STATISTICAL ANALYSIS PLAN

A Phase 1/2, Open-Label, Single-Arm, Dose-Escalation and Dose-Expansion Study of the Safety, Tolerability, Pharmacokinetic, and Antitumor Activity of E-602 as a Single Agent and in Combination with Cemiplimab in Patients with Advanced Cancers

Protocol Number:	PAL-E602-001
Development Phase:	Phase 1/2
Sponsor:	Palleon Pharmaceuticals 266 2nd Ave, Waltham, MA 02451
Protocol Version Number:	8.0
SAP Version:	1.0

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This Statistical Analysis Plan has been reviewed and approved by:

[redacted]

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADA	Antidrug Antibodies
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Plasma Concentration-Time Curve
BOR	Best Overall Response
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
DSUR	Development Safety Update Report
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGJ	Esophagogastric Junction
EOT	End of Treatment
FACS	Fluorescence-Activated Cell Sorting
FIH	First in Human
IB	Investigator Brochure
IHC	Immunohistochemistry
iRECIST	A modified RECIST for immune-based therapeutics
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean Fluorescent Intensity
MTD	Maximum Tolerated Dose
NA	Not Applicable
NACT	New Anti-Cancer Therapy
NCI	National Cancer Institute
NE	Not Evaluable
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease

ABBREVIATION	DEFINITION
PD-L1	Programmed Death Ligand-1
PFS	Progression-free Survival
PK	Pharmacokinetic
PNA	Peanut Agglutinin
PR	Partial Response
PT	Preferred Term
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDRC	Safety Data Review Committee
SDTM	Study Data Tabulation Model
SNP	Single Nucleotide Polymorphism
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings, and Figures
ULN	Upper Limit of Normal
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methodology and analyses to be conducted for the protocol PAL-E602-001. This document may include modifications to the analyses outlined in the protocol. Any major modifications will be documented in the SAP and described in the Clinical Study Report (CSR).

The current SAP is based on protocol v8.0 dated August 24, 2023. A summary of all approved SAP versions is provided below.

Table 1. Summary of the Approved SAP versions

Version	Approval Date	Key Changes	Rationale
1.0	30-Jul-2024	NA	Original SAP

2 STUDY OVERVIEW

2.1 Study Design

This is a Phase 1/2, first-in-human (FIH), open-label, dose escalation and dose expansion study of E-602, administered as a single agent and in combination with cemiplimab, to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and antitumor activity in subjects with advanced cancers.

Each treatment cycle consists of 21 days. E-602 will be administered on Days 1, 8, and 15 of each cycle. Cemiplimab, if given, will be administered on Day 1 of each cycle.

Phase 1 Dose Escalation

The Phase 1 portion of the study follows a modified 3+3 design. Five planned escalating dose cohorts of E-602 monotherapy and 2 planned escalating dose cohorts of combination therapy will be enrolled. The dose for E-602 in the combination cohorts will be initiated at dose level(s) that have previously completed dosing and dose limiting toxicity (DLT) assessments (Cycle 1) as monotherapy. The maximum duration of treatment for each subject will be 1 year. No intrasubject dose escalation of E-602 will be permitted.

Table 1. Planned Escalating Dose Cohorts for Phase 1

Cohort	Number of Subjects	Dose of E-602	Frequency of E-602	Dose of Cemiplimab	Frequency of Cemiplimab
101	3 – 6	1 mg/kg	once a week	n/a	n/a
102	3 – 6	3 mg/kg	once a week	n/a	n/a
103	3 – 6	10 mg/kg	once a week	n/a	n/a
104	3 – 6	20 mg/kg	once a week	n/a	n/a
105	3 – 6	30 mg/kg	Once a week	n/a	n/a
111	3 – 6	20 mg/kg	once a week	350 mg	once every 3 weeks
112	3 – 6	to be determined	once a week	350 mg	once every 3 weeks

Phase 2: Dose Expansion

Phase 2 consists of dose-expansion disease cohorts in subjects with 3 types of advanced tumors: melanoma, non-small cell lung cancer (NSCLC), and the third type to be determined (ovarian, colorectal, pancreatic, breast, gastric/esophagogastric junction [EGJ], head and neck, or urothelial) based on available data including the Phase 1 results. Simon's minimax 2-stage design will be used for each cohort. Each disease cohort (monotherapy or combination) may be evaluated separately.

