Statistical Analysis Plan

Oncologie, Inc.

ONCG100

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Reviewers

The following reviews of the Draft SAP prior to Version 3 were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
Susan MacIntyre	Clinical Development	Draft Version 2.1	Oncologie, Inc.
Kerry Culm-Merdek	Clinical Development	Draft Version 2.1	Oncologie, Inc.
Lukas Makris	Statistics	Draft Version 2.1	Oncologie, Inc.

Version History

Version #	Description of Changes	Version Date
1.0	Not applicable	24 October 2019
2.0	Update per Protocol Amendment 3, 06 February 2020	09 September 2020
3.0	Update per Protocol Amendment 4, 14 September 2020	27 September 2021

Glossary of Abbreviations

Abbreviation	Term
ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
B	Biomarker
β2-GP1	Beta2 glycoprotein 1
BILI	Bilirubin, total
BUN	Blood urea nitrogen
CI	Confidence Interval
CK	Creatine kinase
C_{max}	Maximum concentration
CPS	Combined Positive Score
CR	Complete response
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
C_{trough}	Lowest dose concentration prior to the next dose
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FU	Follow-up
GEJ	Gastroesophageal junction
HER2	Human epidermal growth factor receptor 2
irAE	Immune-related adverse event
Meds	Medications
MedDRA	Medical dictionary for regulatory activities
MSI	Micro satellite instability
NLR	Neutrophil to lymphocyte ratio
PD-1	Programmed cell death protein 1
PDL1	Programmed death-ligand 1
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetic
PP	Per-protocol
PR	Partial response
PS	Performance status EOT
PT	Preferred Term
Q3W	Every 3 weeks

RBC	Red blood cells
RECIST	Response evaluation criteria in solid tumors
RDE	Recommended dose for expansion
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SD	Standard deviation
SE	Standard error
SI	Standard international (International System of Units)
SOC	System organ class
SoD	Sum of Diameters
SRC	Safety review committee
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures and listings
TNM	Tumor, Node, Metastasis

1. Source Documents

The Statistical Analysis Plan was written based on the following documentation:

Document	Date	Version
Protocol Amendment 1	20Mar2019	Amendment 1
Protocol Amendment 1A (United Kingdom only)	05Sep2019	
Production 1.0 Casebook	19Jul2019	

The Amended Statistical Analysis Plan was written based on the following documentation:

Document	Date	Version
Protocol Amendment 3	06Feb2020	Amendment 3
Production 2.0 Casebook	29APR2020	

The Version 3 Statistical Analysis Plan was written based on the following documentation:

Document	Date	Version
Protocol Amendment 4	14Sep2020	Amendment 4
Production 3.0 Casebook	24Sep2020	

2. Protocol Details

2.1 Study Objectives

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

The objectives of the study are:

Primary:

- To assess the safety and tolerability of bavituximab in combination with pembrolizumab in patients with advanced gastric/gastroesophageal junction (GEJ) cancer
- To assess the antitumor activity of the treatment combination based on Response Evaluation Criteria in Solid Tumors (RECIST) Guideline Version 1.1 (Protocol 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

2.2 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 have 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. 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 will be recruited if the initial doses of the regimen are tolerable. Patients will be 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 1).

Safety data monitored throughout the course of the study is including but not limited to; reviewing trends in safety data, laboratory analytes, and adverse events (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.

Table 1: 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 Subse-quent 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													

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 Subse-quent 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				
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	
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 6 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) or 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 Protocol 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 bavituximab

Patients will be assessed for tumor response/progression per RECIST Version 1.1. 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.

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.

2.3 Sample Size and Power

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 approximately 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. As noted above, an ORR of <15% for Group 1 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: approximately 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). Table 2 and Table 3 show how the power varies for with the 2nd and 3rd line cohorts with their respective sample sizes.

Table 2: Power in 2nd line Gastric Cancer or Gastroesophageal Junction

2nd Line Subjects	Responses (CR/PR) for p < 0.1	Power for p1=0.25 (%)	Power for p1=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 3: Power in 3rd line Gastric Cancer or Gastroesophageal Junction

3rd Line Subjects	Responses (CR/PR) for p < 0.1	Power for p1=0.15 (%)	Power for p1=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-relapse patient population, the n was set to 20 patients for the initial assessment of safety, tolerability and initial antitumor activity.

3. Efficacy and Safety Variables

3.1 Primary Endpoints

- Incidence and severity of AEs and SAEs graded according to the National Cancer Institute 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

3.2 Secondary Endpoints

- 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 serum concentrations before and after bavituximab infusions
  - Beta2-glycoprotein 1 (β2-GP1) serum concentrations and change from baseline before and after bavituximab infusions
- Presence of anti-bavituximab antibodies (anti-drug antibodies [ADAs])

3.3 Tertiary Endpoints

- Analysis of tissue to determine percentage of patients with defined genetic signature
  - Tumor micro environment (TME) RNA profile genetic signatures will be evaluated in baseline tumor tissue sample and categorized to Biomarker (B)+/-
  - TME panel-1 scores will also be reported in 4 categories IA = Immune Active; ID = Immune Desert; A = Angiogenic; IS = Immune Suppressed.
- Preliminary correlation of ORR to genetic signature
  - Correlation of DCR and PFS to genetic signature
- Status of genomic and immune biomarkers in blood and tissue samples at baseline and change from baseline upon treatment
  - Biomarker and pharmacodynamic (PD) data for this analysis include:
    - Tumor PDL1 Combined Positive Score (CPS), central laboratory assessment of screening biopsy sample
    - Tumor micro satellite instability (MSI) status at screening
    - Pharmacodynamic (PD) Beta2-glycoprotein 1 (β2-GP1) evaluated prior to dosing
    - Baseline leukocytes, neutrophils (absolute count), and neutrophils/leukocytes (NLR)

- Patient medical history of Human epidermal growth factor receptor 2 (HER2) positivity and Epstein-Barr virus (EBV) status

4. Analysis Populations

4.1 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.

4.2 DLT-evaluable population

The 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.

