Clinical Study Protocol

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
Version Number:	8.0
Compound:	E-602
Brief Title:	Glycan Mediated Immune Regulation with a Bi-Sialidase Fusion Protein (GLIMMER-01)
Study Phase:	Phase 1/2
Sponsor:	Palleon Pharmaceuticals
Address:	266 2nd Ave, Waltham, MA 02451
Contract Research Organization:	Medpace, Inc.
Medical Monitor:	Palleon Pharmaceuticals
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Table of Contents

List of Tables

1. Protocol Summary

1.1. Synopsis

Protocol Title: 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

Rationale:

[redacted] The sialidase moiety of E-602 cleaves off immunosuppressive sialoglycans from immune and tumor cells to enhance antitumor immunity. In preclinical studies, E-602 has been shown to enzymatically remove sialic acids from cell surface sialoglycans and functions as an immune checkpoint blocker by releasing sialoglycan-mediated immunosuppression of antitumor immune cells. E-602 has been shown to enhance immune responses to tumor cells through multiple aspects, including restoring the function of exhausted-like T cells, improving antigen-specific T-cell response, and enhancing dendritic cell (DC) priming and activation of naïve T-cells. In addition, E-602 has a wide safety margin, as it is not an immune agonist and therefore does not cause cytokine activation. In humans, E-602 is expected to have antitumor activities either as a single agent or in combination with an anti-programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) agent.

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 design. • The MTD and/or RP2D based on occurrence of DLTs within a modified 3+3 design.
Secondary	
• To assess the pharmacokinetics (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.	• 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).

• To evaluate preliminary antitumor activity of E-602 in combination with cemiplimab in subjects with advanced cancers.	• 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 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and Immunotherapy Response Evaluation Criteria in Solid Tumors (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).
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.
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 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)

Overall 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, PK, pharmacodynamics, and antitumor activity in subjects with advanced cancers.

Phase 1: Dose Escalation, Monotherapy and Combination Therapy

Phase 1 of the study consists of 5 planned dose escalation cohorts of E-602 as a monotherapy and 2 planned dose escalation cohorts of E-602 in combination with cemiplimab. Phase 1 monotherapy will treat eligible subjects with melanoma, ovarian cancer, non-small cell lung cancer (NSCLC), colorectal cancer, pancreatic cancer, breast cancer, gastric/esophagogastric junction (EGJ) cancer, head and neck cancer, or urothelial cancer. Phase 1 combination with cemiplimab will treat eligible subjects with melanoma, NSCLC, gastric/EGJ cancer, head and neck cancer or urothelial carcinoma. The safety of the dose regimens will be evaluated to identify the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) to be used during Phase 2.

The cohorts of E-602 monotherapy will receive E-602 at the doses of 1, 3, 10, 20 and 30 mg/kg, respectively, via intravenous (IV) infusion once a week. Intermediate dosing cohorts may be added in Phase 1. The first subject dosed in a cohort will be a sentinel subject, with at least 24 hours until any subsequent subjects are dosed in the cohort. No intrasubject dose escalation of E-602 will be permitted.

The cohorts of E-602 in combination with cemiplimab will be initiated at dose level(s) that have previously completed DLT assessments (Cycle 1) as monotherapy. Intermediate dosing cohorts may be added in Phase 1. Subjects in the combination cohorts will receive 20 mg/kg E-602 IV once a week (additional dose levels to be determined) and 350 mg cemiplimab IV once every 3 weeks. The first subject dosed in a cohort will be a sentinel subject, with at least 24 hours until any subsequent subjects are dosed in the cohort. No intrasubject dose escalation of E-602 will be permitted.

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. When the cemiplimab combination is administered, cemiplimab should be administered first and E-602 administered at least 30 minutes after the cemiplimab infusion is completed. Subjects receiving ≥10 mg/kg of E-602 as monotherapy or in combination with cemiplimab should receive premedication including antihistamines and acetaminophen as indicated in the Pharmacy Manual. Corticosteroids should be used as premedication for subjects with previous infusion reaction(s) to E-602 as indicated in the Pharmacy Manual (see Pharmacy Manual, Section 10.5).

Dose escalation guidelines for all Phase 1 dose cohorts will utilize a modified 3+3 design. Assessments of DLTs will occur during 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) for all dose cohorts. Safety monitoring for immune-related toxicities will continue for all subjects for 90 days after treatment discontinuation unless a subsequent cancer therapy is started. All available data will be taken into consideration in selecting the RP2D.

E-602 dose escalation will continue until the MTD is exceeded, unacceptable toxicity is reached, or the RP2D is determined. The Sponsor may terminate dose escalation at a RP2D prior to reaching the MTD based on emerging PK, pharmacodynamic, and safety data.

Any Phase 1 cohort may be backfilled at the judgement of the Sponsor, up to a total of 15 subjects in the dose cohort (dose escalation and backfill) as needed to obtain additional safety, PK and pharmacodynamic data at a particular dose level.

In addition to DLTs, subjects will be evaluated for safety and tumor response as well as PK and pharmacodynamics, as listed in the Schedule of Activities (SoA) in Section 1.3.

Phase 2: Dose Expansion, Monotherapy and Combination Therapy

Phase 2 consists of dose expansion disease cohorts in subjects with 3 types of advanced tumors: melanoma, NSCLC, and the third type to be determined (ovarian, colorectal, pancreatic, breast, gastric/EGJ, head and neck, or urothelial) based on available data including the Phase 1 results. Phase 2 of the study will employ a 2-stage design, as outlined in Section 9.4. Each disease cohort will be analyzed separately. The E-602 dose(s), i.e., RP2D(s), chosen based on Phase 1 data will be used. E-602 as monotherapy and in combination with cemiplimab will be evaluated separately.

Subjects will be evaluated for safety and tumor response as well as PK and pharmacodynamics, as listed in the Schedule of Activities (SoA) in Section 1.3.

Treatment Discontinuation Criteria

Subjects will permanently discontinue study treatment for any of the following:

- Progressive disease (confirmed PD for subjects who continued treatment beyond PD, see Section 4.1.2)
- Initiation of alternative cancer therapy
- Unacceptable toxicity including permanent discontinuation criteria defined in Section 6.5
- Subject's decision to discontinue treatment
- Withdrawal of consent
- Investigator's decision to discontinue treatment
- Sponsor's decision to discontinue treatment
- Inability of the subject to comply with the requirements of the study
- Completion of maximum treatment duration of 1 year from Cycle 1 Day 1

Treatment Beyond Disease Progression

Treatment beyond PD will be allowed as per iRECIST guidelines. The following criteria must be met for continued use of the study treatment beyond PD:

- Absence of symptoms and signs indicating clinically significant progression of disease

- No decline in the Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., symptomatic pleural effusion, spinal cord compression).

At the time of radiographic progression of disease, a subject will be reconsented with emphasis on the FDA-approved therapy and potential clinical benefit that the subject may be foregoing to continue treatment.

Post-treatment Follow-up

For subjects who complete the 1-year treatment, an end-of-treatment (EOT) visit will be conducted, and subjects will return for safety follow-up visits 30 and 90 days after the last dose of study treatment to monitor for safety, including late immune-related toxicities. If prior to completing the 90-day safety follow-up period a subject begins a new cancer treatment, no further safety follow-up is required.

For subjects who discontinue treatment early, an EOT visit will be conducted, and subjects will return for safety follow-up visits 30 and 90 days after the last dose of study treatment. If prior to completing the 90-day safety follow-up period a subject begins a new cancer treatment, no further safety follow-up is required. These subjects will continue to be contacted once every 3 months for disease and survival status through approximately 15 months after the first dose of the study treatment unless the subject has died or withdrawn consent.

Phase 1 Dose-escalation Guidelines:

The following modified 3+3 guidelines will be employed on the basis of the number of DLTs observed during 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):

- Each dose level cohort will treat 3-6 subjects. At each dose level, at least 3 subjects must be DLT-evaluable prior to dose escalation.
- If 0 subjects experience a DLT, the next cohort will be treated at the next higher dose level.
- If only 1 subject experiences a DLT in 6 DLT-evaluable subjects, the next cohort will be treated at the next higher dose level.
- If 2 or more subjects in any cohort experience a DLT, the MTD will have been exceeded and no further subjects will be treated at this or higher dose levels. Additional subjects will be treated at the next lower dose level if needed to have at least 6 subjects treated at that prior dose level. If at least 6 subjects were previously treated at the prior dose level, that prior dose level will be considered the MTD.

Dose-Limiting Toxicity (DLT) Definition:

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. Any of the following events will meet the definition of a DLT if assessed by the investigator to be possibly, probably, or definitely related to study treatment:

- Any death not clearly due to the underlying disease or extraneous causes
- Hy's law:

  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3×the upper limit of normal (ULN) AND
  - Total bilirubin >2×ULN AND
  - Alkaline phosphatase <2×ULN AND
  - No other reason for liver injury
- Neutropenic fever
- Any Grade ≥3 non-hematologic toxicity (with exceptions noted below)
- Grade 4 neutropenia or thrombocytopenia >7 days
- Grade 3 thrombocytopenia with bleeding
- Grade 4 vomiting or diarrhea of any duration
- Grade 3 fatigue ≥7 days
- Grade ≥3 electrolyte abnormality that lasts >72 hours, unless the subject has clinical symptoms, in which case all Grade ≥3 electrolyte abnormality regardless of duration will be a DLT.
- For subjects with hepatic metastases, AST or ALT >8×ULN or AST or ALT >5×ULN for ≥14 days
- Recurrent Grade 3 infusion-related reaction despite pre-medication
- Grade 4 infusion-related reaction on the first occurrence
- Dose delay of >14 days for the study treatment due to an AE

However, the following AEs are NOT considered a DLT:

- Hematologic toxicity:
  - Grade 3 anemia
  - Grade 3 lymphopenia
  - Grade 3 or 4 neutropenia that is not associated with clinical sequelae and lasts <7 days
  - Grade 3 or 4 thrombocytopenia without bleeding
- Cardiovascular toxicity:
  - Grade 3 hypertension
- Other toxicities:
  - Grade 3 fatigue lasting <7 days
  - Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
  - Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated and resolves spontaneously or responds to conventional medical interventions
  - Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
  - Isolated Grade 3 infusion reaction
  - AEs that are clearly and incontrovertibly due to disease progression or extraneous causes.

Subjects treated in the Phase 1 dose escalation part of the study will discontinue treatment if he/she experience DLT(s) during Cycle 1.

Brief Summary:

The purpose of this study is 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. A maximum tolerated dose (MTD) and/or a recommended Phase 2 dose (RP2D) will be determined during Phase 1 to facilitate the conduct of Phase 2.

Study details include:

- Study duration: approximately 2 years from screening of the first subject to the last visit of the last subject (end of study).
- Treatment duration for individual subjects:
  - Screening period: up to 4 weeks before Cycle 1 Day 1
  - Treatment period: up to 1 year from Cycle 1 Day 1 regardless of treatment delays
  - Follow-up period: up to approximately 15 months from Cycle 1 Day 1
- Visit frequency: approximately up to 7 visits in Cycle 1; up to 5 visits in Cycle 2 and from Cycle 3 onward, weekly visits in each 21-day cycle.

Number of Subjects:

The planned total number of subjects to be treated in Phase 1 of the study is up to 87 subjects including up to 42 subjects in dose escalation and 45 subjects in backfilled cohorts. The planned total number of subjects to be treated in Phase 2 of the study is up to 186 subjects.

Total study treatment is up to 273 subjects.

Treatment Groups and Durations:

Phase 1 Treatment (Planned):

Five escalating dose cohorts of E-602 monotherapy and 2 escalating dose cohorts of combination therapy will be treated.

Cohort	Number of Subjects[a]	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

[a] Phase 1 cohorts may be backfilled to a maximum of 15 subjects.

The dose for E-602 in the combination therapy cohorts will be initiated at dose level(s) that have previously completed dosing and DLT assessments (Cycle 1) as monotherapy.

Dose modifications will be made according to the protocol (Section 6.5).

Phase 2 Treatment (Planned):

Subjects in Phase 2 will receive the following treatment:

Cohort	Number of Subjects	Advanced Disease	Dose of E-602	Frequency of E-602	Dose of Cemiplimab	Frequency of Cemiplimab
201	16 − 31	melanoma	monotherapy RP2D	once a week	n/a	n/a
202	16 − 31	NSCLC	monotherapy RP2D	once a week	n/a	n/a
203	16 − 31	TBD[a]	monotherapy RP2D	once a week	n/a	n/a
211	16 − 31	melanoma	combination RP2D	once a week	350 mg	once every 3 weeks
212	16 − 31	NSCLC	combination RP2D	once a week	350 mg	once every 3 weeks
213	16 − 31	TBD[a]	combination RP2D	once a week	350 mg	once every 3 weeks

[a] The third cohort will treat subjects with one of ovarian, colorectal, pancreatic, breast, gastric/EGJ, head and neck, or urothelial cancers based on available data including the Phase 1 results.

