CLINICAL STUDY PROTOCOL

ONCG100

A PHASE 2, MULTICENTER OPEN-LABEL, NON-RANDOMIZED STUDY OF BAVITUXIMAB PLUS PEMBROLIZUMAB IN PATIENTS WITH ADVANCED GASTRIC OR GASTROESOPHAGEAL CANCER WHO HAVE PROGRESSED ON OR AFTER AT LEAST ONE PRIOR STANDARD THERAPY

Sponsor:	Oncologie, Inc. 400 Totten Pond Road, Suite 120 Waltham MA 02451 1-781-907-7810
Protocol Number:	ONCG100
Study Phase:	2
IND:	011947
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Version and Date:	Amendment 4 14 September 2020

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol: ONCG100

Title: A Phase 2, multicenter open-label, non-randomized study of bavituximab plus pembrolizumab in patients with advanced gastric or gastroesophageal cancer who have progressed on or after at least one prior standard therapy.

Date: 14 September 2020

Amendment: 4

Reviewed and Approved by:

September 14, 2020

Name: Hagop Youssoufian, MD Date
Title: Interim Chief Medical Officer
Company: Oncologie, Inc.

PROTOCOL ACCEPTANCE FORM

Protocol: ONCG100

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I have carefully read this protocol and agree that it contains all the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, in compliance with Food and Drug Administration (FDA) regulations 21 CFR Parts 50 and 56, and in conformance with International Council for Harmonization (ICH) Guidelines for Good Clinical Practice (CGP) and all applicable regulatory requirements.

Investigator's Signature Date

Name (printed)

SYNOPSIS

Name of Sponsor/Company: Oncologie, Inc.	
Name of Finished Product: Bavituximab	
Name of Active Ingredient: Chimeric Anti-Phosphatidylserine Monoclonal Antibody	
Name of Combination Product: Pembrolizumab, a programmed cell death protein 1 (PD-1) Inhibitor	
Title of Study: A Phase 2, multicenter open-label, non-randomized study of bavituximab plus pembrolizumab in patients with advanced gastric or gastroesophageal cancer who have progressed on or after at least one prior standard therapy	
Number of Study Sites: Approximately 28	
Study centers: This global, multicenter trial will be conducted in the United States (US), United Kingdom (UK), South Korea, and Taiwan and other countries as deemed appropriate.	
Studied period (years): Date first patient enrolled: Approximately June 2019 Date last patient completed: Approximately June 2021	**Phase of development:** 2

Rationale:

Oncologie, Inc. is developing bavituximab, a chimeric monoclonal antibody (mAb) that inhibits the immunosuppressive effects of phosphatidylserine (PS), for the treatment of cancer. PS modulates the tumor microenvironment as a ligand for multiple receptors on suppressor cells leading to secretion of immunosuppressive cytokines such as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10) from M2-macrophages and myeloid-derived suppressor cells (MDSCs). PS exposure in the tumor microenvironment prevents dendritic cell maturation and inhibits development of tumor-specific cytotoxic T cells. Of importance, expression of PS on the external surface of tumors cell acts as an immunosuppressive ligand for multiple immune receptors, including TIM/TAM. Nonclinical data show that bavituximab blocks PS immunosuppressive signaling, provides specificity for innate immune responses, and activates T-cell-driven adaptive immunopathways that reactivate a therapeutically effective immune response to the tumor.

Pembrolizumab is a mAb that acts by blocking the interaction between PD-1 and its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). Molecules that disrupt the interaction of PD1/PD-L1, also known as immune check point inhibitors (CPI), are emerging as a front-line treatment for several types of cancer. Pembrolizumab is approved in the US for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma after disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy.

Although efficacy is notable and can be sustained, many patients fail pembrolizumab treatment potentially due to exhaustion of specific T-cells. Exhausted T-cells express elevated levels of T cell immunoglobulin and mucin domain 3 (TIM3), as opposed to activated or partially activated T-cells. Bavituximab binding to PS interrupts its binding to TIM3, which

may partially reverse the exhaustion and restore activity to pembrolizumab. Therefore, the combination of bavituximab with pembrolizumab may enhance the antitumor immune response resulting in increased clinical benefit.

Given the potential for this combination to enhance antitumor responses, it is being evaluated in 2 populations of advanced gastric or GEJ cancer patients: patients that have progressed on standard chemotherapy and are naïve to CPI therapy (Group 1); patients that had a confirmed partial response (PR) or complete response (CR) to CPI inhibitor alone or in combination with chemotherapy, then subsequently progressed following treatment with CPI either alone or in combination with chemotherapy (Group 2).

Study Objectives:

Study objectives are the same for both Group 1 (CPI naïve) and Group 2 (CPI relapse).

Primary:

To assess the safety and tolerability of bavituximab in combination with pembrolizumab in patients with advanced gastric/GEJ cancer

To assess the antitumor activity of the treatment combination based on Response Evaluation Criteria in Solid Tumors (RECIST) Guideline version 1.1 (Appendix A)

Secondary:

To further characterize the antitumor activity of the treatment combination based on additional assessments of clinical benefit

To evaluate bavituximab concentrations when administered in combination with pembrolizumab

To assess the potential immunogenicity of bavituximab

Tertiary:

To evaluate a novel biomarker signature panel and correlate with efficacy outcomes in patients treated with bavituximab-pembrolizumab combination

Study Endpoints:

Study endpoints are the same for both Group 1 (CPI naïve) and Group 2 (CPI relapse).

Primary:

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, including changes in clinical laboratory parameters
- Objective response rate (ORR) as assessed by the Investigator per RECIST version 1.1

Secondary:

- Duration of response (DoR), disease control rate (DCR) (as defined by ORR and stable disease rate at 6 weeks), progression-free survival (PFS), and overall survival (OS)
- Bavituximab concentrations before and after bavituximab infusions
- Presence of anti-bavituximab antibodies (anti-drug antibodies [ADAs])

Tertiary:

- Analysis of tissue to determine percentage of patients with defined genetic signature
- Preliminary correlation of ORR to genetic signature
- Status of genomic and immune biomarkers in blood and tissue samples at baseline and change from baseline upon treatment

Study Design:

This is a Phase 2, multicenter, open-label, non-randomized study with an initial safety analysis to assess the safety and tolerability of bavituximab administered in combination with pembrolizumab, a PD-1 inhibitor, in patients with advanced gastric or GEJ adenocarcinoma who have either progressed on standard chemotherapy and are naïve to CPI therapy (Group 1), or have progressed following treatment with CPI either alone or in combination with chemotherapy (Group 2). Approximately 80 patients will be enrolled in the study; a minimum of 40 patients will be enrolled in Group 1 and a minimum of 20 patients will be enrolled in Group 2.
Following a minimum of 3 and a maximum of a 10-patient safety run-in with bavituximab (3 mg/kg intravenous [IV] weekly) and pembrolizumab (200 mg IV every 3 weeks [Q3W]), additional patients will be recruited if the initial doses of the regimen are tolerable. Lower doses of bavituximab may be explored if the initial doses are not tolerable. Primary anti-tumor activity will be documented by Investigator-assessed ORR per RECIST v. 1.1. A total of 80 patients will be enrolled.

The first 3 patients will be evaluated for dose-limiting toxicities (DLTs) for the purpose of declaring the tentative recommended dose for expansion (RDE). The Safety Review Committee (SRC) will review data from these patients for DLTs at the end of the first 3-week cycle:

- If 0 of 3 patients experiences a DLT on any dose level, the RDE will be tentatively declared and further dose expansion will continue.
- If 1 of 3 patients experiences a DLT on any dose level, that cohort will be expanded to 6 patients. If 1 of 6 patients experiences a DLT, the RDE will be tentatively declared and further dose expansion will continue.
- If ≥ 2 of 3 or ≥ 2 of 6 patients experience a DLT on Dose Level 0, Dose Level -1 will be explored. If ≥ 2 of 3 or ≥ 2 of 6 patients experience a DLT on Dose Level -1, Dose Level -2 will be explored.
- If ≥ 2 DLT(s) occur in up to 6 patients at Dose Level -2, further enrollment and dosing will be stopped until there is a full review of all available data, including PK, by the SRC.

After a minimum of 3 and a maximum of 10 eligible patients are enrolled and treated for at least 1 cycle (3 weeks), the SRC will review data from these patients to determine the RDE. In case of DLTs during Cycle 1, de-escalating doses of bavituximab in combination with pembrolizumab will be (**Table A**) as follows:

Table A: Planned Dose Levels

Dose Level	IV Bavituximab (Weekly)	IV Pembrolizumab (Q3W)

0	3 mg/kg	200 mg
-1	2 mg/kg	200 mg
-2	1 mg/kg	200 mg

After the DLT observation period, expansion may proceed. The cumulative safety data from the initial 3 to10 patients will be evaluated by the SRC, as well as subsequent safety data from the expansion population, as deemed appropriate by the SRC.

Definition of Dose-Limiting Toxicities

A DLT is defined as any of the AE described below that occurs during the DLT observation period and is at least possibly related to bavituximab or pembrolizumab. The Investigator will use CTCAE v5.0 guidelines to assign an AE term and severity grade relevant to the DLT.

A DLT is defined as any of the AEs described below that occurs during the DLT observation period and is at least possibly related to bavituximab or pembrolizumab. The Investigator will use CTCAE v5.0 guidelines to assign an AE term and severity grade relevant to the DLT.

Hematological toxicities as follows:

- Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
  - Grade 4 thrombocytopenia of any duration
  - Grade 3 thrombocytopenia associated with clinically significant bleeding
- ≥ Grade 3 febrile neutropenia
  - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour
  - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Grade 4 lymphocyte decreases lasting > 14 days

Non-hematologic toxicities:

- Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
- Any Grade 3 or Grade 4 non-hematologic laboratory value if:

- Clinically significant medical intervention is required to treat the subject, or
- The abnormality leads to hospitalization, or the abnormality persists for >1 week; the abnormality results in a Drug-induced Liver Injury (DILI)
- Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.

- Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
- Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1.
- Missing >25% of planned doses as a result of drug-related AE(s) during the first cycle.
- Grade 5 toxicity.

Isolated laboratory changes without associated clinical signs or symptoms may not be included in this definition. These findings will be discussed and reviewed by the Investigators and the Sponsor's medical monitor.

Safety data in subsequent cycles will also be monitored on an ongoing basis to determine the cumulative incidence of late-onset toxicities.

Adverse events that are not classified as DLTs by the above definition can be designated as DLTs if agreed upon by the Investigators and the Sponsor's medical monitor.

Safety data in subsequent cycles will also be monitored on an ongoing basis to determine the cumulative incidence of late-onset toxicities.

Patients who experience a DLT, but in the opinion of the Investigator can be adequately monitored for recurrence of the toxicity and are otherwise experiencing clinical benefit, may be offered continued treatment with bavituximab and pembrolizumab.

Dosing will continue until criteria for study treatment discontinuation are met (unacceptable toxicity, progressive disease [PD], or withdrawal from the study) or up to a maximum of 35 cycles.

Patients will be assessed for tumor response/progression per RECIST version1.1 (Appendix A). The initial tumor assessment on study therapy will be conducted 6 weeks after initiation of treatment then every 6 weeks until disease progression or another withdrawal criterion is met.

Progressive disease must be confirmed by a second scan 4 weeks after initial PD diagnosis in the absence of clearly symptomatic and/or rapidly progressive clinical deterioration or requirement for urgent intervention. It is anticipated that most patients will remain on treatment during the 4 weeks between scans.

Number of Patients Planned: Up to 80 patients are planned.

Study Duration:

Enrollment is planned to occur over approximately 13 months. Treatment and follow-up projected will be completed within approximately 6 months thereafter. Anticipated duration of the study is at least 21 months.

Diagnosis and Main Criteria for Inclusion / Exclusion:

Inclusion Criteria

For Group 1 only (CPI naïve):

1. Progressed on and/or after at least 1 prior regimen for metastatic disease which includes a fluoropyrimidine and a platinum:
   - Progression within 6 months of prior adjuvant or neoadjuvant chemotherapy will be deemed a rapid progressor and thus equivalent to 1 advanced/metastatic disease treatment regimen.
   - Changing from IV to oral fluoropyrimidine without noted progression is considered only 1 prior regimen.
   - Human epidermal growth factor receptor 2 (HER2)-positive patients must have received prior anti-HER2 therapy and demonstrate PD or was ineligible for such therapy.

For Group 2 only (CPI relapse):

2. Patient achieved stable disease or better in two consecutive scans to PD-1/PD-L1 inhibition alone or in combination with chemotherapy and relapsed following PD-1/PD-L1 inhibition either alone or in combination with chemotherapy
   - All patients must be immediate (defined by within 3 months) progressors of PD-1/PD-L1 inhibition with no intervening treatment with other agents such as chemotherapy alone.

For both Group 1 and Group 2:

3. Signed written informed consent obtained prior to performing any study procedure, including screening procedures.
4. Men and women ≥ 18 years old; ≥ 20 years old in South Korea and Taiwan.
5. Pathologically documented unresectable metastatic or locally advanced gastric or GEJ adenocarcinoma:
   - Must be metastatic/unresectable at the time of enrollment into this study.
6. Willing and able to provide fresh (since most recent progression) formalin-fixed paraffin-embedded tissue tumor sample for screening of signature status prior to study treatment and PD-L1 status. An archival tissue sample should also be provided, if available.
7. Presence of at least one measurable lesion assessed by the Investigator per RECIST version1.1.
8. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.
9. Has adequate organ functions defined as:

System	Laboratory value[a]
Hematological	

• Absolute neutrophil count (ANC)	• 1.5×10^9/L
• Platelets	• 100×10^9/L
• Hemoglobin[b]	• ≥ 9.0 g/dL
Renal	
• Dipstick or routine urinalysis ○ For proteinuria ≥ 2+ or urine protein/creatinine ratio ≥ 0.5, 24-hour urine must be collected	• Urine protein < 2 g/24h
• Creatinine, or	• ≤ 1.5 × ULN
• Glomerular filtration rate (GFR)	• ≥ 50 mL/min (see Appendix B)
Hepatic	
• Total bilirubin	• ≤ 1.5 × ULN (except for known Gilbert's syndrome)
• AST/ALT	• ≤ 2.5 × ULN for patients without liver metastases • ≤ 5 × ULN for patients with liver metastases
Coagulation	
• International normalized ratio (INR) or prothrombin time (PT)	• INR ≤ 1.5 × ULN or PT ≤ 5 sec above ULN, unless the patient is receiving anticoagulant therapy, as long as INR or PT is within therapeutic range of intended use of anticoagulants[c]
• Partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)	• PTT or aPTT ≤ 5 seconds above ULN, unless the patient is receiving anticoagulant therapy, as long as PTT or aPTT is within therapeutic range of intended use of anticoagulants[c]

a All labs will be performed, and values calculated per local institution standards.
b Transfusion and/or erythropoietin therapy to increase the patient's hemoglobin level is not permitted within 1 week prior to the baseline hematology profile.
c Patients on full-dose anticoagulation must be on a stable dose of oral anticoagulant or low molecular weight heparin for ≥ 14 days. If receiving oral anticoagulant, the patient must have an INR ≤ 3.0, no active bleeding (that is, no bleeding within 14 days prior to first dose of study therapy), and no pathological condition with a high risk of bleeding (for example, tumor involving major vessels or known varices).

10. Women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to start of study treatment.
11. Women must not be breastfeeding.
12. Women of childbearing potential defined as not surgically sterile or have not been free from menses for ≥2 years, must agree to follow instructions for highly effective method(s) of contraception for the duration of treatment with study drug bavituximab and pembrolizumab plus 5 months post-treatment completion as described in Section 4.4 Patients or Partners of Patients of Reproductive Potential for the duration of treatment with study drug bavituximab and pembrolizumab plus 5 months post-treatment completion.