In addition, a patient among the first 10 patients who experienced a DLT event during the DLT observation period after receiving a dose of bavituximab less than 70% of the planned dose will be included in the DLT-evaluable population.

The DLT-evaluable population will be used to assess incidence of DLT.

4.3 PK Population

The 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.

This population will be used for PK analyses.

4.4 Efficacy Population

All patients who received at least 1 dose of bavituximab or pembrolizumab, regardless of their eligibility for the study.

The efficacy population will be used for all analyses of tumor response.

5. Data Handling

5.1 Time points and Visit Windows

5.1.1 General Definitions

All assessment days will be related to the first day of first dose of study treatment (C1D1).

Day 1 is defined as the day of first dose of study treatment. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

5.1.2 Screening Period and Baseline

For all subjects, the screening period is defined as the period from informed consent to Day -1. Tumor imaging will be performed within 28 days prior to the first dose of trial treatment. In case available imaging scans performed as part of routine clinical management are used then the baseline tumor assessment may have been collected prior to informed consent.

The baseline value for a variable is defined as the last non-missing value collected before the first dose of treatment. The baseline may then be collected within 28 days prior to first dose, in the screening period, or prior to dose administration on Day 1.

5.1.3 Treatment Period

Unless otherwise specified, assessments/procedures are to be performed prior to dose administration on Day 1 of each cycle. Scheduled assessments on Day 1 will be assigned to baseline unless the time (HH:MM) of data collection and start of infusion time (HH:MM) are both recorded and the data collection time is after start of infusion. In this case, the assessment will be assigned to the treatment period. Adverse events and medications starting on Day 1, will be assigned to the Treatment Period.

The Treatment Period is defined as the period from the date of the first dose of treatment up to and including the date of treatment discontinuation, or, if that is missing then the date of death or withdrawal of consent (where recorded) or the last dose date.

5.1.4 Visit Windows

Safety data will be analyzed using nominal study visits as defined in the Study Schedule (Table 1) and eCRF. No visit windows will be applied for summary and analysis of safety assessments (clinical laboratory tests, vital signs, and ECOG performance status). No visit windows will be applied for summary and analysis of

these endpoints. In case of multiple assessments at a scheduled visit, the first will be considered as the scheduled assessment and later assessments will be repeat or unscheduled.

Study drug dose date relative days after C1D1 will be compared to expected visit relative days. Number of days delayed will be calculated for dose delays > 3 days.

Tumor imaging will be performed 6 weeks (±7 days) after initiation of treatment and then every 6 weeks (±7 days). Patients 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.

Table 4 provides the relative study day ranges to be applied to the imaging date to derive the analysis visit for by visit analyses of tumor response assessments.

The following considerations are to be followed when deriving the analysis visits:

- The relative day number of the assessment lies between the lower and upper boundary of the visit window (the boundary values are included)
- Both scheduled and unscheduled assessments are included for visit windowing
- A scan that meets EOT criteria (that is, within 4 weeks of treatment discontinued and patient discontinued treatment without confirmed PD) will not be classified as scheduled
- If there are two or more valid assessments for a defined window the following rules will be applied:
    - If both scheduled and unscheduled assessments fall within the same visit window, the scheduled assessment with non-missing assessment results will be used for analysis
    - If there are multiple scheduled assessments with non-missing assessment results for any specified visit window and the assessment that is closest to the planned study day will be used for analysis
    - If there are multiple assessments for any specified visit and none of them are from scheduled assessment, the assessment with non-missing results and closest to the planned study day will be used for analysis
    - If there are two or more unscheduled assessments with non-missing results and the same distance to the planned study day, the assessment prior to the planned study day will be used for analysis.

Table 4: Definition of Visit Windows for Tumor Response

Visit	Target Day of Visit[a]	Protocol Visit Windows	Analysis Visit Window
Screening	>= -28	-28 to -1	-28 to -1[b]
Week 6	43	36 to 50	Day 36 to Day 57
Week 12	85	78 to 92	Day 58 to Day 99
Week 18	127	120 to 134	Day 100 to Day 141
Week 24	169	162 to 176	Day 142 to Day 183
. . .	. . .	. . .	. . .
EOT	EOT[c]	EOT – 28, EOT + 28	EOT – 28, EOT + 28[d]

[a] Relative to first dose of treatment.
[b] use latest scan prior to Day C1D1
[c] End of treatment (EOT), date of the discontinuation event
[d] A scan meeting EOT criteria (patient discontinued treatment without confirmed PD) will not be classified as scheduled.
NA= Not Applicable

5.2 Handling of Dropouts, Missing Data, and Outliers

During the Safety run-in phase, patients who are lost to follow up, 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.

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.

Missing or Partial Adverse Event and Prior/Concomitant Medication Start Dates

- If the day is missing but both the month and year are non-missing, then the missing day will be imputed as 01. For an AE, however, if the month and year are the same as the month and year of the date of the first dose of study medication, then the missing day will be imputed to be the day part of the first dose date.
- If both the day and month are missing but the year is non-missing, then the missing day and month will be imputed as 01JAN. For an AE, however, if the year is the same as the year of the date of the first dose of study medication, then the missing day and month will be imputed to be the day and month parts of the first dose date.
- If the date is completely missing, then the start date will be imputed to be the earlier of the date of the first dose of study medication and the AE or medication end date. If the end date is partial, then impute the end date first before imputing the start date.

Missing or Partial Adverse Event and Prior/Concomitant Medication End Dates

If the AE or medication is reported as ongoing (or for an AE, not resolved/not recovered or recovering/resolving), then the end dates should be blank; otherwise, the following rules for imputation should be followed:

- If the day is missing but both the month and year are non-missing, then the missing day will be imputed as the last day of the month.
- If both the day and month are missing but the year is non-missing, then the missing day and month will be imputed as 31DEC. For an AE, however, if the year is the same as the year of the date of the last dose of study medication, then the missing day and month will be imputed to be the day and month parts of the last dose date.
- If the date is completely missing, then the end date will be imputed to be the date of the first visit that is after the AE start date or the subject's last dose date, if there is no visit that is after the AE start date. If the start date is partial, then impute the start date first before imputing the end date.