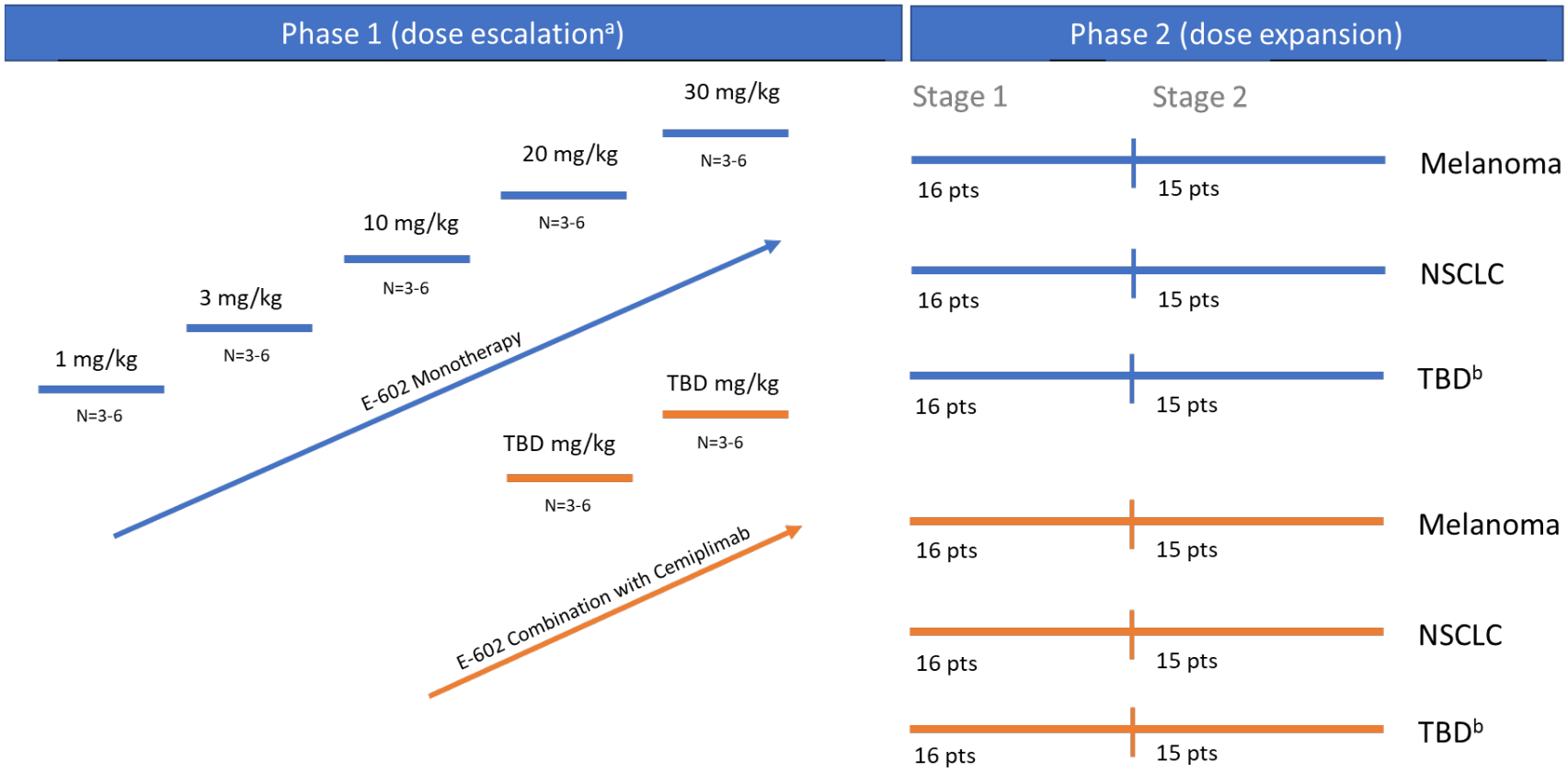
Duration of Treatment:

The maximum duration of treatment for each subject will be 1 year, regardless of treatment delays.

Safety Data Review Committee

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.

1.2. Schema



Abbreviations: NSCLC=non-small cell lung cancer, TBD=to be determined

[a]Tumor types in Phase 1: melanoma, ovarian, NSCLC, colorectal, pancreatic, breast, gastric/EGJ, head and neck, and urothelial. Phase 1 cohorts may be backfilled to a maximum of 15 subjects. The combination therapy cohort(s) will be initiated at dose level(s) that have previously completed DLT assessments (Cycle 1) as monotherapy and include only melanoma, NSCLC, gastric/EGJ, head and neck, or urothelial carcinoma subjects. Intermediate dosing cohorts may be added.

[b]The third cohort will treat subjects with one of ovarian, colorectal, pancreatic, breast, gastric/EGJ, head and neck, or urothelial, based on available data including the Phase 1 results.

1.3. Schedule of Activities (SoA)

1.3.1. Phase 1 E-602 Monotherapy: Dose Escalation and Backfill

Study Period		**Treatment [21]**															**Post Treatment**			
Cycle or Visit	**Screen**	**Cycle 1 [1]**							**Cycle 2 [1]**					**Cycle ≥3**			**EOT [2]**	**Follow-up [3]**		
Day	**-28 to -1**	**1**	**2**	**3**	**8**	**9**	**10**	**15**	**1**	**8**	**9**	**10**	**15**	**1**	**8**	**15**		**+30D**	**+90D**	**Q3M [4]**
Visit Window (days)		-	-	-	±2	-	-	±2	±2	±2	-	-	±2	±2	±2	±2	+14	±7	±7	±7
Clinical Assessments																				
Written informed consent [5]	X																			
Performance status [6]	X	X			X				X					X			X	X	X	
Concomitant medications [7]	X	X			X			X	X	X			X	X	X	X	X	X	X	
Height (cm)	X																			
Weight (kg) [8]	X	X			X			X	X	X			X	X	X	X	X			
Vital signs/oxygen saturation [9]	X	X			X			X	X	X			X	X	X	X	X	X	X	
Medical history [10]	X																			
Adverse event assessment		X			X			X	X	X			X	X	X	X	X	X	X	
12-lead ECG	X																			
Study Treatment																				
E-602 administration		X			X			X	X	X			X	X	X	X				
Laboratory Tests																				
Coagulation [11]	X																			
Urinalysis [11]	X	X							X					X			X			
Chemistry [11]	X	X			X			X	X	X			X	X	X	X	X			
Hematology [11]	X	X			X			X	X	X			X	X	X	X	X			
Thyroid panel [11]	X	X												X						
Plasma for PK analysis [12]		X	X	X	X			X	X	X	X	X	X	X	X		X	X		
Plasma for ADA [13]		X							X					X			X	X		
Pregnancy test [14]	X	X							X					X						
Disease Assessments																				
Physical examination [15]	X	X							X					X			X			
Radiology examination [16]	X													X			X			
Pharmacodynamics and Biomarkers [17]																				
Immune cell desialylation, content and activation status by FACS		X	X	X	X	X	X	X												
Immune cell gene expression profiling (RNAseq)		X	X	X	X	X	X	X												

Study Period	Screen	Treatment [21]															Post Treatment			
Cycle or Visit		Cycle 1 [1]							Cycle 2 [1]					Cycle ≥3			EOT [2]	Follow-up [3]		
Day	-28 to -1	1	2	3	8	9	10	15	1	8	9	10	15	1	8	15		+30D	+90D	Q3M [4]
Visit Window (days)		-	-	-	±2	-	-	±2	±2	±2	-	-	±2	±2	±2	±2	+14	±7	±7	±7
Cytokine panels and C3a		X	X	X	X	X	X	X												
Glycoproteomic profiling		X	X	X	X	X	X	X												
Disease biomarkers [18]		X																		
Circulating tumor DNA analysis [19]		X												X						
Archival Tumor biopsy [20]	X																			
Fresh Tumor biopsy [20]	X								X											
Post-treatment Follow-up																				
Subject Contact [4]																				X

Abbreviations: ADA=antidrug antibody, AE=adverse event, CT=computed tomography, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=end of treatment, FACS=fluorescence-activated cell sorting, MRI=magnetic resonance imaging, PET=positron emission tomography, PK=pharmacokinetic, SAE=serious adverse event

Footnotes:

1. The Day 9 visit should occur approximately 24 hours after the second dose of the cycle and the Day 10 visit should occur approximately 48 hours after the second dose of the cycle.
2. The End-of-Treatment (EOT) visit should occur at the time of discontinuing study treatment prior to completing 1 year of treatment or within 14 days of the last dose for subject who complete 1 year of treatment.
3. Subjects are required to return for safety follow-up visits at 30 days and 90 days after the last dose of study treatment. Any ongoing AEs and SAEs at EOT will continue to be evaluated until resolution or stabilization. If prior to completing the 90-day safety follow-up period a subject begins a new cancer treatment, no further safety follow-up is required.
4. For subjects who discontinue study treatment before 1 year, the study staff will contact the subject once every 3 months up to 15 months after Cycle 1 Day 1 to obtain disease status (if not progressed on study) and survival information.
5. Written informed consent must be obtained before any study procedures that are not part of routine medical care can be performed.
6. Performance status should be assessed using the ECOG scale within 7 days of informed consent during screening, within 72 hours of or on Cycle 1 Day 1 and on the specified cycle days thereafter.
7. Concomitant medications include information regarding all prescription, vaccines, nonprescription, or alternative medicine (including herbal products and vitamins). Use of any supportive care medication (eg, antiemetics, antidiarrheals, hematopoietic growth factors, transfusions) should be noted.
8. Weight should be measured prior to each dose of E-602.
9. Vital signs (pulse, body temperature, blood pressure, and oxygen saturation via pulse oximetry) should be obtained while breathing room air. Vital signs should be obtained at screening and on Cycle 1 Day 1 (predose and 1 (± 15 minutes), 2 (± 15 minutes), 4 (± 30 minutes), and 6 hours (± 30 minutes) after the start of E-602 infusion), Cycle 1 Day 8 (predose), Cycle 2 Day 1 (predose and 1 (± 15 minutes), 2 (± 15 minutes), 4 (± 30 minutes) and 6 hours (± 30 minutes) after the start of E-602 infusion), and predose at all other visits as noted.
10. Medical history includes cancer history including PD-L1 and tumor molecular mutation status, previous cancer therapies, review of systems, past and current medical conditions.
11. See Appendix 10.2 for the laboratory tests required. Cycle 1 Day 1 laboratory tests may be performed up to 72 hours prior to Day 1 to ensure results are available for review prior to dosing. Thyroid panel is required every other cycle, beginning with Cycle 1 (e.g., Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, etc.).
12. Plasma samples for E-602 concentrations will be collected at time points described in Section 8.4. An unscheduled plasma PK sample should be collected in the event of an infusion related reaction.

13. Plasma samples for ADA analysis will be collected pre-dose. An unscheduled plasma ADA sample should be collected in the event of an infusion related reaction.
14. Either serum or urine pregnancy test is allowed. The choice of test is at the investigator's discretion.
15. Physical examination will include, at a minimum, the assessment of cardiovascular, respiratory, gastrointestinal, dermatological and neurological systems along with the lymph nodes and liver. Physical examination should be performed during screening, within 72 hours of or on Cycle 1 Day 1 and on Day 1 of each subsequent cycle.
16. Radiology examination of tumors includes contrast-enhanced CT (preferred) or MRI imaging of the chest, abdomen, and pelvis. The same method (CT, PET/CT, MRI) and the same technique should be used to characterize each identified and reported lesion at screening and during the study. Radiology examinations will be performed during screening (permitted 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 any study treatment(s) delay. An EOT examination should be performed unless the subject already has radiographic confirmation of PD ≤4 weeks prior to the EOT visit. For ovarian cancer subjects, at each radiology examination, CA-125 should also be tested.
17. See Section 8.5 for further information on sample collection and analyses.
18. Biomarkers of disease may be performed up to 72 hours prior to Day 1 as follows: 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.
19. Circulating tumor DNA samples will be collected with radiological assessments. See Footnote 16.
20. Tumor biopsy is optional at screening and on Cycle 2 Day 1 (+4 days) during Phase 1. An archive tissue sample is required for all subjects. See Section 8.5.3 for further information.
21. Dosing visits should not be skipped due to dose delays.

1.3.2. Phase 1 Combination Dose Escalation and Backfill; Phase 2 E-602 Monotherapy and Combination

Study Period	**Screen**	**Treatment [21]**														**Post Treatment**			
Cycle or Visit		**Cycle 1 [1]**						**Cycle 2 [1]**					**Cycle ≥3**			**EOT [2]**	**Follow-up [3]**		
Day	**-28 to -1**	**1**	**2**	**3**	**8**	**9**	**15**	**1**	**8**	**9**	**10**	**15**	**1**	**8**	**15**		**+30D**	**+90D**	**Q3M [4]**
Visit Window (days)		-	-	-	**±2**	-	**±2**	**±2**	**±2**	-	-	**±2**	**±2**	**±2**	**±2**	**+14**	**±7**	**±7**	**±7**
Clinical Assessments																			
Written informed consent [5]	X																		
Performance status [6]	X	X			X			X					X			X	X	X	
Concomitant medications [7]	X	X			X		X	X	X			X	X	X	X	X	X	X	
Height (cm)	X																		
Weight (kg) [8]	X	X			X		X	X	X			X	X	X	X	X			
Vital signs/oxygen saturation [9]	X	X			X		X	X	X			X	X	X	X	X	X		
Medical history [10]	X																		
Adverse event assessment		X			X		X	X	X			X	X	X	X	X	X	X	
12-lead ECG	X																		
Study Treatment																			
E-602 administration		X			X		X	X	X			X	X	X	X				
Cemiplimab administration (combination cohorts)		X						X					X						
Laboratory Tests																			
Coagulation [11]	X																		
Urinalysis [11]	X	X						X					X			X			
Chemistry [11]	X	X			X		X	X	X			X	X	X	X	X			
Hematology [11]	X	X			X		X	X	X			X	X	X	X	X			
Thyroid panel [11]	X	X											X						
Plasma for PK analysis [12]		X	X	X	X		X	X	X	X	X	X	X	X		X	X		
Plasma for ADA [13]		X						X	X				X			X	X		
Pregnancy test [14]	X	X						X					X						
Disease Assessments																			
Physical examination [15]	X	X						X					X			X			
Radiology examination [16]	X												X			X			
Pharmacodynamics and Biomarkers [17]																			
Immune cell desialylation, content and activation status by FACS		X	X		X	X	X		X	X		X							
Glycoproteomic profiling		X	X		X	X	X		X	X		X							
Cytokine panels and C3a [22]		X	X		X	X	X		X	X		X							

Study Period	**Screen**	**Treatment [21]**														**Post Treatment**			
Cycle or Visit		**Cycle 1 [1]**						**Cycle 2 [1]**					**Cycle ≥3**			**EOT [2]**	**Follow-up [3]**		
Day	**-28 to -1**	**1**	**2**	**3**	**8**	**9**	**15**	**1**	**8**	**9**	**10**	**15**	**1**	**8**	**15**		**+30D**	**+90D**	**Q3M [4]**
Visit Window (days)		-	-	-	±2	-	±2	±2	±2	-	-	±2	±2	±2	±2	+14	±7	±7	±7
Single nucleotide polymorphisms (SNPs)		X																	
Disease biomarkers [18]		X																	
Circulating tumor DNA analysis [19]		X											X			X			
Archival Tumor biopsy [20]	X																		
Fresh Tumor biopsy [20]	X							X	[20]										
Post-treatment Follow-up																			
Subject Contact [4]																			X

