I4T-MC-JVDF(b) Clinical Protocol

An Open-Label, Multicenter, Phase 1 Study of Ramucirumab plus Pembrolizumab in Patients with Locally Advanced and Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma, Non-Small Cell Lung Cancer, Transitional Cell Carcinoma of the Urothelium, or Biliary Tract Cancer

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Ramucirumab (LY3009806) and Pembrolizumab (MK3475)

This is an open-label, multicenter, Phase 1 study of ramucirumab plus pembrolizumab: Phase 1a (dose-limiting toxicity) and Phase 1b (safety and preliminary efficacy) will include patients with locally advanced and unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma, non-small cell lung cancer, or transitional cell carcinoma of the urothelium.

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Protocol Electronically Signed and Approved by Lilly on 30 April 2015.
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Approval Date: 11-Feb-2016 GMT

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1. Synopsis

Title of Study: An Open-Label, Multicenter, Phase 1 Study of Ramucirumab plus Pembrolizumab in Patients with Locally Advanced and Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma; Non-Small Cell Lung Cancer; Transitional Cell Carcinoma of the Urothelium; or Biliary Tract Cancer

Summary of Study Design:

Study I4T-MC-JVDF is an open-label, multicenter Phase 1 study to evaluate the safety and efficacy of ramucirumab in combination with pembrolizumab. Phase 1a (dose-limiting toxicity [DLT]) and Expansion Phase 1b (safety and preliminary efficacy) will include patients with locally advanced and unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma; non-small cell lung cancer (NSCLC); transitional cell carcinoma of the urothelium (urothelial cancer); or biliary tract cancer (BTC). If sufficient tolerability and preliminary efficacy are demonstrated in Phase 1, the protocol will be amended to further evaluate efficacy and safety, and re-submitted accordingly.

Objective(s)/Endpoints

	Objectives	**Endpoints**
Phase 1a and 1b	**Primary:** To assess the safety and tolerability of 2 dosing regimens of ramucirumab plus pembrolizumab	Dose-limiting toxicities, observed during a 21-day treatment cycle **Safety (include but are not limited to):** TEAEs, SAEs, deaths, laboratory abnormalities, vital signs, and physical exams
	Secondary: To characterize the PK of ramucirumab when co-administered with pembrolizumab	**PK:** C_{min} and approximate C_{max} of ramucirumab in serum
Phase 1b	**Secondary:** To assess the preliminary efficacy of ramucirumab plus pembrolizumab	**Efficacy:** • ORR (RECIST 1.1 and irRECIST) • DCR, DOR, TTR, PFS, and OS

Abbreviations: C_{max} = maximum concentration; C_{min} = minimum concentration; DCR = disease control rate; DOR= duration of response; irRECIST= immune-related RECIST; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria In Solid Tumors; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events; TTR = time to response.

Treatment Arms and Duration:

DLT Phase 1a

Patients will be treated for up to 21 days (1 cycle); patients without a DLT may continue in Expansion Phase 1b.

Dosing Schedules

- **Schedule 1:** ramucirumab 8 mg/kg on Day 1 and Day 8 and pembrolizumab 200 mg (fixed dose) on Day 1, in 3 patients with gastric-gastroesophageal (GEJ) cancer or biliary tract cancer (BTC)
- **Schedule 2:** ramucirumab 10 mg/kg and pembrolizumab 200 mg (fixed dose) on Day 1, in 3 patients with either gastric-GEJ, NSCLC, or urothelial cancer

Number of patients: up to 12 DLT-evaluable patients (up to 6 enrolled in each dosing schedule)

Expansion Phase 1b

Duration: Continues until approximately 2 years after the first patient received study treatment. Individual patients may continue treatment for up to 35 cycles (approximately 2 years), until confirmed progressive disease or discontinuation for any other reason.

Treatment Cohorts

- **Schedule 1 Dose:**
  - **Gastric-GEJ (2nd - 3rd Line) Cohort A (15 patients),**
  - **BTC (2nd - 3rd Line) Cohort A1 (25 patients), and**
  - **Gastric-GEJ (1st Line) Cohort A2 (25 patients).**
- **Schedule 2 Dose:**
  - **Gastric-GEJ (2nd - 3rd Line) Cohort B (15 patients),**
  - **NSCLC (2nd - 4th Line) Cohort C (25 patients),**
  - **Urothelial (2nd - 4th Line) Cohort D (25 patients), and**
  - **NSCLC (1st Line) Cohort E (25 patients).**

Number of patients: approximately 155 patients

Statistical Analysis:

For the Phase 1a, a 3+3 design will be used to assess the safety of ramucirumab in combination with pembrolizumab. Additional patients will be enrolled in a dosing schedule to achieve the minimum of 3 evaluable patients, if dropouts or dose interruptions or reductions occur that result in a patient being non-evaluable for DLTs. Data will be reviewed by dose schedule group (3 patients).

The final analysis of safety and preliminary efficacy will occur approximately 2 years after the first patient received first study treatment. Interim analyses will occur at a cohort level when the patients have completed approximately 24 weeks of study treatment, or discontinued for any reason. Safety and preliminary efficacy will be analyzed separately for each cohort.

Descriptive statistics will be derived where appropriate. The rate of DLTs will be summarized by cohort; dose exposure and density for each study drug will be calculated for each cohort.

2. Introduction

Ramucirumab (Cyramza™), a human immunoglobulin, subclass 1 anti-vascular endothelial growth factor (VEGF) Receptor 2 monoclonal antibody, has obtained marketing authorization in the United States (US), European Union (EU), and Japan for the treatment of advanced gastric or gastroesophageal junction (gastric-GEJ) adenocarcinoma as monotherapy (Study I4T-IE-JVBD [REGARD]) or in combination with paclitaxel (Study I4T-IE-JVBE [RAINBOW]), with disease progression on or after prior fluoropyrimidine- and/or platinum-containing chemotherapy. Ramucirumab is also approved in the US and EU for the treatment of advanced non-small cell lung cancer (NSCLC) in combination with docetaxel (Study I4T-MC-JVBA [REVEL]), with disease progression on or after prior platinum-based chemotherapy. Patients with epidermal growth factor receptor or anaplastic lymphoma kinase genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving ramucirumab. Ramucirumab is also approved in the US and EU for the treatment of metastatic colorectal cancer (CRC) in combination with FOLFIRI (irinotecan, 5-fluorouracil, and folinic acid; Study I4T-MC-JVBB [RAISE]) with disease progression on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

In a well-controlled, randomized urothelial Phase 2 Study I4Y-IE-JCDC (JCDC), the addition of ramucirumab to the standard docetaxel regimen provided a significant improvement in progression-free survival (PFS) compared with the control therapy. The magnitude of improvement in PFS and investigator-assessed response versus the standard single-agent docetaxel regimen represents a meaningful therapeutic benefit.

In addition, the toxicity profile of ramucirumab has been manageable given as a monotherapy or in combination. REGARD, a single-agent, placebo-controlled, Phase 3 gastric cancer study, 25 patients (10.5%) receiving ramucirumab discontinued study treatment due to adverse events (AEs). The most common adverse drug reactions reported in ≥10% of ramucirumab-treated patients were abdominal pain, diarrhea, and hypertension. Clinically relevant reactions (including Grade ≥3) associated with antiangiogenic therapy observed in ramucirumab-treated patients across clinical trials were proteinuria, infusion-related reactions, and gastrointestinal (GI) perforations.

Pembrolizumab [Keytruda (US)], a humanized monoclonal antibody against the programmed death receptor-1 (PD-1) protein, has been developed by Merck & Co for the treatment of cancer. Pembrolizumab is approved for treatment of melanoma in several countries; in the US and EU it is approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and epidermal growth factor receptor (EGFR) or anaplastic lymphoma (ALK) genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.

There are multiple Phase 3 programs ongoing, including but not limited to NSCLC (KEYNOTE 024, 042), squamous cell head and neck squamous cell carcinoma (KEYNOTE 040), and urothelial cancer (KEYNOTE 045). Results from studies of pembrolizumab used as a monotherapy in advanced NSCLC, gastric-GEJ cancer, and in urothelial cancer have shown preliminary antitumor activity with a manageable safety profile. Single-agent efficacy in each of these tumor types ranged from 22% to 24% objective response rates in PD-L1-positive patients (Table JVDF.1). Additional efficacy and safety information is shown in the table below.

The toxicity profile of pembrolizumab has been manageable, with <10% of patients stopping drug because of side effects. The most common adverse reactions (≥20%) seen with pembrolizumab were fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea. Similar side effect profiles were seen in patients with tumor types other than melanoma. Although less common, immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, hypophysitis, renal failure, immune-mediated nephritis, hypothyroidism, and hyperthyroidism, need to be carefully monitored when treating with these types of agents (Keytruda US package insert [USPI]).

Table JVDF.1 presents a high level summary of the ramucirumab and pembrolizumab safety and efficacy data for the 3 patient populations that are being explored in this study, gastric-GEJ, NSCLC, and urothelial cancer.

More information about the clinical data, including known and expected benefits, risks, and reasonably anticipated AEs of monotherapy with either pembrolizumab or ramucirumab, may be found in the respective Investigator's Brochures (IBs).

Immune Checkpoint Blockers Targeting PD-1/PD-L1

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions.

Immune checkpoints, such as PD-1 and PD-L1, have been targeted with antagonist mAbs, such as PD-1 antibodies nivolumab and pembrolizumab and PD-L1 antibody MEDI4736. In nivolumab and MEDI4736 trials, response rate ranged from 14% to 22% in NSCLC, head and neck cancer, and renal cell carcinoma in unselected patient populations (both PD-L1-positive and PD-L1-negative patients) (Brahmer et al. 2014a, 2014b; Fury et al 2014; Motzer et al. 2014).

Recent publications suggest multiple factors that predict outcomes of patients treated with immune checkpoint inhibitors. Most notably is the evidence that higher expression levels of PD-L1 on the tumor-infiltrating immune cells is associated with better clinical outcomes (Herbst et al. 2014). In pembrolizumab trials, response rate increased approximately 2-fold in PD-L1 "strong positive" patients, ranging from 39% to 50%, in NSCLC and head and neck cancer (Garon et al 2014, Chow et al 2014) In addition, tumor cells develop adaptive immune resistance through up-regulation of PD-L1 expression (Terme et al. 2012). As the immuno-oncology field is gaining further knowledge on the biomarkers to predict antitumor

response, including biomarker assay consensus of expression level and validation, both PD-L1-positive and PD-L1-negative patients will be enrolled in this trial based on the ramucirumab and other PD-1 and PD-L1 blockers' clinical activity in unselected patient population. The Sponsor plans to utilize the current PD-L1 assay, under development with Merck, to explore whether PD-L1 expression further improves the outcome of patients when treating with a combination regimen of immune checkpoint inhibitor pembrolizumab and VEGF Receptor 2 inhibitor ramucirumab.

Further Rationale for the Study

The antitumor activity with manageable safety has been demonstrated by ramucirumab and pembrolizumab in the 3 tumor types (gastric-GEJ, NSCLC, and urothelial cancer) as described above, and the synergistic preclinical activity with the combination of ramucirumab and pembrolizumab described below, laid the foundation for investigating whether the combination therapy might further enhance the efficacy of these agents.

Preclinical Activity of the Combination

A synergistic antitumor effect when blocking VEGF Receptor 2 and PD-1 simultaneously was demonstrated in preclinical murine colon cancer model (Yasuda et al. 2013). Dual blockade of both PD-1 and VEGF Receptor 2 inhibited tumor growth significantly compared to each mAb treatment, individually. There were no overt toxicities in treated mice. Treatment with anti-PD-1 mAb and anti-VEGF Receptor 2 mAb induced a significant increase in the expression of several potent pro-inflammatory cytokines and mediators. There was also a constant tendency of increase in $CD4^+$ and $CD8^+$ T-cell infiltration in tumor tissues treated with the combination.

Preclinical data also demonstrated that vascular-normalizing doses of anti-VEGF Receptor 2 antibody can reprogram the tumor microenvironment away from immunosuppression. With T-cell activation induced by a whole cancer cell vaccine therapy, vascular-normalizing doses of anti-VEGF Receptor 2 antibody enhanced anticancer efficacy in a $CD8^+$ T-cell–dependent manner in both immune-tolerant and immunogenic murine breast cancer models (Huang et al. 2012).

Cellular and Molecular Rationale of the Combination

Voron et al. recently demonstrated that VEGF-A enhances simultaneous expression of several inhibitory receptors, including PD-1, Tim-3, CTLA-4 and LAG3, on CD8+ T cells. Anti-VEGF-R2 antibody, not anti-VEGF-R1 antibody, can revert the expression of these inhibitory molecules that are involved in CD8+ T cell exhaustion (Voron et al. 2015). Thus, combining anti-VEGF-R2 antibody with anti-PD-1 antibody potentially alleviates effector CD8+ T cells from exhaustion in a synergistic way.

This combination may also effectively target the two "parallel lives" as described by Motz and Coukos within the tumor microenvironment: immunosuppression and angiogenesis (Motz and Coukos 2011). Multiple immunosuppressive cells recruited to the tumor microenvironment directly promote angiogenesis by secreting VEGF-A and other factors. Tumor endothelium generated by angiogenesis not only supplies nutrients to the tumor, but also prevents T cell

infiltration through VEGF (derived from tumor)/VEGFR (expressed on endothelium) pathway (Motz and Coukos 2013).

In addition, as summarized by Terme et al, antiangiogenic molecules appear to have several advantages to combine with other immunotherapy agents: (1) they only restore regulatory T-cell proportion to a physiological level, avoiding autoimmune-mediated side effects; (2) they do not deplete activated T-cells; (3) they inhibit other immunosuppressive pathways such as myeloid-derived suppressor cells (MDSC); and (4) they have potential antitumor effect on their own (Terme et al. 2012).

Clinical Safety of the Combination

A recent study combining MPDL3280A (anti-PD-L1) with bevacizumab (anti-VEGF-A) in patients with metastatic CRC demonstrated combining PD1/PD-L1 pathway blocker with antiangiogenic agent was well tolerated with no unexpected toxicities (Bendell et al. 2015). Most common AEs >20% in patients treated with MPDL3280A and bevacizumab were fatigue, diarrhea, nausea, pyrexia, vomiting, headache, and cough. Hodi et al. also demonstrated combining bevacizumab and ipilimumab (cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4] blocker) can be safely administered in melanoma patients. The study findings provided a basis for further investigating future combinations of antiangiogenesis agents and immune checkpoint blockade (Hodi et al. 2014).

The manageable safety profile, clinical efficacy of these 2 agents individually, and the synergistic preclinical antitumor activity demonstrated, provide evidence supporting the rationale for clinically testing whether the simultaneous blockade of PD-1 and VEGF Receptor 2 enhances single-agent activity while maintaining an acceptable safety profile.

Table JVDF.1. Ramucirumab and Pembrolizumab Data Summary: Gastric-GEJ, NSCLC, and Urothelial Indications[a]

Indication	Study Treatment	N	Efficacy	Safety	Reference
Gastric-GEJ	Ram	238	ORR: 3% Median PFS: 2.1 months Median OS: 5.2 months	Adverse reactions occurring at a rate of ≥10% and in ≥2% more in ramucirumab than in placebo group: hypertension (16% [all grades]; 8% [Grade 3-4]) and diarrhea (14% [all grades]; 1% [Grade 3-4])	Cyramza US Package Insert, April 2015
	Ram + Paclitaxel	330	ORR: 28% Median PFS: 4.4 months Median OS: 9.6 months	Adverse reactions occurring at a rate of ≥30% and in ≥2% more in ramucirumab + paclitaxel than in the paclitaxel control group: fatigue/asthenia (57% [all grades]; 12% [Grade ≥3]), neutropenia (54% [all grades]; 41% [Grade ≥3]), diarrhea (32% [all grades]; 4% [Grade ≥3]), and epistaxis (31% [all grades]), 0% [Grade ≥3]).	Cyramza US Package Insert, April 2015
	Pembro	39, PD-L1+ only	ORR: 22% 6-mo PFS rate: 24% 6-mo OS rate: 69%	Grade 3-5 drug-related AEs occurred in 4 patients, peripheral sensory neuropathy, fatigue, decreased appetite, hypoxia, and pneumonitis (n=1 each).	Muro et al. 2015 (ASCO GI Symposium)
NSCLC	Ram+ Docetaxel	628	ORR: 22.9% Median PFS: 4.5 months Median OS: 10.5 months	Adverse reactions occurred at a rate ≥30% and ≥2% more in the ramucirumab + docetaxel than in the docetaxel control group: fatigue/asthenia (55% [all grades]; 14% [Grade 3-4]), neutropenia (55% [all grades]; 49% [Grade 3-4]), and stomatitis/mucosal inflammation (37% [all grades]), 7% [Grade 3-4]).	Cyramza US Package Insert, April 2015
	Pembro	495	ORR: 19.4% overall; 18% previously treated, 24.8% treatment naïve, 45.2% in PD-L1 strong + (≥50%), 16.5% in PD-L1+ (1-49%), 10.7% in PD-L1- (<1%)	Most common AEs were fatigue, pruritus, and decreased appetite. Grade 3-5 drug-related AE occurred in 47 patients (9.5%), most commonly dyspnea (n=19, 3.8%) and pneumonitis (n=9, 1.8%).	Garon et al. 2015

Ramucirumab and Pembrolizumab Data Summary: Gastric-GEJ, NSCLC, and Urothelial Indications (concluded)

Indication	Study Treatment	N	Efficacy	Safety	Reference
Urothelial	Ram+ Docetaxel	46	ORR: 19.6%, median PFS: 5.1 months DCR: 67.4%	Most common AEs were fatigue (80.4%), decreased appetite (54.3%), nausea (54.3%), and neuropathy (50.0%). Grade ≥3 AEs, febrile neutropenia (19.6%), pneumonia (13%), and hypertension (4.3%) were higher with Doc + Ram.	Petrylak et al. 2015 (ASCO GU Symposium)
	Pembro	33, PD-L1+ only	ORR: 24% Median PFS: 8.6 weeks Median OS: 9.3 months (6-month OS rate: 58%)	Most common AEs were fatigue (n=6), peripheral edema (n=4), and nausea (n=3); Grade 3-4 drug-related AEs were reported for 4 patients (12%), with only rash seen in >1 patient (n=2).	O'Donnell et al. 2015 (ASCO GU Symposium)

Abbreviations: AE = adverse event; ASCO = American Society of Clinical Oncology; DCR = disease control rate; Doc = docetaxel; GEJ = gastroesophageal; GI = gastrointestinal; GU = genitourinary; N = number of patients; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; Pembro = pembrolizumab; PFS = progression-free survival; Ram = ramucirumab; US = United States.

[a] Preliminary efficacy and safety data for BTC (2^{nd} -3^{rd} Line), NSCLC (1^{st} Line) and Gastric/GEJ (1^{st} Line) are described below this table.