If the imputation rules above result in an end date being earlier than the start date, where one or both dates are imputed, then end date will be set to start date + 1. If an imputed start date is after the end date, then the start date will be set to the end date – 1. Prior to database lock, all imputed adverse event dates will be reviewed by the study team and approved by the sponsor for clinical relevance. Imputed dates may be adjusted based on this review.

Missing or Partial Diagnosis Dates of Historical Conditions of Interest

- If the day is missing but both the month and year are non-missing, then the missing day will be imputed as 01.
- If both the day and month are missing but the year is non-missing, then the missing day and month will be imputed as 01JAN.
- If the date is completely missing, then it will not be imputed.

Outliers

No rules for outlier detection are planned.

6. Statistical Methods

6.1 General Principles

All data processing, summarization and analyses will be performed using SAS Version 9.4 (or later) of the SAS® statistical software package.

The following principles will be applied to all TFLs unless otherwise stated:

Principle	Value
Significance tests	Two-sided and use a 5% significance level
Group labels and order presented	Tables: Group 1 CPI Naïve, Group 2 CPI Relapse, Overall Listings: Group 1, Group 2
Tables	Data in summary tables presented by Group and visit (where applicable).
Listings	All data collected presented by Group, site, subject, and visit (where applicable)[a].
Descriptive summary statistics for continuous variables	Number of subjects/observations (N), mean, standard deviation (SD), median, and range.
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]
Denominator for percentages	Number of subjects in the analysis population, unless stated otherwise in table shell(s)
Include "Missing" as category	Number missing is greater than zero.
Display for 0 percentages	Blank
Display to the same number of decimal places as collected or standardized value[b]	Minimum Maximum
Display to one more decimal place than collected or standardized value[b]	Mean Median
Display to two more decimal places than collected or standardized value[b]	Standard Deviation Standard Error
Limit of precision for displays	3 decimal places
Date Format	DDMMMYYYY

[a] Data of screen failure patients, where listed, follows data of enrolled patients.
[b] Decimal precision rules for clinical laboratory data are presented in Section 8

6.2 Subject Disposition and Data Sets Analyzed

Subject disposition will be listed and summarized and will include the number and percentage of subjects:

- screened;

- screen failures;
- treated;
- in treatment;
- discontinued treatment and reason for discontinuation;
- in long term follow-up;
- discontinued study and reason;

Patients in the in each study population (Safety, DLT-evaluable, Efficacy, PK and Per-protocol) will also be listed and summarized.

6.3 Protocol Deviations

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

Important protocol deviations will be listed and summarized for the Safety Population.

Important protocol deviations will be reviewed to identify any deviation that may significantly affect the completeness, accuracy, and/or reliability of the study data. Sensitivity analyses that exclude these patients will be performed for the primary and selected secondary efficacy endpoints (refer to Section 6.6.3).

6.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized for the Safety Population. Standard descriptive statistics will be presented for the continuous variables of:

The following demographic data will be summarized:

- Sex
- Age at screening (years)
- Race and ethnicity

The following baseline disease characteristics will be summarized:

- Site of adenocarcinoma (Gastric or GE Junction)
- TNM staging of diagnosis at study entry
- Siewert classification
- Tumor Biomarkers at Screening
    - HER2 status at diagnosis (positive, negative)
    - EBV status at diagnosis (positive, negative)

  - MSI stability (high, low)
  - Central Lab PDL1 Combined Positive Score (CPS)
  - Xerna TME Panel phenotype (IA, A, IS, ID)
  - Xerna TME Panel subtype (B+/ B-)-
- Blood biomarker, β2-GP1 concentration
- Treatment of Gastric/GEJ cancer before enrollment
  - Radiotherapy (yes, no)
    - Procedure
    - Indication
    - Dose
  - Surgery (yes, no)
  - Systemic Anti-cancer therapy
    - Number of previous lines of therapy (1, 2, 3, 4 or more)
    - Received neo-adjuvant, palliative, adjuvant or other indication
    - Best overall response on any previous therapy
    - Reason for treatment discontinuation
- Baseline height (cm) and weight (kg)
- Vital signs: blood pressure (mm Hg), heart rate (bpm), respiratory rate (rpm), and temperature (°C)
- ECOG PS
- Baseline leukocytes, neutrophils (absolute count), and NLR

6.4.1 Screening and Baseline Details

The following baseline characteristics will be presented in cross-tabulated frequency tables by Group for the Efficacy Population. Patient counts in each category will be represented in grouped frequency charts.

- Tumor stage frequency across TME Panel-1

Screening and baseline neutrophils, lymphocyte, and NLR will be listed for all patients with Screening NLR assessed. The NLR values will be presented in a scatterplot by patient.

6.4.2 Medical History

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.

Autoimmune disorders, regardless of onset date.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 22.0]. All medical history will be listed, and the number and

percentage of subjects with any medical history will be summarized for Safety Population by system organ class (SOC) and preferred term (PT).

6.4.3 Prior and 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.

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 will be recorded. Concomitant medications administered for treatment of SAEs and AESIs 30 days or more after the last dose of study treatment will be recorded.

Medications received prior to or concomitantly with treatment will be coded by Covance using the WHODrug Dictionary Version 2019, Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are those with a stop date prior to the first dose date of study treatment.

Concomitant medications are those with a start date on or after the first dose date of study treatment, or those with a start date before the first dose date of study treatment and a stop date on or after the first dose date of study treatment or ongoing end of study.

Prior medications and concomitant medications will be listed and summarized separately for Safety Population.

6.5 Measurements of Treatment Compliance – not applicable

6.6 Efficacy

The efficacy analyses will be based on the Efficacy Population, including predefined biomarker subgroups as needed.

6.6.1 Primary Efficacy Analysis

Based on RECIST Version 1.1 (Protocol Appendix A) criteria, a patient may achieve as best overall response either complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The Objective Response Rate (ORR) is calculated as the number of patients achieving a CR or PR divided by the number of efficacy patients.

