

I4T-MC-JVDC Protocol

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Ramucirumab Plus Docetaxel Versus Placebo Plus Docetaxel in Patients With Locally Advanced or Unresectable or Metastatic Urothelial Carcinoma Who Progressed on or After Platinum-Based Therapy

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## 1. Protocol I4T-MC-JVDC

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#### **Ramucirumab (LY3009806)**

Phase 3, randomized, double-blind, placebo-controlled study of ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or unresectable or metastatic urothelial carcinoma who progressed on or after one prior first-line platinum-based chemotherapy. Patients will be randomized 1:1 to receive one of these study regimens on Day 1 of each 21-day cycle: ramucirumab (10 mg/kg) I.V. plus docetaxel (75 mg/m<sup>2</sup>) I.V. OR placebo (10 mg/kg volume equivalent) I.V. plus docetaxel (75 mg/m<sup>2</sup>) I.V. Provided no prespecified discontinuation criteria have been met (including radiographic documentation of disease progression, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent), treatment with docetaxel may continue for up to six 21-day cycles; further cycles of docetaxel (up to 4 additional cycles [maximum of 10 cycles total]) may be administered with approval of the Lilly clinical research physician/clinical research scientist or designee. Treatment with ramucirumab or placebo (monotherapy) may continue on 21-day cycles until at least one discontinuation criterion is met.

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Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 14-Jan-2015 GMT

## 2. Synopsis

### Study Rationale

Efficacy data from the 75% interim analysis for the Phase 2 Study I4Y-IE-JCDC (JCDC) showed a clinically significant improvement in progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR) when ramucirumab was given with docetaxel versus docetaxel alone. Furthermore, early evaluation of overall survival (OS; 43% censoring) demonstrated survival results trending in favor of the ramucirumab arm. The combination was well tolerated. As a result, the current confirmatory Phase 3 Study I4T-MC-JVDC (JVDC) is planned.

**Clinical Protocol Synopsis: Study I4T-MC-JVDC**

<b>Name of Investigational Product:</b> Ramucirumab (LY3009806)	
<b>Title of Study:</b> A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Ramucirumab plus Docetaxel Versus Placebo plus Docetaxel in Patients with Locally Advanced or Unresectable or Metastatic Urothelial Carcinoma Who Progressed on or After Platinum-Based Therapy	
<b>Number of Planned Patients:</b> Entered: 699 Enrolled/Randomized: 524 Completed (number of patients who will complete the OS endpoint): 382	<b>Phase of Development:</b> 3
<b>Length of Study:</b> approximately 33 months (duration from first patient visit to last patient visit; applies to all patients in trial; excludes the Continued Access Period) Planned first patient visit: JUN 2015 Planned last patient visit, excluding the Continued Access Period: MAR 2018 Planned interim analysis: One interim efficacy analysis for OS (based on all randomized patients) will be performed at the time of PFS final analysis.	
<b>Objectives:</b> The primary objective of this study is to compare the progression-free survival (PFS) of ramucirumab in combination with docetaxel with the PFS of placebo in combination with docetaxel, in patients with locally advanced or unresectable or metastatic urothelial carcinoma who have had disease progression on or after one prior first-line platinum-based chemotherapy. The secondary objectives of this study are to compare each of the following variables between the treatment arms: <ul style="list-style-type: none"> <li>• overall survival (OS) time</li> <li>• objective response rate (ORR; complete response [CR] + partial response [PR]) and disease control rate (DCR)</li> <li>• duration of response (DOR)</li> <li>• safety profile</li> <li>• patient-reported outcome (PRO) measures (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 [EORTC QLQ-C30] and EQ-5D-5L)</li> </ul> Secondary objectives also include the evaluation of: <ul style="list-style-type: none"> <li>• the pharmacokinetic profile of ramucirumab</li> <li>• the immunogenicity of ramucirumab (anti-ramucirumab antibodies)</li> </ul> The exploratory objectives of this study are to: <ul style="list-style-type: none"> <li>• assess the change in tumor size in patients with measurable disease</li> <li>• examine biomarkers relevant to ramucirumab, angiogenesis, and the disease state, and to correlate these markers to clinical outcome</li> </ul>	



**Study Design:** Phase 3, randomized, double-blind, placebo-controlled study of ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or unresectable or metastatic urothelial carcinoma who progressed on or after one prior first-line platinum-based chemotherapy. Patients will be randomized 1:1 to receive one of these study regimens on Day 1 of each 21-day cycle: ramucirumab (10 mg/kg) intravenously (I.V.) plus docetaxel (75 mg/m<sup>2</sup>) I.V. OR placebo (10 mg/kg volume equivalent) I.V. plus docetaxel (75 mg/m<sup>2</sup>) I.V. Provided no prespecified discontinuation criteria have been met (including radiographic documentation of disease progression, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent), treatment with docetaxel may continue for up to six 21-day cycles (up to 4 additional cycles of docetaxel [maximum of 10 cycles total] may be administered with approval of the Lilly clinical research physician [CRP]/clinical research scientist [CRS] or designee). Treatment with ramucirumab or placebo (monotherapy) may continue on 21-day cycles until at least one discontinuation criterion is met. This is an outpatient study.

**Diagnosis and Main Criteria for Inclusion and Exclusion:**

**Key Inclusion Criteria**

- The patient has histologically or cytologically confirmed, locally advanced or unresectable or metastatic urothelial (transitional cell) carcinoma of the bladder, urethra, ureter, or renal pelvis. Patients with mixed pathology are eligible only if they have predominantly transitional cell tumor based on local pathology review.
- The patient has demonstrated disease progression while on a platinum-containing regimen in the first-line setting or within 14 months of completing the first-line platinum regimen. Patients who received treatment with one immune checkpoint inhibitor (for example, PD-1, PDL1, or CTLA4) regimen following platinum therapy may have a longer interval since prior platinum-containing therapy ( $\leq 24$  months); such patients are eligible.
- The patient has received no more than one prior systemic chemotherapy regimen in the relapsed or metastatic setting. Prior cytotoxic therapy in an adjuvant or neoadjuvant setting is not considered as a prior line of systemic chemotherapy in the relapsed or metastatic setting. Prior treatment with intravesicular chemotherapy, bacillus Calmette-Guérin (BCG), or platinum given as a radiation-sensitizing agent will not be considered as a systemic line of treatment. Prior treatment with no more than one prior immune checkpoint inhibitor is permitted and will not be considered as a line of systemic chemotherapy. Patients enrolling after immune checkpoint inhibitor therapy must have demonstrated disease progression while on that therapy or within 24 months after the last dose of that therapy.
- The patient has measurable disease or nonmeasurable but evaluable disease as defined by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).
- The patient has an Eastern Cooperative Oncology Group performance status of 0 or 1.
- The patient is willing to provide blood, urine, and tissue samples for research purposes. Submission of blood and urine specimens is mandatory for participation in this study, unless restricted per local regulations. If prior archived tumor specimens are available, and unless restricted by local regulations, submission of archived tumor tissue is mandatory. If an archived specimen is not available, submission of a newly acquired biopsy is requested when biopsy is safe and feasible.
- The patient has adequate organ function.

**Key Exclusion Criteria**

- The patient has received more than one prior systemic chemotherapy regimen for metastatic disease (except as noted in Inclusion Criteria). A treatment regimen must consist of minimum of 2 cycles to be considered as a prior regimen.

**Test Product, Dosage, and Mode of Administration:**

Ramucirumab drug product 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).

Placebo drug product is a sterile, preservative-free solution for infusion containing histidine buffer in a 50-mL vial to mimic the ramucirumab drug product container and closure.

Patients will receive ramucirumab by I.V. infusion at a dose of 10 mg/kg (or placebo at a dose of 10 mg/kg volume equivalent) over approximately 60 minutes on Day 1 of each 21-day cycle.

**Reference Therapy, Dosage, and Mode of Administration:**

Docetaxel will be administered at a dose of 75 mg/m<sup>2</sup> I.V. over 60 minutes on Day 1 of each 21-day treatment cycle. (A commercial preparation of docetaxel will be used and should be prepared and administered according to the manufacturer's instructions).

**Planned Duration of Treatment:** The following describes the intended duration of treatment for a single patient, excluding the Continued Access Period.

A treatment cycle will be defined as 21 days, with radiographic evaluation of tumor response at these time points:

- at Baseline
- every 6 weeks ( $\pm 7$  days) after randomization (regardless of treatment delays) during the Study Treatment Period, until disease progression OR overall study completion OR 1 year after randomization, whichever occurs first

In addition, any patient whose disease has not progressed by 1 year 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 ( $\pm 7$  days) from 1 year after randomization, until disease progression OR overall study completion OR 3 years after randomization, whichever occurs first; then as per standard clinical practice after that.

Provided no prespecified discontinuation criteria have been met (including radiographic documentation of disease progression, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent), treatment with docetaxel may continue for up to six 21-day cycles (up to 4 additional cycles of docetaxel [maximum of 10 cycles total] may be administered with approval of the Lilly CRP/CRS or designee). Treatment with ramucirumab or placebo (monotherapy) may continue on 21-day cycles until at least one discontinuation criterion is met.

Short-term Follow-up (postdiscontinuation): Approximately 30 days after the date of discontinuation.

Long-term Follow-up (postdiscontinuation): Patients will be followed for survival every 3 months ( $\pm 7$  days) until the patient's death or overall study completion, whichever occurs first.

**Criteria for Evaluation:**Efficacy:

PFS is defined as the time from the date of randomization to the date of first observation of objective progression as defined by RECIST 1.1 or the date of death due to any cause, whichever is earlier.

OS is defined as the time from the date of randomization to the date of death from any cause.

ORR is defined as the proportion of randomized patients achieving a best response of CR or PR, using the investigator response assessments.

DCR is defined as the proportion of randomized patients achieving a best response of CR, PR, or stable disease (SD). SD is defined per RECIST criteria and must last a minimum of 5 weeks from randomization.

DOR is defined only for responders (patients with CR or PR [confirmation not required]) and is measured from the date of first evidence of CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier.

Safety: Drug exposure; adverse events (AEs); treatment-emergent adverse events (TEAEs); deaths; serious adverse events (SAEs); other significant AEs (including TEAEs leading to study treatment discontinuations and dose modifications); vital signs; transfusions; other observations related to safety; and clinical laboratory evaluations. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). AEs and clinical laboratory values will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (v 4.0).

Health Outcomes: Assessment of PROs will be conducted through the use of the EORTC QLQ-C30 and the EQ-5D-5L questionnaires, which measure quality of life and health status, respectively. A change of  $\geq 10$  points on the 100-point EORTC QLQ-C30 scales is considered clinically meaningful.

Immunogenicity (anti-ramucirumab antibodies): Blood samples for immunogenicity (anti-ramucirumab antibodies) testing will be collected from all study patients to determine antibody production against ramucirumab (placebo) at baseline (before the first infusion of ramucirumab/placebo on Cycle 1, Day 1 of treatment); at specified time points during the study; and in the event of an infusion-related reaction, as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event. Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of the ramucirumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ramucirumab.

Pharmacokinetics: Blood samples will be collected from all study patients to assess ramucirumab concentrations in serum, including concentrations prior to ramucirumab infusion ( $C_{\min}$  [trough concentration]) and at 1-hour post end of ramucirumab infusion (approximately  $C_{\max}$  [peak concentration]).

Translational research/Tailoring biomarkers: Deoxyribonucleic acid (DNA) from whole blood samples will be collected for pharmacogenetic analysis. Plasma samples for analysis of circulating markers will be collected prior to infusion on Day 1, Cycle 1 and on Day 1, Cycle 3, and at the (30-day) Short-term Follow-up visit. Urine samples for analysis of biomarkers will be collected at baseline (within 28 days prior to infusion on Day 1, Cycle 1), prior to infusion on Day 1, Cycle 3, and at the (30-day) Short-term Follow-up visit. Submission of prior archived tumor specimen, if available, is mandatory; if archived specimen is not available, submission of newly acquired biopsy obtained at baseline is requested when biopsy is safe and feasible. Tumor tissue and plasma samples will be examined for markers that may include, but are not limited to, those related to locally advanced or unresectable or metastatic urothelial carcinoma, angiogenesis, docetaxel, and/or ramucirumab. Mutation profiling, copy number variability, gene expression, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations with these biomarkers and clinical outcomes. The pharmacogenetic biomarker samples will only be used for investigations related to disease, cancer-related conditions, and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.



**Statistical Methods:**Statistical:

A gatekeeping design will be used to assess PFS, OS, and ORR. PFS, OS, and ORR are tested in a sequential manner. The OS superiority is tested only if the PFS superiority test is significant. Similarly, the ORR superiority is tested only if the OS superiority test is significant. Although the primary endpoint is PFS, the sample size is powered to show a superiority test for comparing OS between the 2 arms.

The sample size to test PFS superiority at the PFS final analysis is determined based on the following assumptions:

- The PFS hazard ratio (HR) for treatment group (ramucirumab plus docetaxel) versus control group (placebo plus docetaxel) is 0.70.
- The randomization ratio is 1:1.
- A 2-tailed significance level of 0.05.
- Control arm median PFS = 2 months.
- The type II error rate is 0.1, i.e., the power of the trial is set to 90%.
- Enrollment rate is approximately 36.3 patients per month. This includes an estimated 25% chance of screen failure patients.

Under these assumptions, the estimated total number of PFS events at the PFS final analysis is 331, from an expected accrual of 371 patients. Assuming a 15% patient dropout rate from PFS follow-up, it is estimated that approximately 437 patients are needed to reach 331 PFS events in approximately 18.4 months.

The sample size to test OS superiority is determined based on the following assumptions:

- $\alpha = 0.049$  (2-sided), statistical power = 80%.
- The randomization ratio is 1:1.
- Control arm median OS = 9 months.
- HR = 0.75
- Interim efficacy analysis for OS (at the PFS final analysis) with testing at  $\alpha = 0.001$  (2-sided).

Under these assumptions, the estimated total number of OS events at the final OS analysis is 382, from an expected accrual of 497 patients. Assuming a 5% dropout rate from survival follow-up, it is estimated that 524 patients will need to be randomized to reach target number of OS events in approximately 32.6 months.

In order to ensure that the PFS final analysis at 331 PFS events reflects both early and later events by having an appropriate censoring rate, the cohort of the first 437 randomized patients will be used for the PFS final analysis, and this analysis will occur when a minimum of 331 PFS events have been observed in this cohort and enrollment is completed. All randomized patients up to that date will be used to compare (interim) OS between the 2 arms.

The final OS analysis is expected at 32.6 months from first patient enrollment. At the final analysis, all randomized patients (planned to be about 524 patients) will be used to compare OS between the 2 arms. The rejection boundary for HR is approximately 0.82.

An independent data monitoring committee (IDMC) will be established to conduct safety reviews (unblinded safety analyses) after at least 100 and 250 evaluable patients total have either started treatment in Cycle 3 or discontinued all study treatment prior to Cycle 3 due to any reasons. Additional safety reviews may be done at the discretion of the IDMC.

**Efficacy:**

The primary analysis will be performed on the intent-to-treat (ITT) population, which will include all randomized patients. Additional sensitivity analysis for PFS and OS will be repeated on the per-protocol population and other criteria. The primary analysis of PFS will be based on stratified log-rank test, stratified by randomization strata (interactive Web response system [IWRS]). PFS survival curves and the median with 95% confidence interval (CI) will be given using the Kaplan-Meier method. The HR will be estimated using a stratified Cox regression model, stratified by randomization strata (IWRS). The time-to-event efficacy endpoints, including PFS, OS, and DOR, will be analyzed with the Kaplan-Meier method by treatment groups, along with a summary of associated statistics (for example, median survival time and survival rates, including the corresponding 2-sided 95% CIs). ORR and DCR will be compared between the treatment groups using the Cochran-Mantel-Haenszel test on the entire ITT population.

**Safety:**

Safety analyses will be performed on the safety population (that is, all randomized patients who received any quantity of any study treatment, including a partial dose [ramucirumab/placebo, docetaxel]), and will include summaries of incidences of TEAEs by maximum CTCAE grade. Additionally, the following (but not limited to) safety-related outcomes will be summarized: study treatment discontinuations due to TEAEs, deaths, SAEs, hospitalizations, and transfusions.

**Health Outcomes:**

Time to deterioration in EORTC QLQ-C30 scales will be estimated with the Kaplan-Meier method. At each postbaseline assessment, patients' scores for each scale will be classified as improved, worsened, or stable; rates of improved/stable will be compared between arms using the ITT population. The EQ-5D-5L will be analyzed using descriptive statistics.

**Immunogenicity:**

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

**Pharmacokinetics:**

Ramucirumab  $C_{min}$  (trough concentration) and concentration at 1-hour post end of ramucirumab infusion (approximately  $C_{max}$  [peak concentration]) in serum will be summarized using descriptive statistics. Additional analysis using the population pharmacokinetic approach may be conducted if deemed appropriate. Relationships between ramucirumab exposure and measures of efficacy and safety will be explored.

**Translational research/Tailoring biomarkers:** The profiles of biomarkers assessed over time will be summarized by treatment. The associations between biomarker measures with clinical outcomes will be analyzed.

### 3. Table of Contents

## A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Ramucirumab plus Docetaxel Versus Placebo plus Docetaxel in Patients with Locally Advanced or Unresectable or Metastatic Urothelial Carcinoma Who Progressed on or After Platinum-Based Therapy

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## 4. Abbreviations and Definitions

Term	Definition
<b>β-hCG</b>	beta human chorionic gonadotropin
<b>AE</b>	adverse event  Any untoward medical occurrence in a patient or clinical investigation subject 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.
<b>ALT</b>	alanine aminotransferase
<b>ANC</b>	absolute neutrophil count
<b>AP</b>	alkaline phosphatase
<b>aPTT</b>	activated partial thromboplastin time
<b>ASCO</b>	American Society of Clinical Oncology
<b>AST</b>	aspartate aminotransferase
<b>ATE</b>	arterial thromboembolic event
<b>Att</b>	Attachment (at the end of the protocol)
<b>audit</b>	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
<b>BCG</b>	bacillus Calmette-Guérin
<b>blinding/masking</b>	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). 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.
<b>BP</b>	blood pressure
<b>BSA</b>	body surface area

<b>BSC</b>	best supportive care
<b>CHF</b>	congestive heart failure
<b>CI</b>	confidence interval
<b>C<sub>max</sub></b>	peak concentration
<b>C<sub>min</sub></b>	trough concentration
<b>CIOMS</b>	Council for International Organizations of Medical Sciences
<b>collection database</b>	A computer database where clinical trial data are entered and validated.
<b>complaint</b>	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
<b>compliance</b>	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
<b>Continued Access Period</b>	The period between study completion and end of trial during which 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.
<b>CR</b>	complete response
<b>CRC</b>	colorectal cancer
<b>CrCl</b>	creatinine clearance
<b>CRF</b>	case report form  Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
<b>CRP</b>	(Lilly) clinical research physician  Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
<b>CRS</b>	(Lilly) clinical research scientist
<b>CSFs</b>	colony-stimulating factors
<b>CT</b>	computed tomography
<b>CTCAE</b>	Common Terminology Criteria for Adverse Events
<b>DC</b>	discontinuation
<b>DC101</b>	a murine-specific anti-VEGF Receptor surrogate antibody for ramucirumab
<b>DCR</b>	disease control rate

<b>DCSI</b>	Development Core Safety Information (part of the Investigator's Brochure)
<b>DNA</b>	deoxyribonucleic acid
<b>DOR</b>	duration of response
<b>ECG</b>	electrocardiogram
<b>ECOG</b>	Eastern Cooperative Oncology Group
<b>EDTA</b>	ethylenediaminetetraacetic acid
<b>end of trial</b>	End of trial is the date of the last visit or last scheduled procedure for the last patient.
<b>enroll</b>	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.
<b>enter</b>	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
<b>EORTC QLQ-C30</b>	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
<b>ERB/IRB</b>	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 trial are protected.
<b>evaluable patients</b>	Must have received at least one dose of study therapy and have either started treatment in Cycle 3 or discontinued all study treatment prior to Cycle 3 due to any reasons. This population applies only to the safety interim analyses.
<b>Flt-1</b>	VEGF Receptor 1
<b>FOLFIRI</b>	folinic acid + fluorouracil + irinotecan chemotherapy regimen
<b>GCP</b>	good clinical practice
<b>G-CSF</b>	granulocyte colony-stimulating factor
<b>GI</b>	gastrointestinal
<b>HCT</b>	hematocrit
<b>HGB</b>	hemoglobin
<b>HIV</b>	human immunodeficiency virus
<b>HR</b>	hazard ratio
<b>IB</b>	Investigator's Brochure
<b>ICF</b>	informed consent form



<b>ICH</b>	International Conference on Harmonisation
<b>icrucumab (generic name)</b>	icrucumab drug product; LY3012212 or IMC-18F1 (code names) recombinant human mAb that binds VEGF Receptor 1
<b>IDMC</b>	independent data monitoring committee
<b>Ig</b>	immunoglobulin
<b>IgG1</b>	immunoglobulin G, subclass 1
<b>IMC-1121B (code name)</b>	a code name for ramucirumab (proprietary name is Cyramza <sup>®</sup> )
<b>IMC-18F1 (code name)</b>	a code name for icrucumab
<b>immunogenicity</b>	anti-drug antibodies (that is, anti-ramucirumab antibodies)
<b>inf</b>	infusion (used only in <a href="#">Attachment 7</a> )
<b>informed consent</b>	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
<b>INR</b>	international normalized ratio
<b>interim analysis</b>	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
<b>investigational product (IP)</b>	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial. Investigational product (IP) includes a product with a marketing authorization when: <ol style="list-style-type: none"> <li>1. used or assembled (formulated or packaged) in a way different from the authorized form,</li> <li>2. used for an unauthorized indication, or</li> <li>3. used to gain further information about the authorized form.</li> </ol>
<b>investigator</b>	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
<b>IRR</b>	infusion-related reaction
<b>ITT (population)</b>	intention-to-treat (or intent-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.