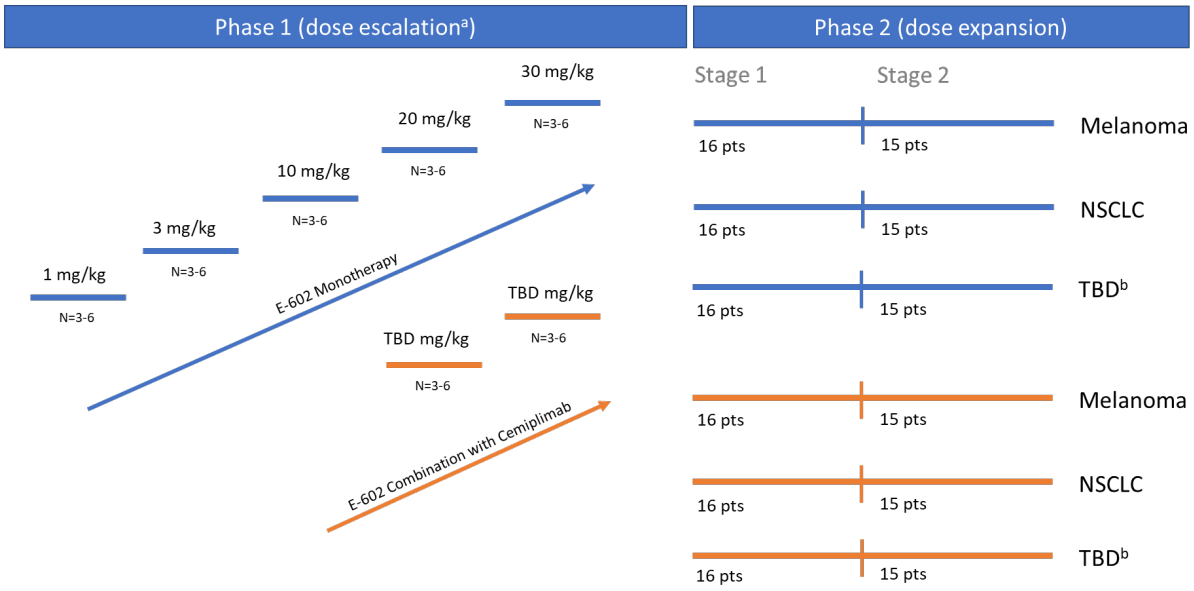
Study Monitoring and Tumor Assessments

A Safety Data Review Committee (SDRC) consisting of the principal investigators and members of the Sponsor will be formed and will meet regularly to review ongoing safety data. The committee will oversee subject safety and make recommendations to the Sponsor for all cohort dosing and dose escalation decisions.

Subjects will undergo radiological tumor assessment at baseline during screening (up to 35 days prior to Cycle 1, Day 1), 9 weeks (±1 week) after the first dose and every 9 weeks (±1 week) thereafter regardless of treatment delays until the End of Treatment (EOT) visit. An examination at EOT visit should be performed unless the subject already has radiographic confirmation of progressive disease (PD) within 4 weeks of the EOT visit. Response to treatment will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and Immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST).

The study schema is provided in Figure 1.

Figure 1 Study Schema



2.2 Study Objectives and Endpoints

The objectives of the study are to evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacodynamics of E-602, as a single agent or in combination with cemiplimab, for the treatment of subjects with advanced tumors.

Table 2. Summary of Study Objectives and Endpoints

Objectives	Endpoints
Dose Escalation Phase (Phase 1)	
Primary	
• To evaluate the safety and tolerability of E-602 as monotherapy in subjects with advanced cancers. • To evaluate the safety and tolerability of E-602 in combination with cemiplimab in subjects with advanced cancers. • To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of E-602 as monotherapy. • To determine the MTD and/or RP2D of E-602 in combination with cemiplimab.	• Incidence of adverse events (AEs) and serious adverse events (SAEs) graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. • Incidence and nature of dose limiting toxicities (DLTs) within a modified 3+3 trial design. • The MTD and/or RP2D based on occurrence of DLTs within a modified 3+3 design.
Secondary	
• To assess the PK of E-602 as monotherapy. • To assess the PK of E-602 in combination with cemiplimab. • To evaluate the immunogenicity of E-602 • To evaluate preliminary antitumor activity of E-602 as monotherapy in subjects with advanced cancers. • To evaluate preliminary antitumor activity of E-602 in combination with cemiplimab in subjects with advanced cancers.	• Noncompartmental PK parameters of E-602 as monotherapy and in combination with cemiplimab, including the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC). • Number and percentage of subjects who develop detectable antidrug antibodies (ADA). • Objective response rate (ORR) of confirmed complete response (CR) and partial response (PR) using RECIST v1.1 and iRECIST. • Duration of response (DoR). • Progression-free survival (PFS), defined as the time from the first dose to first evidence of radiographically detectable disease or death from any cause, whichever occurred first. • Overall survival (OS).

Objectives	Endpoints
Dose Expansion Phase (Phase 2)	
Primary	
• To evaluate the preliminary antitumor activity of E-602 as monotherapy in subjects with advanced cancers. • To evaluate the preliminary antitumor activity of E-602 at the combination RP2D in combination with cemiplimab in subjects with advanced cancers.	• ORR of confirmed CR or PR. • DoR of confirmed CR or PR. • PFS. • OS.
Secondary	
• To evaluate the safety and tolerability of E-602 as monotherapy in subjects with advanced cancers. • To evaluate the safety and tolerability of E-602 in combination with cemiplimab in subjects with advanced cancers. • To assess the PK of E-602 as monotherapy. • To assess the PK of E-602 in combination with cemiplimab. • To evaluate the immunogenicity of E-602	• Incidence of AEs and SAEs graded according to NCI CTCAE v5.0. • Noncompartmental PK parameters of E-602 as monotherapy and in combination with cemiplimab. including C_{max} and AUC. • Number and percentage of subjects who develop detectable ADA.