The ORR and 95% confidence interval (CI) will be presented for the Efficacy Population Group 1, Group 2, and Overall. The 95% CI will be calculated using the Clopper-Pearson method.

A supplementary summary will be presented of the confirmed and unconfirmed best overall response and the overall rate of CR or PR with 95% CI among these responses.

6.6.2 Secondary Efficacy Analysis

6.6.2.1 Disease Control Rate (DCR)

DCR is defined as the percent of patients in the Efficacy population with a CR or PR (patients with OR), or SD, PR or CR evaluated at 6 weeks or later after the date of first dose. The same analysis approach used for the primary efficacy analysis will be applied on DCR.

6.6.2.2 Time to Response and Duration of Response (DoR)

Time to response and DoR are calculated only for patients with a CR or PR response. A supplementary analysis of time to response and DoR will be performed for patients with confirmed or unconfirmed CR or PR.

DoR, defined as the interval in months 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 (1 + date of progression – date of response / 30.4375). Duration of response is expressed as months, and will add 1 day to account for the date measurement criteria was met.

DoR will be analyzed using the Kaplan-Meier (K-M) method to compute the time-to-event curve. The K-M curves for Group 1 and Group 2 will be displayed in a graphic presentation. The median event time as well as times to 25^{th} and 75^{th} percentile event times will be calculated. A 95% confidence interval for each quartile will be calculated using the log-log transformed survival function confidence interval at each time.

Time to response is the interval in months from first treatment until the first date of a confirmed CR or PR response. Months will be reported to 2 decimals as (1+ date of first response – date of first treatment)/30.4375.

6.6.2.3 Progression-Free Survival (PFS)

PFS is defined as the interval in months from the date of first dose of investigational agent until the earliest date of disease progression (date of disease progression –

date of first dose + 1)/30.4375. Disease progression is determined by Investigator assessment of objective radiographic disease assessments per RECIST version1.1 or death due to any cause if occurring sooner than progression in Efficacy population.

PFS will be analyzed Using the K-M method to compute the time-to-event curve. The K-M curves for Group 1 and Group 2 will be displayed in a graphic presentation. The 25th, 50th, and 75th percentile event times will be calculated and 95% confidence intervals for each quartile based on intervals about the log-log transformed survival function.

Time to Progression Censoring Rules

Patients lacking evidence of disease progression, including those who initiate non-study anti-cancer therapy prior to disease progression, will have their DoR and PFS event times censored on the last tumor assessment date at which disease status was determined.

Table 5: Rules for Determining Date of Progression or Censor for Progression-Free Survival

Rule	Situation	Date of Progression or Censor	Outcome
1	No Baseline tumor assessment	Date of first dose	Censored
2	No post-baseline assessments and no death	Date of first dose	Censored
3	No documented progression and no death (with a post-baseline tumor assessment)	Date of last adequate tumor assessment	Censored
4	Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last adequate tumor assessment	Censored
5	Documented progression	Date of documented progression If the tumor assessment was done on multiple days, use the earliest date for that visit	Progressed
6	Death without document progression	Date of death	Progressed
7	Documented progression or death after missing ≥2 consecutive post-baseline tumor assessments	Date of last adequate tumor assessment before missed assessments or date of enrollment, whichever is later	Censored

Note: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than one situation applies

6.6.2.4 Overall survival (OS)

OS is defined as the interval in months from the date of first dose of investigational agent until the date of death (Date of death – date of first dose + 1 / 30.4375) in Safety population. All deaths will be included in the analysis.

OS will be analyzed using the K-M method to compute the time-to-event curve. The K-M curves for Group 1 and Group 2 will be displayed in a graphic presentation. The median event time as well as times to 25th and 75th percentile event times will be calculated and the and a 95% confidence interval for each quantile.

Follow-up time for OS analysis will be assessed using reverse K-M method, reversing censor and event flags. The reverse K-M curves for Group 1 and Group 2 will be displayed in a graphic presentation and median time on study for censored observations estimates will be reported for each group.

Overall Survival Censoring Rules

Patients with no known date of death will have their survival event time censored at the latest date of last completed visit or patient contact or last known date alive recorded on the eCRF. Duration of survival is expressed as months from date of first treatment (Day 1).

6.6.2.5 Time on Study Treatment and Time to Best Overall Response

Time on study treatment and time to confirmed best overall response will be presented in a listing and summary figure (swimmer's plot) representing individual patients on the vertical axis, ordered by months on treatment, horizontal bars to end of treatment and symbols to represent first confirmed CR or PR. For this analysis time on treatment will be calculated to 2 decimal places: months on treatment = ((date of last dose – date of first dose) + 1)/30.4375 and months to best response =((tumor assessment date – date of first dose) + 1)/30.4375.

6.6.2.6 Tumor Response

Tumor response of individual target lesions will be listed and the sum of diameters (SoD) will be listed. Maximum percentage reduction from baseline of the target lesion SoD will be summarized.

Waterfall plots will depict individual patient measurements of maximum percentage reduction on the vertical axis and ordered on the horizontal axis the patients with least to greatest reduction. The plot will use different colors to represent best overall response classification.

Individual patient response, SoD percent change from baseline will also be represented in a spider plot, weeks on study as the horizontal axis, percent change

on the vertical axis, trend lines through the individual SoD percentage change, and line colors to represent best overall response classification.

6.6.3 Sensitivity Analyses for Primary and Secondary Efficacy Analysis

To assess the impact of including subjects with any deviation expected to have significant effect on accuracy or reliability of the study data, the efficacy analysis of OR, DoR, DCR, PFS, and OS will be repeated using the efficacy population with patients excluded. Patients identified in the data classification document will be excluded.

6.6.4 Pharmacokinetic (PK) Analysis

Pharmacokinetic (PK) analysis will include listings by group for minimum serum concentration of bavituximab (C_{trough}) across cycles 1 to 6 and the maximum dose concentration (Cmax) on Day 1 and Day 15 of Cycle 1.