Males who are sexually active with women of childbearing potential must agree to follow instructions for highly effective method(s) of contraception as described in Section 4.4 Patients or Partners of Patients of Reproductive Potential for the duration of treatment with study treatment plus 90 days post-treatment completion.

13. Has adequate treatment washout period before the start of study treatment, defined as:

    Major surgery ≥ 4 weeks; radiation therapy with abdominal radiation ≥ 4 weeks and have recovered from all radiation-related toxicities, not require corticosteroids and not have had radiation pneumonitis; palliative radiation without abdominal radiation ≥ 2 weeks; chemotherapy ≥ 3 weeks; biologic therapy ≥ 3 weeks.

Exclusion Criteria

For Group 1 only (CPI naïve):

1. Prior treatment with any checkpoint inhibitor or other therapies targeting T-cell control.

For Group 2 only (CPI relapse):

2. Primary refractory patients, defined as disease progression at first scan following initiation of PD-1/PD-L1 inhibitor treatment, or if best overall response to PD-1/PD-L1 inhibition was disease progression

For both Group 1 and Group 2:

3. Received any form of anti-phosphatidylserine therapies.
4. Known microsatellite instability-high (MSI-H) gastric or GEJ adenocarcinoma
5. Medical history of myocardial infarction within 6 months before registration, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV; Appendix C), troponin levels consistent with myocardial infarction as defined according to American College of Cardiologists (ACC) guidelines, unstable angina, or serious cardiac arrhythmia requiring treatment.
6. Experienced weight loss >10% over 2 months prior to first dose of study treatment.
7. History of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
8. Has known active CNS metastases/and or carcinomatous meningitis,
   Subjects with previously treated brain metastases may participate provided they are stable without evidence of progression via imaging for at least four weeks prior to first dose of study, and no evidence of neurological symptoms. Carcinomatous meningitis is excluded regardless of clinical stability.
9. Known additional malignancy that is progressing or has required active treatment in within the past 3 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
10. An active infection requiring systemic therapy
11. Known human immunodeficiency virus (HIV) infection or known acute hepatitis B or C infection.

12. Unresolved toxicities from previous cancer treatments (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. Grade 2 toxicities may be eligible at the discretion of the Investigator after consultation with the Sponsor's medical monitor.
13. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
14. Active autoimmune disease or history of chronic recurrent autoimmune disease, requiring systemic treatment for the past two years (i.e. Disease modifying agents, corticosteroids or immunosuppressive drugs).
    - Replacement therapy (thyroxine, insulin, or physiological corticosteroid replacement for either adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
15. History of hypersensitivity to pembrolizumab and/or any of its excipients that in the opinion of the investigator suggests a high risk for a severe hypersensitivity reaction while on treatment.
16. History of infusion reactions to any component/excipient of bavituximab.
17. History of hypersensitivity to mAbs that in the opinion of the investigator suggests a high risk for a severe hypersensitivity reaction while on treatment.
18. Systemic steroid therapy (>10 mg daily prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment (note: topical, inhaled, nasal and ophthalmic steroids are permitted).
19. Has received a live vaccine within 30 days prior to first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
20. Prior organ transplantation including allogeneic or autologous stem-cell transplantation.
21. Currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.
    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
22. Receipt of treatment with immunotherapy, biological therapies, or therapeutic doses of hormonal therapies within 3 weeks of scheduled C1D1 dosing.
23. Known psychiatric, substance abuse disorder, or geographical travel limitations that would interfere with participant's ability to cooperate with the requirements of the study.

24. Pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 5 months after the last dose of study treatment.

Investigational Medicinal Product (IMP), Dose, and Mode of Administration:

Bavituximab is supplied as a sterile, preservative-free solution with a composition of bavituximab, in 10 mM acetate, pH 5.0. It is provided in borosilicate Type 1 glass vials 120 mg/5mL (24 mg/mL) stored at 2°C to 8°C.

Dosage is calculated at 0.125 mL/kg body weight and diluted with normal saline to a volume of no less than 100 mL. Administer as IV with in-line 0.2 μm filter over 90 minutes once weekly. After the 1st infusion, in the absence of Grade 2 or greater hypersensitivity reactions, the infusion time will be reduced to 60 minutes. After the 2nd infusion, in the absence of Grade 2 or greater hypersensitivity reactions, the infusion time will be reduced to 30 minutes.

Pembrolizumab will be administered as 200 mg IV on Day 1 Q3W. Refer to pembrolizumab administration section for more details.

The doses of bavituximab will be adjusted or interrupted as appropriate based on treatment modifications defined in the protocol.

No dose reductions of pembrolizumab are permitted. Doses will be withheld as appropriate based on treatment modifications defined in the protocol.

Duration of Treatment:

Treatment may be continued until one of the following criteria applies:

- Progressive disease (PD): In patients with PD, a confirmatory scan will be performed at least 4 weeks later to confirm PD prior to removing the patient from study treatment.
- Intervening illness that prevents further administration of treatment.
- Unacceptable AEs.
- The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study treatment will occur prior to introduction of the new agent.
- Significant patient non-compliance with the protocol.
- Received 35 cycles of pembrolizumab.
- Pregnancy.
- Patient decision to withdraw from the study.
- Investigator decision to withdraw the patient from the study.
- Patient is lost to follow up.
- Sponsor decision to end the study.

Pharmacokinetics of bavituximab: Peripheral venous blood (4 mL) will be collected from all patients during Cycle 1 on Days 1 and 15 within 24 hours prior to bavituximab infusion, and at 1 hour (± 30 minutes) after the end of bavituximab infusion. Samples are also collected within 24 hours prior to bavituximab infusion on Cycle 2 Days 1 and 15, and Day 1 of Cycles 3, 4, and 6 for quantitation of bavituximab.

Biomarkers:

Peripheral blood and tumor tissue will be collected for biomarker analysis. Tissue will be obtained prior to therapy (mandatory fresh tumor biopsy and, if available, archival sample) and this tissue will be used to measure potential tissue-based predictive biomarkers. Those biomarkers include immunohistochemistry (IHC) as well as RNA signatures. Residual sample material available after completion of the designated analyses may be used in the future for identification of predictive markers or to enhance understanding of disease biology unless prohibited by local laws or regulations. Samples will be de-identified to ensure patient privacy. Serum will be collected at baseline and at timepoints post treatment as specified in the protocol to assess circulating pharmacodynamic biomarkers.

Statistical Methods:

The trial will evaluate safety and efficacy of the bavituximab-pembrolizumab combination in a disease setting in which pembrolizumab has shown promising but modest activity. The hypothesis to be evaluated is whether the bavituximab-pembrolizumab combination will yield an ORR superior to historical ORR of pembrolizumab in the 2nd-line setting in patients who have not previously been exposed to an anti-PD-1 or anti-PD-L1 agent.

Sample Size:

The primary efficacy objective of this Phase 2 study is the evaluation of ORR of bavituximab in combination with pembrolizumab in patients with advanced gastric or GEJ cancer. The overall sample size of 80 patients was chosen to yield adequate information regarding efficacy at the recommended dose and to allow an initial correlation of the preliminary efficacy with biomarker profiles. This includes patients enrolled in both Group 1 and Group 2. Both 2nd and 3rd line patients will be enrolled with no cap on either line of treatment of patients. The 2nd line cohort will have 72% to 86% power to show that the lower bound of the 80% CI is greater than 15% for 30-50 patients is the with a true ORR of 30%, and the 3rd line cohort will have 67% to 78% power to show that the lower bound of the 80% CI is greater than 6% for 30-50 patients is the with a true ORR of 15%.

For Group 1 (CPI naïve),approximately 40 patients are needed to show a statistical superiority of bavituximab-pembrolizumab with 80% statistical power at one-sided type I error rate of α=0.10. For the CPI-relpase patient population, the n was set to 20 patients for the initial assessment of safety, tolerability and initial antitumor activity. See the statistical section of the protocol for further detail.

Criteria for Evaluation:

Safety

All patients who receive at least 1 dose of study treatment will be included in the safety analyses (safety analysis set). DLT evaluable set will be included for the first 3 patients up to

a maximum of 10 patients who have received at least 1 dose and completed 1 full cycle follow up or experienced a DLT.

The safety and tolerability of study treatment will be evaluated based on AEs (incidence and severity), performance status, physical examinations, vital sign measurements, standard clinical laboratory safety evaluations. Laboratory abnormalities and AEs will be graded according to CTCAE v5.0. Immune-related reactions (IRRs) may occur with bavituximab and/or pembrolizumab. Detailed guidance for the handling of IRRs will be presented in the protocol.

Pharmacokinetics

Serum concentrations for bavituximab will be listed and summarized using descriptive statistics by cohort at each time point.

Immunogenicity

The immunogenicity of bavituximab (ADA formation) will be investigated during the course of the study.

Efficacy

Efficacy analysis will be performed on the full analysis set, and per protocol analysis set, including predefined biomarker subgroups (as below). Radiological and clinical tumor assessments will be evaluated based on RECIST version1.1. For patients with PD, a confirmatory scan will be performed at least 4 weeks later to confirm PD prior to removing the patient from study treatment. This confirmatory scan is recommended but not required, it is at the discretion of the treating physician.

Statistical Methods:

Tabular summaries of data will be descriptive in nature (i.e., number of patients [n], mean, standard deviation, median, minimum and maximum for continuous variables and n and percent for categorical variables). A more detailed description of analysis methods will be provided in the statistical analysis plan (SAP) to be completed prior to the clinical database lock.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Abbreviations and Definitions of Terms

Abbreviation or Specialist Term	Explanation
ACC	American College of Cardiologists
ADA	Antidrug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BCG	Bacille Calmette-Guerin
β2-GP1	β2-glycoprotein 1
BP	Blood pressure
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	Complete blood count
CBR	Clinical benefit rate
CD8	Cluster of differentiation 8, a co-receptor for the T-cell receptor
CHF	Congestive heart failure
CI	Confidence interval
CK	Creatine kinase
C_{max}	Maximum concentration
CMP	Complete metabolic panel
CNS	Central Nervous System
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CT	Computerized tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4

Abbreviation or Specialist Term	Explanation
C_{trough}	Lowest dose concentration prior to the next dose
DCR	Disease control rate
DILI	Drug-induced Liver Injury
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EOI	End of infusion
EOT	End of treatment
FoxP3	Forkhead box p3, a marker for regulatory T-cells
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
3G4	Mouse IgG3 mAb that specifically targets anionic phospholipids
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction
GFR	Glomerular filtration rate
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HGB	Hemoglobin
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HR	Heart rate or Hazard Ratio

Abbreviation or Specialist Term	Explanation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgG1	immunoglobulin gamma 1-kappa (IgG1)κ
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial lung disease
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
IRR	Infusion-related reaction
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
LMWH	Low-molecular-weight heparin
mAb	Monoclonal antibody
mch1N11	Mouse chimeric 1N11
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDSC	Myeloid-derived suppressor cell
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	High microsatellite instability
N	Number
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease OR pharmacodynamics
PD-1	Programmed cell death protein 1

Abbreviation or Specialist Term	Explanation
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PE	Physical exam
PET	Positron emission tomography
PFS	Progression-free survival
PI	Prescribing Information
PK	Pharmacokinetics
PLT	Platelets
PO	Orally
PR	Partial response
PS	Phosphatidylserine OR Performance Status
PT	Prothrombin time
PTT	Partial thromboplastin time
Q3W	Every 3 weeks
RBC	Red blood cells
RDE	Recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System organ class
SRC	Safety Review Committee
SUSAR	Serious Unexpected serious adverse reaction
T	Temperature
TAM	Tumor-associated macrophages
T Cell	T lymphocyte
TGF-ß	Transforming growth factor-beta
TIL	Tumor infiltrating lymphocytes
TIM3	T cell immunoglobulin and mucin domain 3
TMDD	Target-mediated drug disposition

Abbreviation or Specialist Term	Explanation
TNBC	Triple negative breast cancer
TNF-α	Tumor necrosis factor-alpha
T-regs	Regulatory T-cells
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
ZAP70	Zeta-chain-associated protein kinase

1. INTRODUCTION

1.1. Overview of Bavituximab

Oncologie, Inc. is developing bavituximab as an immunomodulatory drug for the treatment of cancer. Bavituximab is a chimeric (human/mouse) monoclonal antibody (mAb) derived from murine mAb 3G4 that targets phosphatidylserine (PS) after binding to β2-glycoprotein 1 (β2-GP1).

In normal non-tumorigenic cells, PS is segregated to the inner leaflet of the plasma membrane. Conditions that induce cellular stress, including normal cell death, immune phagocytic cell clearance, oxygen radicals, hypoxia, irradiation, and chemotherapy, cause a shift resulting in the externalization of PS to the outer leaflet of the plasma membrane. Exposed PS is recognized and bound by PS receptors on immune cells where it induces and maintains immune suppression. This relocation also occurs in tumor cells, exosomes, and vascular endothelial cells inducing non-inflammatory signals via multiple receptors which contribute to the immunosuppression of the tumor microenvironment, including binding to TIM/TAM receptors. Phosphatidylserine-targeting agents block PS-mediated immunosuppression by multifocal reprograming of the immune cells in the tumor microenvironment to support immune reactivation. Antibody-mediated PS blockade reduces the levels of myeloid-derived suppressor cells (MDSCs), transforming growth factor-beta (TGF-β), and interleukin (IL)-10, and increases the levels of tumor necrosis factor-alpha (TNF-α) and IL-12. Phosphatidylserine blockade also repolarizes tumor-associated macrophages (TAMs) from predominant M2 to predominant M1 phenotype, promotes the maturation of dendritic cells, and induces potent adaptive antitumor T-cell immunity. In vitro studies have shown that bavituximab binds to PS in the presence of β2-GP1 as a high affinity complex, modulating β2-GP1 binding to PS from 1 μM to 1 nM. In experimental mouse cancer models, the bavituximab surrogate antibody mch1N11 as a single agent reduced tumor growth and prolonged survival. In addition, the anti-tumor effects of mch1N11 were enhanced by co-administration of checkpoint inhibitors (anti- Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA4) and anti-PD-1/L1), as well as chemotherapy or radiation (Yin et al., 2013a; Yin et al., 2013b).

Bavituximab is an attractive immunotherapeutic approach to treating cancer, because its primary mechanism of action involves modulating the tumor microenvironment from a primarily immunosuppressive, angiogenesis-promoting state (with infiltrating MDSCs and M2-macrophages) to an immune activating state (with long-term tumor-specific immunity facilitated by M1 macrophages, mature dendritic cells, and activated T lymphocytes). In essence, expression of PS on the external surface of the cell acts as an immunosuppressive signal in normal cell death and immune phagocytic clearance, thus allowing tumor growth and progression. Exposing PS on the external surface of the cell provides a rich source of ligand for multiple immune receptors expressed on immune cells present in the microenvironment, including PS binding to T cell immunoglobulin and mucin domain 3 (TIM3) receptors.

Nonclinical data suggest that bavituximab and pembrolizumab can be co-administered effectively as demonstrated in murine models for melanoma and triple negative breast cancer. Combining PS-targeting antibody mch1N11 with a single dose of radiotherapy and anti-programmed cell death protein 1 (PD-1) blocking antibody, a triple therapy combination, to treat

mice bearing PD-1 resistant melanoma, results in almost complete tumor elimination and leads to statistically significant prolonged survival (Giese et al., 2018).