<b>I.V.</b>	intravenous(ly)
<b>IWRS</b>	interactive Web response system
<b>legal representative</b>	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
<b>Lilly Safety System</b>	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
<b>LY3009806</b>	A code name for ramucirumab
<b>LY3012212</b>	A code name for icrucumab
<b>mAb</b>	monoclonal antibody
<b>MedDRA<sup>®</sup></b>	Medical Dictionary for Regulatory Activities
<b>MRI</b>	magnetic resonance imaging
<b>MVAC</b>	methotrexate, vinblastine, and adriamycin
<b>NCCN</b>	National Comprehensive Cancer Network
<b>NCI</b>	National Cancer Institute
<b>NSAID</b>	nonsteroidal anti-inflammatory drug
<b>NSCLC</b>	non-small cell lung cancer
<b>ORR</b>	overall response rate (also known as objective response rate)
<b>OS</b>	overall survival
<b>patient</b>	A study participant who has the disease or condition for which the investigational product is targeted.
<b>PD</b>	progressive disease
<b>per protocol population</b>	The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
<b>PET</b>	positron emission tomography
<b>PFS</b>	progression-free survival
<b>PK</b>	pharmacokinetic(s)
<b>PIGF</b>	placental growth factor
<b>PLT</b>	platelets
<b>PR</b>	partial response

<b>primary analysis</b>	The primary analysis will be performed when a minimum of 331 PFS events have been observed from the first 437 randomized patients. If full enrollment is not reached at the point when 331 PFS events have been observed, the primary analysis will be performed when full enrollment is reached, on the number of PFS events observed upon full enrollment from the first 437 randomized patients.
<b>PRO</b>	patient-reported outcome
<b>PS</b>	(ECOG) performance status
<b>PT</b>	prothrombin time
<b>PTT</b>	partial thromboplastin time
<b>QoL</b>	quality of life
<b>ramucirumab (generic name)</b>	ramucirumab drug product; LY3009806 or IMC-1121B (code names); proprietary name is Cyramza <sup>®</sup>  recombinant human mAb that binds VEGF Receptor 2
<b>randomize</b>	the process of assigning patients to an experimental group on a random basis
<b>RBC</b>	red blood cells
<b>RECIST</b>	Response Evaluation Criteria in Solid Tumors
<b>reporting database</b>	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.
<b>re-screen</b>	to screen a patient who was previously declared a screen failure for the same study
<b>ROW</b>	rest of the world (geographic region stratification variable)
<b>RPLS</b>	reversible posterior leukoencephalopathy syndrome
<b>SAE</b>	serious adverse event
<b>SAP</b>	statistical analysis plan
<b>screen</b>	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. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
<b>screen failure</b>	patient who does not meet one or more criteria required for participation in a trial
<b>SD</b>	stable disease
<b>study completion</b>	This study will be considered complete after the final analysis for overall survival is performed.

<b>SUSARs</b>	suspected unexpected serious adverse reactions
<b>TCC</b>	transitional cell carcinoma
<b>TEAE</b>	treatment-emergent adverse event Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
<b>TR</b>	translational research
<b>ULN</b>	upper limit of normal
<b>v 4.0</b>	Version 4.0 (of NCI-CTCAE)
<b>VAS</b>	visual analogue scale
<b>VEGF</b>	vascular endothelial growth factor
<b>vs</b>	versus
<b>VTE</b>	venous thromboembolic event
<b>WBC</b>	white blood cells
<b>WNL</b>	within normal limits
<b>WOCBP</b>	women of childbearing potential

# **A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Ramucirumab plus Docetaxel Versus Placebo plus Docetaxel in Patients with Locally Advanced or Unresectable or Metastatic Urothelial Carcinoma Who Progressed on or After Platinum-Based Therapy**

## **5. Introduction**

### **5.1. Bladder Cancer**

#### **5.1.1. Background and Epidemiology**

Urothelial carcinoma, a cancer involving the transitional epithelial lining of the urinary system, is a type of cancer that typically occurs in the urinary bladder (90% of cases), renal pelvis (8%), or ureters or urethra (remaining 2%, combined). For simplicity, the disease is often referred to as bladder cancer. Transitional cell carcinoma (TCC) is the predominant histologic type of urothelial carcinoma in North America and Europe, where it accounts for  $\geq 90\%$  of all bladder cancers (Billis et al. 2001; Chalasani et al. 2009). Other histologic subtypes are squamous cell, adenocarcinoma, and small-cell tumors. Urothelial tumors with a mixture of histologic subtypes and a transitional cell predominance are generally treated similarly as urothelial (transitional cell) carcinomas (NCCN 2014).

Worldwide, bladder cancer was the ninth most common cancer, with 430,000 new cases diagnosed in 2012 with highest incidence in North America and Europe and lowest incidence in Asia and Latin America and Caribbean. The highest incidence rate of bladder cancer by country is in Belgium, followed by Lebanon, Malta, Turkey, Denmark, and Hungary (IARC 2014). It is expected that more than 74,000 cases (56,000 men and 18,000 women) of bladder cancer will be diagnosed in the United States in 2014, with approximately 16,000 deaths (11,000 men and 5000 women) attributable to this form of malignancy. In the United States, 5-year relative survival rates are 70% for local stage disease at diagnosis but decline to 33% and 5%, respectively, for regional or distant disease (American Cancer Society 2014). In Europe, it is the fourth most frequent malignancy, accounting for 136,000 new cases leading to 49,000 deaths. The incidence of bladder cancer rises with age, peaking between age 50 years and 70 years, and is 3 times more common in men than in women. At initial presentation, 30% of bladder cancer has muscle-invasive disease associated with a high risk of death from distant metastases.

#### **5.1.2. Therapy**

##### **5.1.2.1. First-Line Therapy**

Cisplatin-containing combination chemotherapy, either with gemcitabine or with methotrexate, vinblastine, and adriamycin (MVAC), is standard first-line treatment in advanced metastatic patients. Although bladder cancer is a chemosensitive malignancy, the responses with first-line MVAC or gemcitabine therapy are generally transient and the median survival ranges from 12 to 14 months (Loehrer et al. 1992; Saxman et al. 1997; von der Maase et al. 2000; Galsky 2005).



To date, no improvement in survival has been achieved with newer triplets, novel 4-drug regimens, or dose-dense chemotherapy (Galsky et al. 2007; Milowsky et al. 2009; Bellmunt et al. 2012). Gemcitabine has a safety and tolerability advantage over MVAC particularly around neutropenia, febrile neutropenia, and mucositis (von der Maase et al. 2000).

About 50% of patients are unfit for cisplatin-containing chemotherapy due to a poor performance status, impaired renal function, or comorbidity. Patients unfit for cisplatin-based chemotherapy may be administered a carboplatin-based regimen such as carboplatin plus gemcitabine or single-agent taxane or gemcitabine.

#### **5.1.2.2. Second-Line Therapy**

In the second-line setting, gemcitabine, docetaxel, paclitaxel, and pemetrexed have been tested as single agents with response rates in the 10% to 20% range and median overall survival (OS) of 5 to 10 months. Single agents are typically preferred due to lower toxicity and the absence of a proven survival benefit with combination therapy. Taxanes are accepted by the medical community for treatment of advanced disease based on evidence from Phase 2 studies (McCaffrey et al. 1997; de Wit et al. 1998; Sweeney et al. 1999; Vaughn et al. 2002).

The second-line treatment with docetaxel in patients with advanced or metastatic urothelial carcinoma demonstrated an objective response rate (ORR) of 13.3% and a median OS of 9 months (McCaffrey et al. 1997). Taxanes such as docetaxel are recommended by the National Comprehensive Cancer Network (NCCN) as a palliative option in the metastatic setting and are widely accepted by the medical community in the United States and Canada for treatment of advanced disease (NCCN 2014).

A randomized Phase 3 trial tested vinflunine, a third-generation vinca alkaloid, plus best supportive care (BSC) versus (vs) BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease (Bellmunt et al. 2009). Compared with BSC, treatment with vinflunine resulted in an 8.6% ORR and a non-statistically significant increase in survival (6.9 vs 4.6 months, hazard ratio [HR] 0.88, 95% confidence interval [CI]: 0.69, 1.12;  $p=0.287$ ). A statistically significant difference in OS was observed only in post hoc analyses, which excluded subgroups of patients from the intent-to-treat (ITT) population (HR 0.77 [95% CI: 0.61, 0.98],  $p=0.0360$ ). Vinflunine ORR and OS results from the Phase 3 study show no advantage over other single agents, including taxanes. Nevertheless, vinflunine is the only approved drug in this setting and is approved only in Europe.

A review of the currently available therapies for second-line treatment of metastatic urothelial carcinoma of the bladder suggests that it represents an unmet clinical need, given there is no established and widely available treatment for patients with advanced bladder cancer who experience disease progression on or after first-line platinum-based regimens.

## **5.2. The Role of VEGF and VEGF Receptor 2 in Angiogenesis and Tumor Growth**

Extensive scientific literature suggests that angiogenesis contributes substantially to cancer growth and metastasis. As a result, the pathways that mediate angiogenesis are considered

important targets in cancer drug development. Vascular endothelial growth factors (VEGFs; including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor [PlGF]) have emerged as key regulators of angiogenesis, and the expression of VEGFs has been correlated with poor prognosis in several solid tumor types (Roy et al. 2006a; Roy et al. 2006b; Amini et al. 2012; Oh et al. 2013; Xie et al. 2013). Vascular endothelial growth factor-A is distinct within the VEGF ligand family in that it acts as a dominant endothelial cell-specific mitogen during angiogenesis (Leung et al. 1989; Ferrara 1993; Brown et al. 1997). VEGF Receptor 2 is the primary mediator of proangiogenic effects of VEGF-A, and experimental evidence suggests that the VEGF-A/VEGF Receptor 2 interaction plays an important role in tumor angiogenesis, a process essential for tumor growth and metastasis (Sullivan and Brekken 2010; Tugues et al. 2011; Amini et al. 2012). Therefore, disruption of the interaction between VEGF-A and VEGF Receptor 2 may have therapeutic application in the treatment of cancer.

### 5.3. VEGF and Bladder Cancer

Tumor angiogenesis is considered an essential step for continued tumor growth and progression. High levels of urinary VEGF have been reported in patients with bladder cancer and were correlated with tumor recurrence rates (Crew et al. 1999). In a study of 72 patients with TCC of the bladder, increased VEGF Receptor 2 expression correlated with disease stage and invasive phenotype, demonstrating it as a factor for progression of urothelial cancer. In a small study, 86% of the tissues from 36 invasive bladder cancers were VEGF Receptor 2-positive while 14% of the tissues from 36 superficial cases were VEGF Receptor 2-negative (Xia et al. 2006). These findings support earlier work by Sato and colleagues who noted that the VEGF gene is frequently overexpressed in TCC of the bladder, particularly in muscle-invasive tumors (Sato et al. 1998). Their findings also suggest a paracrine system including VEGF and Flt-1 (VEGF Receptor 1) exists between the TCC cells and the adjacent endothelial cells for regulation of angiogenesis. Studies with a large tissue micro array have also demonstrated that the expression levels of VEGF and VEGF Receptor 1 messenger ribonucleic acid levels were significantly higher in bladder cancer specimens than that of benign urothelial mucosa (Kopparapu et al. 2013). This study further confirmed that expression of VEGF Receptor 2 was significantly higher in muscle-invasive bladder cancer as compared with non-muscle-invasive bladder cancer.

In a human TCC- (253J-BV cells) derived mouse xenograft tumor model, *in vivo* treatment with the combination of a murine-specific anti-VEGF Receptor surrogate antibody for ramucirumab (DC101) and paclitaxel induced a significantly greater reduction in tumor growth compared with that seen with either agent alone (Inoue et al. 2000). In addition, treatment with the combination was associated with a statistically significant reduction in the development of spontaneous lymph node metastasis. Data from animal models suggest that DC101 may be capable of acting as a chemosensitizing agent when given in combination with a cytotoxic chemotherapy. Mobilization of circulating endothelial progenitors from the bone marrow can contribute to recovery of drug-treated tumors after administration of chemotherapeutic agents such as paclitaxel, docetaxel, and fluorouracil. This effect may be blunted by treatment with a VEGF pathway-targeted antiangiogenic drug such as DC101. Such data suggest that the administration



of an anti-VEGF Receptor 2 antibody may improve the antitumor effectiveness of certain cytotoxic agents such as paclitaxel, docetaxel, and fluorouracil (Shaked et al. 2008).

## **5.4. Ramucirumab (IMC-1121B)**

### **5.4.1. Background**

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. 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 1nM), 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 four positive Phase 3 trials, with two in gastric cancer (REGARD and RAINBOW), one in non-small cell lung cancer (NSCLC; REVEL), and one in metastatic colorectal cancer (CRC; RAISE). Ramucirumab (Cyramza<sup>®</sup>) 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, and in combination with docetaxel as a treatment for people with metastatic NSCLC whose cancer has progressed on or after platinum-based chemotherapy. 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.

### **5.4.2. Study JCDC: Phase 2 Study of Ramucirumab in Bladder Cancer**

Study I4Y-IE-JCDC (JCDC), an open-label, multicenter, randomized Phase 2 study, evaluated the safety and efficacy of docetaxel in combination with ramucirumab or icrucumab versus docetaxel alone as second-line therapy in patients with locally advanced or metastatic urothelial (transitional cell) carcinoma of the bladder, urethra, ureter, or renal pelvis with disease progression on or after prior platinum-based treatment. Icrucumab is a recombinant human IgG1 mAb, which specifically targets human VEGF Receptor 1, also known as Flt-1. Icrucumab binds to VEGF Receptor 1 with high affinity and blocks the binding of VEGF, VEGF-B, and PlGF to the receptor, thereby inhibiting subsequent signaling.

A total of 138 patients were planned to be randomized in a 1:1:1 ratio to the treatment arms. Following randomization, 44 patients received docetaxel alone and 46 received ramucirumab plus docetaxel. The primary objective of the study was progression-free survival (PFS);



secondary objectives included OS, ORR, duration of response (DOR), and safety. An interim analysis was performed when the study reached approximately 75% of the expected number of PFS events. For the purposes of this document, data only on the ramucirumab-plus-docetaxel and docetaxel-alone arms are presented.

Ramucirumab in combination with docetaxel reduced the risk of disease progression by 61% (stratified HR = 0.388; 95% CI: 0.222, 0.677), resulting in a 112% longer median time to disease progression in the ramucirumab-plus-docetaxel arm than in the docetaxel arm (22.0 weeks [95% CI: 9.3, 30.0] vs 10.4 weeks [95% CI: 6.7, 16.9]). Ramucirumab in combination with docetaxel increased the median OS compared with that for docetaxel alone (48.9 weeks [95% CI: 30.1, 65.9] vs 33.4 weeks [95% CI: 24.6, 44.4]). This analysis is based on interim data with approximately 43% OS censoring in the 2 arms combined. The ramucirumab-plus-docetaxel arm had a higher ORR than the docetaxel arm at Analysis 2 (19.6% [95% CI: 9.4, 33.9] vs 4.5% [95% CI: 0.6, 15.5]).

In regards to safety, reported adverse events (AEs) were known effects for ramucirumab or docetaxel and most were Grade 1 or 2. The most common treatment-emergent adverse events (TEAEs) reported in patients receiving ramucirumab in combination with docetaxel were fatigue, occurring in 80% of patients (vs 75% in the docetaxel arm), neuropathy (50.0% vs 38.6%), and abdominal pain (32.6% vs 20.5%).

Grade 5 AEs were experienced by 3 patients in the ramucirumab-plus-docetaxel arm (cardiac arrest, decreased appetite, and sepsis) and 3 patients in the docetaxel arm (cardio-respiratory arrest, hypoxia, and multi-organ failure).

The observed rate of all-grade and Grade  $\geq 3$  neutropenia was numerically lower with the ramucirumab-plus-docetaxel combination. Despite this difference, there were higher rates of all-grade pyrexia in the combination arm (26.1% vs 11.4%) and febrile neutropenia (21.7% vs 11.4%). Other noted AEs include epistaxis (41.3% vs 6.8%), hematuria (28.3% vs 2.3%), and hypertension (21.7% vs 4.5%). Higher rates of Grade 3 AEs in the combination arm include fatigue (32.6% vs 11.4%), febrile neutropenia (21.7% vs 6.8%), and stomatitis (6.5% vs 0%).

This study allowed the use of growth factors at the discretion of the investigators. However, the observed incidence of febrile neutropenia in the first cycle and an apparent limited use of prophylactic growth factor use suggest that practice patterns did not fully appreciate the frequency of febrile neutropenia with docetaxel use in this setting. Per current American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2006), use of granulocyte colony-stimulating factor (G-CSF) is recommended prophylactically when the anticipated frequency of febrile neutropenia approximates 20%. These observations support prophylactic use of G-CSF in subsequent studies of this regimen for urothelial carcinoma, and it is anticipated that this intervention could mitigate the risk of febrile neutropenia and related infection-associated AEs such as, pneumonia, cough, or sepsis.

### **5.4.3. Dose Rationale**

Single-agent dose regimens of every-2-week (6-10 mg/kg) and every-3-week (15-20 mg/kg) were evaluated in a dose-ranging study (Study I4T-IE-JVBN [IMCL CP12-0402]). No maximum tolerated dose was identified for either regimen; all dose regimens were well tolerated, and preliminary evidence of clinical efficacy was observed across a range of dose/schedule cohorts.

Two dose regimens, 8 mg/kg every 2 weeks and 10 mg/kg every 3 weeks, were selected for subsequent Phase 2 and Phase 3 studies. These dose regimens were selected because they were associated with pharmacokinetic (PK) profiles, suggesting target receptor saturation and associated with minimum drug concentrations (serum trough levels) that exceeded those of DC101 associated with antitumor activity in preclinical models; preliminary activity was observed at and below these doses and schedules in Phase 1 studies.

The 10-mg/kg every-3-week regimen was used in combination with docetaxel in Study JCDC and proved to be a safe and effective regimen in patients with urothelial cancer and offers a favorable benefit-risk profile in patients with this disease. Thus, this dose regimen will be used in the current Phase 3 study.

### **5.4.4. Study JVDC: Clinical Trial Rationale**

Currently, there are no globally approved agents for the treatment of second-line patients with metastatic urothelial cancer. Several agents have shown modest activity when tested as single-agent therapy, with median survival of 5 to 10 months (Yafi et al. 2011). Combination regimens have shown similar median survival numbers as single agents, however with more toxicities. Second-line treatment for advanced or metastatic urothelial (transitional cell) carcinoma remains a major unmet medical need. Angiogenesis appears to be integral to the development and pathobiology of urothelial carcinoma, and in addition, muscle-invasive bladder cancer has been shown to express VEGF Receptor 2. Clinical investigations with ramucirumab, a recombinant human mAb that binds VEGF Receptor 2 and prevents interaction of this receptor with its activating ligands, have resulted in four positive Phase 3 trials, with two in gastric cancer, one in NSCLC, and one in metastatic CRC. In a Phase 2 study in patients with urothelial carcinoma who had disease relapse following first-line treatment, ramucirumab plus docetaxel showed clinically significant improvement in efficacy with an acceptable safety profile. The combination of docetaxel plus ramucirumab has been administered to approximately 1400 patients across tumor types in one Phase 2 (JCDC) and two Phase 3 trials (REVEL and ROSE) and has been shown to be a tolerable regimen. Therefore, this Phase 3 randomized study is being conducted to confirm results of the Phase 2 Study JCDC in patients with urothelial carcinoma who have progressed on or after treatment with platinum-based therapy.

More information about the known and expected benefits, risks, and reasonably anticipated AEs of ramucirumab may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to ramucirumab may be found in Section 7 (Development Core Safety Information [DCSI]) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate,

periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

More detailed information about the known and expected benefits and risks of docetaxel may be found in the following: Package Insert (Taxotere package insert, 2013) and Section [9.4.1.2](#).

## 6. Objectives

### 6.1. Primary Objective

The primary objective of this study is to compare the progression-free survival (PFS) of ramucirumab in combination with docetaxel with the PFS of placebo in combination with docetaxel, in patients with locally advanced or unresectable or metastatic urothelial carcinoma who have had disease progression on or after one prior first-line platinum-based chemotherapy.

### 6.2. Secondary Objectives

The secondary objectives of this study are to compare each of the following variables between the treatment arms:

- overall survival (OS) time
- objective response rate (ORR; complete response [CR] + partial response [PR]) and disease control rate (DCR)
- duration of response (DOR)
- safety profile
- patient-reported outcome (PRO) measures (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 [EORTC QLQ-C30] and EQ-5D-5L questionnaires)

Secondary objectives also include the evaluation of:

- the pharmacokinetic profile of ramucirumab
- the immunogenicity of ramucirumab (anti-ramucirumab antibodies)

### 6.3. Exploratory Objectives

The exploratory objectives of this study are to:

- assess the change in tumor size in patients with measurable disease
- examine biomarkers relevant to ramucirumab, angiogenesis, and the disease state, and to correlate these markers to clinical outcome



## 7. Study Population

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 clinical research physician (CRP)/clinical research scientist (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.