Objectives	Endpoints
Phase 1 and Phase 2	
Exploratory	
• To evaluate exploratory pharmacodynamic biomarkers of E-602 activity as monotherapy. • To evaluate exploratory pharmacodynamic biomarkers of E-602 activity in combination with cemiplimab.	• Immune cell desialylation and activation using fluorescence-activated cell sorting (FACS) • Immune cell gene expression profiling (RNAseq; Phase 1 E-602 monotherapy only) • Changes in cytokine levels • Changes in circulating tumor DNA • Changes in tumor desialylation by immunohistochemistry (IHC) • Tumor IHC analysis for immune modulation of different immune cell subtypes • Tumor gene expression and mutation profiling • Glycoproteomic profiling • Genetic variation or single nucleotide polymorphisms (SNPs) in select genes (e.g. glycogenes) (Phase 1 combination and Phase 2 only)

2.3 Sample Size Determination

Dose escalation for all cohorts will utilize a modified 3 + 3 design. Five dose escalation cohorts are planned for E-602 monotherapy for a total of up to 30 subjects. Two dose cohorts are planned for the E-602 and cemiplimab combination therapy for a total of up to 12 subjects. Any Phase 1 cohort may be backfilled up to 15 subjects in a dose cohort (dose escalation and backfill) to obtain additional safety, PK and pharmacodynamic data at a particular dose level.

For each cohort in Phase 2, Simon's minimax 2-stage design will be used. Sixteen subjects will be enrolled in the first stage. If ≥2 of 16 subjects respond, Stage 2 will be opened to enroll an additional 15 subjects for a total of 31 subjects in the cohort. At the end of Stage 2, if ≥6 of 31 subjects respond, the treatment will be considered promising for further evaluation. Within each cohort, the design has 80% power and a type I error rate of 0.1 to test the null hypothesis that the response rate is ≤10% against the alternative hypothesis of ≥25%.

3 ANALYSIS POPULATIONS

This section defines the analysis populations to be used for the planned statistical analyses. Study treatment is defined as E-602 monotherapy or E-602 in combination with cemiplimab. Date of first dose of study treatment is defined as the first dose of E-602 for monotherapy and first dose of cemiplimab for combination.

3.1 Safety Population (Intent to Treat)

All subjects who have received any dose of E-602. The Safety Analysis Population will be used for safety analyses. Safety Analysis Population may be further defined by the phase of the study, dose, tumor type, and therapy received (monotherapy or combination therapy).

3.2 DLT Evaluable Population (Phase 1 Dose Escalation)

All subjects treated in the dose escalation part who have had a DLT within Cycle 1 on study or without a DLT but completed safety assessments through Cycle 1 (3 doses of E-602 administered for monotherapy cohorts and 3 doses of E-602 and 1 dose of cemiplimab administered for combination therapy cohorts). The DLT Evaluable Set will be defined for each dose cohort. Subjects who discontinue prior to completing Cycle 1 (3 doses of E-602 administered for monotherapy cohorts and 3 doses of E-602 and 1 dose of cemiplimab administered for combination therapy cohorts) for reasons other than toxicity may be replaced.

3.3 Efficacy Evaluable Population

All subjects who receive any dose of study treatment, have measurable tumor lesions at baseline, and have at least one post-baseline disease assessment per RECIST v1.1.

3.4 Pharmacokinetic (PK) Evaluable Population

All subjects in the Safety Analysis Population for whom adequate E-602 plasma concentration data are available.

3.5 Pharmacodynamic Evaluable Population

All subjects in the Safety Analysis Population for whom there is at least one non-missing baseline measurement and at least one non-missing post-baseline measurement for the pharmacodynamic parameter.

4 CLINICAL OUTCOME VARIABLES

This section provides endpoint definitions. For endpoints based on tumor assessments, such as ORR, BOR, DoR, and PFS, investigator assessments are used per RECIST v1.1.

4.1 Primary Efficacy Endpoint

Objective Response Rate (ORR)

The ORR is defined as the proportion of subjects whose overall response is a confirmed CR or PR per RECIST v1.1. To be assigned a status of confirmed PR or CR, changes in tumor measurements must be confirmed by repeated assessments at least 4 weeks (28 days) after the criteria for response are first met. Tumor assessments after the initiation of new anti-cancer therapy should not be used to derive the ORR.

In addition to ORR, Best Overall Response (BOR) will be summarized based on the response assessments from all visits for each subject. BOR is defined as the best response per RECIST v1.1 in the order of CR, PR, stable disease (SD), PD, not evaluable (NE). For the BOR to be CR or PR, responses need to be confirmed. For the BOR to be SD, measurements must have met the SD criteria at least once at a minimum of 6 weeks from the start of treatment. Tumor assessments after PD per RECIST v1.1 or the initiation of new anti-cancer therapy (NACT) should not be used to derive the BOR.

4.2 Secondary Efficacy Endpoints

Duration of Response (DoR)

Duration of response is defined as the time from the start date of first observed CR or PR (subsequently confirmed) to the date of first documented radiographical progression of disease using RECIST v1.1 or death from any cause, whichever comes first. DoR will be calculated for subjects who are responders, i.e., those who achieve a confirmed CR or PR.