Gray et al. (2016) demonstrated that immune-competent mice implanted with triple negative breast cancer (TNBC) cell lines and treated with a combination of the PS-targeting antibody mch1N11 and anti-PD-1 antibody therapy had significantly greater inhibitory tumor growth activity and significantly increased overall survival compared with either single treatment alone, and is capable of causing complete tumor regression. Additionally, mice treated with the combination experienced complete tumor regression, demonstrated increased splenic IFNɣ production and enhanced number of tumor infiltrating lymphocytes (TILs). Furthermore, on TNBC re-challenge those treated with the combinations were capable of mounting a durable immune response that suppressed tumor growth.

Bavituximab has been administered to 800 patients in early and late phase studies. Initial indication of activity for bavituximab as monotherapy or in combination with chemotherapy is noted in phase 2 trials for breast cancer, non-small cell lung cancer (NSCLC) and pancreatic cancer. A Phase 3 advanced NSCLC trial, SUNRISE, was completed. The primary endpoint of improved overall survival (OS) in bavituximab plus docetaxel versus docetaxel plus placebo was not met. However, subgroup analysis indicated that patients who progressed on study treatment with bavituximab plus docetaxel and went onto a checkpoint inhibitor showed significantly improved OS compared to a similar group of patients with progressive disease (PD) post docetaxel plus placebo who went onto receive a checkpoint inhibitor.

1.1.1. Nonclinical Experience with Bavituximab

In nonclinical studies, no target organs of toxicity were identified in rats and monkeys receiving doses of bavituximab of up to 100 mg/kg. Incidental minimal histological findings were noted in heart and lungs in high-dose monkeys and included left ventricular thrombus, right ventricular subendocardial fibrosis and arteriopathy, and fibrosis in the lung. In rats, subendocardial inflammation was noted in the high-dose group. Bavituximab has been associated with immunogenicity in rats and monkeys. A dose-related prolongation of aPTT in rats and of aPTT and PT in monkeys has been demonstrated to be an in vitro phenomenon due to inhibition of phospholipid-dependent coagulation assays. Bavituximab up to 100 mg/kg did not affect time-to-healing in dermal healing rodent models.

Refer to the bavituximab Investigator's Brochure (IB) for detailed nonclinical data.

1.1.2. Clinical Experience with Bavituximab

Phase 1 (single agent, safety, and pharmacokinetic [PK]) and Phase 1b (safety, tolerability, and PK) studies of bavituximab in combination with chemotherapy have been completed in patients with advanced cancer. Several Phase 2 studies of bavituximab with chemotherapy have been completed, including safety and efficacy studies in patients with locally or advanced metastatic cancers. These studies include patients with NSCLC, previously treated or untreated non-squamous NSCLC, breast cancer, and previously untreated Stage 4 pancreatic cancer. A Phase 3 clinical trial to evaluate the efficacy and safety of bavituximab when given with docetaxel in patients with previously treated Stage 3b/4 non-squamous NSCLC was discontinued following a pre-specified interim analysis. Addition of bavituximab to docetaxel did not improve OS in previously treated advanced NSCLC. Subset analyses suggested possible benefit in high β2GP1

cases and those subsequently receiving immune checkpoint inhibitors. Current development of bavituximab is focused on the combination of bavituximab with other therapeutic approaches including radiation and immunotherapies.

Across all studies, the profile of serious adverse events (SAEs) in subjects receiving bavituximab in combination with chemotherapy or an antiviral was similar to those receiving chemotherapy alone. The most common SAEs were febrile neutropenia (4.6%), neutropenia (4.0%), pneumonia (2.7%), and pulmonary embolism (2.0%), anemia (1.6%), pyrexia (1.6%), dyspnea (1.1%), deep vein thrombosis (1.3%), asthenia (1.2%), diarrhea (1.0%), fatigue (1.0%), and sepsis (1.0%). The only events that occurred at a meaningfully higher frequency (increase by >1.0%) in subjects receiving bavituximab in combination with chemotherapy compared to those receiving chemotherapy alone were febrile neutropenia, neutropenia, and anemia. These events were not observed in the small group of patients receiving bavituximab monotherapy.

Infusion reactions and similar events (e.g. hypersensitivity reactions and anaphylaxis) have occurred in association with bavituximab administration and are a known class effect of chimeric mAbs. These types of reactions have occurred more commonly in oncology studies in which chemotherapy is also administered, but have also occurred in monotherapy studies in both the antiviral and oncology programs. The highest incidence was in Study PPHM 0704, a study conducted in the Republic of Georgia in which patients with advanced breast cancer also received docetaxel therapy. All reactions in that study were mild or moderate in severity, and patients were able to continue to receive bavituximab without an apparent increase (or decrease) in the frequency or severity of the reactions. It is unclear what impact, if any, that the concomitant chemotherapy, patient characteristics, or environment had on the frequency of events in this study.

Grade 3 infusion reactions have occurred in other studies, resulting in discontinuation of patients from treatment with bavituximab. Infusion reactions have occurred both with and without premedication, and it is unclear whether the type of co-administered chemotherapy or premedication with steroids and antihistamines impacts the frequency or severity of infusion reactions. Reports of infusion reactions will continue to be monitored.

Refer to the bavituximab IB for detailed clinical data.

1.1.3. Rationale for Study and Starting Dose of Bavituximab

The approved dose and schedule of pembrolizumab will be used in this trial in combination with the recommended dose of bavituximab for Phase 2 and Phase 3 development. No overlapping toxicities are expected, and the Safety Review Committee (SRC) will review emerging data during the conduct of the trial.

1.2. Overview of Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of

indications. For more details on specific indications and background information, refer to the Investigator's Brochure/approved labeling for pembrolizumab.

1.2.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

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. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in gastric and gastroesophageal junction (GEJ) adenocarcinoma.

1.2.2. Non-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities [Hirano, 2005; Blank, 2004;Weber, 2010; Strome, 2003; Spranger, 2014; Curran, 2010; Pilon, 2010]. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma [Strome, 2003; Curran, 2010; Pilon, 2010; Nomi, 2007; Zhang, 2004]. In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin

expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* [Curran, 2010]. Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

1.2.3. Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity

and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

1.3. Rationale for Combining Bavituximab with Pembrolizumab

Pembrolizumab was recently approved in the US and other countries for later line treatment of recurrent or advanced gastric or GEJ adenocarcinoma based on the KEYNOTE 059 in which patients received 200 mg pembrolizumab intravenously (IV) every 3 weeks until disease progression, Investigator or patient decision to withdraw, or unacceptable toxicity. A total of 259 patients were enrolled; most were male (198 [76.4%]) and white (200 [77.2%]). The median (range) age was 62 (24-89) years. Objective response rate (ORR) was 11.6% (95%CI, 8.0%-16.1%; 30 of 259 patients), with complete response (CR) in 2.3% (95%CI, 0.9%-5.0%; 6 of 259 patients). Median (range) response duration was 8.4 (1.6+ to 17.3+) months. ORR and median (range) response duration were 15.5% (95%CI, 10.1%-22.4%; 23 of 148 patients) and 16.3 (1.6+ to 17.3+) months, and 6.4% (95%CI, 2.6%-12.8%; 7 of 109 patients) and 6.9 (2.4 to 7.0+) months in patients with PD-L1–positive and PD-L1–negative tumors, respectively. Forty-six patients (17.8%) experienced 1 or more Grade 3 to 5 treatment-related adverse events (AEs). Based on these results, albeit positive for gastric cancer patients but still suboptimal in this aggressive disease, and pembrolizumab's manageable safety profile, pembrolizumab will be a rationale combination for the treatment of gastric cancer. In addition, KEYNOTE 061 pembrolizumab versus paclitaxel, pembrolizumab did not significantly improve overall survival compared with paclitaxel as second-line therapy for advanced gastric or gastro-esophageal junction cancer with PD-L1 CPS of 1 or higher, although a better safety profile than paclitaxel was identified. Median overall survival was 9·1 months (95% CI 6·2 –10·7) with pembrolizumab and 8·3 months (7·6 –9·0) with paclitaxel (hazard ratio [HR] 0·82, 95% CI 0·66 – 1·03; one-sided p=0·0421). Median progression-free survival was 1·5 months (95% CI 1·4 –2·0) with pembrolizumab and 4·1 months (3·1 –4·2) with paclitaxel (HR 1·27, 95% CI 1·03 – 1·57). The ORR in these patients was 13.3% (95% CI, 8.2-20.0), including a complete response (CR) rate of 1.4% and a partial response (PR) rate of 11.9%.

Pembrolizumab has received accelerated approval for the treatment of 3rd-line (plus) gastric/GEJ cancer. However, the ORR was 11.6% (95% CI, 8.0%, 16.1%), implying that the majority of such patients fail to derive sufficient benefit from pembrolizumab monotherapy. In experimental mouse cancer models, the bavituximab surrogate antibody used in combination with an anti-PD-1/L1 antibody demonstrated enhanced tumor control. Bavituximab has also demonstrated a tolerable safety profile. Thus, little to no overlapping toxicities are anticipated. The SUNRISE subgroup analysis indicated that patients who progressed on study treatment with bavituximab plus docetaxel and went onto a checkpoint inhibitor showed significantly improved OS. These data in combination with the preclinical data suggest that bavituximab may restimulate T cells or render exhausted T cells susceptible to checkpoint inhibition. Therefore, we hypothesize the addition of bavituximab to pembrolizumab may enhance the antitumor immune response and eventually potentiate the activity of the antibody that is already targeting checkpoint inhibition, resulting in increased clinical benefit.

Given the potential for this combination to enhance antitumor responses, it is being evaluated in 2 populations of advanced gastric or GEJ cancer patients: CPI naïve patients that have

progressed on standard chemotherapy and are naïve to CPI therapy; and CPI relapse patients that had a confirmed PR or CR then subsequently progressed following treatment with CPI either alone or in combination with chemotherapy.

1.4. Benefit-Risk Assessment

Clinical trials in cancer are designed to assess new therapeutic strategies that may provide greater benefit, less toxicity or both than those of existing therapies. This trial is an initial attempt to understand the activity and safety profile of an approved agent for gastric/GEJ cancer when used in combination with an experimental agent that has shown promise in preclinical testing. However, subjects enrolled in clinical trials cannot expect to receive direct benefit from this proposed combination.

Common AEs observed with anti PD-1/PD-L1 agents include diarrhea/colitis, pneumonitis/interstitial lung disease (ILD), hepatitis and increases in transaminases, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), myocarditis, nephritis and increases in serum creatinine, dermatitis/rash and pruritus, neuromuscular toxicity such as myasthenia gravis and Guillain-Barré, and pancreatitis.

Emerging safety data from bavituximab trials, indicates that the overall safety profile appears to be acceptable and consistent across studies. Combination therapy, particularly with docetaxel, did not substantially increase the AE risks. Sporadic infusion reactions have occurred, and it is not clear if corticosteroid premedication mitigates this risk. Refer to the bavituximab IB for additional details.

No patients have been treated with bavituximab and immune checkpoint inhibitors to date in Oncologie-sponsored trials. Overall, the potential additional benefits of the combination of bavituximab and pembrolizumab therapy are likely to outweigh the risks.

2. STUDY OBJECTIVES AND ENDPOINTS

For both Group 1 and Group 2:

Primary Objectives	**Primary Endpoints**
• To assess the safety and tolerability of bavituximab in combination with pembrolizumab in patients with advanced gastric/GEJ cancer • To assess the antitumor activity of the treatment combination based on Response Evaluation Criteria in Solid Tumors (RECIST) version1.1 (Appendix A)	• Incidence and severity of AEs and SAEs graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, including changes in clinical laboratory parameters • Objective response rate (ORR) as assessed by the Investigator per RECIST version1.1
Secondary Objectives	**Secondary Endpoints**
• To further characterize the antitumor activity of the treatment combination based on additional assessments of clinical benefit • To evaluate bavituximab concentrations when administered in combination with pembrolizumab • To assess the potential immunogenicity of bavituximab	• Duration of response (DoR), disease control rate (DCR) (as defined by ORR and stable disease rate at 6 weeks), progression-free survival (PFS), and OS • Bavituxiamb concentrations before and after bavituximab infusions • Presence of anti-bavituximab antibodies (anti-drug antibodies [ADAs])
Tertiary Objective	**Tertiary Endpoints**
• To evaluate a novel biomarker signature panel and correlate with efficacy outcomes in patients treated with bavituximab-pembrolizumab combination	• Analysis of tissue to determine percentage of patients with defined genetic signature • Preliminary correlation of ORR to genetic signature • Status of genomic and immune biomarkers in blood and tissue samples at baseline and change from baseline upon treatment

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 2, multicenter, open-label, non-randomized study with an initial safety analysis to assess the safety and tolerability of bavituximab administered in combination with pembrolizumab, a PD-1 inhibitor, in patients with advanced gastric or GEJ adenocarcinoma who have either progressed on standard chemotherapy and are naïve to CPI therapy (Group 1), or had a confirmed PR or CR then subsequently progressed following treatment with CPI either alone or in combination with chemotherapy (Group 2).

Following a minimum of 3 and a maximum of 10 patient safety run-in with bavituximab (3 mg/kg IV weekly) and pembrolizumab (200 mg IV every 3 weeks [Q3W]), additional patients will be recruited if the initial doses of the regimen are tolerable. Lower doses of bavituximab may be explored if the initial doses are not tolerable. Primary anti-tumor activity will be documented by Investigator-assessed objective response per RECIST 1.1. Approximately 80 patients will be enrolled in the study, a minimum of 40 patients will be enrolled in Group 1 and a minimum of 20 patients will be enrolled in Group 2.

The first 3 patients will be evaluated for dose-limiting toxicities (DLTs) for the purpose of declaring the tentative RDE. The SRC will review data from these patients for DLTs at the end of the first 3-week cycle.

After a minimum of 3 and maximum of 10 eligible patients are enrolled and treated for at least 1 cycle (3 weeks), the SRC will review data from these patients to determine the recommended dose for expansion (RDE). In case of DLTs, de-escalating doses of bavituximab in combination with pembrolizumab will be assessed (see Section 5.6). After the DLT observation period, expansion may proceed. The cumulative safety data from the initial 3 to 10 patients will be evaluated by the SRC, as well as subsequent safety data from the expansion population, as deemed appropriate by the SRC.

Once the RDE of the combination of bavituximab and pembrolizumab has been confirmed, additional patients, for a total of 80 across both groups, will be enrolled in the expansion and assessed for preliminary efficacy and pharmacodynamic effects, as well as safety and tolerability. Patients will be evaluated regularly for safety and efficacy according to the Schedule of Assessments (Table 8).

Safety data will be monitored throughout the course of the study including but not limited to; reviewing trends in safety data, laboratory analytes, and AEs including monitoring of adverse events of special interest (AESIs).

The SRC, comprised of a medical monitor, statistician, the primary Investigator, and ad hoc SRC members, as needed, will be responsible for review of safety data. The SRC will convene regularly to review data to assess DLTs, and will convene at least yearly to review all safety data.

Additional formal meetings for the SRC will occur

(a) when a total of 10 patients have received at least one dose of study therapy and followed for 3 months after the 10th subject patient receives the first dose of study therapy and

(b) when a total of 40 patients have received at least one dose of study therapy and followed for 3 months after the 40th patient receives the first dose of study therapy

Special attention will be paid for later-onset DLT-like toxicities.

Patients will be assessed for tumor response/progression per RECIST version1.1 (Appendix A). The initial tumor assessment on study therapy will be conducted 6 weeks after initiation of treatment for, then every 6 weeks until disease progression or another withdrawal criterion is met.

An End-of-Treatment Visit will be performed at the time of treatment discontinuation followed by a Safety Follow-Up Visit 30 days after the end of treatment.

3.2. Study Duration

Enrollment is planned to occur over approximately 13 months. Treatment and follow-up projected will be completed within approximately 6 months thereafter. The total anticipated duration of the study is at least 21 months.