Rationale for Expanding to Biliary Tract Cancer, First Line Gastric-GEJ, and First Line NSCLC

1). Biliary Tract Cancer:

Vascular endothelial growth factor (VEGF), one of the main proangiogenic factors, is overexpressed in approximately 50% to 60% of cholangiocarcinoma (CCC) (Yoshikawa, et al. 2008). Benckert et al. also showed VEGF was secreted by tumor epithelial cells, and VEGFR1 and VEGFR2 were exclusively expressed on tumor endothelial cells in CCC (Benckert et al. 2003). In gallbladder carcinomas, an increased VEGF secretion was significantly associated with increased angiogenesis (Giatromanolaki et al. 2003). Increased microvascular density (MVD) was also observed in CCC (Benckert et al. 2003; Tang et al. 2006). High MVD (increased angiogenesis) is associated with poor survival in BTC (Giatromanolaki et al. 2003; Möbius et al. 2007). The above observations provided rationale for targeting angiogenesis pathway in developing therapies for BTC.

Anti-angiogenic agents have been investigated in BTC with comparable efficacy as standard chemotherapy, including bevacizumab in combination with gemcitabine and oxaliplatin, bevacizumab in combination with erlotinib, sorafenib, and sunitinib (Bengala et al. 2010; Lubner et al. 2010; Zhu et al. 2010; Yi et al. 2012; Lee et al. 2013). In a more recent study, cediranib, a pan-VEGF receptor tyrosine kinase inhibitor, in combination with gemcitabine/cisplatin, demonstrated an improved efficacy outcome in response rate (44% for cediranib/gemcitabine/cisplatin vs. 19% for placebo/gemcitabine/cisplatin) and 10% improvement in 6-month PFS survival and 1-year overall survival (71% vs. 61%; 58% vs. 48%, respectively) (Valle et al. 2015). However, early discontinuation was observed due to the toxicity of the cediranib/chemotherapy combination. As a result, the early efficacy signal in this study did not translate into sustained anti-tumor activity. Thus, a well-tolerated anti-VEGFR therapy in combination with standard chemotherapy or other targeted therapy should be investigated further to enhance the efficacy outcome in BTC.

Pembrolizumab has demonstrated preliminary efficacy in CRC and non-CRC patients with mismatch-repair (MMR)-deficiency in their tumors (Le et al. 2015). Patients with MMR-deficient non-CRC had similar efficacy outcomes as MMR-deficient CRC. MMR-deficiency is present in 2% to 20% of BTCs and other non-CRC GI cancers (Le et al. 2016). Recent data update confirmed the preliminary efficacy demonstrated previously in MMR–deficient non-CRC patients (n=10): objective response rate (ORR) is 50%, disease control rate (DCR) is 70%, and overall survival (OS) is 21 months (Le et al. 2016).

This study will investigate the combination therapy in previously treated non-selected BTC patients with regard to MMR status based on several considerations: 1) ramucirumab targets angiogenesis that is commonly observed in BTCs; 2) percentage of BTC patients whose tumors have MMR deficiency may be low (for example, occurrence of MMR deficiency in ampullary carcinoma appears less than in CRC [Agaram 2010]); 3) the hypothesis that the combination targets the two processes, angiogenesis and immunosuppression, simultaneously in the tumor microenvironment, may generate synergistic anti-tumor activity.

In summary, ramucirumab and pembrolizumab have demonstrated benefit across multiple tumor types, both as single agents or in combination with cytotoxic chemotherapy, and have been well tolerated. Despite preliminary evidence of activity with both antiangiogenic agents in BTC or with checkpoint inhibitors, no targeted agent has been approved in this setting, and there remains a high unmet need for new treatment options.

2). First Line Gastric-GEJ:

Advanced gastric/GEJ cancer patients treated with current standard first-line chemotherapy have a median OS between 9 and 11 months (Cunningham et al. 2008; Pasini et al. 2011). OS is further extended (13.8 months vs. 11.1 months) when adding trastuzumab to chemotherapy, capecitabine and cisplatin, for patients with HER2 overexpression/amplification, which accounts for only approximately 20% of gastric patients (Bang et al. 2010; Lordick 2011).

Targeted therapies have been investigated to improve OS for the overall gastric patients in first line setting, but have yet to demonstrate significant improvement in OS. AVAGAST trial indicated that adding bevacizumab to chemotherapy, fluoropyrimindine and cisplatin, increased OS as comparison with chemotherapy alone (12.1 months vs. 10.1 months), but failed to demonstrate statistical significance (p=.1002) (Ohtsu et al. 2011). Regional differences in the efficacy outcome were observed between North America/Latin America versus Asia, in which a survival benefit was observed with addition of bevacizumab in North America and Latin America, but not in Asia. Besides a preliminary efficacy signal with addition of bevacizumab, the combination therapy did not substantially alter the safety profile of the chemotherapy backbone. Ramucirumab was also investigated in combination with mFOLFOX-6 in the first line setting for advanced adenocarcinoma of the esophagus, GEJ, or stomach (I4T-MC-JVBT CSR). Although median PFS was similar between the ramucirumab + mFOLFOX-6 arm versus the mFOLFOX-6 alone arm, the PFS rate at 3 months and DCR were improved in the ramucirumab + mFOLFOX-6 arm. In addition, median PFS was improved in patients with primary tumor location in gastric/GEJ/cardia (8.7 months vs. 7.1 months, HR=0.77). Although the safety profile for ramucirumab in this study was consistent with the known safety profile of ramucirumab, a higher discontinuation rate was observed in the ramucirumab + mFOLFOX-6 arm than in the mFOLFOX-6 alone arm. A different chemotherapy backbone, capecitabine and cisplatin, is being utilized to combine with ramucirumab in a Phase 3 study for metastatic gastric/GEJ cancers in the first line setting (I4T-MC-JVCU, RAINFALL).

Pembrolizumab is also being investigated in first line setting for gastric/GEJ cancers as monotherapy and combination therapy with chemotherapy for advanced gastric/GEC cancers, KEYNOTE 059 (Phase 2 study) and KEYNOTE 062 (Phase 3 study). Cisplatin and 5-FU or capecitabine was utilized as chemotherapy backbone for these two Keynote trials. Preliminary results have not been released as of December 2015.

Based on the results of REGARD and RAINBOW, pembrolizumab preliminary data shown in gastric-GEJ cancer patients (KEYNOTE 012), and preliminary data combining anti-angiogenic agents with backbone chemotherapy, exploration of ramucirumab plus pembrolizumab combination is warranted in the first line setting. Simultaneously targeting angiogenesis and

immune checkpoint blocker, PD-1 may potentially further enhance the efficacy of either agent while maintaining tolerable safety profile. This may be a viable first line therapy that does not contain a chemotherapy backbone for gastric/GEJ patients.

3). First Line NSCLC:

Inhibition of the angiogenesis pathway in combination with chemotherapy has been established as a treatment option for NSCLC in the first line setting. Bevacizumab in combination with paclitaxel and carboplatin obtained marketing authorization for non-squamous NSCLC as front line therapy (Sandler et al. 2006). Preliminary efficacy was also demonstrated combining bevacizumab with erlotinib in Japanese patients with EGFR mutation-positive NSCLC as first line therapy in JO25567 study (Kato et al. 2014; Seto et al. 2014). A Phase 3 study combining ramucirumab with erlotinib with safety run-in is currently ongoing in EGFR mutation-positive NSCLC patients in the first line setting (Study I4T-MC-JVCY, RELAY).

Immune checkpoint blockers have also been investigated in clinical studies with or without a chemotherapy backbone in the early line setting. The KEYNOTE-021 evaluated the safety, tolerability, and clinical activity of pembrolizumab in combination with platinum doublet chemotherapy (PDC) for treatment-naive advanced NSCLC (Papadimitrakopoulou et al. 2015). Preliminary results in approximately 50 patients showed 28% and 58% objective response rates, depending on the backbone chemotherapies (pembrolizumab/carboplatin/paclitaxel and pembrolizumab/carboplatin/pemetrexed, respectively). Based on these KEYNOTE 021 results, pembrolizumab is being investigated as a first-line therapy in multiple studies (KEYNOTE-024, 042, and 189). KEYNOTE 024 and 042 are to assess the efficacy of pembrolizumab monotherapy compared with standard of care (SOC) platinum-based chemotherapies in treatment naïve, advanced or metastatic NSCLC patients who are PD-L1 positive. Keynote 189 is to assess the safety and efficacy of pembrolizumab combined with platinum-pemetrexed chemotherapy versus platinum-pemetrexed chemotherapy alone in first line setting for advanced or metastatic non-squamous NSCLC. Based on the established anti-tumor activities and tolerable safety profile of anti-angiogenic agents and anti-PD-1 antibodies in advanced/metastatic NSCLC (ramucirumab with chemotherapy in second line setting in REVEL, bevacizumab in combination with PDC in first line setting, pembrolizumab as monotherapy in later line setting in PD-L1+ patients in Keynote 001, pembrolizumab in combination with PDC in the first-line setting in Keynote 021, and nivolumab in NSCLC in Checkmate studies), investigation of ramucirumab plus pembrolizumab combination is warranted in the first-line NSCLC population as a potentially viable treatment option that does not contain a chemotherapy backbone. Simultaneously targeting angiogenesis and immune checkpoint blocker, PD-1, may potentially further enhance the efficacy of either agent while maintaining tolerable safety profile.

As the PD-L1 assay in NSCLC patients has been validated and approved by regulatory authorities, PD-L1 positivity is required in the first line NSCLC patients to enhance the potential for anti-tumor efficacy of the study treatment. Pembrolizumab has demonstrated efficacy as monotherapy in PD-L1-positive NSCLC patients (KEYNOTE 001). Current KEYNOTE 024 and 042 studies also require PD-L1-positive NSCLC patients in the first line setting.

3. Objectives and Endpoints

Objective(s)/Endpoints

	Objectives	Endpoints
Phase 1a and 1b	**Primary:** To assess the safety and tolerability of 2 dosing regimens of ramucirumab plus pembrolizumab	Dose-limiting toxicities, observed during a 21-day observation period **Safety (include but are not limited to):** TEAEs, SAEs, deaths, laboratory abnormalities, vital signs, and physical exams)
	Secondary: To characterize the PK of ramucirumab when co-administered with pembrolizumab	**PK:** C_{min} and approximate C^{max} of ramucirumab in serum
Phase 1b	**Secondary:** • To assess the preliminary efficacy of ramucirumab plus pembrolizumab	**Efficacy:** • ORR (RECIST 1.1 and irRECIST) • DCR, DOR, TTR, PFS, and OS
	Tertiary/Exploratory: • To explore the association between biomarkers and clinical outcomes • To characterize biomarker measures of immune functioning and angiogenesis • To assess immunogenicity of ramucirumab when co-administered with pembrolizumab	**Biomarkers:** research on genetic and circulating factors **Immunogenicity:** anti-ramucirumab antibody

NOTE: For a more complete description of terms and abbreviations, see Attachment 8.
Abbreviations: C_{max} = maximum concentration; C_{min} = minimum concentration; DCR = disease control rate; DOR= duration of response; irRECIST= immune-related RECIST; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria In Solid Tumors; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events; TTR = time to response.

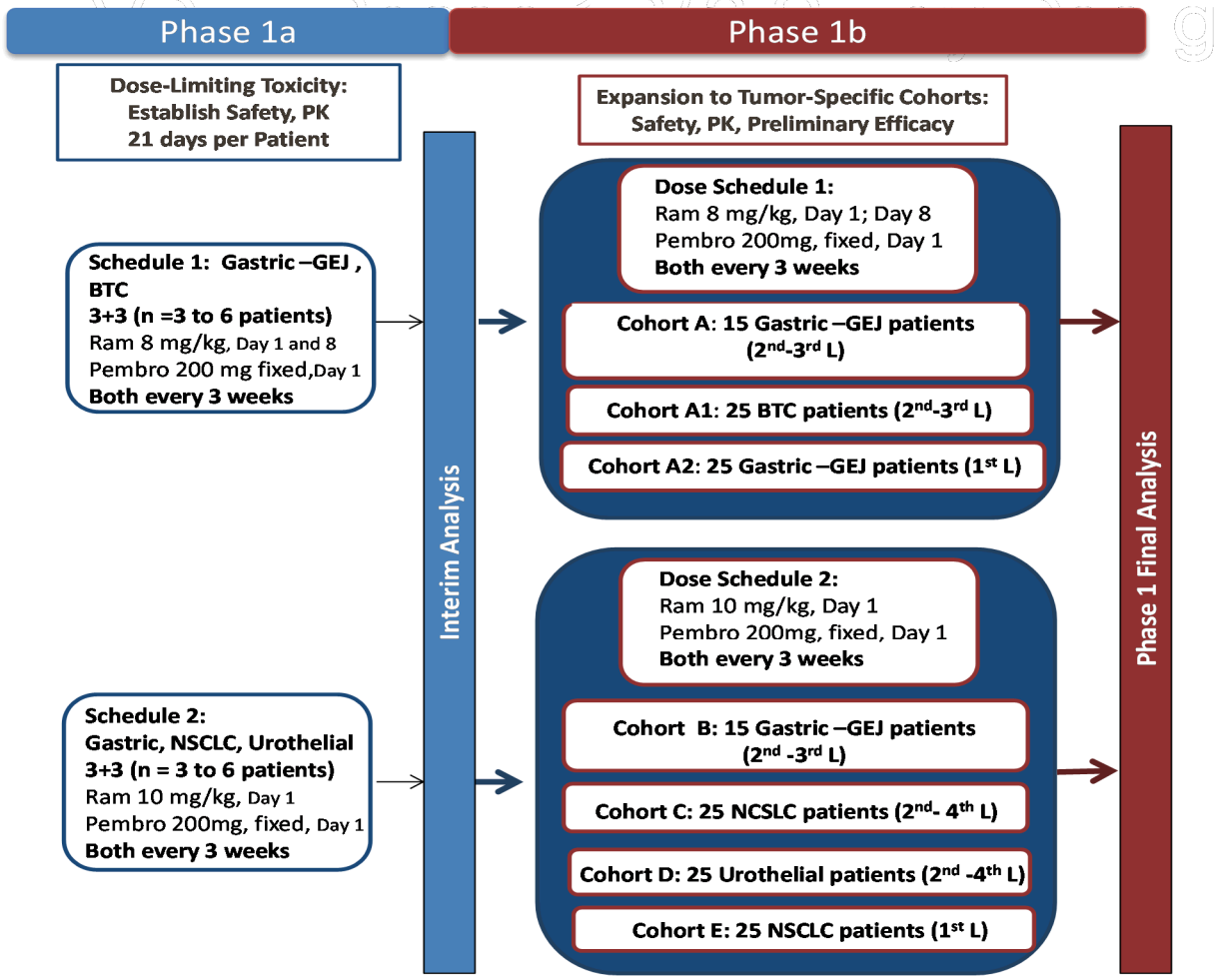
4. Study Design

4.1. Overview of Study Design

Study I4T-MC-JVDF is an open-label, multicenter Phase 1 study to evaluate the safety and preliminary efficacy of ramucirumab in combination with pembrolizumab. Phase 1a (dose-limiting toxicity [DLT] observation) and Phase 1b (expansion; safety and preliminary efficacy) will include patients with locally advanced and unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma (gastric-GEJ cancer), NSCLC, transitional cell carcinoma of the urothelium (urothelial cancer), or biliary tract cancer (BTC).

Based on the results of Phase 1, the Sponsor will consider various approaches toward developing the combination therapy, including but not limited to an adaptive Phase 2/3 trial design, enrolling additional patients, and/or testing alternative dosing levels and schedules. If sufficient tolerability and activity are demonstrated in Phase 1, the protocol will be amended and resubmitted accordingly.

Figure JVDF.1 illustrates the study design.



Abbreviations: BTC = biliary tract cancer; GEJ = gastroesophageal; L = line; n = number of patients; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; Ram = ramucirumab.

Note: The results of the Phase 1a interim analysis will confirm the dosing regimens to be used in Phase 1b. Dose reductions (ramucirumab), delays, and discontinuations may occur per the guidelines in Section 6.6.

Figure JVDF.1. Illustration of study design.

4.1.1. Phase 1a: Dose-Limiting Toxicity Observation

The DLT observation period of Phase 1a will employ a 3+3 design, enrolling up to 6 patients per dose schedule. Patients will be allocated into one of 2 dose schedules, based on their diagnosis at baseline, as shown in Figure JVDF.1.

The DLT observation period will last for one 21-day treatment cycle (see Section 6.1.1 for selection and timing of doses).

The definition for DLTs and the criteria used to determine progress of the study are provided in Section 6.1.1.1.

4.1.2. Phase 1b: Expansion

If results yield an acceptable number of DLTs (≤1) in the observation period of Phase 1a, then the Expansion Phase 1b (Expansion Portion) will start.

The results of the Phase 1a interim analysis will confirm the dosing regimens to be used in Phase 1b. Dose reductions (ramucirumab), delays, and discontinuations may occur per the guidelines in Section 6.6.

Patients will be added to include 7 separate expansion cohorts, with dosing schedules corresponding to those in DLT Phase 1a, as shown in Figure JVDF.1. Gastric patients will be assigned to Cohort A, A2, or B (Section 6.2).

The final analysis of safety and preliminary efficacy will occur approximately 2 years after the first patient received first study treatment. Interim analyses will occur at a cohort level when the patients have completed approximately 24 weeks of study treatment. The Phase 1b data will provide additional safety, tolerability, pharmacokinetics (PK) and pharmacodynamics, and preliminary efficacy data for the combination.

4.1.3. Study Period and Continued Access Definitions

Terms used to describe the periods during the study are defined below and illustrated in Figure JVDF.2.

- **Baseline/Screening:** begins when the informed consent form (ICF) is signed, and ends at the first study treatment (defined as receiving either ramucirumab or pembrolizumab); if no study treatment is given, baseline/screening ends at discontinuation. Lasts up to 28 days.
- **Study Period:** begins at the time of first study treatment and ends at study completion, which occurs approximately 2 years after the first patient received first study treatment (Section 4.4).
    - **Study Treatment Period:** begins with the day of the first patient's first study treatment and ends the day that the decision is made to discontinue study treatment (discontinuation of both study drugs; Section 7.1). Individual patients who enroll in Study JVDF may continue treatment for up to 35 cycles (approximately 2 years), until they have confirmed progressive disease or discontinued study treatment for any other reason.
    - **Postdiscontinuation Follow-Up** consists of the following 2 phases.
        - **Short-Term (Safety) Follow-Up**: begins the day after the patient and the investigator agree that the patient will discontinue study treatment and ends with the short-term follow up visit, to occur approximately 30 days thereafter.
        - **Long-Term (Survival) Follow-Up:** begins the day after short-term follow-up is completed and ends with the patient's death, loss to

follow-up, or overall study completion, whichever is earlier. The long-term follow-up visit will occur approximately 90 days after the decision is made to discontinue from study treatment. Subsequent follow-up (not a formal visit) will occur approximately every 90 days thereafter, for up to approximately 2 years from the first study treatment (Attachment 1).

- **Continued Access Period:** begins after study completion (final analysis and evaluation of the study endpoints) and ends at end of trial (defined in Section 4.4). In the continued access period, individual patients may continue the current study treatment after study completion, as long as they experience ongoing clinical benefit (details in Section 6.10). Sites will be notified when the continued access period is to begin and end.