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

### 7.1. Inclusion Criteria

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

- [1] The patient has histologically or cytologically confirmed, locally advanced or unresectable or metastatic urothelial (transitional cell) carcinoma of the bladder, urethra, ureter, or renal pelvis. Patients with mixed pathology are eligible only if they have predominantly transitional cell tumor based on local pathology review.
- [2] The patient has demonstrated disease progression while on a platinum-containing regimen in the first-line setting or within 14 months ( $\leq 14$  months) after completing the first-line platinum regimen. Patients who received treatment with one immune checkpoint inhibitor (for example PD-1, PDL1, or CTLA4) regimen may have a longer interval since prior platinum-containing therapy ( $\leq 24$  months), as noted in Inclusion Criterion [4]; such patients are eligible.
- [3] The patient has a life expectancy of  $\geq 3$  months, in the judgment of the investigator.
- [4] The patient has received no more than one prior systemic chemotherapy regimen in the relapsed or metastatic setting. Prior cytotoxic therapy in an adjuvant or neoadjuvant setting is not considered as a prior line of systemic chemotherapy in the relapsed or metastatic setting. Prior treatment with intravesicular chemotherapy, bacillus Calmette-Guérin (BCG), or platinum given as a radiation-sensitizing agent will not be considered as a systemic line of treatment. Prior treatment with no more than one prior immune checkpoint inhibitor is permitted and will not be considered as a line of systemic chemotherapy. Patients enrolling after immune checkpoint inhibitor therapy must have demonstrated disease progression while on that therapy or within 24 months ( $\leq 24$  months) after the last dose of that therapy.

- [5] The patient has measurable disease or nonmeasurable but evaluable disease as defined by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009).
- [6] The patient has resolution, except where otherwise stated in the inclusion criteria, of all clinically significant toxic effects of prior chemotherapy, surgery, or radiotherapy to Grade  $\leq 1$  by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (v 4.0).
- [7] The patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 ([Attachment 4](#)).
- [8] The patient has adequate hematologic function as defined by an absolute neutrophil count (ANC)  $\geq 1.5 \times 10^3/\mu\text{L}$  ( $1.5 \times 10^9/\text{L}$ ), hemoglobin  $\geq 9$  g/dL (90 g/L), and platelets  $\geq 100 \times 10^3/\mu\text{L}$  ( $100 \times 10^9/\text{L}$ ) and has not received blood or blood components transfusion within 2 weeks ( $\leq 2$  weeks) prior to the laboratory test.
- [9] The patient has adequate coagulation function as defined by international normalized ratio (INR)  $\leq 1.5$  and a partial thromboplastin time (PTT)  $\leq 1.5 \times$  upper limit of normal (ULN) if not receiving anticoagulation therapy. Patients on full-dose anticoagulation must be on a stable dose of oral anticoagulant or low molecular weight heparin. If on warfarin, the patient must have an INR  $\leq 3$  and have no active bleeding (defined as within 14 days [ $\leq 14$  days] prior to randomization, excluding trace hematuria) or pathological condition that carries a high risk of bleeding (for example, tumor involving major vessels or known varices).
- [10] The patient has adequate hepatic function as defined by bilirubin within normal limits (WNL), aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 3.0 \times$  ULN, and alkaline phosphatase (AP)  $\leq 2.5 \times$  ULN.
- [11] The patient does not have:
- cirrhosis at a level of Child-Pugh B (or worse) (Child and Turcotte 1964; Pugh et al. 1973), or
  - cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.
- [12] The patient has adequate renal function as defined by creatinine clearance  $>30$  mL/min either as measured by 24-hour urine collection or as calculated (for example, by Cockcroft-Gault [Cockcroft and Gault 1976] or another standard equation; [Attachment 5](#)).

- [13] The patient's urinary protein is  $\leq 1+$  on dipstick or routine urinalysis; if urine protein  $\geq 2+$ , a 24-hour urine collection must demonstrate  $< 2$  g of protein in 24 hours to allow participation in the study.
- [14] The patient, if female, is surgically sterile, postmenopausal<sup>\*</sup>, or agrees to use a highly effective<sup>†</sup> method of contraception during and for 12 weeks after the treatment period (oral hormonal contraception alone is not considered highly reliable and must be used in combination with a barrier method). The patient, if male, is surgically sterile or agrees to use a reliable method of contraception and to not donate sperm during and for 12 weeks after the treatment period or country requirements, whichever is longer.

\*A "postmenopausal woman" is a woman meeting either of the following criteria:

1. spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives, hormones, gonadotropin-releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy)
2. spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone level  $> 40$  mIU/mL

<sup>†</sup>A highly effective method of contraception is defined as one that results in a low failure rate (that is,  $< 1\%$  per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices, sexual abstinence, or a vasectomized partner. For patients using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.

- [15] The patient is able to provide signed informed consent and is amenable to compliance with protocol schedules and testing.
- [16] The patient is  $\geq 18$  years of age or of an acceptable age to provide informed consent according to local regulations, whichever is older.
- [17] The patient is willing to provide blood, urine, and tissue samples for research purposes. Submission of blood and urine specimens is mandatory for participation in this study, unless restricted per local regulations. If prior archived tumor specimens are available, and unless restricted by local regulations, submission of archived tumor tissue is mandatory. If an archived specimen is not available, submission of a newly acquired biopsy is requested when biopsy is safe and feasible.



## 7.2. Exclusion Criteria

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

- [18] The patient has received more than one prior systemic chemotherapy regimen for metastatic disease (except as noted in Inclusion Criterion [4]). A treatment regimen must consist of a minimum of 2 cycles to be considered as a prior regimen.
- [19] The patient has received prior systemic taxane therapy for TCC of the bladder, urethra, ureter, or renal pelvis in any setting (neoadjuvant, adjuvant, metastatic). Prior intravesical taxane therapy is allowed and will not be considered as a prior line of systemic therapy.
- [20] The patient has received more than one prior antiangiogenic agent (that is, bevacizumab, sorafenib, sunitinib) for TCC of the urothelium.
- [21] The patient has received radiation therapy (including full-dose pelvic radiotherapy) within 4 weeks ( $\leq 4$  weeks) prior to randomization or has not recovered from toxic effects of the treatment that was given  $>4$  weeks prior to randomization. Single fraction radiotherapy for palliative bone stabilization within 4 weeks ( $\leq 4$  weeks) prior to randomization is allowed. If any tumor lesion is administered radiotherapy, then it cannot be considered for response assessment.
- [22] The patient has a history of uncontrolled hereditary or acquired bleeding or thrombotic disorders.
- [23] The patient has experienced a Grade  $\geq 3$  bleeding event (for example, via gastric ulcers, gastric varices, rectal bleeding, or gross hematuria) within 3 months ( $\leq 3$  months) prior to randomization. Patients must have complete resolution of any prior bleeding event prior to randomization.
- [24] The patient has uncontrolled intercurrent illness, including, but not limited to symptomatic anemia, uncontrolled hypertension ( $>160$  mm Hg systolic and/or  $>100$  mm Hg diastolic, despite antihypertensive medication), symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, psychiatric illness, or any other serious uncontrolled medical disorders in the opinion of the investigator.
- [25] The patient has experienced any arterial or venothrombotic or thromboembolic events, including, but not limited to myocardial infarction, transient ischemic attack, or cerebrovascular accident, within 6 months ( $\leq 6$  months) prior to randomization.
- [26] The patient has known untreated brain metastases, uncontrolled spinal cord compression, or leptomeningeal disease. (Note: A brain scan via computed tomography [CT] with contrast or magnetic resonance imaging [MRI] is to be performed only after study eligibility is confirmed, to detect the presence of intracranial metastasis.)



- [27] The patient has an ongoing or active infection requiring antibiotic, antifungal, or antiviral therapy.
- [28] The patient has known human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome-related illness.
- [29] The patient has received a prior autologous or allogeneic organ or tissue transplantation.
- [30] The patient:
- received chemotherapy within 21 days ( $\leq 21$  days) prior to randomization; and/or
  - is currently enrolled in, or discontinued within 21 days ( $\leq 21$  days) prior to randomization from, a clinical trial involving an investigational product (IP) or non-approved use of a drug or device, or is concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study; and/or
  - was treated with antiangiogenic therapy within 28 days ( $\leq 28$  days) prior to randomization.
- [31] The patient has undergone major surgery within 28 days ( $\leq 28$  days) prior to randomization or subcutaneous venous access device placement within 7 days ( $\leq 7$  days) prior to randomization.
- [32] The patient has had a serious nonhealing wound, ulcer, or bone fracture within 28 days ( $\leq 28$  days) prior to randomization.
- [33] The patient has an elective or planned major surgery to be performed during the course of the trial.
- [34] The patient is pregnant (confirmed within 7 days [ $\leq 7$  days] prior to randomization by serum beta human chorionic gonadotropin [ $\beta$ -hCG] pregnancy test) or lactating.
- [35] The patient has a concurrent malignancy or had another malignancy within 5 years ( $\leq 5$  years) of study enrollment (with the exception of adequately treated non-melanomatous skin cancer, in-situ cervical cancer, other noninvasive carcinoma or in situ neoplasm, or localized prostate cancer with no evidence of biochemical or clinical recurrence over a minimum of 6 months [ $\geq 6$  months]).
- [36] The patient has an acute/subacute bowel obstruction or history of chronic diarrhea requiring ongoing medical intervention.
- [37] The patient has a history of gastrointestinal perforation and/or fistula within 6 months ( $\leq 6$  months) prior to randomization.
- [38] The patient has active diverticulitis.

- [39] The patient has a known hypersensitivity to docetaxel or other drugs formulated with polysorbate 80.
- [40] The patient has a known hypersensitivity to agents of similar biologic composition as ramucirumab, or other agents that specifically target VEGF.

### **7.3. Discontinuation**

The reason for discontinuation and the date of discontinuation will be collected for all patients. All randomized patients who discontinue, regardless of whether or not they received study drug, will have procedures performed as shown in the Study Schedule ([Attachment 1](#)).

Patients who are discontinued from all study drug will have follow-up procedures performed as shown in the Study Schedule ([Attachment 1](#)).

If a patient withdraws informed consent, he or she must not be contacted unless he or she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

#### **7.3.1. Discontinuation of Inadvertently Enrolled Patients**

The criteria for enrollment must be followed explicitly. If the investigator identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor CRP/CRS or designee and the investigator to determine whether it is medically appropriate for the patient to continue in the study, with or without study treatment. The investigator must obtain documented approval from the sponsor CRP/CRS or designee to allow an inadvertently enrolled patient to continue in the study, with or without study treatment.

#### **7.3.2. Discontinuation of Study Treatment**

This section lists the reasons for permanent discontinuation of all study treatment, except as indicated otherwise. For details regarding study treatment delays and dose modifications, refer to Section [9.4.1](#).

Patients will be replaced only if inadvertently enrolled and found to be ineligible.

All patients who are discontinued from all study treatment (except those patients who request withdrawal of consent from the study) should be followed (for disease progression and/or survival, as applicable) until study completion or as instructed by Lilly.

After termination of all study therapy, the patient will be treated as clinically indicated by the investigator or referring physician. All patients will be followed until resolution or stabilization of any study-related toxicity.

Patients will be permanently discontinued from all study therapy (except as indicated otherwise) in the following circumstances:

- Enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Screen failure or failure to meet enrollment criteria (refer also to Section 7.3.1).
- 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 occurs prior to introduction of the new agent.
- The investigator decides that the patient should be discontinued from study treatment.
- The patient or the patient's designee (for example, parent, legal guardian, or caregiver) requests to be discontinued from study treatment (this reason should not be used if there is clinical deterioration or an AE).
  - In the event that a patient withdraws consent for study treatment, he or she may still enter Short-term and/or Long-term Follow-up if consent for follow-up is not also withdrawn. It should be clarified with the patient and documented in the patient's file whether follow-up information on tumor assessment and survival can be still obtained, and if so, to what extent.
- The patient is significantly noncompliant with study procedures and/or treatment.
- Radiographic documentation of disease progression.
- Symptomatic deterioration/clinical disease progression.
  - Symptomatic deterioration sufficient to warrant discontinuation of therapy will not be considered a descriptor of response, but rather only a reason for stopping therapy. Whenever possible, patients removed from therapy solely for symptomatic progression should be followed for subsequent radiographic progression. Response evaluation in a patient who discontinues treatment due to symptomatic deterioration in the absence of radiological confirmation of disease progression should be based on evaluation of target, nontarget lesions, and new lesions.
- An unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient), including any of the following:
  - A Grade 3 or 4 infusion-related reaction (IRR).
  - 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. Patients with evidence of portal hypertension (splenomegaly, platelets  $<100 \times 10^3/\mu\text{L}$  [ $100 \times 10^9/\text{L}$ ], or any prior history of variceal bleeding) who develop Grade 3 or 4 venous thromboembolism will have study therapy discontinued.
  - A Grade 4 hypertension (uncontrolled hypertension, hypertensive crisis, hypertensive encephalopathy).
  - A Grade 3 or 4 bleeding or hemorrhagic event.



- Any event that would require study therapy to be modified by >2 dose reductions or that necessitates 2 or more consecutive missed doses of study therapy. In this case, all study therapy does not necessarily need to be discontinued; the particular study drug that was responsible for such a dose modification or missed dose should be discontinued, and the other study drug may be continued. In situations where 2 (or more) consecutive doses have been missed, events related to the missed doses have resolved, and there is evidence of ongoing disease control, continuation of study therapy may be considered and must be discussed with the Lilly CRP/CRS or designee.
- Any study therapy-related event that is deemed life-threatening, regardless of grade, warrants discontinuation of that therapy and/or discontinuation from all therapy, if appropriate, in the opinion of the investigator. If other identifiable risk factors are felt to be associated with the observed event and could be modified to substantially mitigate the risk of recurrence, continued therapy may be permitted following discussion between investigator and Lilly CRP/CRS or designee.
- Event of a gastrointestinal (GI) perforation.
- A confirmed occurrence of a GI or non-GI fistula.
- Proteinuria level is >3 g/24 hours in the setting of nephrotic syndrome or there is a third occurrence of proteinuria  $\geq 2$  g/24 hours.
- A concurrent illness or change in the patient's condition that renders the patient unsuitable for further treatment, in the opinion of the investigator.
- The patient becomes pregnant or fails to use adequate birth control during treatment.

### **7.3.3. Discontinuation from the Study**

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

- The investigator decides that the patient should be discontinued from the study.
- 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 or the patient's designee (for example, parent, legal guardian, or caregiver) requests that the patient be withdrawn from the study.

### **7.3.4. Patients Who Are 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 attempts to contact the patient are unsuccessful. 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.

Site personnel, or an independent third party, will attempt to collect the vital status (that is, alive or dead) for all randomized patients who are lost to follow-up, including randomized patients who do not receive study drug, within legal and ethical boundaries. Site personnel, or an independent third party, may search public sources for vital status information. If the patient's vital status is determined, the vital 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 vital status information.

### **7.3.5. *Discontinuation of Study Sites***

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges discontinuation of study site participation necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

### **7.3.6. *Discontinuation of the Study***

The study will be discontinued at any time if Lilly judges discontinuation of the study necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

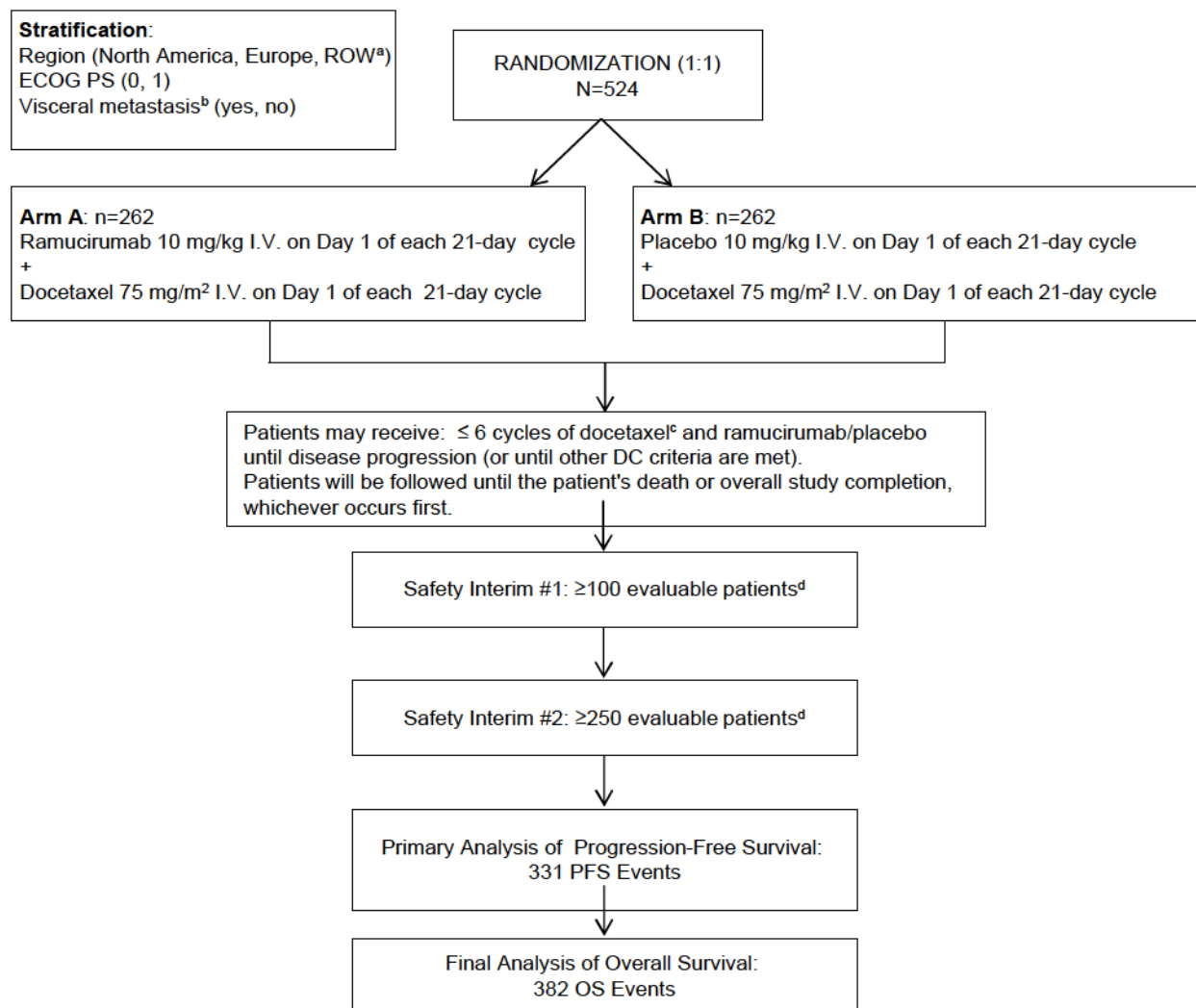
## 8. Investigational Plan

### 8.1. Summary of Study Design

Study I4T-MC-JVDC is a Phase 3, global, multicenter, randomized, double-blind, placebo-controlled trial in patients with locally advanced, or unresectable, or metastatic urothelial carcinoma who had disease progression on or after one prior first-line platinum-based chemotherapy regimen. Urothelial carcinoma includes those arising in the bladder, urethra, ureter, and/or renal pelvis.

Figure JVDC.1 illustrates the study design.





<sup>a</sup> ROW region includes countries outside the continents of Europe and North America.

<sup>b</sup> Where visceral metastases involve the liver, lung, and/or bone.

<sup>c</sup> Up to 4 additional cycles of docetaxel (maximum of 10 cycles total) may be administered with approval of the Lilly CRP/CRS or designee. Refer to Section 9.1 for further details regarding the number of cycles allowed for each study drug.

<sup>d</sup> To be evaluable for safety interim analyses, patients must have received at least one dose of study therapy and have either started treatment in Cycle 3 or discontinued all study treatment prior to Cycle 3 due to any reasons.

Abbreviations: CRP = (Lilly) clinical research physician; CRS = (Lilly) clinical research scientist; DC = discontinuation; ECOG PS = Eastern Cooperative Oncology Group performance status; I.V. = intravenous(ly); N = number of randomized patients; n = number of patients in arm; OS = overall survival; PFS = progression-free survival; ROW = rest of the world (geographic region stratification variable).

**Figure JVDC.1. Illustration of study design.**

Approximately 524 patients are planned to be randomized in a 1:1 ratio to the following treatment arms:

- **Arm A** - ramucirumab (10 mg/kg) plus docetaxel (75 mg/m<sup>2</sup>) on Day 1 (± 3 days) of each 21-day cycle; **n=262**
- **Arm B** - placebo (10 mg/kg volume equivalent) plus docetaxel (75 mg/m<sup>2</sup>) on Day 1 (± 3 days) of each 21-day cycle; **n=262**

Refer to Section 12.2.13 for details on the safety interim analyses, Section 12.2.6 for details on the primary endpoint (PFS) analysis, and Section 12.2.7 for details on the final OS analysis.