Bavituxmab serum concentrations will be summarized by group for the PK population using descriptive statistics at each cycle and study day (see Table 6). Listings will represent actual elapsed time post dose. Further PK and PK/PD analysis may be described in separate plans.

6.6.5 Pharmacodynamic Variables

Beta2 glycoprotein 1 concentrations and change from baseline will l be listed and summarized using descriptive statistics by group, cycle and study day per the sample collection schedule described in Table 6. Change from baseline β2 GP1 by time on treatment will be presented in individual and summary graphs.

6.6.6 Immunogenicity Analysis

Anti-drug antibodies (ADA) will be collected as described in Table 6. The number and percentage of patients with pre-existing ADA will be reported and incidence of seroconversion (patient's ADA changed from negative to positive) will be summarized by time point. Descriptive summaries (n, median, minimum and maximum) of antibody titers will be provided at each time point for the Safety population. Negative ADA will be set =1 for numeric titer summaries. Results of immunogenicity testing will be provided in listings.

Table 6: 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

6.6.7 Subgroup Correlation Analysis

Efficacy correlation analyses will be based on the Efficacy Population, and will evaluate the relationship between key efficacy parameters including ORR, PFS, DCR, and OS and the following predefined key biomarker subgroups:

- NLR evaluated at baseline
- Xerna TME Panel subtype B+/B-
- Tumor PDL1 CPS

More specifically, correlation analyses will be evaluated for the following subgroups for all patients and by patient group (group 1, group 2):

- Major Subgroup Analyses

- NLR<4/ NLR≥4
- B+/B- (Frequencies and proportions are represented in Barchart for B+/B- and also for TME Panel-1 classes)
- B+ and NLR<4
- B- and NLR<4

- Subgroup Analyses by CPS
  - CPS<1 and NLR<4
  - CPS<1 and NLR≥4
  - CPS<1 and B+
  - CPS<1 and B-
  - CPS<1 and B+ and NLR<4
  - CPS<1 and B- and NLR<4
  - CPS≥1 and NLR<4
  - CPS≥1 and NLR≥4
  - CPS≥1 and B+
  - CPS≥1 and B-
  - CPS≥1 and B+ and NLR<4
  - CPS≥1 and B- and NLR<4
- Subgroup Analyses by MSS
  - MSS and NLR<4
  - MSS and NLR≥4
  - MSS and B+
  - MSS and B-
  - MSS and B+ and NLR<4
  - MSS and B- and NLR<4
- Subgroup Analyses by Line of Therapy

- 2nd line
- 2nd line and NLR <4
- 2nd line and NLR≥4
- 2nd line and CPS<1 and B+
- 2nd line and CPS<1 and B-
- 2nd line and CPS<1 and B+ and NLR<4
- 2nd line and CPS<1 and B- and NLR<4
- 3rd line and higher
- 3rd line and NLR<4
- 3rd line and NLR≥4
- 3rd line and CPS<1 and B+
- 3rd line and CPS<1 and B-
- 3rd line and CPS<1 and B+ and NLR<4
- 3rd line and CPS<1 and B- and NLR<4

- NLR time profiles will be presented in a listing, time profile plot and spider plot
  - Individual NLR by visit
  - NLR % change from baseline grouped by best response (CR, Confirmed PR, SD or PD)

6.7 Safety

All safety analysis will be based on the Safety population.

6.7.1 Extent of Exposure

Dose record: The number of dose omissions, reductions, and delays, number of cycles received, percentage compliance, and dose intensity will be summarized for all treated patients in safety population. Percentage compliance will be defined as 100 times the number of infusions received divided by the number of infusions expected during the interval from first to last dose. For pembrolizumab, the number of infusions expected is the number of cycles of treatment completed by the patient. For bavituximab, the number of infusions expected is the number of cycles times 3. Dose intensity (mg/week) will be defined as the cumulative dose (mg) divided by the treatment duration (weeks).

Study drug exposure: Exposure will be summarized for pembrolizumab and bavituximab separately. The exposure variables are defined as;

- Duration of exposure (days) = (date of last dose – date of first dose) + 1;
- Cumulative dose (mg) = the sum of doses during all treatment cycles;
- Actual dose (mg/cycle) = cumulative dose (mg)/ (duration of treatment (cycle));
- Relative dose (%) = (actual dose (mg/cycle)/scheduled dose (mg/cycle)) * 100

Dose records and summary calculations of dose omissions, reductions, and delays, number of cycles received, percentage compliance, dose intensity, duration, cumulative dose, actual dose and relative dose will be listed and summarized using descriptive statistics for the Safety population.

6.7.2 Adverse Events

6.7.2.1 Adverse Events Reporting

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

AEs and laboratory abnormalities will be graded according to the CTCAE v5.0 grading system and recorded on the eCRF. Verbatim terms for each AE will be coded using MedDRA Version 22.0.

The relationship between an AE and study treatment is assessed as Yes (possible, probably or definitely related), No (not related or definitely not related). Relationship between an AE and study treatment is recorded as related to bavituximab, related to pembrolizumab, or related to both.

An SAE 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
- is immediately life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity

- results in a congenital abnormality or birth defect an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

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, will be reported.

Investigators will 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 will be followed beyond the 30-day Safety Follow-up Visit. If the patient dies, this will be captured as the outcome of the AE. Death will be reported as a separate event only if no link between the AE and patient death can be established.

Adverse events of special interest (AESIs) are required to be reported to the Sponsor immediately. Adverse events of special interest for this study are defined in protocol Section 8.8.

All AEs are classified as either pre-treatment AEs or treatment–emergent AEs (TEAEs) as follows:

- Pre-treatment AEs are events that start prior to the date of first dose of study treatment.
- TEAEs are events with start date on or after the date of first dose of study treatment whose severity worsens on or after the date of first dose of study treatment.