4. STUDY POPULATION

4.1. Number of Patients

Up to approximately 80 patients are planned for inclusion in this study. A minimum of 40 patients will be enrolled in Group 1 and a minimum of 20 patients will be enrolled in Group 2.

4.2. Patient Inclusion Criteria

Patients must meet all the following inclusion criteria to be enrolled.

For Group 1 only (CPI naïve):

1. Progressed on and/or after at least 1 prior regimen for metastatic disease which includes a fluoropyrimidine and a platinum therapy:
    - Progression within 6 months of prior adjuvant or neoadjuvant chemotherapy will be deemed a rapid progressor and thus, equivalent to 1 advanced/metastatic disease treatment regimen.
    - Changing from IV to oral fluoropyrimidine without noted progression is considered only 1 prior regimen.
    - Human epidermal growth factor receptor 2 (HER2)-positive patients must have received prior anti-HER2 therapy and demonstrate PD or was ineligible for such therapy.

For Group 2 only (CPI relapse):

2. Patient achieved stable disease or better in two consecutive scans to PD-1/PD-L1 inhibition alone or in combination with chemotherapy and relapsed following PD-1/PD-L1 inhibition either alone or in combination with chemotherapy
    - All patients must be immediate (defined by within 3 months) progressors of PD-1/PD-L1 inhibition with no intervening treatment with other agents such as chemotherapy alone.

For both Group 1 and Group 2:

3. Signed written informed consent obtained prior to performing any study procedure, including screening procedures.
4. Men and women ≥ 18 years old; ≥ 20 years old in South Korea and Taiwan.
5. Pathologically documented unresectable metastatic or locally advanced gastric or GEJ adenocarcinoma
    - Must be metastatic/unresectable at the time of enrollment into this study
6. Willing and able to provide fresh (since most recent progression) formalin-fixed paraffin-embedded tissue tumor sample for screening of signature status prior to study treatment and to measure PD-1 status. An archival tissue sample should also be provided, if available.

7. Presence of at least one measurable lesion assessed by the Investigator per RECIST version 1.1.
8. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.
9. Has adequate organ functions defined as:

System	Laboratory value[a]
Hematological	
• Absolute neutrophil count (ANC)	• 1.5×10^9/L
• Platelets	• 100×10^9/L
• Hemoglobin[b]	• ≥ 9.0 g/dL
Renal	
• Dipstick or routine urinalysis ○ For proteinuria ≥ 2+ or urine protein/creatinine ratio ≥ 0.5, 24-hour urine must be collected	• urine protein < 2 g/24 h
• Creatinine, or	• ≤ 1.5 × upper limit of normal (ULN)
• Glomerular filtration rate (GFR)	• ≥ 50 mL/min (see Appendix B)
Hepatic	
• Total bilirubin	• ≤ 1.5 × ULN (except for known Gilbert's syndrome)
• Aspartate transaminase (AST)/ alanine transaminase (ALT)	• ≤ 2.5 × ULN for patients without liver metastases • ≤ 5 × ULN for patients with liver metastases
Coagulation	
• International normalized ratio (INR) or prothrombin time (PT)	• INR ≤ 1.5 × ULN or PT ≤ 5 sec above ULN, unless the patient is receiving anticoagulant therapy, as long as INR or PT is within therapeutic range of intended use of anticoagulants[c]
• Partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)	• PTT or aPTT ≤ 5 seconds above ULN, unless the patient is receiving anticoagulant therapy, as long as PTT or aPTT is within therapeutic range of intended use of anticoagulants[c]

a All labs will be performed, and values calculated per local institution standards.
b Transfusion and/or erythropoietin therapy to increase the patient's hemoglobin level is not permitted within 1 week prior to the baseline hematology profile.
c Patients on full-dose anticoagulation must be on a stable dose of oral anticoagulant or low molecular weight heparin for ≥ 14 days. If receiving oral anticoagulant, the patient must have an INR ≤ 3.0, no active bleeding (that is, no bleeding within 14 days prior to first dose of study therapy), and no pathological condition with a high risk of bleeding (for example, tumor involving major vessels or known varices).

10. Women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to start of study treatment.

11. Women must not be breastfeeding.
12. Women of childbearing potential defined as not surgically sterile or have not been free from menses for ≥ 2 years, must agree to follow instructions for highly effective method(s) of contraception as described in Section 4.4 Patients or Partners of Patients of Reproductive Potential for the duration of treatment with study drug bavituximab and pembrolizumab plus 5 months post-treatment completion.

    Males who are sexually active with women of childbearing potential must agree to follow instructions for highly effective method(s) of contraception as described in Section 4.4 s or Partners of Patients of Reproductive Potential for the duration of treatment with study treatment plus 90 days post-treatment completion.
13. Has adequate treatment washout period before start of study treatment, defined as:
    - Major surgery ≥ 4 weeks; radiation therapy with abdominal radiation ≥ 4 weeks and have recovered from all radiation-related toxicities, not require corticosteroids and not have had radiation pneumonitis; palliative radiation without abdominal radiation ≥ 2 weeks; chemotherapy ≥ 3 weeks; biologic therapy ≥ 3 weeks.

4.3. Patient Exclusion Criteria

Patients who meet any of the following criteria may not be enrolled.

For Group 1 only:

1. Prior treatment with any checkpoint inhibitor or other therapies targeting T-cell control.

For Group 2 only:

2. Primary refractory patients, defined as disease progression at first scan following initiation of PD-1/PD-L1 inhibitor treatment, or if best overall response to PD-1/PD-L1 inhibition was disease progression.

For both Group 1 and Group 2:

3. Received any form of anti-phosphatidylserine therapies.
4. Known MSI-H gastric or GEJ adenocarcinoma
5. Medical history of myocardial infarction within 6 months before registration, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV; Appendix C), troponin levels consistent with myocardial infarction as defined according to American College of Cardiologists (ACC) guidelines, unstable angina, or serious cardiac arrhythmia requiring treatment.
6. Experienced weight loss >10% over 2 months prior to first dose of study treatment.
7. History of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
8. Known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable without evidence of progression via imaging for at least four weeks prior to first dose of study, and no evidence of neurological symptoms. Carcinomatous meningitis is excluded regardless of clinical stability.

9. Known additional malignancy that is progressing or has required active treatment in within the past 3 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

10. Active infection requiring systemic therapy.
11. Known human immunodeficiency virus (HIV) infection, or known acute hepatitis B or C infection.
12. Unresolved toxicities from previous cancer treatments (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. Grade 2 toxicities may be eligible at the discretion of the Investigator after consultation with the Sponsor's medical monitor.
13. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
14. Active autoimmune disease or history of chronic recurrent autoimmune disease, requiring systemic treatment for the past two years (i.e., disease modifying agents, corticosteroids, or immunosuppressive drugs).
    - Replacement therapy (thyroxine, insulin, or physiological corticosteroid replacement for either adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
15. History of hypersensitivity to pembrolizumab and/or any of its excipients that in the opinion of the investigator suggests a high risk for a severe hypersensitivity reaction while on treatment.
16. History of infusion reactions to any component/excipient of bavituximab.
17. History of a hypersensitivity to mAbs that in the opinion of the investigator suggests a high risk for a severe hypersensitivity reaction while on treatment.
18. Systemic glucocorticoid therapy (>10 mg daily prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment (note: topical, inhaled, nasal and ophthalmic steroids are permitted).
19. Received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
20. Prior organ transplantation including allogeneic or autologous stem-cell transplantation.

21. Currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

22. Receipt of treatment with immunotherapy, biological therapies, or therapeutic doses of hormonal therapies within 3 weeks of scheduled C1D1 dosing.
23. Known psychiatric, substance abuse disorder, or geographical travel limitations that would interfere participant's ability to cooperate with the requirements of the study.
24. Pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 5 months after the last dose of study treatment.

4.4. Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study.

It is unknown whether bavituximab or pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

Female patients of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to start of study treatment. A serum or urine pregnancy test will be performed at the End-of-Treatment (EOT) Visit.

To be considered of non-childbearing potential, a female patient must meet at least one of the following criteria:

- Postmenopausal (i.e., amenorrheic for ≥ 2 years) AND a follicle-stimulating hormone (FSH) value within the institution's post-menopausal range at screening
- Hysterectomy OR bilateral oophorectomy
- Tubal ligation at least 5 years prior to screening with no subsequent pregnancies

Fertile female patients must practice a highly effective method of contraception during treatment and for 5 months following the last dose of study treatment. Highly effective contraception includes:

- an intrauterine device (IUD; alone or in combination with other birth control)
- bilateral tubal occlusion
- vasectomized partner (provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success)

- sexual abstinence as defined as complete abstinence, acceptable only when it is the usual and preferred lifestyle of the patient; periodic abstinence (e.g., calendar, symptothermal, post-ovulation methods) is not acceptable
- Combination of any 2 of the following (a + b or a + c or b + c)
    a) Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%) (e.g., hormone vaginal ring or transdermal hormone contraception)
    b) Placement of an intrauterine device or intrauterine system
    c) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/cream/vaginal suppository.

Male patients with a female partner of childbearing potential must have either had a prior vasectomy with medical assessment of the surgical success or agree to double-barrier methods of contraception during treatment, and for 90 days after the last dose of either study treatment to allow for clearance of any altered sperm.

Patients will be instructed to notify the Investigator if pregnancy is discovered either during or within 5 months of the last dose of study treatment.

4.5. Waivers of Inclusion/Exclusion Criteria

No waivers of these inclusion or exclusion criteria will be granted by the Investigator and the Sponsor or its designee for any patient enrolling into the study.

No deviations from the protocol should be initiated without prior discussion with Sponsor and written Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects.

4.6. Criteria for Treatment Discontinuation

Patients may withdraw voluntarily from participation in the study or from study treatment at any time and for any reason. A patient's participation in the study may terminate at his/her request or on the basis of the Investigator's clinical judgment. The reason for patient withdrawal will be documented in the source data and noted on the electronic case report form (eCRF).

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations at the 30-Day Safety Follow-up visit.

If such withdrawal occurs, or if the patient fails to return for visits, the Investigator must determine the primary reason for a patient's withdrawal from the study and record the information on the eCRF. If the reason for withdrawal is an AE, monitoring should continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF. At the discretion of the Sponsor, patients may also be removed from the study.

It should be clearly documented in the source data whether patients withdrew their consent and will not enter the follow-up phase, or if patients withdrew their consent for study treatment but will continue further participation in the study. If patients withdraw consent for the survival follow-up phase, the study site is still obligated to follow the patient's survival status through publicly available forms of information (i.e. death registries).

Treatment may be continued until one of the following criteria applies:

- Progressive disease (PD): In patients with PD, a confirmatory scan should be performed at least 4 weeks later to confirm PD prior to removing the patient from study treatment. The confirmatory scan is recommended but not required, it is at the discretion of the treating physician
- Intervening illness that prevents further administration of treatment.
- Recurrent Grade 2 pneumonitis
- Unacceptable AE(s).
- The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study treatment will occur prior to introduction of the new agent.
- Significant patient non-compliance with the protocol.
- Completion of 35 cycles (approximately 2 years) with pembrolizumab.
    - Note: The number of treatments is calculated starting with the first dose of pembrolizumab.
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), beyond the date when the initial CR was declared.
- Pregnancy.
- Patient decision to withdraw from the study.
- Investigator decision to withdraw the patient from the study.
- Patient is lost to follow up.
- Sponsor decision to end the study.

5. DESCRIPTION OF STUDY TREATMENT

5.1. Doses and Schedule of Administration

Table 1: Doses and Schedule of Administration

Study Treatment Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Sourcing
Pembrolizumab	Solution for infusion	100 mg/vial	200 mg Q3W	IV infusion	Day 1 of each 3-week cycle	Sponsor
Bavituximab	Solution for infusion	120 mg/vial	3 mg/kg*	IV infusion	Days 1,8,15 of each 3-week cycle	Sponsor

*The first 3-10 patients will receive 3mg/kg bavituximab, unless DLTs require de-escalation (see Section 5.6).

On days when both pembrolizumab and bavituximab are administered, pembrolizumab will be administered first. After a window of at least 60 minutes, bavituximab will be administered. In the absence of Grade 2 or greater hypersensitivity reactions, the window of time between the two infusion may be reduced to 30 minutes after the first two cycles.

Dose escalations from starting dose are not allowed for bavituximab or pembrolizumab

Bavituximab must occur within a 3 day window of the scheduled treatment. Outside a 3 day window, such doses will be skipped and dosing will resume at the next scheduled time. A missed dose due to holiday, bad weather, or other unforeseen circumstances will not be not counted as a protocol deviation.

A delay of a pembrolizumab dose due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days. Outside of a 7 day delay, the dose will be skipped and resumed at the next scheduled time.

The safety outcome of the run-in phase will determine the RDE for subsequent patients. Bavituximab dose may be reduced pending DLT analysis of the first 3 to 10 patients (See Section 5.6).

Patients enrolled in the safety run- in phase the dose of bavituximab will be adjusted or interrupted as appropriate; see Section 5.6

Patients enrolled in the expansion phase (once RDE is determined) may not have a reduction in the dose of bavituximab. The dose of bavituximab will be interrupted as appropriate, see Section 5.7 and Table 6.

No dose reductions of pembrolizumab are permitted. Doses will be withheld as appropriate based on treatment modifications defined in Table 7.

Administration of bavituximab and pembrolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

If continued treatment with bavituximab is contraindicated due to AEs, the patient may continue treatment with pembrolizumab after consultation with the medical monitor. If continued treatment with pembrolizumab is contraindicated due to AEs, bavituximab administration may continue upon consultation with the medical monitor.

5.2. Description of Bavituximab

Bavituximab is a chimeric (human/mouse) version derived from the original murine PS-targeting mAb 3G4. It is a genetically engineered immunoglobulin gamma 1-kappa (IgG1)κ consisting of human IgG1κ constant regions linked by recombinant deoxyribonucleic acid (DNA) techniques to murine 3G4 variable regions.

Bavituximab is supplied as a sterile, preservative-free solution with a composition of bavituximab, in 10 mM acetate, pH 5.0. It is provided in borosilicate Type 1 glass vials and stored at 2°C to 8°C containing 120 mg/5mL (24mg/mL).

Vials containing bavituximab drug product will be labeled according to national regulations for investigational products.

5.3. Description of Pembrolizumab

Pembrolizumab is a PD-1 blocking antibody.

Pembrolizumab is supplied as 100 mg/4 mL (25 mg/mL) solution in a single-dose vial.

Pembrolizumab vials should not be used beyond the expiration date provided by the manufacturer. Each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

5.4. Method of Assigning Patients to Treatment Groups

Patients will be enrolled through an interactive web response system (IWRS).

5.5. Preparation and Administration of Study Treatment

5.5.1. Bavituximab

The Investigator or designee will be responsible for administering the appropriate dose of IV bavituximab to all patients. Bavituximab must be stored at 2°C to 8°C in its original package.

Infusion reactions have occurred both with and without premedication, and it is unclear whether the type of co-administered chemotherapy or premedication with steroids and antihistamines impacts the frequency or severity of infusion reactions. Reports of infusion reactions will continue to be monitored. Prior to each bavituximab infusion, the patient should be premedicated with an antihistamine to decrease the risk of an infusion reaction. A recommended regimen is 50 mg diphenhydramine IV and 325 mg acetaminophen orally (PO) administered 1.5 hours (± 30 minutes) prior to infusion. See Section 6.2 for full recommendations for IRRs. The regimen, dosages, and timing of the premedications can be adjusted at the Investigator's discretion.

