A Phase 1 Dose Escalation and Expansion Study of EO-3021, an Anti-claudin 18.2 (CLDN18.2) Antibody Drug Conjugate, in Patients with Solid Tumors Likely to Express CLDN18.2

Elevation Oncology, Inc.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
ADC	Antibody drug conjugate
AE	Adverse event
AESI	Adverse event of special interest
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration time curve
AUC_{INF}	Area under the curve from time zero extrapolated to infinity
BCVA	Best-corrected visual acuity
BOIN	Bayesian optimal interval
BOR	Best overall response
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CAR-T	Chimeric antigen receptor T-cell
CBC	Complete blood count
CFR	Code of Federal Regulations
C1D1	Cycle 1 Day 1
C2D1	Cycle 2 Day 1
CI	Confidence interval
CL	Clearance
CLDN	Claudin
C_{max}	Maximum observed concentration
CMP	Comprehensive metabolic profile
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRO	Clinical research organization
CSF	Cerebrospinal fluid
CSPC	CSPC Megalith Biopharmaceutical Co., Ltd.
CT	Computerized tomography
CTCAE	Common terminology criteria for adverse events
DCR	Disease control rate
DLT	Dose-limiting toxicity
dMMR	mismatch repair deficient
DOR	Duration of response
DRESS	Drug reaction with eosinophilia and systemic symptoms
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
EOX	Epirubicin, oxaliplatin, and capecitabine
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GCP	Good clinical practice
GEJ	Gastro-esophageal junction
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HED	Human equivalent dose
HEENT	Head, eyes, ears, nose, and throat
HER2	Receptor tyrosine-protein kinase erbB-2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
ICI	Immune checkpoint inhibitor
ICMJE	International Committee of Medical Journal Editors
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
ILD	Interstitial lung disease
imAE	Immune-mediated AEs
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
ISF	Investigator study file
IV	Intravenous
LFT	Liver function test
LMWH	Low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl auristatin E
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MSI-H	Microsatellite instability-high
MTD	Maximum tolerated dose
nAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
NE	Not evaluable
NOAEL	No observed adverse effect level
OCT	Optimal coherence tomography
ORR	Objective response rate
OS	Overall survival

Abbreviation	Definition
PD	Progressive disease
PD-1	Programmed death receptor-1
PD-L1	Programmed death receptor ligand-1
PE	Pulmonary embolism
PIS	Patient information sheet
PFS	Progression-free survival
PHI	Protected health information
PK	Pharmacokinetic
PO	Orally
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
Q3W	Once every 3 weeks
Q4W	Once every 4 weeks
QTcF	QT interval corrected for heart rate by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SJS	Stevens-Johnson syndrome
SOC	System organ class
SpO_2	Oxygen saturation
SRC	Safety Review Committee
STD	Severely toxic dose
$t_{½}$	Half-life
TEAE	Treatment emergent adverse event
TEN	Toxic epidermal necrolysis
T_{max}	Time of maximum concentration
TNF	Tumor necrosis factor
TRAE	Treatment-related adverse events
UA	Urinalysis
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
WBC	White blood count

PROTOCOL SIGNATURE PAGE

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this study as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I will identify study personnel conducting study specific procedures and appropriately document their training and/or delegated responsibilities. I understand that the study may be terminated, or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the patients in the study.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

_____ _____

Signature of Investigator Date

_____

Print Name of Investigator

_____ _____

Signature of Sponsor Date

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SYNOPSIS

Sponsor:	Elevation Oncology, Inc. 101 Federal Street, Suite 1900 Boston, MA 02110
Protocol Title:	A Phase 1 Dose Escalation and Expansion Study of EO-3021, an Anti-claudin 18.2 (CLDN18.2) Antibody Drug Conjugate, in Patients with Solid Tumors Likely to Express CLDN18.2
Protocol Number:	ELVCAP-002-01
Phase of Development:	1
Study Locations:	Multicenter, International
Number of Sites:	Approximately 10 to 40 institutions will be recruited for participation in this study.
Patient Population:	Part A (Dose Escalation) enrolls patients with gastric/gastro-esophageal junction (GEJ) adenocarcinoma that are refractory to or intolerant of standard treatment, or for which no standard treatment is available). Part B (Expansion) enrolls patients with gastric/GEJ adenocarcinoma.
Estimated Number of Patients:	Approximately 70 patients are planned to be enrolled in Part A (Dose Escalation). The actual number enrolled will depend on overall safety and tolerability. Approximately 120 patients with gastric/GEJ adenocarcinoma are planned to be enrolled in Part B (Expansion).
Primary Objective:	To determine the recommended phase 2 dose(s) (RP2D) for the single-agent EO-3021, and when in combination with either ramucirumab or dostarlimab, for further exploration in patients with advanced/metastatic gastric/GEJ adenocarcinoma or advanced solid tumors that are likely to express CLDN18.2.
Secondary Objectives:	• To document the overall safety profile for EO-3021 when administered as a single agent, and when in combination with either ramucirumab or dostarlimab • To evaluate the pharmacokinetic (PK) profile of EO-3021 as a single agent, and when in combination with either ramucirumab or dostarlimab • To assess the immunogenicity of EO-3021 as a single agent, and when in combination with either ramucirumab or dostarlimab • To document any early indication of clinical efficacy in patients with advanced/metastatic gastric/GEJ adenocarcinoma or advanced solid tumors that are likely to express CLDN18.2 as a single agent, and when in combination with either ramucirumab or dostarlimab
Exploratory Objectives:	• To evaluate the association of anti-tumor activity of EO-3021 with CLDN18.2 expression by immunohistochemistry (IHC) (at various biomarker cut-offs) in advanced/metastatic gastric/GEJ

	adenocarcinoma or advanced solid tumors that are likely to express CLDN18.2 as a single agent, and when in combination with either ramucirumab or dostarlimab • To evaluate if mechanistically-linked biomarkers correlate with clinical outcomes as a single agent, and when in combination with either ramucirumab or dostarlimab
Study Design:	This is a Phase 1 multicenter, open-label, dose escalation and expansion study conducted in patients with advanced unresectable or metastatic solid tumors that are likely to express CLDN18.2. With the release of a Protocol Administrative Letter dated 09April2024, only patients with gastric/GEJ adenocarcinoma will be enrolled in this study. Patients with other solid tumors likely to express CLDN18.2 will be excluded from trial participation. The study consists of 2 parts: Part A (Dose Escalation) and Part B (Expansion). Approximately 70 patients may be treated in Part A (Dose Escalation). Part A (Dose Escalation) consists of 3 arms: • Arm A1 (monotherapy): EO-3021 as a single agent in patients with gastric/GEJ adenocarcinoma that are refractory to or intolerant of standard treatment, or for which no standard treatment is available. Dose escalation will start with EO-3021 at 1.0 mg/kg following the Bayesian Optimal interval (BOIN) design with a target dose-limiting toxicity (DLT) rate of 25% for the maximum tolerated dose (MTD) (Yuan et al., 2016; Zhou et al., 2018). Dose escalation will proceed according to Figure 1 and Figure 2. Monotherapy dose escalation has completed at the time of this protocol amendment. • Arm A2 (combination with ramucirumab): EO-3021 in combination with ramucirumab in patients with gastric/GEJ adenocarcinoma that are refractory to or intolerant of standard treatment, or for which no standard treatment is available. Combination dose escalation will start with EO-3021 at 2.0 mg/kg intravenously (IV) once every 3 weeks (Q3W) following a standard 3+3 design and proceed according to Figure 3. Ramucirumab will be administered at 10 mg/kg IV Q3W after EO-3021. The dose of Ramucirumab will be held constant while the dose of EO 3021 is escalated according to Figure 3 until RP2D/MTD is reached. • Arm A3 (combination with dostarlimab): EO-3021 in combination with the anti-PD1 inhibitor dostarlimab in patients with gastric/GEJ adenocarcinoma that are refractory to or intolerant of standard treatment, or for which no standard treatment is available. Dose escalation will start with EO-3021 at 2.0 mg/kg IV Q3W following a standard 3+3 design and proceed according to Figure 4. Dostarlimab will be administered at 500 mg IV Q3W after EO-3021. The dose of dostarlimab will be held constant while the dose of EO-3021 is escalated according to Figure 4 until RP2D/MTD is reached.

	Dose escalation rules of each arm are outlined in Table 2 and discussed in Section 6.3. In all 3 arms, dose escalation follows the prespecified dose increments. Intermediate dose levels of EO-3021 as well as doses higher or lower than those described in Section 6.3 and/or alternative dosing frequencies (e.g., once every 4 weeks [Q4W]) may be explored, if warranted, based on overall safety, tolerability, and/or PK data if available and agreed upon by the SRC and Sponsor. At the discretion of the SRC and Sponsor, additional backfill patients may be included to further characterize the MTD/RP2D. Upon identifying the RP2D and/or MTD, Part B (Expansion) will commence in patients with gastric/GEJ adenocarcinoma. Part B (Expansion) aims to confirm the RP2D and to assess early signals of efficacy. A total of approximately 120 patients could be enrolled in Part B (Expansion). The Dose Expansion cohort consists of 3 arms: • Arm B1 (monotherapy): EO-3021 as a single agent in patients with gastric/GEJ adenocarcinoma who have received at least 1 but no more than 3 prior lines of therapy in the advanced metastatic setting. Patients will be randomized to 2.0 mg/kg or 2.5 mg/kg in a 1:1 fashion in monotherapy expansion. Prospective CLDN18.2 selection will be implemented during enrollment of the monotherapy expansion. • Arm B2 (combination with ramucirumab): EO-3021 in combination with ramucirumab in patients with locally advanced or metastatic gastric/GEJ adenocarcinoma who previously were treated with only 1 prior line of therapy in the metastatic setting. Prior fluoropyrimidine and platinum-containing chemotherapy is required. The dose of EO-3021 will be the RP2D/MTD determined in the combination dose escalation Arm A2. Ramucirumab will be administered at 10 mg/kg IV Q3W after EO-3021. Prospective CLDN18.2 selection will be implemented during enrollment of the combination expansion. • Arm B3 (combination with dostarlimab): EO-3021 in combination with dostarlimab in patients with locally advanced or metastatic gastric/GEJ adenocarcinoma who have not received any prior systemic therapy in the advanced metastatic setting. The dose of EO-3021 will be the RP2D/MTD determined in the combination dose escalation Arm A3. Dostarlimab will be administered at 500 mg IV Q3W after EO-3021. Prospective CLDN18.2 selection will be implemented during enrollment of the combination expansion. Prior to any study-specific activities, all patients or legal representatives must sign an informed consent form (ICF). Patients meeting the eligibility criteria are enrolled and treated at the dose level specified by the dose escalation scheme. Patients receive study treatment until disease

	progression, unacceptable toxicity, or one or more protocol-specific treatment discontinuation criteria are met as described in Section 6.8.1. Logistically, the study is divided into observational windows of 21 days for data collection purposes; each 21-day period is considered a cycle of treatment. Patients will be treated on an outpatient basis and closely monitored for safety, being seen at the clinic on a weekly basis in the first cycle and then every 3 weeks when the patients receive dosing throughout therapy. Once off study treatment, survival data is collected via written communication (e.g., email, electronic medical record), telephone call, or clinic visits every 3 months (±28 days) from the date of last treatment until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor.
Study Endpoints	*Safety endpoints*: Dose-limiting toxicities, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), vital signs, and laboratory data. *Efficacy endpoints*: Objective response rate (ORR; complete response [CR]+partial response [PR]), disease control rate (DCR; CR+PR+ stable disease [SD]), and time to event parameters (duration of response [DOR], progression-free survival [PFS] and overall survival [OS]). *PK and anti-drug antibody (ADA) endpoints*: Serum PK parameters (maximum observed concentration [C_{max}], area under the concentration time curve [AUC], and half-life [$t_{½}$]) and ADA levels (percentage of subjects developing detectable ADAs and percentage of neutralizing antibodies [nAbs]) at prespecified time points.
Inclusion Criteria:	To be eligible for participation in the study, patients must meet the following inclusion criteria: 1. Age ≥18 years 2. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 at screening 3. Histologically and/or cytologically confirmed diagnosis of advanced metastatic gastric/GEJ adenocarcinoma not amenable to resection or radiation therapy with curative intent 4. Availability of tumor tissue for evaluation of biomarker including: For Part A (Escalation) all arms: a. Archived formalin-fixed paraffin-embedded [FFPE] block or slides of tumor tissue from a previous biopsy obtained within last 24 months (Note: Only applicable to dose escalation and non-prospective selection portion of expansion arms), **AND** b. Fresh (new) biopsy prior to start of treatment, if medically feasible. Tumor biopsies should be considered by the treating physician in accordance with site standard procedures and obtained using a low-risk, medically routine procedure (Levit et al. 2019) (Note: Only applicable to dose

	escalation and non-prospective selection portion of expansion arms) i. *Note: Tumor biopsy obtained prior to consent but no more than 3 months prior to Cycle 1 Day 1 (C1D1) without any intervening treatment between the biopsy and C1D1 may be used to fulfill the fresh tumor tissue requirement with Sponsor approval* c. Patients who meet only one of the above tumor tissue requirements may still be eligible for the study after discussion and approval from the Sponsor For Part B (Expansion) all arms: d. For the prospective selection portion of the expansion arms, a FFPE block or a minimum of 6 unstained slides of tumor tissue from a biopsy obtained within 6 months of enrollment must be available to submit for central review. (Note: If the patient received any CLDN18.2 directed therapy after the date of the archival biopsy a new biopsy must be performed and a FFPE block or 6 unstained slides must be available for central review.) e. For the prospective selection portion of expansion arms, patients must have tumor CLDN18.2 expression of greater than or equal to 25% 1+/2+/3+ by central laboratory review. 5. Progressed on or after standard therapy, or are intolerant of available standard therapy, or there is no available standard therapy a. For Part A (Dose Escalation) with monotherapy EO-3021 (Arm A1) and in combination with ramucirumab (Arm A2) or dostarlimab (Arm A3), there is no limit on the number of prior lines of therapy b. For Part B (Expansion) for monotherapy EO-3021 (Arm B1), at least 1 but no more than 3 prior lines of therapy in the advanced/metastatic setting is allowed c. For Part B (Expansion) for combination of EO-3021 plus ramucirumab (Arm B2), only 1 prior line of therapy in the advanced/metastatic setting is allowed; prior fluoropyrimidine and platinum-containing chemotherapy is required d. For Part B (Expansion) for combination of EO-3021 plus dostarlimab (Arm B3), no prior systemic therapy in the advanced/metastatic setting is allowed 6. At least one measurable extra-cranial lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 a. For Part A (Dose Escalation), patients with evaluable but non-measurable disease per RECIST v1.1 may be eligible after discussion and approval from the Sponsor 7. Adequate organ function, defined as:

	a. ***Hematology:*** defined as absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelet ≥90 x 10^9/L, hemoglobin ≥9.0 g/dL (in the absence of transfusion within the last 7 days and use of growth factors within the last 14 days prior to C1D1) i. For Arms A2 and B2 (Combination of EO-3021 plus ramucirumab): platelet ≥100 x 10^9/L b. ***Renal function:*** defined as estimated glomerular filtration rate (eGFR) ≥40 mL/min (using the Cockcroft-Gault formula): Female creatinine clearance (CrCl) = ((140 - age in years) x weight in kg x 0.85) / (72 x serum creatinine in mg/dL) Male CrCl = ((140 - age in years) x weight in kg x 1.00) / (72 x serum creatinine in mg/dL) i. For Arms A2 and B2 (Combination of EO-3021 plus ramucirumab): 1. The patient has adequate renal function as defined by a serum creatinine ≤1.5 times the upper limit of normal (ULN), or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (that is, if serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed 2. The patient's urinary protein is ≤1+ on dipstick or routine urinalysis (UA); if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to allow participation in Arms A2 and B2) c. ***Hepatic Function***: i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN) for patients without liver metastases or ≤5 x ULN if liver metastases are present ii. Total bilirubin ≤1.5 x ULN for patients without liver metastases or ≤3 x ULN if liver metastases are present, or the patient has bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin d. ***Coagulation function:*** International Normalized Ratio (INR) ≤1.5; Activated Partial Thromboplastin Time (APTT) ≤1.5 × ULN (patients on chronic anticoagulants are eligible)

	i. Note: Patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin (LMWH). If receiving warfarin, the patient must have an INR ≤3.0. Patients should have no active bleeding (that is, no bleeding within 14 days prior to C1D1) or pathological condition present that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices). 8. Albumin level ≥3.0 g/dL 9. Life expectancy >12 weeks 10. Ability to understand the nature of this study, comply with protocol requirements, and give written informed consent 11. Willingness of men and women of reproductive potential to observe conventional and effective birth control for the duration of treatment and for 6 months following study completion (or longer as required by local regulations including 6 months plus 5 half-lives for female patients in South Korea and 3 months plus 5 half-lives for male patients in South Korea). Please refer to Appendix A for detailed criteria for men and women of reproductive potential.
Exclusion Criteria:	**Exclusion Criteria (All Parts and Treatment Arms, Unless Noted)** To be eligible for participation in the study, patients must **not** meet any of the following exclusion criteria: 1. Have non-adenocarcinoma histologic subtype of gastric/GEJ cancer (e.g., adenosquamous carcinoma, squamous carcinoma, etc.) 2. Have unresolved toxicities from prior anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, grade ≤1 or baseline. Patients with chronic grade 2 toxicities (except for Grade 2 peripheral neuropathy) may be eligible per the discretion of the Investigator after discussion and approval from the Sponsor 3. Have a history of several allergic and/or anaphylactic reactions to known chimeric, human, or humanized antibodies, fusion proteins or known allergies to components of EO-3021, ramucirumab, or dostarlimab 4. Have serious concurrent illness or clinically relevant active bacterial, fungal or viral infection including but not limited to the following: a. Active hepatitis B or C infection (whether on active antiviral therapy or not) i. For Arms A3 and B3 (Combination of EO-3021 plus dostarlimab), patients must have documented negative Hepatitis B surface antigen (HBsAg) and

	Hepatitis C antibody tests within 3 months prior to C1D1, see Section 4.2.3. b. Known human immunodeficiency virus (HIV) infection c. Other concurrent infectious disease requiring IV antibiotics within 2 weeks prior to C1D1 *Note: testing for HIV or hepatitis B or C is not required unless clinically indicated* 5. Have diagnosis of another malignancy, or history of systemic treatment for invasive cancer within last 3 years. *Note: Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. Diagnosis of non-melanoma skin cancer, carcinoma in situ of the cervix or breast, or noninvasive tumor does not affect eligibility* 6. Have active central nervous system (CNS) disease involvement, defined by cerebrospinal fluid (CSF) cytology, magnetic resonance imaging (MRI) or computerized tomography (CT) a. Patients with asymptomatic CNS metastases are eligible if they have been clinically stable for at least 4 weeks prior to C1D1 and do not require interventions such as surgery, radiation, or any corticosteroid therapy for management of symptoms related to CNS disease. b. Patients with history of brain metastasis previously treated with radiation and/or surgical resection and without evidence of progression at screening are eligible, including those on stable low-dose of steroids (i.e., 10 mg orally (PO) daily of prednisone or equivalent) c. Screening for CNS disease is not required. Patients with history of CNS disease should have head imaging within the last 3 months documenting no active CNS disease. Patients with signs/symptoms concerning for CNS involvement should undergo head imaging to rule out active CNS disease at screening. 7. Have history of non-infectious pneumonitis/interstitial lung disease 8. Have peripheral neuropathy Grade ≥2 9. Have active ocular surface disease defined as symptomatic or Grade ≥2 disease involving the cornea at baseline (based on screening ophthalmic examination) 10. Have history of Grade ≥2 gastritis 11. Are pregnant or breastfeeding 12. Have previously received anti-CLDN18.2 antibody drug conjugates (ADCs) or any ADC containing an auristatin payload 13. Have had major surgery (excluding tumor biopsy) within 28 days prior to C1D1 14. Have received systemic anticancer therapy including chemotherapy, radiotherapy, biological therapy, targeted therapy, immunotherapy and investigational therapies within 28 days or

	5 half-lives, whichever is shorter, before the first dose of EO-3021 and the combination with ramucirumab or dostarlimab a. Use of palliative radiotherapy for bone metastases or local radiotherapy for pain relief within 2 weeks before the first dose of EO-3021 and the combination with ramucirumab or dostarlimab is allowed b. Ongoing use of drugs for bone metastasis related events (e.g., zoledronic acid) will not affect eligibility 15. Have history of allogenic hematopoietic stem cell transplantation or solid organ transplantation 16. Use of any drugs or substances known to be strong inducers or inhibitors of CYP3A enzymes (Table 9) and/or P-glycoprotein within 7 days prior or 3 half-lives, whichever is shorter, before the first dose of EO-3021 and the combination with ramucirumab or dostarlimab 17. Have clinically significant cardiac disease, including but not limited to, any of the following within 6 months prior to C1D1: a. Myocardial infarction b. Unstable angina pectoris c. Cerebrovascular accident, transient ischemic attack, cerebral infarction d. Uncontrolled congestive heart failure (New York Heart Association Class III or IV) e. Uncontrolled or poorly controlled hypertension (defined as >160 mmHg systolic or >100 mmHg diastolic for >4 weeks despite standard medical management) f. Unstable cardiac arrhythmia requiring acute therapy (including torsades de pointes) g. Prolongation of the QT interval corrected for heart rate (QTcF) > 480 ms on at least 2 of 3 consecutive electrocardiograms (ECGs) and/or mean QTcF > 480 ms on all 3 ECGs during screening. Correction of suspected drug induced QTcF prolongation may be attempted at the investigator's discretion if considered clinically safe. 18. Have received any live vaccine within 30 days of enrollment. Vaccination against coronavirus disease 2019 (COVID-19) using vaccines that are authorized via the appropriate regulatory mechanisms (e.g., Emergency Use Authorization, Conditional Marketing Authorization, or Marketing Authorization Application) are not exclusionary. *Note: mRNA and adenoviral-based COVID-19 vaccines are considered non-live. If a COVID-19 vaccine is administered at any time, the date of COVID-19 vaccination must be entered in the eCRF.* 19. Patients who are not appropriate candidates for participation in this clinical study for any other reason as deemed by the investigator

	Exclusion Criteria for Part B (Expansion) (All Treatment Arms B1, B2, B3) In addition to the main exclusion criteria, patients must **not** meet any of the following exclusion criteria: 1. Have receptor tyrosine-protein kinase erbB-2 (HER2)+ disease as defined by American Society of Clinical Oncology-College of American Pathologists guidelines for gastric/GEJ adenocarcinoma 2. Have non-measurable disease per RECIST v1.1 **Additional Exclusion Criteria for Combination with Ramucirumab (Arms A2 and B2)** In addition to the main exclusion criteria, patients must **not** meet any of the following exclusion criteria: 1. Received prior treatment with ramucirumab and other VEGFR2 inhibitors 2. Have experienced any Grade 3-4 gastrointestinal (GI) bleeding within 3 months prior to C1D1. 3. Have a history of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to C1D1. 4. Have cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and with a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. a. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis. 5. Is receiving chronic antiplatelet therapy, including dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted. 6. Have a prior history of GI perforation/fistula (within 6 months of first dose of protocol therapy) or risks factors for perforation. 7. Have a serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to C1D1. 8. Have a minor surgery/subcutaneous venous access device placement within 7 days prior to C1D1. 9. The patient has elective or planned major surgery to be performed during the course of the clinical trial. **Additional Exclusion Criteria for Combination with Dostarlimab (Arms A3 and B3)** In addition to the main exclusion criteria, patients must **not** meet any of the following exclusion criteria:

	1. Prior treatment with immune checkpoint inhibitors (ICI) including dostarlimab and other anti-programmed death receptor-1 (PD-1), anti-programmed death receptor ligand-1 (PD-L1), etc. 2. Have an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. 3. Have experienced any of the following with prior immunotherapy: any immune-related adverse event ≥Grade 3, immune-mediated severe neurologic events of any grade (e.g., myasthenic syndromic/myasthenia gravis, encephalitis, Guillain Barré syndrome, or transverse myelitis), exfoliative dermatitis of any grade (Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], or drug reaction with eosinophilia and systemic symptoms [DRESS] syndrome), or myocarditis of any grade. Non-clinically significant laboratory abnormalities are not exclusionary. 4. Have documented presence of HBsAg at Screening or within 3 months prior to C1D1. Patients with a negative HBsAg and positive Hepatitis B core antibody result are eligible only if HBV DNA is negative. 5. Have a positive Hepatitis C virus (HCV) antibody test result at Screening visit or within 3 months prior to C1D1. *Note: Patients with a positive HCV antibody test result due to prior resolved disease can be enrolled, only if a confirmatory negative HCV RNA test is obtained.*
Length of Study:	The total duration of the study is planned to be approximately 3 years
Investigational Product:	EO-3021, ramucirumab, and dostarlimab are administered by IV infusion once every 21 days (±3 days). Patients should receive EO-3021 infused over 90 to 120 (±10) minutes for the first dose in C1D1. In the absence of infusion reactions, subsequent infusion time may gradually be decreased to 60 to 90 (±10) minutes, as tolerated. Patients should receive ramucirumab infused over 60 (±10) minutes; subsequent infusion time may gradually be decreased to 30 (±10) minutes as tolerated by the patient. Patients should receive dostarlimab infused over 30 (±10) minutes.
Statistical Considerations:	The sample size during Part A (Dose Escalation) of the study follows the BOIN design for Arm A1 (monotherapy) and traditional 3+3 design for Arm A2 (combination with ramucirumab) and Arm A3 (combination with dostarlimab. Approximately 70 patients are expected (approximately 30 patients in Arm A1, 20 patients in Arm A2, and 20 patients in Arm A3). The actual sample size (including backfills) will depend on the number of DLTs observed and the number of doses explored.

	For Part B (Expansion), approximately 120 patients will be treated at the RP2D, including approximately 80 patients in Arm B1 (monotherapy) and 20 patients each in Arm B2 (combination with ramucirumab) and Arm B3 (combination with dostarlimab). The analysis populations are defined as follows: • Safety Analysis Population includes all patients who received at least one dose of study treatment • DLT Evaluable Population includes all patients who received at least one dose of EO-3021 and complete the DLT observation period or experience DLT(s) within the DLT observation period • Efficacy Evaluable Population includes all patients who received at least one dose of EO-3021 and have baseline measurable disease and at least one post-baseline imaging assessment • PK Analysis Population will include all patients in the Safety Analysis Population who have at least one evaluable PK assessment • ADA Analysis Population will include all patients in the Safety Analysis Population who have at least one valid ADA result In general, descriptive analyses will be provided for all data including patient disposition, demographics, baseline characteristics, PK, safety, and efficacy. A Statistical Analysis Plan (SAP) will be finalized prior to the database lock. Safety analyses will include summary of incidence and severity of TEAEs, SAEs, laboratory values, physical exams, ECGs, and vital signs. Efficacy analyses will focus on patients enrolled in Part B (Expansion). However, patients in Part A (Dose Escalation) with the same type of disease and receiving the same dose as in Part B (Expansion) may be pooled into the appropriate disease cohorts as sensitivity analysis. For the ORR (CR or PR) endpoint, the Clopper-Pearson 95% confidence intervals (CIs) will be provided. Duration of response will be calculated among responders (CR and PR). Progression-free survival, OS and DOR will be analyzed using the Kaplan-Meier method. Graphical displays of data such as Kaplan-Meier curves and waterfall plots of best tumor changes from baseline will be provided.