Patients who are in short-term follow-up when the continued access period begins will complete the 30-day short-term follow-up visit and then discontinue the study.

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

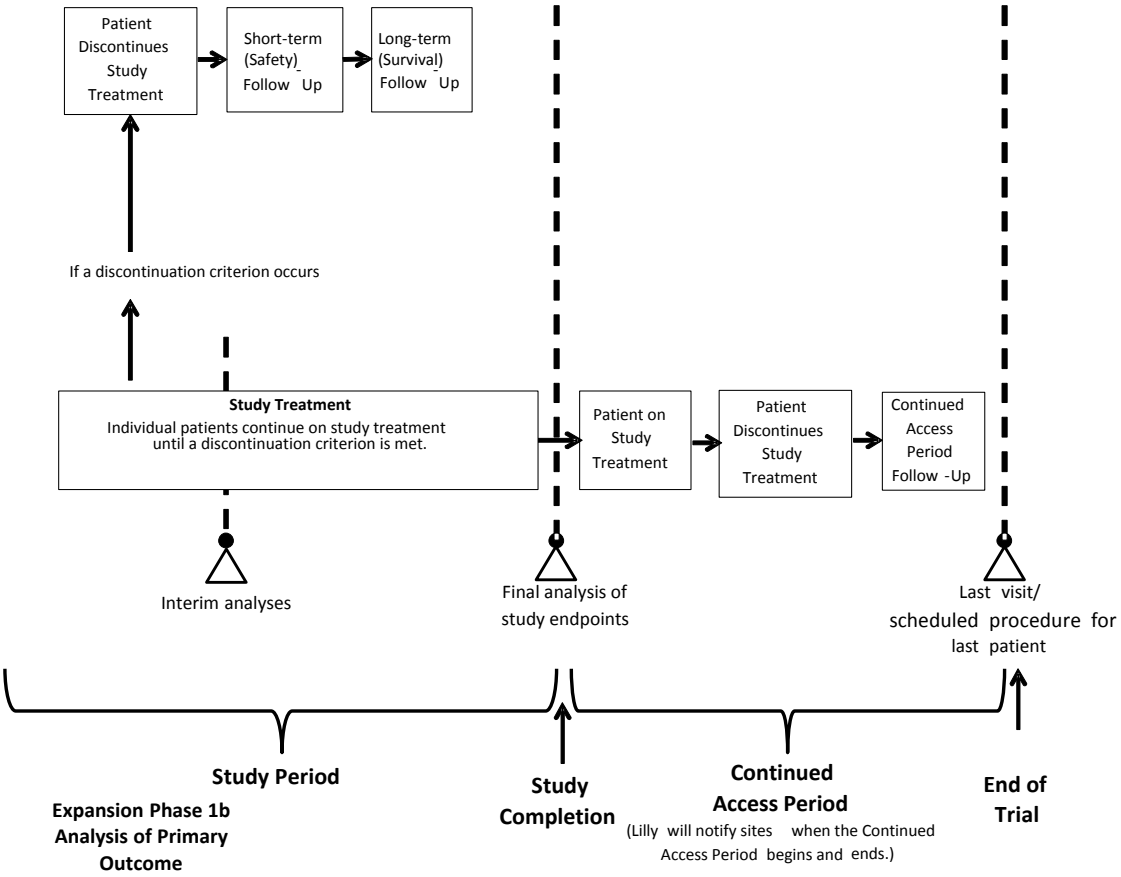


Figure JVDF.2. Study period and continued access diagram.

4.2. Rationale for Study Design

The general rationale for the study design is described in the Introduction (Section 2). The details regarding dose selections are described below.

4.2.1. Dose Selection for Ramucirumab

4.2.1.1. Rationale for Selection of Ramucirumab Dose Schedule 1 (8mg/kg every 3 weeks on Day 1 and Day 8 in Patients with Gastric-GEJ Cancer and BTC)

Ramucirumab Dose Schedule 1 (8 mg/kg on Days 1 and 8; 21-day cycle) was based on exposure-response analyses in REGARD (8 mg/kg every 2 weeks [Q2W]) and RAINBOW (8 mg/kg on Days 1 and 15; 28-day cycle).

Efficacy

Exposure-efficacy response analyses performed on data obtained from REGARD and RAINBOW demonstrated that an increase in exposure is associated with improved efficacy in terms of both overall survival (OS) and progression-free survival (PFS). In both studies, patients with greater-than-median ramucirumab exposure demonstrated significantly longer OS and PFS (smaller hazard ratio [HR]) as compared to patients with less-than-median ramucirumab exposure.

These findings were consistent for all 4 exposure measures tested: minimum concentration after first dose administration ($C_{min,1}$), minimum concentration at steady state ($C_{min,ss}$), maximum concentration at steady state ($C_{max,ss}$), and average concentration at steady state ($C_{ave,ss}$).

Safety

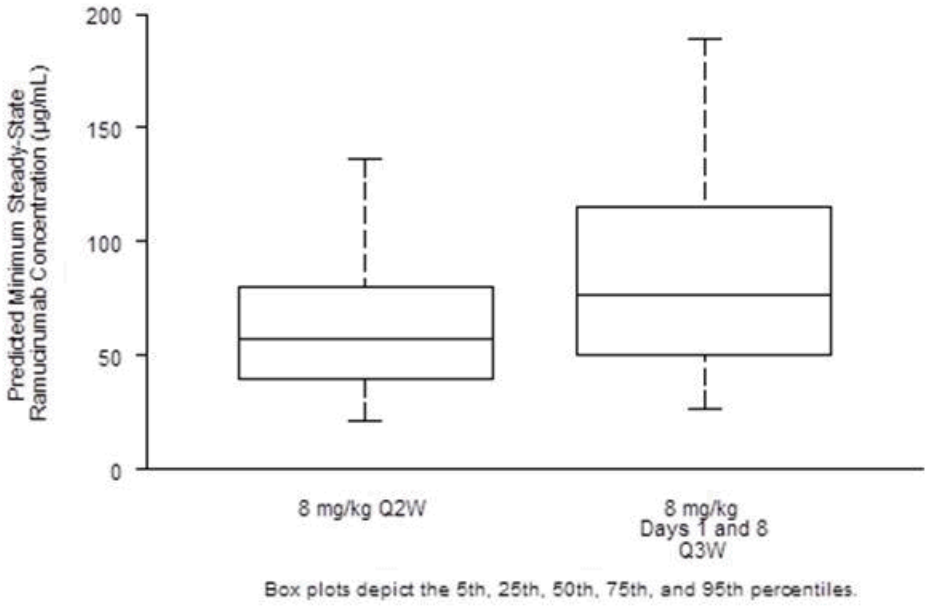
Weekly doses of ramucirumab ranging from 2 to 16 mg/kg were evaluated in the Phase 1 Study JVBM. A maximum tolerated dose (MTD) for weekly dosing was identified as 13 mg/kg. Every-2-week (6 to 10 mg/kg) and every-3-week (15 to 20 mg/kg) dose regimens were evaluated in another dose-ranging Study JVBN.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

REGARD demonstrated a well-tolerated safety profile in the gastric-GEJ cancer monotherapy setting. Due to the low incidence of hypertension and neutropenia, no safety-exposure relationship was identified for these treatment-emergent adverse events.

In RAINBOW, the overall safety profile was also considered manageable, although increasing ramucirumab exposure was correlated with increased incidence of Grade 3 or greater hypertension, neutropenia, and leukopenia. There were no Grade 4 or 5 hypertension events. Hypertension was managed primarily by the use of standard antihypertensive medication, and the association of neutropenia with ramucirumab exposure did not appear to translate to an increased risk of febrile neutropenia with higher ramucirumab exposure.

These data indicate that there may be an opportunity to further improve ramucirumab activity in the gastric-GEJ indication. Based on PK simulation, Dose Schedule 1 (8 mg/kg on Days 1 and

8; 21-day cycle) may produce $C_{min,ss}$ greater than the median $C_{min,ss}$ obtained from the standard 8-mg/kg Q2W regimen in at least 70% of the patient population (Figure JVDF.3) and therefore may produce better clinical efficacy outcomes relative to the 8-mg/kg Q2W regimen. The ramucirumab-related safety risk in the gastric-GEJ cancer indication may not be significantly increased using Dose Schedule 1, as this dose is approximately 60% lower than the maximum tolerated weekly dose identified in the Phase 1 dose-escalation Study JVBM (13 mg/kg weekly). Thus, Dose Schedule 1 may further enhance the efficacy in Gastric-GEJ indication, and may be the appropriate dosing regimen for BTC as well.



Abbreviations: $C_{min,ss}$ = minimum concentration at steady state; Q = every; W = week. Box plots depict the 5th, 25th, 50th, 75th, and 95th percentiles calculated from 1000 simulation iterations.

Figure JVDF.3. Predicted $C_{min,ss}$ following different dose regimens.

4.2.1.2. Rationale for Selection of Dose Schedule 2 (10mg/kg every 3 weeks)

A ramucirumab dose of 10 mg/kg every 3 weeks (Q3W) in combination with docetaxel is the approved dose in second-line NSCLC, and has also been studied in second-line urothelial cancer (JCDC).

In Study JCDC, ramucirumab 10 mg/kg Q3W in combination with docetaxel also demonstrated clinical safety and preliminary efficacy in previously treated urothelial cancer patients. No new unexpected safety findings were identified; the Grade ≥3 AEs occurring at a greater frequency in the docetaxel-plus-ramucirumab arm compared with the docetaxel-alone arm were fatigue (33% vs. 11%), febrile neutropenia (20% vs. 11%), diarrhea (7% vs. 2%), stomatitis (7% vs. 0%), and thrombocytopenia (7% vs. 0%). Additionally, the preliminary efficacy results showed a median PFS of 10.4 weeks in the docetaxel monotherapy arm and 22.0 weeks in the docetaxel-plus-ramucirumab arm (stratified HR, 0.388; p<.001). This improvement in PFS represents a meaningful therapeutic benefit and warrants further exploration.

Thus, Dose Schedule 2 (ramucirumab 10 mg/kg Q3W) was chosen for gastric-GEJ, NSCLC, and urothelial patients in Study JVDF.

4.2.2. Dose Selection for Pembrolizumab

An open-label Phase 1 trial (KEYNOTE 001) is being conducted to evaluate the safety and clinical activity of single-agent pembrolizumab (MK-3475). The dose-escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered Q2W in patients with advanced solid tumors. All 3 dose levels were well tolerated and no DLTs were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W). No MTD has been identified.

In KEYNOTE 001, 2 randomized cohort evaluations of melanoma patients receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating of 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma patients who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The objective response rate (ORR) was 26% (21/81) in the 2-mg/kg group and 26% (20/76) in the 10-mg/kg group. The proportion of patients with drug-related AE, Grade 3-5 drug-related AE, serious drug-related AE, death, or discontinuation due to an AE was comparable between groups or lower in the 10-mg/kg group. In Cohort B3, advanced melanoma patients (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab at 10 mg/kg Q2W versus 10 mg/kg Q3W. The ORR was 30.9% (38/123) in the 10-mg/kg Q2W group and 24.8% (30/121) in the 10-mg/kg Q3W group (APaT). The proportion of patients with drug-related AE, Grade 3-5 drug-related AE, serious drug-related AE, death, or discontinuation due to an AE was comparable between groups.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (Pembrolizumab IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). These early PK and pharmacodynamic data provide scientific rationale for testing a Q3W dosing schedule. Because Q3W dosing is more convenient for patients, Q3W dosing will be further studied.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model), and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed

dose of 200 mg Q3W will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose Q3W, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response, and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

4.3. Benefit/Risk Assessment

This study will provide benefit-risk data on the coadministration of pembrolizumab with ramucirumab. An assessment of the hypothesized benefits and risks of co-administration is described in the Introduction (Section 2), and more details are included in the ramucirumab and pembrolizumab IBs.

4.4. End of Study/Trial Definition

Study completion for Phase 1 of Study JVDF occurs after the clinical trial database is locked and the final analysis and evaluation of the study endpoints of dose-expansion Cohorts A through E has occurred based on data available approximately 2 years after the first patient received first study treatment. The end of trial occurs after study completion and when the last patient has discontinued study treatment and completed any applicable continued access follow-up (last patient last visit). Section 6.1 describes the maximum duration of study treatment.

5. Study Population

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

5.1. Inclusion Criteria

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

[1] Have diagnosis with one of the following types of cancer:

a) Gastric-GEJ cancer (Cohort A [2^{nd}-3^{rd} Line] and Cohort B [2^{nd}-3^{rd} Line])

- Histopathologically confirmed gastric or gastroesophageal junction (GEJ) adenocarcinoma (GEJ: Siewert Type I, II, and III)
- Metastatic disease or locally advanced, unresectable disease
- Documented disease progression to at least one prior line of systemic therapy and no more than two (2). Prior therapy for advanced disease must include a platinum and/or fluoropyrimidine. Prior therapy in an adjuvant or neoadjuvant setting is not considered as a prior line of systemic chemotherapy, unless patient has rapidly progressed as defined by ≤ 6 months of last dose in this setting. If it is ≤ 6 months, it will be regarded as a prior line of treatment.

b) Biliary Tract Cancer (Cohort A1 [2^{nd}-3^{rd} Line])

- Have a histologically or cytologically confirmed diagnosis of non-resectable, recurrent, or metastatic biliary tract adenocarcinoma (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or Ampula of Vater).
- Have adequate biliary drainage (per investigator's discretion), with no evidence of ongoing infection.
- Documented disease progression to at least 1 prior line of systemic therapy and no more than 2 prior lines of chemotherapy or biological therapy. Prior therapy for advanced disease must include gemcitabine and cisplatin. Prior therapy in an adjuvant or neoadjuvant setting is not considered as a prior line of systemic chemotherapy, unless patient has rapidly progressed, as defined by ≤ 6 months since the last dose of chemotherapy.

c) First-Line Gastric-GEJ Cancer (Cohort A2)

- Histopathologically confirmed gastric or gastroesophageal junction (GEJ) adenocarcinoma (GEJ: Siewert Type I, II, and III)
- Metastatic disease or locally advanced, unresectable disease
- No prior systemic chemotherapy for the treatment of the subject's advanced or metastatic (patients whose disease has progressed after>12 months following the last dose of systemic treatment in the adjuvant/neoadjuvant setting are eligible).
- Patients are ineligible for or refuse standard chemotherapy approved for first line treatment

d) Second Line and later NSCLC (Cohort C [2^{nd}-4^{th} Line])

- Histologically confirmed nonsquamous or squamous NSCLC
- Metastatic disease or locally advanced, unresectable disease
- Documented disease progression to at least one prior line of systemic therapy and no more than three (3). Prior therapy for advanced disease must include a platinum. Prior therapy in an adjuvant or neoadjuvant setting is not considered as a prior line of systemic chemotherapy, unless patient has rapidly progressed as defined by ≤ 6 months of last dose in this setting. If it is ≤ 6 months, it will be regarded as a prior line of treatment.
- Patients with known EGFR or ALK mutations are eligible only if they have received at least one line of prior targeted therapy for these mutations.
- A brain scan via computed tomography [CT] with contrast or magnetic resonance imaging [MRI] is to be performed to confirm absence of intracranial metastasis.

e) Urothelial Cancer (Cohort D [2^{nd}-4^{th} Line])

- Histologically confirmed transitional cell carcinoma of the urothelium (bladder, urethra, or renal pelvis). Patients with mixed pathology are eligible only if they have predominantly transitional cell tumor based on local pathology review.
- Metastatic disease or locally advanced, unresectable disease
- Documented disease progression to at least one prior line of systemic therapy and no more than three (3). Prior therapy for advanced disease must include a platinum. Prior therapy in an adjuvant or neoadjuvant setting is not considered as a prior line of systemic chemotherapy, unless patient has rapidly progressed as defined by ≤ 6months of last dose in this setting. If it is ≤ 6 months, it will be regarded as a prior line of treatment.
- 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.
- A brain scan via CT with contrast or MRI is to be performed to confirm absence of intracranial metastasis.

f) First-Line NSCLC (Cohort E)

- Histologically confirmed nonsquamous or squamous NSCLC
- No prior systemic chemotherapy or radiotherapy for the treatment of the subject's advanced or metastatic (patients whose disease has progressed after>12 months following the last dose of systemic treatment in the adjuvant/neoadjuvant setting are eligible).
- Patients are ineligible for or refuse standard chemotherapy approved for first line treatment
- Metastatic disease or locally advanced, unresectable disease
- Tumor specimen evaluable for PD-L1 expression by the central study laboratory and confirmation of PD-L1 expression level of at least 1% is required to be eligible

- A brain scan via computed tomography (CT) with contrast or magnetic resonance imaging (MRI) is to be performed to confirm absence of intracranial metastasis.

[2] Have the presence of measurable disease based on the Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1; Eisenhauer et al. 2009; Attachment 6) as determined by the site study team. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

[3] Have provided signed informed consent and are amenable to compliance with protocol schedules and testing

[4] Have submitted an evaluable tissue sample for biomarker analysis from a newly obtained core or excisional biopsy of a tumor lesion prior to enrollment. Formalin-fixed paraffin embedded tumor tissue sample blocks are preferred. Repeat samples may be required if adequate tissue is not provided.

Notes:

Patients for whom newly obtained samples cannot be obtained (for example, inaccessible or patient safety concern) may submit an archived specimen only upon agreement from the Sponsor. General guidance for archival samples is in the biomarker section (Section 8.4.2). See Criterion 1f for additional requirements for patients with 1st-Line NSCLC.

[5] Have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at the time of enrollment (Attachment 4)

[6] Have urinary protein that is <2 on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, then a 24-hour urine must be collected and must demonstrate <2 g of protein in 24 hours to allow participation in the study.

[7] Have adequate organ function, as defined in the table below, with all screening labs performed within 28 days of treatment initiation

Note: adequate organ function should be confirmed within 7 days prior to first dose on Cycle 1 Day 1.

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L
Platelets	≥100 x 10^9/L
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L (packed red blood cell transfusions are not allowed within one week prior to baseline hematology profile)
Renal	
Creatinine **OR** Measured or calculated creatinine clearance (see Attachment 5)	≤1.5 x ULN **OR** ≥60 mL/min
Hepatic	
Total bilirubin	≤1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤2.5 x ULN **OR** ≤5 x ULN for patients with liver metastases
Coagulation[b]	
International Normalized Ratio (INR) or Prothrombin Time (PT)	INR ≤1.5 x ULN or PT ≤ 5 seconds above ULN unless patient is receiving anticoagulant therapy as long as INR or PT is within therapeutic range of intended use of anticoagulants
Partial Thromboplastin Time (PTT) or Activated Partial Thromboplastin Time (aPTT)	PTT or aPTT ≤ 5 seconds above ULN unless patient is receiving anticoagulant therapy as long as PTT or aPTT is within therapeutic range of intended use of anticoagulants
Thyroid	
TSH, T3, and T4	TSH within the normal limits **OR** Total T3 or free T3 and free T4 are within the normal limits.

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] Creatinine clearance should be calculated per institutional standard.