DoR in days will be calculated as:

DoR (days) = [Date of PD, or Death, (whichever is earlier)] – (First Date of PR/CR) + 1

DoR in months will be calculated as:

DoR (months) = [12 x DoR (days)]/365.25

Responders who have not experienced disease progression or death at the time of the analysis will be censored at the date of the last tumor assessment. If no tumor assessments are available after the date of the first occurrence of response, the subject will be censored on the date of the first occurrence of the response.

Progression-Free Survival (PFS)

Progression-free survival is defined as the time from the date of first dose (study day 1) of study treatment to the first documented radiographical progression of disease using RECIST v1.1, or death from any cause, whichever comes first.

PFS in days will be calculated as:

PFS (days) = [Date of PD or Death (whichever is earlier)] – (First Dose Date) + 1

PFS in months will be calculated as:

$$\text{PFS (months)} = [12 \times \text{PFS (days)}]/365.25$$

The following table summarizes the PFS censoring rules:

Table 3: Progression-Free Survival Censoring Rules

	Primary Analysis (Censoring Rules)	**Sensitivity Analysis (Censoring Rules)**
No PD, No death	Censored at last tumor assessment. If no evaluable tumor assessment, censored on the first dose date.	Censored at last tumor assessment. If no evaluable tumor assessment, censored on the first dose date.
PD or death after 1 missed tumor assessment	PFS event at the date of PD or death	PFS event at the date of PD or death
PD or death after 2 or more missed tumor assessments	Censored at last tumor assessment prior to PD or death	PFS event at the date of PD or death
PD or death after NACT	Censored at the last tumor assessment prior to NACT	PFS event at the date of PD or death
No PD, no death, NACT initiated	Censored at the last tumor assessment prior to NACT	Censored at last tumor assessment regardless of NACT

Overall Survival (OS)

Overall survival is defined as the time from the date of first dose (Dose 1) of study treatment to the date of death from any cause.

OS in days will be calculated as:

$$\text{OS (days)} = \text{Date of Death} - \text{First Dose Date} + 1$$

OS in months will be calculated as:

$$\text{OS (months)} = [12 \times \text{OS (days)}]/365.25$$

Subjects who are alive at the time of analysis or lost to follow-up will be censored on the date the subject is last known to be alive based on data collected in the database. The maximum follow-up is 15 months from the first dose of study treatment for each subject.

4.3 Safety Endpoints

Treatment-Emergent Adverse Events (TEAEs)

Adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary v24.1 or later. Severity will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All AEs, complaints, or symptoms that occur from the time of written informed consent

through the 90-day safety follow-up are to be recorded on the appropriate case report form (CRF).

A TEAE is any adverse event with an onset date on or after the date of first dose of study treatment through 90-day safety follow-up or the initiation of new anti-cancer therapy, whichever is earlier. TEAEs will be summarized in the safety analysis.

Dose-Limiting Toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as the occurrence of any of the events listed in Section 4.1.5 of the protocol that are assessed by the investigator to be possibly, probably, or definitely related to study treatment. The DLT window of observation for the purposes of dose escalation will be Cycle 1 defined as a subject receiving 3 doses of E-602 for monotherapy cohorts and 3 doses of E-602 and 1 dose of cemiplimab for combination therapy cohorts.

Exposure to Treatment

Exposure to E-602 and cemiplimab will be summarized separately. The following variables will be derived for each drug.

Total Treatment Duration will be calculated as:

Total Treatment Duration (days) = Date of Last Dose – Date of First Dose + 1

Total Treatment Duration (months) = 12 x Total Treatment Duration (days)/365.25

Actual Dose Administered (mg) will be calculated as:

Actual Dose Administered (mg) = Actual Cumulative Dose Administered up to the Date of Last Dose

Relative Dose Intensity (RDI) is the percentage of actual dose administered relative to the cumulative dose planned through to treatment discontinuation.

RDI will be calculated as follows:

$$RDI = 100\% \times (d/D)$$

where d (mg) is actual total dose administered and D (mg) is cumulative dose planned. D is the cumulative dose that would be administered if there were no modification to dose or schedule.

4.4 Other Definitions

Study Day 1

This is the day of the first dose of E-602 in monotherapy or first dose of either cemiplimab or E-602 in combination.

Baseline

Unless stated otherwise, the baseline value for any variable in the statistical analysis is defined as the last non-missing measurement prior to the first administration of study treatment.

Change from Baseline

Change from baseline is the arithmetic difference between any post-baseline assessments (i.e., assessments made after the first dose) and the baseline value.

Change from Baseline = Post-baseline Value – Baseline Value.

Visit Windows

Safety parameters such as laboratory values and vital signs are collected at certain scheduled visits over time. By-visit summaries are planned in the analysis. The definition of visit windows should cover the entire time to allow the potential for all scheduled and unscheduled visit data to be included in the by-visit analysis. For example, hematology and chemistry panels are scheduled on days 1, 8, and 15 in each cycle with a +/-2 days variation per protocol. The following visit windows may be defined for a particular Cycle X.

Cycle X Visit 1 = Days 1-4 in Cycle X

Cycle X Visit 2 = Days 5-12 in Cycle X

Cycle X Visit 3 = Days 13-21 in Cycle X.