Abbreviations: ADA=antidrug antibody, AE=adverse event, CT=computed tomography, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=end of treatment, FACS=fluorescence-activated cell sorting, MRI=magnetic resonance imaging, PET=positron emission tomography, PK=pharmacokinetic, SAE=serious adverse event

Footnotes:

1. The Day 9 visit should occur approximately 24 hours after the second dose of the cycle and the Day 10 visit should occur approximately 48 hours after the second dose of the cycle.
2. The End-of-Treatment (EOT) visit should occur at the time of discontinuing study treatment(s) prior to completing 1 year of treatment or within 14 days of the last dose for subject who complete 1 year of treatment.
3. Subjects are required to return for safety follow-up visits at 30 days and 90 days after the last dose of study treatment. Any ongoing AEs and SAEs at EOT will continue to be evaluated until resolution or stabilization. If prior to completing the 90-day safety follow-up period a subject begins a new cancer treatment, no further safety follow-up is required.
4. For subjects who discontinue study treatment before 1 year, the study staff will contact the subject once every 3 months up to 15 months after Cycle 1 Day 1 to obtain disease status (if not progressed on study) and survival information.
5. Written informed consent must be obtained before any study procedures that are not part of routine medical care can be performed.
6. Performance status should be assessed using the ECOG scale within 7 days of informed consent during screening, within 72 hours of or on Cycle 1 Day 1 and on the specified cycle days thereafter.
7. Concomitant medications include information regarding all prescription, vaccines, nonprescription, or alternative medicine (including herbal products and vitamins). Use of any supportive care medication (eg, antiemetics, antidiarrheals, hematopoietic growth factors, transfusions) should be noted.
8. Weight should be measured prior to each dose of E-602.
9. Vital signs (pulse, body temperature, blood pressure, and oxygen saturation via pulse oximetry) should be obtained while breathing room air. Vital signs should be obtained at screening and on Cycle 1 Day 1 (predose and 1 (± 15 minutes), 2 (± 15 minutes) and 4 hours (± 30 minutes), after the start of E-602 infusion), Cycle 1 Day 8 (predose), Cycle 2 Day 8 (predose and 1 (± 15 minutes), 2 (± 15 minutes) and 4 hours (± 30 minutes) after the start of E-602 infusion), and predose at all other visits as noted.
10. Medical history includes cancer history including PD-L1 and tumor molecular mutation status, previous cancer therapies, review of systems, past and current medical conditions.
11. See Appendix 10.2 for the laboratory tests required. Cycle 1 Day 1 laboratory tests may be performed up to 72 hours prior to Day 1 to ensure results are available for review prior to dosing. Thyroid panel is required every other cycle, beginning with Cycle 1 (e.g., Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, etc.).
12. Plasma samples for E-602 concentrations will be collected at time points described in Section 8.4. An unscheduled plasma PK sample should be collected in the event of an infusion related reaction. Cycle 1 Day 3 and Cycle 2 Day 10 sample collection is not required for Phase 2.
13. Plasma samples for ADA analysis will be collected pre-dose. An unscheduled plasma ADA sample should be collected in the event of an infusion related reaction.
14. Either serum or urine pregnancy test is allowed. The choice of test is at the investigator's discretion.

15. Physical examination will include, at a minimum, the assessment of cardiovascular, respiratory, gastrointestinal, dermatological and neurological systems along with the lymph nodes and liver. Physical examination should be performed during screening, within 72 hours of or on Cycle 1 Day 1 and on Day 1 of each subsequent cycle.
16. Radiology examination of tumors includes contrast-enhanced CT (preferred) or MRI imaging of the chest, abdomen, and pelvis. The same method (CT, PET/CT, MRI) and the same technique should be used to characterize each identified and reported lesion at screening and during the study. Radiology examinations will be performed during screening (permitted 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 any study treatment(s) delay. An EOT examination should be performed unless the subject already has radiographic confirmation of PD ≤4 weeks prior to the EOT visit. For ovarian cancer subjects, at each radiology examination, CA-125 should also be tested.
17. See Section 8.5 for further information on sample collection and analyses.
18. Biomarkers of disease may be performed up to 72 hours prior to Day 1 as follows: 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.
19. Circulating tumor DNA samples will be collected with radiological assessments and at EOT visit. See Footnote 16.
20. Fresh tumor biopsy is required for all subjects in Phase 1 combination at screening and on Cycle 2 Day 1 post-dose (+4 days). Fresh tumor biopsy is required for all subjects in Phase 2 at screening and post-dose on Cycle 2 Day 1 or Day 8. The biopsy should be performed on Day 2 or 3 if performed post Cycle 2 Day 1 E-602 administration or Day 9 or 10 if performed post Cycle 2 Day 8 E-602 administration. An archive tissue sample is required for all subjects. See Section 8.5.3 for further information.
21. Dosing visits should not be skipped due to dose delays.
22. Unscheduled cytokine panel samples should be collected in the event of an infusion related reaction.

2. Introduction

E-602, also known as Bi-Sialidase, [redacted] E-602 is being developed as an immune therapy to treat advanced cancers.

2.1. Study Rationale

The sialidase moiety of E-602 cleaves off immunosuppressive sialoglycans from immune and tumor cells to enhance antitumor immunity. In preclinical studies, E-602 has been shown to enzymatically remove sialic acids from cell surface sialoglycans and functions as an immune checkpoint blocker by releasing sialoglycan-mediated immunosuppression of antitumor immune cells. E-602 has been shown to enhance immune responses to tumor cells through multiple aspects, including restoring the function of exhausted-like T cells, improving antigen-specific T-cell response, and enhancing dendritic cell (DC) priming and activation of naïve T cells. In addition, E-602 has a wide safety margin, as it is not an immune agonist and therefore does not cause cytokine activation. In humans, E-602 is expected to have antitumor activities either as a single agent or in combination with an anti-programmed death-1 (PD-1)/ programmed death ligand-1 (PD-L1) agent.

2.2. Background

Sialoglycans have recently emerged as a critical glyco-immune checkpoint that impairs the efficacy of antitumor treatment by inhibiting innate and adaptive immunity (Rodriguez et al, 2018). Sialoglycans are structurally heterogeneous and upregulated on activated and exhausted T cells as a compensatory regulation mechanism that is similar to the programmed death-ligand 1 (PD-L1) / programmed cell death protein 1 (PD-1) immune checkpoints. Multiple types of tumors upregulate cell-surface sialoglycans as an immune escape mechanism. Sialoglycans interact with various immune receptors, including 15 Siglecs and other receptors on immune cells. Several decades of literature have shown various upregulated sialoglycans, such as sialyl ST, STn, sialyl Lewis X/A, GD2, GD3, GM3, and α2-3 sialylation, correlate with poor clinical outcomes in over a dozen tumor types (Crocker and Varki, 2001; Varki and Gagneux, 2012). As such, therapeutic interventions targeting this pathway remains challenging due to receptor redundancy and glyco-ligand heterogeneity (Xiao et al, 2016).

E-602, a human sialidase-based modality, overcomes this challenge by enzymatically removing the critical common immunosuppressive moiety, terminal sialic acids, from cell surface sialoglycans, regardless of their structures or receptor preferences. E-602 functions as an immune checkpoint blockade by releasing sialoglycan-mediated immunosuppression without causing systematic immune activation.

In preclinical research, E-602 has been shown to enhance immune responses in multiple assays with primary human immune cells, including restoring the immune function of exhausted-like T cells, improving antigen-specific T-cell response, and enhancing DC priming and activation of naïve T cells. E-602 monotherapy has shown antitumor activity in immune-competent syngeneic mouse tumor models. Synergistic antitumor activity has also been observed when its desialylation mechanism, ie, blocking sialoglycan-mediated immunosuppression, is combined with anti-PD-1/PD-L1 blockade. Furthermore, E-602 shows a wide safety margin in nonclinical research.

Because E-602 is not an immune agonist but instead works by releasing sialoglycan-mediated immunosuppression, it does not cause cytokine activation in human peripheral blood mononuclear cell (PBMC) assays.

This is the first-in-human clinical trial of E-602.

During this trial, E-602 will be combined with cemiplimab. Cemiplimab (REGN2810) is a high affinity hinge-stabilized IgG4P human antibody to the PD-1 receptor (PDCD1, CD279) that blocks PD-(L)1 mediated T cell inhibition. Binding of the PD-1 ligands PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Blockade of the PD-1 signaling pathway has demonstrated clinical benefit by inducing regression of advanced and metastatic tumors and improving survival with a favorable safety profile with manageable immune-related adverse events (Topalian 2014, Chen 2015).

2.2.1. Nonclinical Studies

2.2.1.1. E-602 Pharmacology

In *in vitro* models, E-602 was shown to desialylate synthetic sialic acid probes and natural cell surface sialoglycans. E-602 does not bind to sialoglycan-abundant T cells and does not cause antibody-dependent cellular toxicity (ADCC). E-602 desialylated activated or exhausted-like T cells and restores the function of exhausted-like T cells. By cleaving off sialoglycans, E-602 enhanced T-cell response against antigens. Further, E-602 augmented T-cell activation and proliferation in a human mixed lymphocyte reaction (MLR) with naïve T cells, suggesting that desialylation during T-cell priming could enhance its activation and contribute to a more robust immune response.

In a mouse model, E-602 enhanced antigen-specific CD8+ T-cell proliferation and activation in cultured and purified naïve CD8+ T cells from OT-I transgenic mouse splenocytes.

In an immunocompetent syngeneic mouse A20 (murine B cell) tumor model, treatment with single-agent E-602 led to evidence of antitumor activity. Desialylation was shown to result in antitumor response in a cold B16F10 (melanoma) tumor model, which is known to be resistant to PD-1/PD-L1 blockade.

In a mouse MC38 (colon) tumor model, combination treatment with anti-mouse PD-L1 treatment and E-601, a precursor molecule structurally similar to E-602, showed synergistic antitumor activity that was higher than either treatment alone.

For the assessment of safety, a cytokine release assay was performed on human peripheral blood mononuclear cells (PBMC) from 4 donors after treatment with E-602 in the range of 125 µg/mL to 15.6 µg/mL with 1:2 dilutions. E-602 did not cause cytokine secretion such as IL-6, IL-10, IFN-γ, TNF-α, and IL-2 even at a high concentration of 125 µg/mL, compared with immune agonist controls. The results were consistent with the immune-checkpoint mechanism of sialoglycans, since desialylation only releases sialoglycan-mediated immunosuppression, which does not activate immune cells in the absence of immune stimuli.

2.2.1.2. E-602 Pharmacokinetics

The PK profile of E-602 in cynomolgus monkeys was evaluated in a toxicokinetic study, in which single and repeat doses ranging from 5 to 200 mg/kg were administered as 30-minute IV infusions.

E-602 exposure (measured by AUC_{tau}) increased greater than 2-fold over the dose range of 100 to 200 mg/kg. The apparent $t_{1/2}$ and V_{ss} were comparable among the repeated dosing groups. No accumulations were observed between Day 8 and Day 1 (weekly dosing) or Day 11 and Day 1 (twice-weekly dosing). The accumulation ratios of C_{max} and AUC_{tau} ranged from 0.805 to 1.04. The exposures were comparable between the 100 mg/kg weekly and 100 mg/kg twice-weekly dosing schedules. Please refer to the current E-602 investigator's brochure (IB) for additional information.

2.2.1.3. E-602 Toxicology

The toxicity of E-602 IV infusion was evaluated in male and female cynomolgus monkeys in a toxicology and toxicokinetic study. E-602 was administered at doses of 5 to 200 mg/kg as a single dose at 5 or 30 mg/kg, weekly at 100 or 200 mg/kg, or twice weekly at 100 mg/kg. All infusions were given in 30 minutes.

E-602 at all doses was well tolerated and resulted in only minimal changes in liver enzymes (minimal increases in ALT and AST and minimal decreases in ALP and gamma-glutamyl transferase (GGT) in animals administered ≥100 mg/kg), which were generally within the normal range of levels for cynomolgus monkeys at the test facility and considered of uncertain relationship to E-602 administration and non-adverse. The no-observed-adverse-effect level (NOAEL) was considered 100 mg/kg for weekly dosing.

Please refer to the current E-602 IB for additional information.

2.2.2. Cemiplimab Pharmaceutical and Therapeutic Background

Cemiplimab is a fully-human monoclonal antibody targeting the immune checkpoint receptor PD-1 on T-cells. By binding to PD-1, cemiplimab has been shown to block cancer cells from using the PD-1 pathway to suppress T-cell activation.

Anti-PD-1 immunotherapy and chemotherapy combination studies have been conducted in patients with NSCLC. A wealth of clinical data shows that anti-PD-1 monotherapy prolongs progression free survival (PFS) and overall survival (OS) in NSCLC, with the greatest clinical benefit observed in tumors expressing high levels of PD-L1. In addition, clinical data in patients with advanced NSCLC suggest that first line treatment with cemiplimab in combination with chemotherapy, irrespective of PD-L1 expression levels, provides clinically meaningful and statistically significant improvement in OS, PFS, objective response rate (ORR) and duration of response (DOR) vs chemotherapy alone, with a safety profile consistent with cemiplimab monotherapy and platinum-based chemotherapy (Gogishvilli, 2022). Recently, the FDA and the European Commission approved cemiplimab (Libtayo®) for first-line treatment of patients with locally advanced or metastatic, non-small cell lung cancer (NSCLC) whose tumors have ≥50% PD-L1 expression. On November 8, 2022, the Food and Drug Administration approved cemiplimab in combination with platinum-based chemotherapy for adult patients with advanced NSCLC with no EGFR, ALK, or ROS1 aberrations.

Refer to the IB/approved labeling for detailed background information on cemiplimab (REGN2810).

2.3. Benefit/Risk Assessment

This is the first-in-human study of E-602, which is designed to evaluate the safety profile of the drug as a monotherapy and in combination with cemiplimab. Although E-602 has never been administered before to humans, the nonclinical research findings to date have not shown significant toxicities from administration of E-602 to non-human primates. The subjects treated in this study will have advanced cancers with limited or no other treatment options. Subjects will be closely monitored after receiving the study treatment, and dose-modification and discontinuation criteria are prespecified in the protocol. A safety data review committee will meet regularly to review the data and provide oversight in trial conduct and protection of patient safety.