Terms used to describe the periods during the study are defined as follows:

- **Baseline:** begins when the ICF is signed and ends at the first study treatment (or at discontinuation, if no treatment is given).
- **Study Period:** begins at the first study treatment and ends at study completion. The study period does not include the Continued Access Period.
  - **Study Treatment Period:** begins at the first study treatment and ends when the patient and the investigator agree that the patient will no longer continue (any) study treatment. The date of this agreement is to be reported on the case report form (CRF) as the Date of Discontinuation from study treatment. Refer to Section 9.1 for details regarding treatments administered.
  - **Postdiscontinuation Follow-up:** begins the day after the patient and the investigator agree that the patient will no longer continue (any) study treatment.

*Short-term Follow-up* begins the day after the patient and the investigator agree that the patient will no longer continue (any) study treatment and lasts approximately 30 days (until the [30-day] Short-term Follow-up visit is completed).

*Long-term Follow-up* begins the day after Short-term Follow-up is completed and continues until the patient's death or overall study completion. Patients who discontinue (all) study treatment for reasons other than disease progression will continue to undergo radiographic tumor assessments (as described in Section 10.1) until radiographic documentation of disease progression as defined by RECIST 1.1 or until overall study completion, whichever occurs first. Patients will be followed for survival every 3 months (±7 days) until the patient's death or overall study completion, whichever occurs first.

- **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.

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

### **8.1.1. Study Completion and End of Trial**

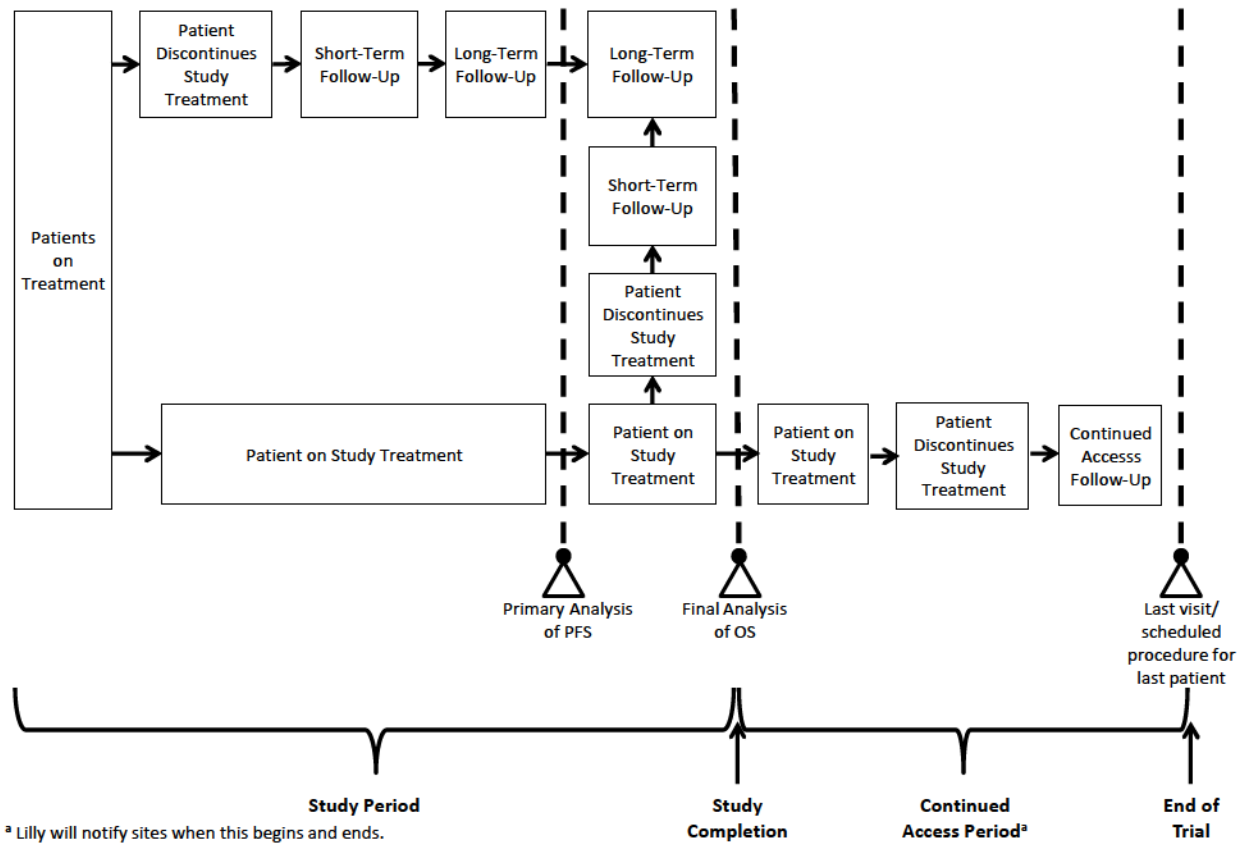
The primary analysis will be performed when a minimum of 331 PFS events have been observed from the first 437 randomized patients. If full enrollment is not reached at the point when 331 PFS events have been observed, the primary analysis will be performed when full enrollment is reached, on the number of PFS events observed upon full enrollment from the first 437 randomized patients.

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis for OS, as determined by Lilly. Note that patients will be followed for disease progression and/or survival, as applicable, until 382 OS events (deaths) have been confirmed or until study completion, as determined by Lilly.

Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. “End of trial” refers to the date of the last visit or last scheduled procedure for the last patient.

Upon study completion, investigators and patients may be unblinded to study treatment assignment.

The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable Continued Access Follow-up.



Abbreviations: OS = overall survival; PFS = progression-free survival.

**Figure JVDC.2. Study period and continued access diagram.**

### **8.1.2. Continued Access Period**

The Continued Access Period will apply to this study only if at least one patient is still on study treatment when study completion occurs.

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 7.3). During the Continued Access Period, placebo will no longer be administered; the decision to permit crossover or not will be made by Lilly after the final analysis of OS is completed. First, written notification will be sent to the sites specifying the outcome of this decision. Then, each patient will be evaluated individually (case-by-case basis) for eligibility of adding ramucirumab treatment to docetaxel, following discussion with Lilly. Lilly will notify investigators when the Continued Access Period begins.

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.

During the Continued Access Period, all AEs, SAEs, and exposure to study drug will be reported on the CRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.3.1.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE. Blood samples for PK and immunogenicity analysis will be collected in the event of an IRR that occurs during the Continued Access Period.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; 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.



## 8.2. Discussion of Design and Control

A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study treatment and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study treatment and minimizes bias in the assessment and interpretation of observed treatment effects. Patients will be stratified for differences in factors thought to be associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses. Assessment of bias is further minimized by the use of a double blind and placebo control.

Investigational treatment administration in this study is double blind; that is, patients, investigational sites, and the sponsor study team do not have immediate access to treatment assignments for any patients. This design feature minimizes potential bias due to knowledge of patient's treatment during evaluation of study endpoints, at the patient level or aggregated across patients.

## 9. Treatment

### 9.1. Treatments Administered

Patients in this study will be randomly assigned 1:1 to receive one of the following treatments:

**Arm A (experimental arm)** - ramucirumab (10 mg/kg) intravenously (I.V.) plus docetaxel (75 mg/m<sup>2</sup>) I.V. on Day 1 (± 3 days) of each 21-day cycle

**Arm B (comparator arm)** - placebo (10 mg/kg volume equivalent) I.V. plus docetaxel (75 mg/m<sup>2</sup>) I.V. on Day 1 (± 3 days) of each 21-day cycle

Following necessary premedication (Section 9.1.1), patients will receive the treatment regimen shown in Table JVDC.1, in the order shown in the table, according to the study arm to which they were assigned.

Treatment (that is, the Study Treatment Period) will continue until there is radiographic documentation of disease progression, toxicity or intolerance requiring cessation, protocol noncompliance, or withdrawal of consent. Provided no prespecified discontinuation criteria have been met for a given patient (see Section 7.3), the following duration of treatment for each study drug applies for that patient:

- Treatment with docetaxel may continue for up to six 21-day cycles; further cycles of docetaxel (up to 4 additional cycles [maximum of 10 cycles total]) may be administered if adequate disease response (that is, stable disease [SD] or better [PR, CR], based on the investigator's assessment) is observed and with approval of the Lilly CRP/CRS or designee.
- Treatment with ramucirumab or placebo (monotherapy) may continue until at least one discontinuation criterion is met.

No other anticancer therapy, including chemotherapy, is permitted until radiographic documentation of disease progression, except as allowed in the protocol. Once a patient has demonstrated disease progression and is in postdiscontinuation follow-up, he/she may receive other anticancer treatment per investigator discretion.

**Table JVDC.1. Treatment Regimens and Dosing Schedule**

*All treatments to be administered in the order shown in this table.*

<b>Combination Therapy - Up to six 21-day cycles<sup>a</sup> of the following:</b>		
<b>Drug</b>	<b>Starting Dose<sup>b</sup></b>	<b>Time for Administration</b>
<b>Arm A (experimental arm)</b>		
Ramucirumab	10 mg/kg I.V. infusion	Administered over approximately 60 minutes on Day 1 of each 21-day cycle.
Docetaxel <sup>c</sup>	75 mg/m <sup>2</sup> I.V. infusion	Administered over 60 minutes on Day 1 of each 21-day cycle. <sup>d</sup>
<b>Arm B (comparator arm)</b>		
Placebo	10 mg/kg volume equivalent I.V. infusion	Administered over approximately 60 minutes on Day 1 of each 21-day cycle.
Docetaxel <sup>c</sup>	75 mg/m <sup>2</sup> I.V. infusion	Administered over 60 minutes on Day 1 of each 21-day cycle. <sup>e</sup>
<b>Monotherapy as follows, after patient has DCed treatment with docetaxel<sup>c</sup>:</b>		
<b>Drug</b>	<b>Starting Dose<sup>b</sup></b>	<b>Time for Administration</b>
<b>Arm A</b>		
Ramucirumab	10 mg/kg I.V. infusion	Administered over approximately 60 minutes on Day 1 of each 21-day cycle.
<b>Arm B</b>		
Placebo	10 mg/kg volume equivalent I.V. infusion	Administered over approximately 60 minutes on Day 1 of each 21-day cycle.
<b>Monotherapy as follows, after patient has DCed treatment with ramucirumab/placebo<sup>a</sup>:</b>		
<b>Drug</b>	<b>Starting Dose<sup>b</sup></b>	<b>Time for Administration</b>
<b>Arm A</b>		
Docetaxel <sup>c</sup>	75 mg/m <sup>2</sup> I.V. infusion	Administered over 60 minutes on Day 1 of each 21-day cycle.
<b>Arm B</b>		
Docetaxel <sup>c</sup>	75 mg/m <sup>2</sup> I.V. infusion	Administered over 60 minutes on Day 1 of each 21-day cycle.

Abbreviations: CR = complete response; CRP = clinical research physician; CRS = clinical research scientist; DCed = discontinued; IRR = infusion-related reaction; I.V. = intravenous(ly); PR = partial response; SD = stable disease.

<sup>a</sup> Provided no prespecified discontinuation criteria have been met for a given patient, treatment with docetaxel may continue for up to six 21-day cycles; further cycles of docetaxel (up to 4 additional cycles [maximum of 10 cycles total]) may be administered if adequate disease response (that is, SD or better [PR, CR], based on the investigator's assessment) is observed and with approval of the Lilly CRP/CRS or designee.

<sup>b</sup> Refer to Section 9.4.1 for details regarding dose modifications.

<sup>c</sup> Taxotere package insert, 2013.

<sup>d</sup> IRRs may occur during or following administration of ramucirumab (placebo). See Attachment 8 for a definition of IRRs. For the first and second treatment cycles: Docetaxel administration 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 (that is, first and second treatment cycles), then no observation period is required for subsequent (third and later) treatment cycles, and docetaxel can be administered immediately after the infusion of ramucirumab/placebo.

<sup>e</sup> Treatment with ramucirumab/placebo may continue until at least one discontinuation criterion is met.

Refer to Section 9.4 for the selection and timing of doses.

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 site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

**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.

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.

### **9.1.1. Premedication**

Per ASCO guidelines (Smith et al. 2006) and based on the observed rates of febrile neutropenia in both arms of the Phase 2 study and in prior studies with single-agent docetaxel in urothelial cancer (McCaffrey et al. 1997), the use of colony-stimulating factors (CSFs) as primary prophylaxis (first and subsequent-cycle use) is recommended in patients randomized to either arm of Study JVDC.

#### **9.1.1.1. Premedication for Ramucirumab or Placebo**

Premedication is required for all patients prior to each infusion of ramucirumab or placebo. Recommended premedication agents include histamine H1 antagonists 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 CRF.

#### **9.1.1.2. Premedication for Docetaxel**

Sites should consult the manufacturer's instructions for docetaxel (Taxotere package insert, 2013) for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of docetaxel. Patients should be premedicated with corticosteroids such as dexamethasone 16 mg/day (for example, 8 mg twice a day) for 3 days starting 1 day prior to each docetaxel infusion to reduce the severity of fluid retention and hypersensitivity reactions. Additional antiemetic premedication may be employed at the discretion of the investigator. All premedication administered must be adequately documented in the CRF.

### **9.1.2. Study Drugs**

#### **9.1.2.1. Ramucirumab or Placebo**

Patients will receive ramucirumab by I.V. infusion at a dose of 10 mg/kg (or placebo at a dose of 10 mg/kg volume equivalent) on Day 1 of each 21-day cycle, in the absence of disease progression or other discontinuation criteria.



Ramucirumab is compatible with common infusion containers. The use of a low protein binding 0.22-micron in-line filter is required. Based on the calculated volume of ramucirumab, add (or remove from pre-filled [with 0.9% normal saline] I.V infusion container) a sufficient quantity of sterile normal saline (0.9% weight/volume) to the container to make the total volume 250 mL. For dose volumes greater than 250 mL, the addition of sterile normal saline is not required. Do not use dextrose-containing solutions. The container should be gently inverted to ensure adequate mixing. The infusion should be delivered via infusion pump in approximately 60 minutes. The infusion rate should not exceed 25 mg/minute. Infusions of durations longer than 60 minutes are permitted in specific circumstances (that is, for larger patients in order to maintain an infusion rate that does not exceed 25 mg/minute, or in the setting of a prior ramucirumab IRR; refer to [Attachment 8](#) for definitions of IRRs); the infusion duration must always be accurately recorded. The infusion set must be flushed post infusion with sterile 0.9% normal saline equal to or greater than infusion set hold-up volume to ensure delivery of the calculated dose.

Aseptic technique is to be used when preparing and handling ramucirumab (or placebo) for infusion. Different drug product lots must not be mixed in a single infusion. Refer to the pharmacy dispensing manual and the ramucirumab IB for detailed information on reconstitution, infusion compatibility, infusion, storage, and accountability of ramucirumab (or placebo).

Ramucirumab (or placebo) drug product: The drug product must be stored under refrigeration at 2°C to 8°C (36°F-46°F) with protection from light. **DO NOT FREEZE OR SHAKE RAMUCIRUMAB OR PLACEBO.** Stability studies have demonstrated that the drug product can withstand transient excursion to room temperature without adverse effect; however, storage at this temperature is not recommended.

Prepared ramucirumab (or placebo) for infusion: Chemical and physical in-use stability for the prepared ramucirumab (or placebo) drug product has been demonstrated for up to 24 hours below 25°C (77°F). However, it is recommended that the prepared drug product be used immediately in order to minimize the risk of microbial contamination. If not used immediately, the prepared ramucirumab (or placebo) solution must be stored for no more than 24 hours at 2°C to 8°C (36°F-46°F) (refrigeration) or no more than 4 hours if held at room temperature (below 25°C [77°F]). **DO NOT FREEZE OR SHAKE PREPARED RAMUCIRUMAB (OR PLACEBO) FOR INFUSION.**

**CAUTION:** IRRs may occur during or following ramucirumab (or placebo) administration. Refer to [Attachment 8](#) for definitions of Grade 3 and 4 IRRs. During the administration of ramucirumab (or placebo), patients should be in an area with resuscitation equipment and treatments necessary for advanced life-support and cardiopulmonary resuscitation, such as bronchodilators, vasopressor agents (for example, epinephrine), oxygen, glucocorticoids, antihistamines, I.V. fluids, etc. A 1-hour observation period is required after the administration of the first and second doses of ramucirumab (or placebo). Docetaxel administration should start only after this observation period. If there is no evidence of an IRR during the initial 2 infusions of ramucirumab (or placebo) (that is, first and second treatment cycles), then no observation period is required for subsequent (third and later) treatment cycles, and docetaxel can be



administered immediately after the infusion of ramucirumab (or placebo). In the event an IRR occurs thereafter, the 1-hour observation should be reinstated.

#### **9.1.2.2. Docetaxel**

Docetaxel will be administered at a dose of 75 mg/m<sup>2</sup> I.V. over 60 minutes on Day 1 of each 21-day treatment cycle, in the absence of disease progression or other discontinuation criteria. Refer to Section 9.1 for details regarding the maximum number of cycles of docetaxel permitted.

Aseptic technique is to be used when preparing and handling docetaxel.

A commercial preparation of docetaxel will be used and should be prepared and administered according to the manufacturer's instructions. Investigators should consult the approved docetaxel package insert (Taxotere package insert, 2013) for complete prescribing information, and follow institutional procedures for the administration of docetaxel.

### **9.2. Materials and Supplies**

Ramucirumab will be provided by Lilly. Commercial docetaxel will be used. Clinical trial materials will be labeled according to the country's regulatory requirements.

#### **9.2.1. Ramucirumab Drug Product or Placebo**

Ramucirumab drug product 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 10mM histidine, 75mM sodium chloride, 133mM glycine, and 0.01% polysorbate 80. The pH is 6.0.

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

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

#### **9.2.2. Docetaxel**

A commercial preparation of docetaxel will be used in this study, and will be packaged, labeled, and stored according to manufacturer standards and according to the country's regulatory requirements, if supplied by the sponsor.

### **9.3. Method of Assignment to Treatment**

Patients who meet all criteria for enrollment will be randomly assigned to receive either ramucirumab plus docetaxel (Arm A [experimental arm]) or placebo plus docetaxel (Arm B [comparator arm]) 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: geographic region (North America, Europe, or rest of the world); ECOG performance status at baseline (0 or 1); and visceral metastasis (yes or no), where visceral metastases involve the liver, lung, and/or bone. The chosen stratification factors have been identified as important adverse prognostic factors or regional considerations that could affect efficacy in this disease. Randomization will be performed separately within each of the 12 strata (or cells) defined by all combinations of these 3 variables.

#### **9.4. Selection and Timing of Doses**

Local laboratory values will be used to determine the patient dose and/or dose adjustments.

A cycle is defined as an interval of 21 days (a delay of the start of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 days and not counted as a protocol deviation).

The actual doses of ramucirumab/placebo administered will be determined by measuring the patient's weight in kilograms at the beginning of each cycle. If the patient's weight does not fluctuate by more than  $\pm 10\%$  from the weight used to calculate the prior dose, the dose will not need to be recalculated.

The actual doses of docetaxel administered will be determined by calculating the patient's body surface area (BSA) at the beginning of each cycle. If the patient's weight does not fluctuate by more than  $\pm 10\%$  from the weight used to calculate the prior dose, the BSA will not need to be recalculated.

For the first and second treatment cycles, docetaxel administration should start only after at least a 1-hour observation period after ramucirumab or placebo administration. If there is no evidence of an IRR after the ramucirumab or placebo infusion during the first and second treatment cycles, then no observation period is required for subsequent (third and later) treatment cycles, and docetaxel can be administered immediately after the infusion of ramucirumab or placebo.

A patient may continue to receive docetaxel until he or she has received a maximum of 6 cycles or until he or she meets at least one of the specified reasons for discontinuation (as described in Section 7.3); further cycles of docetaxel (up to 4 additional cycles [maximum of 10 cycles total]) may be administered if adequate disease response (that is, SD or better [PR, CR], based on the investigator's assessment) is observed and with approval of the Lilly CRP/CRS or designee. A patient may continue to receive ramucirumab or placebo (monotherapy) until he or she meets at least one of the specified reasons for discontinuation (as described in Section 7.3).

Study treatment will be administered as described in Section 9.1.

### 9.4.1. Dose Adjustments and Delays

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 9.4.1.1) or docetaxel (Section 9.4.1.2).

Ramucirumab/placebo dose modifications are permanent; no dose escalations are allowed after dose reduction.

Ramucirumab/placebo therapy should continue as scheduled if there is a delay or discontinuation of docetaxel. Likewise, if there is a delay or modification of ramucirumab/placebo due to toxicity, treatment with docetaxel can continue as scheduled.

#### 9.4.1.1. Dose Modifications for Ramucirumab/Placebo

Table JVDC.2 presents the dose reduction schedule for ramucirumab/placebo.

**Table JVDC.2. Ramucirumab/Placebo Dose Reduction Schedule**

Starting Dose	Dose Level -1	Dose Level -2
10 mg/kg	8 mg/kg	6 mg/kg

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  $\leq 1$  or pretreatment level within the same treatment cycle without treatment interruption. However, if the event required treatment interruption or delay or in the event of a second instance of the event, upon recovery (Grade  $\leq 1$  or pretreatment level), the dose should be reduced by one level (Table JVDC.2). 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. Dose adjustments or delays are not required for Grade  $\leq 2$  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. When restarting ramucirumab/placebo, an attempt should be made to resynchronize administration with docetaxel (that is, at Day 1 of the next normally scheduled cycle). If clinically appropriate, the investigator can delay all treatment components up to a maximum of 7 days to allow synchronized administration of both agents.