If the start of the next cycle after Cycle X is advanced or delayed, Cycle X Visit 3 window is defined up to the day before the first day of the next cycle.

When two values are included in a visit window, the worst value (minimum or maximum depending on which direction is worse for the parameter of interest) will be used.

5 DATA REVIEW AND QUALITY

5.1 Data Management

Study data will be entered and stored in a database using Electronic Data Capture (EDC). Data fields are reviewed, checked, and source verified by the data management function of the Sponsor, or the Sponsor-designated contract research organization (CRO) specializing in data management. Data quality reviews and checks are specified in the data management plan.

5.2 Electronic Data Transfer

For all statistical analyses, a snapshot of the data will be taken from the EDC database along with snapshots of data external to the EDC database, if applicable. This will allow reproducibility of the analyses. The data snapshots will be stored and transferred to the responsible statistician(s) and programmer(s) at the Sponsor, or the Sponsor-designated CRO.

5.3 Handling of Missing Data

In general, missing data will not be imputed. Incomplete dates (missing day or month) associated with AE and concomitant medication dates may be imputed.

5.4 Data Transformation

If required by the Sponsor, source data from the EDC may be programmatically transformed to datasets more amenable for statistical analysis. These may include data formats for regulatory submissions in the form of Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM). The statistical programs used to perform the transformation will be validated to ensure accuracy and no loss of content. Otherwise, raw and ADaM-like datasets will be utilized for reporting purposes including generation of TLFs.

5.5 Validation of Statistical Analyses and Outputs

Analysis programs will be developed in SAS v9.4 or later, unless otherwise specified. Other statistical software, such as R, may be used as appropriate. All analyses and outputs intended for the CSR will be validated following the CRO's standard operating procedures to ensure accuracy, traceability, and reproducibility.

6 STATISTICAL ANALYSES

This section describes the statistical analyses to be conducted in relation to the primary, secondary, and exploratory objectives of the study.

6.1 General Statistical Considerations

In general, all analyses will be summarized by dose level and study treatment (e.g. monotherapy, combination with cemiplimab). Safety analysis will be based on the safety analysis population. The primary efficacy analysis will be based on the efficacy evaluable population by study treatment and/or tumor indication.

For each tumor indication, subjects administered the same study treatment may be combined for analysis purposes, regardless of study phase. Statistical inference, when performed, will be assessed at the 2-sided nominal 5% significance level without multiplicity adjustment. Point estimates will be accompanied by 95% confidence intervals (CIs). For the ORR endpoint assessed per the Simon's 2-stage design, the 2-sided 80% CI may be used.

For continuous variables, the number of observations (n), mean, standard deviation, median, minimum, and maximum will be provided as summary statistics. The mean and median will be reported to one additional decimal place compared to the original data. The standard deviation will be reported to two additional decimal places compared to the original data and the minimum and maximum will be reported to the same number of decimal places as the original data.

For categorical variables, the frequency and percentage in each category will be displayed. Percentages (e.g., for AEs and concomitant medications) will be calculated out of the population total for each cohort. Footnotes will clarify the denominator used in each output if other than the analysis set stated in the title. Percentages will be reported to one decimal place throughout unless the percentage is 100 (in which case no decimal places will be presented) or if the frequency count is zero (in which case no percentage will be presented).

For time to event data, unless otherwise noted, the median value, 25th percentile and 75th percentile will be calculated using the Kaplan-Meier method. The Brookmeyer and Crowley method will be used to calculate the CI of the median value (Brookmeyer and Crowley 1982). Also, the Greenwood formula will be used to calculate the CI of the rate of interest pertaining to the time to event data, at a given time point estimated using the Kaplan-Meier method (Kalbfleisch and Prentice 2002). The time to event analysis will be calculated only if an adequate number of responses are observed to warrant.

6.2 Subject Characteristics and Disposition

The safety population will be used for all tables and listings.

6.2.1 Subject Disposition

Subject disposition will be summarized in terms of counts and percentages for all subjects who have signed the informed consent regardless of study treatment. The following subject disposition categories will be summarized:

- Subjects consented
- Subjects consented but not treated (screen failure)
- Subjects treated with E-602 and E-602 + cemiplimab
- Subjects discontinued E-602 and E-602 + cemiplimab
- Subjects discontinued the study
- Subjects completed the study (end of study reason from the Case Report Form [CRF])

For subjects who discontinued study treatment or discontinued the study, a summary will be provided by reason of discontinuation.

The number and percentage of subjects in each defined analysis population will be tabulated.

Individual listings will be generated for the screen failures and safety populations.

6.2.2 Protocol Deviations

Protocol deviations will be identified and reported following the process described in the Protocol Deviation Plan. Important protocol deviations considered reportable in the CSR per the Protocol Deviation Plan will be summarized and listed by subject.

The number and percentage of subjects with CSR reportable protocol deviations will be summarized by dose/cohort and overall, for all treated subjects. Protocol deviations will be classified by CSR reportability prior to database lock.

A subject listing with all deviations will be provided.