[b] Patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If receiving warfarin, the patient must have an INR ≤ 3.0 and no active bleeding (i.e., no bleeding within 14 days prior to first dose of study treatment) or pathological condition present that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices). Patients on anticoagulation therapy with unresected primary tumors or local tumor recurrence following resection are not eligible.

[8] Be males or females at least 18 years of age on day of signing informed consent

[9] Have an anticipated life expectancy of ≥3 months

[10] Have resolution, except where otherwise stated in the inclusion criteria, of all clinically significant toxic effects of prior systemic cancer therapy, surgery, or radiotherapy to Grade ≤1 by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (v 4.0)

[11] For male patients, are sterile (including vasectomy confirmed by post-vasectomy semen analysis) or agree to use a reliable method of birth control and to not donate sperm during the study and for at least 120 days following the last dose of study treatment

Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

[12] For female patients, are surgically sterile, are postmenopausal, or agree to use a highly effective method of birth control (2 methods preferred) during the study and for 120 days following the last dose of study treatment

Note: A "highly effective method of birth control" is defined in Section 6.8.2.

[13] If female and of childbearing potential, must have a negative serum or urine pregnancy test within 7 days prior to enrollment.

Note: Non-childbearing potential (by other than medical reasons) is defined in Section 6.8.2.

Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

5.2. Exclusion Criteria

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

[14] Have non-measurable disease

[15] Have known brain metastases, uncontrolled spinal cord compression, or leptomeningeal disease

[16] Have received equal to or greater than 3 lines of prior systemic anticancer therapy for advanced disease in GEJ patients, and equal to or greater than 4 in patients in NSCLC and urothelial cancer patients

[17] Have a serious illness or medical condition(s) including, but not limited to, the following:

- Diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

- Active autoimmune disease that has required systemic treatment in past 2 years (that is, with use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (for example, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- Received a prior autologous or allogeneic organ or tissue transplantation
- Evidence of active, non-infectious pneumonitis
- History of interstitial lung disease
- Known human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related illness
- Known active Hepatitis B or Hepatitis C infection
- Liver cirrhosis at a level of Child-Pugh B (or worse)
- Liver 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.
- Have a serious cardiac condition, such as congestive heart failure; unstable angina pectoris; myocardial infarction within the last 6 months; valvulopathy that is severe, moderate, or deemed clinically significant; or arrhythmias that are symptomatic or require treatment (not including patients with rate-controlled atrial fibrillation)
- Active or uncontrolled clinically serious infection
- Known psychiatric or substance abuse disorders
- Known allergy or hypersensitivity reaction to any of the treatment components
- Have ongoing or recent (≤6 months) hepatorenal syndrome

[18] History of hematologic malignancy, malignant primary brain tumor, malignant sarcoma, or other malignant priory solid tumor not under study, except:

- no evidence of that disease for 5 years
- adequately treated non-melanomatous skin cancer
- curatively treated cervical carcinoma in situ or other noninvasive carcinoma or in situ neoplasm

[19] Have received any previous systemic therapy (including investigational agents) targeting VEGF/VEGF receptor, PD-1/PDL-1, or PD-1/PDL-2 signaling pathways. Prior therapy with other immune checkpoint inhibitor, including but not limited to, anti-CD137 antibody or anti-CTLA-4 antibody, is not permitted. ONLY for NSCLC patients: prior VEGF/VEGF receptor treatment is allowed.

[20] Have received a live vaccine within 30 days prior to enrollment. Seasonal flu vaccines that do not contain live virus are permitted.

[21] Have received transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF], or recombinant erythropoietin) within 4 weeks prior to Cycle 1 Day 1

[22] Have a significant bleeding disorder or vasculitis or had a Grade ≥3 bleeding episode within 12 weeks prior to enrollment

[23] Have experienced any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to enrollment

[24] Have experienced any Grade 3 or 4 venous thromboembolic event (VTE) that is considered by the investigator to be life threatening or that is symptomatic and not adequately treated by anticoagulation therapy, within 6 months prior to enrollment

[25] Have a history of gastrointestinal perforation and/or fistula within 6 months prior to enrollment

[26] Have a bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (hemicolectomy or extensive small intestine resection, either condition with chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea

[27] Have uncontrolled hypertension, as defined as Grade >2 CTCAE Version 4.0 (clinically, the patient continues to experience elevated blood pressure [systolic >160 mmHg and/or diastolic >100 mmHg] despite medications)

[28] Are receiving chronic therapy with any of the following within 7 days prior to enrollment:

- nonsteroidal anti-inflammatory agents (NSAIDs; such as indomethacin, ibuprofen, naproxen, or similar agents)
- other anti-platelet agents (such as clopidogrel, ticlopidine, dipyridamole, or anagrelide)
- Aspirin use at doses up to 325 mg/day is permitted.

[29] Have had a serious or non-healing wound, ulcer, or bone fracture within 28 days prior to enrollment

[30] Have an elective or a planned major surgery during the course of the trial or has undergone major surgery within 28 days prior to enrollment, or central venous access device placement within 7 days prior to enrollment.
Note: If patient received major surgery, the patient must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

[31] Have had chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks and/or monoclonal antibody treatment within 4 weeks prior to enrollment or not recovered (that is, ≤ Grade 1 or at baseline) from previously administered agents

Note: Neuropathy (≤ Grade 2) or nonserious and nonlife-threatening toxicities, such as alopecia, altered taste, or nail changes, are an exception to this criterion.
Note: Palliative radiotherapy during the study, if clinically indicated, can be considered after consultation with the Lilly clinical research physician (CRP).

[32] Are currently enrolled in a clinical trial involving an investigational product or non-approved use of a drug, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study or discontinued study drug within 28 days prior to enrollment. Patients participating in surveys or observational studies are eligible to participate in this study.

[33] Are or have an immediate family member (for example, spouse, parent/legal guardian, sibling, or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective institutional review board (IRB) approval (by chair or designee) is given allowing exception to this criterion for a specific patient

Additional Key Exclusion Criteria specific to all Gastric-GEJ patients:

[34] Have squamous cell or undifferentiated gastric-GEJ cancer

[35] Received previous systemic chemotherapy with a cumulative dose of >900 mg/m^2 of epirubicin or >400 mg/m^2 of doxorubicin

Additional Key Exclusion Criteria specific to all NSCLC patients:

[36] Have radiologically documented evidence of major blood vessel invasion or encasement by cancer

[37] Have radiographic evidence of intratumor cavitation, regardless of tumor histology

[38] Have a history of gross hemoptysis (defined as bright red blood or ≥1/2 teaspoon) within 2 months prior to enrollment

[39] Have pleural effusion, pericardial fluid, or ascites requiring drainage every other week or more frequently

[40] Have superior vena cava syndrome

[41] Have preexisting idiopathic pulmonary fibrosis as evidenced by CT scan/X-ray at baseline; have or had any disease of acute lung injury, idiopathic pulmonary fibrosis, or pneumoconiosis evident on an X-ray; have or had any disease of radiation pneumonia or drug-induced pneumonia

Additional Key Exclusion Criteria specific to First Line NSCLC patients (Cohort E):

[42] Epidermal growth factor receptor (EGFR)-sensitizing mutation and/or is echinoderm microtubule-associated protein-like 4(EML4) gene/anaplastic lymphoma kinase (ALK) gene fusion positive, or these status never tested.

Additional Key Exclusion Criteria specific to BTC patients (Cohort A1):

[43] Has received more than 2 lines of therapy for advanced or metastatic disease.

[44] TACE or radiotherapy, including use of radioactive beads, is not allowed.

[45] Received photodynamic treatment and does not have measurable or evaluable disease at the site. Exception: there is clear evidence of disease progression at the local site or measurable and progressing disease is present at another site.

[46] Have mixed hepatocellular biliary tract cancer histology.

Additional Key Exclusion Criteria specific to First Line Gastric-GEJ patients (Cohort A2):

[47] HER2-positive status or HER2 status never tested

5.3. Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened, only after discussion with and permission from the Lilly CRP or designee.

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.

6. Treatment

6.1. Treatments Administered

Ramucirumab and pembrolizumab will be administered per Table JVDF.2. For Gastric/GEJ, Urothelial, 2nd-4th line NSCLC and BTC, patients can receive study treatment after evaluable tumor tissue has been shipped to central study laboratory. For first line NSCLC, patient can receive study treatment after PD-L1 expression has been confirmed to be at least 1% (Section 5.1).

Across all study periods, including the continued access period, individual patients will be treated with ramucirumab and/or pembrolizumab, as follows:

- until confirmed progressive disease (Section 8.1.1.3), unacceptable toxicity, or discontinuation for any other reason
- for a maximum duration of study treatment of 35 cycles, approximately 2 years

Table JVDF.2. Phase 1 Treatment Regimens/Dosing Schedule

Tumor Type	Drug	Dose (IV)	Dose Frequency	Dose Day (21-day cycle)
Schedule 1 (Gastric-GEJ, BTC)	Ramucirumab	8 mg/kg	Q3W	Day 1, Day 8
	Pembrolizumab	200 mg	Q3W	Day 1
Schedule 2 (Gastric-GEJ, NSCLC or Urothelial)	Ramucirumab	10 mg/kg	Q3W	Day 1
	Pembrolizumab	200 mg	Q3W	Day 1

Abbreviations: BTC = biliary tract cancer; GEJ = gastroesophageal junction; IV = intravenous; NSCLC = non-small cell lung cancer; Q3W = every 3 weeks.
NOTE: Ramucirumab will be administered prior to pembrolizumab for every cycle (Section 6.1.1).

6.1.1. Selection and Timing of Doses

The ramucirumab and the pembrolizumab Pharmacy Manuals contain specific instructions for premedication, the preparation of infusion, and administration of each infusion solutions, separately.

A cycle is defined as an interval of 21 days (a delay of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 7 days and not counted as a protocol deviation).

The actual doses of ramucirumab administered will be determined by measuring the patient's weight at the beginning of each cycle. If the patient's weight fluctuates by more than ±10% from the weight used to calculate the prior dose, the dose must be recalculated. Recalculation of the ramucirumab dose for weight fluctuations of <10% is permitted but not required.

Ramucirumab will be administered prior to pembrolizumab, over an approximately 60-minute intravenous (IV) infusion. The maximum ramucirumab infusion rate is 25 mg/min.

Pembrolizumab 200 mg (fixed dose) will be administered over a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (that is, infusion time is 30 minutes -5 min/+10 min).

The first 2 cycles will require a 1-hr observation period i) between ramucirumab and pembrolizumab administration, and ii) after pembrolizumab infusion. For all cycles thereafter, no observation period will be required unless clinically indicated.

6.1.1.1. Phase 1a: Dose-Limiting Toxicity Observation

For the 21-day Phase 1a DLT observation period, the following criteria will be used to determine the progress of the study:

- If none of the initial 3 patients within a dose schedule develops a DLT, Expansion Phase 1b will start.
- If 1 of the initial 3 patients within a dose schedule develops a DLT, 3 additional patients will be added.
- If ≤1 of 6 patients within a dose schedule develops a DLT, Expansion Phase 1b will start.
- If 2 or more patients develop a DLT, enrollment will stop and an alternative dose level may be considered (in which case the protocol would be amended).

No intra-patient dose escalation or reduction is allowed during DLT observation. For the purpose of patient management, DLTs will lead to dose interruption during the observation period. Dose modifications will be allowed after the observation period.

For either group, if dropouts, dose interruptions, or reductions occur that result in a patient being nonevaluable for DLTs ("evaluable" is defined in Section 6.7), additional patients will be enrolled to achieve the minimum of 3 evaluable patients. The need for patient replacement will be determined based on consultation with the investigator and Lilly CRP/clinical research scientist (CRS). Patients who withdraw from the study during the DLT period for reasons other than a DLT may be replaced within the same dose level.

6.1.1.1.1. Definition of Dose-Limiting Toxicities

A DLT is defined as one of the following AEs reported during the DLT observation period, if considered to be definitely, probably, or possibly related to either study regimen by the investigator; and fulfills any one of the following criterion using NCI CTCAE Version 4.0:

1. Nonhematologic toxicity as follows:
   a) Grade 4 nonlaboratory toxicity
   b) Grade 3 nonlaboratory toxicity (for example, nausea, vomiting, and diarrhea) lasting >3 days despite optimal supportive care
   c) Any Grade 3 or Grade 4 laboratory value if:
      i) Medical intervention is required to treat the patient, or
      ii) The abnormality persists for >1 week.

Note: Liver function abnormality: For patients with liver metastasis who begin treatment with Grade 2 asparatate aminotransferase (AST) or alanine amino transferase (ALT), if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 7 days

2. Hematologic toxicity, as follows:
    a) Grade 4 toxicity lasting ≥ 7 days, or
    b) Grade 3 thrombocytopenia if associated with bleeding and requires platelet transfusion, or
    c) Febrile neutropenia Grade 3 or Grade 4
3. Grade 5 toxicity (that is, death)
4. Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting, for example:
    a) Any toxicity that is possibly related to study treatment that requires the withdrawal of the patient from the study during Cycle 1, or
    b) A delay of > 14 days due to persistent Grade ≥ 2 toxicities in initiating Cycle 2, with the exception of Grade 2 fatigue

Any infusion or hypersensitivity reactions occurring during the infusion of the drug are not considered dose-related and therefore will NOT be considered to be a DLT.

After each of the 3 patients in a dose schedule completes the observation period, a safety analysis will occur; the data will be reviewed by study investigators and the Lilly CRP/CRS, and the findings documented, indicating whether each dose schedule is or is not well tolerated. The results will inform the decision whether or not to move onto Expansion Phase 1b.

6.1.2. Investigator Responsibilities

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 and appropriate records, including those of investigational product (IP) dispensing and collection,
- ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations,
- 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 IP so that the situation can be assessed.

6.2. Treatment Assignment

Patients meeting all inclusion/exclusion criteria will be assigned to a dose schedule based upon their diagnosis at baseline (Table JVDF.2). Study drug will be allocated to patients using an interactive web response system.

6.3. Blinding

This is an open-label study.

6.4. Packaging and Labeling

All IP materials will be provided by Lilly. Clinical trial materials will be labeled according to the country's regulatory requirements. Ramucirumab and pembrolizumab vials should be stored under refrigeration at 2°C to 8°C (36°F to 46°F).

6.5. Preparation/Handling/Storage

Refer to the respective IBs for detailed information about preparation, handling, and storage of ramucirumab and pembrolizumab.

6.6. Dose Adjustments, Delays, and Discontinuation

Doses of either study drug may need to be delayed, reduced (ramucirumab only), or discontinued to manage specific AEs or other toxicities.

When a study drug is delayed, if possible and appropriate, patients should resume study treatment within 21 days, with every effort made to start on Day 1 of the next dosing schedule.

6.6.1. Ramucirumab Dose Adjustments, Delays, and Discontinuation

The ramucirumab dose may need to be delayed and/or reduced if the patient experiences an adverse event, including an adverse event of special interest (AESI) (Section 8.2.1.1.1). Doses may be delayed to allow time for the patient to recover from the event. Certain AEs require immediate and permanent discontinuation of study treatment. Any patient who requires a dose reduction will continue to receive a reduced dose until discontinuation from ramucirumab or discontinuation from the study. Any patient who has had 2 dose reductions and who experiences a toxicity that would cause a third dose reduction must be discontinued from ra mucirumab.

Table JVDF.3 presents the ramucirumab dose reductions for each treatment cohort.

Table JVDF.4 presents the criteria for dose modifications and dose discontinuations applicable if the patient experiences a ramucirumab AESI or other AEs at least possibly related to ramucirumab.

Table JVDF.3. Ramucirumab Dose Reductions[a]

	Dose Schedule 1: Gastric-GEJ/BTC (21-day Cycle)	Dose Schedule 2 Gastric-GEJ/NSCLC/Urothelial (21-day Cycle)
Starting dose	8 mg/kg on D1, D8	10 mg/kg on Day 1
First dose reduction	6 mg/kg on Day 1, Day 8	8 mg/kg on Day 1
Second dose reduction	5 mg/kg on Day 1, Day 8	6 mg/kg on Day 1

Abbreviations: BTC = biliary tract cancer; D = Day; GEJ = gastroesophageal; NSCLC = non-small cell lung cancer.

[a] Ramucirumab dose reductions are allowed between cycles and within a given cycle.

Table JVDF.4. Dose-Modification Guidelines for Ramucirumab for Adverse Events at Least Possibly Related to Ramucirumab, including Adverse Events of Special Interest

	Adverse Event ***NOTE: All Specific Adverse Events Listed are defined as AESIs in Section 8.2.1.1.1).***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in*** Table JVDF.3. *Treating physicians can modify or discontinue ramucirumab more conservatively than in the guidance below.*
1.	**Infusion-related reaction**		
1.a.	Infusion-related reaction	2	Interrupt and reduce the infusion rate by 50% for the duration of the infusion and for all future infusions. Prior to all future infusions of ramucirumab, premedicate with: • an intravenous histamine H1 antagonist, such as diphenhydramine hydrochloride • dexamethasone or equivalent • acetaminophen/paracetamol
1.b.	Infusion-related reaction	3-4	Immediately and permanently discontinue ramucirumab
2.	**Hypertension**		
2.a.	Hypertension (non-life-threatening and associated with symptoms) NOTE: Hypertension should be monitored prior to each ramucirumab infusion.	3	• Delay ramucirumab until the hypertension is controlled with medication and is resolved to Grade 0-2. o If controlled with medication and resolved to Grade 0-2, then may resume ramucirumab at current dose. o If NOT controlled with medication and not resolved to Grade 0-2 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion.
2.b.	Uncontrolled hypertension, hypertensive crisis, or hypertensive encephalopathy	4	Immediately and permanently discontinue ramucirumab.

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

	Adverse Event ***NOTE: All Specific Adverse Events Listed are defined as AESIs in Section 8.2.1.1.1).***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTE: Dose reductions to occur as defined in*** Table JVDF.3.
3.	**Proteinuria**		
3.a.	Proteinuria = 2+ (dipstick or routine urinalysis)[a]		• Administer ramucirumab at the current dose if clinically indicated. • Obtain 24-hour urine protein results within 3 days prior to the next ramucirumab dose. o If urine protein is <2 g/24 h, administer ramucirumab at the patient's current dose. o If urine protein is ≥2 g/24 h, modify the ramucirumab dose based on 24-hour collection. See *Proteinuria ≥2 g/24 h (24-hour urine collection)*, Line 3.c in this table.
3.b.	Proteinuria >2+ (dipstick or routine urinalysis)[a]		• Delay ramucirumab until urine protein returns to <2 g/24 h. • Obtain 24-hour urine protein results within 3 days prior to the next ramucirumab dose. o If urine protein is <2 g/24 h, no further dose delay or dose reduction is required. o If urine protein remains ≥2 g/24 h and is not resolved within a reasonable timeframe, discontinue ramucirumab at investigator's discretion.
3.c.	Proteinuria ≥2 g/24 h (24-hour urine collection)[a]		• **First or second occurrence**: delay ramucirumab until urine protein returns to <2 g/24 h. o If urine protein returns to <2 g/24 h, reduce ramucirumab dose. o If urine protein remains ≥2 g/24 h and is not resolved within a reasonable timeframe, discontinue ramucirumab at investigator's discretion. • **Third occurrence**: discontinue ramucirumab.
3.d.	Proteinuria >3 g/24 h **or** in the setting of nephrotic syndrome[a]		Immediately and permanently discontinue ramucirumab.
4.	**Arterial thromboembolic events, venous thromboembolic events**	3 or 4	Immediately and permanently discontinue ramucirumab.
5.	**Bleeding/hemorrhage**	3 or 4	Immediately and permanently discontinue ramucirumab.
6.	**Gastrointestinal perforation**		Immediately and permanently discontinue ramucirumab.