The bavituximab dosage is calculated at 0.125 mL/kg body weight and diluted with normal saline to a volume of no less than 100 mL. The total dose will not be recalculated based on body weight unless there is a ≥ 10% change in weight from Day 1. Administer as IV with in-line 0.2 μm filter over 90 minutes once weekly. After the 1st infusion, in the absence of Grade 2 or greater hypersensitivity reactions, the infusion time will be reduced to 60 minutes. After a 2nd infusion, in the absence of Grade 2 or greater hypersensitivity reactions, the infusion time will be reduced to 30 minutes.

The individual bavituximab infusion will be prepared under aseptic conditions and administered at the study site, according to the directions of the Sponsor, which will be provided in a Pharmacy Manual. In general, a vial of bavituximab must be used as soon as possible after reaching room temperature. Any solution remaining in the vial must be discarded. After dilution for infusion, administration of bavituximab should take place as soon as possible. Maximum allowed storage times and conditions will be detailed in the Pharmacy Manual.

Bavituximab is administered as an infusion. Bavituximab should not be administered as an IV push or bolus.

5.5.2. Pembrolizumab

Pembrolizumab will be administered using IV infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed. Bavituximab compound to be administered post administration of pembrolizumab.

Pembrolizumab will be administered as a dose of 200 mg using 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 (i.e., infusion time is 30 minutes (-5 min/+10 min).This is an open-label study; study treatments will not be blinded.

5.6. DLT Dose De-escalation/Modification

Patients who complete the DLT observation period without a DLT will continue study treatment until a criterion for discontinuation is met (Section 4.6). See Section 5.7 for information about administration of bavituximab dose modifications for patients who continue on study treatment after they complete the DLT observation period.

If the patient experiences a DLT during the DLT observation period (see Section 3.1), dosing of bavituximab and pembrolizumab must be interrupted, as shown in Table 2. If a DLT resolves to Grade ≤ 1, dosing may be resumed at the next available reduced dose level for bavituximab or the same dose for pembrolizumab if agreed to by the Investigator and the Sponsor's medical monitor. If the patient was on the lowest dose level of bavituximab when the DLT occurred, they must be discontinued from the study. No intra-patient dose re-escalation is allowed after a dose reduction.

Table 2: Dose Interruption for Dose-Limiting Toxicity During the DLT Observation Period

DLT is at least possibly related to:	Bavituximab Dosing	Pembrolizumab Dosing
Bavituximab	Hold dose/reduce	Administer

Pembrolizumab	Administer	Hold dose
Bavituximab and Pembrolizumab	Hold dose/reduce	Hold dose

A patient will be considered evaluable for DLTs if he or she (1) receives at least one dose of either study treatment and completes the DLT observation period or (2) discontinues because of a DLT. A patient will be considered nonevaluable for DLTs if he or she discontinues during the DLT observation period for a reason other than a DLT; patients who are not evaluable for DLTs will be replaced.

The first 3 patients will be evaluated for DLTs for the purpose of declaring the tentative RDE. The SRC will review these patients for DLTs at the end of the first 3-week cycle:

- If 0 of 3 patients experiences a DLT on any dose level, the RDE will be tentatively declared and further dose expansion will continue.
- If 1of 3 patients experiences a DLT on any dose level, that cohort will be expanded to 6 patients. If 1 of 6 patients experiences a DLT, the RDE will be tentatively declared and further dose expansion will continue.
- If ≥ 2 of 3 or ≥ 2 of 6 patients experience a DLT on Dose Level 0, Dose Level -1 will be explored. If ≥ 2 of 3 or ≥ 2 of 6 patients experience a DLT on Dose Level -1, Dose Level -2 will be explored.
- If ≥ 2 DLT(s) occur in up to 6 patients at Dose Level -2, further enrollment and dosing will be stopped until there is a full review of all available data, including PK, by the SRC.

Table 3: Planned Dose Levels

Dose Level	IV Bavituximab (Weekly)	IV Pembrolizumab (Q3W)
0	3 mg/kg	200 mg
-1	2 mg/kg	200 mg
-2	1 mg/kg	200 mg

The SRC may decide to meet at any time to evaluate a dosing cohort if a safety signal arises or other data become available to justify re-evaluation of the dosing cohort before it is fully enrolled.

Patients who are lost to follow up or withdraw consent for study participation prior to receiving study treatment or who withdraw prior to completing Cycle 1 for reasons other than DLT may be replaced. Approximately ten patients will be evaluated for safety by SRC, even if no DLTs have been identified to ensure early safety monitoring of the combination.

5.6.1. Definition of Dose-Limiting Toxicities

A DLT is defined as any of the AEs described below that occurs during the DLT observation period and is at least possibly related to bavituximab or pembrolizumab. The Investigator will use CTCAE v5.0 guidelines to assign an AE term and severity grade relevant to the DLT.

Hematological toxicities as follows:

- Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:

- Grade 4 thrombocytopenia of any duration
- Grade 3 thrombocytopenia associated with clinically significant bleeding

- ≥ Grade 3 febrile neutropenia
  - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour
  - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Grade 4 lymphocyte decreases lasting > 14 days

Non-hematologic toxicities:

- Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤ 3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
  - Any Grade 3 or Grade 4 non-hematologic laboratory value if:
    - Clinically significant medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or the abnormality persists for >1 week; the abnormality results in a Drug-induced Liver Injury (DILI)
    - Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.
- Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
- Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1.
- Missing >25% of planned doses as a result of drug-related AE(s) during the first cycle.
- Grade 5 toxicity.

Isolated laboratory changes without associated clinical signs or symptoms may not be included in this definition. These findings will be discussed and reviewed by the Investigators and the Sponsor's medical monitor.

Safety data in subsequent cycles will also be monitored on an ongoing basis to determine the cumulative incidence of late-onset toxicities.

Patients who experience a DLT, but in the opinion of the Investigator can be adequately monitored for recurrence of the toxicity and are otherwise experiencing clinical benefit, may be offered continued treatment with bavituximab and pembrolizumab.

Dosing will continue until criteria for study treatment discontinuation are met (unacceptable toxicity, PD, or withdrawal from the study) or up to a maximum of 35 cycles.

5.7. Dose Modification Guidelines

CTCAE v5.0 must be used to grade the severity of AEs.

If appropriate, the Investigator may attribute each toxicity event to either bavituximab or pembrolizumab alone or in combination.

Bavituximab Dose Reductions: Once RDE derived from the DLT observation period is established, bavituximab doses may not be reduced.

Bavituximab Dose Interruptions: Treatment with bavituximab may be interrupted for up to 21 days (1 cycle) for toxicity or reasons unrelated to toxicity. If bavituximab is withheld because of AEs for > 21 days, then the patient will be discontinued from bavituximab. If, in the judgment of the Investigator, the patient is likely to derive clinical benefit from bavituximab after a hold of > 21 days, study drug may be restarted with the approval of the medical monitor.

Recommendations for bavituximab dose modifications for the management of specific AEs are presented in Section 6.3.

Pembrolizumab Dose Reductions: Dose reductions of pembrolizumab are not permitted.

Pembrolizumab Dose Interruptions: Treatment with pembrolizumab may be temporarily suspended for up to 12 weeks (3 cycles) beyond the last dose to allow for resolution of immune-related AEs and tapering of corticosteroids.

If a patient must be tapered off steroids used to treat AEs, pembrolizumab may be withheld for up to 12 weeks from the last dose until steroids are discontinued or reduced to prednisone dose equivalent ≤ 10 mg/day. The acceptable length of interruption will depend on an agreement between the Investigator and the medical monitor.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with medical monitor approval. The acceptable length of interruption will depend on agreement between the Investigator and the medical monitor.

5.8. Treatment Compliance

The study treatments will be administered to subjects at the study site, under the supervision of the Investigator or designee in accordance with the protocol. Compliance with schedule infusions during study visits will be recorded on the CRF.

5.9. Study Drug Accountability

Study personnel will maintain accurate records of study treatment shipments/receipts and administration. The site is responsible for the return or destruction of study treatment as required.

5.10. Concomitant Medications

Patients are allowed to continue the medications that they are taking at baseline. Patients may also receive concomitant medications that are medically indicated as standard care for the treatment of symptoms and intercurrent illnesses. Medications to treat concomitant diseases, e.g., diabetes, hypertension, and chronic obstructive pulmonary disease (COPD) are allowed. Patients may also receive therapy to mitigate side effects of the study medication as clinically indicated, as well as best supportive care as per institutional guidelines. This may include, e.g., anti-emetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics, and other medications intended to treat symptoms. The Investigator should instruct the patient not to take any additional medications (including over-the-counter products) during the study without prior consultation.

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and AESIs,

5.11. Premedication for Infusion Reactions

Routine premedication (e.g., diphenhydramine and acetaminophen) is required prior to infusion of bavituximab (Section 5.5.1). Management of infusion-related reactions is described in Section 6.2.

5.12. Corticosteroid Use

Systemic corticosteroids and tumor TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with bavituximab and pembrolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study.

5.13. Hematopoietic Growth Factor and Blood Products

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Prophylactic use of these agents is not permitted.

Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

5.14. Prohibited Therapies

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol

- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment, while participating in the study, and for 4 months following the last dose of either pembrolizumab or bavituximab, whichever is later. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Medical Monitor

  Note: Inhaled steroids are allowed for management of asthma.

Participants who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

5.15. Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or ≥5 times the indicated dose.

For this study and overdose of bavituximab will be defined as any dose of 15mg/kg or ≥5 times the indicated dose.

No specific information is available on the treatment of overdose of bavituximab or pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In the event of a known or suspected overdose, the patient should be monitored with appropriate hematology and clinical chemistry and should receive supportive therapy, as necessary. Please also refer to Section 6.3 for guidelines on the management of potential study treatment-related toxicities.

Decisions regarding dose interruptions or modifications for bavituximab and/or pembrolizumab (interruptions only) in the case of a suspected overdose will be made by the Investigator in consultation with the medical monitor based on the clinical evaluation of the patient.

A plasma sample for PK analysis may be requested by the medical monitor or Sponsor on a case-by-case basis. This plasma sample should be collected as soon as possible, but within 10 days from the date of the last dose of on-study dosing.

Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the appropriate eCRF.

6. MONITORING AND MANAGEMENT OF EXPECTED OR POTENTIAL TREATMENT-RELATED TOXICITY

6.1. Patient Monitoring

Staff administering study drug are required to closely monitor all patients for possible systemic hypersensitivity reactions (e.g., generalized exanthema, urticaria, paraesthesia, bronchoconstriction, palpitations) during and after the first infusion of both study drugs.

All systemic hypersensitivity manifestations will be captured on the appropriate eCRF page(s) and identified as being due to a hypersensitivity reaction.

6.2. Management of Infusion Reactions – Bavituximab and Pembrolizumab

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist, as per standard practice.

Precautions for anaphylaxis should be observed during both bavituximab and pembrolizumab administration. Vital signs should be measured as outlined in Section 7.1.10 during both bavituximab and pembrolizumab infusions. All supportive measures consistent with optimal patient care will be provided throughout the study according to institution standards. Emergency resuscitation equipment and medications should be readily available. Additional supportive measures should also be available and may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen (paracetamol).

Infusion-related reactions (IRRs) will be defined according to Table 4.

Table 4: Definition of Infusion-Related Reactions (IRRs)

Grade 1	Grade 2	Grade 3	Grade 4
Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (i.e., not rapidly responsive to symptomatic medication, brief interruption of infusion, or both); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated

Abbreviations: IRR=infusion-related reaction; IV=intravenous; NSAIDs=non-steroidal anti-inflammatory drugs.

Note: An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspthatnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritis/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); vomiting.

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on bavituximab and pembrolizumab associated infusion reaction are provided in Table 5.

Table 5: Management of IRRs Induced by Bavituximab or Pembrolizumab

NCI CTCAE v5.0 Grade	Treatment	Premedication at Subsequent Dosing
Grade 1: Mild reaction, infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None.
Grade 2: Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids) prophylactic medications indicated for ≤ 24 hours	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include, but is not limited to: -IV fluids -Antihistamines -NSAIDs -Acetaminophen -Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. If symptoms resolve within one hour of stopping treatment infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be premedicated 1.5 hours (± 30 minutes) prior to infusion of pembrolizumab with: -Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). -Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).

Grade 3 or 4: *Grade 3:* Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) *Grade 4:* Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include, but is not limited to: -IV fluids -Antihistamines -NSAIDs -Acetaminophen -Narcotics -Oxygen -Pressors -Corticosteroids -Epinephrine** Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **** in cases of anaphylaxis, epinephrine should be used immediately.** **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing.
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of study treatment.		

6.3. Bavituximab Expected or Potential Treatment-related Toxicities

6.3.1. Management of Thromboembolic Events

Very high doses of bavituximab (100 mg/kg) in animals have been associated with evidence of minimal to mild thrombi (see bavituximab IB). Although it is known that tumor disease causes thromboembolic events, it is unknown whether treatment with bavituximab in the doses utilized in this study poses an increased risk of thrombosis in humans. Therefore, the Investigator should maintain a high degree of vigilance for thrombotic events in study patients.

Should thrombotic or thromboembolic events be suspected at any time after the start of bavituximab treatment, whether on the basis of clinical signs or symptoms, abnormalities of platelets, aPTT, PT, or d-dimer results, or some combination of abnormalities and/or clinical findings, additional diagnostic and/or therapeutic measures should be undertaken without delay. Evaluation and management of such events should include Doppler examination and consideration of additional coagulation studies, imaging studies as appropriate, as well as consideration of treatment with low-molecular-weight heparin (LMWH) and/or transfusion of blood products as appropriate. Events that meet seriousness criteria should be reported to and discussed with the medical monitor (as with any other SAEs).

6.3.2. Management of Other Adverse Events

For dose modifications of bavituximab based on the occurrence of related AEs, see Table 6.

Table 6: Bavituximab Dose Reductions for Treatment-Related Adverse Events

Severity of Event	Dose Adjustment for Bavituximab
Grade 1	Maintain bavituximab dose level and provide treatment to control symptoms, if applicable.
Grade 2 (tolerable)	Maintain bavituximab dose level and provide treatment to control symptoms, if applicable.
Grade 2 (intolerable)	Hold administration of bavituximab until the AE recovers to Grade 0-1 or to pretreatment baseline AE level, whichever is more abnormal. Then, resume treatment.
Grade 3	Hold administration of bavituximab until the AE recovers to Grade 0-1 or to pretreatment baseline AE level, whichever is more abnormal.
Grade 4	Discontinue

Abbreviations: AE = adverse event.

6.4. Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes.

Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 7.

Table 7: Management of Potential Pembrolizumab Toxicities

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and
	Grade 4 or recurrent Grade 3	Permanently discontinue		

				electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine	Monitor for signs and symptoms of thyroid disorders.

			or liothyroinine) per standard of care	
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis		

	Grade 4 or recurrent Grade 3	Permanently discontinue		
[1]Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

The Investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of pembrolizumab. In patients who have met the criteria for permanent discontinuation, resumption of pembrolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-related event. Patients can be re-challenged with pembrolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the medical monitor.

7. STUDY ASSESSMENTS

The procedures and assessments that will be conducted during this study are described in this section and summarized in the Schedule of Assessments (Table 8). Study assessments are identical for patients enrolled in Group 1 and Group 2. Detailed instructions regarding all laboratory procedures, including collection and handling of samples, will be included in the study Laboratory Manual provided by the Sponsor.

Pharmacokinetic, pharmacodynamic, and ADA assessments are presented in Table 9.

Written informed consent must be granted by each patient prior to the initiation of any study procedure or assessment (other than those considered standard of care).