6.2.3 Demographics and Baseline Characteristics

Demographic characteristics such as age at consent, sex at birth, race, and ethnicity will be summarized. Age will also be categorized as <65 vs ≥65. Baseline height (cm), body weight (kg), and Eastern Cooperative Oncology Group (ECOG) performance status will be summarized using frequencies and percentages.

Demographics and baseline characteristics will be listed by subject.

6.2.4 Medical History

Medical history will be collected during Screening. All pertinent prior medical conditions, surgeries or other medical procedures, allergies, and medications will be collected.

The reported medical history terms may be coded using MedDRA v24.1 or later. Medical history will be summarized by system organ class (SOC) and preferred term (PT).

Frequencies and percentages of subjects reporting each PT will be presented by SOC and PT. For each subject, multiple events of the same PT will be counted once in the summary. All reported medical history data including those with incomplete dates will be included in the analysis.

Reported medical history data will be presented in a by-subject listing.

6.2.5 Cancer History

Cancer history will be collected during Screening. Time since initial diagnosis (days) (Cycle 1 Day 1 [first dose study drug] – date of initial diagnosis) +1 and time since most recent progression (days) (Cycle 1 Day 1 [first dose study drug] – date most recent progression) +1 will be summarized with descriptive statistics. Categorical variables, including primary cancer type, tumor stage at time of initial diagnosis, histology/cytology, grade, and tumor stage at study entry, will be summarized using frequencies and percentages.

Cancer history data will be presented in a by-subject listing.

6.2.6 Prior Cancer Therapies

For systemic anti-cancer treatments, the number of prior lines of treatment received will be summarized. The reported cancer therapy terms will be coded using the World Health Organization (WHO) Drug Dictionary (September 2021 or later). Prior cancer therapies will be summarized by Anatomical Therapeutic Chemical (ATC) and preferred name. A subject will be counted only once within an ATC classification but may contribute to two or more preferred names in the same classification.

The number and percentage of subjects who received prior radiation therapy and prior cancer surgery will be summarized.

All prior therapies will be listed, including prior systemic anti-cancer treatments (preferred name by ATC and verbatim term), prior radiation therapy, and prior cancer surgery.

6.3 Efficacy Analyses

The primary efficacy analyses will be based on the efficacy evaluable population. For each tumor indication, subjects administered the same study treatment may be combined for analysis purposes, regardless of study phase. All data from scheduled or unscheduled tumor assessments will be included in the efficacy analyses except for tumor assessments after the initiation of new anti-cancer therapy for the ORR and DoR endpoints as described in Section 4.

Sensitivity efficacy analysis may be performed based on the ITT Population if it is sufficiently different from the efficacy evaluable population and the additional analysis may be informative. Subjects with no measurable baseline disease or no evaluable post-baseline disease assessments (i.e., NE) will be considered non-responders and included in the denominator in the calculation of the ORR for the ITT population.

6.3.1 Primary Efficacy Analyses

Objective Response Rate (ORR)

Point estimate of the ORR will be provided for each study treatment and/or tumor indication with the 2-sided 80% and 95% exact Clopper-Pearson CIs (Clopper and Pearson 1934) and if an adequate number of responses are observed to warrant. Confidence intervals adjusting for the 2-stage nature of the design may also be provided.

The best overall response (confirmed CR, confirmed PR, SD, PD, NE) will also be tabulated to show the number and percentage of subjects in each response category.

ORR between the monotherapy and combination therapy cohorts of the same tumor type may be compared as an exploratory analysis. The difference and its 95% CI will be provided using the continuity corrected Wilson score method (Newcombe 1998). This analysis will be calculated only if an adequate number of responses are observed to warrant.

6.3.2 Secondary Efficacy Analyses

Duration of Response (DoR)

DoR will be estimated using the Kaplan-Meier method along with the Kaplan-Meier plot if an adequate number of responses are observed to warrant.

The number and percentage of subjects who had events (response discontinued) or were censored will be summarized. The median, 25th percentile, 75th percentile, minimum and maximum will be provided along with the 95% CI for the median. The proportion and 95% CI for the number of subjects with durable responses at 6 months and 12 months from the onset of response will be provided. Other clinically relevant time points may also be included if data warrant.

Progression-free Survival (PFS)

PFS based on investigator assessments will be estimated using the Kaplan-Meier method and will be presented graphically if adequate data warrant. Censoring rules for the primary and sensitivity analyses are described in Table .

The number and percentage of subjects who had a PFS event or were censored will be summarized. The median, 25th percentile, 75th percentile, minimum and maximum will be provided along with the 95% CI for the median. The proportion and 95% CI for the number of subjects progression-free at clinically significant time points (e.g., 6 months, 12 months) from the date of the first dose will be provided. Other clinically relevant time points may also be included if data warrant.

Overall Survival (OS)

OS will be estimated using the Kaplan-Meier method along with the Kaplan-Meier plot if adequate data warrant.

The number and percentage of subjects who died or were censored will be summarized. The median, 25th percentile, 75th percentile, minimum and maximum will be provided along with the 95% CIs for the median. The proportion and 95% CI for the number of subjects alive at clinically significant time points (e.g., 6 months, 12 months) from first treatment will be provided. Other clinically relevant time points may also be included if data warrant.