	Adverse Event ***NOTE: All Specific Adverse Events Listed are defined as AESIs in Section 8.2.1.1.1).***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTE: Dose reductions to occur as defined in*** Table JVDF.3.
7.	**Reversible posterior leukoencephalopathy syndrome**		Immediately and permanently discontinue ramucirumab.
8.	**Congestive heart failure**	3-4	Immediately and permanently discontinue ramucirumab.
9.	**Fistula formation**		Immediately and permanently discontinue ramucirumab.
10.	**Impaired wound healing**		
10.a.	Prior to planned surgery		Withhold ramucirumab.
10.b	After surgery		Resume ramucirumab based on clinical judgment.
10.c.	Wound-healing complications developed during study treatment		Delay ramucirumab dosing until the wound is fully healed.
11.	Liver injury/liver failure		
11.a.	Hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis		Immediately and permanently discontinue ramucirumab.
12	**Hypothyroidism**	2-4	Therapy with ramucirumab can be continued while treatment for the thyroid disorder is instituted.
13	**Other adverse events considered at least possibly related to ramucirumab**[b]		
13.a	Non-life threatening and reversible	3	May delay ramucirumab until resolved to Grade 0-1. • If resolved to Grade 0-1, may reduce ramucirumab dose. • If NOT resolved to Grade 0-1 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion
13.b	Adverse Event	4	Permanently discontinue treatment immediately, with the exception of Grade 4 fever or Grade 4 laboratory abnormality, in which case: • **First occurrence:** Delay ramucirumab until resolved to Grade 0-1. o If resolved to Grade 0-1, may resume ramucirumab original dose at the discretion of the investigator. o If NOT resolved to Grade 0-1 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion. • **Second occurrence:** Delay ramucirumab until resolved to Grade 0-1. o If resolved to Grade 0-1, reduce ramucirumab dose. o If NOT resolved to Grade 0-1 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion.

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

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

a Perform urinalysis within 3 days prior to each infusion of ramucirumab. If 24-hour urine collection is also performed, the results of 24-hour urine collection should be used for clinical decision-making.

b Patients who enter the study with symptoms or laboratory values equivalent to NCI-CTCAE Version 4.0 Grade 1-2 adverse events should not necessarily have dose delays or reductions related to the persistence or mild worsening of those symptoms or laboratory values. Grade 2 toxicities which represent clinically significant worsening of symptoms from baseline, ramucirumab dose may be delayed at the discretion of the investigator. If the toxicity is resolved to Grade 0-1, may reduce ramucirumab dose. If the toxicity is not resolved to Grade 0-1, may discontinue ramucirumab.

6.6.2. Pembrolizumab Dose Delays and Discontinuation

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld (dose reductions are not permitted) for drug-related toxicities and severe or life-threatening AEs. See Section 6.9.1.3 for supportive care guidelines, including use of corticosteroids. Table JVDF.5 presents the guidelines for treatment delays and discontinuation of pembrolizumab for specific AEs associated with pembrolizumab treatment.

Table JVDF.5. Pembrolizumab Treatment Discontinuation Guidelines for Specific Adverse Events at Least Possibly Related to Pembrolizumab

	Adverse Event	CTCAE Grade	Treatment Delay and Discontinuation
1	**Diarrhea/Colitis**	2-3	Delay pembrolizumab until resolved to Grade 0-1. • If resolved to Grade 0-1 within 12 weeks of last dose, then resume pembrolizumab. • Within 12 weeks of last dose, if toxicity does not resolve to Grade 0-1 *or* with inability to reduce corticosteroid to ≤10 mg/day of prednisone or equivalent per within 12 weeks, discontinue pembrolizumab.
		4	Immediately and permanently discontinue pembrolizumab.
2	**Increased AST, ALT, or Bilirubin**[a]	2	Delay pembrolizumab until resolved to Grade 0-1. • If resolved to Grade 0-1 within 12 weeks of last dose, then resume pembrolizumab. • If NOT resolved to Grade 0-1 within 12 weeks of last dose, then discontinue pembrolizumab.
		3-4	Immediately and permanently discontinue pembrolizumab. See exceptions below.
3	**Type 1 Diabetes Mellitus (if new onset) or Hyperglycemia associated with evidence of beta cell failure**	T1DM or 3-4	Delay pembrolizumab until patients are clinically and metabolically stable. • If clinically and metabolically within 12 weeks of last dose, then resume pembrolizumab. • If NOT clinically and metabolically stable within 12 weeks of last dose, then immediately and permanently discontinue pembrolizumab.
4	**Hypophysitis**	2-4	Delay pembrolizumab until resolved to Grade 0-1. • If resolved to Grade 0-1 within 12 weeks of last dose, then resume pembrolizumab. • Within 12 weeks of last dose, if toxicity does not resolve to Grade 0-1 *or* with inability to reduce corticosteroid to ≤10 mg/day of prednisone or equivalent per within 12 weeks, immediately and permanently discontinue pembrolizumab.

Pembrolizumab Treatment Discontinuation Guidelines for Specific Adverse Events at Least Possibly Related to Pembrolizumab (continued)

	Adverse Event	CTCAE Grade	Treatment Delay and Discontinuation
5	**Hyperthyroidism**	2	Therapy with pembrolizumab can be continued; non-selective beta-blockers (e.g., propranolol) are suggested as initial therapy for hyperthyroidism (Section 6.9.1.3.5).
		3	Delay pembrolizumab until resolved to Grade 0-1. • If resolved to Grade 0-1 within 12 weeks of last dose, then resume pembrolizumab. • Within 12 weeks of last dose, if toxicity does not resolve to Grade 0-1 *or* with inability to reduce corticosteroid to ≤10 mg/day of prednisone or equivalent per within 12 weeks, immediately and permanently discontinue pembrolizumab.
		4	• Immediately and permanently discontinue pembrolizumab.
	Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
6	**Infusion Reaction**	2	• First occurrence: Stop infusion of pembrolizumab until resolved to Grade 0-1. o If resolved to Grade 0-1 within 1 hour of stopping infusion, then restart infusion at 50% of the original rate (e.g., from 100 mL/hr to 50 mL/hr). o If NOT resolved to Grade 0-1 within 1 hour of stopping infusion, delay pembrolizumab until symptoms resolve, and premedicate for the next scheduled dose. • Second occurrence: If toxicity develops despite premedication, immediately and permanently discontinue pembrolizumab.
		3-4	Immediately and permanently discontinue pembrolizumab.

Pembrolizumab Treatment Discontinuation Guidelines for Specific Adverse Events at Least Possibly Related to Pembrolizumab (continued)

	Adverse Event	CTCAE Grade	Treatment Delay and Discontinuation
7	**Pneumonitis**	2	Delay pembrolizumab until resolved to Grade 0-1. • If resolved to Grade 0-1 within 12 weeks of last dose, then resume pembrolizumab. Within 12 weeks of last dose, if toxicity does not resolve to Grade 0-1 *or* with inability to reduce corticosteroid to ≤10 mg/day of prednisone or equivalent per within 12 weeks, immediately and permanently discontinue pembrolizumab.
		3-4	Immediately and permanently discontinue pembrolizumab.
8	**Renal Failure or Nephritis**	2	Delay pembrolizumab until resolved to Grade 0-1. • If resolved to Grade 0-1 within 12 weeks of last dose, then resume pembrolizumab. • Within 12 weeks of last dose, if toxicity does not resolve to Grade 0-1 *or* with inability to reduce corticosteroid to≤10 mg/day of prednisone or equivalent per within 12 weeks, immediately and permanently discontinue pembrolizumab.
		3-4	Immediately and permanently discontinue pembrolizumab.
9	**Other Adverse Events**[b]	3 or severe	Delay pembrolizumab until resolved to Grade 0-1. • If resolved to Grade 0-1 within 12 weeks of last dose, then resume pembrolizumab. • Within 12 weeks of last dose, if toxicity does not resolve to Grade 0-1 *or* with inability to reduce corticosteroid to ≤10 mg/day of prednisone or equivalent per within 12 weeks, immediately and permanently discontinue pembrolizumab.
		4	Immediately and permanently discontinue pembrolizumab.

Pembrolizumab Treatment Discontinuation Guidelines for Specific Adverse Events at Least Possibly Related to Pembrolizumab (concluded)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; T1DM = type 1 diabetes mellitus.

Note: **Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event. Reoccurrence of Grade 2 pneumonitis also warrants permanent discontinuation.**

a For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week, then patients should be discontinued.

b Patients with intolerable or persistent Grade 2 drug-related AE(s) may hold study medication at physician discretion. Permanently discontinue pembrolizumab for persistent Grade 2 adverse reactions for which pembrolizumab has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

6.6.3. Dose Delays for Reasons Not Related to Study Treatment

Dosing interruptions of either study drug are also permitted for reasons not related to study treatment (for example, elective surgery, unrelated medical events, patient vacation, and/or holidays).

Patients should resume the delayed study drug(s) within 21 days of the scheduled interruption, with every effort made to start on Day 1 of the next dosing schedule, unless otherwise discussed with the Sponsor. The reason for interruption should be documented on the case report form (CRF).

6.7. 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.

During Phase 1a, DLT-evaluable population is defined as all enrolled patients in DLT Phase 1a who either completed 21 days of observation or discontinued study treatment or study participation before completing 1 cycle due to a DLT.

Any patient who discontinued from the study before completing safety monitoring for the 21-day DLT observation period for any other reason than a DLT will be considered non-evaluable for DLT assessment.

Patients who are not evaluable for pharmacokinetics, but who complete 1 cycle of therapy, may be replaced upon consultation with the investigator(s) and the Lilly CRP/CRS to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT.

6.8. Lifestyle and/or Dietary Requirements

6.8.1. Diet

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6.8.2. Contraception

Based on ramucirumab's mechanism of action, it is likely that ramucirumab will inhibit angiogenesis and may potentially result in adverse effects during pregnancy and postnatal development.

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

Therefore, 1) non-pregnant, non-breast-feeding women may only be enrolled if they are willing to use a highly effective method of birth control or are considered to be of non-childbearing potential and 2) only men may be enrolled who use a reliable method of birth control, or who are sterile (including confirmed vasectomy) and do not donate sperm (Section 5.1).

For female patients, non-childbearing potential (by other than medical reasons) is defined as any one of the following:

- ≥45 years of age and has not had menses for greater than 2 years
- Amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon pretrial (screening) evaluation (FSH level >40 mIU/mL)
- At least 6 weeks following surgical bilateral oophorectomy or tubal ligation with or without hysterectomy. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure; otherwise, the patient must be willing to use an adequate barrier method throughout the study, starting with the screening visit through 120 days after the last dose of study treatment.
- not heterosexually active for the duration of the study

A "highly effective method of birth control" 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.

Two birth control methods are preferred, and can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide as per local regulations or guidelines.

Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents). For patients using a hormonal contraceptive method, information regarding pembrolizumab and its potential effect on the contraceptive should be addressed.

Patients should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study treatment.

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

6.9. Concomitant Therapy

A list of restricted and excluded concomitant therapies and exceptions is provided in Attachment 7. All premedication, supportive care, and concomitant medication must be reported on the CRF at each visit.

6.9.1. Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. For both study drugs, specific AEs have been identified based on past data for special monitoring and, when necessary, supportive care. For ramucirumab, these are referred to as Adverse Events of Special Interest (AESI).

See Table JVDF.4 and Table JVDF.5 for dose reductions (ramucirumab only), delays, or discontinuations for AEs considered to be at least possibly related to study treatment (pembrolizumab or ramucirumab).

6.9.1.1. Infusion-Related Reactions- Ramucirumab and Pembrolizumab

Infusion-related reactions (IRRs) have been identified as events of interest for both ramucirumab and pembrolizumab. In the event of an IRR, blood samples will be collected for both PK and immunogenicity analysis for each drug at the following time points: (i) as close as possible to the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days following the IRR.

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

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

The first 2 cycles will require a 1-hour observation period i) between ramucirumab and pembrolizumab administration, and ii) after pembrolizumab infusion. For all cycles thereafter, no observation period will be required unless clinically indicated. If the patient shows no evidence of an IRR with the first 2 cycles of each study drug, no observation period is required for subsequent cycles, unless clinically indicated. In the event an IRR occurs thereafter, the 1-hour observation should be reinstituted.

6.9.1.1.1. Infusion-Related Reactions-Ramucirumab

Table JVDF.4 presents ramucirumab dose modification and supportive care guidelines for patients who experience an IRR associated with ramucirumab.

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

6.9.1.1.2. Infusion-Related Reactions-Pembrolizumab

Table JVDF.5 presents pembrolizumab dose modification and supportive care guidelines for patients who experience an IRR associated with pembrolizumab. For Grade 3-4 IRRs, the patient is immediately and permanently discontinued from pembrolizumab.

6.9.1.2. Supportive Care for Ramucirumab

6.9.1.2.1. Supportive Care by Adverse Event of Special Interest

6.9.1.2.1.1. Hypertension

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

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

6.9.1.2.1.2. Proteinuria

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

6.9.1.2.1.3. Thromboembolic Events

6.9.1.2.1.3.1. Arterial Thromboembolic Events

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

6.9.1.2.1.3.2. Venous Thromboembolic Events

Venous thromboembolic events are associated with cancer; however, the incidence of VTEs likely varies depending on the type of cancer, stage, and intensity of imaging. Additionally, VTEs have been associated with some antiangiogenic therapy, although the incidence varies depending on the type of therapy, use of concomitant chemotherapy agents, and specific disease state. 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.

6.9.1.2.1.4. Bleeding/Hemorrhage

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

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

6.9.1.2.1.5. Gastrointestinal Perforation

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

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

6.9.1.2.1.6. Reversible Posterior Leukoencephalopathy Syndrome

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

Across the clinical program to date, 2 cases of RPLS have been reported: One case occurred in each arm of the recently completed double-blind, randomized, placebo-controlled Phase 3 Study RAISE evaluating ramucirumab in combination with FOLFIRI versus FOLFIRI in combination with placebo for patients with metastatic colorectal cancer.

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

6.9.1.2.1.7. 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. A small number of CHF events (including fatal) were also reported in patients who had received ramucirumab after prior treatment with anthracyclines in the Phase 2 and Phase 3 studies.

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

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

6.9.1.2.1.8. Fistula Formation

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

6.9.1.2.1.9. Surgery and Impaired Wound Healing

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

6.9.1.2.1.10. Liver Failure and Other Significant Liver Injury

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

6.9.1.2.2. Supportive Care Agents for Ramucirumab- Guidelines

Supportive care measures may include but are not limited to antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Guidelines regarding the use of specific supportive care agents are presented below.

6.9.1.2.2.1. Antiemetic Agents

Although emesis is not an expected side effect of ramucirumab, the use of antiemetic agents is permitted at the discretion of the investigator. Acceptable antiemetic agents include 5-HT_3 receptor antagonists (for example, ondansetron), dopamine receptor antagonists (for example, metoclopramide), corticosteroids (for example, dexamethasone), and others.

6.9.1.2.2.2. Analgesic Agents

The use of analgesic agents is permitted at the discretion of the investigator. Opiate and nonopiate analgesic agents are permitted (including acetaminophen/paracetamol); however, use of NSAIDs and/or aspirin is restricted (Attachment 7).

6.9.1.2.2.3. Appetite Stimulants

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

6.9.1.2.2.4. Granulocyte-Colony Stimulating Factors

The as-needed use of G-CSFs is permitted at the discretion of the investigator based on American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2006) (Attachment 7).

6.9.1.2.2.5. Erythroid Growth Factors

The as-needed use of erythroid-stimulating factors (for example, erythropoietin) is permitted at the discretion of the investigator based on ASCO guidelines (Rizzo et al. 2008) (Attachment 7).

6.9.1.2.2.6. Other Supportive Care Agents

The use of benzodiazepines, antidepressants, laxatives, and other agents that may be helpful in controlling disease-related symptoms are also permitted and encouraged, except as prohibited in Attachment 7.

6.9.1.3. Supportive Care for Pembrolizumab

Supportive care guidelines for the management of specific AEs with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Several courses of steroid tapering may be necessary, as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance as outlined below.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.9.1.3.1. Pneumonitis - Pembrolizumab

Apply the following supportive care guidance for pneumonitis:

For Grade 2 events, treat with systemic corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent). When symptoms improve to Grade 0-1, steroid taper should start and be continued over no less than 4 weeks.

For Grade 3-4 events, immediately treat with intravenous steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1 to 2 mg/kg/day or dexamethasone 4 mg every 4 hours). Administer additional anti-inflammatory measures, as needed.

Add prophylactic antibiotics for opportunistic infections, in the case of prolonged steroid administration.

6.9.1.3.2. Diarrhea/Colitis - Pembrolizumab

Patients should be monitored carefully for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, and blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis**, administer oral corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent).
- For **Grade 3 or 4 diarrhea/colitis (**or **Grade 2 diarrhea**), treat with intravenous steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1 to 2 mg/kg/day or dexamethasone 4 mg every 4 hours).
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

6.9.1.3.3. Type 1 Diabetes Mellitus or Hyperglycemia - Pembrolizumab

For Grade 3-4 hyperglycemia or new onset type 1 diabetes mellitus (T1DM), including diabetic ketoacidosis (DKA) or ≥ Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA),supportive care guidance is as follows:

- Insulin replacement therapy is recommended for T1DM and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

6.9.1.3.4. Hypophysitis - Pembrolizumab

Apply the following supportive care guidance for hypophysitis:

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

6.9.1.3.5. Hyperthyroidism or Hypothyroidism - Pembrolizumab

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Apply the following supportive care guidance:

- **Grade 2** hyperthyroidism events and **Grade 2-4** hypothyroidism:
  - In hyperthyroidism, non-selective beta-blockers (for example, propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

6.9.1.3.6. Hepatic Events - Pembrolizumab

See Site Guidance Document for Hepatic Monitoring/Drug-Induced Liver Injury. Apply the following supportive care guidance for hepatic events:

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids.
- For **Grade 3-4** events, treat with IV corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

6.9.1.3.7. Renal Failure or Nephritis - Pembrolizumab

Apply the following supportive care guidance for renal failure or nephritis:

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

6.10. Continued Access Period

The continued access period begins after study completion and ends at end of trial (Figure JVDF.2 and Section 4.4).

Attachment 1 presents the schedule of events, including AE/serious adverse event (SAE) data collection and a continued access follow-up visit, to occur 30 days after discontinuation from the

continued access period or when the patient starts a new anticancer therapy, whichever happens first.