6.7.2.2 Adverse Events Listings and Overall Summary

All AE data will be listed. Pre-treatment AEs will be presented and a separate listing. All other listings and AE summary tables will present only TEAEs. Listings of serious TEAEs (SAEs), AEs leading to discontinuation of study treatment and TEAEs resulting in death will be produced. The AEs related to study drug and AEs leading to study drug interrupted or withdrawn will be listed. Any DLT will be listed with information of the DLT criteria.

Summary tables of TEAEs will be produced for the Safety population.

The categories of AE relationship to study drug will be combined for separate summaries of AEs related to bavituximab and AEs related to pembrolizumab.

An overview table will summarize the number and percentage of study subjects with at least one of the following TEAEs, where subjects with more than one TEAE in a particular category are counted only once in that category:

- any AE;
- Any DLT;
- Any AE with severity grade ≥ 3;
- any AE by maximum severity (Grade 1 to 5), a subject is counted only once at the highest severity grade of all AEs experienced by the subject;
- any AE related to bavituximab
  and AE related to bavituximab with severity grade ≥ 3
- any AE related to pembrolizumab
  and AE related to pembrolizumab with severity grade ≥ 3
- any AE related to bavituximab and pembrolizumab
  and AE related to bavituximab and pembrolizumab with severity grade ≥ 3
- AE leading to treatment discontinuation (bavituximab, pembrolizumab, or either);
- AE leading to dose modification (bavituximab dose reduced, bavituximab interrupted, pembrolizumab drug interrupted)
- AE related to bavituximab leading to treatment discontinuation (bavituximab, pembrolizumab, or either)
- AE related to pembrolizumab leading to treatment discontinuation (bavituximab, pembrolizumab, or either)
- AE related to bavituximab and pembrolizumab leading to treatment discontinuation (bavituximab, pembrolizumab, or either)
- SAE;
- treatment-related SAE (bavituximab, pembrolizumab, or both);
- SAE leading to death;
- treatment-related SAE leading to death;

6.7.2.3 Adverse Events by System Organ Class (SOC) and Preferred Term (PT)

The number and percentage of subjects reporting each TEAE will be summarized by System Organ Class (SOC) and Preferred Term (PT) for the Safety population. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- AEs, by SOC and PT;
- AEs by PT;
- AEs related to study treatment, by SOC and PT (grouped to bavituximab, pembrolizumab, or both);
- AEs related to study treatment, by PT (grouped to bavituximab, pembrolizumab, or both);
- AEs severity grade ≥ 3, by SOC and PT;
- AEs severity grade ≥ 3, by PT;
- AEs severity grade ≥ 3 related to study treatment, by SOC and PT (grouped to bavituximab, pembrolizumab, or both);
- AEs severity grade ≥ 3 related to study treatment, by PT (grouped to bavituximab, pembrolizumab, or both);
- AEs by relationship to study treatment, by SOC and PT;
- AEs by maximum severity, by SOC and PT;
- AEs related to study treatment by severity, by SOC and PT (grouped to bavituximab, pembrolizumab, or both);
- AEs causing discontinuation from bavituximab study treatment, by SOC and PT;
- AEs causing discontinuation from pembrolizumab study treatment, by SOC and PT;
- AEs related to study treatment leading to discontinuation from study treatment, by SOC and PT (related to bavituximab and leading to bavituximab discontinued or related to pembrolizumab and leading to pembrolizumab discontinued);
- AEs leading to bavituximab dose reduced, by SOC and PT;
- AEs related to study treatment leading to bavituximab dose reduced, by SOC and PT (related to bavituximab);

- AE leading to study treatment interrupted (bavituximab interrupted, pembrolizumab drug interrupted)
- AEs related to study treatment leading to study treatment interrupted, by SOC and PT (related to bavituximab and leading to bavituximab interrupted or related to pembrolizumab and leading to pembrolizumab interrupted);

In the above summaries, subjects with more than one AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT. For summaries by severity, subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. AEs with missing intensity/severity will be included (as severe) in the overall count of subjects with AEs, but will not be included in the counts of subjects with AEs within a SOC or PT.

6.7.2.4 Serious Adverse Events (SAE), Adverse Events of Special Interest (AESI) and Deaths

The number and percentage of subjects reporting TE SAE and TE AESI will be summarized by System Organ Class (SOC) and Preferred Term (PT) for the Safety population. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- SAEs, by SOC and PT;
- SAEs related to study treatment, by SOC and PT;
- TEAEs leading to death, by SOC and PT;
- Treatment-emergent AESI by SOC and PT;
- Treatment related, treatment-emergent AESI by maximum severity, by SOC and PT (related grouped to bavituximab, pembrolizumab, or both)

All deaths will be listed including deaths resulting from AEs, from disease progression, and deaths reported during survival follow-up period. The death listing will present study period, primary cause of death and the number of days between the date of the last dose of study drug and death. The number and percentage of patients who died will be summarized by study period: pre-treatment, treatment period through 30-day follow-up, and survival follow-up period.

6.7.3 Laboratory Evaluations

Blood and urine samples will be collected at the time points specified in Table 1. Screening results for study eligibility will 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 will be performed prior to study treatment administration.

Laboratory tests of Table 7 will be performed by local labs and converted to International System of Units (SI) units. The SI units and decimal presentation format for laboratory data listings are presented in Section 8.

Quantitative hematology, coagulation, clinical chemistry (including thyroid), and urinalysis results will be listed and summarized by visit using standard descriptive statistics for the Safety population. Changes from baseline will also be summarized. For each laboratory test, the baseline value will be defined as last scheduled value collected prior to the first dose of study treatment. Only data from scheduled visits will be included in the descriptive summary tables. Qualitative urinalysis and pregnancy test results will be listed only.

Out-of-reference-range values will be flagged as high (H) or low (L) in the listings. A shift table will be presented to summarize shifts from baseline to the scheduled Day 1 assessment of each treatment cycle.

Clinically significant laboratory abnormalities will be recorded to the AE eCRF and will be graded according to the CTCAE v5.0 grading system. In addition, criteria to assign laboratory toxicity grade based on CTCAE Version 5.0 will be used to assign severity grades to selected abnormal laboratory results. Details of statistically derived CTCAE grades are presented below in Section 9. These derived severity grades will be reported in the clinical laboratory listings and summarized in laboratory shift tables.