6.4 Safety Analyses

Safety will be assessed based on reported AEs, clinical laboratory evaluations, vital signs, physical examinations, and ECOG performance status. Treatment exposure, concomitant medications, and concomitant medical procedures will also be summarized.

The safety analysis will be based on the Safety Population and will be presented by dose and study treatment, respectively. In addition, safety analyses pooling from all phases of the study (monotherapy or combination therapy) may be provided.

6.4.1 Treatment Exposure

Descriptive statistics will be provided for treatment duration (days), number of doses, cumulative dose administered, and relative dose intensity for E-602 and cemiplimab, respectively. The number and percentage of subjects with dose interruption will be summarized. The reasons for dose modifications will also be tabulated.

6.4.2 Adverse Events

All TEAEs will be summarized. For subjects who are still on study treatment, all TEAEs reported up to the data cutoff date will be included.

AEs with incomplete start date will be considered treatment emergent if:

- Day and month are missing, and the year is equal to or after the year of the first dose date of study treatment;
- Day is missing and the year is after the year of the first dose date of study treatment;
- Day is missing and the year is equal to the year of the first dose date of study treatment and the month is equal to or after the year of the first doe date of study treatment;
- Year is missing; or
- Start date is completely missing.

However, if the end date of the AE is before the first dose date of study treatment, the AE will not be treatment emergent regardless of the completeness of its start date. AEs reported in the CRF but not considered TEAEs will be listed.

All TEAEs and SAEs will be coded using the most current version of MedDRA and graded by the Investigator according to the NCI CTCAE v5.0. Frequencies and percentage of subjects reporting each PT will be presented by SOC and PT. For each subject, multiple events of the same PT will be counted once in the summary. For summaries involving severity, the worst grade among events of the same PT will be used. The following summary tables of subject incidence will be provided by study treatment:

- All TEAEs
- SAEs
- Treatment-related TEAEs
- Treatment-related TEAEs by Severity
- Treatment-related SAEs by Severity
- TEAEs by Maximum Severity
- SAEs by Severity
- Treatment-related SAEs by Severity
- Treatment-related SAEs
- SAEs leading to treatment discontinuation (E-602, cemiplimab, E-602 in combination with cemiplimab)
- TEAEs leading to treatment discontinuation (E-602, cemiplimab, E-602 in combination with cemiplimab)
- TEAEs leading to dose interruptions (E-602, cemiplimab, E-602 in combination with cemiplimab)

- TEAEs leading to study drug delays (E-602, cemiplimab, E-602 in combination with cemiplimab)

The summary tables will include SOC and PT, and where applicable, severity grade will be added. An overall summary table with the number and percentage in the major AE categories listed above will also be provided.

Listings of TEAEs, fatal TEAEs, SAEs, and TEAEs leading to treatment discontinuation will be provided. For subjects treated in Phase 1 Dose Escalation, DLTs, if any, will be listed.

6.4.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations (hematology, chemistry, coagulation, thyroid panel and urinalysis) will be summarized using descriptive statistics for select laboratory parameters including absolute measurements and changes from baseline by visit.

For laboratory parameters, shift tables (with categories of low, normal, high based on normal ranges) from baseline to post-baseline assessments may be produced. Both scheduled and unscheduled post-baseline visits will be considered in tabulations.

A listing will be generated for subjects potentially meeting Hy's Law criteria (Total Bilirubin $\geq$ (2×ULN) and AST or ALT > (3×ULN) at any time during the study). Graphical displays may also be provided to help identify potential Hy's Law cases.

Clinical laboratory evaluations will be listed by subject.

6.4.4 Vital Signs

Vital signs measurements (systolic and diastolic blood pressure, pulse rate, oxygen saturation, body temperature, and weight) will be summarized using descriptive statistics including absolute measurements and changes from baseline by visit.

All vital sign assessments will be presented in a by-subject listing.

6.4.5 Physical Examinations

Results of physical examinations (normal or abnormal) at each time point (including scheduled and unscheduled) will be listed by subject and body system.

6.4.6 ECOG Performance Status

The ECOG performance status at each visit on study will be presented using frequencies and percentages. Both scheduled and unscheduled visits will be tabulated.

ECOG performance status results will be presented in a by-subject listing.

6.4.7 Anti-drug Antibody

The ADA analysis and methods will be described in the Pharmacokinetic and Immunogenicity Analysis Plan.

6.4.8 Concomitant Medications and Procedures

The medications collected will be coded using WHO Drug Dictionary and summarized by ATC and PT. Medications with a stop date before the first dose date will not be included in the summary for concomitant medications. Frequencies and percentages of subjects reporting each PT will be presented by ATC and PT. For each subject, multiple medications with the same PT will be counted once in the summary.

All concomitant medications and medical procedures will be presented in data listings by subject.

6.4.9 Other Safety Assessments

Results from other safety assessments (e.g., pregnancy test) will be presented in by-subject listings if applicable.

6.4.10 Periodic Safety Reporting

The analyses required for DSUR (Development Safety Update Report) and IB (Investigator Brochure) should follow the SAP as applicable. In general, these analyses are subsets of the analyses planned for the CSR.