1. INTRODUCTION

Claudin 18 is a transmembrane protein that is a component of the tight junctions between epithelial or endothelial cell plates and plays an important role in maintaining cell polarity and signal transduction. Claudin 18 has 2 isoforms, CLDN18.1 and CLDN18.2; these isoforms are specific for pulmonary and gastric tissue, respectively (Sahin et al., 2008). CLDN18.2 expression in normal tissues is strictly limited to the differentiated epithelial cells that are typically buried within the gastric mucosa and are therefore largely inaccessible to monoclonal antibodies (Bergquist et al., 2019). CLDN18.2 is overexpressed in several cancer types, including pancreatic, stomach, esophageal, lung, and ovarian cancers (Hong et al., 2020; Kim 2018; Wöll et al., 2014). An assessment of CLDN18.2 transcripts in human cancer tissues as determined by end-point real-time polymerase chain reaction demonstrated that 96%, 60%, 63%, and 41% of gastric, esophageal, pancreatic, and lung cancer samples, respectively, showed CLDN18.2 positivity; 77%, 78%, and 80% of gastric, esophageal, and pancreatic cancer samples, respectively, were positive for CLDN18.2 protein expression as determined by immunostaining (Sahin, et al., 2008). The development of carcinogenesis leads to disruptions in tight junctions, which exposes the CLDN18.2 epitopes on the surfaces of tumor cells, thereby enabling the access of a CLDN18.2 antibody (Sahin, et al. 2008).

In recent years, CLDN18.2 has become a promising target for patients with gastric cancer and pancreatic cancer due to its high and selective expression within these malignant tumor types. Drug development for the CLDN18.2 target has primarily included monoclonal antibodies, antibody drug conjugates (ADCs), bispecific antibodies, and chimeric antigen receptor T-cell (CAR-T) therapies. Of these, the most advanced of antibody drugs targeting CLDN18.2 is the monoclonal antibody zolbetuximab (also referred to as claudiximab or IMAB362) developed by Ganymed (acquired by Astellas), for which the completed phase 3 SPOTLIGHT study showed a significant reduction in the risk of disease progression or death compared to placebo when combined with modified FOLFOX chemotherapy and administered to previously untreated, locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma (Shitara et al., 2023). The phase 3 GLOW study reported an improvement in progression-free and overall survival for the addition of zolbetuximab to capecitabine and oxaliplatin chemotherapy as first-line treatment for CLDN18.2-positive, receptor tyrosine-protein kinase erbB-2 (HER2)-negative, locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma (Shah et al., 2023b). Other monoclonal antibodies, bispecific antibodies, and CAR-T therapies developed for this target are in phase 1 clinical trials (Zhang et al., 2020).

Monomethyl auristatin E (MMAE) is a synthetic, highly potent mitotic inhibitor and is too toxic to be used as a chemotherapeutic drug by itself. However, in recent years, MMAE has widely been used as a cytotoxic payload component of ADCs for targeted therapy.

EO-3021 (also referred to as SYSA1801 or CPO102) is an ADC that consists of an immunoglobulin G1 (IgG1) anti-CLDN18.2 monoclonal antibody conjugated via stable amide bonds with two MMAE moieties. The intended clinical indication for EO-3021 is advanced solid tumors that are likely to express CLDN18.2, including pancreatic cancer and adenocarcinoma of the stomach and gastroesophageal junction. Gastric and pancreatic cancers are among the malignancies with the highest unmet medical need. Gastric cancer remains a prevalent cancer worldwide and is responsible for over 1 million new cases in 2020 and an estimated 769,000 deaths (equating to 1 in every 13 deaths globally), ranking fifth for incidence and the fourth for mortality

globally (Sung et al., 2021). Most patients with gastric cancer present with unresectable or metastatic disease at the time of diagnosis, with a poor prognosis and median survival of less than a year (Hsu et al., 2020). Pancreatic cancer is presently the seventh leading cause of cancer death worldwide, with a 5-year survival rate of 9% (Rawla et al., 2019; Sung et al., 2021). Only about 10% to 20% of pancreatic cancers are surgically resectable, and even after surgical resection, only about 20% of those patients live longer than 5 years (McGuigan et al., 2018; Neoptolemos et al., 2018). The poor prognosis of these cancer types highlights the need for additional treatment approaches. New targeted therapies with better efficacy and safety profiles will greatly benefit these patients.

Since high expression of CLDN18.2 is primarily restricted to malignant tissues, coupled with the selective binding to CLDN18.2 and conjugation with the potent mitotic inhibitor MMAE, EO-3021 has the potential to offer a specific targeted therapy for solid tumors expressing CLDN18.2.

1.1. Clinical Application of CLDN18.2 in Solid Tumors

Gastric cancer: In an effort to develop CAR-T therapies for the treatment of gastric cancer, Jiang et al. evaluated CLDN18.2 protein expression by immunohistochemistry (IHC) in 24 types of human normal tissue samples (Jiang et al., 2019). They found that normal CLDN18.2 expression was only observed in stomach tissues. Normal tissues surrounding gastric tumors retained a high level of CLDN18.2 expression (≥2+ intensity). CLDN18.2 seemed to be homogeneously expressed in gastric cancer tissues. In metastatic gastric tumors, 77.4% (24/31) expressed CLDN18.2 and in 61.3% (19/31), CLDN18.2 was highly expressed (≥2+ intensity). Furthermore, the CLDN18.2 expression level in metastatic lesions is consistent with that in the corresponding primary gastric cancer tissues.

Pancreatic cancer: Sahin et al. reported that the CLDN18.2 transcripts were restricted to normal gastric tissue and were also detected in several epithelial tumor types (Sahin et al., 2008). In 7 of 11 pancreatic adenocarcinomas examined, elevated mRNA levels of CLDN18.2 were noted. Various studies (Karanjawala et al., 2008; Lee et al., 2011; Tanaka et al., 2011; Hong et al., 2020) have also been carried out to assess the CLDN18.2 protein expression in different cancer types and have reported a range of 14% to 63% CLDN18.2 positivity rates in pancreatic tumors. The limited expression of CLDN18.2 in normal tissues coupled with the enhanced expression in pancreatic cancer suggests a clinically relevant application of therapies targeted to patients with CLDN18.2.

Further supporting the clinical evaluation of EO-3021, clinical trials of the anti-claudin 18.2 monoclonal antibody, zolbetuximab (IMAB362), have shown encouraging clinical activity. Patients with advanced gastric, GEJ or esophageal adenocarcinomas with moderate-to-strong CLDN18.2 expression in ≥50% of tumor cells received zolbetuximab intravenously (IV) every 2 weeks for 5 planned infusions. Anti-tumor activity data were available for 43 patients, of whom 4 achieved partial response (PR) (objective response rate [ORR] 9%) and 6 (14%) had stable disease (SD) for a clinical benefit rate of 23% (Türeci et al., 2019). Following this small but encouraging study, more clinical studies for zolbetuximab have been conducted, including the SPOTLIGHT and GLOW studies which reported reduction of disease progression and death (Shitara et al., 2023; Shah et al., 2023b).

1.2. EO-3021, Anti-claudin 18.2 MMAE Antibody Drug Conjugate

EO-3021 has a molecular weight of approximately 147.6 kilodaltons (kDa, deglycosylated form). The drug product contains 10 mg/mL EO-3021 ADC in a 20 mM histidine buffer containing 6% (w/v) sucrose and 0.02% (w/v) polysorbate 20 at pH 5.5. For clinical use, the EO-3021 drug product is diluted in 0.9% sodium chloride injection solution to obtain a solution for a single IV infusion.

1.2.1. Nonclinical Pharmacology

The binding specificity of EO-3021 was demonstrated in vitro using cellular binding assays. EO-3021 only binds to the HEK293 cells expressing human CLDN18.2 but not human CLDN18.1 proteins. Upon binding with membrane CLDN18.2, EO-3021 is endocytosed and the active moiety MMAE is released. Incubation of EO-3021 with CLDN18.2-expressing cells induced cell cycle arrest at G2/M phase and apoptosis. As an IgG1 antibody, EO-3021 also retains substantial antibody-dependent cell-mediated and complement-dependent cytotoxic activities.

The anti-tumor activity of EO-3021 was demonstrated in xenograft models. EO-3021 dose dependently inhibited tumor growth in 5 human cancer models that endogenously or ectopically expressed human CLDN18.2, including gastric (NUGC4 and NUGC4-CLDN18.2), pancreatic (PATU8988s and BxPC3-CLDN18.2), and non-small cell lung cancer (NSCLC) (NCI-H460-CLDN18.2) models. The effective dose for NUGC4 and PATU8988s models were 10 mg/kg as a single dose at the beginning of 3-week period, and those for the ectopic models NUGC4-CLDN18.2, BxPC3-CLDN18.2, and NCI-H460-CLDN18.2 were 0.5, 2, and 4 mg/kg as single dose, respectively. EO-3021 showed superior anti-tumor efficacy than the conventional chemotherapeutic drugs gemcitabine and cisplatin.

1.2.2. Nonclinical Pharmacokinetics

Nonclinical pharmacokinetics (PK) of EO-3021 were studied following a single dose IV administration in Sprague Dawley rats and cynomolgus monkeys. The low, middle, and high dose levels for rats and monkeys were 1, 3, and 10 mg/kg and 0.5, 1.5, and 5 mg/kg, respectively. The intact EO-3021, total antibody (EO-3021 + naked antibody) and free MMAE were measured.

The results showed no statistically significant sex differences in the primary PK parameters of EO-3021 including the maximum observed concentration (C_{max}), area under the concentration time curve (AUC), half-life ($t_{½}$) and drug clearance (CL) in all dose groups in both species. The exposure of ADC and total antibody in serum in different dose groups proportionally increased with the increasing administration doses tested.

In both rats and monkeys, the PK behavior of ADC and total antibody was very similar. The mean $t_{1/2}$ ranged from 47 to 132 hours in rats and 143 to 189 hours in monkeys. The median time of maximum concentration (T_{max}) was 0.25 hours in rats and 0.5 hours in monkeys. The CL measurements ranged from 0.635 to 0.871 mL/h/kg in rats and 0.420 to 0.502 mL/h/kg in monkeys.

The plasma exposure of free MMAE was minimal, less than 0.1%, as compared with the serum exposure of the intact ADC, suggesting that negligible MMAE shedding from EO-3021 occurred in the blood stream. The stability of ADC was further confirmed by in vitro serum/plasma incubation studies.

Anti-drug antibodies (ADA) were detected in both rats and monkeys, and more frequently in rats. Following a single IV administration, 1/6, 1/6, and 2/6 monkeys in the low, medium, and high dose groups, respectively, were positive for ADA, and they showed slightly reduced drug exposure than other animals that were ADA-negative.

1.2.3. Nonclinical Safety Toxicology and Pharmacology

The safety of EO-3021 has been evaluated in both in vitro systems and in animals. The maximum tolerated doses (MTDs) after single IV administration of EO-3021 were 75 and 30 mg/kg in Sprague Dawley rats and cynomolgus monkeys, respectively. The repeat-dose toxicity studies showed that the highest non-severely toxic doses (HNSTDs) were 25 and 20 mg/kg in Sprague Dawley rats and cynomolgus monkeys, respectively, after IV administration of EO-3021 once every 3 weeks for 6 weeks (3 doses in total) followed by a 4-week recovery period. The main toxic target organs are the digestive system (stomach) and lymph-hematopoietic system (thymus, bone marrow in sternum) in both species. In Sprague Dawley rats, the target organs also include the digestive system (ileum, liver), reproductive system (testes and epididymis), administration site, eyeballs, Hada's gland, and mammary gland. Similar findings were observed in MMAE-treated Sprague Dawley rats. The pattern of effects observed in the toxicology studies is consistent with the anti-mitotic mechanism of action of MMAE and is similar to those observed with other antibody-MMAE conjugates (e.g., polatuzumab vedotin, Li et al., 2019). Additional EO-3021-related effects in the stomach are not unexpected based on the stomach-specific expression of CLDN18.2. All adverse effects had recovered or were recovering by the end of the 4-week recovery period, with the exception of microscopic findings in the stomach, testes, and epididymides in rats.

Safety pharmacological studies showed that EO-3021 had no potential effects on the central nervous system in rats, or on the cardiovascular system and respiratory systems in cynomolgus monkeys, with the no observed adverse effect level (NOAEL) of ≥50 mg/kg in rats and ≥20 mg/kg in monkeys following a single IV administration.

In addition, in vitro tests confirmed that EO-3021 at concentrations of 5 mg/mL did not induce hemolysis or agglutination of rabbit red blood cells.

Based on in vitro pharmacology, in vivo efficacy in mouse models, PK, and safety results, EO-3021 has the potential to be a specific, safe, and efficacious method to treat advanced/metastatic gastric/GEJ adenocarcinoma or advanced solid tumors that are likely to express CLDN18.2.

1.2.4. Clinical Experience with Anti-Claudin 18.2 Agents and EO-3021

There is limited data available for CLDN18.2-targeted agents. While there are currently no CLDN18.2-targeted agents approved commercially, there are ongoing clinical stage compounds in development, such as zolbetuximab. Early clinical safety data indicate common treatment-emergent adverse events (TEAEs) reported to include abdominal pain, decreased appetite, drug hypersensitivity, fatigue, pneumonia, vertigo, vomiting, weight loss, nausea, and general physical health deterioration. The majority of reported TEAEs were grade 1 or 2; grade 3 nausea and vomiting were also reported.

Nausea and vomiting were the most common TEAEs and occurred early during infusion of zolbetuximab. Given the organ-specific expression of CLDN18.2 in the stomach, the frequency of

these events was analyzed post hoc in relation to prior gastrectomy. Patients without prior gastrectomy were more likely to report nausea and vomiting. Incidence of these TEAEs decreased over time as patients were exposed to repeated zolbetuximab infusions (Türeci et al., 2019).

A first-in-human study of EO-3021 titled A Phase I Trial to Evaluate Safety, Tolerability, Pharmacokinetics, Immunogenicity and Initial Efficacy of SYSA1801 in the Treatment of CLDN18.2 Positive Advanced Malignant Solid Tumor (SYSA1801-CSP-001; NCT05009966) is ongoing in China with CSPC Megalith Biopharmaceutical Co., Ltd. (CSPC) as the Sponsor.