Patients receiving IPs and experiencing ongoing clinical benefit, without disease progression, and no undue risks may continue to receive IP after study completion in the continued access period until one of the criteria for discontinuation is met, including unacceptable toxicity or pregnancy (Section 7.1). Patients may receive a maximum of 35 cycles (approximately 2 years) of study treatment.

Lilly will notify investigators when the continued access period begins and ends.

7. Discontinuation Criteria

The reason for discontinuation and the date of discontinuation will be collected for all patients. All enrolled patients who discontinue, regardless of whether or not they received IPs, will have procedures performed as shown in the Time and Events Table (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.

7.1. Discontinuation from Study Treatment

Patients are considered to have discontinued from study treatment when BOTH pembrolizumab and ramucirumab will no longer be administered.

Details regarding discontinuation due to an AE or due to pregnancy are found in Section 6.6, Section 8.2.1, and Section 8.2.1.2). Patients will be discontinued from study treatment if they meet any of the following additional criteria:

- 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
- 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 the study occurs prior to introduction of the new agent.
- The investigator decides that the patient should be discontinued from study treatment.
- The patient requests that the patient be withdrawn from study treatment.
- The patient is significantly noncompliant with study procedures and/or treatment.
- disease progression (must be confirmed if patient is clinically stable [Section 8.1.1.3])
- Discontinuation of treatment may be considered for patients who have attained a confirmed CR that have been treated for at least 24 weeks and had at least 2 cycles of study treatments beyond the date when the initial CR was declared.

7.1.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the Sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Sponsor CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with study drug(s).

7.2. 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.
- The patient requests that the patient be withdrawn from the study.

- The patient becomes pregnant during the study. See Section 8.2.1.3 regarding reporting requirements on fetal outcome and breastfeeding.
- Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

7.2.1. 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 is unable to be contacted by the study site. 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.

8. Study Assessments and Procedures

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

Study procedures assessments and their timing are described in the sections below and shown in the Time and Events Table (Attachment 1).

8.1. Efficacy

8.1.1. Efficacy Assessments at Baseline and during Study Treatment

RECIST 1.1 (Attachment 6) will be applied as the primary measure for assessment of tumor response and date of disease progression. Local tumor imaging (investigator assessment with site radiological reading) will be used.

Tumor imaging should be performed by CT, which is preferred for the majority of patients, as the more commonly used modality. Magnetic resonance imaging (MRI) should only be used when CT is contraindicated or for imaging in the brain. The same imaging technique should be used for a patient throughout the trial. Imaging should include the chest, abdomen, and pelvis.

The subsections below describe in detail the tumor imaging and assessment measures at baseline and during study treatment (one or both study drugs, Section 4.1.3).

8.1.1.1. Baseline Tumor Imaging

Initial tumor imaging at screening must be performed within 21 days prior to the date of enrollment (assignment to treatment) or within 28 days of the first dose of study treatment. The site study team must review screening images to confirm the patient has measurable disease per RECIST 1.1.

Scans performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within protocol required time frame as described above.

8.1.1.2. Tumor Imaging During Study Treatment

During study treatment, tumor response will be assessed every 6 weeks (± 7 days) by investigator, with confirmatory assessment obtained at the next routine scheduled imaging time point (that is, after 6 weeks ±7 days). After 24 weeks, tumor assessment will be conducted every 12 weeks (± 7 days).

Per RECIST 1.1, partial or complete response should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (that is, 6 weeks $\pm$ 7 days later), whichever is clinically indicated.

Continue to perform imaging until whichever of the following occurs first:

- disease progression confirmed by the second radiographic exam

- the start of new anticancer treatment
- withdrawal of consent
- death
- end of trial

8.1.1.3. Immune-Related RECIST (irRECIST)

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, for Study JVDF, RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab (immune-related RECIST [irRECIST]). irRECIST will be applied as detailed below for treatment-related decisions, and the resulting data will be included in the clinical database.

If radiologic imaging verifies initial progressive disease (PD), tumor assessment should be repeated approximately 4 weeks later in order to confirm PD with the option of continuing study treatment per below while awaiting radiologic confirmation of progression.

If repeat imaging shows < 20% target lesion compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued / resumed.

If repeat imaging confirms PD due to any of the scenarios listed below, patients will be discontinued from study treatment. In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions (see Site Guidance Document for RECIST/irRECIST).

Scenarios where PD is confirmed at repeat imaging:

- Target lesions remains ≥ 20% and at least 5-mm absolute increase compared to nadir.
- Non-target disease resulting in initial PD is worse (qualitative).
- New lesion resulting in initial PD is worse (qualitative).
- Additional new lesion(s) since last evaluation

In patients who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a patient on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- absence of signs and symptoms indicating disease progression
- no decline in ECOG performance status
- absence of rapid progression of disease

- absence of progressive tumor at critical anatomical sites (for example, cord compression) requiring urgent alternative medical intervention

When feasible, patients should not be discontinued from study treatment until progression is confirmed by the second radiographic exam. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Patients who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

Table JVDF.6 summarizes the guidance for imaging and treatment after the first radiologic evidence of PD.

Table JVDF.6. Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of PD	Repeat imaging approximately 4 weeks later at site to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging approximately 4 weeks later to confirm PD, per investigator discretion only	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments every 6 weeks	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments every 6 weeks	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

Abbreviations: CR = complete response; N/A = not applicable; PD = progressive disease; PR = partial response; SD = stable disease.

NOTE: Discontinuation of study treatment may be considered for patients who have attained a confirmed CR that have been treated for at least 24 weeks with study treatment and had at least 2 treatment cycles beyond the date when the initial CR was declared.

In determining whether or not the tumor burden has increased or decreased, study site investigators should consider all target lesions as well as non-target lesions (see Procedure Manual). Patients that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation. If radiologic progression is confirmed by subsequent scan, then the patient will be discontinued from study treatment. If radiologic progression is not confirmed,

then the patient should resume or continue trial treatment and have their next tumor imaging according to the protocol schedule of every 6 weeks (± 7 days).

8.1.2. Efficacy Assessments during Postdiscontinuation Follow-Up

Postdiscontinuation follow-up during the study period will be conducted per the Time and Events Table (Attachment 1).

Tumor assessments may continue for patients who are withdrawn from the study for reasons other than disease progression every 6 to 12 weeks depending on standard of care.

8.1.3. Efficacy Measures

The objective response rate (ORR) is the proportion of enrolled patients who have received any amount of either study drug, have at least 1 postbaseline tumor image, and achieve a best overall response of complete response (CR) or partial response (PR). The ORR will be assessed based on RECIST 1.1 (Eisenhauer et al. 2009) and irRECIST.

Time-to-response (TTR) is the time from the date of first study treatment until the first evidence of a confirmed CR or PR, as defined in Section 8.1.1.3.

Duration of response (DoR) is defined only for responders (patients with a confirmed CR or PR). It is measured from the date of first evidence of a confirmed 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.

Disease Control Rate (DCR) is defined as the proportion of enrolled patients who have a best overall response of CR, PR, or stable disease (SD).

Progression-free survival (PFS) is defined as the time from the date of first study treatment until the date of the first observed radiographically documented PD or 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 enrollment date, regardless of whether or not objectively determined disease 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 complete objective progression-free disease assessment date.

TTR, DoR, DCR, and PFS will be assessed based on RECIST 1.1. Exploratory analysis of TTR, DoR, and PFS may be conducted using irRECIST.

Overall survival (OS), including 1- and 2- year survival rates, is determined from the date of first study treatment until death due to any cause. If the patient was alive at the data inclusion cutoff date for the analysis (or was lost to follow-up), OS will be censored on the last date the patient was known to be alive.

8.1.4. Appropriateness of Measurements

The measures used in this study are consistent with those used in most conventional oncology trials.

8.2. Safety

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, 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 Time and Events Table (Attachment 1). Table JVDF.7 presents a summary of AE and SAE reporting guidelines and shows which database or storage system is used.

Table JVDF.7. Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to be Reported[a]	Collection Database[b]	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions	x	
	All AEs	x	
	SAEs related to protocol procedures	x	X
Study treatment period	All AEs	x	
	All SAEs	x	X
Short-term postdiscontinuation follow-up (30 days)	All AEs	x	
	All SAEs	x	X
Long-term postdiscontinuation period			
Through post-discontinuation follow-up visit (90 days)	All SAEs	x	X
Additional long-term discontinuation follow up (every 90 days to study completion)	All SAEs related to protocol procedures or IP	x	X
Continued access period	All AEs	x	
	All SAEs	x	X
Continued access follow-up (30 days; or sooner, to occur when patient begins a new anti-cancer therapy)	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 IP that the investigator becomes aware of		X

Abbreviations: AEs = adverse events; CRF = case report form; IP = Investigational Product (ramucirumab or pembrolizumab); SAEs = serious adverse events.

a Although not strictly adverse events, pregnancy and breastfeeding are reported as SAEs. The reporting period starts after receiving IP(s) and ends 120 days after discontinuing study treatment or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier.

b CRF collection guidelines will be followed.

8.2.1. Adverse Events

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), labs, vital sign measurements, or other procedures that result in a diagnosis should be reported to Lilly or its designee.

After the informed consent form (ICF) is signed, 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. Site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). Progression of the cancer under study is not considered an adverse event unless it is considered to be drug-related by the investigator. 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 IP must be reported to Lilly or its designee via CRF.

Investigators should report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure or IP via CRF.

The investigator decides whether he or she interprets the observed AEs as reasonably possibly related to disease, to the study regimen, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the IP, the following is defined:

> Reasonably Possibly **Related**: Reasonable possibility that there is a cause and effect relationship between the IP, study device, and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

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

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 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) dictionary.

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.

8.2.1.1. Reporting Ramucirumab Adverse Events of Special Interest and Pembrolizumab Events of Clinical Interest

8.2.1.1.1. Infusion-Related Reactions-Ramucirumab and Pembrolizumab

Any treatment-related IRRs are defined according to the CTCAE Version 4.0 definition (*General Disorders and Administration Site Conditions*). Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (*Immune System Disorders*). In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event.

8.2.1.1.2. Adverse Events of Special Interest- Ramucirumab

Section 6.9.1.2.1 describes supportive care measures for each ramucirumab AESI.
Table JVDF.3 presents the dose-modification guidelines for ramucirumab AESIs. Contact the Lilly CRP if questions arise concerning AESIs.

8.2.1.1.3. Events of Clinical Interest- Pembrolizumab

The 2 categories of ECIs include:

1. an overdose of pembrolizumab (≥1000 mg [5 times the dose]) not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal (ULN) and an elevated total bilirubin lab value that is greater than or equal to 2X ULN and, at the same time, an alkaline phosphatase lab value that is less than 2X ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing. Please refer to the Site Guidance Document for Drug-induced Liver Injury.

ECIs identified from the date of first dose through 90 days following discontinuation of study treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported to the Sponsor (ECIs that are SAEs are reported within 24 hours, per Section 8.2.1.2).

8.2.1.2. 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, including, but not limited to:
    - Is a new cancer (that is, not a condition under study. NOTE: metastases are not considered to be a new cancer).
    - Is associated with an overdose (as defined in Section 8.2.1.1.3 for pembrolizumab and greater than the appropriate absolute dose based on the patient's weight as specified in Section 6.1.1).

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 IP and ends 90 days following cessation of treatment, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier. If a patient experiences an SAE after signing informed consent, but prior to receiving IPs, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

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.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the IPs.

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 IPs, 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 pembrolizumab and ramucirumab IBs.

8.2.1.3. Pregnancy

Cases of pregnancy that occur during maternal or paternal exposures to IPs (ramucirumab or pembrolizumab) should be reported within 24 hours. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, congenital abnormality, fetal death, intrauterine death, miscarriage and stillbirth, or other disabling or life-threatening complication to the mother or newborn must be reported as AEs. Data on fetal outcome (including and breastfeeding) are collected for regulatory reporting and drug safety evaluation. The following additional measures will be taken in the case of pregnancy:

- A patient who becomes pregnant will be immediately removed from the study.
- It is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the trial or within 120 days of completing the trial or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier.
- All patients who become pregnant must be contacted by the site at least monthly and the patient's status documented to the completion/termination of the pregnancy; the investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

8.2.1.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Development Core Safety Information in the IB and that the investigator identifies as

related to the IPs 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.

8.2.2. Other Safety Measures

8.2.2.1. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected according to the Time and Events Table (Attachment 1) as single ECGs for 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.

After enrollment, if a clinically significant increase in the QT/corrected QT interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to determine if the patient can continue in the study. 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.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation. Local ECG findings at baseline and end of treatment, and any on study clinically significant abnormal findings, will be reported into the electronic CRF (eCRF) and any alert reports.

8.2.2.2. Echocardiogram or Multiple-Gated Acquisition Scan

An echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan will be performed according to the Time and Events Table (Attachment 1). Additional evaluations are not required but should be performed in the setting of cardiac symptoms, at the discretion of the investigator.

Patients will undergo baseline left ventricular ejection fraction (LVEF) determination by ECHO or MUGA scan. This evaluation may be repeated at any time during the study if clinically indicated.

8.2.3. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes (Attachment 3)
- adverse events, including ramucirumab AESI and pembrolizumab ECI (Section 8.2.1.1).
- 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 may consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Site Guidance Document for Drug-Induced Liver Injury.

8.3. Pharmacokinetics

Pharmacokinetic samples to determine ramucirumab PK will be collected as specified in Attachment 2.

Blood samples will be drawn for all patients for the assessment of ramucirumab concentrations in serum (also known as bioanalytical samples). Sampling times were selected to coincide with expected C_{max} and C_{min} and with consideration to draw minimum volume of blood from patients and ensuring that the patients do not to need to make an extra visit to provide these samples.

Instructions for the collection and handling of bioanalytical blood samples will be provided by the Sponsor. The actual start and end date and time of ramucirumab infusion administration must be recorded on the eCRF. The actual date and time that each bioanalytical blood sample was drawn must be recorded on the laboratory accession page after the sample is drawn.

Ramucirumab concentrations in bioanalytical serum samples will be measured using a validated assay methodology in a laboratory designated by the Sponsor.

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

8.4. Biomarkers

Where local regulations and ethical review boards (ERBs) allow, these samples will be collected for biomarker research as discussed below and specified in the Sampling Schedule (Attachment 2).

All biomarker samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel. Samples will be destroyed according to a process consistent with local regulations.

It is possible that biomarker data for patients in the study has already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data

generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Section 8.4.2.

8.4.1. Genetics

Whole Blood Sample for DNA Collection:

A whole blood sample will be collected for pharmacogenetic analysis where local regulations and ERBs allow. These samples **are not** being collected to create a biobank for conducting unspecified disease or population genetic research either now or in the future.

Samples may be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in cancer. Assessment of variable response may include evaluation of AEs or differences in efficacy. These studies may include but are not limited to the VEGF pathway and immunomodulatory mechanisms to evaluate their association with observed response to study treatment.

Samples will be retained for a maximum of 15 years after the last patient visit, or as local regulations and ERBs allow, for the study at a facility selected by the Sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

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

8.4.2. Tailoring and Pharmacodynamic Biomarkers

Samples will be collected for potential non-pharmacogenetic biomarker research. Samples will be collected at the times specified in the Schedule of Activities.

Samples may be used for research on the drug targets (PD-1 and VEGF Receptor 2), disease process, pathways associated with cancer, mechanism of action of ramucirumab and/or pembrolizumab, and/or research method or in validating diagnostic tools or assay(s) related to cancer.

Samples will be retained for a maximum of 15 years after the last patient visit, or as local regulations and ERBs allow, for the study at a facility selected by the Sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

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

- EDTA plasma

- peripheral mononuclear blood cells from whole blood
- tumor tissue at baseline (see Inclusion Criterion [4] and the paragraph below).

For the submission of baseline tumor tissue sample, formalin-fixed paraffin-embedded tumor tissue sample blocks are preferred. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 7 days from when the slides are cut. In addition, all archival samples should be discussed with the Sponsor before submission. A formalin-fixed paraffin-embedded tumor tissue block obtained within 3 months prior to enrollment and following most recent systemic treatment will be considered by the Sponsor.

Optional samples for biomarker research that should be collected from patients in the study where possible are the following:

- tumor tissue/biopsy that becomes available during the study treatment period

8.5. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine anti-drug antibody (ADA) production against ramucirumab. The specific time points are listed in Attachment 2. Sample collection, storage, and shipment instructions for blood samples will also be provided in the Procedures Manual.

Pretreatment and post-treatment samples will be collected and assayed for the presence of ADA using an immunoassay. The number and percentage of patients with positive antidrug response will be summarized. In the event of an IP- related infusion reaction, every effort should be made to collect a blood sample for anti-ramucirumab antibody determination, as well as a blood sample for ramucirumab serum concentration, as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

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.

8.6. Health Economic and Outcomes Research

This section is not applicable to this protocol.

9. Statistical Considerations and Data Analysis

9.1. Determination of Sample Size

The primary objective for the DLT Phase 1a and Expansion Phase 1b is to evaluate safety and tolerability. The sample size of Expansion Phase 1b was selected to allow adequate assessment of safety at the recommended doses for ramucirumab and pembrolizumab for each tumor type and dose schedule, separately.

The following sample sizes apply to each phase of the study:

Phase 1a Dose-Limiting Toxicity Observation: up to 12 DLT-evaluable patients

Phase 1b Expansion: 155 patients;

- 15 patients each for Gastric-GEJ (2^{nd} - 3^{rd} Line) Cohorts A and B (2^{nd} - 3^{rd} Line)
- 25 patients each for:
    - BTC (2^{nd} - 3^{rd} Line) Cohort A1
    - Gastric-GEJ (1^{st} Line) Cohort A2
    - NSCLC (2^{nd} - 4^{th} Line) Cohort C
    - Urothelial (2^{nd} - 4^{th} Line) Cohort D
    - NSCLC (1^{st} Line) Cohort E

The primary objective of Study JVDF is the safety and tolerability of ramucirumab in combination with pembrolizumab. During Expansion Phase 1b, 25 to 30 patients per tumor type will be treated, to provide a preliminary assessment of tumor response and an assessment of safety. For each of the tumor types, the ORR values in the simulations are provided as a reference for estimation of statistical power rather than a basis of any decision criteria. All efficacy endpoints will be utilized to determine next steps of development of the combination.

For Gastric-GEJ and BTC (2^{nd} -3^{rd} line), and NSCLC and Urothelial (2^{nd} to 4^{th} line), the null hypothesis is based on the assumption that the ORR is no greater than 10% to 15% and the target treatment effect (alternative response rate) of the combination treatment on ORR is greater than 20% to 30%. Based on these assumptions, a sample size of n=25 to 30 (n=30 for combined Gastric Cohorts A and B) provides statistical power of approximately 60% to 90%, with a 1-sided 0.20 significance level (Table JVDF.8).