Although E-602 is not expected to significantly stimulate cytokine release in humans based on the preclinical data, precautions are recommended for any drug product that interacts with immune cells to monitor for and manage suspected cytokine or immune-related adverse reactions. This includes frequent assessment of vital signs, blood pressure, and observation for emergent symptoms consistent with cytokine release. Premedication including standard prophylaxis such as antihistamines and acetaminophen are recommended at doses ≥10 mg/kg of E-602 as infusion related reactions have been observed. As of 02-Dec-2022, preliminary data indicate that 12 of 26 treated subjects had infusion related reactions at doses ≥10 mg/kg of E-602 which were primarily ≤Grade 2 and manageable, resolving with concomitant medication and/or slowing of the infusion rate. An isolated Grade 3 infusion related reaction occurred in one subject at the 20 mg/kg E-602 monotherapy dose level which resolved with concomitant medication and did not recur following premedication and slowing of the infusion rate. Two subjects have discontinued study treatment due to ≤Grade 2 recurrent infusion related reactions.

More detailed information about the known and expected benefits, risks, and adverse events (AEs) of E-602 and cemiplimab may be found in the respective IBs.

3. 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 design. • The MTD and/or RP2D based on occurrence of DLTs within a modified 3+3 design.
Secondary	
• To assess the pharmacokinetics (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 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and Immunotherapy Response Evaluation Criteria in Solid Tumors (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).
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 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.
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 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)

4. Study Design

4.1. Overall 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, PK, pharmacodynamics, and antitumor activity in subjects with advanced cancers.

4.1.1. Study Design Overview

Phase 1: Dose Escalation, Monotherapy and Combination Therapy

Phase 1 of the study consists of 5 planned dose escalation cohorts of E-602 as a monotherapy and 2 planned dose escalation cohorts of E-602 in combination with cemiplimab. Phase 1 monotherapy will treat eligible subjects with melanoma, ovarian cancer, non-small cell lung cancer (NSCLC), colorectal cancer, pancreatic cancer, breast cancer, gastric/EGJ cancer, head and neck cancer, or urothelial cancer. Phase 1 combination with cemiplimab will treat eligible subjects with melanoma, NSCLC, gastric/EGJ cancer, head and neck cancer or urothelial carcinoma. The safety of the dose regimens will be evaluated to identify the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) to be used during Phase 2.

The cohorts of E-602 monotherapy will receive E-602 at the doses of 1, 3, 10, 20 and 30 mg/kg, respectively, via intravenous (IV) infusion once a week. Intermediate dosing cohorts may be added in Phase 1. The first subject dosed in a cohort will be a sentinel subject, with at least 24 hours until any subsequent subjects are dosed in the cohort. No intrasubject dose escalation of E-602 will be permitted.

The cohorts of E-602 in combination with cemiplimab will be initiated at dose level(s) that have previously completed DLT assessments (Cycle 1) as monotherapy. Intermediate dosing cohorts may be added in Phase 1. Subjects in the combination cohorts will receive 20 mg/kg E-602 IV once a week (additional dose levels to be determined) and 350 mg cemiplimab IV once every 3 weeks. The first subject dosed in a cohort will be a sentinel subject, with at least 24 hours until any subsequent subjects are dosed in the cohort. No intrasubject dose escalation of E-602 will be permitted.

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. When the cemiplimab combination is administered, cemiplimab should be administered first and E-602 administered at least 30 minutes after the cemiplimab infusion is completed. Subjects receiving ≥10 mg/kg of E-602 as monotherapy or in combination with cemiplimab should receive premedication including antihistamines and acetaminophen as indicated in the Pharmacy Manual. Corticosteroids should be used as premedication for subjects with previous infusion reaction(s) to E-602 as indicated in the Pharmacy Manual (see Pharmacy Manual, Section 10.5).

Dose escalation guidelines for all Phase 1 dose cohorts will utilize a modified 3+3 design. Assessments of DLTs will occur during 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) for all dose cohorts. Safety monitoring for immune-related toxicities will continue for all

subjects for 90 days after treatment discontinuation unless a subsequent cancer therapy is started. All available data will be taken into consideration in selecting the RP2D.

E-602 dose escalation will continue until the MTD is exceeded, unacceptable toxicity is reached, or the RP2D is determined. The Sponsor may terminate dose escalation at an RP2D prior to reaching the MTD based on emerging PK, pharmacodynamic, and safety data.

Any Phase 1 cohort may be backfilled at the judgement of the Sponsor, up to a total of 15 subjects in the dose cohort (dose escalation and backfill) as needed to obtain additional safety, PK, and pharmacodynamic data at a particular dose level.

In addition to DLTs, subjects will be evaluated for safety and tumor response as well as PK and pharmacodynamics, as listed in the Schedule of Activities (SoA) in Section 1.3.

Phase 2: Dose Expansion, Monotherapy and Combination Therapy

Phase 2 consists of dose expansion disease cohorts in subjects with 3 types of advanced tumors: melanoma, NSCLC, and the third type to be determined (ovarian, colorectal, pancreatic, breast, gastric/EGJ, head and neck, or urothelial) based on available data including the Phase 1 results. Phase 2 of the study will employ a 2-stage design, as outlined in Section 9.4. Each disease cohort will be analyzed separately. The E-602 dose(s), i.e., RP2D(s), chosen based on Phase 1 data will be used. E-602 as monotherapy and in combination with cemiplimab will be evaluated separately.

Subjects will be evaluated for safety and tumor response as well as PK and pharmacodynamics, as listed in the Schedule of Activities (SoA) in Section 1.3.

Study Duration and Visit Frequency

- Study duration: approximately 2 years from screening of the first subject to the last visit of the last subject (end of study).
- Treatment duration for individual subjects:
    - Screening period: up to 4 weeks before Cycle 1 Day 1
    - Treatment period: up to 1 year from Cycle 1 Day 1 regardless of treatment delays
    - Follow-up period: up to approximately 15 months from Cycle 1 Day 1
- Visit frequency: approximately up to 7 visits in Cycle 1, up to 5 visits in Cycle 2 and from Cycle 3 onward, approximately weekly visits in each 21-day cycle.

Number of Subjects

The planned total number of subjects to be treated in Phase 1 of the study is up to 87 subjects including up to 42 subjects in dose escalation and 45 subjects in backfilled cohorts. The planned total number of subjects to be treated in Phase 2 of the study is up to 186 subjects.

Total study treatment is up to 273 subjects.

4.1.2. Continued Treatment Beyond Disease Progression

Each subject will receive the study treatment for 1 year, unless the treatment is discontinued for any of the reasons listed in Section 7.1.

Treatment beyond progressive disease (PD) will be allowed as per iRECIST guidelines (Seymour 2017). The following criteria must be met for continued use of the study treatment beyond PD:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in the Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., symptomatic pleural effusion, spinal cord compression).

At the time of radiographic progression of disease, a subject will be reconsented with emphasis on the FDA-approved therapy and potential clinical benefit that the subject may be foregoing to continue treatment.

4.1.3. Post-treatment Follow-up

For subjects who complete the 1-year treatment, an end-of-treatment (EOT) visit will be conducted, and subjects will return for safety follow-up visits 30 and 90 days after the last dose of study treatment to monitor for safety, including late immune-related toxicities. If prior to completing the 90-day safety follow-up period a subject begins a new cancer treatment, no further safety follow-up is required.

For subjects who discontinue treatment early, an EOT visit will be conducted, and subjects will return for safety follow-up visits 30 and 90 days after the last dose of study treatment. If prior to completing the 90-day safety follow-up period a subject begins a new cancer treatment, no further safety follow-up is required. These subjects will continue to be contacted once every 3 months for disease and survival status through approximately 15 months after the first dose of the study treatment unless the subject has died or withdrawn consent.

4.1.4. Phase 1 Dose-escalation Guidelines

The following modified 3+3 guidelines will be employed on the basis of the number of DLTs observed during 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):

- Each dose level cohort will initially treat 3-6 subjects. At each dose level, at least 3 subjects must be DLT-evaluable prior to dose escalation.
- If 0 subjects experience a DLT, the next cohort will be treated at the next higher dose level.
- If only 1 subject experiences a DLT in 6 DLT-evaluable subjects, the next cohort will be treated at the next higher dose level.
- If 2 or more subjects in any cohort experience a DLT, the MTD will have been exceeded and no further subjects will be treated at this or higher dose levels. Additional subjects will be treated at the next lower dose level if needed to have at least 6 subjects treated at that prior dose level. If at least 6 subjects were previously treated at the prior dose level, that prior dose level will be considered the MTD.

4.1.5. Dose-Limiting Toxicity (DLT) Definition

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. Any of the following events will meet the definition

of a DLT if assessed by the investigator to be possibly, probably, or definitely related to study treatment:

- Any death not clearly due to the underlying disease or extraneous causes
- Hy's law:
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3×the upper limit of normal (ULN) AND
  - Total bilirubin >2×ULN AND
  - Alkaline phosphatase <2×ULN AND
  - No other reason for liver injury
- Neutropenic fever
- Any Grade ≥3 non-hematologic toxicity (with exceptions noted below)
- Grade 4 neutropenia or thrombocytopenia >7 days
- Grade 3 thrombocytopenia with bleeding
- Grade 4 vomiting or diarrhea of any duration
- Grade 3 fatigue ≥7 days
- Grade ≥3 electrolyte abnormality that lasts >72 hours, unless the subject has clinical symptoms, in which case all Grade ≥3 electrolyte abnormality regardless of duration will be a DLT.
- For subjects with hepatic metastases, AST or ALT >8×ULN or AST or ALT >5×ULN for ≥14 days
- Recurrent Grade 3 infusion-related reaction despite pre-medication
- Grade 4 infusion-related reaction on the first occurrence
- Dose delay of >14 days for the study treatment due to an AE

However, the following AEs are NOT considered a DLT:

- Hematologic toxicity:
  - Grade 3 anemia
  - Grade 3 lymphopenia
  - Grade 3 or 4 neutropenia that is not associated with clinical sequelae and lasts <7 days
  - Grade 3 or 4 thrombocytopenia without bleeding
- Cardiovascular toxicity:
  - Grade 3 hypertension
- Other toxicities:
  - Grade 3 fatigue lasting <7 days
  - Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
  - Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated and resolves spontaneously or responds to conventional medical interventions
  - Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis

- Isolated Grade 3 infusion reaction
- AEs that are clearly and incontrovertibly due to disease progression or extraneous causes.

Subjects treated in the Phase 1 dose escalation part of the study will discontinue treatment if he/she experience DLT(s) during Cycle 1.

4.2. Scientific Rationale for Study Design

This study is a combination of a Phase 1, FIH, dose escalation study and a Phase 2, dose expansion study. Subjects to be treated in the study are those with advanced cancers, and a control group is not deemed appropriate.

In this study, the effects of desialylation of immune and tumor cells on the antitumor immunity will be explored, with E-602 given as a monotherapy and together with a PD1-pathway inhibitor. The tumor types chosen to be studied are populations enriched for patients with tumors that have greater amounts of sialoglycan modifications with immunoinhibitory potential, such as melanoma (Prendergast 2021), lung, colon, pancreatic, ovarian, breast, gastric/EGJ, head and neck and urothelial cancers (data on file).

In Phase 1 of the study, dose escalation (5 dose levels planned) will follow a modified 3+3 design for the E-602 monotherapy, and dose escalation (2 dose levels) for the combination therapy with cemiplimab will be carried out after the same dose level in monotherapy has been deemed tolerable. This design will assure protection of subject safety while identifying an MTD and an appropriate dose for dose expansion in Phase 2. Phase 1 cohorts can be backfilled at the judgement of the Sponsor in a dose cohort as needed to obtain additional safety, PK, and pharmacodynamic data at a particular dose level.

The RP2D(s) for monotherapy and combination therapy will be selected separately based on the totality of data including safety, pharmacodynamic, and PK data collected during Phase 1.

4.3. Justification for Dose

4.3.1. Justification for E-602 Dose

The starting dose in this FIH study is based on the maximum safe starting dose based on the highest non-severely toxic dose (HNSTD) or the no-observed-adverse-effect level (NOAEL) from the preclinical Good Laboratory Practice (GLP) toxicology studies and data from *in vitro* human cytokine release assays. The dose increment between cohorts is based on a modified Fibonacci pattern. Details for each method to estimate starting dose can be found in the IB.

Since immune desialylation serves as both a critical pharmacodynamic indicator for the overall activity of E-602 and a logical surrogate marker for the potential of E-602 to cause immune-related toxicity, the EC_{20} for E-602 desialylation of human CD8 T cells *in vitro* was estimated to be 15.5 µg/mL and 14.4 µg/mL for CD4 T cells (Table 1). Taken together, the EC_{20} for immune cell desialylation is approximately 15 µg/mL.

Table 1 50% And 20% effective concentrations (EC_{50} and EC_{20}) of E-602 for desialylation of human CD8 and CD4 T cells

	CD8+ T cells (µg/mL)	CD4+ T cells (µg/mL)
EC_{50}	62.0	57.5
EC_{20}	15.5	14.4

A human PK model was developed for E-602 based on the NHP data to estimate the amount of delivered E-602 that would yield a blood concentration of 15 µg/mL at C_{max}. A range of 5 dose levels, 0.1, 0.5, 1, 1.5, and 3 mg/kg, were simulated to produce concentrations over a 21-day period, with weekly dose administration. The simulated concentrations of dose levels 1 and 1.5 mg/kg produced a C_{max} of 10 and 15 µg/mL, respectively.

Thus, the human dose delivered that would likely produce the pharmacodynamic EC_{20} for desialylation of immune cells at the C_{max} would be approximately 1.5 mg/kg. Based on these data, the first cohort dose level will be 1 mg/kg.