Based on available data from CSPC, the C_{max} of ADC was observed near the end of the infusion from 0.5 to 2 mg/kg IV once every 3 weeks (Q3W) after the first dose, with a mean C_{max} of 8.10 to 35.66 µg/ml and a mean AUC_{inf} of 41.42 to 162.93 day*µg/ml. The C_{max} and AUC_{inf} increased proportionally to the increase in dose. The mean elimination $t_{½}$ of ADC was 5.65 to 6.23 days.

The most common adverse event (AE; >20%) related to EO-3021, by system organ class (SOC), were mainly: gastrointestinal (GI) disorders, mainly manifested as nausea (64%), vomiting (57%), upper abdominal pain (21%); eye disorders, manifested as dry eye (29%), corneal disorders (21%); and general disorders mainly manifested as asthenia (21%). See the Investigator's brochure (IB) for a full summary of the safety profile.

Initial preliminary clinical data presented by Wang et al. (2023) at the Annual Meeting of the American Society of Clinical Oncology (ASCO) highlighted the potential of EO-3021 to confer clinical benefit in patients with gastric cancer that expressed CLDN18.2 (defined as at least 1% of tumor cells with 1+ IHC by central laboratory testing). As of the data cut-off of 05 November 2022, 33 eligible patients were enrolled: 6 patients with pancreatic cancer and 27 patients with gastric cancer. Patients received 0.5 mg/kg to 3 mg/kg of EO-3021 administered IV Q3W as part of the dose escalation portion of the study (n=17); in the dose expansion portion of the study, patients (n=16) were treated at effective doses (2.0 mg/kg IV Q3W and 2.5 mg/kg IV Q3W). Twenty-one patients (gastric cancer n=17, pancreatic cancer n=4) were evaluable for efficacy per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The ORR was 38.1% (8 PRs, including 4 confirmed PRs), and the disease control rate (DCR) was 57.1% (including 4 SDs).

In gastric cancer, the ORR was 47.1% (8 PRs, including 4 confirmed PRs) and the DCR was 64.7%, including three patients with SD. The preliminary clinical data with an ORR of 47.1% in gastric cancer suggest EO-3021 has the potential to provide greater clinical benefit to patients with gastric cancer expressing CLDN18.2 than the currently available standard therapy (ORR 3-28%) (Wilke et al., 2014; Chan et al., 2019).

The current study, ELVCAP-002-01 (NCT05980416), was initiated in August 2023 and is currently enrolling patients in the US and Japan. As of 10 JUNE 2024, 32 patients with gastric (n=17), GEJ (n=9), pancreatic (n=5), or esophageal (n=1) cancer have been enrolled in dose escalation at dose levels of 1.0 mg/kg to 2.9 mg/g IV Q3W. The safety profile remains favorable; the most common AEs (reported in ≥20% of patients) related to EO-3021 included nausea (53%), decreased appetite (41%), and fatigue (38%). There was no MMAE-associated toxicity reported (e.g., peripheral neuropathy, neutropenia, and elevations in liver function tests [LFTs]) in the initial safety dataset. Additionally, premedications with anti-emetics were strongly encouraged which seemed to reduce the rate of vomiting (3.8%). Four dose-limiting toxicities (DLTs) were observed in the 6 patients treated at 2.9 mg/kg IV Q3W. DLTs of Grade 3 encephalopathy and Grade 3 fatigue were observed in 2 patients with advanced metastatic pancreatic cancer in the global

protocol. In addition, DLTS of Grade 3 decreased appetite and Grade 2 decreased appetite requiring a dose reduction were observed in 2 patients with advanced gastric cancer in the Japanese dose escalation cohort which was being conducted under a 3 + 3 design. The SRC declared the MTD to be 2.5 mg/kg IV Q3W based on the totality of data from the global and Japanese dose escalation arms. See the IB for a full summary of the safety profile. Early signs of clinical benefit and anti-tumor activity have also been observed. Of the 18 patients with gastric/GEJ adenocarcinoma who had measurable disease and were evaluable for tumor response per RECIST v1.1, tumor reduction was observed in ~50% of the patients, with 3 patients achieving tumor reduction of greater than 30% (2 confirmed PR; 1 as yet to be confirmed PR). In a CLDN18.2 biomarker-enriched patient population (defined as CLDN18.2 in ≥20% of tumor cells at 2+/3+ IHC), the confirmed ORR was 42.8% in patients with gastric/GEJ adenocarcinoma.

Taken together, these data support the continued evaluation of EO-3021 in gastric/GEJ adenocarcinoma that express CLDN18.2.

1.2.5. Rationale for the Implementation of Claudin 18.2 Expression in the Expansion Part of this Phase 1 Study

Clinical trials of the anti-CLDN18.2 antibody, zolbetuximab have demonstrated encouraging clinical efficacy; however responses require the majority (>70%) of tumors cells to express moderate-to-strong (2+/3+ IHC) expression of CLDN18.2 (Türeci et al., 2019; Sahin et al., 2021; Shitara et al., 2023). In the phase 2a study (NCT01197885, MONO 2013), patients with advanced gastric, GEJ or esophageal adenocarcinomas with moderate-to-strong CLDN18.2 expression demonstrated by IHC analysis in ≥50% of tumor cells received zolbetuximab IV every 2 weeks for 5 planned infusions. Antitumor activity data were available for 43 patients, of whom 4 achieved PR (ORR 9%) and 6 (14%) had SD for a clinical benefit rate of 23% (Türeci et al., 2019). All 4 PR responders had >70% CLDN18.2 expression in tumor cells, suggesting a possible correlation between CLDN18.2 expression and therapeutic benefit with zolbetuximab.

A phase 2b study (NCT01630083, FAST 2015) evaluated zolbetuximab in combination with epirubicin, oxaliplatin, and capecitabine (EOX) chemotherapy in patients with advanced/recurrent gastric/GEJ adenocarcinoma. In this study, in patients with moderate-to-strong CLDN18.2 expression in >70% of tumor cells, distinct improvements in progression-free survival (PFS) and overall survival (OS) were observed with zolbetuximab + EOX versus EOX. However, in patients where 40%-69% of tumor cells had moderate-to-strong CLDN18.2, neither PFS nor OS were significantly different between treatment arms (Sahin et al., 2021). Subsequently, two phase 3 studies (SPOTLIGHT and GLOW) confirmed the benefit of adding zolbetuximab to chemotherapy in patients with gastric/GEJ adenocarcinoma that were CLDN18.2-positive, defined as moderate-to-strong CLDN18.2 expression in ≥75% of tumor cells (Shitara et al., 2023; Xu et al., 2023).

While these results with zolbetuximab, a monoclonal antibody to CLDN18.2, suggest high expression of CLDN18.2 is likely to correlate with patient benefit, EO-3021 is an anti-CLDN18.2 antibody conjugated to a cytotoxic payload. It is plausible high expression of CLDN18.2 is not necessary for EO-3021's mechanism of action. This hypothesis is supported by early clinical data from the ongoing study with EO-3021 conducted by CSPC; tumor shrinkage and confirmed tumor responses have been observed at a range of CLDN18.2 expression, including tumors with at least 1+ (weak) CLDN18.2 expression in 5-97% of tumor cells (data on file). Therefore, enrollment into

the dose escalation portion of this phase 1 clinical trial is not dependent on CLDN18.2 expression provided the patients have a confirmed diagnosis of gastric/GEJ adenocarcinoma. For Part A all arms, the provision of tumor tissue (archival formalin-fixed paraffin-embedded [FFPE] biopsy obtained within the last 24 months and a fresh [new] FFPE tumor biopsy, if medically feasible) is required for retrospective exploratory analysis of CLDN18.2 as a potential predictive biomarker of response to EO-3021. Enrolling tumors with a broad range of CLDN18.2 expression will further support correlative analysis of clinical outcomes with varying CLDN18.2 expression in order to potentially establish a more defined cut-off that is clinically meaningful to predict and enrich for efficacy with EO-3021. It has been reported that the majority (~80%) of gastric, esophageal, and pancreatic adenocarcinomas express some level of CLDN18.2 (Sahin et al., 2008). Furthermore, EO-3021 exhibits bystander killing of tumor cells that do not express CLDN18.2 coupled with tumor heterogeneity (Fisher et al., 2013). Therefore, the benefits outweigh the risks for a preselection biomarker at this stage of development.

In Part A of monotherapy dose escalation/backfill, 3 PRs were observed in tumors with higher CLDN18.2 expression and SD was the best response seen in tumors with little to no CLDN18.2 expression to date. The assessment of CLDN18.2 expression and response for participants in Part A is ongoing. As the data around CLDN18.2 as a predictive biomarker for EO-3021 monotherapy mature, the Sponsor plans to implement a prospective CLDN18.2 biomarker selection strategy to identify and enroll patients who would likely derive the most benefit from EO-3021 as monotherapy or in combination with ramucirumab or dostarlimab in future studies. In Part B (Expansion), expression of CLDN18.2 in 25% or more of tumor cells at 1+/2+/3+ IHC staining intensity as determined in a central laboratory will be required for enrollment in order to enrich for CLDN18.2-expressing tumors to support exploratory analyses of potential biomarker cutoffs in future studies.

1.3. EO-3021 in Combination Therapy

CLDN18.2, a tight junction protein normally expressed only on gastric mucosa, is highly expressed in gastric, pancreatic and other solid tumors (Türeci et al., 2011; Sahin et al., 2008). EO-3021 is an ADC composed of a monoclonal antibody targeting CLDN18.2 with an MMAE payload (Dan et al., 2023). EO-3021 selectively delivers the MMAE cytotoxic payload directly to cancer cells resulting in immunogenic cell death.

First-line platinum-based doublet or triplet chemotherapy is the standard of care treatment in advanced (HER2 negative, programmed death receptor ligand-1 [PD-L1] low) gastric/GEJ adenocarcinoma with a median OS rate around 1 year (Kim et al., 2012; Baek et al., 2011; Al-Batran et al., 2008; Koizumi et al., 2010; Koizumi et al., 2008; Yamada et al., 2015; Shah et al., 2023; Lordick et al., 2022). Systemic therapy in the second and subsequent lines of therapy include ramucirumab in combination with paclitaxel (ORR 28%; median OS 9.6 months), or FOLFIRI (ORR 20-29%; median OS 6.4-6.7 months) if not used previously in the first-line setting (Fuchs et al., 2014; Sym et al., 2013; Assersohn et al., 2004). Additional options include single agent paclitaxel, docetaxel or irinotecan which achieve a median OS benefit between 5-9.5 months (Fuchs et al., 2014; Ford et al, 2014; Thuss-Patience et al., 2011). The low ORR and median OS rates of the established treatments in the second-line setting provide an opportunity for improvement. It is hypothesized that combining an established agent with EO-3021 may achieve

superior ORR and median OS in the first-line and second-line setting for patients with advanced or metastatic gastric/GEJ adenocarcinoma.

1.3.1. Rationale for Combination with Ramucirumab

Proangiogenic signaling through the vascular endothelial growth factor (VEGF) family of receptors, including the VEGF receptor 2 (VEGFR2) signaling pathway, is associated with increased tumor growth and invasion and reduced survival in patients with gastric cancer (Ferrara et al, 2003; Lieto et al, 2008; Peng et al, 2012). Ramucirumab (Cyramza) is a recombinant human IgG1 monoclonal antibody VEGFR2 antagonist (Miao et al, 2006). Ramucirumab is approved for use as a single agent or in combination with paclitaxel as a second-line therapy for patients with metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy based on the results from two phase III trials (REGARD, RAINBOW) (CYRAMZA, 2022; Fuchs et al, 2014; Wilke et al, 2014). The REGARD study exhibited a survival benefit with ramucirumab monotherapy for patients with advanced GC or GEJ adenocarcinoma who progressed after receiving first-line chemotherapy (5.2 vs 3.8 months) (Fuchs et al, 2014). However, no difference in ORR between study arms was observed (3% vs. 3%) (Fuchs et al, 2014). In the RAINBOW study, patients with advanced GC or GEJ adenocarcinoma who progressed after receiving first-line chemotherapy and received paclitaxel in combination with ramucirumab had significantly longer median OS benefit compared to paclitaxel monotherapy (9.6 vs 7.4 months) and higher ORR (28% vs 16%) (Wilke et al, 2014). The established use of ramucirumab in 2L, a poor ORR rate with ramucirumab monotherapy (Fuchs et al, 2014), and the distinct mechanism of action of EO-3021 from ramucirumab provide the rationale for combining EO-3021 with ramucirumab to treat metastatic gastric/GEJ adenocarcinoma.

For patients with advanced or metastatic gastric/GEJ adenocarcinoma whose disease has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy, ramucirumab as a single agent or with the addition of paclitaxel is recommended by the NCCN, ASCO and ESMO (Shah et al, 2023; Lordick et al, 2022; Ajani et al, 2022). Known overlapping toxicities (reported in ≥20% of patients) between EO-3021 and ramucirumab in patients with gastric cancer include fatigue/asthenia and vomiting. Mitigation strategies for AEs are provided in Section 6.5 of this protocol.

1.3.2. Rationale for Combination with Dostarlimab

Programmed death receptor-1 (PD-1)/ PD-L1 inhibitors have been approved for use in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients with advanced or metastatic GC/GEJ adenocarcinoma (KEYTRUDA, 2020; OPDIVO, 2018) based on improvement of median survival and overall response rates (Rha et al, 2023; Sun et al, 2021; Doki et al, 2022; Janjigian et al, 2021).

Preclinical evidence investigating PD-L1 expression in CLDN18.2-expressing gastric cancer cells correlated an increase in both PD-L1 upregulation and tumor infiltrating lymphocytes following treatment with an anti-CLDN18.2 monoclonal antibody (Qian et al, 2023). Additionally, clinical studies with MMAE-containing ADCs in solid tumors have provided evidence of MMAE-induced immunogenic cell death including recruitment and activation of immune cells, and extracellular release of adenosine triphosphate (ATP) (Liu et al, 2020; Trang et al, 2023; Heiser et al, 2024).