Table JVDF.8. Summary of Statistical Power for Overall Response Rates for NSCLC 2-4L, Bladder 2-4L, BTC 2-3L, and Gastric 2-3L

	NSCLC, Bladder, and BTC				Gastric (combined preliminary efficacy)			
	Low Case	High Case	Low Case	High Case	Low Case	High Case	Low Case	High Case
	N=25	N=25	N=25	N=25	N=30	N=30	N=30	N=30
Null response rate	10%	10%	15%	15%	10%	10%	15%	15%
Alternative response rate	20%	25%	25%	30%	20%	25%	25%	30%
Power	57.9%	78.6%	62.2%	80.7%	74.5%	90.2%	65.2%	84.0%

Abbreviations: BTC = biliary tract cancer; L = line; N = number of patients; NSCLC = non-small cell lung cancer.
Note: Low case = 10% difference between alternative response rate and null response rate for overall response rate; High case = 15% difference between alternative response rate and null response rate for overall response rate.

For the first-line NSCLC and Gastric-GEJ, the null hypothesis is based on the assumption that the ORR is no greater than 30% to 35% and the target treatment effect (alternative response rate) of the combination treatment on ORR is greater than 45% to 55%. Based on these assumptions, a sample size of n=25 provides statistical power of approximately 65% to 90%, with a 1-sided 0.20 significance level (Table JVDF.9).

Table JVDF.9. Summary of Statistical Power for Overall Response Rates for NSCLC 1L and Gastric 1L

	NSCLC (1L) and Gastric (1L; combined preliminary efficacy)			
	Low Case	High Case	Low Case	High Case
	N=25	N=25	N=25	N=25
Null response rate	30%	30%	35%	35%
Alternative response rate	45%	50%	50%	55%
Power	75.8%	88.5%	65.5%	81.7%

Abbreviations: 1L = First-Line; N = number of patients; NSCLC = non-small cell lung cancer.
Note: Low case = 15% difference between alternative response rate and null response rate for overall response rate; High case = 20% difference between alternative response rate and null response rate for overall response rate.

9.2. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly.

For the Phase 1a, a 3+3 design will be used to assess the safety of ramucirumab in combination with pembrolizumab (Section 6.1.1.1). Additional patients will be enrolled in a dosing schedule to achieve the minimum of 3 evaluable patients, if dropouts or dose interruptions or reductions occur that result in a patient being non-evaluable for DLTs. Data will be reviewed by dose schedule group (3 patients).

The final analysis of safety and preliminary efficacy will occur approximately 2 years after the first patient received first study treatment. Separate interim analyses will occur after all patients in each cohort have completed approximately 24 weeks of study treatment or discontinued for any reason. Safety and preliminary efficacy will be analyzed separately for each cohort (details in Section 9.8).

Descriptive statistics will be derived where appropriate. The rate of DLTs will be summarized by cohort; dose exposure and density for each study drug will be calculated by each cohort.

Pharmacodynamics/Biomarkers

Pharmacodynamic and/or tailoring biomarker analyses will be based on the subset of patients from the above cohorts from whom a valid assay result (according to laboratory guideline) has been obtained.

General

Additional details will be provided in a separate statistical analysis plan (SAP) for the study. 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.

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

9.3. Patient Characteristics

Patient characteristics which will be summarized by cohort:

- Patient demographics will be reported using descriptive statistics. Demographic data are collected and reported to demonstrate that a trial population represents the target patient population considered for regulatory approval.
- Baseline disease characteristics will be summarized by presenting frequency counts and percentages (for example, for pathological diagnosis [histological or cytological] and disease stage).
- 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 number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation).
- Disease-related therapies, including prior anticancer treatments, prior radiotherapies (such as type of therapy, regimen, and prior surgery)

Other patient characteristics will be summarized as deemed appropriate.

9.3.1. Concomitant Therapy

Concomitant medications will be summarized for the safety population.

9.3.1.1. Postdiscontinuation Therapy

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

9.3.2. Treatment Compliance

The number of dose omissions, reductions, and delays, number of cycles received, and dose intensity will be summarized for all treated patients and for both study drugs.

9.4. Efficacy Analysis: Phase 1b

The objective response rate and disease control rate, and the corresponding confidence interval, will be provided by cohort (according to RECIST v1.1 and irRECIST). Time-to-event variables, such as time to response, duration of response, PFS, and OS will be estimated by Kaplan-Meier (1958) methodology by cohort. Presentations of efficacy may include patients enrolled in DLT Phase 1a with the same tumor type and treatment schedule.

Individual changes in the tumor burden over time will be presented graphically within a tumor type (that is, Waterfall plots). Subgroup analysis of interest will be further defined in the SAP. Association between tumor PD-L1 expression at baseline will also be correlated with clinical outcomes such as overall response rate, and further assessed and characterized by appropriate statistics.

9.5. Safety Analyses

All patients who receive at least 1 dose of ramucirumab or pembrolizumab will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE, Version 4.0.

Safety analyses will include summaries of the following:

- DLTs: the number of patients who experienced any DLTs during Cycle 1 will be summarized by dose schedule in Phase 1a
- AEs, including severity and possible relationship to study drug
- AEs by MedDRA System Organ Class (SOC) by decreasing frequency of Preferred Term within SOC
- Laboratory and nonlaboratory AEs by CTCAE term and maximum CTCAE grade (regardless of causality and at least possibly related to study treatment)

9.6. Pharmacokinetic/Pharmacodynamic Analyses

The sampling schedule for drawing blood samples for ramucirumab PK is provided in Attachment 2. Serum concentrations of ramucirumab prior to infusion (C_{min}) and at 1 hour after the end of the ramucirumab infusion (approximately maximum concentrations) will be summarized using descriptive statistics.

Population PK analyses for ramucirumab may be conducted using population PK approach. The relationship between ramucirumab exposure and selected safety outcomes may be explored.

9.7. Other Analysis

9.7.1. Immunogenicity

Immunogenicity (anti-ramucirumab antibody) incidence will be tabulated, and correlation to ramucirumab drug level, activity, and safety will be assessed, as appropriate, respectively. The measures that will be analyzed include baseline presence and level of ADA, treatment-emergent ADA, levels of neutralizing ADA, and incidence and levels of ADA related to IRRs.

9.7.2. Biomarker Analysis

Biomarkers will be summarized and assessed for correlations with clinical outcomes. Biomarker relationships by tumor type, changes in biomarker levels over time, and differences among dose levels or exposure will be explored as possible.

9.8. Interim Analyses

For Phase 1a, safety and PK data will be reviewed on a cohort-by-cohort basis during the study. The purpose of these data reviews is to evaluate the safety and tolerability for each dose schedule and determine if a DLT has been observed. The investigators and the Lilly study team will evaluate the totality of data to determine whether or not to move into the Expansion Phase 1b.

Separate interim analyses will occur after all patients in each cohort have completed approximately 24 weeks of study treatment or discontinued for any reason. The interim analyses may be combined if they are expected to occur within approximately a month, and interim analyses may also be combined with the ongoing trial-level safety review or annual safety review for annual safety update reporting.

An independent data monitoring committee may be initiated if one or more additional cohorts will be expanded to further explore safety and efficacy for the ramucirumab and pembrolizumab combination.

10. Regulatory and Ethical Considerations, Including the Informed Consent Process

10.1. 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 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 investigational product.

10.2. Ethical Review

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

The investigator must give assurance that the ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

The study site's ERB(s) should be provided with the following:

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

10.3. Regulatory Considerations

This study will be conducted in accordance with:

1) 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

2) the ICH GCP Guideline [E6]

3) applicable laws and regulations

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

Some of the obligations of the Sponsor 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.

10.4. Investigator Information

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

10.5. 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.

10.6. 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 coordinating investigator will be the investigator with the most enrolled patients; if this investigator is unable to fulfill this function, another investigator will be chosen by the Sponsor.

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

10.7. Complaint Handling

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

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

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.

10.8. 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 training 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 the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

10.8.1. Data Capture System

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

Case report form data will be encoded and stored in a clinical trial database.

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

10.9. Study and Site Closure

10.9.1. Discontinuation of Study Sites

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

10.9.2. Discontinuation of the Study

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

11. References

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Attachment 1. Protocol JVDF Time and Events Tables

Time and Events Table: Baseline, Study Treatment, and Postdiscontinuation Follow-Up Periods

	Study Period							Notes
	Baseline (within 28 days prior to enrollment)			**Treatment (21-day cycles)** ±7 days		**Postdiscontinuation Follow-Up**		The first study treatment will be administered within 7 days following enrollment. Postdiscontinuation follow-up begins when the decision is made that the patient will no longer continue study treatment.
Procedure	≤28 days	≤21 days	≤7 days	Day 1	Day8	Short-Term Follow-Up Visit (30 ±7 days)	Long-Term Follow-Up Visit (every 90 ±7 days)	Day 8 procedures are only for Cohort A, A1, and A2 (Gastric-GEJ or BTC Ram 8 mg/kg, Days 1 and 8). Long-term follow-up should be attempted at regularly scheduled intervals (every 90 days [±7 days]) until death, loss to follow-up, or study completion (whichever occurs first).
Informed consent form (ICF)	X							Obtain ICF prior to any study-specific procedures. If the ICF is revised during the course of the study, re-consenting of patients may be required if deemed necessary by Lilly or the ERB.
Inclusion/exclusion criteria	X							
Medical history	X							Including preexisting conditions and historical illnesses
ECG	X					X		Baseline, short-term follow–up, and when clinically indicated
Echocardiogram or MUGA scan	X							Baseline, and when clinically indicated
ECOG Performance Status	X			X		X		A time window of -3 days of Day 1 is permitted for the ECOG assessment.
Brain Scan	X							Baseline brain scan by CT or MRI for NSCLC patients and Urothelial patients only. Refer to eligibility criteria.
Concomitant therapy	X			X		X		Concomitant medications will be recorded, including any taken within 30 days prior to enrollment and those taken during the 30 days after the last dose of study treatment.
Physical exam	X			X		X		A time window of ±3 days with respect to the other study visit procedures is permitted.

	Study Period							Notes
	Baseline (within 28 days prior to enrollment)			**Treatment (21-day cycles)**		**Postdiscontinuation Follow-Up**		The first study treatment will be administered within 7 days following enrollment. Postdiscontinuation follow-up begins when the decision is made that the patient will no longer continue study treatment.
Procedure	≤28 days	≤21 days	≤7 days	Day 1	Day 8	Short-Term Follow-Up Visit (30 ±7 days)	Long-Term Follow-Up Visit (every 90 ±7 days)	Day 8 procedures are only for Cohort A, A1, and A2 (Gastric-GEJ or BTC Ram 8 mg/kg, Days 1 and 8). Long-term follow-up should be attempted at regularly scheduled intervals (every 90 days [±7 days]) until death, loss to follow-up, or study completion (whichever occurs first).
Height, weight	X			X				Measure height at baseline only. Measure weight at the beginning of each cycle. Recalculate the ramucirumab dose if weight change is ≥10% compared to previous measurement(s).
Vital signs	X			X	X			For the first 2 ramucirumab infusions, measure blood pressure and pulse as follows: (i) within 15 minutes prior; (ii) after infusion completion; and (iii) at the end of the 1-hr post-infusion observation period. Measure blood pressure and pulse prior to each subsequent ramucirumab infusion. Measure other vital signs as clinically indicated.
AE collection; CTCAE grading	X							During short-term follow-up, all AEs/SAEs will be collected. At the 90-day long-term follow-up visit, all SAEs will be collected. Thereafter, during long-term follow-up, only SAEs that are related to study regimen or protocol procedures will be collected.

	Study Period							Notes
	Baseline (within 28 days prior to enrollment)			**Treatment (21-day cycles)**		**Postdiscontinuation Follow-Up**		The first study treatment will be administered within 7 days following enrollment. Postdiscontinuation follow-up begins when the decision is made that the patient will no longer continue study treatment.
Procedure	≤28 days	≤21 days	≤7 days	Day 1	Day 8	Short-Term Follow-Up Visit (30 ±7 days)	Long-Term Follow-Up Visit (every 90 ±7 days)	Day 8 procedures are only for Cohort A, A1, and A2 (Gastric-GEJ or BTC Ram 8 mg/kg, Days 1 and 8). Long-term follow-up should be attempted at regularly scheduled intervals (every 90 days [±7 days]) until death, loss to follow-up, or study completion (whichever occurs first).
Laboratory Assessment								Baseline laboratory assessments can be used for Cycle 1 Day 1 if the baseline assessments were performed within 7 days prior to Cycle 1 Day 1 and the results are deemed still clinically valid by the treating investigator. Starting with the second cycle, where required, labs are to be performed within 3 days prior to first day of each cycle. More frequent assessment should be performed if clinically indicated. Results of blood tests must be reviewed prior to start of cycle.
Hematology	X			X		X		Local only. Within 3 days prior to Day 1 of each cycle.
Chemistry	X			X		X		Local and central: Local chemistry laboratory testing will be used to determine patient eligibility and decisions for treatment. Central chemistry laboratory testing will be used for subsequent scheduled analyses. Within 3 days prior to Day 1 of each cycle.
Urinalysis	X			X		X		Local only. Within 3 days prior to Day 1 of each cycle. 24-hr urine protein analysis if urine protein is ≥2+ at baseline, >2+ during study treatment.
T3, free T4, TSH	X			X		X		Central and local as needed. At baseline, within 3 days prior to Day 1 of Cycle 3, Day 1 of Cycle 6, and every 2 cycles thereafter; and more frequently if clinically indicated.
Coagulation	X			X		X		Local only. Within 3 days prior to Day 1 of every odd-numbered cycle.
Pregnancy test			X			X		Local only. Required for women of child-bearing potential. If required per local regulations and/or institutional guidelines, testing can occur at other times during the study treatment period.

	Study Period							Notes
	Baseline (within 28 days prior to enrollment)			**Treatment (21-day cycles)**		**Postdiscontinuation Follow-Up**		The first study treatment will be administered within 7 days following enrollment. Postdiscontinuation follow-up begins when the decision is made that the patient will no longer continue study treatment.
Procedure	≤28 days	≤21 days	≤7 days	Day 1	Day 8	Short-Term Follow-Up Visit (30 ±7 days)	Long-Term Follow-Up Visit (every 90 ±7 days)	Day 8 procedures are only for Cohort A, A1, and A2 (Gastric-GEJ or BTC Ram 8 mg/kg, Days 1 and 8). Long-term follow-up should be attempted at regularly scheduled intervals (every 90 days [±7 days]) until death, loss to follow-up, or study completion (whichever occurs first).
Efficacy Assessment								
Tumor imaging and assessment		X		X		X	X	Assessments previously obtained as part of routine clinical care may be used as the baseline assessment if performed within 21 days prior to enrollment. Imaging is not required on Cycle 1 Day 1. SEE FOOTNOTE.
Survival information						X	X	Follow-up for the collection of survival data and subsequent anticancer treatments should be attempted at regularly scheduled intervals (every 90 days [±7 days]) for up to 2 years after patients receive the first dose. This follow-up might be a phone call to the patient, her/his family, or local doctor.
Additional Analyses								
Tumor tissue	X							New biopsy at baseline (recent to Cycle 1 Day 1) is required. For first line NSCLC, PD-L1 >=1% is required. Tumor tissue collection during the treatment period is optional, and can be provided if available, for example in case of a clinically-indicated biopsy.
Genetics Whole Blood Sample				X				Collect 1 sample prior to treatment on Cycle 1 Day 1.
• Biomarker • Pharmacokinetics • Immunogenicity	See Attachment 2.							

	Study Period							Notes
	Baseline (within 28 days prior to enrollment)			**Treatment (21-day cycles)**		**Postdiscontinuation Follow-Up**		The first study treatment will be administered within 7 days following enrollment. Postdiscontinuation follow-up begins when the decision is made that the patient will no longer continue study treatment.
Procedure	≤28 days	≤21 days	≤7 days	Day 1	Day 8	Short-Term Follow-Up Visit (30 ±7 days)	Long-Term Follow-Up Visit (every 90 ±7 days)	Day 8 procedures are only for Cohort A, A1, and A2 (Gastric-GEJ or BTC Ram 8 mg/kg, Days 1 and 8). Long-term follow-up should be attempted at regularly scheduled intervals (every 90 days [±7 days]) until death, loss to follow-up, or study completion (whichever occurs first).
Administration of Study Drugs								Administer ramucirumab first per the dose schedule to which the patient is allocated. For first 2 cycles, implement a 1-hr observation period i) between ramucirumab and pembrolizumab administration, and ii) after pembrolizumab infusion. For all cycles thereafter, no observation period will be required unless clinically indicated.
Administer Ramucirumab								
BTC 8 mg/kg				X	X			
Gastric-GEJ 8 mg/kg				X	X			
Gastric-GEJ 10 mg/kg				X				
NSCLC 10 mg/kg,				X				
Urothelial 10 mg/kg				X				
Administer Pembrolizumab								
200 mg fixed				X				

Time and Events Table (concluded)

Abbreviations: AE = adverse event; Att. = attachment; BTC = biliary tract cancer; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ERB = ethical review board; Gastric-GEJ= Gastric-Gastroesophageal Junction; ICF = informed consent form; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NSCLC = non-small cell lung cancer; PD = progressive disease; Prot. Ref. = protocol reference; Ram = ramucirumab; SAE= serious adverse event; TSH = thyroid-stimulating hormone.

FOOTNOTES Regarding Tumor Assessment:

- During treatment cycles, perform tumor assessment and imaging as follows: (i) every 6 weeks (±7 days) for the first 6 months after enrollment, and (ii) every 12 weeks (±7 days) thereafter. Perform as scheduled even if study treatment is delayed, except when tumor assessment and imaging are not feasible in the opinion of the investigator because of the patient's clinical status.
- If radiologic imaging verifies initial progressive disease (PD), tumor assessment should be repeated approximately 4 weeks later in order to confirm PD with the option of continuing study treatment while awaiting radiologic confirmation of progression (Section 8.1.1.3).
- During the short-term and long-term follow-up periods, for patients who discontinue study treatment without objectively measured PD, continue to perform tumor assessment and imaging every 6 to 12 weeks depending on standard of care.

Time and Events Table: Continued Access Period

	Continued Access Period			Notes
	Continued Access Treatment (21-day cycles)		Continued Access Follow-Up	Day 1 and Day 8 assessments are performed only if study drug dosing is scheduled to occur on that day. Continued access follow-up begins 1 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. Efficacy assessments will be performed at the investigator's discretion based on the standard of care.
Relative Day within a Cycle	Day 1	Day 8		
Procedures				
Weight	X			
Administer Ramucirumab				
BTC 8 mg/kg	X	X		
Gastric-GEJ 8 mg/kg	X	X		
Gastric-GEJ 10 mg/kg	X			
NSCLC 10 mg/kg	X			
Urothelial 10 mg/kg	X			
Administer Pembrolizumab 200 mg (fixed)				
All treatment cohorts	X			
AE Collection, CTCAE Grading	X	X	X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System. After the patient is no longer participating in the study (that is, no longer receiving study treatment and no longer in follow-up), only SAEs that the investigator is made aware of and are related to study regimen or protocol procedures will be collected.
Immunogenicity and PK Sample				If a patient experiences an IRR to ramucirumab, blood samples for immunogenicity and PK analysis 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.

Abbreviations: AE = adverse event; BTC = biliary tract cancer; CTCAE = Common Terminology Criteria for Adverse Events; GEJ = gastroesophageal junction; IRR = infusion-related reaction; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; SAE =serious adverse events.