An additional monotherapy dose escalation cohort of 30 mg/kg is planned for evaluation. As limited desialylation of peripheral immune cells has been observed at the 1 and 3 mg/kg dose levels, addition of 30 mg/kg dose level is expected to further inform the PK/PD relationship and identification of the recommended Phase 2 dose of E-602 monotherapy. The pharmacodynamic activity of E-602 in NHP GLP toxicology studies demonstrated a linear dose response of immune cell desialylation following E-602 administration across the dose range with maximum desialylation at 200 mg/kg (human equivalent dose of 60 mg/kg). The 30 mg/kg dose remains below the human equivalent dose (approximately 33 mg/kg) of the NHP NOAEL (100 mg/kg). Clinical experience (as of 23-September-2022) supports the tolerability of E-602 monotherapy. Doses up to 10 mg/kg of E-602 monotherapy have been evaluated with no DLTs reported and the 20 mg/kg E-602 monotherapy dose level is currently enrolling. Preliminary data indicate that the adverse events are consistent with an advanced cancer population. No E-602 related serious adverse events have been reported.

4.3.2. Justification for Cemiplimab Dose

A 350 mg Q3W dose of cemiplimab was chosen based on the safety and anti-tumor activity observed across >20 clinical studies (see cemiplimab IB). Analysis of the 350 mg Q3W dose regimen demonstrated that median steady-state concentrations (CV%) of cemiplimab ranged between a maximum concentration ($C_{max,ss}$) of 166 mg/L (28%) and a minimum concentration ($C_{min,ss}$) of 59 mg/L (48%). Cemiplimab exposure in serum at the fixed dose of 350 mg Q3W is similar to that at the body weight adjusted dose of 3 mg/kg once every 2 weeks (Q2W). The dose of 350 mg Q3W is consistent with the current USPI (Libtayo® USPI, 2022).

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last subject in the study.

A subject is considered to have completed the study if he/she has completed the final study visit or follow-up contact, whichever is later.

5. Study Population

5.1. Inclusion Criteria

1. Criteria for each cancer type are as follows:
    a. Melanoma:
        - Histologically confirmed unresectable Stage III or Stage IV cutaneous or mucosal melanoma.
        - Subject must have known BRAF genetic mutation status.
            - BRAF mutation-positive subjects are eligible without prior treatment or after failure of BRAF directed inhibitor therapy.
        - Subjects must have had prior therapy with an anti-PD-(L)1 pathway therapy and been deemed resistant (had progression on therapy or within 3 months of discontinuation of therapy).
    b. Ovarian:
        - Histologically or cytologically confirmed diagnosis of advanced, epithelial ovarian cancer (except carcinosarcoma), primary peritoneal, or fallopian tube cancer.
        - Subject has received at least 1 line of platinum-containing therapy or must be platinum-intolerant.
        - A subject with homologous repair deficiency (HRD) positive disease may participate if he/she has received prior polyadenosine diphosphate ribose polymerase (PARP) inhibitor therapy.
        - Subject has no standard therapy options that are likely to convey clinical benefit.
    c. NSCLC:
        - Histologically or cytologically documented Stage IV NSCLC not amenable to curative surgery or radiation.
        - Subject must have progressed on standard therapy that includes platinum-based chemotherapy and anti-PD-(L)1 pathway therapy.
            - Subjects must have been deemed resistant (had progression on therapy or within 3 months of discontinuation of therapy) to an anti-PD-(L)1 therapy.
        - Subjects with known active driver mutations that confer insensitivity to immune checkpoint inhibitors are excluded, including those with driver mutations in EGFR, ALK, ROS-1, and RET.
    d. Colorectal cancer:
        - Histologically or cytologically documented metastatic colorectal cancer.
        - Subject must have been previously treated with chemotherapy regimens based on fluoropyrimidine, oxaliplatin, and irinotecan; and anti-VEGF biological therapy; and, if RAS wild-type, an anti-EGFR therapy.
        - Subjects with microsatellite instability-high (MSI-H) or mismatch repair deficient tumors (dMMR) must have had prior therapy with an anti-PD-(L)1

pathway therapy and been deemed resistant (had progression on therapy or within 3 months of discontinuation of therapy).

e. Pancreatic:
   - Histologically or cytologically confirmed metastatic pancreatic adenocarcinoma.
   - Subjects has no standard therapy options available that could be of benefit as per the treating investigator.

f. Breast:
   - Other than Triple-Negative Breast Cancer (TNBC):
     - Histologically or cytologically confirmed diagnosis of hormone receptor (HR) positive and/or human epidermal growth factor receptor-2 (HER-2) positive breast cancer (Allison, 2020) not amenable to curative surgery or radiation.
     - Subject has received at least 2 lines of systemic therapy in the recurrent or metastatic setting:
       - Relapse within 6 months of completing neoadjuvant/adjuvant therapy can be considered 1 line of therapy
       - Regimens may include treatments such as anthracycline, platinum or taxane chemotherapy, aromatase inhibitor, endocrine therapy, PARPi, or, if HER-2$^+$, HER-2-targeting agent.
       - If HR$^+$, must have progressed on or was offered and deferred a cyclin-dependent kinase4/6 (CDK4/6) inhibitor.
   - TNBC:
     - Histologically or cytologically confirmed diagnosis of triple-negative breast cancer (Allison, 2020) not amenable to curative surgery or radiation.
     - Subject has received at least 1 line of systemic therapy including an anti-PD-(L)1 pathway therapy if PD-L1 Combined Positive Score (CPS) > 10. Relapse within 6 months of completing neoadjuvant/adjuvant therapy can be considered 1 line of therapy.
       a. For subjects with CPS>10 receiving a PD-(L)1 pathway therapy, subjects must have been deemed resistant (had progression on therapy or within 3 months of discontinuation of therapy) to the anti-PD-(L)1 pathway therapy.

g. Gastric/EGJ:
   - Histologically or cytologically documented locally advanced or metastatic gastric/EGJ carcinoma not amenable to curative surgery.
   - Subject must have been previously treated with chemotherapy regimens based on fluoropyrimidine and platinum.
   - A subject with HER-2$^+$ cancer must have progressed on or was offered and deferred a prior HER-2-targeting agent and/or if known NTRK gene fusion a tropomyosin receptor kinase (TRK) inhibitor.

- Subjects with microsatellite instability-high (MSI-H) or mismatch repair deficient tumors (dMMR) or PD-L1 CPS > 5 must have had prior therapy with an anti-PD-(L)1 pathway therapy and been deemed resistant (had progression on therapy or within 3 months of discontinuation of therapy).

h. Head and Neck cancer:
   - Histologically or cytologically confirmed squamous or adenocarcinoma of the head and neck (oral cavity, oropharynx, hypopharynx and larynx), not amenable to local therapy with curative intent surgery or radiation therapy ± chemotherapy. Carcinomas of the nasopharynx, paranasal sinus, or salivary glands are excluded.
   - Subject must have progressed on standard therapy that includes platinum-based chemotherapy and anti-PD-(L)1 pathway therapy.
     - Subjects must have been deemed resistant (had progression on therapy or within 3 months of discontinuation of therapy) to an anti-PD-(L)1 pathway therapy.

i. Urothelial Carcinoma:
   - Histologically or cytologically documented locally advanced or metastatic (Stage IV) muscle invasive urothelial carcinoma not amenable to curative surgery or radiation.
   - Subject must have progressed on standard therapy that includes platinum-based chemotherapy, and/or an anti-PD-(L)1 pathway therapy.
     - Subjects must have been deemed resistant (had progression on therapy or within 3 months of discontinuation of therapy) to an anti-PD-(L)1 pathway therapy.
   - Subject with known fibroblast growth factor receptor (e.g., FGFR2 or FGFR3) genetic alternations must have progressed on or was offered and deferred the standard treatments approved for these settings.

2. Age ≥18 years old.
3. Mentally competent and able to understand and sign the informed consent form.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
5. Life expectancy of greater than 12 weeks per the investigator.
6. Subject has disease that is measurable by Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1.
7. Female subjects of childbearing potential and male subjects are willing and able to use a highly effective method of contraception (see Appendix 10.4.2) from the first dose of study treatment through 6 months after the last dose.
8. Laboratory values at screening meet the following criteria:
   a. Hematology:
      - absolute neutrophil count ≥1,500 cells/mm^3
      - platelet count ≥100,000 cells/mm^3
      - hemoglobin ≥9.0 g/dL without packed red blood cell transfusion within the prior 2 weeks. Prior and concomitant erythropoietin is permitted.
   b. Renal:
      - creatinine clearance ≥30 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

(140-age)×(weight in kg)×(0.85 if female)/[72× (serum creatinine in mg/dL)]

c. Coagulation:
   - International Normalized Ratio (INR) and prothrombin time (PT) ≤1.5×ULN or activated partial thromboplastin time (aPTT) ≤1.5×ULN, unless undergoing anticoagulation therapy

d. Liver:
   - AST and ALT ≤2×ULN or ≤2.5×ULN with liver metastasis
   - Bilirubin ≤1.5×ULN, unless genetic cause of elevated bilirubin is known (such as Gilbert's Syndrome).

5.2. Exclusion Criteria

1. For cohorts receiving E-602 and cemiplimab combination therapy:
   - Moderate or Severe hypersensitivity to cemiplimab or any of the following excipients that are used for formulation: histidine, sucrose, L-proline, polysorbate 80.
   - Previous treatment with an anti-PD-(L)1 pathway therapy as a monotherapy and a history of ≥Grade 3 autoimmune complications or discontinuation due to toxicity, with the exception of asymptomatic Grade 3 elevations in lipase and/or amylase not associated with clinical manifestations of pancreatitis.
   - Subject has an active autoimmune disease. The following are not exclusionary: vitiligo, type 1 diabetes, autoimmune endocrinopathies that are stable on hormone replacement therapy, or psoriasis that does not require systemic treatment.
   - Previously received idelalisib.
2. Cardiovascular exclusions:
   - Subject has a medical history of an arterial thrombotic event, stroke, or transient ischemia attack within the past 12 months.
   - A medical history of symptomatic congestive heart failure (CHF) (New York Heart Association classes II-IV) or a cardiac arrhythmia that requires treatment.
   - A medical history of myocardial infarction or unstable angina within 6 months before Cycle 1 Day 1.
   - QTc prolongation to >470 milliseconds (ms) based on a 12-lead electrocardiogram (ECG).
3. History of age-related macular degeneration (AMD).
4. Subject has been previously administered study treatment in this study.
5. Subject is actively enrolled in another clinical study, unless it is an observational (noninterventional) clinical study or the follow-up component of an interventional study.
6. Major surgery < 4 weeks from Cycle 1 Day 1.
7. Use of another therapy within 4 weeks prior to Cycle 1 Day 1 or within 5 half-lives of the previous drug, whichever is shorter. Note: Subjects must have recovered from all AEs due to previous therapies to ≤ Grade 1 or baseline prior to Cycle 1 Day 1. Subjects with ≤ Grade 2 neuropathy may be eligible. Subjects with endocrine-related AEs ≤ Grade 2 requiring treatment or hormone replacement may be eligible.

8. Evidence of active infection requiring antimicrobials (IV or oral) within 7 days prior to Cycle 1 Day 1.
9. Active uncontrolled bleeding or a bleeding diathesis within 7 days before Cycle 1 Day 1.
10. Serious or non-healing wound, fistula, skin ulcer, or non-healing bone fracture within 7 days prior to Cycle 1 Day 1.
11. Subject has had a vaccine within 14 days prior to Cycle 1 Day 1.
12. Prior history of interstitial lung disease that required steroids or ≥ Grade 2 immune-related pneumonitis or has current non-infectious pneumonitis or interstitial lung disease.
13. Known human immunodeficiency virus (HIV) infection, active hepatitis B infection, or active hepatitis C infection.
14. Subjects with central nervous system (CNS) metastasis, and/or carcinomatous meningitis. However, subjects with CNS metastasis may participate if the subject has completed treatment of CNS metastasis and is:
    - >4 weeks from prior therapy for CNS metastasis (including radiation and/or surgery),
    - >2 weeks from receiving steroid therapy for treating CNS metastasis and are asymptomatic, and
    - clinically stable with respect to CNS metastasis at Screening.
15. Subject is taking the equivalent of >10 mg/day oral prednisone or the equivalent systemic exposure by any other route of administration.
16. Pregnant or breastfeeding woman.
17. Subject is unwilling or unable to follow protocol requirements.
18. Subject has had an allogeneic tissue or organ transplantation or is on systemic immunosuppressive therapy.
19. Subject has a known additional malignancy that is progressing or has required active treatment within the past 3 years, with the following exceptions:
    - Subjects with history of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, non-muscle invasive bladder cancer, carcinoma in situ, or localized breast cancer previously treated with curative intent are not excluded.
    - Localized prostate cancer that has been treated with curative intent or which does not require active treatment is not excluded.
20. Any condition or serious illness that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of the subject's safety or study results.
21. History of thromboembolic event unless the event occurred > 6 months from Cycle 1 Day 1 and the subject is on anti-coagulation treatment. Note: subjects with history of thromboembolic event which occurred >6 months from Day 1 of study treatment administration but who are not on anti-coagulation treatment may be allowed to participate if, in the judgment of the investigator, the thromboembolic event was provoked by a temporary factor that is resolved (e.g. by temporary immobility due to surgery) and the subject does not have a predisposition to or elevated risk of thromboembolic event.

22. Subject has received prior radiotherapy within 2 weeks of Cycle 1 Day 1, has a history of ≥Grade 3 radiation pneumonitis, or Grade 2 radiation pneumonitis that has been active within the last 6 months. Note: Subjects must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout prior to Cycle 1 Day 1 is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

5.3. Lifestyle Considerations

Partners (male and female) of subjects should use effective methods of contraception.

5.4. Screen Failures

A screen failure occurs when a subject who consents to participate in the study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened after discussion with Medical Monitor. Rescreened subjects should be assigned a new subject number.

6. Study Treatment and Concomitant Therapy

6.1. Study Treatment Administered

E-602 is supplied as a sterile solution for IV infusion in glass vials. Each container is filled with 10 mL solution which contains 100 mg E-602 active ingredient in 20 mM glutamic acid-sodium hydroxide buffer with 8% (w/v) sucrose and 0.04% (w/v) polysorbate 80 at a pH value of 4.7. Cemiplimab is provided as a sterile solution (350 mg/7 ml vial) for IV infusion.

