and drug classes that either have restricted use (see the Conditions for Use column and referenced guidelines) or are not permissible for use while the patient is on Arm A of the study.

Therapy	As Needed	Chronic Use	Conditions for Use
Anticoagulants other than warfarin	no	no	Use of warfarin is prohibited. Refer to Inclusion Criterion [8]d and Exclusion Criterion 21.
Biologic response modifiers	no	no	
Chemotherapy	no	no	
Colony-stimulating factors	yes	no	Follow local guidelines.
Erythroid growth factors	yes	no	Follow local guidelines.
Experimental medicines	no	no	
Investigational agents	no	no	
NSAIDs	yes	no	Chronic use of aspirin up to 325 mg/day is permitted.
Radiotherapy	yes	no	Palliative radiotherapy during the study, if clinically indicated, can be considered after consultation with the Lilly CRP/CRS.

Abbreviations: CRP = (Lilly) clinical research physician; CRS = (Lilly) clinical research scientist; NSAIDs = nonsteroidal anti-inflammatory drugs.

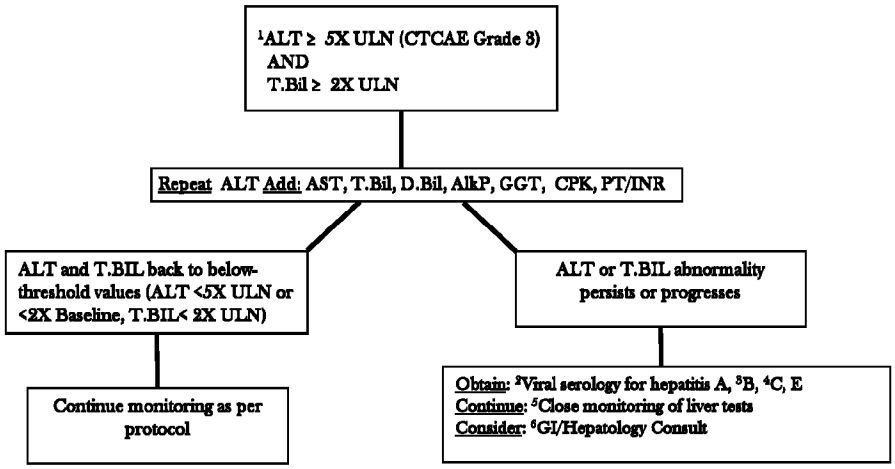
Appendix 10. NCI-CTCAE v 4.0 Infusion-Related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤ 24 h	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					

Abbreviations: IV = intravenous(ly); NSAIDs = nonsteroidal anti-inflammatory drugs.

Appendix 11. Hepatic Monitoring Algorithm for Patients in Oncology Clinical Trials

Hepatic Monitoring Algorithm for Patients in Oncology Clinical Trials



1. For patients entering the study with ALT≥ 8X ULN monitoring will be triggered at ALT ≥2X baseline
2. Recommended viral serology tests (may be adjusted based on geography and risk factors):
   - Hepatitis A Virus (HAV): HAV Ab total, IgM
   - Hepatitis B Virus (HBV): HBsAg, HBsAb, HBcAb
   - Hepatitis C Virus (HCV): HCV Ab
   - Hepatitis E Virus (HEV): HEV Ab IgG, IgM
3. In patients with detectable HBsAg consider testing for HBV DNA by PCR
4. In immune suppressed patients consider testing for HCV RNA by PCR
5. Recommended liver tests monitoring: ALT, AST, T.Bil, D.Bil, AlkP, GGT, CPK, PT/INR
6. Consider hepatobiliary ultrasound to assess for gallstone or gallbladder disease

Note:
- AlkP levels are not used as initiating conditions in this algorithm as they may frequently change due to the underlying illness in oncology patients.
- Significant changes in ALT are more likely to be related to a liver injury not directly related to the underlying illness.
- In the absences of ALT changes, changes in T.BIL are less likely to be related to DILI or viral hepatitis.

Appendix 12. Protocol Amendment I3O-MC-JSBF(a) Summary: Randomized, Double-Blind, Phase 2 Study of Ramucirumab or Merestinib or Placebo plus Cisplatin and Gemcitabine as First-Line Treatment in Patients with Advanced or Metastatic Biliary Tract Cancer

Overview

Protocol I3O-MC-JSBF, Randomized, Double-Blind, Phase 2 Study of Ramucirumab or Merestinib or Placebo plus Cisplatin and Gemcitabine as First-Line Treatment in Patients with Advanced or Metastatic Biliary Tract Cancer, has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

Changes were made to this protocol based on regulatory authority feedback, from the US FDA. Additionally, minor changes were made in Sections 7.1.1.3, 7.1.1.4, and 7.2.1.5 to provide clarity to the site personnel.