A listing of laboratory tests for review of potential drug induced liver injury (patient cases) will include results of all scheduled and unscheduled alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (BILI), and alkaline phosphatase tests evaluated from baseline through safety follow-up of any patient with (ALT > 3xULN or AST > 3xULN) and (BILI > 2xULN). The criterion will be assessed using the patient's maximum ALT, AST, and BILI over the interval from baseline through safety follow-up. All test results will be reported as a ratio to the corresponding test upper limit of normal range.

For hematology, coagulation, and serum chemistry, shift tables presenting changes CTCAE grading from baseline to worst post-baseline result will be provided. Where defined, low and high shifts will be summarized separately. This analysis will include scheduled and unscheduled post-baseline assessments.

6.7.4 Vital Signs

The following vital signs will be listed and summarized by visit.

- systolic and diastolic blood pressure (mmHg);
- pulse rate (bpm);
- respiration rate (breaths/min);
- body temperature (°C).
- weight (kg)

Vital signs data and changes from baseline in vital signs will be summarized by visit using standard descriptive statistics for the Safety population. The baseline value will be defined as last scheduled value collected prior to the first dose of study treatment. For post-baseline, only data from scheduled visits will be included in the summary tables.

Height (meter) will be measured at screening only. Height will be summarized on baseline characteristics for the Safety population.

6.7.5 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures once at screening.

The quantitative ECG measurements will be listed for the Safety population.

The Investigator assessment of ECG (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant") will be listed. Clinically significant abnormal findings will be listed as medical history.

6.7.6 Physical Examination

Clinically significant abnormal physical examination findings noted during screening will be listed as medical history.

New clinically significant abnormal findings should be recorded as AEs.

6.7.7 ECOG Performance Status

ECOG performance status will be assessed at the time points specified in

For each assessment, the status scores and percentage of subjects will be summarized by visit for the Safety Population.

6.8 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.

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. Treatment exposure, AEs and laboratory results will be listed for DLT-evaluable and Safety populations. Summary tables of demographics, disposition, AEs and SAEs by CTCAE grade and relationship to study treatment, and laboratory shift will be presented.

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. ORR will be summarized and supporting listings will be presented. Primary and secondary efficacy endpoints will be listed by study treatment for Efficacy population. Safety variables like treatment exposure, AEs, lab results will be summarized. 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.

7. Changes in Planned Analysis

Protocol states 'Efficacy analysis will be performed on the full analysis set, and per protocol analysis set, including predefined biomarker subgroups'. Per protocol analysis set is not defied in this SAP, but a sensitivity analysis that excludes patients with specified important protocol deviations will be performed for the primary and secondary efficacy endpoints. These important protocol deviations will be identified in a data classification document, which is finalized prior to database lock.

8. Laboratory Tests, Standard International (SI) Units and Decimal Precision

Table 7: 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	
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.

Listings and tables will report all quantitative laboratory tests using SI units and decimal precision indicated below:

Hematology	LBTESTCD	LBTEST	SI Units (LBSTRESU)	Decimal Precision
Leukocytes (WBC	WBC	Leukocytes	10^9/L	1
Neutrophils	NEUT	Neutrophils	10^9/L	1
Lymphocytes	LYM	Lymphocytes	10^9/L	1
Monocytes	MONO	Monocytes	10^9/L	2

Hematology	LBTESTCD	LBTEST	SI Units (LBSTRESU)	Decimal Precision
Eosinophils	EOS	Eosinophils	10^9/L	2
Basophils	BASO	Basophils	10^9/L	2
Erythrocytes (RBC)	RBC	Erythrocytes	10^12/L	1
Hemoglobin (HGB)	HGB	Hemoglobin	g/L	0
Hematocrit (HCT)	HCT	Hematocrit	L/L	2
Mean corpuscular volume (MCV)			fL	0
Mean corpuscular hemoglobin concentration (MCHC)			g/L	0
Platelets (PLT)	PLAT	Platelets	10^9/L	0

Coagulation	LBTESTCD	LBTEST	SI Units (LBSTRESU)	Decimal Precision
activated partial thromboplastin time (aPTT)	APTT	Activated Partial Thromboplastin Time	sec	0
partial thromboplastin time (PTT)	PTT		sec	0
International normalized ratio (INR)	INR	Thyroxine, Free	No unit	1
Prothrombin time (PT)	PT	Prothrombin Time	sec	1
% Prothrombin time (PT)	PT	Prothrombin Time	%	0

Chemistry	LBTESTCD	LBTEST	SI Units (LBSTRESU)	Decimal Precision
Alanine aminotranferase (ALT)	ALT	Alanine Aminotransferase	microkat/L	2
Albumin	ALB	Albumin	g/L	0
Alkaline phosphatase	ALP	Alkaline Phosphatase	microkat/L	2
Aspartate aminotranferase (AST)	AST	Aspartate Aminotransferase	microkat/L	2
Bilirubin, direct	BILDIR	Direct Bilirubin	µmol/L *	2
Bilirubin, total	BILI	Bilirubin	µmol/L *	2
Blood Urea Nitrogen (BUN)	UREAN	Urea Nitrogen	mmol/L	1
Blood Urea	UREA	Blood Urea	mmol/L	1
Calcium (Ca)	CA	Calcium	mmol/L	1
Chloride (Cl)	CL	Chloride	mmol/L	0
Creatine kinase (CK)	CK	Creatine kinase	microkat/L	2

Chemistry	LBTESTCD	LBTEST	SI Units (LBSTRESU)	Decimal Precision
Creatinine	CREAT	Creatinine	µmol/L *	0
Glucose, nonfasting	GLUC	Glucose	mmol/L	1
Magnesium	MG	Magnesium	mmol/L	1
Potassium (K)	K	Potassium	mmol/L	1
Sodium (Na)	SODIUM	Sodium	mmol/L	0
Uric acid	URATE	Urate	µmol/L *	0

* µmol/L may print as umol/L

Thyroid Function Testing	LBTESTCD	LBTEST	SI Units (LBSTRESU)	Decimal Precision
T3 (free)	T3		nmol/L	2
T3 (total)	T3FR		pmol/L	2
T4 (free)	T4		nmol/L	1
T4 (total)	T4FR		pmol/L	1
TSH	TSH		microIU/L	0

Urinalysis (dipstick)	LBTESTCD	LBTEST	SI Units (LBSTRESU)	Decimal Precision
pH	PH	pH	(no unit)	1
Specific gravity	SPGRAV	Specific Gravity	(no unit)	3

Blood, Glucose, Ketones, Protein, and Urine leukocyte esterase are qualitative assessments.