For all subjects treated in the study, E-602 will be administered via IV infusion once a week at the assigned doses summarized below. For the combination therapy cohorts, 350 mg of cemiplimab will be administered via IV infusion once every 3 weeks. Subjects receiving ≥10 mg/kg of E-602 as monotherapy or in combination with cemiplimab should receive premedication including antihistamines and acetaminophen as indicated in the Pharmacy Manual. Corticosteroids should be used as premedication for subjects with previous infusion reaction(s) to E-602 as indicated in the Pharmacy Manual (see Pharmacy Manual, Section 10.5). All procedures and assessments must be completed prior to the start of dosing.

In each 21-day cycle, E-602 will be administered on Days 1, 8, and 15, and cemiplimab will be administered on Day 1. When the cemiplimab combination will be administered, cemiplimab should be administered first and E-602 administered at least 30 minutes after the cemiplimab infusion is completed. No intrasubject dose escalation of E-602 will be permitted. Details of study treatment administration methods will be provided in the Pharmacy Manual.

Cemiplimab should be administered in compliance with the manufacturer's labeling information (Libtayo® Prescribing Information 2022).

Phase 1 Treatment (Planned):

Five escalating dose cohorts of E-602 monotherapy and 2 escalating dose cohorts of combination therapy will be treated.

Cohort	Number of Subjects[a]	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

[a] Phase 1 cohorts may be backfilled to a maximum of 15 subjects.

The dose for E-602 in the combination therapy cohorts will be initiated at dose level(s) that have previously completed dosing and DLT assessments (Cycle 1) as monotherapy.

Dose modifications will be made according to Section 6.5.

Phase 2 Treatment (Planned):

Subjects in Phase 2 will receive the following treatment:

Cohort	Number of Subjects	Advanced Disease	Dose of E-602	Frequency of E-602	Dose of Cemiplimab	Frequency of Cemiplimab
201	16 − 31	melanoma	monotherapy RP2D	once a week	n/a	n/a
202	16 − 31	NSCLC	monotherapy RP2D	once a week	n/a	n/a
203	16 − 31	TBD[a]	monotherapy RP2D	once a week	n/a	n/a
211	16 − 31	melanoma	combination RP2D	once a week	350 mg	once every 3 weeks
212	16 − 31	NSCLC	combination RP2D	once a week	350 mg	once every 3 weeks
213	16 − 31	TBD[a]	combination RP2D	once a week	350 mg	once every 3 weeks

[a] The third cohort will treat subjects with one of ovarian, colorectal, pancreatic, breast, gastric/EGJ, head and neck or urothelial cancers, based on available data including the Phase 1 results.

The maximum duration of treatment for each subject will be 1 year, regardless of treatment delays. See Section 7.1 for early treatment discontinuation criteria.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received, and any discrepancies are reported and resolved before use of the study treatment.

Only subjects consented to the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy Manual.

As E-602 is a large molecule, the drug product is supplied as a frozen liquid. E-602 should be handled and prepared by qualified study personnel using aseptic technique and administered through an IV infusion as described in the Pharmacy Manual. Details for the storage, handling, and preparation of E-602 will be provided in the Pharmacy Manual.

Cemiplimab (manufactured by Regeneron Pharmaceuticals, Inc.) is supplied as a solution (350 mg/7 mL) and administered via IV infusion. Cemiplimab should be prepared by qualified study personnel in accordance with the manufacturer's labeling.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable. This is an open-label study. No control group will be used.

6.4. Study Treatment Compliance

All study subjects will receive E-602 and cemiplimab (if assigned to a combination therapy cohort) at the study site and will receive the study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment(s) and study subject identification will be confirmed at the time of treatment by a member of the study site staff other than the person administering the study treatment(s).

6.5. Dose Modification

To mitigate treatment-related toxicities, the following dosing modifications will be made for both E-602 monotherapy and for E-602 in combination with cemiplimab. When E-602 is used in combination, cemiplimab should be administered first and E-602 administered at least 30 minutes after the cemiplimab infusion is completed. Dose modifications for combination therapy apply to both E-602 and cemiplimab, and both study treatments must be held or restarted according to recommended dose modifications in Table 2. Dosing visits should not be skipped due to dose delays.

All therapies should be permanently discontinued if the study treatment is not restarted within 12 weeks after the last dose for the following:

- treatment-related toxicity, per Dose Modification (Table 2), does not resolve to Grade 0–1
- corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day
- any non-treatment related toxicity does not permit restarting study treatment

Table 2 Dose modifications for E-602 monotherapy and combination therapy with cemiplimab

Adverse Reaction	Severity (CTCAE v5.0)	Dose Modification/ Action with study treatment
Hematologic events	Any Grade 3 except thrombocytopenia with bleeding as specified below Grade 4 neutropenia not associated with clinical sequelae Grade 4 thrombocytopenia without bleeding	Withhold until adverse reaction recovers to Grade 0–1
	Grade 3 thrombocytopenia with bleeding Any Grade 4 unless specified above or recurrent Grade 3 Neutropenic fever	Permanently discontinue

Adverse Reaction	Severity (CTCAE v5.0)	Dose Modification/ Action with study treatment
Non-hematologic events unless specified below	Any Grade 3 Grade 4 electrolyte abnormality without clinical complications Grade 4 amylase or lipase increases not associated with symptoms or clinical manifestations of pancreatitis	Withhold until adverse reaction recovers to Grade 0–1
	Any Grade 4 unless specified above	Permanently discontinue
Pneumonitis	Grade 2	Withhold until adverse reaction recovers to Grade 0–1
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue
Diarrhea or Colitis	Grade 2 or 3	Withhold until adverse reaction recovers to Grade 0–1
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis (CTCAE grading according to increase creatinine or acute kidney injury)	Grade 2 with creatinine >1.5 to ≤3 times ULN	Withhold until adverse reaction recovers to Grade 0–1
	Grade ≥3 with creatinine >3 times ULN	Permanently discontinue
Endocrinopathies	Grade 2 adrenal insufficiency or hypophysitis	Withhold treatment until controlled by hormone replacement
	Grade 3 or 4 adrenal insufficiency or symptomatic hypophysitis Type 1 diabetes associated with Grade ≥3 hyperglycemia (glucose >250 mg/dL or >13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥3	Withhold until adverse reaction recovers to Grade 0–1 For any subject with Grade 3 or Grade 4 endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of study treatment may be considered after corticosteroid taper, if needed. Otherwise, treatment should be discontinued.
	Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption.
AST or ALT elevation or Increased Bilirubin	Grade 2	Withhold until adverse reaction recovers to Grade 0-1
	Grade ≥3	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥50% and lasts ≥1 week	Permanently discontinue

Adverse Reaction	Severity (CTCAE v5.0)	Dose Modification/ Action with study treatment
Immune-mediated skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or drug rash eosinophilia and systemic symptoms (DRESS)	Withhold until adverse reaction recovers to Grade 0–1
	Grade 4 or confirmed SJS or TEN or DRESS	Permanently discontinue
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold until adverse reaction recovers to Grade 0–1
	Grade 2, 3 or 4 myocarditis	Permanently discontinue
Other immune-related adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reaction recovers to Grade 0–1
	Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barré syndrome Grade 4 or recurrent Grade 3	Permanently discontinue
Infusion-related reactions	Recurrent Grade 2 or isolated Grade 3	Consider a one week study drug delay
	Recurrent Grade 3 despite pre-medication or Grade 4	Permanently discontinue

6.6. Management of Infusion Reactions

As a biologic product, infusion reaction is possible with E-602 and/or cemiplimab. Investigators should assess infusion reactions from the start of an infusion through one hour after the end of the infusion. See Appendix 10.5 for CTCAE version 5.0 severity grading and acute clinical management guidelines.

6.7. Treatment of Overdose

For this study, any dose of E-602 administered greater than the 125% assigned dose will be considered an overdose. No specific information is available on the treatment of an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the subject to determine, in consultation with the medical monitor, whether study treatment should be interrupted and/or delayed.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities. Appropriate supportive treatment should be provided if clinically indicated.
- Document the quantity of the excess dose as well as the duration of the infusion.

6.8. Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from study treatment may be required.

Vaccines including those against the SARS-CoV-2 virus are allowed during the study, after the subject completes a minimum of 30 days on treatment or has discontinued treatment and is in follow-up. Vaccines should not be administered the same day (+2 days) as study treatment administration.

Any medication or vaccine (including premedications, medications used to manage adverse events, over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the subject is receiving from 28 days prior to Cycle 1 Day 1, until study treatment discontinuation must be recorded. Any medication to treat adverse events during the 90-day safety follow-up must also be recorded. The following information must be included:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Rescue Medicine

The study site will supply rescue medication that will be obtained locally to treat potential occurrence of anaphylaxis and/or severe allergic reactions. Local standard of care medications will be used in such emergency situations.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7. Discontinuation of Study Treatment and Withdrawal of Consent

7.1. Discontinuation of Study Treatment

Subjects will permanently discontinue study treatment for any of the following:

- PD (confirmed PD for subjects who continued treatment beyond PD, see Section 4.1.2)
- Initiation of alternative cancer therapy
- Unacceptable toxicity including permanent discontinuation criteria defined in Section 6.5
- Subject's decision to discontinue treatment
- Withdrawal of consent
- Investigator's decision to discontinue treatment
- Sponsor's decision to discontinue treatment
- Inability of the subject to comply with the requirements of the study
- Completion of maximum treatment duration of 1 year from Cycle 1 Day 1

If study treatment is permanently discontinued, the subject will return for an EOT visit as well as 30 days and 90 days after the last dose for safety follow-up, as indicated in the SoA (Section 1.3). In addition, the subject will be contacted every 3 months for disease status (if the discontinuation is not due to progression of disease) and survival, until 15 months after Cycle 1 Day 1.

Subjects treated in the Phase 1 dose escalation part of the study will discontinue treatment if he/she experience DLT(s) during Cycle 1 (see Section 4.1.5).

For all subjects, see Section 6.5 for toxicity-related treatment-discontinuation criteria.

For subjects receiving the combination therapy of E-602 and cemiplimab, both treatments should be discontinued simultaneously.

7.1.1. Temporary Interruption of Study Treatment

Temporary interruption of study treatment due to adverse drug reactions is permitted. See Section 6.5 for guidelines.

7.1.2. Subject Replacement

During Phase 1 dose escalation, subjects who cannot be evaluated for DLT (e.g., discontinued before completing Cycle 1 for reasons other than study treatment-related toxicity) may be replaced. Backfill and Phase 2 subjects will not be replaced.

7.1.3. Study Stopping Criteria

The study will be stopped and an assessment of the risk/benefit for subjects evaluated if any of the following criteria are met:

- Study treatment related deaths
- Recommendation of the SDRC based on the risk/benefit no longer warranting continuation of the study

The study may be restarted if appropriate measures to protect the safety of study subjects can be implemented.

7.2. Subject Withdrawal from the Study

A subject may withdraw his or her consent for study participation at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws consent from the study, he/she may request destruction of any blood or tissue samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor or designee as soon as possible upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Study Periods

Overall, this study encompasses the following periods:

- Screening: up to 28 days
- Treatment: from Cycle 1 Day 1 to End-of-Treatment (EOT) visit, up to 1 year, regardless of treatment delays
- Post-treatment safety follow-up: up to 90 days after the last dose
- Survival follow-up: up to approximately 15 months from Cycle 1 Day 1

Written informed consent must be obtained before any study procedures are performed, unless the procedure is a part of routine care. The Eastern Cooperative Oncology Group (ECOG) performance status at screening should be evaluated within 7 days of informed consent. Screening tests should be completed within 28 days before Cycle 1 Day 1, and study personnel should ensure each subject meets the eligibility criteria before the initial dose of study treatment is administered. Radiology examinations during screening are permitted up to 35 days prior to Cycle 1, Day 1.

8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA.

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 EOT visit. An examination at EOT visit should be performed unless the subject already has radiographic confirmation of PD within 4 weeks of the EOT visit.

Tumor assessment should include contrast-enhanced computed tomography (CT, preferred) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. The same method (positron emission tomography [PET]/CT, MRI, or CT) and the same technique should be used to characterize each identified and reported lesion throughout the study. Lesions in a previously irradiated field may be assessed as target lesions if progression since irradiation has been demonstrated.

Response to treatment will be evaluated using the RECIST version 1.1 (Eisenhauer 2009) and iRECIST (Seymour 2017). Subject responses will be classified as progressive disease (PD), stable disease, partial response (PR), and complete response (CR). A per timepoint response of Stable Disease requires a minimum of 56 days between two measures. To assess a Best Overall Response (BOR) of CR or PR per RECIST version 1.1, confirmation of the CR or PR is required at the subsequent timepoint at least 4 weeks later.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatologic, and neurological systems along with the lymph nodes, and liver.

8.2.2. Vital Signs

Vital signs will be assessed and include body temperature, pulse, blood pressure, and oxygen saturation via pulse oximetry and be assessed as outlined in the SOA (Section 1.3).

8.2.3. Weight and Height

Height will be measured during screening. Body weight will be measured at visits indicated in Section 1.3.

8.2.4. Electrocardiograms

A 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECG should be conducted at screening.

8.2.5. Clinical Safety Laboratory Tests

See Appendix 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.

8.2.6. Pregnancy Testing

Subjects who are women of childbearing potential are required to undergo either serum or urine pregnancy test, (choice of test at the investigator's discretion), during the study at timepoints indicated in the SoA (Section 1.3).

8.3. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 10.3.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all adverse events until resolved or clinical stable.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Note: The causality of each AE should be assessed and recorded separately for E-602 and cemiplimab for subjects receiving combination therapy.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing the informed consent form (ICF) until the final safety follow-up visit at the timepoints specified in the SoA (Section 1.3). If prior to completing the 90-day safety follow-up period a subject begins a new cancer treatment, no further safety follow-up is required.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor or designee.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and Adverse Events of Special Interest (AESI) (as defined in Section 8.3.7) will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and forwarded to investigators.

8.3.5. Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects will be collected from the first dose of study treatment until 6 months after the last dose (see Section 5.1).

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the female subject or female partner of male subject (after obtaining the necessary signed informed consent from the female partner) pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any subject/female partner who becomes pregnant during the study will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject/female partner, and the neonate and the information will be forwarded to the Sponsor or designee.