Table 8: Schedule of Assessments

Procedure or Assessment	Screening	Cycle 1 (21 days)[a] Day in Cycle			Cycle 2 (21 days)[a] Day in Cycle ± 1 day			Cycle 3 (21 days)[a] Day in Cycle ± 1 day			Cycle 4 and Subsequent Cycles[a] ± 3 days	EOT Visit[b]	Safety FU Visit 30 ± 3 days	Survival FU Every 12 wks
	Days -28 to -1	1 ±3 days	8 ±3 days	15±3 days	1 ±3 days	8 ±3 days	15±3 days	1 ±3 days	8 ±3 days	15±3 days				
Optional Future Tissue Study Informed Consent	X													
Informed Consent	X													
Tumor Tissue Biopsy	X[c]											X[d]		
Inclusion/Exclusion	X													
Demographics	X													
Medical History/ Signs and Symptoms	X													
Prior Cancer Treatment	X													
Prior/Concomitant Meds Review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Exam	X											X		
Directed Physical Exam		X	X	X	X	X	X	X	X	X	X		X	
Review of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[P]	X	X	X	X	X	X	X	X	X	X	X	X		
Body Weight/Height (Height at screening only)	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG PS[e]	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG	X													
Administer Bavituximab		X	X	X	X	X	X	X	X	X	X (Day 1,8,15)			
Administer Pembrolizumab		X			X			X			X (Day 1)			
PK/PD[f]		X		X	X		X	X			X			
ADA[f]		X			X						X		X	
Biomarker Blood Sample[f]		X		X	X		X						X	
Hematology[g,h]	X	X			X			X			X (Day 1)	X	X	

Procedure or Assessment	Screening	Cycle 1 (21 days)[a] Day in Cycle			Cycle 2 (21 days)[a] Day in Cycle ± 1 day			Cycle 3 (21 days)[a] Day in Cycle ± 1 day			Cycle 4 and Subsequent Cycles[a] ± 3 days	EOT Visit[b]	Safety FU Visit 30 ± 3 days	Survival FU Every 12 wks
	Days -28 to -1	1 ±3 days	8 ±3 days	15±3 days	1 ±3 days	8 ±3 days	15±3 days	1 ±3 days	8 ±3 days	15±3 days				
Coagulation[g,i]	X	X			X			X			X (Day 1)			
Clinical Chemistry[g,j]	X	X			X			X			X (Day 1)	X	X	
Thyroid Panel][i]	X							X			X (Day 1 every other cycle)		X	
Urinalysis[g,k]	X	X												
Pregnancy Test[l]	X	X			X			X			X	X		
Tumor Imaging[m,n]	X							X				X[o]		
Post-study Anti-cancer Treatment													X	X
Survival Status														X

Abbreviations: ADA=antidrug antibody, AE=adverse event, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, FU=follow-up; Meds=medications, PK=pharmacokinetic, PS=performance status, Q3W=every 3 weeks, SAE=serious adverse event, TSH=thyroid-stimulating hormone, W=weeks.

[a] Unless otherwise specified, assessments/procedures are to be performed prior to dose administration on Day 1 of each cycle.

[b] Patients who discontinue both study treatments should be scheduled for an EOT visit within 15 days following the last dose date of study treatment.

[c] Baseline tumor tissue will be collected prior to enrollment on study for exploratory biomarker and PDL1 status (see study manual for details)

[d] An optional biopsy is also requested at the time of discontinuation for PD.

[e] Screening ECOG should be performed within 72 hours prior to first dose of treatment.

[f] Refer to Table 9 for details on PK, ADA and biomarker blood sample scheduling.

[g] Laboratory Screening Tests should be performed within 72 hours prior to first dose of treatment. For all subjects, unresolved abnormal labs resulting in drug-related AEs should be followed until resolution.

[h] CBC w/differentials will be collected and assessed within 72 hours of Day 1 of each cycle prior to dosing.

[i] T3 (free or total), T4 (free or total), and TSH will be collected and assayed prior to C1D1, C3D1, and every other cycle thereafter (e.g., C5D1, C7D1, etc.).

[j] Chemistry will be collected within 72 hours of Day 1 of each cycle prior to dosing.

[k] Urinalysis is conducted post screening every other cycle as clinically indicated.

[l] For women of reproductive potential, a negative pregnancy test should be performed within 72 hours prior to first dose of trial treatment. Pregnancy tests (serum and/or urine tests) should be repeated prior to dosing on Day 1 of every cycle in the UK. In all other countries pregnancy tests should be repeated as required by local guidelines.

[m] Tumor imaging at screening: Imaging will be performed within 28 days prior to the first dose of trial treatment. For all subjects, already available imaging scans performed as part of routine clinical management are acceptable if they are of diagnostic quality and performed within the acceptable timeframe.

[n] The first on-study tumor imaging will be performed 6 weeks (±7 days) after initiation of treatment and then every 6 weeks (±7 days) thereafter (or more frequently if clinically indicated). Timing of imaging follows calendar days and should not be adjusted due to dose interruptions. The same imaging technique, acquisition, and processing parameters for a subject should be used throughout the trial.

[o] Subjects without confirmed PD who discontinue treatment will have imaging performed at the time study treatment is discontinued (i.e. date of discontinuation ± 4-week window). If a scan was obtained within 4 weeks prior to discontinuation of treatment, then imaging at treatment discontinuation is not required. Continue to monitor disease status as indicated in Section 7.2.1.3.

[P] Vital signs will be captured approximately 30 minutes prior to pembrolizumab; 30 minutes prior to bavituximab administration and within 60 minutes post bavituxumab

Table 9: Pharmacokinetic/Pharmacodynamic/Biomarker Blood Sample Specific Collections – Collection Times

Visit	Time Point	Bavituximab[a]		Biomarker Blood Sample	Window
		PK/PD	ADA		
Cycle 1 Day 1	Prior to dosing[b]	X	X	X	Within 24 hours prior to bavituximab administration
Cycle 1 Day 1	1 hour post EOI[c]	X			+/-30 minutes post bavituximab infusion
Cycle 1 Day 15	Prior to dosing[b]	X		X	Within 24 hours prior to bavituximab administration
Cycle 1 Day 15	1 hour post EOI[c]	X			+/-30 minutes post bavituximab infusion
Cycle 2 Day 1	Prior to dosing[b]	X	X	X	Within 24 hours prior to bavituximab administration
Cycle 2 Day 15	Prior to dosing[b]	X		X	Within 24 hours prior to bavituximab administration
Cycle 3 Day 1	Prior to dosing[b]	X			Within 24 hours prior to bavituximab administration
Cycle 4 Day 1	Prior to dosing[b]	X	X		Within 24 hours prior to bavituximab administration
Cycle 6 Day 1	Prior to dosing[b]	X			Within 24 hours prior to bavituximab administration
30-day Follow-up	Follow-up		X	X	Any time during the Safety Follow-up Visit

Abbreviations: EOI = end of infusion; ADA=antidrug antibody; PK = pharmacokinetics.

[a] In the event of an infusion-related reaction (IRR), blood samples will be collected for both PK and ADA at the following time points: (i) as soon as possible after the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days (±3 days) following the IRR.

[b] Pre-dose PK samples are collected within 24 hours prior to infusion of bavituximab.

[c] Post-dose PK samples are collected 1 hour (+/-30 minutes) post bavituximab infusion

7.1. Summary of Assessments

7.1.1. Screening

All screening procedures must be performed within 28 days prior to first treatment (C1D1), unless otherwise stated. The screening procedures include the following (See Table 8 above for the list of assessments to be performed.):

Informed Consent

Informed consent may be obtained any time prior to screening procedures being performed. Screening procedures performed as standard of care prior to informed consent need not be repeated if they were done within protocol defined windows. These are the anticipated consents to be used in the trial. However individual IRBs/ECs may require additional consent.

1) General Informed Consent: To consent patients for all study procedures
2) Optional Future Tissue Study Informed Consent: To obtain consent to use tumor tissue for possible future tissue study.

Eligibility Checklist (Inclusion/Exclusion)

In order to determine and confirm the eligibility of the patient, all screening procedures must be documented and completed.

Patient Demographics and other Baseline Characteristics

The data that will be collected on patient characteristics at screening includes:

Demographic (name, age), sex, race/ethnicity;

Diagnosis, and extent of cancer;

Pertinent medical history;

Prior cancer treatment;

AEs related to study procedures

All medications taken within 30 days before first treatment. If there are any changes, medications are to be updated on a continual basis.

Furthermore, the following assessments will be performed:

Vital signs (BP, HR, T, RR);

Concomitant medications;

Height and weight;

Physical examination (PE);

ECOG PS;

Laboratory evaluations (complete metabolic panel [CMP], complete blood count [CBC], PT/INR and PTT/aPTT, thyroid panel);

12-lead electrocardiogram (ECG);

Radiological assessments (RECIST version1.1) (computed tomography [CT] - chest/abdomen/pelvis or magnetic resonance imaging [MRI] – abdomen/pelvis). Chest CT will be performed at baseline only. During the treatment phase, a chest CT will be performed as clinically indicated;

Urinalysis;

Urine or serum pregnancy test (women of childbearing potential only).

Pre-Treatment - Biomarker Tissue Biopsy (Required)

After obtaining informed consent, the fresh tumor biopsy must be obtained prior to initial treatment (C1D1), and can be since progression of last treatment. Archival formalin fixed paraffin embedded tumor tissue is requested from any early tissue sample for same disease, as well.

7.1.2. Treatment Phase

Study Treatment

Patients will be treated with bavituximab (3 mg/kg IV weekly) and pembrolizumab (200 mg IV Q3W). Patients will be treated until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason. For details of assessment, refer to Table 8.

Additional Treatment Phase Assessments will be performed:

Vital signs (BP, HR, T, RR);

AEs / Concomitant medications;

Weight;

PE;

ECOG PS;

Laboratory evaluations (Day 1 of every cycle: CMP, CBC, PT/INR and aPTT; Day 1 of every other cycle: thyroid panel and urinalysis as clinically indicated)

Radiological assessments (RECIST 1.1) (CT - chest/abdomen/pelvis or MRI – abdomen/pelvis). During the treatment phase, a Chest CT will be performed as clinically indicated.

Urine or serum pregnancy test (women of childbearing potential only).

Biomarker Blood Collection

Biomarker blood samples will be collected, during treatment, and at the 30 day follow up visit. This procedure is for research and will not be used to make medical decisions regarding the patient's treatment.

7.1.3. Post – Treatment Follow-up Phase

7.1.3.1. End of Treatment

Patients who discontinue both study treatments should be scheduled for an EOT visit within 15 days following the last dose date of study treatment, at which time all the assessments listed for the EOT visit will be performed. For details of the assessment, see Table 8.

An optional fresh tumor biopsy is requested for patients who discontinue due to PD

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for study evaluations during the 30 days following the last dose date of study treatment.

7.1.3.2. 30-Day Safety Follow-Up Visit

All patients will be followed up for safety up to 30 days after last dose of study drug (bavituximab and pembrolizumab) treatment. Patients whose treatment is interrupted or permanently discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first.

The Investigator will review all new anti-cancer therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up Visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.3.3. Survival Follow-up

Patients will be followed for survival every 12 weeks after the 30-Day Safety Follow-up Visit. Telephone contacts will be documented every 12 weeks to confirm survival, withdrawal of consent, lost to follow-up or to notify patient of the end of the study, whichever occurs first.

At least 3 documented attempts should be made to contact the patient before the patient is considered lost to follow-up.

If patients withdraw consent for the survival follow-up phase, the study site is still obligated to follow the patient's survival status through publicly available forms of information (i.e. death registries).

7.1.4. Beginning and End of the Trial

The study begins when the first patient signs the informed consent. The end of the study may be designated as a maximum of 12 months from the last patient receiving the last dose of study therapy or the time point when all patients have discontinued the study, whichever is sooner.

7.1.5. Informed Consent

The investigator or qualified designee must obtain documented consent from each potential patient or each patient's legally acceptable representative prior to participating in a clinical trial. Consent must be documented by the patient's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the patient prior to trial participation.

The Investigator is responsible for:

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

7.1.6. Ethical Review

Documentation of IEC/IRB approval of the protocol, ICF and any other patient materials must be provided to Oncologie, Inc. or its representative before the study may begin at the investigative site(s). Oncologie, Inc. or its representatives must approve the ICF, including any changes made by the IEC/IRBs, before it is used at the investigative site(s). All ICFs must be compliant with the International Council for Harmonisation (ICH) guideline for GCP) and local regulations.

7.1.7. Adverse Event Assessment

The Investigator has the responsibility for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. Patients will be monitored for AEs during study participation (beginning after informed consent is signed) and until 30 days after the last dose of study treatment. Any ongoing SAEs will be followed until resolution or stabilization. AEs and laboratory abnormalities will be graded according to the CTCAE v5.0 grading system and recorded on the eCRF.

Complete details for monitoring AEs, including the definition of drug-related AEs, are provided in Section 8.

7.1.8. Inclusion/Exclusion Criteria

All inclusion/exclusion criteria will be reviewed by the Investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.9. Demographic/Medical History/Prior Treatments

Patient demographics and significant medical history including prior treatments will be recorded by the Investigator or qualified designee. Medical history will include all active conditions and any condition diagnosed within the last 10 years that are considered clinically significant by the Investigator. Details regarding the patient's gastric or GEJ adenocarcinoma will be recorded separately and NOT listed as medical history.

If patient has lost at least 15 pounds over the three months prior to screening, "weight loss" should be considered an active condition and noted in Medical History. Autoimmune disorders, regardless of onset date, should be recorded.

7.1.10. Vital Signs

The Investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of bavituximab and again prior to administration of each dose of pembrolizumab, and at treatment discontinuation. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

Vital signs will be captured approximately 30 minutes prior to pembrolizumab; 30 minutes prior to bavituximab administration and within 60 minutes post bavituxumab

7.1.11. Weight and Height

Height will be measured only during screening. Weight will be measured at Day 1 of each cycle. The patient should be in light indoor clothes.

7.1.12. Full Physical Examination

Physical examinations will include an assessment of all the major body systems. A complete physical examination will be performed at the time points specified in Table 8. Clinically significant abnormal findings noted during screening period should be recorded as medical history.

7.1.13. Directed Physical Exam

For cycles that do not require a full physical exam per Table 8, the Investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle. New clinically significant abnormal findings should be recorded as AEs.

7.1.14. ECOG Performance Status

ECOG performance status will be assessed at the time points specified in Table 8. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

7.1.15. 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

7.1.16. Laboratory Assessments

Blood and urine samples will be collected at the time points specified in Table 8. Screening results for study eligibility should be performed within 72 hours prior to first dose of treatment. Additional clinical laboratory tests can be obtained at any time during the study at the Investigator's discretion. Local laboratories will perform the assessments.

All blood and urine collections for clinical laboratory tests occurring on the same day as study treatment administration must be performed prior to study treatment administration and Investigator must review results to ensure acceptability prior to initiating each new cycle of treatment.

Clinically significant treatment-related findings at the EOT/Safety Follow-Up Visit should be followed to resolution or stabilization.

Clinical Laboratory Tests

Hematology - local laboratory	
Leukocytes (WBC)	Erythrocytes (RBC)
Neutrophils[a]	Hemoglobin (HGB)
Lymphocytes	Hematocrit (HCT)
Monocytes	Mean corpuscular volume (MCV)
Eosinophils	Mean corpuscular hemoglobin concentration (MCHC)
Basophils	Platelets (PLT)

Coagulation - local laboratory
Activated partial thromboplastin time (aPTT) or Partial thromboplastin time (PTT)
International normalized ratio (INR) or Prothrombin time (PT)

Clinical Chemistry - local laboratory	
Serum Concentrations of:	
Alanine aminotransferase (ALT)	Creatine kinase (CK)
Albumin	Creatinine
Alkaline phosphatase	Glucose, nonfasting
Aspartate aminotransferase (AST)	Magnesium
Bilirubin, direct	Potassium
Bilirubin, total	Sodium
Blood urea nitrogen (BUN) or blood urea	Uric acid
Calcium	T3 (free or total)
Chloride	T4 (free or total)
	TSH

Urinalysis - local laboratory	
Blood	Protein
Glucose	Specific gravity
Ketones	Urine leukocyte esterase
pH	

Pregnancy Test (for female patients of childbearing potential) - local laboratory
Serum pregnancy test
Urine pregnancy test

Abbreviations: RBC = red blood cells; TSH = thyroid-stimulating hormone; WBC = white blood cells.