6.5 Covariates and Subgroups

If the sample sizes permit, subgroup analyses will be performed, at a minimum, for the primary efficacy endpoint (ORR). For the ORR endpoint, forest plots may be provided to assess the consistency of treatment effect by subgroups. The covariates and subgroups of interest include but are not limited to:

- Age, age groups (e.g., <65, ≥65 years)
- Sex at birth
- Number of prior lines of treatment (e.g., 1 versus >1)
- Baseline PD-L1 expression levels (e.g. positive versus negative; >50%)
- Baseline biomarker of disease: carcinoembryonic antigen (CEA) and CA-125 for subjects with NSCLC, CEA and CA19-9 for subject with colorectal or pancreatic cancer, and CA-125 for subjects with ovarian cancer.
- Baseline IHC HYDRA/hypersialylation levels (e.g. combined H-score >50 or >20)

6.6 COVID-19

Protocol deviations resulting from COVID-19 will be recorded and included in the protocol deviation listing.

6.7 Pharmacokinetic Analyses

The PK analysis and methods will be described in the Pharmacokinetic and Immunogenicity Analysis Plan.

6.8 Exploratory Analyses

6.8.1 Exploratory Pharmacodynamic Biomarker Analyses

Exploratory pharmacodynamic biomarker analyses will be performed using the pharmacodynamic evaluable population.

6.8.1.1 Pharmacodynamic Biomarker Definitions

Baseline

For the purposes of the pharmacodynamic biomarker analyses, baseline will be defined as indicated for each parameter:

- **Chemokine Panel, Pro-inflammatory Panel, and C3a**: last non-missing measurement prior to the first administration of E-602 treatment.
- **Immunophenotyping parameters:** Average of non-missing measurements prior to the first administration of E-602 treatment or the only available measurement prior to the first administration of E-602 should only one measurement be available.
- **IHC:** last non-missing measurement prior to the first administration of E-602 treatment.

Fold-change from Baseline

Fold-change from baseline is the ratio of the post-baseline value over the baseline value.

Fold-change from Baseline = Post-baseline Value/Baseline Value.

*Note: "value" in MFI of PNA = MFI (timepoint) - MFI (FMO)

Data Handling and Exclusions

The following quality metrics will be used to exclude entire visit/timepoint results from the analysis. Any visit/timepoint meeting the exclusion criteria will be noted in the listing of the corresponding Biomarker Panel.

Biomarker Panel	**Exclusion Criteria**
Immunophenotyping (FACS)	<65% live cells by Cellometer count OR Received for PBMC processing >72 hours after collection
Tissue IHC	H&E Adequacy = "N"

6.8.1.2 Pharmacodynamic Biomarker Analysis

Immunophenotyping (FACS), Chemokine Panel, Pro-inflammatory Panel and C3a biomarkers will be summarized using descriptive statistics for select parameters including absolute measurements and fold change from baseline by visit. Tissue IHC biomarkers will be summarized using descriptive statistics for select parameters including absolute measurements and change from baseline.

Sensitivity pharmacodynamic biomarker analyses may also be performed. For Tissue IHC biomarkers, data may be summarized for the patients for which there are matched pre- and on-treatment and the on-treatment biopsy was collected within 48 hours after the last dose of E-602. All biomarker results will be presented in a by-subject listing.

6.8.2 Exploratory Efficacy Analyses Based on iRECIST

If an adequate number of responses are observed to warrant, additional efficacy endpoints such as iORR, iDoR, iPFS based on iRECIST criteria may be analyzed similarly as their counterparts defined based on the RECIST criteria. For the iORR endpoint, iCR and iPR after iUPD will be included. For iDoR and iPFS, the event will be iCPD (confirmed PD) or death, whichever is earlier.

7 INTERIM ANALYSIS

7.1 Phase 1

An SDRC, consisting of the principal investigators and members of the Sponsor, will review safety data on an ongoing basis and after at least 3 subjects have completed the DLT-assessment period during dose escalation for a dose cohort. The committee will make dose de-escalation/escalation recommendations based on accumulating data. Details of the committee structure and meetings are described in the SDRC charter.

7.2 Phase 2

In addition to the ongoing review of safety data, the SDRC will also review the efficacy data at the end of Stage 1 per the Simon's 2-stage design. For the expansion cohort in Phase 2, efficacy data including but not limited to the number of subjects who achieved objective response and duration of response will be reviewed by the SDRC to determine if criteria to proceed to Stage 2 are met.

Additional interim analyses not planned as a part of the study design may also be performed and documented.

8 CHANGES FROM PROTOCOL-SPECIFIED ANALYSIS

There are no changes from the analysis specified in protocol v8.0.

9 REFERENCES

Brookmeyer, R., & Crowley, J. (1982). A confidence interval for the median survival time. *Biometrics*, 29-41.

Kalbfleisch, J. D. & Prentice, R. L. (2002). *The statistical analysis of failure time data* (2nd ed.). Hoboken, NJ: John Wiley & Sons, Inc.

Clopper, C.; Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". Biometrika. 26 (4): 404–413. doi:10.1093/biomet/26.4.404

Newcombe, R., “Interval Estimation for the Difference Between Independent Proportions: Comparison of Eleven Methods”, Statist. Med. 17, 873-890 (1998).