Dostarlimab (Jemperli) is an anti-PD-1 humanized IgG4 monoclonal antibody (Laken et al, 2016). While dostarlimab is not broadly approved for the treatment of GC/GEJ, it has accelerated approval as a single agent for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors including gastric/GEJ adenocarcinoma (JEMPERLI, 2024). In patients with locally advanced or metastatic dMMR gastric/GEJ cancers who had progressive disease following systemic therapy, dostarlimab monotherapy achieved a confirmed ORR of 37.5% (Andre et al, 2021). While dostarlimab can induce responses in this subset of the patient population, combining dostarlimab with a targeted ADC may improve patient responses in a broader patient population with gastric/GEJ adenocarcinoma. Clinical trials investigating MMAE-containing ADCs directed towards various targets in combination with a PD-1 inhibitor in solid tumors, including gastric/GEJ cancer, are underway (NCT05934331; NCT05180799; NCT05941507). Notably, a nectin 4-directed ADC with an MMAE payload administered in combination with a PD-1 inhibitor yielded better outcomes compared to chemotherapy for first-line treatment in patients with locally advanced or metastatic urothelial cancer (Powles et al, 2024) resulting in an FDA approval for eligible patients.

The use of PD-1 inhibitors in the first line along with the distinct mechanism of action of EO-3021 monotherapy support the rationale for combining EO-3021, which can activate antigen-presenting cells and immunogenic cell death, with dostarlimab, a PD-1 inhibitor, to treat gastric/GEJ cancer. Based on the potential enhancement of an immune response from a PD-1 inhibitor, it is hypothesized that combining EO-3021 with dostarlimab may result in improved outcomes in patients with locally advanced or metastatic gastric/GEJ adenocarcinoma. Overlapping toxicities (reported in ≥20% of patients) between EO-3021 and dostarlimab include anemia, nausea, and fatigue/asthenia; dostarlimab related immune-mediated adverse events with potential overlap with EO-3021 include pneumonitis and ocular toxicities. Mitigation strategies for AEs are provided in Section 6.5 of this protocol.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

The primary objective of this study is to determine the recommended phase 2 dose(s) (RP2D) for the single-agent EO-3021, and when in combination with either ramucirumab or dostarlimab, for further exploration in patients with advanced/metastatic gastric/GEJ adenocarcinoma or advanced solid tumors that are likely to express CLDN18.2.

2.2. Secondary Objectives

The secondary objectives of this study include the following:

- To document the overall safety profile for EO-3021 when administered as a single agent, and when in combination with either ramucirumab or dostarlimab
- To evaluate the PK profile of EO-3021 as a single agent, and when in combination with either ramucirumab or dostarlimab
- To assess the immunogenicity of EO-3021 as a single agent, and when in combination with either ramucirumab or dostarlimab

- To document any early indication of clinical efficacy in patients with advanced/metastatic gastric/GEJ adenocarcinoma or advanced solid tumors that are likely to express CLDN18.2 as a single agent, and when in combination with either ramucirumab or dostarlimab

2.3. Exploratory Objectives

The exploratory objectives of this study include the following:

- To evaluate the association of anti-tumor activity of EO-3021 with CLDN18.2 expression by IHC (at various biomarker cut-offs) in advanced/metastatic gastric/GEJ adenocarcinoma or advanced solid tumors that are likely to express CLDN18.2 as a single agent, and when in combination with either ramucirumab or dostarlimab
- To evaluate if mechanistically-linked biomarkers correlate with clinical outcomes as a single agent, and when in combination with either ramucirumab or dostarlimab

2.4. Study Endpoints

Safety endpoints:

- Dose-limiting toxicities, TEAEs, serious adverse events (SAEs), vital signs, and laboratory data

Efficacy endpoints:

- ORR (complete response [CR]+PR), DCR (CR+PR+SD), and time to event parameters (duration of response, PFS and OS)

PK and ADA endpoints:

- Serum PK parameters (C_{max}, AUC, $t_{½}$) and ADA levels (percentage of subjects developing detectable ADAs and percentage of nAbs) at prespecified time points

3. STUDY DESIGN

This Phase 1 study is a multicenter, open-label, dose escalation and expansion study conducted in patients with advanced/metastatic gastric/GEJ adenocarcinoma or advanced solid tumors that are likely to express CLDN18.2. With the release of a Protocol Administrative Letter dated 09April2024, only patients with gastric/GEJ adenocarcinoma will be enrolled in this study. Patients with other solid tumors likely to express CLDN18.2 will be excluded from trial participation.

The study design overview is presented in Figure 1 below. The study consists of 2 parts: Part A (Dose Escalation) and Part B (Expansion).

Approximately 70 patients may be treated in Part A (Dose Escalation). Dose escalation consists of 3 arms:

- Arm A1 (monotherapy): EO-3021 as a single agent in patients with gastric/GEJ adenocarcinoma that are refractory to or intolerant of standard treatment, or for which no standard treatment is available. Dose escalation will start with EO-3021 at 1.0 mg/kg following the Bayesian Optimal interval (BOIN) design with a target DLT rate of 25% for

the MTD (Yuan et al., 2016; Zhou et al., 2018). Dose escalation will proceed according to Figure 1 and Figure 2.

- Arm A2 (combination with ramucirumab): EO-3021 in combination with ramucirumab in patients with gastric/GEJ adenocarcinoma that are refractory to or intolerant of standard treatment, or for which no standard treatment is available. Combination dose escalation will start with EO-3021 at 2.0 mg/kg IV Q3W following a standard 3+3 design and proceed according to Figure 3. Ramucirumab will be administered at 10 mg/kg IV Q3W after EO-3021. The dose of Ramucirumab will be held constant while the dose of EO-3021 is escalated according to Figure 3 until RP2D/MTD is reached.
- Arm A3 (combination with dostarlimab): EO-3021 in combination with the anti-PD1 inhibitor dostarlimab in patients with gastric/GEJ adenocarcinoma that are refractory to or intolerant of standard treatment, or for which no standard treatment is available. Dose escalation will start with EO-3021 at 2.0 mg/kg IV Q3W following a standard 3+3 design and proceed according to Figure 4. Dostarlimab will be administered at 500 mg IV Q3W after EO-3021. The dose of dostarlimab will be held constant while the dose of EO-3021 is escalated according to Figure 4 until RP2D/MTD is reached.

Dose escalation rules of each arm are outlined in Table 2 and Table 3 and discussed in Section 6.3. In all 3 arms, dose escalation follows the prespecified dose increments. Intermediate dose levels of EO-3021 as well as doses higher or lower than those described in Section 6.3 and/or alternative dosing frequencies (e.g., once every 4 weeks [Q4W]) may be explored, if warranted, based on overall safety, tolerability, and/or PK data if available and agreed upon by the SRC and Sponsor.

At the discretion of the SRC and Sponsor, additional backfill patients may be included to further characterize the MTD/RP2D. Patients enrolled to backfill do not contribute to the evaluation of the DLT rate in Part A1 dose escalation. Overall data from backfill and dose escalation cohorts will be used to determine the RP2D.

Upon attaining an RP2D and/or MTD, Part B (Expansion) will commence in patients with gastric/GEJ adenocarcinoma. Part B (Expansion) aims to confirm the RP2D and to assess early signals of efficacy in the selected cancer patient populations. The Sponsor, in conjunction with the SRC, may decide to evaluate more than 1 dose in Part B. In this scenario, randomization may be employed to assign patients to 1 of 2 candidate RP2Ds. The sponsor may manage enrollment through the IRT to ensure balanced representation of evaluable patients in each arm by select covariates of interest (e.g., geographical location, lines of therapy, etc.)

A total of approximately 120 patients could be enrolled in Part B (Expansion). The Dose Expansion cohort consists of 3 arms:

- Arm B1 (monotherapy): EO-3021 as a single agent in patients with gastric/GEJ adenocarcinoma who have received at least 1 but no more than 3 prior lines of therapy in the advanced metastatic setting. Patients will be randomized to 2.0 mg/kg or 2.5 mg/kg in a 1:1 fashion in monotherapy expansion. Prospective CLDN18.2 selection will be implemented during enrollment of the monotherapy expansion.
- Arm B2 (combination with ramucirumab): EO-3021 in combination with ramucirumab in patients with locally advanced or metastatic gastric/GEJ adenocarcinoma who previously were treated with only 1 prior line of therapy in the metastatic setting. Prior

fluoropyrimidine and platinum-containing chemotherapy is required. The dose of EO-3021 will be the RP2D/MTD determined in the combination dose escalation Arm A2. Ramucirumab will be administered at 10 mg/kg IV Q3W after EO-3021. Prospective CLDN18.2 selection will be implemented during enrollment of the combination expansion.

- Arm B3 (combination with dostarlimab): EO-3021 in combination with dostarlimab in patients with locally advanced or metastatic gastric/GEJ adenocarcinoma who have not received any prior systemic therapy in the advanced metastatic setting. The dose of EO-3021 will be the RP2D/MTD determined in the combination dose escalation Arm A3. Dostarlimab will be administered at 500 mg IV Q3W after EO-3021. Prospective CLDN18.2 selection will be implemented during enrollment of the combination expansion.

In Part A (Dose Escalation), archived FFPE tumor tissue from a prior biopsy/surgical specimen (obtained within the last 24 months) and a fresh (new) tumor biopsy, if medically feasible, is required for retrospective evaluation of tumor CLDN18.2 expression performed by the Sponsor in a central laboratory. Tumor biopsy obtained prior to consent but no more than 3 months prior to Cycle 1 Day 1 (C1D1) without any intervening treatment between the biopsy and C1D1 may be used to fulfill the fresh tumor tissue requirement with Sponsor approval. Documentation of CLDN18.2 expression is not a requirement for participation in Part A (monotherapy and combination) of this study.

In Part B (Expansion), a FFPE block or a minimum of 6 unstained slides of tumor tissue from a biopsy obtained within 6 months of enrollment must be available to submit for prospective central review. (Note: If the patient received any CLDN18.2 directed therapy after the date of the archival biopsy a new biopsy should be performed and FFPE block or 6 unstained slides must be available for prospective central review.)

Prior to any study-specific activities, all patients or legal representatives must sign an informed consent form (ICF). Patients meeting the eligibility criteria are enrolled and treated at the dose level specified by the dose-escalation scheme. Patients receive study treatment until disease progression, unacceptable toxicity, or one or more protocol-specific treatment discontinuation criteria have been met as described in Section 6.8.1. Logistically, the study is divided into observational windows of 21 days for data collection purposes; each 21-day period is considered a cycle of treatment.

Patients will be treated on an outpatient basis and will be closely monitored for safety, being seen in the clinic on a weekly basis in the first cycle and then every 3 weeks when the patients receive dosing throughout therapy. Once off study treatment, survival data will be collected via written communication (e.g., email, electronic medical record), telephone call, or clinic visits every 3 months (±28 days) from the date of last treatment until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor.

Figure 1: Study Design Overview

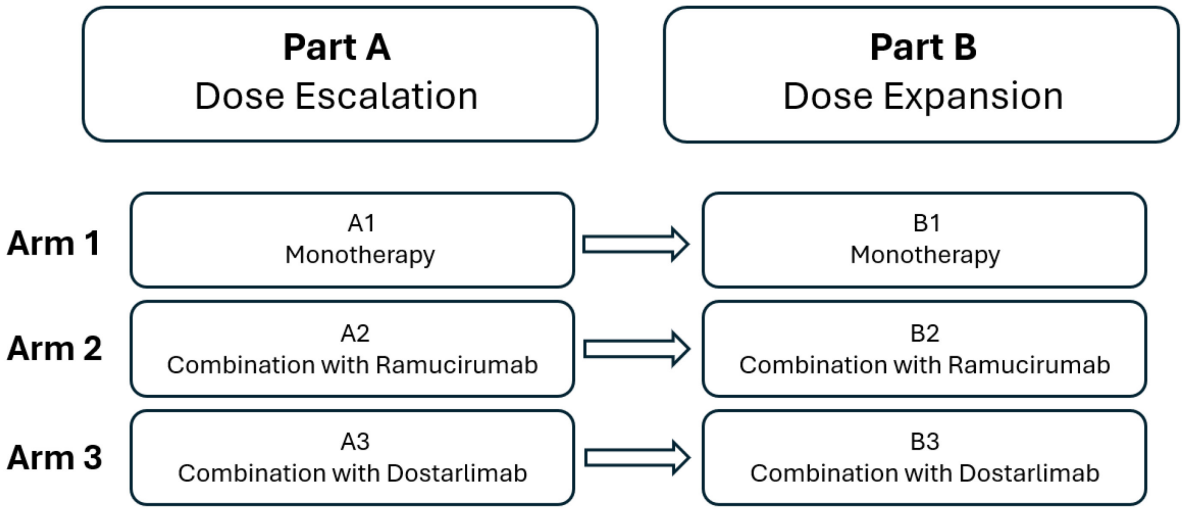
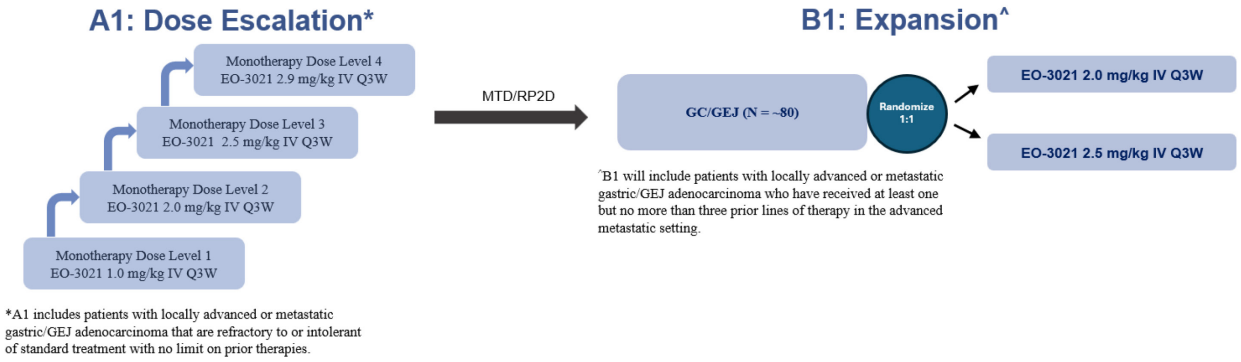
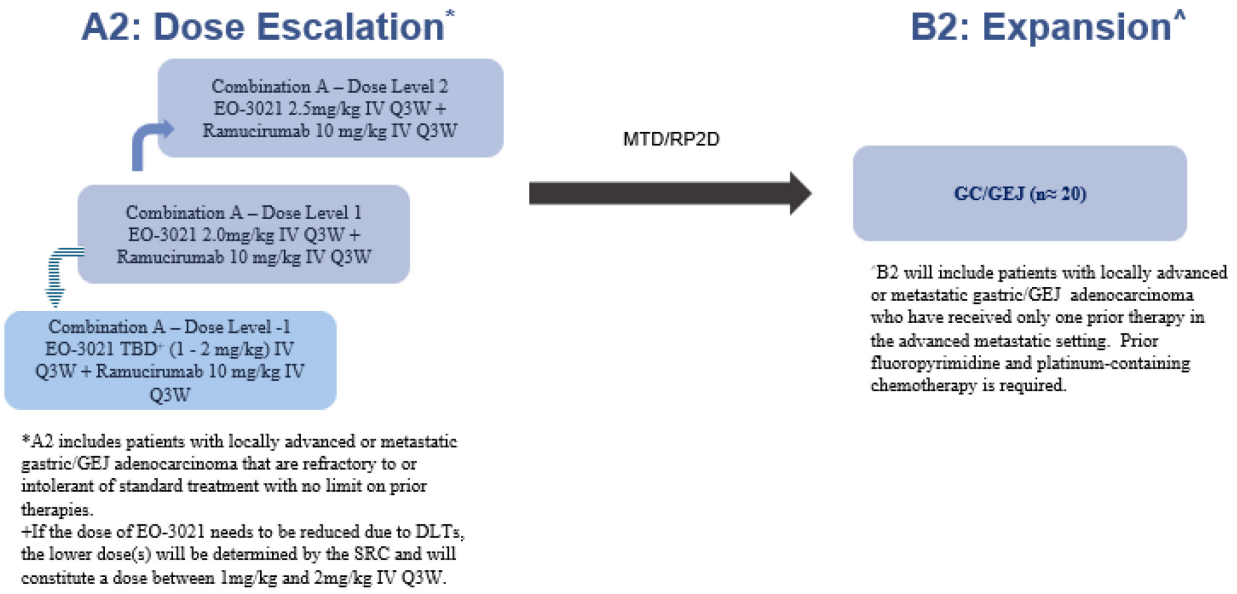