Any post-study pregnancy-related SAE considered reasonably related to the study treatment(s) by the investigator will be reported to the Sponsor or designee as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study subjects/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will discontinue all study treatments.

8.3.6. Death Events

After the safety follow-up visit, information on subjects' survival status will be collected via telephone or other methods, including date and cause of death, during the post-treatment period (up to 15 months from Cycle 1 Day 1).

8.3.7. Adverse Events of Special Interest

The adverse events of special interest (AESI) in this study will be potential immune-related toxicities. The following assessments will be conducted throughout the study:

- Clinical observation for immune-related signs and symptoms.
- Select laboratory tests for endocrine, hepatic, or renal dysfunction.

8.4. Pharmacokinetics

Plasma samples will be collected for PK analysis of E-602 concentration at time points shown in Table 3. Sample collection and handling instructions will be provided in the Laboratory Manual.

Table 3 Blood sample collection time points for pharmacokinetic analyses

Cycle	Day	Time[a]	PK
1	1	predose	X
		0.5 h (EOI) ± 5 min[b]	X
		2 h ± 10 min[c]	X
		4 h ± 30 min	X
		6 h ± 30 min[d]	X
	2	24 h ± 2 h	X
	3	48 h ± 4 h[e]	X
	8	predose	X
	15	predose	X
2	1 (Day 22)	predose	X
		0.5 h (EOI) ± 5 min[b]	X
	8	predose	X
		0.5 h (EOI) ± 5 min[b]	X
		2 h ± 10 min[c]	X
		4 h ± 30 min	X
		6 h ± 30 min[d]	X
	9	24 h ± 2 h	X
	10	48 h ± 4 h[e]	X
	15	predose	X

Cycle	Day	Time[a]	PK
≥ 3	1	predose	X
		0.5 h (EOI) ± 5 min[b]	X
	8	predose	X
EOT Visit	NA	NA	X
Follow-up 30 day	NA	NA	X

[a]All time points except predose are after the start of E-602 infusion. Predose should be collected prior to the start of any study treatment.
[b]The 0.5 h sample collection is ± 5 mins from the end of E-602 infusion. In instances when the infusion time is >30 minutes, the ± 5 mins window still applies to the end of the infusion.
[c]In the event the E-602 infusion exceeds 2 hours, the 2 h timepoint will be permitted as a missed assessment.
[d]The 6 h sample is only required for Phase 1 E-602 monotherapy cohorts.
[e]Cycle 1 Day 3 and Cycle 2 Day 10 sample collection is not required for Phase 2.

8.5. Biomarkers

The samples collected for pharmacodynamic, genetic and biomarker research, and any additional samples derived from the original samples, may be analyzed and stored for up to 15 years after the study ends and the final results are reported. These samples may be used for scientific research to support this study protocol, to design or improve methods for analyzing, comparing or combining study data. The Sponsor and its authorized representatives will ensure that samples are destroyed at the end of the storage period.

8.5.1. Pharmacodynamics

Whole blood and serum samples will be collected according to SoA. The time points for sample collection are listed in Table 4 and

Table 5. In addition, results for baseline biomarkers of disease will be performed locally up to 72 hours prior to Day 1 as follows: 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.

The exploratory biomarker investigations include but are not limited to:

- Immune cell desialylation using FACS
- Immune cell content and activation status by FACS
- Pro-inflammatory cytokine and chemokine levels, including but not limited to: IL-2, IL-6, TNFα, IFN-γ, IL-8, IP-10, monocyte chemoattractant proteins (MCP)
- Complement C3a
- Changes in the glycoproteomic profile

These samples may also be used for other biomarker research to further elucidate E-602 mechanism of action, identify potential resistance mechanisms, understand variability in response and/or adverse events, identify other biomarkers of response, and to better understand the disease understudy. Analyses may include, but are not limited to protein, metabolite and antibody profiling methodologies.

Additional exploratory biomarkers related to tumor and immune biology may be analyzed, using methods such as gene expression profiling, mutational, protein and tissue image analysis.

Details of sample collection, storage, and shipping instructions will be provided in the Laboratory Manual.

Table 4 Phase 1 E-602 monotherapy biomarker sample collection time points for pharmacodynamic, genetic and immunogenicity analyses

Cycle	Day	Time[a]	Cytokine Panels and C3a	FACS (desialylation and activation)	RNASeq (blood)	Circulating Tumor DNA	Tumor Biopsy	ADA	Glycoproteomic Profile
Screening							X		
1	1	predose	X[b]	X[b]	X[b]	X[b]		X	X
	2	24 h ± 2 h	X	X	X				X
	3	48 h ± 4 h	X	X	X				X
	8	predose	X	X	X				X
	9	24 h ± 2 h	X	X	X				X
	10	48 h ± 4 h	X	X	X				X
	15	predose	X	X	X				X
2	1 (Day 22)	predose					X	X	
≥ 3	1	predose				X[c]		X	
EOT	NA	NA						X	
Follow-up 30 day	NA	NA						X	

[a]All time points except predose are after the start of infusion.
[b]Two predose samples should be collected at least 1 hour apart and up to 72 hours prior to Cycle 1 Day 1.
[c]Circulating tumor DNA samples will be collected with radiological assessments.

Table 5 Phase 1 combination and Phase 2 biomarker sample collection time points for pharmacodynamic, genetic and immunogenicity analyses

Cycle	Day	Time[a]	Cytokine Panels and C3a	FACS (desialylation and activation)	SNPs	Circulating Tumor DNA	Tumor Biopsy	ADA	Glycoproteomic Profile
Screening							X[d]		
1	1	predose	X[b]	X[b]	X	X[b]		X	X
	2	24 h ± 2 h	X	X					X
	8	predose	X	X					X
	9	24 h ± 2 h	X	X					X
	15	predose	X	X					X

Cycle	Day	Time[a]	Cytokine Panels and C3a	FACS (desialylation and activation)	SNPs	Circulating Tumor DNA	Tumor Biopsy	ADA	Glycoproteomic Profile
2	1 (Day 22)	predose					X[d]	X	
	8	predose	X	X			X[d]	X	X
	9	24 h ± 2 h	X	X					X
	15	predose	X	X					X
≥ 3	1	predose				X[c]		X	
EOT	NA	NA				X		X	
Follow-up 30 day	NA	NA						X	

[a]All time points except predose are after the start of any study treatment infusion. Predose should be collected prior to the start of any study treatment.
[b]Two predose samples (prior to start of any study treatment administration) should be collected at least 1 hour apart and up to 72 hours prior to Cycle 1 Day 1.
[c]Circulating tumor DNA samples will be collected with radiological assessments and at EOT visit.
[d]Fresh tumor biopsy is required for all subjects in Phase 1 combination at screening and on Cycle 2 Day 1 post-dose (+4 days). Fresh tumor biopsy is required for all subjects in Phase 2 at screening and post dose on Cycle 2 Day 1 or Day 8. The biopsy should be performed on Day 2 or 3 if performed post Cycle 2 Day 1 E-602 administration or Day 9 or 10 if performed post Cycle 2 Day 8 E-602 administration. An archive tissue sample is required for all subjects.

8.5.2. Genetics

Blood samples in the Phase 1 E-602 monotherapy portion of the study will be collected to analyze circulating tumor DNA for target gene expression and immune cell gene expression profiling (RNAseq) at timepoints specified in the SoA and in Table 4.

Table 5 summarizes the blood sample collection in Phase 1 combination and Phase 2 including collection of samples for circulating tumor DNA assessment and a whole blood single nucleotide polymorphism (SNP) sample for DNA sequencing.

The SNP sample will be used to assess genetic variation or single nucleotide polymorphisms in select genes, including and not limited to genes involved in the metabolism and catabolism of sialoglycans and glycoproteins (i.e., glycogenes) or other genes that may predispose subjects to E-602 benefit or adverse events. Additional uses of the DNA sequencing data from the whole blood SNP sample may include correlations with clinically-relevant biomarkers identified by other methodologies described in this section to identify genotypic associations, as well as for comparison to tumor mutation data to identify genetic variants specific to the tumor.

These blood samples may also be used for other pharmacogenomic/biomarker research to further elucidate E-602 mechanism of action, identify potential resistance mechanisms, understand variability in response and/or adverse events, identify other biomarkers of response, and to better understand the disease under study.

Tissue samples (Section 8.5.3) may also be analyzed for immune cell gene expression profiling (RNAseq) and tumor mutational burden.

8.5.3. Tumor Biopsy

For subjects in Phase 1 monotherapy, tumor biopsy at screening and Cycle 2 Day 1 are optional. For subjects treated in Phase 1 combination and Phase 2, a tumor biopsy at screening and in Cycle 2 as indicated in Table 5 are required. If the investigator considers that performing a tumor biopsy at Cycle 2 puts a subject at undue safety risk and the subject is otherwise eligible to continue study participation, the subject may be allowed to continue the study. Additionally for Phase 2, the Sponsor may elect to permit subjects on study who do not have lesions amenable to biopsy in the investigator's judgement but would otherwise be eligible for the study following discussion with the investigator. The reason for not performing a required biopsy will be documented in the CRF.

An archival tumor tissue sample is required for all subjects. A fresh tumor biopsy is permissible at screening if tumor tissue from a subject's previous biopsy cannot be obtained.

Table 6 Collection time point requirements for tumor biopsy

	Phase 1 monotherapy	Phase 1 combination	Phase 2
Archival Biopsy Sample	X	X	X
Screening	Optional	X	X
Cycle 2	Optional: Cycle 2 Day 1 post-dose + 4 days	Cycle 2 Day 1 post-dose + 4 days	Cycle 2 Day 1 or Day 8 post dose[a]

[a]The biopsy should be performed on Day 2 or 3 if performed post Cycle 2 Day 1 E-602 administration or Day 9 or 10 if performed post Cycle 2 Day 8 E-602 administration.

During screening and during Cycle 2 as indicated in Table 6, subjects who undergo a tumor biopsy will have a sample collected and preserved in a representative formalin-fixed paraffin-embedded (FFPE) block (preferred) or at least 20 unstained, freshly cut, serial sections (on slides) from an FFPE tumor specimen will be collected. The specimen should be accompanied by the associated pathology report. The following specimen types are acceptable: resections, core needle biopsies, excisional, incisional, or forceps biopsies. For core needle biopsy specimens, preferably, at least 3 cores embedded in a single paraffin block should be submitted for evaluation. Fine needle aspirate is not an acceptable tissue collection method.

Tumor cells will be analyzed for immune modulation of different immune cell subtypes, including T cells, macrophages, dendritic cells, and neutrophils. The following analyses may include but is not limited to:

- Tumor desialylation by immunohistochemistry (IHC)
- Tumor IHC analysis for immune markers (PD-L1) and modulation of different immune cell subtypes (T cells, macrophages, DC, neutrophils)

These samples may also be used for other biomarker research to further elucidate E-602 mechanism of action, identify potential resistance mechanisms, understand variability in response and/or adverse events, identify other biomarkers of response, and to better understand the disease

under study. Additional exploratory biomarkers related to tumor and immune biology may be analyzed, using methods such as gene expression profiling, mutational, protein and tissue image analysis.

8.6. Immunogenicity Assessments

Antibodies to E-602 will be evaluated in plasma samples collected from all subjects according to the SoA. These samples will be collected pre-dose at the designated visits, including a pre-dose sample before the initial dose on Cycle 1 Day 1.

The detection and characterization of the ADAs will be performed using a validated assay method.

9. Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Analysis Sets

DLT Evaluable Set:

Will include 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.

Safety Analysis Set:

Will include all subjects who have received any dose of study treatment. The Safety Analysis Set will be used for safety analyses. Safety Analysis Set may be further defined by the phase of the study, dose, and tumor type.

Efficacy Evaluable Set:

Will include all subjects who receive any dose of study treatment, meet eligibility criteria, have measurable tumor lesions at baseline, and have at least one post-baseline disease assessment per RECIST v1.1. Efficacy Evaluable Set is defined for each cohort in the Phase 2 separately.

Pharmacokinetics (PK) Analysis Set:

Will include all subjects in the Safety Analysis Set for whom adequate data on E-602 plasma concentration are available.

9.2. Statistical Analyses

9.2.1. General Considerations

The statistical analyses will generally be descriptive in nature. Data collected will be presented using summary tables, data listings, and figures. For continuous variables, descriptive summaries will include the mean, median, standard deviation, the first and third quartiles, minimum, and maximum. For categorical variables, the number and percentage of subjects in each category will be presented.

9.2.2. Subject Disposition

The number and percent of subjects who have consented, treated, discontinued (including reasons for discontinuation), and completed the study will be summarized. The number of subjects for each analysis set will be tabulated.

9.2.3. Baseline Characteristics

Descriptive summary statistics will be provided for demographic variables (age at consent, sex at birth, race, ethnicity) and baseline disease characteristics (e.g., ECOG performance status). Relevant medical history and prior anti-cancer therapies/medications will also be summarized.

9.2.4. Safety Analyses

9.2.4.1. Treatment Exposure

Duration of treatment, cumulative dose administered, relative dose intensity, frequency of dose adjustment, and treatment discontinuation will be summarized. For the combination therapy cohorts, E-602 and cemiplimab doses will be summarized separately.

9.2.4.2. Treatment Emergent Adverse Events

All adverse events will be coded to a system organ class and a preferred term based on the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later.

Treatment-emergent adverse events (TEAEs) are defined as AEs with an onset date on or after the date of first dose of study treatment until 90 days after the last dose.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuation of treatment, and fatal adverse events will be tabulated by system organ class and preferred term.

The number and percent of subjects reporting TEAEs will be evaluated overall and by dose level and will also be tabulated by severity and relationship to study treatment. The severity of each adverse event will be graded using The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or later criteria.

For the Phase 1 component of the study, DLTs (if any) will be summarized by dose and will be listed separately.

9.2.4.3. Laboratory Values

Descriptive statistics for laboratory test values and changes from baseline at each visit will be tabulated and, in some cases, presented graphically. Additional analyses based on shift from baseline in test values in multiples of the lower/upper limit of normal range (LLN/ULN) of a parameter will be detailed in the statistical analysis plan.