9. Severity Grades in Clinical Laboratory Listings and Tables

Clinically significant laboratory abnormalities and CTCAE grades will be recorded to the AE eCRF and will be graded according to the CTCAE v5.0 grading system. In addition, the following tables of criteria to assign laboratory toxicity grade are based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017. These will be used to assign severity grades to selected abnormal laboratory results. The derived severity grades will be reported in the clinical laboratory listings and summarized in laboratory shift tables.

In the following tables, 'Clinical' indicates that the CTCAE definition includes clinical signs and symptoms. Assignment of severity grade by statistical programming will not evaluate clinical signs or symptoms.

Table 8: Hematology Severity Grades of Laboratory Abnormal Results

Hematology	Hypo/ Hyper	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes (WBC)	Hyper	Leukocytosis	NA	NA	>100,000/mm3	Clinical
Leukocytes (WBC)	Hypo	White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 – 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophils	Hypo	Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocytes	Hypo	Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Lymphocytes	Hyper	Lymphocyte count increased	NA	> 4 - 20 x10e9/L	> 20 10e9/L	NA
Hemoglobin	Hypo	Anemia	<LLN - 100 g/L	<100 - 80g/L	<80 g/L; Clinical	Clinical
Hemoglobin	Hyper	Hemoglobin increased	>0 - 2 g/dL above max(ULN, BL)	>2 - 4 g/dL above max(ULN, BL)	>4 g/dL above max(ULN, BL)	NA
Platelets	Hypo	Platelet count decreased	<LLN - 75.0 x 10e9 /L	<75.0 - 50.0 x 10e9 /L	<50.0 - 25.0 x 10e9 /L	<25.0 x 10e9/L

BL = baseline; LLN = lower limit of normal range; NA = not applicable, no toxicology grade will be assigned;
ULN = upper limit of normal range.

Table 9: Coagulation Severity Grades of Laboratory Abnormal Results

Coagulation	Hypo/ Hyper	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Activated partial thromboplastin time (aPTT)	Hyper	aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; Clinical	NA
International normalized ratio (INR) [1]	Hyper	INR increased	**>1.2 - 1.5**; >1 - 1.5 x baseline if on anticoagulation	**>1.5 - 2.5**; >1.5 - 2.5 x baseline if on anticoagulation	**>2.5**; >2.5 x baseline if on anticoagulation; Clinical	NA

BL = baseline; LLN = lower limit of normal range; NA = not applicable, no toxicology grade will be assigned; ULN = upper limit of normal range.

[1] The calculation will not reference concomitant medication but will use the second rule if baseline INR > 1.1.

Table 10: Clinical Chemistry Severity Grades of Laboratory Abnormal Results

Serum Chemistry	Hypo/ Hyper	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransferase (ALT)	Hyper	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Albumin	Hypo	Hypoalbuminemia	<LLN - 30 g/L	<30 - 20 g/L	<20 g/L	Clinical
Alkaline phosphatase	Hyper	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was Abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was Abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase (AST)	Hyper	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Bilirubin, Direct	Hyper	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Bilirubin, Total	Hyper	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Calcium (Ca) [Corrected serum calcium] [1]	Hyper	Hypercalcemia	[>ULN - 2.9 mmol/L]	[>2.9 - 3.1 mmol/L]	[>3.1 - 3.4 mmol/L]; Clinical	[>3.4 mmol/L]; Clinical

Serum Chemistry	Hypo/ Hyper	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Calcium (Ca) [Corrected serum calcium] [1]	Hypo	Hypocalcemia	[<LLN - 2.0 mmol/L]	[<2.0 - 1.75 mmol/L]	[<1.75 - 1.5 mmol/L]; Clinical	[<1.5 mmol/L]; Clinical
Creatinine (Cr)	Hyper	Creatinine increased	>ULN - 1.5 x ULN; >1 - 1.5 x baseline	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Magnesium (Mg)	Hyper	Hypermagnesemia	>ULN - 1.23 mmol/L	NA	>1.23 - 3.30 mmol/L	>3.30 mmol/L; Clinical
Magnesium (Mg)	Hypo	Hypomagnesemia	<LLN - 0.5 mmol/L	<0.5 - 0.4 mmol/L; Clinical	<0.4 - 0.3 mmol/L; Clinical	<0.3 mmol/L; Clinical
Potassium (K)	Hyper	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; Clinical	>6.0 - 7.0 mmol/L; Clinical	>7.0 mmol/L; Clinical
Potassium (K)	Hypo	Hypokalemia	<LLN - 3.0 mmol/L; Clinical	<LLN - 3.0 mmol/L; Clinical	<3.0 - 2.5 mmol/L; Clinical	<2.5 mmol/L; Clinical
Sodium (Na)	Hyper	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; Clinical	>155 - 160 mmol/L; Clinical	>160 mmol/L; Clinical
Sodium (Na)	Hypo	Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L; Clinical	120-124 mmol/L; Clinical	<120 mmol/L; Clinical

BL = baseline; LLN = lower limit of normal range; NA = not applicable, no toxicology grade will be assigned; ULN = upper limit of normal range.
[1] Corrected serum calcium (mmol/L) = total calcium (mmol/L) + 0.02 [40 – albumin (g/L)]. Corrected calcium will be used for assignment of toxicology grade by statistical programming.