Figure 2: Study Schema for Arm 1 (EO-3021 Monotherapy)



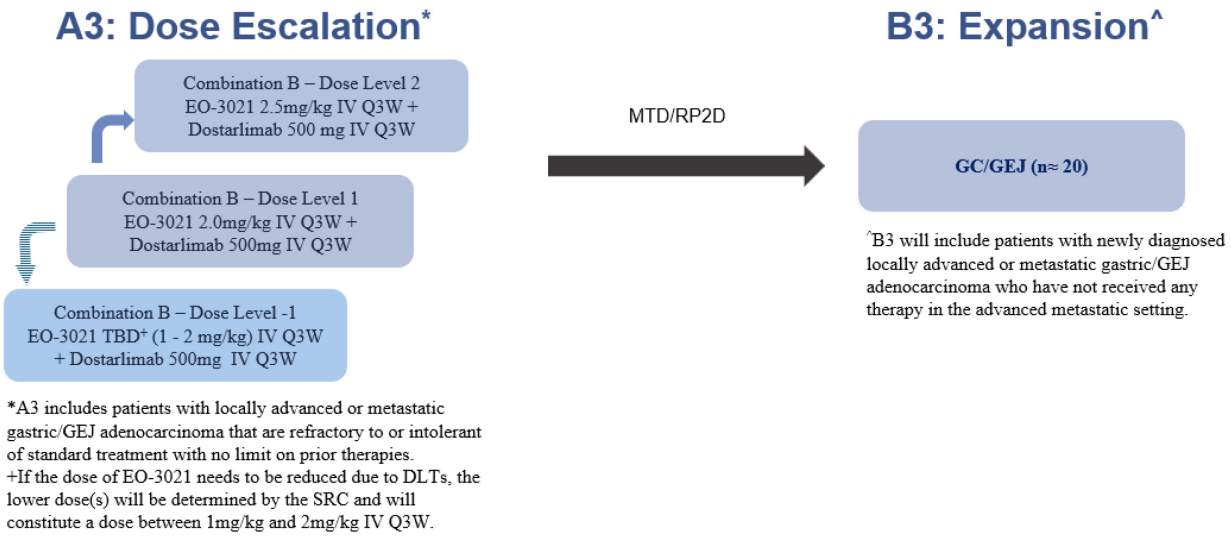
GC = Gastric cancer; GEJ = Gastro-esophageal junction; IV = Intravenous; MTD = Maximum tolerated dose; Q3W = Once every 3 weeks; RP2D = Recommended phase 2 dose

Figure 3: Study Schema for Arm 2 (Combination with Ramucirumab)



DLT = Dose-limiting toxicity; GC = Gastric cancer; GEJ = Gastro-esophageal junction; IV = Intravenous; MTD = Maximum tolerated dose; Q3W = Once every 3 weeks; RP2D = Recommended phase 2 dose; SRC = Safety Review Committee; TBD = to be determined

Figure 4: Study Schema for Arm 3 (Combination with Dostarlimab)



DLT = Dose-limiting toxicity; GC = Gastric cancer; GEJ = Gastro-esophageal junction; IV = Intravenous; MTD = Maximum tolerated dose; Q3W = Once every 3 weeks; RP2D = Recommended phase 2 dose; SRC = Safety Review Committee; TBD = to be determined

4. STUDY POPULATION

Patient selection criteria include general criteria applicable to all patients (Section 4.1) as well as additional exclusion criteria included in Section 4.2.1 and Section 4.2.3 for combination of EO-3021 with ramucirumab and dostarlimab, respectively.

4.1. Inclusion Criteria (All Parts and Treatment Arms, Unless Noted)

To be eligible for participation in the study, patients must meet the following inclusion criteria:

1. Age ≥18 years
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 at screening
3. Histologically and/or cytologically confirmed diagnosis of advanced metastatic gastric/GEJ adenocarcinoma not amenable to resection or radiation therapy with curative intent
4. Availability of tumor tissue for evaluation of biomarker including:
   For Part A (Dose Escalation) all arms:
   a. Archived FFPE block or slides of tumor tissue from a previous biopsy obtained within last 24 months (Note: Only applicable to dose escalation and non-prospective selection portion of expansion arms) **AND**
   b. Fresh (new) biopsy prior to start of treatment, if medically feasible. Tumor biopsies should be considered by the treating physician, in accordance with site standard procedures, and obtained using a low-risk, medically routine procedure (Levit et al., 2019) (Note: Only applicable to dose escalation and non-prospective selection portion of expansion arms)
      i. *Note: Tumor biopsy obtained prior to consent but no more than 3 months prior to C1D1 without any intervening treatment between the biopsy and C1D1 may be used to fulfill the fresh tumor tissue requirement with Sponsor approval*
   c. Patients who meet only one of the above tumor tissue requirements for retrospective testing may still be eligible for the study after review and approval from the Sponsor.

   For Part B (Expansion) all arms:
   d. For the prospective selection portion of the expansion arms, a FFPE block or a minimum of 6 unstained slides of tumor tissue from a biopsy obtained within 6 months of enrollment must be available to submit for central review. (Note: If the patient received any CLDN18.2 directed therapy after the date of the archival biopsy a new biopsy must be performed and a FFPE block or 6 unstained slides must be available for central review.)
   e. For the prospective selection portion of expansion arms, patients must have tumor CLDN18.2 expression of greater than or equal to 25% 1+/2+/3+ by central laboratory review.
5. Progressed on or after standard therapy, or are intolerant of available standard therapy, or there is no available standard therapy
   a. For Part A (Dose Escalation) with monotherapy EO-3021 (Arm A1) and in combination with ramucirumab (Arm A2) or dostarlimab (Arm A3), there is no limit on the number of prior lines of therapy
   b. For Part B (Expansion) for monotherapy EO-3021 (Arm B1), at least 1 but no more than 3 prior lines of therapy in the advanced/metastatic setting is allowed

c. For Part B (Expansion) for combination of EO-3021 plus ramucirumab (Arm B2), only 1 prior line of therapy in the advanced/metastatic setting is allowed; prior fluoropyrimidine and platinum-containing chemotherapy is required
d. For Part B (Expansion) for combination of EO-3021 plus dostarlimab (Arm B3), no prior systemic therapy in the advanced/metastatic setting is allowed

6. At least one measurable extra-cranial lesion as defined by RECIST v1.1
   a. For Part A (Dose Escalation), patients with evaluable but non-measurable disease per RECIST v1.1 may be eligible after discussion and approval from the Sponsor
7. Adequate organ function, defined as:
   a. ***Hematology:*** defined as absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelet ≥90 x 10^9/L, hemoglobin ≥9.0 g/dL (in the absence of transfusion within the last 7 days and use of growth factors within the last 14 days prior to C1D1)
      i. For Arms A2 and B2 (Combination of EO-3021 plus ramucirumab): platelet ≥100 x 10^9/L
   b. ***Renal function:*** defined as estimated glomerular filtration rate (eGFR) ≥40 mL/min (using the Cockcroft-Gault formula):

      Female CrCl = ((140 - age in years) x weight in kg x 0.85) / (72 x serum creatinine in mg/dL)

      Male CrCl = ((140 - age in years) x weight in kg x 1.00) / (72 x serum creatinine in mg/dL)

      i. For Arms A2 and B2 (Combination of EO-3021 plus ramucirumab):
         1. The patient has adequate renal function as defined by a serum creatinine ≤1.5 times the upper limit of normal (ULN), or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (that is, if serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed
         2. The patient's urinary protein is ≤1+ on dipstick or routine urinalysis (UA); if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to allow participation in Arms A2 and B2)
   c. ***Hepatic Function***:
      i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN) for patients without liver metastases or ≤5 x ULN if liver metastases are present
      ii. Total bilirubin ≤1.5 x ULN for patients without liver metastases or ≤3 x ULN if liver metastases are present, or the patient has bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin
   d. ***Coagulation function:*** International Normalized Ratio (INR) ≤1.5; Activated Partial Thromboplastin Time (APTT) ≤1.5 × ULN (patients on chronic anticoagulants are eligible)
      i. Note: Patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin (LMWH). If receiving warfarin, the patient must have an INR ≤3.0. Patients should have no active bleeding (that is, no bleeding within 14 days

prior to C1D1) or pathological condition present that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices).

8. Albumin level ≥3.0 g/dL
9. Life expectancy >12 weeks
10. Ability to understand the nature of this study, comply with protocol requirements, and give written informed consent
11. Willingness of men and women of reproductive potential to observe conventional and effective birth control (consistent with local regulations) for the duration of treatment and for 6 months following study completion (or longer as required by local regulations including 6 months plus 5 half-lives for female patients in South Korea and 3 months plus 5 half-lives for male patients in South Korea). Please refer to Appendix A for detailed criteria for men and women of reproductive potential.

4.2. Exclusion Criteria (All Parts and Treatment Arms, Unless Noted)

To be eligible for participation in the study, patients must **not** meet any of the following exclusion criteria:

1. Have non-adenocarcinoma histologic subtype of gastric/GEJ cancer (e.g., adenosquamous carcinoma, squamous carcinoma, etc.)
2. Have unresolved toxicities from prior anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, grade ≤1 or baseline. Patients with chronic grade 2 toxicities (except for Grade 2 peripheral neuropathy) may be eligible per the discretion of the Investigator after discussion and approval from the Sponsor
3. Have a history of several allergic and/or anaphylactic reactions to known chimeric, human, or humanized antibodies, fusion proteins or known allergies to components of EO-3021, ramucirumab, or dostarlimab
4. Have serious concurrent illness or clinically relevant active bacterial, fungal or viral infection including but not limited to the following:
    a. Active hepatitis B or C infection (whether or not on active antiviral therapy)
        i. For Arms A3 and B3 (Combination of EO-3021 plus dostarlimab), patients must have documented negative Hepatitis B surface antigen (HBsAg) and Hepatitis C antibody tests within 3 months prior to C1D1, see Section 4.2.3.
    b. Known human immunodeficiency virus (HIV) infection
    c. Other concurrent infectious disease requiring IV antibiotics within 2 weeks prior to C1D1