[a] Neutrophils reported by automated differential hematology instruments include both segmented and band forms.

7.1.17. Pregnancy Test

A woman of child bearing potential must have a negative urine pregnancy test (e.g. within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

A pregnancy test must be repeated prior to dosing on Day 1 of every cycle and at the end of treatment visit. Pregnancy tests (serum and/or urine tests) should be repeated prior to dosing on Day 1 of every cycle in the UK. In all other countries pregnancy tests should be repeated as required by local guidelines.

If a subject inadvertently becomes pregnant while on treatment with study treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study 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. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 8.5.

7.2. Efficacy Assessments

7.2.1. Tumor Assessments

Tumor response and progression will be assessed by the Investigator according to RECIST, Version 1.1 (Appendix A). Tumor assessments, including tumor markers, will be performed at the time points specified in Table 8.

Tumor assessments should consist of clinical examination and appropriate imaging techniques (preferably CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST); other studies (MRI, X-ray, positron emission tomography [PET] scan, and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. Investigators should perform scans of the anatomical sites that, in their judgment, are appropriate to assess based on each patient's tumor status.

7.2.1.1. Baseline Tumor Imaging

To meet screening criteria, baseline tumor imaging must be performed within 28 days prior to the first dose of study treatment.

Scans performed as part of routine clinical management are acceptable for use as the baseline scan if they are of diagnostic quality and performed within 28 days prior to the first dose of study treatment.

7.2.1.2. Tumor Imaging During Trial

Tumor imaging will be conducted every 6 weeks (± 7 days) after initiation of treatment. until one of the following occurs:

- disease progression
- start of new anti-cancer treatment
- withdrawal of consent
- death
- end of study

Imaging should follow calendar days and not be delayed for any dose interruptions that may occur.

7.2.1.3. Timing of Repeat Imaging

In patients with PD, a confirmatory scan should be performed at least 4 weeks later to confirm PD prior to removing the patient from study treatment. The confirmatory scan is recommended but not required, it is at the discretion of the treating physician.

Per RECIST 1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response must be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (6 weeks later), whichever is clinically indicated.

7.3. Immunogenicity Assessments

7.3.1. Antidrug Antibody Assessments

Venous blood samples for the assessment of ADA levels will be drawn at the time points presented in Table 9 for bavituximab.

Blood samples should be collected from the arm opposite from the investigational drug infusion, or from another site if collected within 24 hours of dosing.

Residual ADA serum samples used for ADA analysis may also be used for exploratory PK and/or pharmacodynamic analyses related to bavituximab treatment. This could include using leftover serum for exploratory, alternative PK assay development and analysis.

ADA samples will also be collected in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if ADA is suspected, at which time those samples could be used to measure any relevant biomarkers, to understand the infusion reaction/adverse event better. After the primary clinical study report data cut-off date is reached, no additional ADA samples will be collected for the patients still on-going on the study.

In the event of an IRR, blood samples will be collected for both PK and ADA at the following time points: (i) as soon as possible after the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days (±3 days) following the IRR.

Please refer to the Laboratory Manual for details on collection and processing of blood ADA samples.

7.4. Pharmacokinetic Assessments

7.4.1. Blood Sample Collection

Venous blood samples for the PK analysis of bavituximab will be drawn at the time points presented in Table 9.

Blood samples should be collected from the arm opposite from the investigational drug infusion, or from another site if collected within 24 hours of dosing.

Residual PK serum samples used for PK analysis may also be used for exploratory PK and/or PD analyses related to bavituximab treatment. This could include using leftover serum for exploratory, alternative PK assay development and analysis.

In the event of an IRR, blood samples will be collected for both PK and ADA at the following time points: (i) as soon as possible after the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days (±3 days) following the IRR.

7.4.2. Sample Analysis

PK parameters will be determined for bavituximab and pembrolizumab using non-compartmental methods. Possible compartmental analysis and possible relationships between PK and pharmacodynamic variables, efficacy and/or selected toxicities will be explored, as appropriate.

PK profiles to assess PK properties of single-agent bavituximab will be collected from all enrolled patients.

PK and ADA samples will also be collected in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if ADA is suspected, at which time those samples could be used to measure any relevant biomarkers, to understand the infusion reaction/adverse event better. After the primary clinical study report data cut-off date is reached, no additional PK and ADA samples will be collected for the patients still on-going on the study.

Central laboratories will be used for bioanalysis of study drug in human serum. Please refer to the Laboratory Manual for details on collection and processing of blood PK samples.

7.5. Biomarker Assessments

7.5.1. Tumor Biopsies

Patients must be consented for a mandatory fresh tissue biopsy to be performed in order to enroll in this trial. The fresh tumor biopsy must be prior to initial treatment (C1D1). If available, archival samples will also be collected. An optional fresh tumor biopsy is requested at the EOT for patients who discontinue due to PD

The baseline fresh tumor tissue will be used to investigate potential response-predictive biomarkers. Those biomarkers include immunohistochemistry (IHC) as well as RNA signatures.The signatures generated will have the potential to inform patient stratification strategies for future trials. See the Laboratory Manual for sample processing details.

Patient tissue samples will be assessed to determine 4 unique RNA signatures as well as whole exome sequencing for exploratory analysis. The putative RNA signatures will be analyzed to determine whether any correlate to response to the combination treatment. Classifying patients to these four putative signatures will be derived from an expanded gene set from that described in Uhlik et at 2016 and a unique classifier algorithm. These four classification signatures encompass immunological and angiogenic characteristics in the tumor stroma. If patients with a particular signature/s are more responsive to this combination treatment, future studies may be planned to select patients. .

Residual sample material available after completion of the designated analyses may be used in the future for identification of predictive markers or to enhance understanding of disease biology unless prohibited by local laws or regulations.

7.5.2. Biomarker Blood Samples

All patients will have venous blood samples drawn at the time points specified in Table 9 for blood biomarkers including, but not limited to, immunomodulating cytokines and related factors.

Complete instructions for processing, handling and shipment of blood samples will be provided in the Laboratory Manual.

8. ADVERSE EVENT MANAGEMENT

8.1. Definition of Adverse Events

8.1.1. Adverse Event (AE)

Patients will be monitored for all AEs from the time the first dose of study treatment is administered through 30 days after the last dose of study treatment. All AEs that occur from the signing of the ICF until the first dose of study treatment should be recorded on the AE eCRF page only if the event was related to a study procedure. Study procedure-related AEs that occur after signing of the ICF and before administration of study treatment will also be collected.

An AE is the development of an undesirable medical condition or the worsening of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the study treatment.

8.1.2. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

Results in death

It is immediately life-threatening

It requires in-patient hospitalization or prolongation of existing hospitalization

It results in persistent or significant disability or incapacity

Results in a congenital abnormality or birth defect

It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

8.2. Clarifications to Serious Adverse Event Reporting

Death is an outcome of an SAE and not an SAE in itself. When death is an outcome, report the event(s) resulting in death as the SAE term (e.g., “pulmonary embolism”). If the cause of death is unknown, report “Death, unknown cause” as the SAE term.

Pre-planned or elective hospitalizations including social and/or convenience situations (e.g. respite care) are excluded from SAE reporting. In addition, emergency room visits and admission under 23-hour observation are excluded from SAE reporting; however, such events should still be reported on the appropriate AE eCRF page.

Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a SAE unless the outcome is fatal during the study or within the safety reporting period. If the event has a fatal outcome during the study or within the safety reporting period, then the event causing the death must be recorded as an AE and as a SAE with CTC Grade 5 (fatal outcome) indicated. The AE/SAE term of Disease Progression should only be used when the Investigator is not able to distinguish the actual event that caused the death.

Serious adverse events specifically related to subsequent anticancer therapies administered during the 30-day Safety Follow-up period are excluded from SAE reporting, as are hospitalizations for the administration of such therapy. If it is not known whether the SAE is related to the subsequent anticancer therapy, the SAE should be reported.

8.3. Assessment of Causality

The relationship of each AE to the study treatment (bavituximab and pembrolizumab) administration will be assessed by the Investigator after careful consideration of all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to receipt of the study medication and de-challenge or re-challenge according to the following guidelines:

YES (possible, probably or definitely related): there is a reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

The event follows a reasonable temporal sequence from administration of study drug.

The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environment or toxic factors or other modes of therapy administered to the patient.

The event follows a known pattern of response to study drug.

The event disappears or decreases on cessation or reduction in dose of the study drug. In some situations, an AE will not disappear or decrease in intensity upon discontinuation of the study drug despite other clear indications of relatedness.

NO (not related or definitely not related): There is no reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

The event does not follow a reasonable temporal sequence from administration of study drug.

The event could be reasonably attributed to the known characteristics of the patient's clinical state, concurrent illness, environment or toxic factor or other modes of therapy administered to the patient.

The event does not follow a known pattern of response to study drug.

The event does not disappear or decrease on cessation or reduction in dose of the study drug, and it does not reappear or worsen when the study drug is re-administered.

8.4. Assessment of Severity

The severity rating of an AE refers to its intensity. The severity of each AE will be categorized using the NCI CTCAE v5.0. For any term that is not specifically listed in the CTCAE scale, intensity should be assigned a grade of 1 through 5 using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 8.1.2. An AE of severe intensity may not be considered serious.

8.5. Pregnancy or Drug Exposure during Pregnancy

If a participant inadvertently becomes pregnant while on treatment with bavituximab and /or pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study 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. All pregnancies and exposure during breastfeeding, must be collected and reported from the time of treatment through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy

Pregnancies must be reported within 24 hours of the Investigator's knowledge using the pregnancy form.

Pregnancy in itself is not regarded as an AE or SAE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

8.6. Laboratory Abnormalities

To the extent possible, all laboratory abnormalities observed during the course of the study will be included under a reported AE term describing a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an AE of "renal failure"). In these cases (e.g., an AE of renal failure), the laboratory abnormality itself (e.g., elevated creatinine) does not need to be recorded as an AE.

If a laboratory abnormality cannot be reported as a clinical syndrome, AND if the laboratory abnormality results in a therapeutic intervention (i.e., concomitant medication or therapy), is a DLT, or is judged by the Investigator to be of other particular clinical relevance, then the laboratory abnormality should be reported as an AE.

Patients experiencing AEs or clinically significant laboratory abnormalities will be assessed and appropriate evaluations performed until all parameters have returned to baseline levels, or are consistent with the patient's then-current physical condition.

8.7. Reporting Adverse Events

All AEs, serious and nonserious, will be fully documented on the appropriate eCRF. For each AE, the Investigator must provide its duration (start and end dates or ongoing), intensity, assessment of causality and whether specific action or therapy was required.

All AEs that occur from the signing of the ICF until the first dose of study treatment should be recorded on the AE eCRF page only if the event was related to a study procedure. All other AEs/findings prior to first dose of study treatment should be recorded as medical history on the applicable eCRF page. All AEs occurring from the first dose of study treatment until 30 days after the last dose of study treatment must be recorded on the AE eCRF.

All AEs meeting serious criteria, from the time of treatment/ allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

All SAEs and AESIs must be reported to the Sponsor's designee within 24 hours of the Investigator's knowledge. This should be done by completing the eCRF SAE Report Form. Detailed instructions for reporting SAEs are provided in a study manual.

Investigators must follow patients with AEs/SAEs until the event has resolved, the condition has stabilized, withdrawal of consent, initiation of subsequent anticancer therapy, the patient is lost to follow up or death OR until the 30-day Safety Follow-up Visit, whichever occurs first. New and ongoing treatment-related SAEs should be followed beyond the 30-day Safety Follow-up Visit. If the patient dies, this should be captured as the outcome of the AE unless no link between the AE and the patient death can be established, in which case the AE will be marked as ongoing and the death will be reported as a separate event.

If a patient is lost to follow up, this should be captured accordingly within the AE eCRF and on the follow up SAE report.

The Sponsor or designee is responsible for notifying the relevant regulatory authorities of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs as required by their IEC/IRB.

8.8. Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest (AESIs) are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 8.7 for reporting instructions). Adverse events of special interest for this study are as follows:

An overdose of pembrolizumab as defined as any dose of 1000 mg or ≥5 times the indicated dose, that is not associated with clinical symptoms or abnormal laboratory results.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

An overdose of bavituximab is define as any dose of 15mg/kg or ≥5 times the indicated dose.

No specific information is available on the treatment of overdose of bavituximab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In the event of a known or suspected overdose, the patient should be monitored with appropriate hematology and clinical chemistry and should receive supportive therapy, as necessary. Please also refer to Section 6.3 for guidelines on the management of potential study treatment-related toxicities.

An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

> *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not AESIs for this trial.

9. STATISTICS

This trial will evaluate safety and efficacy of the bavituximab-pembrolizumab combination in a disease setting in which pembrolizumab has shown promising but modest activity. The hypothesis to be evaluated is whether the bavituximab-pembrolizumab combination will yield an ORR superior to historical ORR of pembrolizumab in the 2nd-line or 3rd-line settings in patients who have not previously been exposed to an anti-PD-1 or anti-PD-L1 agent. Detail on all planned statistical analyses will be presented in a separate Statistical Analysis Plan (SAP).

The minimum efficacy analysis will be conducted 3 months after 40 patients have received at least one dose of study treatment. There will be no more than 4 additional patients enrolled during the time the minimum efficacy analysis is taking place. Conducting an analysis at approximately 40 patients will limit patients risks if the combination is not trending towards an added benefit, as defined by a response rate of 15% or greater (6/40) further exploration will be warranted before further enrollment to 80 patients (details provided in interim analysis section).

9.1. Sample Size

The primary efficacy objective of this Phase 2 study is the evaluation of ORR of bavituximab in combination with pembrolizumab in patients with advanced gastric or GEJ cancer. The sample size of 80 patients across both Group 1 and Group 2 was chosen to allow minimal enrollment within each of our four putative biomarker signatures to allow for exploration of differential responses, more information about the biomarkers can be found in section 7.5.1. As noted above, an ORR of <15% will be regarded as futile as it will be unlikely to exceed the activity of pembrolizumab as a single agent in this study population.

The following sample sizes apply:

DLT Observation: up to 10 DLT-evaluable patients in total

Phase 2: Minimum efficacy analysis: 40 total patients across both Group 1 and Group 2; Full enrollment: 80 patients

For the CPI-naïve patient population assumptions, the historical ORR of pembrolizumab in the 2nd-line setting was approximately 15% and an ORR of the bavituximab-pembrolizumab combination was set to 30%. Approximately 40 patients are needed to show a statistical superiority of bavituximab-pembrolizumab with 80% statistical power at one-sided type I error rate of α=0.10. In the 3rd-line setting if the historical ORR is assumed as 6%, if the true ORR of Bavituximab-Pembrolizumab combination is 15%, then approximately 40 patients are needed to show a statistical superiority of Bavituximab-Pembrolizumab with 74% statistical power at one-sided type I error rate of α=0.10. In addition, PDL1 status was able to impact outcomes in all lines of treatment with PDL1+ patients having better outcomes than negative. By combining patients from DLT and the expansion phase, safety and efficacy information will be available for a total of 80 patients, assuming >6 responders are observed by 40. Enrollment will not be controlled for the number of patients in each line nor PD-L1 status (2nd vs. 3rd line, positive vs. negative), these numbers could vary for each patient type (e.g. 2nd line PDL1+ vs. Third line PDL1 negative). Tables 9.1.1 and 9.1.2 show how the power varies for with the 2nd and 3rd line cohorts with their respective sample sizes.