A total of up to 2 dose-level decreases are allowed during the study; the patient needs to be discontinued from treatment if any further dose reduction beyond 2 dose-level decreases is needed.

The preceding information in this section pertains only to general dose modifications for ramucirumab/placebo. The following information (in this section and the following subsections) pertains to dose modifications and delays for and management of AEs of concern, which may or may not be associated with ramucirumab therapy, including the following:

- IRR
- Hypertension
- Arterial and venous thromboembolic events
- Bleeding (hemorrhagic) events
- Gastrointestinal perforation
- Fistula
- Proteinuria
- Congestive heart failure
- Surgery and impaired wound healing
- Liver injury/failure
- Reversible posterior leukoencephalopathy syndrome (RPLS)

Table JVDC.3 presents ramucirumab/placebo dosing guidelines for managing infusion reactions, hypertension, and proteinuria, which are common ramucirumab toxicities.



**Table JVDC.3. Ramucirumab/Placebo Dosing Guidelines for Managing Infusion Reactions, Hypertension, and Proteinuria**

<b>Event and Grade<sup>a</sup></b>	<b>Specifics</b>	<b>Ramucirumab/Placebo Dosing Guidelines, including Dose Reductions and Delays</b>
<b>IRR Events</b>		
Grade 1 or 2		Reduce the infusion rate by 50% for the duration of the infusion and for all future infusions.  If the patient has a second Grade 1 or 2 IRR, premedicate (also) with dexamethasone (or equivalent) and acetaminophen.
Grade 3 or 4		Discontinue ramucirumab/placebo
<b>Hypertension</b>		
Grade 1 (hypertension controlled with medications)		10 mg/kg (full dose) without interruption
Grade 2 or 3 (hypertension [non-life-threatening])	Resolution to Grade <2 within 3 weeks	Delay ramucirumab/placebo administration. Administer 10 mg/kg (full dose) once hypertension is controlled with medications and is Grade <2 within 3 weeks.
	Resolution to Grade <2 within 3 to 6 weeks	Delay ramucirumab/placebo administration. Administer ramucirumab/placebo at 8 mg/kg if hypertension is Grade <2 by the fourth week. Administer ramucirumab/placebo at 6 mg/kg if hypertension is Grade <2 by the sixth week. Discontinue ramucirumab/placebo if blood pressure does not improve to Grade <2 by the sixth week (42 days), despite >2 oral agents.
Grade 4 (uncontrolled hypertension, hypertensive crisis, hypertensive encephalopathy)		Discontinue ramucirumab/placebo.



Event and Grade <sup>a</sup>	Specifics	Ramucirumab/Placebo Dosing Guidelines, including Dose Reductions and Delays
<b>Proteinuria</b>		
Dipstick (or routine urinalysis) <2 <sup>b</sup>		Administer baseline or full previous dose of ramucirumab/placebo without interruption.
Dipstick (or routine urinalysis) =2 <sup>b</sup>		Administer full previous dose of ramucirumab/placebo without interruption.  Perform a 24-h urine collection within 3 d prior to next dose of ramucirumab/placebo. <ul style="list-style-type: none"> <li>If &lt;2 g/24 h, administer unchanged dose of ramucirumab/placebo.</li> <li>If ≥2 g/24 h, then follow dose adjustment based on 24-h collection (below in this table).</li> </ul>
Dipstick (or routine urinalysis) >2 <sup>b</sup>		Delay ramucirumab/placebo dose up to 21 days.  Perform a 24-h urine collection within 3 d prior to the next planned dose of ramucirumab/placebo. <ul style="list-style-type: none"> <li>If &lt;2 g/24 h, administer unchanged dose of ramucirumab/placebo.</li> <li>If ≥2 g/24 h, then follow dose adjustment based on 24-h collection (below in this table).</li> </ul>
24-h Urine collection: ≥2 g/24 h <sup>b</sup>	First instance	8 mg/kg once urinary protein returns to <2 g/24 h
	Second instance	6 mg/kg once urinary protein returns to <2 g/24 h
	Third instance	Discontinue ramucirumab/placebo (if a third dose reduction is required)
24-h Urine collection: >3 g/24 h in the setting of nephrotic syndrome <sup>b</sup>		Discontinue ramucirumab/placebo

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction; NCI = National Cancer Institute.

a NCI-CTCAE v 4.0 (CTEP 2009).

b A dipstick test (or routine urinalysis) for proteinuria should be performed prior to each infusion of ramucirumab/placebo. If both dipstick (or routine urinalysis) and 24-hour tests are performed, the results of 24-hour collection should be used for clinical decision-making.

#### 9.4.1.1.1. Infusion-Related Reactions

Any treatment-related, infusion-related reactions are defined according to the NCI-CTCAE v 4.0 definition (section “General disorders and administration site conditions”). Symptoms occurring during or following infusion of ramucirumab/placebo may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (NCI-CTCAE, v 4.0 section “Immune system disorders”). In the setting of symptoms occurring during or following infusion of ramucirumab/placebo, 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. These reactions should be graded as shown in [Attachment 8](#).

As with other mAbs, IRRs were reported in clinical trials with ramucirumab, with the majority of events occurring during or following a first or second ramucirumab infusion. It is thus required that patients are premedicated prior to each administration of ramucirumab/placebo.

Recommended agents include histamine H1 antagonists such as diphenhydramine hydrochloride. Monitor patients during the infusion for signs of hypersensitivity reactions with resuscitation equipment readily available. Symptoms included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension.

Reduce the infusion rate of ramucirumab/placebo by 50% for Grade 1 or 2 IRRs. For patients who have experienced a Grade 1 or 2 infusion reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each ramucirumab/placebo infusion.

Immediately and permanently discontinue ramucirumab/placebo for Grade 3 or 4 IRRs.

#### **9.4.1.1.2. Hypertension**

An increased incidence of severe hypertension was reported in patients receiving ramucirumab as compared with those receiving placebo. In most cases, hypertension was controlled using standard antihypertensive treatment.

Preexisting hypertension should be controlled before starting ramucirumab/placebo treatment. Monitoring of blood pressure (BP) is recommended during therapy.

Temporarily suspend ramucirumab/placebo for severe hypertension until controlled with medical management. Permanently discontinue ramucirumab/placebo if medically significant hypertension such as hypertensive crisis, malignant hypertension, or hypertensive encephalopathy occurs or cannot be controlled with antihypertensive therapy.

Patients whose hypertension is poorly controlled for >4 weeks (>160 mm Hg systolic or >100 mm Hg diastolic) despite appropriate oral medication (>2 oral agents at maximum tolerated dose) is considered refractory. The patient will be discontinued from ramucirumab/placebo. Treatment with docetaxel may be continued, if appropriate in the opinion of the investigator.

#### **9.4.1.1.3. Thromboembolic Events**

##### **9.4.1.1.3.1. 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. Permanently discontinue ramucirumab/placebo in patients who experience a severe ATE.

##### **9.4.1.1.3.2. 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.

Most VTEs lack early warning signs; therefore, awareness and prompt treatment is important, especially in those patients with risk factors and/or previous history of VTEs (Chen and Cleck 2009; Suter and Ewer 2013).

Ramucirumab/placebo therapy should be discontinued in the event of any Grade 3 or 4 VTE that is considered by the investigator to be life-threatening or symptomatic and not adequately treated by anticoagulation therapy. At the investigator's discretion, ramucirumab/placebo therapy may be continued in the setting of an incidentally diagnosed, asymptomatic deep vein thrombosis or pulmonary embolism, or following a symptomatic deep vein thrombosis or pulmonary embolism when symptoms have resolved with the institution of anticoagulation therapy.

Ramucirumab/placebo should also be discontinued in the setting of a deep vein thrombosis or pulmonary embolism that occurs or intensifies while the patient is receiving therapeutic anticoagulation therapy.

#### **9.4.1.1.4. Bleeding (Hemorrhagic) Events**

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

Permanently discontinue ramucirumab/placebo in patients who experience Grade 3 or 4 bleeding.

#### **9.4.1.1.5. Gastrointestinal Perforation**

Ramucirumab is an antiangiogenic therapy and has the potential to increase the risk of GI perforations. Permanently discontinue ramucirumab/placebo in patients who experience GI perforations.

#### **9.4.1.1.6. Fistula**

Gastrointestinal and non-GI fistula formation have been associated with other antiangiogenic agents, including bevacizumab and sunitinib (Kamba and McDonald 2007). 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).

Patients may be at increased risk for the development of fistula when treated with ramucirumab. Ramucirumab/placebo treatment should be discontinued in patients who develop fistula.

#### **9.4.1.1.7. Proteinuria**

Proteinuria is an adverse effect for all therapies targeting the VEGF/VEGF Receptor 2 pathway. Proteinuria has been associated with ramucirumab in clinical studies. The majority of events were Grade 1 or 2.



If, while on ramucirumab/placebo therapy, a patient has proteinuria  $>2+$  per a dipstick or routine urinalysis test, delay ramucirumab/placebo administration up to 21 days and perform a 24-hour urine collection within 3 days prior to the next planned dose of ramucirumab/placebo. If the protein level is  $<2$  g/24 hours, the patient will continue on ramucirumab/placebo therapy at the same dose.

If the dipstick is  $2+$ , administer full previous dose of ramucirumab/placebo without interruption. Perform a 24-hour urine collection within 3 days prior to the next dose of ramucirumab/placebo. If the protein level is  $<2$  g/24 hours, administer unchanged dose of ramucirumab/placebo. If the protein level is  $\geq 2$  g/24 hours, perform a 24-hour urine collection prior to the next planned dose of ramucirumab/placebo. Ramucirumab/placebo treatment will resume at a reduced dose level (8 mg/kg) once the protein level returns to  $<2$  g/24 hours. A second dose reduction of ramucirumab/placebo to 6 mg/kg is permitted in case of a second instance of proteinuria  $\geq 2$  g/24 hours. The patient will be discontinued from ramucirumab/placebo treatment if the protein level is  $>3$  g/24 hours in the setting of nephrotic syndrome or if there is a third occurrence of proteinuria  $\geq 2$  g/24 hours.

#### **9.4.1.1.8. Congestive Heart Failure**

An increased risk of congestive heart failure (CHF) has been associated with some antiangiogenic therapeutic agents, particularly in patients with metastatic breast cancer previously treated with anthracyclines or with other risk factors for CHF, including prior radiotherapy to the left chest wall. 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.

While the mechanism of action is currently unknown, based on the safety data received to date, it is likely that treatment with ramucirumab enhances the cardiotoxicity associated with mitoxantrone and has the potential to enhance cardiotoxicity of other agents within the anthracycline/anthracendione 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. Patients with symptomatic CHF, unstable angina pectoris, or symptomatic or poorly controlled cardiac arrhythmia should not be enrolled in clinical trials with ramucirumab. Ramucirumab/placebo should be discontinued in the event of any Grade 3 or 4 events consistent with CHF.

#### **9.4.1.1.9. Surgery and Impaired Wound Healing**

The impact of ramucirumab has not been evaluated in patients with serious or non-healing wounds. In a study conducted in animals, ramucirumab did not impair wound healing. However, since ramucirumab is an antiangiogenic therapy and may have the potential to adversely affect wound healing, ramucirumab treatment should be withheld for at least 4 weeks prior to scheduled surgery. Note: Central venous line replacement, such as a Hickman line,

should not be considered a significant surgery and would not require discontinuation of ramucirumab.

If a patient develops wound healing complications during therapy, temporarily discontinue ramucirumab/placebo until the wound is fully healed. Should the wound persist beyond 2 cycles (42 days\*), permanently discontinue ramucirumab/placebo.

\* This 42-day period is approximate and begins on the day that the next cycle of ramucirumab/placebo should have been administered but was withheld specifically for toxicity.

#### **9.4.1.1.10. Liver Injury/Liver Failure**

Liver failure or other significant liver injury events, such as hepatic encephalopathy, have been observed in patients receiving ramucirumab. Patients with the following conditions should not be enrolled in clinical trials with ramucirumab: 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 or hepatorenal syndrome. “Clinically meaningful ascites” is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

Ramucirumab/placebo should be discontinued in the event of any new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis.

##### **9.4.1.1.10.1. 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). Magnetic resonance imaging (MRI) represents the most reliable method for the 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, 2 cases of RPLS have been reported. Both cases occurred in the double-blind, randomized, placebo-controlled Phase 3 Study I4T-MC-JVBB (IMCL CP12-0920; RAISE) evaluating folinic acid/fluorouracil/irinotecan chemotherapy (FOLFIRI) in combination with ramucirumab versus FOLFIRI in combination with placebo for patients with metastatic CRC. One RPLS case was reported in each arm of the study (1 patient in the ramucirumab-plus-FOLFIRI arm and 1 patient in the placebo-plus-FOLFIRI arm).

RPLS should be identified and treated promptly 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).



If the diagnosis of RPLS is confirmed, ramucirumab/placebo should be permanently discontinued.

#### 9.4.1.2. Dose Modifications for Docetaxel

Investigators should consult the manufacturer's instructions for docetaxel (Taxotere package insert, 2013) for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of docetaxel. All implemented dose modifications are permanent. The doses must be modified according to the lowest hematology values and the highest degree of nonhematologic toxicities observed at any time during the previous cycle. If a patient develops several different toxic effects and there are conflicting recommendations, the dose reduction required for the clinically most severe toxic effect must be chosen.

The docetaxel dose reduction schedule is presented in [Table JVDC.4](#).

**Table JVDC.4. Docetaxel Dose Reduction Schedule**

Dose	Dose Reduction Level
Starting dose	75 mg/m <sup>2</sup>
First dose reduction	60 mg/m <sup>2</sup>
Second dose reduction	50 mg/m <sup>2</sup>

Dose modifications for hypersensitivity reactions and for hematologic toxicity ([Table JVDC.6](#)) are discussed in Sections [9.4.1.2.1](#) and [9.4.1.2.2](#), respectively.

General guidelines for docetaxel dose modifications for nonhematologic toxicity are presented in [Table JVDC.5](#).

**Table JVDC.5. Docetaxel Dose Modifications for Nonhematologic Toxicity**

Toxicity (NCI-CTCAE Grade <sup>a</sup> )	Docetaxel Dose
<b>Hepatic</b>	
AST/ALT and AP WNL and bilirubin >1× ULN	Delay treatment until recovery <sup>b</sup> up to 3 weeks.
AST/ALT ≤2 × ULN and AP ≤2 × ULN and bilirubin WNL	No change.
AST/ALT >2 - ≤5 × ULN and AP ≤2.5 × ULN and bilirubin WNL	No change.
AST/ALT >2 - ≤5 × ULN and AP >2.5 - ≤5 × ULN and bilirubin WNL	Delay treatment until recovery <sup>c</sup> up to 3 weeks.
AST/ALT >5 × ULN and AP >5 × ULN and bilirubin WNL	Delay treatment until recovery <sup>c</sup> up to 3 weeks.
AST/ALT >5 × ULN and AP >5 × ULN and bilirubin >1 × ULN	Delay treatment until recovery <sup>b,c</sup> up to 3 weeks.
<b>Gastrointestinal</b>	
Grade 1-4 nausea and/or vomiting	No change. Control with adequate antiemetics.
<b>Mucositis</b>	
Grade 1-2	Delay treatment until recovery to Grade ≤1 up to 3 weeks.
Grade 3-4	Delay treatment until recovery to Grade ≤1 up to 3 weeks, then dose reduce.
<b>Fluid Retention</b>	
Grade 1	No change.
Grade 2	No change. Treat with oral diuretics.
Grade 3-4	Treat with oral diuretics. Delay treatment until Grade ≤1 up to 3 weeks. Discontinue treatment if fluid retention is not responsive to diuretic therapy.
<b>Neurologic</b>	
Grade 1	No change.
Grade 2	With the exception of peripheral neuropathy, delay treatment until toxicity recovers to Grade 1, then reduce docetaxel dose. If Grade 2 toxicity persists >3 weeks, discontinue docetaxel.
Grade 3-4	Discontinue treatment.

Toxicity (NCI-CTCAE Grade <sup>a</sup> )	Docetaxel Dose
<b>Other toxicities</b>	
Grade $\leq 2$	Manage symptomatically, if possible and retreat without dose reduction or dose delay.
Grade 3	Delay treatment until toxicity resolves to Grade $\leq 1$ (no longer than 3 weeks) unless baseline value was Grade $>1$ . If medically appropriate, reduce docetaxel dose.
Grade 4	Discontinue treatment.

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; ULN = upper limit of normal; WNL = within normal limits.

- a Toxicity grades per NCI-CTCAE v 4.0.
- b Bilirubin  $\leq 1 \times$  ULN.
- c AST/ALT/AP returns to level at trial entry or better.

Patients who are discontinued from docetaxel will continue in the study and may continue to receive further treatment with ramucirumab/placebo, if the toxicity that caused discontinuation of docetaxel is not considered by the investigator to be related to ramucirumab/placebo.

#### **9.4.1.2.1. Hypersensitivity Reactions**

Hypersensitivity reactions may occur within a few minutes following initiation of a docetaxel infusion. All patients should be premedicated with a corticosteroid prior to the initiation of the infusion of docetaxel (see Section 9.1.1.2).

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and administration of appropriate therapy. Patients with a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80 must not be given (re-challenged with) docetaxel.

Descriptions and suggested management of docetaxel hypersensitivity reactions are as follows:

Mild symptoms: flushing or localized cutaneous reaction such as mild pruritus or rash

- Consider decreasing the rate of infusion until recovery of symptoms; stay at bedside.
- Then, complete docetaxel infusion at the initial planned rate.
- Interruption of docetaxel is not required.

Moderate symptoms: any symptom not listed as mild or severe, such as generalized pruritus, flushing, rash, dyspnea, or hypotension with systolic BP >80 mm Hg.

- Stop docetaxel infusion.
- Give I.V. dexamethasone 10 mg and/or diphenhydramine 50 mg I.V.
- Resume docetaxel infusion after recovery of symptoms.
- Docetaxel should be administered over 2 hours for subsequent treatments.
- If symptoms recur, stop the docetaxel infusion and remove patient from docetaxel treatment.

Severe or life-threatening symptoms (CTCAE Grade 3 or 4): such as bronchospasm, generalized urticaria, systolic BP  $\leq$ 80 mm Hg, angioedema, or anaphylaxis

- Stop docetaxel infusion.
- Give I.V. diphenhydramine and dexamethasone as for moderate symptoms. Add epinephrine or bronchodilators if indicated.
- The patient should be permanently discontinued from docetaxel treatment.

Management of subsequent treatment cycles: The recommended pretreatment for subsequent infusions is 50 mg diphenhydramine I.V. and 10 mg dexamethasone I.V. 30 minutes prior to the docetaxel infusion. This is in addition to the prescribed dexamethasone (corticosteroid premedication).

Patients with hypersensitivity reactions to docetaxel are at risk for recurrent reactions. For patients who experience moderate hypersensitivity reactions, the docetaxel should be administered over 2 hours for subsequent treatment courses in addition to premedication as noted in Section 9.1.1.2. These patients must be informed of the potential risk of recurrent allergic reactions and must be carefully monitored.

In cases of late-occurring (for example, appearance within 1 week after treatment) hypersensitivity symptoms of a localized or generalized pruritus, symptomatic treatment may be given (for example, oral antihistamine). Additional oral or I.V. premedication with antihistamine may also be given for the next cycle of treatment, depending on the intensity of the reaction observed. No dose reductions will be made in any case.

#### **9.4.1.2.2. Hematologic Toxicity**

Neutropenia ( $<2.0 \times 10^3/\mu\text{L}$  [ $<2.0 \times 10^9/\text{L}$ ]) occurs in almost all patients treated with docetaxel 60 to 100 mg/m<sup>2</sup>, and Grade 4 neutropenia ( $<0.5 \times 10^3/\mu\text{L}$  [ $<0.5 \times 10^9/\text{L}$ ]) occurs in 85% of patients given 100 mg/m<sup>2</sup> and 75% of patients given 60 mg/m<sup>2</sup>. Frequent monitoring of blood counts is therefore essential so that the dose can be adjusted. Docetaxel should not be administered to patients with neutrophils  $<1.5 \times 10^3/\mu\text{L}$  ( $<1.5 \times 10^9/\text{L}$ ). Primary prophylaxis with growth factor support is recommended.

**Table JVDC.6. Docetaxel Dose Modifications for Hematologic Toxicity**

	Docetaxel Dose Modification	
	ANC on Day 1 of cycle	
	$<1.5 \times 10^3/\mu\text{L}$ ( $<1.5 \times 10^9/\text{L}$ )	$\geq 1.5 \times 10^3/\mu\text{L}$ ( $\geq 1.5 \times 10^9/\text{L}$ )
<b>Nadir of ANC during last course:</b>		
CTCAE Grade 1 LLN- $1.5 \times 10^3/\mu\text{L}$ ( $1.5 \times 10^9/\text{L}$ )	No change	No change
CTCAE Grade 2 $<1.5-1.0 \times 10^3/\mu\text{L}$ ( $<1.5-1.0 \times 10^9/\text{L}$ )	Delay up to 3 weeks	No change
CTCAE Grade 3 $<1.0-0.5 \times 10^3/\mu\text{L}$ ( $<1.0-0.5 \times 10^9/\text{L}$ )	Delay up to 3 weeks	No change if asymptomatic, otherwise dose reduce
CTCAE Grade 4 $<0.5 \times 10^3/\mu\text{L}$ ( $<0.5 \times 10^9/\text{L}$ )	Delay up to 3 weeks	No change if asymptomatic, otherwise dose reduce
Febrile neutropenia	Delay up to 3 weeks	Dose reduce
	Platelet count on Day 1 of cycle	
	$<100 \times 10^3/\mu\text{L}$ ( $<100 \times 10^9/\text{L}$ )	$\geq 100 \times 10^3/\mu\text{L}$ ( $\geq 100 \times 10^9/\text{L}$ )
<b>Nadir of platelet count during last course:</b>		
$\geq 25 \times 10^3/\mu\text{L}$ ( $\geq 25 \times 10^9/\text{L}$ )	Delay up to 3 weeks	No change
$<25 \times 10^3/\mu\text{L}$ ( $<25 \times 10^9/\text{L}$ )	Delay up to 3 weeks	Dose reduce

Abbreviations: ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal.