    Note: testing for HIV or hepatitis B or C is not required unless clinically indicated or required by local regulations
5. Have diagnosis of another malignancy, or history of systemic treatment for invasive cancer within last 3 years. *Note: Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. Diagnosis of non-melanoma skin cancer, carcinoma in situ of the cervix or breast, or noninvasive tumor does not affect eligibility.*
6. Have active central nervous system (CNS) disease involvement, defined by cerebrospinal fluid (CSF) cytology, magnetic resonance imaging (MRI) or computerized tomography (CT)

   a. Patients with asymptomatic CNS metastases are eligible if they have been clinically stable for at least 4 weeks prior to C1D1 and do not require interventions such as surgery, radiation, or any corticosteroid therapy for management of symptoms related to CNS disease.
   b. Patients with history of brain metastasis previously treated with radiation and/or surgical resection and without evidence of progression at screening are eligible, including those on stable low-dose of steroids (i.e., 10 mg orally (PO) daily of prednisone or equivalent).
   c. Screening for CNS disease is not required. Patients with history of CNS disease should have head imaging within the last 3 months documenting no active disease. Patients with signs/symptoms concerning for CNS involvement should undergo head imaging to rule out active CNS disease at screening.
7. Have history of non-infectious pneumonitis/interstitial lung disease
8. Have peripheral neuropathy Grade ≥2
9. Have active ocular surface disease defined as symptomatic or Grade ≥2 disease involving the cornea at baseline (based on screening ophthalmic examination)
10. Have history of Grade ≥2 gastritis
11. Are pregnant or breastfeeding
12. Have previously received anti-CLDN18.2 ADCs or any ADC containing an auristatin payload
13. Have had major surgery (excluding tumor biopsy) within 28 days prior to C1D1
14. Have received systemic anticancer therapy including chemotherapy, radiotherapy, biological therapy, targeted therapy, immunotherapy and investigational therapies within 28 days or 5 half-lives, whichever is shorter, before the first dose of EO-3021 and the combination with ramucirumab or dostarlimab

    a. Use of palliative radiotherapy for bone metastases or local radiotherapy for pain relief within 2 weeks before the first dose of EO-3021 and the combination with ramucirumab or dostarlimab is allowed.
    b. Ongoing use of drugs for bone metastasis related events (e.g., zoledronic acid) will not affect eligibility.
15. Have history of allogenic hematopoietic stem cell transplantation or solid organ transplantation
16. Use of any drugs or substances known to be strong inducers or inhibitors of CYP3A enzymes (Table 9) and/or P-glycoprotein within 7 days prior or 3 half-lives, whichever is shorter, before the first dose of EO-3021 and the combination with ramucirumab or dostarlimab
17. Have clinically significant cardiac disease, including but not limited to, any of the following within 6 months prior to C1D1:
    a. Myocardial infarction
    b. Unstable angina pectoris
    c. Cerebrovascular accident, transient ischemic attack, cerebral infarction
    d. Uncontrolled congestive heart failure (New York Heart Association Class III or IV)
    e. Uncontrolled or poorly controlled hypertension (defined as >160 mmHg systolic or >100 mmHg diastolic for >4 weeks despite standard medical management)
    f. Unstable cardiac arrhythmia requiring acute therapy (including torsades de pointes)

g. Prolongation of the QT interval corrected for heart rate (QTcF) > 480 ms on at least 2 of 3 consecutive electrocardiograms (ECGs) and/or mean QTcF > 480 ms on all 3 ECGs during screening. Correction of suspected drug induced QTcF prolongation may be attempted at the investigator's discretion if considered clinically safe.

18. Have received any live vaccine within 30 days of enrollment. Vaccination against coronavirus disease 2019 (COVID-19) using vaccines that are authorized via the appropriate regulatory mechanisms (e.g., Emergency Use Authorization, Conditional Marketing Authorization, or Marketing Authorization Application) are not exclusionary. *Note: mRNA and adenoviral-based COVID-19 vaccines are considered non-live. If a COVID-19 vaccine is administered at any time, the date of COVID-19 vaccination must be entered in the eCRF.*
19. Patients who are not appropriate candidates for participation in this clinical study for any other reason as deemed by the investigator.

4.2.1. Exclusion Criteria for Part B Expansion (All Treatment Arms B1, B2, B3)

In addition to the main exclusion criteria, patients must **not** meet any of the following exclusion criteria:

1. Have HER2+ disease as defined by American Society of Clinical Oncology-College of American Pathologists guidelines for gastric/GEJ adenocarcinoma
2. Have non-measurable disease per RECIST v1.1

4.2.2. Additional Exclusion Criteria for Combination with Ramucirumab (Arms A2 and B2)

In addition to the main exclusion criteria, patients must **not** meet any of the following exclusion criteria:

1. Received prior treatment with ramucirumab and other VEGFR2 inhibitors
2. Have experienced any Grade 3-4 gastrointestinal bleeding within 3 months prior to C1D1.
3. Have a history of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to C1D1.
4. Have cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and with a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis.
    a. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.
5. Is receiving chronic antiplatelet therapy, including dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.
6. Have a prior history of GI perforation/fistula (within 6 months of first dose of protocol therapy) or risks factors for perforation.
7. Have a serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to C1D1.
8. Have a minor surgery/subcutaneous venous access device placement within 7 days prior to C1D1.
9. The patient has elective or planned major surgery to be performed during the course of the clinical trial.

4.2.3. Additional Exclusion Criteria for Combination with Dostarlimab (Arms A3 and B3)

In addition to the main exclusion criteria, patients must **not** meet any of the following exclusion criteria:

1. Prior treatment with immune checkpoint inhibitors (ICI) including dostarlimab and other anti-PD-1, anti-PD-L1, etc.
2. Have an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
3. Have experienced any of the following with prior immunotherapy: any immune-related adverse event ≥Grade 3, immune-mediated severe neurologic events of any grade (e.g., myasthenic syndromic/myasthenia gravis, encephalitis, Guillain Barré syndrome, or transverse myelitis), exfoliative dermatitis of any grade (Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], or drug reaction with eosinophilia and systemic symptoms [DRESS] syndrome), or myocarditis of any grade. Non-clinically significant laboratory abnormalities are not exclusionary.
4. Have documented presence of HBsAg at Screening or within 3 months prior to C1D1. Patients with a negative HBsAg and positive Hepatitis B core antibody result are eligible only if HBV DNA is negative.
5. Have a positive Hepatitis C virus (HCV) antibody test result at Screening visit or within 3 months prior to C1D1. *Note: Patients with a positive HCV antibody test result due to prior resolved disease can be enrolled, only if a confirmatory negative HCV RNA test is obtained.*

5. ENROLLMENT AND REGISTRATION PROCEDURES

5.1. Enrollment of Patients

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side effects, risks, and discomforts. Human protection committee (institutional review board [IRB]/ethics committee [EC]) approval of this protocol and the ICF is required. Eligible patients who wish to participate will be enrolled into the study after fulfilling the eligibility criteria for the study.

5.2. Screen Failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore are not enrolled into the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a patient is excluded from the study, the reasons for exclusion are documented in the patient's source documents, and on the Screening and Enrollment log. Patients who screen fail may be re-screened according to inclusion and exclusion criteria after appropriate treatment or observation at the discretion of the Investigator. Re-screened subjects are assigned a new screening number and signed a new ICF. Each patient has one re-screening opportunity. If a patient re-screens, some study assessments (e.g., baseline

imaging, baseline ophthalmic exams, etc.) may not need to be repeated if they originally occurred within the appropriate screening window for the new C1D1.

5.3. Registration of Patients

Registration must occur prior to the initiation of protocol therapy (i.e., C1D1). Patient registration and dose level assignment are performed by the Sponsor or Clinical Research Organization (CRO) designee. The Sponsor or CRO designee documents the patient identification number, dose level, and date of enrollment on the Registration Form and sends the completed form back to the site following the registration request.

Sites cannot enroll or administer a dose of EO-3021 (or EO-3021 in combination with ramucirumab or dostarlimab) to any patient without receiving the assigned patient number, treatment arm and dose cohort (if applicable) from the CRO. The patient should commence treatment as soon as practical after receiving the registration confirmation.

For additional information regarding study registration, please refer to the Study Reference Manual.

5.4. Replacement of Patients

If a patient withdraws or is withdrawn from the study either prior to C1D1, or prior to the completion of the DLT observation period in Part A (Dose Escalation) for any reason other than DLT and does not meet the minimum requirements for inclusion in the MTD-determining population described in Section 6.3.5, that patient may be replaced, if fewer than 3 patients are dosed that dose level.

Any patient receiving at least one dose of EO-3021 will be asked to have all end of treatment safety evaluations performed as described in the protocol schedule of assessments (Appendix C).

5.5. Blinding Procedures

This is an open-label study. No blinding procedures will be applied.

6. STUDY TREATMENT

All patients entering this study will receive EO-3021 (alone or in combination with ramucirumab or dostarlimab) by IV infusion at a dose level based on data evaluation from the prior cohort(s). Patients should receive EO-3021 infused over 90-120 (±10) minutes for the first dose in C1D1. In the absence of infusion reactions, subsequent infusion time may gradually be decreased to 60-90 (±10) minutes, as tolerated. Longer infusion times with EO-3021 may be acceptable based on patient tolerance and adverse events. Patients in Arms A2 and B2 should receive ramucirumab infused over 60 (±10) minutes; subsequent infusion time may gradually be decreased to 30 (±10) minutes as tolerated by the patient. Patients in Arms A3 and B3 should receive dostarlimab infused over 30 (±10) minutes as tolerated by the patient. All doses should be administered on an outpatient basis. Patients will receive the protocol therapy until disease progression, unacceptable toxicity, or one or more protocol-specific treatment discontinuation criteria have been met as described in Section 6.8.1.

6.1. Selection of Starting Dose of EO-3021 (Monotherapy)

The proposed starting dose in the clinical study of EO-3021 sponsored by Elevation Oncology is 1.0 mg/kg IV Q3W. The starting dose is based on the safety, tolerability, and efficacy data obtained in the clinical study of SYSA1801-CSP-001 sponsored by CSPC in China.

The starting dose in the clinical study of SYSA1801-CSP-001 was 0.5 mg/kg IV Q3W, which was estimated based on toxic dose levels in Sprague Dawley rat and cynomolgus monkeys, toxicokinetic data in animal species, and with consideration of the pharmacological activity observed in the efficacy study in mouse models. One patient received EO-3021 at this dose of 0.5 mg/kg IV Q3W. The patient did not experience a DLT or intolerance during the treatment cycles as defined in the study protocol. The patient had a best overall tumor response of SD, and discontinued study treatment due to progressive disease (PD) after 5 months of study treatment. At the next dose level at 1.0 mg/kg IV Q3W, 3 patients were enrolled and treated under the 3+3 study design; no DLT was experienced, and only mild/moderate (Grade 1/2) adverse events were reported. One patient had a best overall tumor response of confirmed PR and 2 patients with PD. Based on the overall benefit/risk of EO-3021, and to limit the number of patients exposed to a potentially subtherapeutic dose, the starting dose in the study sponsored by Elevation Oncology is set at 1.0 mg/kg IV Q3W.

As the toxicities of EO-3021 are related mainly to the conjugated small molecule cytotoxin MMAE, the starting clinical dose in the study SYSA1801-CSP-001 sponsored by CSPC in China was determined using the recommended approaches to setting a first-in-human starting dose for small molecule cytotoxic drugs. The guidance provided in the *International Conference on Harmonisation (ICH) S9 guideline ("Nonclinical Evaluation for Anticancer Pharmaceutical")* recommends setting the starting dose at 1/10th the severely toxic dose (STD) in 10% of animals (STD10) in rodents or 1/6th the HNSTD in nonrodents according to body surface area (BSA) calculation.

In the 6-week repeat-dose toxicity study in Sprague Dawley rats, there was 4% mortality at 50 mg/kg EO-3021 (less than STD10); this is equivalent to a human dose of 10.1 mg/kg based on BSA conversion. Applying a safety factor of 10 on rodent STD results in a maximum recommended starting dose (MRSD) of 1.01 mg/kg. In the 6-week repeat-dose toxicity study in cynomolgus monkeys, the HNSTD of EO-3021 was 20 mg/kg. Based on its human equivalent dose (HED) of 8.09 mg/kg and a safety factor of 6 based on non-rodent HNSTD, the MRSD was calculated to be 1.35 mg/kg. The data from both relevant species suggest a similar starting dose.

In animal efficacy model studies, the effective doses (single dose in 3-week period) for the 3 CLDN18.2 overexpressing models were 0.5 mg/kg (0.04 mg/kg HED; NUGC4-CLDN18.2), 2 mg/kg (0.16 mg/kg HED; BxPC3CLDN18.2), and 4 mg/kg (0.33 mg/kg HED; NCI-H460-CLDN18.2).

6.2. Selection of Starting Dose for Combination

6.2.1. EO-3021

Prior to this amendment, the starting dose in monotherapy dose escalation was 1.0 mg/kg IV Q3W as described above. Three patients (2 with gastric/GEJ adenocarcinoma and 1 with pancreatic cancer) were treated at 1.0 mg/kg IV Q3W with no DLTs. Doses of up to 2.9 mg/kg IV Q3W have been evaluated and are ongoing with a manageable safety profile. No DLTs were observed at

2.0 mg/kg IV Q3W and 2.5 mg/kg IV Q3W. DLTs were observed at 2.9 mg/kg IV Q3W. These DLTs were Grade 3 encephalopathy and Grade 3 fatigue in patients with pancreatic cancer. In the combination dose finding part of the study, the starting dose of EO-3021 will be 2.0 mg/kg IV Q3W. The dose can be escalated to 2.5 mg/kg IV Q3W or de-escalated to doses between 2.0 mg/kg and 1.0 mg/kg IV Q3W based on the SRC recommendation following standard 3+3 study design.

6.2.2. Ramucirumab

In gastric/GEJ cancer, the approved dose of ramucirumab is 8 mg/kg every 2 weeks as monotherapy and 8 mg/kg on Days 1 and 15 in combination with paclitaxel 80 mg/m^2 on Days 1, 8, 15 of a 28-day cycle. In NSCLC, the approved dose of ramucirumab is 10 mg/kg on Day 1 in combination with docetaxel 75 mg/m^2 on Day 1 of a 21-day cycle (CYRAMZA, 2022). Based on the ramucirumab IB, two dose regimens, 8 mg/kg Q2W and 10 mg/kg Q3W, were selected for the 8 Phase 3 studies, including gastric cancer (REGARD and RAINBOW), NSCLC (REVEL), colorectal cancer (RAISE), hepatocellular carcinoma (REACH and REACH-2), urothelial carcinoma (RANGE), and breast cancer (ROSE). The choice of Q2W dosing versus Q3W dosing was primarily determined by the regimen of combination therapies. Furthermore, outcomes from 2 dose-response studies demonstrated that ramucirumab 8 mg/kg Q2W or 10 mg/kg Q3W dosing regimens are appropriate for second-line gastric cancer, NSCLC, and colorectal cancer. Given that EO-3021 is administered once every 3 weeks, the dose of ramucirumab administered in the combination arm will be 10 mg/kg IV Q3W.