Attachment 2. Protocol JVDF Pharmacokinetic, Immunogenicity, and Biomarker Sampling Schedules

PK and immunogenicity (IK) samples will be collected for ramucirumab only, in both Phase 1a and Phase 1b portions of the study. Predose samples should be taken as close as possible to the start of first infusion, that is ramucirumab infusion, but can be drawn up to 1 hour (60 minutes) prior start of infusion, and exact clock reading should be recorded. Postdose (post end-of-infusion) samples for PK for ramucirumab should be drawn preferably at 1 hour (±15 minutes) after the end of the ramucirumab infusion, and exact clock reading for the sample draw should be recorded.

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

In addition, if a patient experiences an infusion-related reaction (IRR), blood samples for anti-ramucirumab antibody and PK should be drawn. 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.

Table ATT.2.1. Schedule 1 (Gastric GEJ Cohort A [2nd-3rd Line] and Gastric GEJ A2 [1st Line]; and BTC Cohort A1 [2nd-3rd Line]): Pharmacokinetic (PK), Immunogenicity (IK), and Biomarker Collection Timepoints for Ramucirumab for Schedule 1 Dosing Regimen (1h Infusion Ramucirumab followed by 0.5h Infusion Pembrolizumab on Day 1 and 1h Infusion Ramucirumab on Day 8, every 3 weeks)

Visit/Cycle Day	Study Day	Sample Time (relative to start of Ram infusion) (HR:MIN)[a]	Ram PK[f] (Serum)	Ram Immunogenicity[e,f] (Serum)	Biomarker	
					EDTA Plasma	PBMCs
Cycle 1 Day 1 (1-hr observation period between Ram and Pem infusions)	1	**0:00 hr** Predose sample[b,d]	**X** (collect prior to start of first infusion)	X	X	X
		2.00 hr Postdose sample[c,d]	**X** (collect approx. 1 hr after Ram infusion ends)			
Cycle 1 Day 8 (Ram only)	8	0:00 hr Predose sample[b,d]	**X** (collect prior to start of infusion)		X	X
Cycle 2 Day 1	22	0:00 hr Predose sample[b,d]	X (collect prior to start of first infusion)	X	X	X
Cycle 3 Day 1	43	0:00 hr Predose sample[b,d]	X (collect prior to start of first infusion)		X	X
Cycle 4 Day 1	64	0:00 hr Predose sample[b,d]	X (collect prior to start of first infusion)	X	X	X
Cycle 5 Day1	85	0:00 hr Predose sample[b,d]	X (collect prior to start of first infusion)	X	X	X
Cycle 7 Day 1	127	0:00 hr Predose sample[b,d]	**X** (collect prior to start of first infusion)	X	X	X
Cycle 7 Day 8 (Ram only)	134	0:00 hr Predose sample[b,d]	**X** (collect prior to start of infusion)		X	X
Cycle 9, Day 1	169	0:00 hr Predose[b,d]	**X** (collect prior to start of first infusion)	X	X	X
		2:00 hr Postdose[c,d]	**X** (collect approx. 1 hr after Ram infusion ends)			
30 days Post treatment DC		Anytime[g]	X	X	X	X

Schedule 1 (Gastric GEJ Cohort A [2nd-3rd Line] and Gastric GEJ A2 [1st Line]; and BTC Cohort A1 [2nd-3rd Line]): Pharmacokinetic (PK), Immunogenicity (IK), and Biomarker Collection Timepoints for Ramucirumab for Schedule 1 Dosing Regimen (1h Infusion Ramucirumab followed by 0.5h Infusion Pembrolizumab on Day 1 and 1h Infusion Ramucirumab on Day 8, every 3 weeks) (concluded)

Note: Ram and Pem infusions are given every 3 weeks. 1-hr Ram infusion is given prior to half-hour Pem infusion. There is one-hour observation period (for infusion reactions) between Ram and Pem infusions at Cycle 1 Day 1 visit. Each cycle is a 21-day cycle.

Abbreviations: DC = Discontinuation; eCRF = electronic case report form; GEJ = gastroesophageal junction; IK = immunogenicity; IRR = infusion-related reaction; Pem = pembrolizumab; PMBC = peripheral blood mononuclear cells; PK = pharmacokinetics; Ram = ramucirumab.

a All sample times are relative to start of first (Ram) infusion.

b Predose sample for Ram PK, IK, and biomarkers should be preferably collected within 1 hour prior to start of first infusion, and within 15 minutes of one another.

c Two-hour sample for Ram PK should be preferably collected at 1 hr ±15 minutes from the end of Ram infusion.

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

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

f Record ACTUAL date and time of blood collection for PK/IK sample on the Requisition Form AFTER drawing the sample.

Table ATT.2.2. Schedule 2 (Gastric-GEJ Cancer Patients Cohort B [2nd-3rd Line], NSCLC Cohort C [2nd-4th Line], Urothelial Cancer Cohort D [2nd-4th Line], and NSCLC Cohort E [1st Line]): Pharmacokinetic (PK), Immunogenicity (IK), and Biomarker Collection Timepoints for Ramucirumab for Schedule 2 Dosing regimen (1h infusion Ramucirumab followed by 0.5h infusion Pembrolizumab on Day 1 every 3 weeks)**

Visit/Cycle Day	Study Day	Sample Time (relative to start of Ram infusion) (HR:MIN)[a]	Ram PK[f] (Serum)	Ram Immunogenicity[e,f] (Serum)	Biomarker Collection	
					EDTA Plasma	PBMCs
Cycle 1 Day 1 (1-hr observation period between Ram and Pem infusions)	1	**0:00 hr** Predose sample[b,d]	**X** (collect prior to start of first infusion)	X	X	X
		2.00 hr Postdose sample[c,d]	**X** (collect approx. 1 hr after Ram infusion ends)			
Cycle 2 Day 1	22	0:00 hr Predose sample[b,d]	X (collect prior to start of first infusion)	X	X	X
Cycle 3 Day 1	43	0:00 hr Predose sample[b,d]	X (collect prior to start of first infusion)		X	X
Cycle 4 Day1	64	0:00 hr Predose sample[b,d]	X (collect prior to start of first infusion)	X	X	X
Cycle 5 Day 1	85	0:00 hr Predose sample[b,d]	**X** (collect prior to start of first infusion)	X	X	X
Cycle 7 Day 1	127	0:00 hr Predose sample[b,d]	X (collect prior to start of first infusion)	X	X	X
Cycle 9 Day 1	169	0:00 hr Predose[b,d]	**X** (collect prior to start of first infusion)	X	X	X
		2:00 hr Postdose[c,d]	**X** (collect approx. 1 hr after Ram infusion ends)			
30 days Post treatment DC		Anytime[f]	X	X	X	X

Schedule 2 (Gastric-GEJ Cancer Patients Cohort B [2nd-3rd Line], NSCLC Cohort C [2nd-4th Line], Urothelial Cancer Cohort D [2nd-4th Line], and NSCLC Cohort E [1st Line]): Pharmacokinetic (PK), Immunogenicity (IK), and Biomarker Collection Timepoints for Ramucirumab for Schedule 2 Dosing regimen (1h infusion Ramucirumab followed by 0.5h infusion Pembrolizumab on Day 1 every 3 weeks) (concluded)**

Notes:

Ram and Pem infusions are given Q3W. 1-hr Ram infusion is given prior to half-hour Pem infusion. There is one hour observation period (for infusion reactions) between Ram and Pem infusions at Cycle 1 Day 1 visit. Each cycle is a 21-day cycle.

Abbreviations: DC = Discontinuation; eCRF = electronic case report form; GEJ = gastroesophageal junction; IK = immunogenicity; IRR = infusion-related reaction; NSCLC = non-small cell lung cancer; Pem = pembrolizumab; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetics; Ram = ramucirumab.

[a] All sample times are relative to start of first (Ram) infusion.

[b] Predose sample for Ram PK, IK, and biomarkers should be preferably collected within 1 hour prior to start of first infusion, and within 15 minutes of one another.

[c] Two-hour sample for Ram PK should be preferably collected at 1 hr ±15 minutes from the end of Ram infusion.

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

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

[f] Record ACTUAL date and time of blood collection for PK/IK sample on the Requisition Form AFTER drawing the sample.

Attachment 3. Protocol JVDF Clinical Laboratory Tests

Hematology-Local only	**Clinical Chemistry-Local and Central** [a]
Hemoglobin Hematocrit Erythrocyte count (RBC) Leukocytes (WBC) Absolute Neutrophil Count Lymphocytes Monocytes Eosinophils Basophils Platelets	**Serum Concentrations of:** Sodium Magnesium Potassium Total bilirubin Direct bilirubin (if total bilirubin is above ULN) Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Blood urea nitrogen (BUN) Creatinine Uric acid Calcium Glucose, random Albumin Cholesterol Creatine kinase (CK) Chloride Total protein Phosphorus Lactate dehydrogenase (LDH)
Thyroid Function Tests-Central Only	
Thyroid-stimulating hormone (TSH) Total triiodothyronine (T3) Free tyroxine (T4)	
Urinalysis[b]**- Local Only**	
Protein Specific gravity Blood Glucose	**Pregnancy Test** Urine or Serum[c]–**Local Only**
	β-human chorionic gonadotropin (β-hCG)
Coagulation Test[d] **Local Only**	
Prothrombin time (PT) /INR Partial thromboplastin time (PTT) or activated PTT (aPTT)	

Abbreviations: INR= International Normalized Ratio; RBC = red blood cells; ULN = upper limit of normal; WBC = white blood cells.

a. Local chemistry laboratory testing will be used to determine patient eligibility and decisions for treatment. Central chemistry laboratory testing will be used for subsequent scheduled analyses.

b A microscopic exam is required for abnormal results. If urinalysis indicates proteinuria ≥2+ at baseline or during the treatment period, a 24 hour urine collection (to assess protein) must be obtained.

c. Minimum sensitivity 25 IU/L or equivalent units of β-human chorionic gonadotropin (β-HCG), for women of childbearing potential (WOCBP). If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

d. For both prothrombin time and partial thromboplastin time, the laboratory for each is selected at baseline, and should be followed during the study period.

Attachment 4. Protocol JVDF ECOG Performance Status

ECOG Performance Status

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

Source: Oken et al. 1982.

Attachment 5. Protocol JVDF Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

a age in years, weight (wt) in kilograms.

Reference: Cockcroft and Gault 1976.

Attachment 6. Protocol JVDF RECIST Criteria 1.1

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 ≤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 ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥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. For Study JVDF (Section 8.1.1.3), total of 10 lesions (and a maximum of 5 lesions per organ) could be collected if clinically relevant. 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 ≥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 ≥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 IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV 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 ≥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 ≤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, 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 (<10mm 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 (± Non-target) 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[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

[a] 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. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

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 [first dose].

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, 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 end point, 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.

Attachment 7. Protocol JVDF Restricted and Prohibited Concomitant Therapy

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

Generally, medications or live vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial.

Therapy	As Needed	Chronic Use	Exceptions or Conditions for Use
Anti-platelet therapy	yes	no	Chronic use of aspirin up to 325 mg/day is permitted.
Anticoagulation therapy	no	Yes, with restrictions	At enrollment, patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin or similar agent. If on warfarin, the patient must have an INR ≤ 3 and no active bleeding or pathological condition present that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices).
Anti-cancer biological therapy	no	no	
Chemotherapy	no	no	
Colony-stimulating factors	yes	no	Follow local guidelines.
Erythroid growth factors	yes	no	Follow local guidelines.
Experimental medicines or investigational agents	no	no	Other than ramucirumab or pembrolizumab
Glucocorticoids	no	no	Systemic glucocorticoids are permitted to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Note: Inhaled steroids are allowed for management of asthma.
Immunotherapy (including vaccinations)	no	no	Other than pembrolizumab OR inhaled steroids Live vaccines are NOT allowed within 30 days prior to the first study treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., Flu - Mist®) are live attenuated vaccines, and are not allowed.
NSAIDs	yes	no	Chronic use of aspirin up to 325 mg/day is permitted. In addition, in certain medical situations, NSAIDs may be the best treatment option (for example, for pain management). Increased risk of bleeding should be considered by the treating physician and the patient.
Radiation therapy	no	no	Localized radiation therapy to a symptomatic, solitary lesion or to the brain may be allowed after consultation with the Sponsor.

Abbreviations: INR = international normalized ratio; NSAIDs = nonsteroidal anti-inflammatory drugs.

Attachment 8. Protocol JVDF Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
audit	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).
BCG	bacillus Calmette-Guérin
blinding/masking	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.
$C_{ave,ss}$	average concentration at steady state
CHF	congestive heart failure
$C_{max,ss}$	maximum concentration at steady state
$C_{min,1}$	minimum concentration after first dose administration
$C_{min,ss}$	minimum concentration at steady state

collection database	A computer database where clinical trial data are entered and validated.
complaint	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.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
continued access period	The period between study completion and end of trial during which patients on study treatment (ramucirumab and/or pembrolizumab) 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.
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF/eCRF	case report form/electronic 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.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRS	clinical research scientist
CSFs	colony-stimulating factors
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DCR	disease control rate
DKA	diabetic ketoacidosis
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest

ECOG PS	Eastern Cooperative Oncology Group performance status
end of trial	End of trial is after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
EU	European Union
FOLFIRI	irinotecan, 5-fluorouracil, and folinic acid
FSH	follicle-stimulating hormone
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GEJ	gastroesophageal junction
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IK	immunogenicity
Informed consent	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.
INR	international normalized ratio

interim analysis	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.
investigational product (IP)	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: 1. used or assembled (formulated or packaged) in a way different from the authorized form, 2. used for an unauthorized indication, or 3. used to gain further information about the authorized form. In this study, the IPs are ramucirumab and pembrolizumab.
investigator	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.
IRR	infusion-related reaction
irRECIST	immune-related Response Evaluation Criteria In Solid Tumors
IV	intravenous
legal representative	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.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMR	mismatch-repair
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI	National Cancer Institute

non-investigational product (non-IP)	A non-investigational product (non-IP) is a product that is not being tested or used as a reference in the trial but is provided to patients and used in accordance with the protocol. Examples of non-IPs include the following: • Concomitant or rescue/escape medication for preventive, diagnostic, or therapeutic reasons • Concomitant or rescue/escape medication to ensure that adequate medical care is provided for the patient • A product used in accordance with the protocol to induce a physiological response.
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed death-1 T-cell co-receptor
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
Q2W	every 2 weeks
Q3W	every 3 weeks
randomize	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria In Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event

SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SOC	system organ class
Study completion	This study will be considered complete after the final analysis and evaluation of the Phase 1b study endpoints is performed.
SUSAR	suspected unexpected serious adverse reactions
T1DM	type 1 diabetes mellitus
TEAE	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.
TSH	thyroid stimulating hormone
TTR	time to first response
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event

Attachment 9. Protocol JVDF Amendment(b) Summary An Open-Label, Multicenter, Phase 1 Study of Ramucirumab plus Pembrolizumab in Patients with Locally Advanced and Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma, Non-Small Cell Lung Cancer, Transitional Cell Carcinoma of the Urothelium, or Biliary Tract Cancer

Overview

Protocol I4T-MC-JVDF, An Open-Label, Multicenter, Phase 1 Study of Ramucirumab plus Pembrolizumab in Patients with Locally Advanced and Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma, Non-Small Cell Lung Cancer, or Transitional Cell Carcinoma of the Urothelium, has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Addition of title, rationale, study design, entry criteria, study procedures and statistical elements for 3 new Phase 1b expansion Cohorts, to include first-line Gastric-GEJ (Schedule 1), first-line NSCLC patients (Schedule 2), and second or third line BTC patients (Schedule 1). At the time of this amendment, Phase 1A Schedule 1 DLT observation is ongoing; Phase 1A Schedule 2 DLT observation has been completed. For first line Gastric/GEJ and first line NSCLC patients, more frequent tumor imaging schedule (every 4 weeks for the first 12 weeks) is required to monitor anti-tumor response to study treatment and initiate alternative treatment as determined by treating investigators.
- Clarifications and refinements, as follows:
    - The final analysis of safety and preliminary efficacy will occur approximately 2 years after the first patient received first study treatment. Separate interim analyses will occur after all patients in each cohort have completed approximately 24 weeks of study treatment or discontinued for any reason. Safety and preliminary efficacy will be analyzed separately for each cohort. *Rationale:* This change was implemented to harmonize the interim analysis and final analysis with the intent of the trial design. There is no change to the study treatment duration for each individual patient (35 cycles, approximately 2 years).
    - In Inclusion Criterion [20], clarified that baseline tumor tissue samples must be evaluable, and elaborated on guidance regarding the submission of tumor tissue samples in Section 8.4.2.

  - The timing of the required 1-hour observation periods, to occur between ramucirumab and pembrolizumab administration *and* after pembrolizumab administration, for the first 2 cycles. Rationale: this change was implemented to ensure the consistent implementation of the 1-hour observation periods for Schedule 1 and Schedule 2 patients.
  - Two additional categories of events are to be reported as SAEs: 1) new cancers (exception: metastases of cancer under study), and 2) any event associated with an overdose of either study drug, as defined in Section 8.2.1.2.
  - For pembrolizumab, immune-related adverse events are no longer labeled as Events of Clinical Interest (ECIs). Similarly, references in the protocol to the detailed Site Guidance Document for Events of Clinical Interest were removed. Two (2) categories of ECIs remain: overdose and abnormal liver function tests (as defined in Section 8.2.1.1.3).
  - Pembrolizumab dose modification table "Note" was updated to specify that Grade 2 pneumonitis warrants permanent discontinuation of pembrolizumab (see "Note" in table footnote).
  - Pembrolizumab supportive care guidelines for Diarrhea/Colitis (Section 6.9.1.3.2) were updated to eliminate any waiting period before beginning treatment for any Grade 2, 3, or 4 event.
- Other typographical, formatting errors or very minor clarifications (key examples below):
  - The Introduction was updated to reflect current regulatory approval status for ramucirumab and pembrolizumab.
  - In Inclusion Criterion [7], to clarify that the screening period is 28 days.
  - Exclusion Criterion [20], to allow seasonal flu vaccines that do not contain live virus.
  - Dose management for ramucirumab in case of Grade 2 toxicity, investigator "may" reduce ramucirumab dose or discontinue ramucirumab. See footnote b in Table JVDF.4.
  - If radiologic imaging verifies initial progressive disease, tumor assessment should be repeated approximately (not "at least") 4 weeks later to confirm PD.
  - That "whole" blood sample is collected for pharmacogenetic analysis where local regulations and ERBs allow.
  - That the overall response rates presented in the simulations represented by Table JVDF.8 and Table JVDF.9 are provided as a reference for estimation of statistical power rather than as a basis for any decision criteria.
  - A baseline brain scan by CT or MRI was added in the schedule of events (Attachment 1) to be consistent with inclusion criteria for NSCLC and urothelial cancer patients.
  - Correction of formatting error in baseline biomarker samples collection for Schedule 1 patients (Attachment 2). Baseline sample should be collected pre-dose.

Note: Changes that are applied globally to the document were described above. A brief section of text with strikethrough/underscore as an example of the type of change that occurs throughout the amended protocol is provided below.

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