#### **9.4.1.2.3. Fluid Retention**

Severe fluid retention has been reported following docetaxel therapy. It is characterized by poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, and pronounced abdominal distention (due to ascites).

Patients should be premedicated with corticosteroids prior to each docetaxel administration to reduce the incidence and severity of fluid retention (see Section 9.1.1.2). When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg. Patients with preexisting pleural effusions should be closely monitored from the first dose of docetaxel for the possible exacerbation of the effusion.

#### **9.4.1.2.4. Cutaneous**

Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended.

## **9.5. Blinding**

This is a double-blind, placebo-controlled study.

To preserve the blinding of the study, ramucirumab will be visibly indistinguishable from placebo, unblinding will not occur at disease progression. Additionally, there are no anticipated or identified toxicities of ramucirumab that would potentially unblind investigators to treatment



assignment. Unblinding of the study team will not occur until after the reporting database is validated and locked for final statistical analysis (that is, final analysis of OS).

For this study, the independent data monitoring committee (IDMC) will be permitted to access unblinded safety data from the initial approximately 100 and 250 evaluable patients (refer to Section 4, Abbreviations and Definitions, for a definition of evaluable patients). Access to unblinded data/documents will be controlled by restricting access to the data/documents to the IDMC. Details of the unblinding plan will be described in the IDMC Charter.

Interim analyses for safety will be conducted by an IDMC, using unblinded data. See Section 12.2.13 for further details. Only the IDMC is authorized to evaluate unblinded interim safety analyses. Appropriate team members will be identified and documented (to be unblinded) prior to the database lock for the primary PFS analysis. At that point, these team members will no longer be involved in trial management activities. No by-patient level treatment data will be accessible to anyone else (for example, the rest of the study team and investigators) until the database lock for the final analysis of OS. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Upon study completion (following final analysis of the OS endpoint), investigators and patients may be unblinded to study treatment assignment.

### **9.5.1. 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 for medical management of the event. 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 or designee 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.

### **9.5.2. 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 performing assessments, or patient is unblinded, the unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study treatment or excluded from any safety or efficacy analyses.

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

## **9.6. 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 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.

### **9.6.1. 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 on the CRFs.

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

Premedication and treatment of hypersensitivity (infusion-related) reactions is described in Section [9.4.1.1.1](#).

#### **9.6.1.1. Colony-Stimulating Factors**

The use of G-CSF is permitted at the discretion of the investigator based on ASCO (Smith et al. 2006) and European Society for Medical Oncology (Crawford et al. 2009) guidelines. G-CSF or similar agents are recommended as primary prophylaxis and are strongly recommended following Grade 3 or 4 neutropenia of duration >5 days or following any incidence of febrile neutropenia (ANC <1.0 × 10<sup>9</sup>/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.

#### **9.6.1.2. 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. 2008).

#### **9.6.1.3. 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 I.V. 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 I.V. hydration and correction of electrolyte imbalance.

#### **9.6.1.4. Antiemetic Therapy**

The routine use of standard antiemetics, including dexamethasone plus 5-HT<sub>3</sub> antagonists (such as granisetron or ondansetron) as premedication and/or symptomatic management, should be administered as per the Multinational Association of Supportive Care in cancer and ASCO, or institutional guidelines.

#### **9.6.1.5. Analgesic Agents**

The use of analgesic agents is permitted at the discretion of the investigator. The chronic use of nonsteroidal anti-inflammatory drugs (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. Chronic use of analgesic agents with no or low bleeding risk (for example, paracetamol/acetaminophen, metamizole, dipyrrone, or propyphenazone) is recommended.

### **9.6.2. 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 9.6.3.

Concomitant interferon-alpha is not permitted while on study.

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 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 therapy will be cause for discontinuation of study therapy.

### **9.6.3. Restricted Therapies**

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

Patients stabilized on chronic oral anticoagulation therapy are eligible, provided that the coagulation parameters defined in the inclusion criteria are met.



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).

#### **9.6.4. 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 study treatment. 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.

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 (see Section 10.1).

#### **9.7. Treatment Compliance**

The study medication will be administered only at the investigational sites by the authorized study personnel. As a result, treatment compliance is ensured.

## 10. Efficacy, Health Outcomes Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

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

Study procedures related to efficacy, safety, health outcomes measures, sample collection and testing assessments and their timing are described in the sections below and shown in the Study Schedule ([Attachment 1](#)).

### 10.1. Efficacy Measures

Patients will be evaluated for tumor response according to RECIST 1.1, which are provided in [Attachment 6](#) (Eisenhauer et al. 2009). All patients will be evaluated for response at these time points:

- at baseline
- every 6 weeks ( $\pm 7$  days) after randomization (regardless of treatment delays) during the Study Treatment Period, until disease progression OR overall study completion OR 1 year after randomization, whichever occurs first

In addition, any patient whose disease has not progressed by 1 year 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 ( $\pm 7$  days) from 1 year after randomization, until disease progression OR overall study completion OR 3 years after randomization, whichever occurs first; then as per standard clinical practice after that.

Response assessments during the ongoing trial (and related treatment decisions) will be performed by the treating investigator at the site in cooperation with the local radiologist(s).

The preferred methods of tumor measurement are computed tomography (CT; including spiral CT scans) and MRI. Imaging studies include a CT scan of the chest and a contrast-enhanced CT scan of the abdomen and pelvis or an equivalent MRI scan. For any patient with bone metastasis at baseline, bone lesions (that is, nontarget) need to be followed by bone scan or another modality based on local clinical practice.

#### 10.1.1. *Efficacy Assessments at Baseline and during Study Treatment*

Within 28 days prior to randomization, baseline tumor measurement(s) will be performed on each patient. Computed tomography, including spiral CT, scans and MRI are the preferred methods of measurement.

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 I.V. and oral contrast). Low-dose or attenuation-corrected CT portions of a



combined PET-CT are not a substitute for dedicated diagnostic contrast-enhanced CT scans for RECIST measurements. 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.

The method of assessment used at baseline must be used consistently for tumor assessment and will be repeated as per Section 10.1.

During the Continued Access Period, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care.

#### **10.1.1.1. Centralized Radiologic Collection**

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 frequency described in Section 10.1. Lilly will collect and store tumor measurement images on all randomized patients.

Further details are provided in the manual of central radiology.

#### **10.1.2. Efficacy Assessments during Postdiscontinuation Follow-up**

For patients who discontinue study treatment without objectively measured disease progression, the investigative sites will continue to monitor patients and periodically evaluate tumor response (for timing, refer to Section 10.1), 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 overall study completion (that is, the final analysis of OS), whichever occurs first. After the patient has objective disease progression, radiographic tests are no longer required and the patient will be followed up approximately every 3 months ( $\pm 7$  days) until the patient's death or overall study completion, whichever occurs first (see Section 8.1.1).

After radiographic documentation of disease progression, patients may receive additional anticancer therapy at the discretion of the investigator. The additional treatments should be documented in the CRF.

#### **10.1.3. Primary Efficacy Measure**

The primary efficacy measure is progression-free survival (PFS).

Lilly or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study (refer to Section 10.1.1.1).

The PFS time is measured from the date of randomization to the date of first observation of objective progression as defined by RECIST 1.1 or the date of death due to any cause, whichever is earlier. The censoring is taken in the following order:

- If a patient does not have a complete baseline disease assessment, then the PFS time will be censored at the randomization date, regardless of whether or not objectively determined progression or death has been observed for the patient; otherwise,
  - if a patient is not known to have died or have objective progression as of the data inclusion cutoff date for the analysis, the PFS time will be censored at the last adequate objective progression-free disease assessment date.
- If death or disease progression occurs after 2 or more consecutive missing radiographic visits, censoring will occur at the date of the last adequate radiographic visit prior to the missed visits.
- If death or disease progression occurs after postdiscontinuation systemic anticancer therapy, censoring will occur at the date of last adequate radiographic visit prior to the start of postdiscontinuation systemic anticancer therapy.

Refer to the statistical analysis plan (SAP) for further details.

#### 10.1.4. Secondary Efficacy Measures

The following secondary efficacy measures (Table JVDC.7) will be collected at the times shown in the Study Schedule (Attachment 1).

**Table JVDC.7. Secondary Efficacy Endpoints**

Endpoint	Definition
Overall survival (OS)	The time from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data inclusion cutoff date for a particular analysis, OS will be censored for that analysis at the last known alive date prior to the data inclusion cutoff date.
Objective response rate (ORR)	The number of randomized patients who achieve a best response of CR or PR, using the investigator response assessments, divided by the total number of patients randomized to that study arm, based on the achievement of measurement criteria. RECIST 1.1 will be used to make the determination in this trial.
Disease control rate (DCR)	The proportion of randomized patients achieving a best response of CR, PR, or SD. Stable disease definition per RECIST (Attachment 6) and must achieve a minimum duration of 5 weeks from randomization.
Duration of response (DOR)	DOR is defined only for responders (patients with CR or PR [confirmation not required]). It is measured from the date of first evidence of CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. If a responder is not known to have died or have objective progression as of the data inclusion cutoff date, DOR will be censored at the date of the last complete objective progression-free disease assessment.

Abbreviations: CR = complete response; DCR = disease control rate; DOR = duration of response; ORR = objective response rate; OS = overall survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

## 10.2. Health Outcomes Measures

Assessment of PROs will be conducted through the use of the EORTC QLQ-C30 and the EQ-5D-5L questionnaires, which measure quality of life (QoL) and health status, respectively. The questionnaires will be completed at baseline, prior to each cycle of therapy (starting at Cycle 2), and at the (30-day) Short-term Follow-up visit as detailed in [Attachment 1](#). It is recommended that the instruments be administered together and in sequence order, at the beginning of the visit prior to other study procedures, with the EORTC QLQ-C30 presented first, followed by presentation of the EQ-5D-5L. At each applicable time point, the instruments should be completed before any extensive contact and consultation, which may bias patient responses.

The questionnaires will be completed only by those patients who are fluent in an available translation.

### 10.2.1. EORTC QLQ-C30

Patients will complete the EORTC QLQ-C30 questionnaire (Version 3). The EORTC QLQ-C30 is a self-administered, cancer-specific questionnaire with multidimensional scales (Aaronson et al. 1993). It consists of both multi-item and single-item scales, including 5 functional domains, a global QoL domain, 3 multi-item symptom domains, and 6 single-item domains. A change of  $\geq 10$  points on the 100-point scales is considered clinically meaningful (Osoba et al. 1998).

### 10.2.2. EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of self-reported health status (Herdman et al. 2011). Patients will complete the 5-level (no problem, slight problem, moderate problem, severe problem, and inability or extreme problem), 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) questionnaire concerning their current health state. A unique EQ-5D 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 visual analogue scale (VAS) ranging from 100 (best imaginable health state) to 0 (worst imaginable health state).

## 10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered 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 investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment regimen or study procedure, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.



The timing of all safety evaluations is shown in the Study Schedule ([Attachment 1](#)).

[Table JVDC.8](#) presents a summary of AE and SAE reporting guidelines. [Table JVDC.8](#) also shows which database or system is used to store AE and SAE data.

**Table JVDC.8. Adverse Event and Serious Adverse Event Reporting Guidelines**

Period	Types of AEs/SAEs to Be Reported	Collection Database	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions	X	
	All AEs <sup>a</sup>	X	
	SAEs related to protocol procedures	X	X
Study Treatment Period	All AEs	X	
	All SAEs	X	X
Short-term Postdiscontinuation Follow-up	All AEs	X	
	All SAEs	X	X
Long-term Postdiscontinuation Follow-up	All SAEs related to protocol procedures or study drug(s)	X	X
Continued Access (treatment) Period	All AEs	X	
	All SAEs	X	X
Continued Access Follow-up	All AEs	X	
	All SAEs	X	X
After the patient is no longer participating in the study (that is, no longer receiving study treatment and no longer in follow-up)	All SAEs related to protocol procedures or study drug(s) that the investigator becomes aware of		X

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

Note: The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment or procedures, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained.

<sup>a</sup> For patients who fail screening, only AEs related to protocol procedures are collected in the collection database.

### 10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from electrocardiograms (ECGs), laboratory results, and vital signs measurements that result in a diagnosis should be reported to Lilly or its designee.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs related to protocol procedures are reported to Lilly or its designee.

In addition, all AEs occurring after the patient receives the first dose of study drug must be reported to Lilly or its designee via CRF.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure and/or study drug via CRF.

The investigator decides whether he or she interprets the observed AEs as related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to study medication or study procedure, the following terminologies are defined:

- **Probably related:** a direct cause-and-effect relationship between the study treatment and the AE is likely.
- **Possibly related:** a cause-and-effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Does not know:** the investigator cannot determine.
- **Not related:** without question, the AE is definitely not associated with the study treatment.

The investigator should classify all “probably related,” “possibly related,” or “does not know” AEs and SAEs as related to IP/study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The NCI-CTCAE v 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate System Organ Class and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA®).

If a patient’s dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via CRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.



### 10.3.1.1. Serious Adverse Events

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

- death
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- 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 adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse event collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

Study site personnel must alert Lilly or its designee of any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event via a sponsor-approved method. If study site personnel contact Lilly or its designee by telephone regarding an SAE, study site personnel must also immediately provide official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study 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 caused by disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

The investigator does not need to actively monitor patients for AEs once the trial has ended, unless provided otherwise in the protocol; however, if an investigator becomes aware of an SAE occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

### **10.3.1.2. Suspected Unexpected Serious Adverse Reactions**

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the DCSI in the IB and that the investigator identifies as related to the study drug 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.

### **10.3.2. Other Safety Measures**

#### **10.3.2.1. Electrocardiograms**

For each patient, 12-lead digital ECGs will be collected according to the Study Schedule ([Attachment 1](#)) as single ECGs (no overread). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

### **10.3.3. Safety Monitoring**

The Lilly CRP/CRS or designee will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP/CRS or designee will, as is appropriate, consult with the functionally independent Lilly Global Patient Safety therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes
- adverse events
- If a patient experiences elevated ALT  $>5 \times$  ULN and elevated total bilirubin  $>2 \times$  ULN, clinical and laboratory monitoring should be initiated by the investigator.

- 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 or designee regarding collection of specific recommended clinical information and follow-up laboratory tests. See [Attachment 3](#).

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 (an advisory group for this study formed to protect the integrity of data; refer to Section [12.2.13](#)) can conduct additional unblinded analyses of the safety data.

Refer to Section [12.2.13](#) for details regarding interim safety analyses.

#### **10.3.4. Complaint Handling**

Lilly collects product complaints on study drugs used in clinical trials in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

Complaints related to unblinded comparator drugs or concomitant drugs are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or its designee will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

### **10.4. Sample Collection and Testing**

Samples collected for this study will be coded with the patient number. The samples and any data generated from them can be linked back to the patient only by investigator site personnel.

[Attachment 1](#) lists the schedule for sample collections in this study.

[Attachment 2](#) lists the specific tests that will be performed for this study and whether these will be performed at a central or local laboratory.

[Attachment 7](#) lists the schedules for sample collections for PK, immunogenicity, and translational research (tumor tissue, plasma, urine, and whole blood).

#### **10.4.1. Samples for Study Qualification and Health Monitoring**

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Samples will be collected at the times specified in the Study Schedule ([Attachment 1](#)).



Standard laboratory tests, including chemistry, hematology, coagulation, pregnancy testing (as applicable, in women of childbearing potential), and urinalysis panels will be performed. Chemistry will be analyzed locally and centrally; hematology, coagulation, pregnancy testing, and urinalysis panels will be analyzed locally. [Attachment 2](#) lists the laboratory tests that will be performed for this study. Local laboratory results will be used to determine patient eligibility at baseline, except for central analysis of chemistry results. Local laboratory results may be used for on-study dosing decisions; if so, testing must also still be performed by the central laboratory for chemistry results (only). These central chemistry laboratory results will be used for subsequent safety analyses. In the event of minor discrepancies between local and central laboratory results, the investigator may use the local results for treatment decisions, and the central laboratory results will remain part of the safety database.

Based on laboratory safety values, unscheduled hepatic monitoring tests (see [Attachment 3](#)) may be performed as part of patient follow-up, in consultation with the Lilly CRP/CRS or designee.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

#### **10.4.2. Samples for Translational Research**

As part of the sponsor's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study may analyze biomarkers relevant to ramucirumab, docetaxel, and/or urothelial carcinoma. The study will analyze the clinical correlation between biomarkers and clinical outcome and may be used for related research methods or validation of diagnostic tools or assay(s).

Samples for translational research (TR) will be collected at the times specified in [Attachment 7](#).

The following samples are mandatory (required) for biomarker research, except as indicated otherwise:

- Tumor tissue (newly biopsied or archived) (see Section [10.4.2.1](#))
- Plasma for biomarkers (see Section [10.4.2.2](#))
- Urine for biomarkers (see Section [10.4.2.2](#))
- Whole blood for DNA sample (pharmacogenetic analysis) (see Section [10.4.2.3](#))

For these mandatory samples: All sites are required to participate in the TR portion of the study, and patient participation in the TR portion of the study is mandatory, unless restricted by local regulations.

Patients will not receive results of these investigations except where required by local law.

#### 10.4.2.1. Tumor Tissue

Collection of tumor tissue samples (either newly biopsied or archived) is mandatory (required) for participation in this study, as follows, except as indicated otherwise:

- If a prior archived tumor specimen is available, and unless restricted by local regulations, submission of archived tumor tissue is mandatory.
- If an archived specimen is not available, submission of a newly acquired biopsy (obtained at baseline) is requested when biopsy is safe and feasible.

The availability of tumor tissues is important to better characterize the relationship of tumor biology and response evaluation in this study. As such, this study is requesting submission of tumor tissue (newly biopsied or archived) to support correlative studies.

Pretreatment formalin-fixed paraffin-embedded tumor tissue obtained from the primary tumor or metastatic site should be provided as a block or (20) unstained slides. Due diligence should be used to make sure that tumor specimen (not a normal adjacent or a tumor margin sample) is provided. Pathology notes accompanying archival tissue may also be requested.

Tumor tissue will be examined for biomarkers that may include, but are not limited to, those related to locally advanced or unresectable or metastatic urothelial carcinoma, angiogenesis, docetaxel, and/or ramucirumab. Mutation profiling, copy number variability, gene expression, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations with these biomarkers and clinical outcomes.

Tumor samples that become available secondary to a surgical procedure or a biopsy during the study should be collected. Similar analysis as described for the baseline sample may be conducted.

The samples will be stored for a maximum of 15 years after the last patient visit for the study at a facility selected by the sponsor. Any block of original tumor tissue will be sectioned and returned to the site. Any slides submitted or cut from the block at a central laboratory will be discarded within 15 years after the last patient visit for the study.

#### 10.4.2.2. Plasma and Urine for Biomarkers

CCI





CCI

#### 10.4.2.3. Whole Blood for DNA Collection

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the availability of receptors, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis.

Sampling for this analysis will be a one-time collection (refer to [Attachment 7](#) for timing of the collection). Samples will be stored and analysis may be performed on genetic variants/copy number variations that are thought to play a role in locally advanced or unresectable or metastatic urothelial carcinoma, angiogenesis, docetaxel, and/or ramucirumab.

In the event of an unexpected AE or the observation of an unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to ramucirumab and/or docetaxel. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease, cancer-related conditions, and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation. Pharmacogenetic data will not be provided to the investigator or the patient except where required by local law.

#### 10.4.3. Samples for Immunogenicity Research

Blood samples for immunogenicity (anti-ramucirumab antibody) testing will be collected from all study patients to determine antibody production against ramucirumab (placebo) at baseline (before the first infusion of ramucirumab/placebo on Cycle 1, Day 1 of treatment); at specified time points during the study; and in the event of an IRR, as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event (see [Attachment 7](#)). Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of the ramucirumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ramucirumab.

When any immunogenicity sample is drawn, a sample for drug concentration measurement (PK) should also be drawn and analyzed to allow interpretation of immune response (see Section 10.4.4).

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

#### **10.4.4. Samples for Drug Concentration Measurements (Pharmacokinetics)**

Blood samples will be collected from all study patients to assess ramucirumab concentrations in serum, as specified in Attachment 7.

In the event of an IRR, every attempt should be made to collect a blood sample for anti-ramucirumab antibody and serum ramucirumab concentration determination at time points noted in Attachment 7.

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

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

## 11. 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.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

### 11.1. Data Capture System

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

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 generic laboratory system.

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 PRO measures (for example, a rating scale).