The overall main changes made to this protocol are as follows:

- Table JSBF.2 (Treatment Period) is amended to include a full chemistry profile on Day 8 of each study Cycle during Cycles 1 through 8. Thereafter, collection for testing of a full chemistry profile on Day 8 of each study cycle is optional as clinically indicated at the discretion of the treating investigator.
- Table JSBF.1 (Schedule of Screening Activities), Table JSBF.2 (Treatment Period), and Table JSBF.3 (Postdiscontinuation Follow-Up Schedule) are amended to include testing of serum TSH, free thyroxine (T4), and free triiodothyronine (T3). Testing is added to baseline assessment, Cycle 8, the short-term follow-up visit, and as clinically indicated at the discretion of the treating investigator.
- Text has been added to Section 10.1 (Sample Size Determination) related to analysis of OS for the study.
- Text has been added to Section 7.4 (Dose modification) as guidance for investigators to make attributions for the purpose of dose modifications, in the event of observed toxicities that may be associated with more than one agent.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of <u>double underscore</u>.

Section 2. Schedule of Activities

Table 1. Schedule of Screening Activities I3O-MC-JSBF

			Baseline			
		Cycle	BL			
		Visit	0			
		Relative Day Prior to Cycle 1 Day 1	**≤28**	**≤14**	**≤7**	**Notes**
Procedure Category	**Prot. Ref.**	**Procedure**				
Laboratory/ Diagnostic Tests	6.1, Appendix 3	Serum Chemistry profile		X		Two measurements are required that are separated by at least 5 days. Serum chemistry to include TSH, free thyroxine (T4), and free triiodothyronine (T3).

Abbreviations: …TSH = thyroid-stimulating hormone;….

Table 2. Treatment Period, I3O-MC-JSBF

			Treatment Period								
		Study Period									**Notes**
		Cycle (21-day cycle)	**1-8**				**9+**				
		Relative Day within Cycle)	**1**	**2-7**	**8**	**9-21**	**1**	**2-7**	**8[a]**	**9-21**	
Procedure Category	**Protocol Section**	**Procedure**									
Laboratory/ Diagnostic Tests	Appendix 3	Full chemistry profile	X		X		X				Assessments performed within 3 days prior to Day 1 of the cycle may be used for treatment decisions, if the results are deemed still clinically valid by the treating investigator. Day 8 chemistry to be collected during Cycles 1 through 8. Thereafter, Day 8 collections will be optional as clinically indicated at the discretion of the treating investigator. In Cycle 8, serum chemistry on any day in the cycle to include TSH, free thyroxine (T4), and free triiodothyronine (T3).

Abbreviations: …TSH = thyroid-stimulating hormone;….

Table 3. Postdiscontinuation Follow-Up Schedule, I3O-MC-JSBF

			Postdiscontinuation Follow-up		
		Cycle	**Short-term Follow-up**	**Long-term Follow-up**	**Notes**
		Visit	801	802-8XX	
		Duration	Refer to footnote for duration	Refer to footnote for duration	
Procedure Category	**Protocol Reference**	**Procedure**			
Laboratory/ Diagnostic Tests	Appendix 3	Chemistry	X		Serum chemistry to include TSH, free thyroxine (T4), and free triiodothyronine (T3).

Abbreviations: …TSH = thyroid-stimulating hormone;….

7.1.1.3. Gemcitabine

Gemcitabine will be supplied in commercially available dosage forms and provided according to the country's regulatory requirements. Gemcitabine should be stored in accordance with the ~~package insert~~ product information.

7.1.1.4. Cisplatin

Cisplatin will be supplied in commercially available dosage forms and provided according to the country's regulatory requirements. Cisplatin should be stored in accordance with the ~~package insert~~ product information.

7.2.1.5. Administration of Gemcitabine

Patients will receive 1000 mg/m2 gemcitabine administered over approximately 30 minutes on Days 1 and 8 of each 21-day treatment cycle. Treatment with gemcitabine may continue for a planned maximum of 8 cycles, or until a criterion for discontinuation is met (as described in Section 8). Investigators should consult the approved gemcitabine ~~package insert~~ product information for complete packaging and labeling information.

7.4. Dosage Modification

In the event of observed toxicities that may be associated with more than one agent (for example, hepatic toxicity or unexpected hematologic toxicity) a temporal association should be evaluated to aid in assessment of drug relatedness and dose modification. Other potentially reversible risk factors for the AE should be identified and addressed as appropriate. For example, in the case of hepatic toxicity, patients should be evaluated for the need to undergo biliary drainage. In the absence of temporal association or other potentially reversible or modifiable risks factors for the AE, for overlapping toxicities, consideration should be given to first reduce the dose of the investigational drugs and try to maintain the dose of gemcitabine and cisplatin.

10.1. Sample Size Determination

The analysis of OS for the comparison of each investigational treatment to pooled control will be performed when a minimum of a total of 225 events in the study have been observed. Assuming an OS hazard ratio of 0.75, this sample size yields approximately 68% statistical power to detect superiority of each investigational treatment over the pooled control with the use of a log-rank test and a 1-sided type I error rate of 0.10.

Attachment 3. Clinical Laboratory Tests

Serum Thyroid Function Tests (central)
TSH
Free thyroxine (T4)
Free triiodothyroxine (T3)
Abbreviations: …TSH = thyroid-stimulating hormone;….

Leo Document ID = 5d184a92-4920-47c9-b069-c7d97cde7b20

Approver: PPD
Approval Date & Time: 30-Mar-2016 14:48:16 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 30-Mar-2016 15:46:23 GMT
Signature meaning: Approved