Table 9.1.1. Power in 2nd line Gastric Cancer

2nd Line Subjects	Responses (CR/PR) for p < 0.1	Power for p_1=0.25 (%)	Power for p_1=0.3 (%)
20	6	38.3	58.3
30	8	48.5	71.8
40	10	56.0	80.4
50	12	61.8	86.1
60	14	66.5	90.0

Assume historical ORR with p_0=0.15.

Table 9.1.2. Power in 3rd line Gastric Cancer

3rd Line Subjects	Responses (CR/PR) for p < 0.1	Power for p_1=0.15 (%)	Power for p_1=0.2 (%)
20	4	59.5	79.3
30	4	67.8	87.7
40	5	73.6	92.4
50	6	78.0	95.2
60	6	90.3	98.7

Assume historical ORR with p_0=0.05.

For the CPI-relpase patient population, the n was set to 20 patients for the initial assessment of safety, tolerability and initial antitumor activity.

9.2. Analysis Populations

The following analysis populations are defined for the study:

Safety population: all patients who received at least 1 dose of bavituximab or pembrolizumab, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose a patient actually received. The safety population will be used for all analyses of dosing, exposure, and safety.

DLT-evaluable population: will include the first 3 patients up to a maximum of 10 patients who (1) receive at least 70% of the dose of bavituximab (2) complete the DLT observation period or discontinue (from study treatment or from the study) during the DLT observation period (Cycle 1) because of a DLT.

PK population: will include all treated patients who received at least 1 full dose of bavituximab and pembrolizumab and have baseline and at least one postbaseline evaluable PK sample.

Efficacy population: will include all patients (including DLT patients) who receive any quantity of study treatment at the dose recommended for the Phase 2 population.

9.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Oncologie, Inc. or its designee.

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

9.3.1. Safety Analyses

All patients who receive at least 1 dose of bavituximab or pembrolizumab will be evaluated for safety and toxicity. Data will be reviewed by group and dose level.

Safety analyses will include summaries of the following:

- DLTs: the number of patients who experienced any DLTs during the DLT observation period will be summarized by dose level
- AEs, including severity and possible relationship to study treatment
- AEs by Medical Dictionary for Regulatory Activities System Organ Class (SOC) by decreasing frequency of Preferred Term within SOC
- Laboratory and nonlaboratory AEs by CTCAE v5.0 term, maximum CTCAE grade, and CTCAE Grade 3 and above (regardless of causality and at least possibly related to study treatment

The final analysis will occur approximately 6 months after the last patient received his or her first dose of study treatment. Descriptive statistics will be derived where appropriate. Adverse events will be summarized by study arm; dose exposure and density for each study drug will be calculated for each group and dose level.

Incidence tables of patients with AEs will be presented for all AEs by maximum severity, SAEs, AEs assessed as related to study treatment, and AEs resulting in discontinuation of study treatment.

Listings of all safety data sorted by dose, group, patient and assessment date will be provided.

9.3.2. Pharmacokinetic/Pharmacodynamic Analyses

Serum concentrations for bavituximab will be listed and summarized using descriptive statistics by cohort and group at each time point.

Pharmacodynamic biomarkers will be listed and summarized using descriptive statistics by cohort and group at each time point.

The PK/PD relationship and relationship to tumor response may be explored.

9.3.3. Efficacy Analyses

In order to characterize the preliminary efficacy signal, the primary efficacy endpoint will be the best overall response rate (CR and PR) according to RECIST Version 1.1 (Appendix A) as determined by the Investigator. Corresponding confidence intervals (CIs) will also be provided.

For planning purposes, ORR of <15% will be regarded as futile as the combination will be unlikely to exceed the activity of pembrolizumab as a single agent.

Efficacy analysis will be performed on the full analysis set, and per protocol analysis set, including predefined biomarker subgroups (Section 9.3.2).

Duration of Response (DoR), defined as the interval from the date measurement criteria are met for CR or PR (whichever is first recorded) until the earliest date of disease progression, as determined by Investigator assessment of objective radiographic disease assessments per RECIST 1.1 or death due to any cause if occurring sooner than progression. Only subjects who achieve an initial response will be evaluated for DOR.

Stable disease (SD) at 6 weeks will also be used to derive the clinical benefit rate (CBR), consisting of ORR and SD.

Progression-Free Survival (PFS) will be defined as the interval from the date of first dose of investigational agent until the earliest date of disease progression, as determined by Investigator assessment of objective radiographic disease assessments per RECIST version1.1 or death due to any cause if occurring sooner than progression.

Overall survival (OS) defined as the interval from the date of first dose of investigational agent until the date of death.

Presentations of efficacy will include patients enrolled in Part 1 as well as patients treated at the recommended dose. Individual changes in tumor burden over time will be presented graphically (for example, Waterfall plots). Details regarding statistical methodologies associated with analyses of the initial efficacy signal will be further defined in the SAP.

9.3.4. Primary Analysis

The primary analysis will be conducted approximately 6 months after the last patient receives his or her first dose of study treatment

9.3.5. Other Analyses

9.3.5.1. Patient Characteristics

Patient characteristics will be summarized:

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 the number and percentage of patients discontinuing (overall and by reason for discontinuation).

Disease-related therapies, including prior anticancer treatments and prior radiotherapies (such as type of therapy, regimen, and prior surgery)

A summary of prior and concomitant medications by study arm will be reported. Other patient characteristics will be summarized as deemed appropriate.

9.3.5.2. Poststudy-Treatment-Discontinuation Therapy

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

9.3.5.3. Treatment Compliance

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

9.3.5.4. Interim Analysis

Safety data will be reviewed during the study. The purpose of these data reviews is to evaluate the safety and tolerability for the initial dose schedule and determine if a DLT has been observed. Additional safety analyses will be performed when a total of 10 subject patients have received at least one dose of study therapy and followed for 3 months after the 10^{th} patients receives the first dose of study therapy. At that point the available clinical safety data as well as laboratory data will be evaluated particularly for late-onset DLT-like toxicities.

Interim analyses of the safety and efficacy data will be performed approximately 3 months after a total 40 patients across both Group 1 and Group 2 have received at least one dose of study treatment. The data from the interim analyses will be considered directional and used primarily for minimal efficacy analysis considerations. After the analysis of 40 patients for ORR, the activity of study therapy across the entire population as well as in the combined pool of biomarker groups will be analyzed, and, if the data appear to be promising, the study population or the overall sample size may be adjusted via an amendment.

The study will be assessed for futility if the interim analysis finds no evidence for the activity of the study therapy beyond that expected for pembrolizumab monotherapy. No formal statistical testing will be done at the interim analysis. Details on the procedures for the interim analysis will be provided in the SAP.

9.4. Statistical Methods

Tabular summaries of data will be descriptive in nature (i.e., number of patients [n], mean, standard deviation, median, minimum and maximum for continuous variables and n and percent for categorical variables). A more detailed description of analysis methods will be provided in the SAP to be completed prior to the clinical database lock.

10. STUDY ADMINISTRATION

10.1. Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol; GCPs, including ICH Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; Food and Drug Administration (FDA) regulatory requirements; other regulatory authorities, and in accordance with the ethical principles of the Declaration of Helsinki.

10.1.1. Regulatory Authority Approvals

The Sponsor or designee will submit the study protocol plus all relevant study documents to applicable regulatory agencies for approval before the study start. No patient will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

Each Investigator must complete a Form FDA 1572 or equivalent and provide the completed form according to written instructions to the Sponsor (or designee). Each Investigator must submit to the Sponsor (or designee) financial disclosure information according to national law and/or local regulations.

Data generated in the US will be handled in accordance with the Health Information Portability and Accountability Act (HIPAA). The study will be registered at www.clinicaltrials.gov using the Protocol Registration System.

10.1.2. Institutional Review Board/Ethics Committees

This protocol and any material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator to an IEC/IRB. This also applies to protocol amendments.

The Sponsor will supply relevant data for the Investigator to submit the study protocol and additional study documents to the IEC/IRB. The Principal Investigator will submit the study protocol for review and approval by an IEC/IRB, according to national law and/or local regulations, and will provide the IRB with all appropriate materials.

Verification of the IEC/IRB's unconditional approval of the study protocol and the written ICF will be transmitted to the Sponsor. This approval must refer to the study by exact study protocol title and number, identify the documents reviewed, and state the date of the review.

No patient will be admitted to the study until appropriate IEC/IRB approval of the study protocol has been received, the Investigator has obtained the signed and dated ICF, and the Sponsor is notified.

The Principal Investigator will submit appropriate reports on the progress of the study to the IEC/IRB in accordance with applicable national law and/or local regulations and in agreement with the policy established by the IEC/IRB.

The IEC/IRB must be informed by the Principal Investigator of all subsequent study protocol amendments and of SAEs or SUSARs occurring during the study that are likely to affect the safety of the patients or the conduct of the study.

10.2. Confidentiality of Information

The Investigator must ensure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. The Investigator must keep logs on screened and enrolled patients. In addition, the Investigator must have a list where the identity of all treated patients can be found.

The Investigator agrees that all information received from the Sponsor, including, but not limited to, the IB, this protocol, eCRFs, the protocol-specified treatment, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain. The Investigator shall be under additional obligations related to non-disclosure confidential information and the handling of intellectual property as set forth in the Clinical Trial Agreement.

10.3. Patient Informed Consent

All information about the clinical study, including the patient information and the ICF, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines, the Declaration of Helsinki and local regulations.

It is the responsibility of the Investigator to obtain signed ICFs from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.

The ICF, prepared by the Investigator with the assistance of the Sponsor, must be approved along with the study protocol by the IEC/IRB and be acceptable to the Sponsor.

The patient must be provided with the patient information and ICF consistent with the study protocol version used and approved by the relevant IRB. The ICF must be in a language fully comprehensible to the prospective patient. Patients (and/or relatives, guardians, or legal representatives, if necessary) must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their participation in the study with the Investigator concerned. The patient and the person explaining about the study and with whom they discuss the informed consent will sign and date the ICF. A copy of the signed ICF will be retained by the patient and the original will be filed in the Investigator file unless otherwise agreed.

10.4. Study Monitoring

On behalf of the Sponsor, a clinical research organization monitor will contact and visit the Investigator at the study center before the entry of the first patient and at predetermined appropriate intervals during the study until after the last patient has completed. The monitor will also perform a study closure visit.

In accordance with ICH GCP guidelines, the Investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are

for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The Investigator will make all source data (i.e., the various study records, the eCRFs, laboratory test reports, other records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (i.e., source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs.

By agreeing to participate in the study, the Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved. Contact information for the study monitor is located in the Investigator file. Representatives from the Sponsor may also contact and visit the Investigators and monitor data during the study.

10.5. Electronic Case Report Form (eCRF)

The data will be collected using an electronic data capture (EDC) system. Sites will receive training on the EDC system. All users will be supplied with unique login credentials.

Before study start, the Investigator will prepare a list showing the signature and handwritten initials of all individuals authorized to make or change entries on eCRFs. This "study center personnel and delegation list" must be kept current throughout the study.

For each patient enrolled, an eCRF must be completed, reviewed, signed, and dated by the Principal Investigator or Co-Investigator within a reasonable time period (< 2 weeks) after data collection. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

Full information regarding EDC and completing eCRFs is included in a study manual. All questions or comments related to electronic capture should be directed to the assigned monitor.

10.6. Study Termination and Site Closure

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

The Sponsor reserves the right to discontinue the study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be given.

The entire study will be stopped if:

The protocol-specified treatment is considered too toxic to continue the study;

Evidence has emerged that, in the opinion of the Sponsor or the Investigator(s), makes the continuation of the study unnecessary or unethical;

The stated objectives of the study are achieved;

The Sponsor discontinues the development of study treatment.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow up must be recorded on the eCRF. All reasons for discontinuation of treatment must be documented. In terminating the study, the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

10.7. Modification of the Study Protocol

Protocol amendments, except when necessary to eliminate an immediate hazard to patients, must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/IRB must be informed of all amendments and give approval before their implementation. The Sponsor will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the Investigator(s) updated as detailed in the ICH GCP guidelines.

10.8. Retention of Study Documents

The study site will maintain a study file, which should contain, at minimum, the IB, the protocol and any amendments, drug accountability records, correspondence with the IRB and the Sponsor, and other study-related documents.

The Investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the Sponsor or its designees.

The Investigator shall retain records required to be maintained for a period of 5 years after the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In addition, the Investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of the Sponsor. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing of the new responsible person and/or the new location. The Sponsor will inform the Investigator, in writing, when the study-related records are no longer needed.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

10.9. Clinical Study Report

A clinical study report will be prepared under the responsibility and supervision of the Sponsor and signed by a Sponsor representative, thereby indicating their agreement with the analyses, results, and conclusions of the clinical study report.

10.10. Study Publication

The conditions regulating dissemination of the information derived from this study are described in the Clinical Trial Agreement.

10.11. Quality Assurance Audits

Clinical centers may be audited by the Sponsor's Quality Unit (QU) qualified auditor or designee as required per approved schedule. The purpose of an audit, which is independent of and separate from routine monitoring or Quality Unit (QU) functions, is to evaluate study conduct and compliance with the protocol, standard operating procedures, ICH GCPs, and the applicable regulatory requirements. The Investigator and the Sponsor may also be subject to an inspection by FDA, European regulatory authorities, or other applicable regulatory authorities at any time.

The auditor and regulatory authorities will require authority from the Investigator to have direct access to the patients' medical records. It is important that the Investigator(s) and their staff cooperate with the auditor or regulatory authorities during this audit or inspection.

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12 APPENDICES

Appendix A: Response Evaluation Criteria in Solid Tumor (RECIST) Version 1.1

The RECIST guidelines (version 1.1) are described in Eisenhauer (2009) and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm);
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable);
- A minimum size of 20 mm by chest X-ray.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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 slice thickness recommended to be not greater than 5 mm). At baseline and in follow up, only the short axis will be measured and followed.

Nonmeasurable Disease:

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions

Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment. Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of 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 as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are nonmeasurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the overall tumor response.

Non-target Lesions

RECIST criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

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 preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Evaluation of Non-Target Lesions

Complete Response	Disappearance of all non-target lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete *responder*.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Time Point Response

A response assessment will occur at the protocol-specified time points. The tables below provide a summary of the overall response status calculation at each time point for patients who have measurable and non-measurable disease (non-target disease only).

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 evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; NE, Not evaluable.

Evaluation of Best Overall Response When Confirmation of CR and PR Required

Overall Response: First Time Point	Overall Response: Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; NE, Not evaluable.

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes this disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Time point Response: Patients with Nontarget Lesion Assessments

Nontarget Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
Non-CR/non-PD	No	Non-CR/non-PD	
Not all evaluated	No	NE	
Unequivocal PD	Any	PD	
Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response, which is most likely to occur in the case of PD; e.g., if only 2 of 3 baseline target lesions are assessed and result in a > 20% increase in the sum, then the patient would be assessed as a PD regardless of the missing lesion.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) before confirming the CR status.

Confirmatory Measurement/Duration of Response

Confirmation

Radiographic tumor assessments are required. If an initial CR or PR is noted, confirmatory scans must be performed at least 4 weeks later. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of no less than 4 weeks.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

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

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Reference:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

Appendix B: Creatinine Clearance Formula

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

Abbreviations: CrCl = creatinine clearance; wt = weight.

[a] Age in years, weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

Appendix C: New York Heart Association Classification of Functional Cardiac Capacity

Class	Description
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

From: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.