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

## 12. Sample Size and Statistical Methods

### 12.1. Determination of Sample Size

The primary objective of this study is to compare ramucirumab plus docetaxel with placebo plus docetaxel in terms of PFS in patients with locally advanced or unresectable or metastatic urothelial carcinoma who progressed on or after platinum-based therapy. The study will enroll approximately 524 patients in a 1:1 randomization (262 patients in the ramucirumab-plus-docetaxel arm and 262 patients in the placebo-plus-docetaxel arm). The primary analysis of PFS will be performed when a minimum of 331 PFS events have been observed from the first 437 randomized patients (that is, 24% censoring rate). If full enrollment is not reached at the point when 331 PFS events have been observed, the primary analysis will be performed when full enrollment is reached, on the number of PFS events observed upon full enrollment from the first 437 randomized patients. Although PFS is the primary endpoint, this study is powered on OS. Assuming an OS hazard ratio of 0.75, this sample size yields at least 80% statistical power to detect superiority of the ramucirumab-plus-docetaxel arm over the placebo-plus-docetaxel arm with the use of a 2-sided log-rank test and a 2-sided type I error of 0.05.

A gatekeeping design will be used to assess PFS, OS, and ORR. The PFS, OS, and ORR are tested in a sequential manner. The OS superiority is tested only if the PFS superiority test is significant. Likewise, the ORR superiority is tested only if the OS superiority test is significant. For OS, an interim analysis for efficacy is planned at time of PFS final analysis; the Bonferroni method will be used for alpha splitting, with  $\alpha=0.001$  (2-sided) spent at the interim analysis and  $\alpha=0.049$  (2-sided) spent at the final analysis for OS. Although the primary endpoint is PFS, the sample size is powered to show a superiority test for comparing OS between the 2 arms.

The sample size to test PFS superiority at the PFS final analysis is determined based on the following assumptions:

- The PFS hazard ratio for treatment group (ramucirumab plus docetaxel) versus control group (placebo plus docetaxel) is 0.70.
- The randomization ratio is 1:1.
- A 2-tailed significance level of 0.05.
- Control arm median PFS = 2 months.
- The type II error rate is 0.1, that is, the power of the trial is set to 90%.
- Enrollment rate is approximately 36.3 patients per month. This includes an estimated 25% chance of screen failure patients.

Under these assumptions, the estimated total number of PFS events at the PFS final analysis is 331, from an expected accrual of 371 patients. Assuming a 15% patient dropout rate from PFS follow-up, it is estimated that approximately 437 patients are needed to reach 331 PFS events in approximately 18.4 months.



The sample size to test OS superiority was determined based on the following assumptions:

- $\alpha = 0.049$  (2-sided), statistical power = 80%.
- The randomization ratio is 1:1.
- Control arm median OS = 9 months.
- HR=0.75
- Interim efficacy analysis for OS (at the PFS final analysis) with testing at  $\alpha = 0.001$  (2-sided).

Under these assumptions, the estimated total number of OS events at the final OS analysis is 382, from an expected accrual of 497 patients. Assuming a 5% dropout rate from survival follow-up, it is estimated that 524 patients will need to be randomized to reach 382 OS events in approximately 32.6 months.

At the PFS final analysis, the first 437 randomized patients will be used for the analysis. An interim OS analysis will be performed; all patients who have been randomized at that point will be used to compare OS between the 2 arms, based on Bonferroni alpha splitting of 0.001 (2-sided).

The final OS analysis is expected at 32.6 months from first patient enrollment. At the final analysis, all randomized patients will be used to compare OS between the 2 arms. The type I error spend for OS is 0.049 (2-sided), which approximately corresponds to observed HR <0.82.

The estimated number of events and efficacy boundaries and probabilities of first crossing the boundaries at each analysis are summarized in [Table JVDC.9](#). EAST<sup>®</sup> 6.2 is used to calculate the sample size and boundaries.

**Table JVDC.9. Study Design and Operating Characteristics**

Statistical Analysis		Primary PFS	Final OS
Duration of study (months)*		18.4	32.6
Estimated	# events	331	382
	# patients	437	524
	P value boundary	$p \leq 0.05$	$p \leq 0.049$
	Rejection boundary for HR	0.806	0.82

Abbreviations: HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

\* Estimated numbers.

## 12.2. Statistical and Analytical Plans

### 12.2.1. General Considerations

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All CIs will be given at a 2-sided 95% level, unless otherwise stated.

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. Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the SAP. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

If study data violate key statistical assumptions of an analysis method, alternative statistical methods may be used.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

#### 12.2.1.1. Analysis Populations

The following populations will be defined for this study:

- Intention-to-Treat 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 outcome analyses.
- Per-Protocol population: will include all patients who are randomized and received at least 1 cycle 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 SAP prior to database lock, and will be used for sensitivity analyses of OS and PFS; other efficacy endpoints may also be analyzed.
- 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 actual study treatment a patient has received, regardless of the arm to which he or she was randomized. The safety population will be used for all dosing/exposure, AEs, and resource utilization analyses.

#### 12.2.2. Patient Disposition

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

### **12.2.3. Patient Characteristics**

Description of patient characteristics at baseline, such as patient demographics, baseline disease characteristics, preexisting conditions, and prior therapies, will be reported using descriptive statistics.

### **12.2.4. Concomitant Therapy**

Concomitant medications will be summarized for the safety population.

#### **12.2.4.1. Postdiscontinuation Anticancer Therapy**

The numbers and percentages of patients reporting postdiscontinuation anticancer therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name, for the ITT population.

### **12.2.5. Treatment Compliance**

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

### **12.2.6. Primary Outcome and Methodology**

PFS time is defined as the time from randomization until the first radiographic documentation of progression as defined by RECIST 1.1, or death due to any cause, whichever is earlier.

The analysis of PFS will be based on stratified log-rank test, stratified by randomization strata (IWRS). The testing boundaries are summarized in [Table JVDC.9](#). The actual test boundary will be adjusted according to actual number of events. PFS survival curves, the median with 95% CI, and survival rates at various time points for each treatment group will be estimated using Kaplan-Meier method (Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model (Cox 1972), stratified by randomization strata (IWRS).

The first 437 randomized patients at final PFS analysis as primary analysis and all randomized patients at final PFS analysis as sensitivity analysis, according to the ITT principle, will be included in the analysis of this endpoint.

### **12.2.7. Other Analyses of Efficacy**

Other analyses of efficacy, including sensitivity analysis of the primary endpoint PFS, are described in the following subsections.

#### **12.2.7.1. Sensitivity Analysis for Progression-Free Survival**

The following sensitivity analyses will be performed for PFS:

- unstratified log-rank test and Cox regression models
- stratified log-rank test and Cox regression models, stratified by strata collected in the CRF
- analysis including both radiographic and symptomatic progressions as PFS events
- analysis for the per-protocol population
- sensitivity analysis for various PFS censoring rules (details will be provided in the SAP)

- at the primary analysis, sensitivity analysis using all PFS events from ITT population, that is, all PFS events from all patients randomized at the time of the primary analysis
- univariate and multivariate Cox regression model will be used to explore potential prognostic and/or predictive factors

#### **12.2.7.2. Overall Survival**

The analysis of OS will be based on stratified log-rank test, stratified by randomization strata (IWRS). The Bonferroni alpha splitting method will be used for type I error allocation to interim and final analyses. The expected events number and testing boundaries are summarized in [Table JVDC.9](#).

OS survival curves, the median with 95% CI, and survival rates at various time points for each treatment group will be estimated using Kaplan-Meier method (Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model, stratified by randomization strata (IWRS).

OS will be analyzed for all randomized patients (ITT population) at both the primary PFS and final analyses.

The following sensitivity analyses will be performed for OS:

- unstratified log-rank test and Cox regression models
- stratified log-rank test and Cox regression models, stratified by strata collected in the CRF
- analysis for the per-protocol population
- univariate and multivariate Cox regression model will be used to explore potential prognostic and/or predictive factors

Additional sensitivity analyses may be specified in the SAP.

#### **12.2.7.3. Objective Response Rate and Disease Control Rate**

The best overall response will be determined using the RECIST 1.1 guidelines.

The ORR will be calculated 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 group (ITT population). Additionally, a subgroup analysis will be performed for patients with measurable disease and for patients with nonmeasurable disease. Patients who do not have a tumor response assessment for any reason are considered as nonresponders and are included in the denominator when calculating the response rate. The ORR with 95% CI observed in each treatment group will be summarized and compared using the Cochran-Mantel-Haenszel test adjusting for the randomization strata at time of OS final analysis.

#### **12.2.7.4. Duration of Response**

The survival curves and medians with 95% CIs will be estimated using the Kaplan-Meier method and will be compared using Cox regression model and log-rank test. The analysis is for responders only.



#### **12.2.7.5. Other**

Additional exploratory analyses may be performed as deemed appropriate.

#### **12.2.8. Pharmacokinetic and Immunogenicity Analyses**

Serum concentrations of ramucirumab prior to infusion ( $C_{\min}$  [trough]) and at 1-hour post end of (ramucirumab) infusion (approximately  $C_{\max}$  [peak]) will be summarized using descriptive statistics. Additional analysis using the population pharmacokinetic approach may be conducted if deemed appropriate. Relationships between ramucirumab exposure and measures of efficacy and safety will be explored. Details will be provided in the SAP.

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

#### **12.2.9. Translational Research Analyses**

The profiles of biomarkers assessed over time will be summarized by treatment. The associations between biomarker measures with clinical outcomes will be analyzed.

#### **12.2.10. Health Outcomes Analyses**

The compliance of completing the questionnaires will be summarized at each scheduled assessment. Percentage compliance will be calculated based on the number of patients who completed the assessment divided by the number of patients expected (that is, still on study and alive). If there is a response to at least one item, the questionnaire will be considered completed. Reasons for noncompliance will be summarized.

##### **12.2.10.1. EORTC QLQ-C30**

Quality-of-life assessments will be scored according to the algorithm described in the EORTC QLQ-C30 Scoring Manual (Fayers et al. 2001). All scales and single items are scored on categorical scales and linearly transformed to 0-to-100 scales where:

- a high score for a functional scale represents a high or healthy level of functioning
- a high score for the global health status/QoL represents a high level of QoL
- a high score for a symptom scale or an item represents a high level of symptoms/problems

For each scale, time to deterioration will be estimated with the Kaplan-Meier method and analyzed with Cox regression models. Time to deterioration is defined as date of randomization to first worsening of  $\geq 10$  points. Patients without deterioration will be censored at their last non-deteriorated assessment.

For each scale, proportions of patients with improved or stable scores will be compared using Cochran-Mantel-Haenszel test adjusting for the randomization strata will be used, unless number of strata make Cochran-Mantel-Haenszel unstable, then a Fisher's Exact test will be used, with the ITT population as the denominator. Scores will be classified as improved or worsened if change from baseline is  $\geq 10$  points; change  $< 10$  points will be classified as stable.

Data will also be analyzed using descriptive statistics, including change from baseline.

**12.2.10.2. EQ-5D-5L**

The index score will be calculated from a set of item weights to derive a score based on a scale of 0 to 1, with 0 representing death and 1 representing the best health status; negative scores are possible. Item weights for the 5-level version of the EQ-5D are still being developed, but will be described in the SAP prior to final analysis. Responses to the 5 dimensions will be summarized. Descriptive statistics for the index and VAS will be calculated.

**12.2.11. Safety Analyses**

All safety summaries and analyses will be based upon the safety population as defined in Section 12.2.1, unless otherwise indicated, and include:

- Treatment-emergent AEs will be summarized by MedDRA System Organ Class/Preferred Term, classified from verbatim terms. The incidence and percentage of patients with at least one occurrence of a Preferred Term will be included, according to the most severe NCI-CTCAE v 4.0 grade. Causality (relationship to study drug), action taken, severity or CTCAE grade, and outcome will be summarized separately. Duration of TEAE will be determined and included in the listings.
- Study drug exposure will be summarized for each arm with following variables: number of infusions (except docetaxel), number of cycles, duration of therapy, cumulative dose, dose intensity, and relative dose intensity.
- Laboratory results will be classified according to the NCI-CTCAE, v 4.0. Incidence of laboratory abnormalities will be summarized.
- Hospitalizations and transfusions will be summarized.
- Vital signs will be summarized.

Additionally, the following (but not limited to) safety-related outcomes will be summarized: study treatment discontinuations due to TEAEs, deaths, and SAEs.

**12.2.12. Subgroup Analyses**

Subgroup analyses of PFS and OS may be performed for the following subgroup variables:

- Sex (males vs females)
- Age (<65 year vs ≥65 years)
- Race (white vs Asian vs all others)
- Geographical region (North America, Europe, rest of world)
- ECOG performance status (0 vs 1)
- Time from diagnosis to randomization
- Prior immune checkpoint inhibitor (Y/N)
- Primary tumor location (bladder vs kidney/ureter/urethra)
- Visceral metastasis (Y/N), where metastases involve the liver, lung, and/or bone
- Specific sites of metastases (Y/N)
- Hemoglobin level (<10 g/dL, ≥10 g/dL)

If number of patients in a subgroup is too small for an informative analysis, that particular subgroup may be omitted or combined with other subgroups. Other subgroup analyses may be performed as deemed appropriate.

### **12.2.13. Interim Analyses**

In this study, the following interim analyses will be performed:

- An unblinded safety analysis after at least 100 and 250 evaluable patients total have either started treatment in Cycle 3 or discontinued all study treatment prior to Cycle 3 due to any reasons. Additional safety reviews may be done at the discretion of the IDMC.
- Analysis for OS interim (based on all randomized patients) will be performed at the time of PFS final analysis.

#### **12.2.13.1. Predefined Time Points for IDMC Safety Reviews**

An independent data monitoring committee (IDMC) will be established to conduct safety reviews. The membership, roles, and responsibilities of the IDMC are defined in the IDMC Charter.

There will be no prespecified rules for stopping or modifying the trial due to safety concerns. The IDMC members will review unblinded safety data at prespecified time points to determine whether there are sufficient safety concerns to justify modifying the study or the termination of study treatment and/or enrollment.

Only the IDMC is authorized to evaluate unblinded safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Unblinding details are provided in the blinding section of the protocol (Section 9.5).

IDMC safety reviews will be performed for **all randomized** patients at the following time points:

- After at least 100 and 250 patients total have either started treatment in Cycle 3 or discontinued all study treatment prior to Cycle 3 due to any reasons. Additional safety reviews may be done annually, adjusted at the discretion of the IDMC.
- The IDMC will evaluate unblinded safety data to make recommendations for study modification, if required. Details on the process flow/communication plan are provided in the IDMC Charter.

Patient enrollment will continue during data assessment by the IDMC.

#### **12.2.13.2. Predefined Time Points for Lilly Efficacy Reviews**

Lilly will conduct one OS interim efficacy analysis during study conduct. The interim efficacy analysis for OS will occur at time of PFS final analysis.

The multiple testing and gatekeeping approach to be used in this study, including testing (alpha) levels at the primary and final analyses, is summarized in [Table JVDC.9](#). All the testing boundaries will be adjusted based on actual number of events at each analysis.

All interim analyses will include complete assessments of safety-related data. Pharmacokinetic data will be available for PFS final analysis only and not for the safety interim analyses at 100 and 250 patients.



## 13. Informed Consent, Ethical Review, and Regulatory Considerations

### 13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including 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.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or, where permitted by local law or regulation, by the patient's legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drugs.

As used in this protocol, the term "informed consent" includes all consent given by patients or their legal representatives.

### 13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at the investigative sites. All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative sites.

The study site's ERBs should be provided with the following, at a minimum:

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

### 13.3. 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
- ICH GCP Guideline (E6)
- applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

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

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

### **13.3.1. Investigator Information**

Physicians with a specialty or experience in treating patients with urological malignancies will participate as investigators in this clinical trial.

### **13.3.2. Protocol Signatures**

The sponsor'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.

### **13.3.3. Final Report Signature**

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 chosen by Lilly or a designee 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 sign/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.

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## Attachment 1. Protocol JVDC Study Schedule

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**Study Schedule, Protocol I4T-MC-JVDC**

Perform procedure as indicated in the following schedules.

Baseline Schedule, I4T-MC-JVDC

Procedure Category	Protocol Section or Attachment	Procedure	Baseline		Comments
			Cycle	BL	
			Visit	0	
			Relative day to Cycle 1, Day 1 (unless indicated otherwise)	≤28      ≤7	
Study Entry/ Enrollment	7.1, 13.1	Informed consent form signed	X		ICF must be signed prior to performance of any protocol-specific tests/procedures.
	7.1, 7.2, 9.3, 12.2.12	Inclusion/exclusion evaluation and IWRS randomization	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	7.1, 7.2, 10.3, 10.3.1, 10.3.1.1, 12.2.3	Initial history/preexisting conditions	X		
	12.2.3, 12.2.12	Demography	X		
	7.1, 7.2	Historical illnesses	X		
Physical Examination		Height	X		Height measurement to be performed at baseline only.
	9.4	Weight	X		
	7.2, 9.4.1.1.2, 10.3.1, 12.2.11	Blood pressure/pulse	X		
	7.1, 9.3, 12.2.12, Att 4	ECOG performance status	X		
Brain Scan	7.2	CT with contrast or MRI	X		To be performed only after study eligibility is confirmed, to detect the presence of intracranial metastasis.
Patient-Reported Outcomes	10.2.1, 12.2.10.1	EORTC QLQ-C30 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 EORTC QLQ-C30 completed first, followed by the EQ-5D-5L.
	10.2.2, 12.2.10.2	EQ-5D-5L questionnaire	X		
Efficacy Assessment	10.1, 10.1.1, Att 6	Radiologic imaging (according to RECIST 1.1) and tumor measurement	X*		Imaging studies include a CT scan of the chest and a contrast-enhanced CT scan of the abdomen and pelvis or an equivalent MRI scan. Routine bone scans should be performed only in the setting of bone disease, or as deemed appropriate if there is clinical suspicion of new or worsening bone metastases. * To be performed within 28 days prior to randomization.
Adverse Events	10.3, 10.3.1, 10.3.1.1, 10.3.3, 12.2.11	AE collection and CTCAE grading	X		Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.
Concomitant Medications	9.6, 12.2.4	Concomitant medication notation	X		

Procedure Category	Protocol Section or Attachment	Procedure	Baseline		Comments
			Cycle		
			Visit		
			Relative day to Cycle 1, Day 1 (unless indicated otherwise)		
			BL		
			0		
			≤28	≤7	
Laboratory/ Diagnostic Tests	10.3.1, 10.3.3, 10.4.1, 12.2.11, 12.2.12, Att 2	Hematology	X		
	10.3.1, 10.3.3, 10.4.1, 12.2.11, Att 2	Chemistry	X		Central laboratory results to be used to determine eligibility.
	10.3.1, 10.3.3, 10.4.1, 12.2.11, Att 2	Coagulation	X		
	7.2, 10.3.1, 10.4.1, Att 2	Pregnancy test		X*	Serum β-hCG (minimum sensitivity 25 IU/L or equivalent units of β-hCG). Pregnancy test results will not be collected on the CRF. * To be performed within 7 days prior to randomization.
	7.1, 10.3.1, 10.3.3, 10.4.1, 12.2.11, Att 2	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.
	7.1, 10.4.2.1, 12.2.9, Att 7	Tumor tissue (requested; mandatory where applicable)	Refer to Attachment 7.		If prior archived tumor specimens are available, and unless restricted by local regulations, submission of archived tumor tissue is mandatory. If an archived specimen is not available, submission of a newly acquired specimen is requested when biopsy is safe and feasible.
	7.1, 10.4.2.2, 12.2.9, Att 7	Urine samples (biomarkers)	Refer to Attachment 7.		
	7.1, 10.4.2.3, 12.2.9, Att 7	Whole blood for DNA sample (pharmacogenetic analysis)	Refer to Attachment 7.		
	10.3.1, 10.3.2.1	ECG	X		

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; Att = Attachment; BL = baseline; CRF = case report form; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; ICF = informed consent form; IWRS = interactive web response system; MRI = magnetic resonance imaging; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = serious adverse event.

Treatment Period Schedule, I4T-MC-JVDC

		Treatment Period		Comments	
		1-6	7-N		
		1-6	7-N		
		1	1		
				Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.	
Procedure Category	Protocol Section or Attachment	Procedure			
Physical Examination	9.4	Weight	X	X	BSA to be calculated, as needed, at each cycle until docetaxel is discontinued. (If the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior dose, the BSA will not need to be recalculated.)
	9.4.1.1.2, 10.3.1, 12.2.11	Blood pressure/pulse	X	X	
	9.3, 12.2.12, Att 4	ECOG performance status	X	X	
Patient-Reported Outcomes	10.2.1, 12.2.10.1	EORTC QLQ-C30 questionnaire	X	X	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 EORTC QLQ-C30 completed first, followed by the EQ-5D-5L. Patients do not need to complete prior to Cycle 1, if completed at baseline.
	10.2.2, 12.2.10.2	EQ-5D-5L questionnaire	X	X	
Efficacy Assessment	10.1, 10.1.1, Att 6	Radiologic imaging (according to RECIST 1.1) and tumor measurement	X*	X*	<p>*To be performed according to the following timing (also stated in Section 10.1): Every 6 weeks (±7 days) after randomization (regardless of treatment delays) during the Study Treatment Period, until disease progression OR overall study completion OR 1 year after randomization, whichever occurs first. In addition, any patient whose disease has not progressed by 1 year 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 1 year after randomization, until disease progression OR overall study completion OR 3 years after randomization, whichever occurs first; then as per standard clinical practice after that.</p> <p>Imaging studies include a CT scan of the chest and a contrast-enhanced CT scan of the abdomen and pelvis or an equivalent MRI scan. Throughout the study, use the same imaging modality used at baseline. Routine bone scans should be performed only in the setting of bone disease, or as deemed appropriate if there is clinical suspicion of new or worsening bone metastases.</p>
Adverse Events	10.3, 10.3.1, 10.3.1.1, 10.3.3, 12.2.11	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.
Concomitant Medications	9.6, 12.2.4	Concomitant medication notation	X	X	



		Treatment Period		Comments
Cycle (21-day cycle)		1-6	7-N	
Visit		1-6	7-N	
Relative day within a cycle		1	1	
Procedure Category	Protocol Section or Attachment	Procedure		
Premedication	9.1.1, 9.1.1.1, 9.1.1.2	Premedication notation	X	X
Study Drug	9.1, 9.1.2.1, 9.2.1, 9.3, 9.4, 9.4.1.1, 9.7, 12.2.11	Ramucirumab/Placebo	X*	X
	9.1, 9.1.2.2, 9.3, 9.4, 9.4.1.2, 9.7, 12.2.11	Docetaxel	X*	(X)†

Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.