9.2.4.4. Vital signs

Vital sign parameters (blood pressure, pulse, and body temperature), oxygen saturation, and weight observed at each visit will be summarized along with the change values from baseline. Clinically important physical exam findings will be listed and summarized.

9.2.5. Efficacy analysis

The primary analysis for efficacy will be based on the cohort-specific efficacy evaluable analysis set. Sensitivity analysis may include pooling additional subjects treated in Phase 1 at the same dose level in the same tumor type.

For objective response rate (ORR), the Clopper-Pearson 80% and 95% confidence intervals (CIs) will be provided. Confidence intervals adjusting for the 2-stage nature of the design may also be provided.

Duration of response (DoR) will be calculated among responders (CR and PR). The Kaplan-Meier method will be used to estimate median DoR and the confidence intervals. Subjects who continue to respond at the time of the analysis will be censored at the last assessment of response.

Progression-free survival (PFS) is measured from the date of first study treatment dose until the first date when progressive disease (PD) is objectively documented or death from any cause. Subjects without PD or death will be censored at the last available tumor assessment. PFS will be summarized using the Kaplan-Meier method.

Overall survival (OS) is measured from the date of first study treatment dose until death. Subjects who are alive will be censored at the last known alive date. OS will be summarized using the Kaplan-Meier method.

9.2.6. Pharmacokinetics and Immunogenicity

Pharmacokinetics

Individual and mean plasma E-602 concentration versus time data will be tabulated, summarized, and plotted by dose level. Noncompartmental PK parameters of E-602 including but not limited to AUC, C_{max}, and C_{trough}, will be tabulated and summarized (e.g., mean, standard deviation, and coefficient of variation). Inter-subject variability and drug accumulation may be evaluated.

Immunogenicity

The number and percentage of subjects who develop detectable ADA will be summarized by dose level. The impact of ADA on PK may be analyzed as appropriate.

9.2.7. Exploratory Analysis: Pharmacodynamics

Serum immune cell desialylation and ctDNA levels will be monitored for potential changes due to the various therapies tested in this study.

9.2.8. Covariates and Subgroup analysis

Additional safety and efficacy subgroup analyses may be performed based on, but not limited to, the following covariates:

- Age or age categories
- Gender (sex at birth)
- Prior anti-cancer treatment
- Baseline PD-L1 expression levels

9.3. Interim Analysis

During the phase 2 portion of the study, the safety data review committee will review both safety and efficacy data. Efficacy data at the end of Stage 1 of the Phase 2 portion will be used to determine Stage 2 expansion. Any additional interim analyses not built in as a part of the study design will be documented.

9.4. Sample Size Determination

Phase 1 Dose Escalation:

Dose escalation for all cohorts will utilize a modified 3+3 design.

A total of 5 dose escalation cohorts are planned for E-602 monotherapy for a total of up to 30 subjects.

A total of up to 2 dose cohorts are planned for the E-602 and cemiplimab combination therapy for a total of up to 12 subjects.

Phase 1 Backfill:

Any Phase 1 cohort may be backfilled up to a total of 15 subjects in a dose cohort (dose escalation and backfill) to obtain additional safety, PK and pharmacodynamic data at a particular dose level.

Phase 2:

For each cohort in Phase 2, Simon's minimax 2-stage design will be used. Sixteen subjects will be treated in the first stage. If ≥2 of 16 subjects respond, Stage 2 will be opened to treat 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%.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information by completing a financial disclosure form as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the subject and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB or study center.

The medical record must include a statement that written informed consent was obtained before the subject underwent any study required procedures beyond standard of care and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject.

Subjects can be rescreened if they are within the protocol-specified screening window and do not need to re-consent. If the subject falls outside of the protocol-specified screening window, the subject must re-sign the ICF and receive a new subject number.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4. Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

A Safety Data Review Committee (SDRC) will be formed to oversee the study conduct and safety of subjects, including dose-escalation recommendations. The committee will consist of the principal investigators and members of the Sponsor.

Details of committee structure and meetings will be described in the committee charter.

10.1.6. Dissemination of Clinical Study Data

The study protocol and results will be reported in compliance with US FDA regulations.

10.1.7. Data Quality Assurance

All subject data relating to the study will be recorded on electronic CRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

Guidance on completion of CRFs will be provided.

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the monitoring plan.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of subjects and the site has all required documents in place prior to screening potential subjects.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further development of E-602

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator
- Total number of subjects included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to discuss publication opportunities with the Sponsor for approval in advance. All agreed upon manuscripts or abstracts will be reviewed and approved by the Sponsor before submission.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 7 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as deemed necessary by the investigator or required by local regulations.

Table 7 Protocol-required safety laboratory tests

Laboratory Tests	Parameters			
Hematology	hemoglobin hematocrit platelet count (absolute)	RBC indices: mean corpuscular volume (MCV)	White blood cell (WBC) count with differential (absolute): neutrophils lymphocytes monocytes eosinophils basophils	
Chemistry	Blood urea nitrogen (BUN) creatinine uric acid[a] lactate dehydrogenase (LDH)[b] Glucose	chloride sodium potassium bicarbonate calcium[c] magnesium[c] phosphorus[c]	aspartate aminotransferase (AST) alanine aminotransferase (ALT) total bilirubin alkaline phosphatase (ALP)	albumin[c] lipase[c] amylase[c]
Routine urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen (if available), nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential), choice of test at the investigator's discretion			
Thyroid Panel	Thyroid stimulating hormone (TSH), Triiodothyronine (T3) or Free Triiodothyronine (FT3), and Free thyroxine (FT4)			

Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Coagulation: prothrombin time (PT), activated partial thromboplastin (aPTT), International Normalized Ratio (INR)

[a]Test should be performed at screening only.
[b]Test should be performed at screening and each restaging visit (Cycle 4 Day 1, Cycle 7 Day 1, etc.).
[c]Test should be performed at screening and Day 1 of each cycle.

Safety laboratory tests including pregnancy test for Cycle 1 Day 1 may be collected up to 72 hours prior to Day 1 to ensure results are available for review prior to dosing on Day 1. For all other dosing days, serum electrolytes, ALT/AST and hematology test results need to be reviewed prior to dosing.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study treatment(s), whether or not considered related to the study treatment(s). • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment(s). • Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.
Definition of Unsolicited and Solicited AE
• An unsolicited adverse event is an adverse event that was not solicited and that is communicated by a subject who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The subject will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the subject's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the subject will be collected during an interview with the subjects and by review of available medical records at the next visit. • Solicited AEs are predefined local (at the injection site) and systemic events for which the subject is specifically questioned.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition

- New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of dependency or abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor or its designee in lieu of completion of the SAE required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsors or its designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor or its designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study using the NCI CTCAE version 5.0.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment(s) and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship (not related, unlikely related, possibly related, probably related or definitely related).
- Relationship to E-602 and to cemiplimab will be determined separately.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor or its designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or its designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or its designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor or its designee with a copy of any postmortem findings including histopathology, if available.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to Sponsor or its designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to the Sponsor or Designee via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor or its designee will be entry into the EDC system.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the EDC system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor or SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the Investigator Site File.

SAE Reporting to the Sponsor or Designee via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the backup method to transmit this information to the medical monitor or SAE coordinator if the EDC system is unavailable.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the Investigator Site File.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

- Following menarche
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required. If the subject cannot meet these criteria as written, the subject will be considered to be WOCBP and pregnancy testing is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment(s), additional evaluation should be considered.

10.4.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a to medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male subject can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] –oral –intravaginal –transdermal –injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] –oral –injectable
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment(s). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

10.5. Appendix 5: Infusion Reaction Assessments and Management

NCI CTCAE version 5.0 Grading Criteria for Infusion Reactions

Infusion related reactions will be considered the adverse event and graded following the below CTCAE criteria.

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

Source: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

Clinical Management Guidelines for Infusion Reactions

Unscheduled plasma PK, ADA and cytokine panel samples should be collected in the event of an infusion related reaction.

Infusion Reactions	Immediate Clinical Management
Mild (Grade 1) *Mild-transient reaction; infusion interruption is not indicated; intervention is not indicated.* ***Any of the following symptoms may be observed:** • Mild chills • Mild flushing • Pruritus • Transient rash (covering less than 10% BSA with or without symptoms) • Dizziness (not interfering with activity) • Mild allergic rhinitis	• Assess and monitor subject closely. • Ensure equipment and medication are readily available should thereaction progress. • Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. • Remain with subject until symptoms have resolved. **If symptoms progress to Grade 2, proceed as described below.**
Moderate (Grade 2) *Therapy or infusion interruption is indicated but subject responds promptly to treatment (such as NSAIDs, antihistamines, narcotics, IV fluids);*	Apply Grade 1 clinical management and: • Stop infusion. • Consider giving diphenhydramine 50 mg IV and/or hydrocortisone sodium succinate 100 mg IV.

Infusion Reactions	Immediate Clinical Management
medications are indicated for less than or equal to 24 hours. ***Any of the following symptoms may be observed:** • Moderate flushing • Pruritus • Mild to moderate chest discomfort • Mild to moderate back pain • Mild to moderate nausea, vomiting, and/or diarrhea • Transient rash (covering 10 to 30% BSA with or without symptoms) • Dizziness (moderate unsteadiness or sensation of movement) • Moderate dyspnea • Urticaria (lesions covering 10 to 30% BSA) • Moderate allergic rhinitis • Fever 39 to 40°C • Mild to moderate abdominal discomfort • Mild hypotension (less than or equal to 20 mmHg drop from baseline) • Rigors	• If symptoms resolve within 1 hour of stopping drug infusion, may resume infusion at the following rates at the investigator's discretion: o 25% of the rate at time of reaction for 5 minutes o 50% of the rate at time of reaction for 5 minutes o 75% of the rate at time of reaction for 5 minutes o 100% of the rate at time of reaction o Slowed infusion rates and durations beyond those above are permitted at the discretion of the investigator o Otherwise, dosing will be held until symptoms resolve and corticosteroids, dose at the discretion of the investigator, should be added to the premedication regimen for the next scheduled dose and at subsequent E-602 doses. **Participants who develop recurrent Grade 2 toxicity despite adequate premedication should be evaluated for individual risk/benefit prior to further study treatment.** A one week study drug delay may be considered.
Severe (Grade 3) *Prolonged (i.e., not rapidly responsive to symptomatic medication and/or a brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization is indicated for clinical sequelae.* ***Any of the following symptoms may be observed:** • Fever greater than 40°C • Hypoxia: decreased oxygen saturation at rest (e.g., pulse oximeter less than 88%) • Severe rash (covering greater than 30% BSA with or without associated symptoms) • Symptomatic bronchospasm with or without urticaria • One or more symptoms of respiratory distress requiring treatment (e.g., repetitive cough, wheeze, throat tightness/change in voice) • Generalized urticaria (covering greater than 30% BSA) • Dizziness: severe unsteadiness or sensation of	Apply Grade 1 clinical management and: • Stop infusion and do not restart. • Consider giving diphenhydramine 50 mg IV and/or hydrocortisone sodium succinate 100 mg IV. • Consider giving normal saline if needed for hypotension. • Consider giving epinephrine 0.5 mg* intramuscularly STAT. Consider repeating epinephrine at 5-minute intervals twice more as needed (i.e., if breathing becomes more labored or level of consciousness decreases). • Consider giving oxygen if needed for dyspnea. • Consider giving bronchodilators if indicated. • Initiate Emergency Response Call as appropriate if subject condition warrants. • Hospitalization may be considered as indicated for clinical sequalae. • If isolated Grade 3, attempt to retreat on another occasion after premedication including corticosteroids using a slower infusion rate as

Infusion Reactions	Immediate Clinical Management
movement • Edema/angioedema • Uncontrolled hypotension (more than 20 mmHg drop from baseline) requiring therapy • Severe nausea, vomiting, and/or diarrhea **Severe (Grade 4)** *Life-threatening consequences: urgent intervention indicated* ***Any of the following symptoms may be observed:** • Cyanosis • Life-threatening hypoxia or airway compromise • Severe angioedema (periorbital/facial) • Altered level of consciousness	indicated for Grade 2. • If Grade 4 or recurrent Grade 3, permanently discontinue study treatment. *Note: epinephrine 1:1,000 = 1 mg/mL and epinephrine 1:10,000 = 1 mg/10 mL

*Symptoms noted are intended as potential examples at each grade. Severity grading of the infusion related reaction will be based on the investigator's judgement per CTCAE v5.0.

10.6. Appendix 6: Abbreviations

ADA	antidrug antibody
ADCC	antibody-dependent cellular toxicity
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BOR	best overall response
BUN	blood urea nitrogen
CDK	cyclin-dependent kinase
CEA	carcinoembryonic antigen
CHF	congestive heart failure
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum concentration
CNS	central nervous system
CPS	combined positive score
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DC	dendritic cell
dMMR	mismatch repair deficient tumors
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DRESS	drug rash with eosinophilia and systemic symptoms
EC_{20}	20% effective concentration
EC_{50}	50% effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGJ	esophagogastric junction
EOI	end of infusion
EOT	end of treatment
FACS	fluorescence-activated cell sorting
FFPE	formalin-fixed paraffin-embedded
FIH	first in human
FGFR	fibroblast growth factor receptor
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hCG	human chorionic gonadotropin
HER-2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR^+	hormone receptor positive

HRD	homologous repair deficiency
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
INR	International Normalized Ratio
IRB	institutional review board
iRECIST	Immunotherapy Response Evaluation Criteria in Solid Tumors
IV	intravenous
LDH	lactate dehydrogenase
MCP	monocyte chemoattractant proteins
MCV	mean corpuscular volume
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHP	nonhuman primate
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PARP	polyadenosine diphosphate ribose polymerase
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SJS	Stevens-Johnson syndrome
SNP	single nucleotide polymorphism
SoA	Schedule of Activities
$T_{1/2}$	half-life
T3	triiodothyronine
TEN	toxic epidermal necrosis
TNBC	triple-negative breast cancer

TNF	tumor necrosis factor
TRK	tropomyosin receptor kinase
TSH	thyroid stimulating hormone
ULN	upper limit of normal
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WOCBP	Woman of Childbearing Potential

11. References

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