Ramucirumab/Placebo: Premedication is required for all patients prior to each infusion of ramucirumab or placebo.  
Docetaxel: Premedication is required for 3 days starting 1 day prior to infusion of docetaxel.

\*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 and not more than 72 hours prior to Day 1.  
Treatment with ramucirumab or placebo (monotherapy) may continue on cycles until at least one discontinuation criterion is met.

†Treatment with docetaxel may continue for up to six 21-day cycles; further cycles of docetaxel (up to 4 additional cycles [maximum of 10 cycles total]) may be administered if adequate disease response (that is, SD or better [PR, CR], based on the investigator's assessment) is observed and with approval of the Lilly CRP/CRS or designee.

Procedure Category	Protocol Section or Attachment	Procedure	Treatment Period		Comments	
			Cycle (21-day cycle)	1-6		7-N
			Visit	1-6		7-N
			Relative day within a cycle	1		1
					Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.	
Laboratory/ Diagnostic Tests	10.3.1, 10.3.3, 10.4.1, 12.2.11, 12.2.12, Att 2	Hematology	X	X		
	10.3.1, 10.3.3, 10.4.1, 12.2.11, Att 2	Chemistry	X	X	Local chemistry laboratory results will be used for dosing decisions; the tests scheduled on the study protocol must also be performed by the central laboratory. Pretreatment laboratory data may not be older than 72 hours (Day 1 of each cycle).	
	10.3.1, 10.3.3, 10.4.1, 12.2.11, Att 2	Coagulation	X			
	10.3.1, 10.4.1, Att 2	Pregnancy test	X*	X*	* 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.	
	10.3.3, Att 3	Hepatic monitoring	(X)*	(X)*	* Hepatic monitoring tests (per Attachment 3; performed by Lilly-designated [central] laboratory) may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly CRP/CRS or designee.	
	10.4.4, 12.2.8, Att 7	PK	Refer to Attachment 7.		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.	
	10.4.3, 12.2.8, Att 7	Immunogenicity: Anti-ramucirumab antibodies				
	10.4.2.1, 12.2.9, Att 7	Tumor tissue (requested)	Refer to Attachment 7.		At any time during the study, if tumor tissue becomes available, a sample should be provided.	
10.4.2.2, 12.2.9, Att 7	Plasma and urine samples (biomarkers)	Refer to Attachment 7.				

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; Att = Attachment; BSA = body surface area; CR = complete response; CRF = case report form; CRP = (Lilly) clinical research physician; CRS = (Lilly) clinical research scientist; CT = computed tomography; CTC/AE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PK = pharmacokinetic(s); PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = serious adverse event; SD = stable disease; WOCBP = women of childbearing potential.

Postdiscontinuation Follow-up Schedule, I4T-MC-JVDC

		Postdiscontinuation Follow-up			Comments
		Cycle	Short-term Follow-up	Long-term Follow-up	
		Visit	801	802-8XX	
		Duration	Refer to footnote for duration	Refer to footnote for duration	
Procedure Category	Protocol Section or Attachment	Procedure			
Physical Examination		Weight	X		
	9.4.1.1.2, 10.3.1, 12.2.11	Blood pressure/pulse	X		
	9.3, 12.2.12, Att 4	ECOG performance status	X		
Patient-Reported Outcomes	10.2.1, 12.2.10.1	EORTC QLQ-C30 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 EORTC QLQ-C30 completed first, followed by the EQ-5D-5L.
	10.2.2, 12.2.10.2	EQ-5D-5L questionnaire	X		
Efficacy Assessment	10.1, 10.1.1, 10.1.2, Att 6	Radiologic imaging (according to RECIST 1.1) and tumor measurement	X	X	<p>Patients who discontinue study treatment for any reason other than disease progression will continue to undergo radiographic tumor assessments according to the following timing (also stated in Section 10.1), by the same method used at baseline and throughout the study:</p> <p>Every 6 weeks (<math>\pm 7</math> days) until disease progression OR overall study completion OR 1 year after randomization, whichever occurs first. In addition, any patient whose disease has not progressed by 1 year after randomization will be evaluated for response every 12 weeks (<math>\pm 7</math> days) from 1 year after randomization, until disease progression OR overall study completion OR 3 years after randomization, whichever occurs first; then as per standard clinical practice after that.</p> <p>After the patient has objective disease progression, radiologic tests are no longer required and the patient will be followed for survival every 3 months (<math>\pm 7</math> days) until the patient's death or overall study completion, whichever occurs first.</p> <p>Imaging studies include a CT scan of the chest and a contrast-enhanced CT scan of the abdomen and pelvis or an equivalent MRI scan. Throughout the study, use the same imaging modality used at baseline. Routine bone scans should be performed only in the setting of bone disease, or as deemed appropriate if there is clinical suspicion of new or worsening bone metastases.</p>

Procedure Category	Protocol Section or Attachment	Procedure	Postdiscontinuation Follow-up		Comments	
			Short-term Follow-up	Long-term Follow-up		
			Visit	801		802-8XX
			Duration	Refer to footnote for duration		Refer to footnote for duration
Survival information	7.3.4, 8.1, 10.1.2	Collection of survival information	X	X	Collection of survival data every 3 months ( $\pm 7$ days) until the patient's death or overall 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	10.3, 10.3.1, 10.3.1.1, 10.3.3, 12.2.11	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. During Postdiscontinuation Long-term Follow-up, only SAEs that are related to protocol procedures or study treatment will be collected.	
Concomitant Medications	9.6, 12.2.4	Concomitant medication notation	X			
Laboratory/ Diagnostic Tests	10.3.1, 10.3.3, 10.4.1, 12.2.11, 12.2.12, Att 2	Hematology	X			
	10.3.1, 10.3.3, 10.4.1, 12.2.11, Att 2	Chemistry	X			
	10.3.1, 10.3.3, 10.4.1, 12.2.11, Att 2	Coagulation	X			
	10.3.1, 10.3.3, 10.4.1, 12.2.11, Att 2	Urinalysis	X		Routine dipstick measurements, and if clinically indicated, microscopic analysis. If urine dipstick or routine analysis indicates proteinuria $\geq 2+$ at evaluations, a 24-hour urine collection (to assess protein) must be obtained.	
	10.3.3, Att 3	Hepatic monitoring	(X)*		* Hepatic monitoring tests (per Attachment 3; performed by Lilly-designated [central] laboratory) may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly CRP/CRS or designee.	
	10.4.4, 12.2.8, Att 7	PK	Refer to Attachment 7.			
	10.4.3, 12.2.8, Att 7	Immunogenicity: Anti-ramucirumab antibodies				
10.4.2.2, 12.2.9, Att 7	Plasma and urine samples (biomarkers)					



Procedure Category	Protocol Section or Attachment	Procedure	Postdiscontinuation Follow-up		Comments	
			Short-term Follow-up	Long-term Follow-up		
			Visit	801		802-8XX
			Duration	Refer to footnote for duration		Refer to footnote for duration
Other	12.2.4.1	Collection of postdiscontinuation anticancer therapy	X	X		

Abbreviations: AE = adverse event; Att = Attachment; CRP = (Lilly) clinical research physician; CRS = (Lilly) clinical research scientist; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; MRI = magnetic resonance imaging; OS = overall survival; PK = pharmacokinetic(s); RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAEs = serious adverse events.

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 overall 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 10.1, 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 overall 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 overall study completion, whichever occurs first.

Continued Access Schedule, I4T-MC-JVDC

Procedure Category	Protocol Section or Attachment	Procedure	Continued Access Period		Comments
			Treatment Period	Continued Access Follow-up	
			Cycle	Follow-up	
			Visit	901	
			X-Y		
			501-5XX	901	
		Relative day within a cycle	1		
Physical Examination	9.4	Weight	X		BSA to be calculated at each cycle until docetaxel is discontinued.
Adverse Events	10.3, 10.3.1, 10.3.1.1, 10.3.3, 12.2.11	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.
Laboratory/Diagnostic Tests	10.4.4, 12.2.8, Att 7 10.4.3, 12.2.8, Att 7	PK Immunogenicity: Anti-ramucirumab antibodies	Refer to Attachment 7.		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.
Premedication	9.1.1, 9.1.1.1, 9.1.1.2	Premedication notation	X		Ramucirumab: Premedication is required for all patients prior to each infusion of ramucirumab or placebo. Docetaxel: Premedication is required for 3 days starting 1 day prior to infusion of docetaxel.
Study Drug	8.1.2, 9.1, 9.1.2.1, 9.2.1, 9.3, 9.4, 9.4.1.1, 9.7, 12.2.11	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 7.3). During the Continued Access Period, placebo will no longer be administered, the decision to permit crossover or not will be made by Lilly after the final analysis of OS is completed.
	8.1.2, 9.1, 9.1.2.2, 9.3, 9.4, 9.4.1.2, 9.7, 12.2.11	Docetaxel	X		

Abbreviations: AE = adverse event; Att = Attachment; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction; PK = pharmacokinetics; OS = overall survival; 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.

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## Attachment 2. Protocol JVDC Clinical Laboratory Tests

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### Clinical Laboratory Tests

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#### Hematology<sup>a</sup>:

Hemoglobin (HGB)  
 Hematocrit (HCT)  
 Erythrocytes (RBC)  
 Mean corpuscular volume (MCV)  
 Mean corpuscular hemoglobin concentration (MCHC)  
 Leukocytes (WBC)  
 Neutrophils<sup>c</sup>  
 Lymphocytes  
 Monocytes  
 Eosinophils  
 Basophils  
 Platelets (PLT)

#### Coagulation<sup>a,d</sup>:

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

#### Urinalysis<sup>a</sup>:

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

#### Other<sup>b</sup> (see Attachment 7):

Anti-ramucirumab antibody (immunogenicity)  
 Ramucirumab concentrations in serum (PK)  
 Translational research/biomarkers

#### Clinical Chemistry<sup>a,b</sup>

##### Serum Concentrations of:

Sodium  
 Magnesium  
 Potassium  
 Bilirubin, total  
 Bilirubin, direct  
 Uric acid  
 Alkaline phosphatase  
 Alanine aminotransferase (ALT)  
 Aspartate aminotransferase (AST)  
 Blood urea nitrogen (BUN)  
 Creatinine  
 Calcium  
 Glucose, random  
 Albumin  
 Total protein  
 Lactate dehydrogenase  
 Chloride  
 Phosphorus

#### Pregnancy Test (WOCBP only)<sup>a,e</sup>

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Abbreviations:  $\beta$ -hCG = beta human chorionic gonadotropin; aPTT = activated partial thromboplastin time; CRF = case report form; INR = international normalized ratio; PK = pharmacokinetic(s); PT = prothrombin time; RBC = red blood cells; WBC = white blood cells; WOCBP = women of childbearing potential.

- <sup>a</sup> Assayed by local or investigator-designated laboratory.
- <sup>b</sup> Assayed by Lilly-designated (central) laboratory.
- <sup>c</sup> 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.
- <sup>d</sup> For coagulation parameters PT and PTT/aPTT, the laboratory selected for each at baseline should be followed throughout the study.
- <sup>e</sup> 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  $\beta$ -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.

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## Attachment 3. Protocol JVDC Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

### Hepatic Monitoring Tests

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<p><b>Hepatic Hematology<sup>a</sup></b>            Hemoglobin (HGB)            Hematocrit (HCT)            Erythrocytes (RBC)            Leukocytes (WBC)            Neutrophils<sup>b</sup>            Lymphocytes            Monocytes            Eosinophils            Basophils            Platelets (PLT)</p> <p><b>Hepatic Chemistry<sup>a</sup></b>            Total bilirubin            Direct bilirubin            Alkaline phosphatase            Alanine aminotransferase (ALT)            Aspartate aminotransferase (AST)            Gamma glutamyl transferase (GGT)            Creatine phosphokinase (CPK)</p>	<p><b>Haptoglobin<sup>a</sup></b></p> <p><b>Hepatic Coagulation<sup>a</sup></b>            Prothrombin time            Prothrombin time, INR</p> <p><b>Hepatic Serologies<sup>a,c</sup></b>            Hepatitis A antibody, total            Hepatitis A antibody, IgM            Hepatitis B surface antigen            Hepatitis B surface antibody            Hepatitis B Core antibody            Hepatitis C antibody            Hepatitis E antibody, IgG            Hepatitis E antibody, IgM</p> <p><b>Anti-nuclear antibody<sup>a</sup></b></p> <p><b>Anti-smooth muscle antibody<sup>a</sup></b></p>
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Abbreviations: CRP = (Lilly) clinical research physician; CRS = (Lilly) clinical research scientist;

Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

<sup>a</sup> Assayed by Lilly-designated (central) laboratory.

<sup>b</sup> 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.

<sup>c</sup> Reflex/confirmation dependent on regulatory requirements and/or testing availability.



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**Attachment 4. Protocol JVDC ECOG Performance Status**

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<b>Activity Status</b>	<b>Description</b>
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, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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Source: Oken et al. 1982.

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## Attachment 5. Protocol JVDC Creatinine Clearance Formula

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**Note:** This formula (or another standard formula) may be used for calculating creatinine clearance (CrCl) from **local laboratory results only**.

*For serum creatinine  
concentration in mg/dL:*

$$\text{CrCl} = \frac{(140 - \text{age}^a) \times (\text{wt}) \times 0.85 \text{ (if female), or } \times 1.0 \text{ (if male)}}{72 \times \text{serum creatinine (mg/dL)}} \text{ (mL/min)}$$

*For serum creatinine concentration in  $\mu\text{mol/L}$ :*

$$\text{CrCl} = \frac{(140 - \text{age}^a) \times (\text{wt}) \times 0.85 \text{ (if female), or } \times 1.0 \text{ (if male)}}{0.81 \times \text{serum creatinine } (\mu\text{mol/L})} \text{ (mL/min)}$$

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<sup>a</sup> age in years, weight (wt) in kilograms.

Reference: Cockcroft and Gault 1976.

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## Attachment 6. Protocol JVDC RECIST Criteria 1.1

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Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

### **Measurability of Tumor at Baseline**

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

#### ***Measurable***

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness  $\leq 5$  mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan thickness recommended to be  $\leq 5$  mm).

#### ***Nonmeasurable***

All other lesions, including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

#### ***Special Considerations for Lesion Measurability***

##### Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

**Baseline Documentation of Target and Non-Target Lesion*****Target Lesions***

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of  $\geq 15$  mm by CT scan. All measurements are to be recorded in the case record form (CRF) in millimeters (or decimal fractions of centimeters [cm]).

***Nontarget Lesions***

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as ‘present,’ ‘absent,’ or in rare cases ‘unequivocal progression.’ In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis  $\geq 10$  mm but  $< 15$  mm should be considered nontarget lesions. Nodes that have a short axis  $< 10$  mm are considered nonpathological and are not recorded or followed.

**Specifications by Methods of Measurement**

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is



should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with I.V. contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without I.V. contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

*Clinical Lesions:* Clinical lesions will only be considered measurable when they are superficial and  $\geq 10$  mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

*Chest X-ray:* Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

*CT and MRI:* CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is  $\leq 5$  mm. When CT scan have slice thickness  $> 5$  mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

*Ultrasound:* Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

*Endoscopy, Laparoscopy:* The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

*Tumor Markers:* Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

*Cytology, Histology:* These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

*Pet Scan (FDG-PET, PET CT):* PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

*Bone Scan:* If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

## **Response Criteria**

### ***Evaluation of Target Lesions***

*Complete Response (CR):* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

*Partial Response (PR):* At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

*Progressive Disease (PD):* At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

*Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD (for a minimum of 5 weeks from randomization), taking as reference the smallest sum diameters while on study.

*Not Evaluable:* When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

***Evaluation of Nontarget Lesions***

*Complete Response:* Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10 mm short axis).

*Non-CR/ non-PD:* Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

*Progressive Disease:* Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

*Not Evaluable:* When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

**Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

***Time Point Response***

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

**Table 1. Time Point Response: Patients with Target (± Nontarget) Disease**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable.



Table 2 is to be used when patients have *nonmeasurable* disease only.

**Table 2. Time Point Response: Patients with Nontarget Disease Only**

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD <sup>a</sup>
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease; NE = inevaluable.

<sup>a</sup> non-CR/non-PD is preferred over SD for nontarget disease.

### Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

### Confirmatory Measurement/Duration of Response

#### *Confirmation:*

The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed.

In randomized trials (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from randomization.

#### *Duration of Overall Response*

The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

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

#### *Duration of Stable Disease*

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met (minimum interval not less than 5 weeks from Day 1 must be achieved), taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).



**Independent Review of Response and Progression**

When objective response (CR + PR) is the primary endpoint, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

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## **Attachment 7. Protocol JVDC Pharmacokinetic, Immunogenicity, and Translational Research Sampling Schedule Sampling Schedule**

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It is essential that the exact infusion start and stop times (actual clock readings) 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.

Pharmacokinetic, Immunogenicity, and Translational Research Sampling Schedule

		Baseline	Study Treatment Period (21-day cycles)							Post-DC Follow-up
			Cycle 1, Day 1		Cycle 2, Day 1	Cycle 3, Day 1	Cycle 5, Day 1	Cycle 9, Day 1		
			<i>1st infusion</i>		<i>2nd infusion</i>	<i>3rd infusion</i>	<i>5th infusion</i>	<i>9th infusion</i>		
Sample for:	Protocol Section	≤28 days	Pre-inf	Post-inf	Pre-inf	Pre-inf	Pre-inf	Pre-inf	Post-inf	Short-term Follow-up <sup>a</sup>
PK <sup>b</sup>	10.4.4		X <sup>c</sup>	X <sup>d</sup>	X <sup>c</sup>	X <sup>c</sup>	X <sup>c</sup>	X <sup>c</sup>	X <sup>d</sup>	X
Immunogenicity <sup>b</sup>	10.4.3		X <sup>c</sup>			X <sup>c</sup>				X
Tumor tissue	10.4.2.1	X <sup>e</sup>								
Plasma for biomarkers	10.4.2.2		X			X				X <sup>f</sup>
Urine for biomarkers	10.4.2.2	X				X				X
Whole blood sample for DNA analysis	10.4.2.3	X <sup>g</sup>								

Abbreviations: DC = discontinuation; DNA = deoxyribonucleic acid; EDTA = ethylenediaminetetraacetic acid; inf = infusion; IRR = infusion-related reaction; PK = pharmacokinetic(s).

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

Note: For all samples collected prior to an infusion, it is recommended that samples be collected after it is confirmed that the patient is qualified to receive the infusion at that time point.

- a Short-term Follow-up begins the day after the patient and the investigator agree that the patient will no longer continue (any) study treatment (during the Study Treatment Period) and lasts approximately 30 days (until the [30-day] Short-term Follow-up visit is completed).
- b If a patient experiences an IRR at any time while on study treatment (including during the Continued Access Period), separate blood samples for immunogenicity (anti-ramucirumab antibody) and PK analysis should be drawn, within 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.
- c At Cycle 1, Day 1: A preinfusion sample is to be drawn at any time prior to the first (ramucirumab/placebo) infusion. For all other time points: A preinfusion sample is to be drawn within 4 hours prior to the beginning of the infusion. The exact time of collection of each blood sample needs to be recorded.
- d A postinfusion sample is to be drawn within 0.5 hours after the completion of the ramucirumab/placebo infusion. The exact time of collection of each blood sample needs to be recorded.

**Pharmacokinetic, Immunogenicity, and Translational Research Sampling Schedule (concluded)**

- e If prior archived tumor specimens are available, and unless restricted by local regulations, submission of archived tumor tissue is mandatory. If an archived specimen is not available, submission of a newly acquired biopsy is requested when biopsy is safe and feasible. In addition, at any time during the study, if tumor tissue becomes available, a sample should be provided.
- f When applicable, EDTA plasma should be collected as near as possible to the time of disease progression, during the Study Treatment Period. If, for any reason, the post-progression sample cannot be collected at the time of progression, it should be collected at (or by) the (30-day) Short-term Follow-up visit. The post-progression sample should be collected before the initiation of any new anticancer therapy.
- g Collected at baseline (preferred) or at later visits.



## Attachment 8. Protocol JVDC 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, I.V. 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, I.V. 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: I.V. = intravenous(ly); NSAIDs = nonsteroidal anti-inflammatory drugs.