6.2.3. Dostarlimab

The approved dose of dostarlimab as monotherapy for the treatment of dMMR recurrent or advanced endometrial cancer and solid tumors is 500 mg IV every 3 week for the first 4 doses then 1000 mg IV every 6 weeks until disease progression or unacceptable toxicity. The approved dose of dostarlimab as combination therapy for the treatment of dMMR/microsatellite instability-high (MSI-H) primary or recurrent endometrial cancer is 500 mg IV every 3 weeks with carboplatin and paclitaxel for 6 doses then 1000 mg IV monotherapy every 6 weeks until disease progression, unacceptable toxicity, or up to 3 years (JEMPERLI, 2024). The transition from Q3W to Q6W dosing regimen of dostarlimab reduced the frequency of dosing visits for patients after the initial 4 or 6 doses. However, given that EO-3021 is dosed Q3W until disease progression, unacceptable toxicity, or 1 or more protocol-specific treatment discontinuation criteria have been met, the dosing regimen of dostarlimab will be as 500 mg IV Q3W for the duration of study treatment in combination with EO-3021. The maximum duration of the combination of dostarlimab and EO-3021 is 3 years from the date of therapy start.

6.3. Study Part A: Dose-Escalation Procedure

6.3.1. Monotherapy Dose-Escalation (Arm A1)

The study explores a Q3W schedule in which a dose is administered once every 3 weeks.

Arm A1 (monotherapy dose escalation) follows the BOIN MTD (Yuan 2016, Zhou 2018). The starting dose of EO-3021 in Arm A1 (monotherapy) is 1.0 mg/kg IV Q3W with 4 planned dose levels (Table 1). Intermediate dose levels or higher dose levels of EO-3021 may be explored, depending on the observed safety profile and PK data analysis, if deemed appropriate.

Table 1 Illustrative Dose Escalation of EO-3021 in Arm A1 (Monotherapy)

Dose Level	EO-3021 (mg/kg)	% Increase from Prior Dose Level	Patients (n)
1	1.0	-	3-12
2	2.0	100%	3-12
3	2.5	25%	3-12
4	2.9	16%	3-12

The target toxicity rate for the MTD is 25% and the target sample size in Arm A1 (monotherapy dose escalation) is approximately 30. Patients enrolled are treated in cohorts of 3. Dose limiting toxicities are defined in Section 6.3.4 and the DLT evaluation period is 21 days. The BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- if the observed DLT rate at the current dose is ≤0.197, escalate the dose to the next higher dose level
- if the observed DLT rate at the current dose is >0.298, de-escalate the dose to the next lower dose level
- otherwise, stay at the current dose.

At each dose level, a 3+3 run-in is applied to override the above rules when the number of subjects treated at the current dose is 3. Specifically, it will escalate the dose if 0 of 3 DLT, stay at the current dose if 1 of 3 DLT, and de-escalate the dose if ≥2 of 3 DLTs. As a result of the incorporation of the 3+3 run-in, the updated dose escalation/de-escalation and elimination rules are summarized in Table 2, which will be used to conduct the trial. Dose is not escalated to the next higher level unless 3 subjects are treated and are DLT evaluable. The dose escalation phase of Arm A1 is complete if the sample size reaches approximately 30 or the number of evaluable subjects treated at the current dose reaches 12 and the dosing decision according to Table 2 is to stay at the current dose. At the discretion of the SRC and Sponsor, additional backfill patients may be included to further characterize the MTD/RP2D. Further, the SRC and Sponsor may choose to evaluate two candidate RP2Ds in expansion.

Table 2 Dose Escalation/De-escalation Rules for the BOIN Design

# of Evaluable Subjects Treated at Current Dose	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Escalate if # of DLT ≤	0	0	0	0	0	1	1	1	1	1	2	2
De-escalate if # of DLT ≥	1	1	2*	2	2	2	3	3	3	3	4	4
Eliminate if # of DLT ≥	NA	NA	3	3	3	4	4	4	5	5	6	6

BOIN = Bayesian optimal interval; DLT=dose-limiting toxicity; NA = not evaluable

Note: "# of DLT" is the number of patients with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate, or eliminate) is triggered, stay at the current dose for treating the next cohort of subjects. "NA" means that a dose cannot be eliminated before treating 3 evaluable subjects. "*" indicates the 3+3 design run-in.

When using Table 2, please note the following:

- "Eliminate" means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
- When a dose is eliminated, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, the study will be terminated or amended.
- If none of the actions (i.e., escalation, de-escalation, or elimination) is triggered, treat the new patients at the current dose.
- If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate or amend the study.
- If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.

6.3.2. Combination Dose-Escalation (Arms A2 and A3)

The starting dose of EO-3021 in Arm A2 (combination with ramucirumab) and Arm A3 (combination with dostarlimab) is 2.0 mg/kg IV Q3W and will be escalated to 2.5 mg/kg IV Q3W or de-escalated to doses between 2 mg/kg and 1 mg/kg IV Q3W as recommended by the SRC following the standard 3+3 design (Table 3). Ramucirumab will be administered as 10 mg/kg IV Q3W after EO-3021. Dostarlimab will be administered as 500 mg IV Q3W after EO-3021.

Table 3: Illustrative Dose Escalation of EO-3021 in Arm A2 (combination with ramucirumab) and Arm A3 (combination with dostarlimab)

Dose Level	EO-3021 (mg/kg)	% change from starting dose	Patients (n)
0	1.0-2.0*	Up to 50% decrease	3-6
1	2.0	Starting dose	3-6
2	2.5	25% increase	3-6

*As recommended by the SRC if de-escalation is needed

At each dose level within Arm A2 (combination with ramucirumab) and Arm A3 (combination with dostarlimab), a standard 3+3 design will be applied. Specifically, the design starts off by treating 3 patients at the starting dose. If no DLTs are observed, the study proceeds to the next higher dose with 3 more patients. If 1 DLT is observed among the previous 3 patients, 3 more patients are treated at the current dose. If 1-2 DLTs are observed among the 3-6 patients, respectively, at the starting dose, then the dose of EO-3021 will be de-escalated to a lower dose determined by the SRC. If ≥2 DLTs occur in 3 or 6 patients at any level, the previously evaluated dose becomes the maximum tolerated dose. Dose escalation continues until an MTD is defined. Dose is not escalated to the next higher level unless 3 subjects are treated and are DLT evaluable. The dose escalation phase of Arm A2 and Arm A3 is complete if the sample size reaches approximately 18 or the number of evaluable subjects treated at the current dose reaches 6 and the dosing decision according to Table 3 is to stay at the current dose. At the discretion of the SRC and Sponsor, additional backfill patients may be included to further characterize the MTD/RP2D. Further, the SRC and Sponsor may choose to evaluate two candidate RP2Ds in expansion.

6.3.3. Intermediate Dose Levels

Intermediate dose levels of EO-3021 other than the target doses stipulated in the study schemas (Figure 2, Figure 3, and Figure 4), Table 1, and Table 3 may be explored following the demonstration of a DLT to ascertain a safe and effective dose(s). Selection of doses will be determined by the SRC based on risk/benefit to patients.

6.3.4. Dose-Limiting Toxicity (DLT)

A TEAE is defined as an adverse event (AE, according to CTCAE Version 5.0) that starts on or after the first administration of study medication.

A DLT is defined as a TEAE that is considered at least possibly related to study treatment, occurs within the first 21 days of treatment initiation (i.e., during Cycle 1), meets at least one of the criteria listed below (with severity graded according to CTCAE v5.0), and is not reasonably attributed to the patient's underlying disease or another medical condition.

Patients enrolled to backfill do not contribute to the DLT rate for the determination to escalate/de-escalate the dose level.

Hematological DLT will be defined as:

- Grade 4 neutropenia (ANC <0.5 x 10^9/L) present for more than 7 days
- Febrile neutropenia (defined as ANC <1.0×10^9/L with a single temperature >38.3°C [101°F] or a sustained temperature of ≥38°C [100.4°F] for more than 1 hour)
- Grade 4 thrombocytopenia (platelets <25 x 10^9/L)
- Grade 3 thrombocytopenia (platelets <50 x 10^9/L) with clinically significant bleeding
- Grade 4 anemia (life-threatening consequences; urgent intervention indicated)

Non-hematological DLT will be defined as:

- Grade 3 or 4 non-hematologic toxicity. The following will **not** be considered DLTs:
  - Grade 3 nausea and/or vomiting or diarrhea lasting <72 hours with maximal supportive therapy
  - Grade 3 fatigue for <7 days

In addition, the following events are also qualified as DLTs:

- Grade 3 and above infusion-related reaction
- Treatment delay of EO-3021 for Cycle 2 Day 1 (C2D1) by >21 days due to unresolved treatment related toxicity.
- Dose reduction of EO-3021 for any reason at C2D1 (e.g., the patient receives a lower dose at C2D1 than C1D1)
- Concurrent elevation of ALT or AST ≥3 × ULN and total bilirubin >2 × ULN (>35% direct bilirubin; >3 × ULN total bilirubin for subjects with Gilbert's syndrome) or ALT or AST ≥3 × ULN, which may indicate severe liver injury (potential Hy's Law), in the absence of cholestasis and other causes (e.g., viral hepatitis, other preexisting or acute

liver disease, or another drug capable of the observed). Any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the Sponsor Medical Monitor.

- For patients with hepatic metastases, AST or ALT >8 x ULN or AST or ALT >5 x ULN for ≥14 days excluding other causes (e.g., viral hepatitis, other preexisting or acute liver disease, or another drug capable of the observed).
- Any death during DLT-period not clearly due to the underlying disease or extraneous causes

The following non-hematologic TEAEs will **not** be considered DLTs:

- Asymptomatic Grade 3 or 4 electrolyte abnormalities or lab abnormalities that are not clinically significant per the investigator and resolve spontaneously or with standard medical treatment within 72 hours

6.3.5. Determination of Dose-Limiting Toxicities

The patient population used for determination of DLTs will consist of patients who have received the intended dose of EO-3021 and have met the minimum 21-day DLT observation period in Part A (Dose Escalation). Toxicity appearing following this minimum observation period may be considered a DLT, if clinically relevant. Patients enrolled to backfill do not contribute to the DLT rate for the determination to escalate/de-escalate the dose level.

6.3.6. Maximum Tolerated Dose

The EO-3021 MTD for Arm A1 (monotherapy) will be estimated based on all DLT evaluable patients using isotonic regression. The target toxicity rate for the MTD is 25% in Arm A1 based on the BOIN design.

The EO-3021 MTD in combination with ramucirumab (Arm A2) or dostarlimab (Arm A3) is defined as the highest dose level of EO-3021 at which no more than 0 of 3 or 1 of 6 patients experiences a DLT during the first cycle of therapy. The target toxicity rate for the MTD in combination is 33% in Arm A2 (combination with ramucirumab) and Arm A3 (combination with dostarlimab) based on the standard 3+3 design.

6.3.7. Recommended Phase 2 Dose

The RP2D will not be greater than the MTD. However, the RP2D may be a lower dose level in certain circumstances:

- If emerging toxicity at the MTD is unpredictable or undesirable for other reasons
- If clear evidence of efficacy is noted at lower doses with a cleaner safety profile
- If longer follow-up on earlier patient cohorts suggests the emergence of delayed toxicity

The SRC will review the totality of the data from dose escalation and recommend one or more candidate RP2D for Part B (Expansion). If two candidate RP2Ds are selected for expansion simultaneously, randomization may be employed to assign patients to one of two candidate RP2Ds.

6.3.8. Safety Overview and Dose-Escalation Decisions

A SRC is established to monitor study conduct and to assess the safety and tolerability and PK (if available) of EO-3021. The SRC is composed of Sponsor representatives, site Investigators, and CRO representatives. Regular conference calls between participating centers, the designated CRO, and the Sponsor will be scheduled bi-weekly during the dose-escalation phase. Additional calls may be scheduled at any time if warranted by the emerging safety profile. The purpose of each call will be to review patient enrollment and emerging safety data. Participating investigators and the Sponsor's Medical Monitor will review study drug-related toxicities, current patient PK profiles if available, and any other relevant data from the current cohort before escalating to the next dose. The SRC will provide a recommendation for the RP2D including the potential to evaluate intermediate doses, higher doses or more than one RP2D. Additional information on the SRC can be found in the study SRC Charter.

6.4. Study Part B: Dose-Expansion at the RP2D

Once the RP2D has been selected for a treatment arm in Part A (e.g. A1, A2, or A3) then the treatment arm may proceed to Part B (e.g. B1, B2, or B3).

A total of approximately 120 patients could be enrolled in Part B (Expansion), including approximately 80 patients in Arm B1 (monotherapy) and 20 patients each in Arm B2 (combination with ramucirumab) and Arm B3 (combination with dostarlimab). The plan for the expansion group may be adjusted based on the enrollment of patients in the dose escalation phase and evolving data.

Part B (Expansion) will allow the following:

- Further characterization of the safety and PK profile
- Confirmation or modification of the ultimate EO-3021 dose to be used in future studies
- Early exploration of efficacy in relevant patient population

If two candidate RP2Ds are selected for expansion simultaneously within a treatment arm, randomization may occur during Part B (Expansion) to assign patients to one of two candidate RP2Ds in each cohort.

6.5. Dose Modifications

6.5.1. Dose Modification Rules

Dose reductions or treatment delays are allowed as clinically indicated by the treating physician. Scheduled prophylaxis for management of nausea/vomiting is recommended for all patients prior to C1D1 as outlined in Section 6.5.3. If EO-3021 or combination therapy (e.g., ramucirumab or dostarlimab) meets the criteria for dose delay for drug-related AEs regardless of whether the event is attributed to E0-3021, ramucirumab, or dostarlimab, then administration of both drugs must be delayed if any of the delay criteria are met. Patients whose treatment is **delayed** due to toxicity will either discontinue study treatment or will proceed with the next cycle of treatment when toxicity has improved (as long as the toxicity resolves within 21 days or with approval from the Sponsor) according to the dose modifications below.

Any allowed dose modification and any deviation from the intended dose (e.g., missed doses or overdoses) should be documented on the dose electronic Case Report Form (eCRF).

If the study drug is interrupted for >21 days, the patient has to be rescanned to ensure no disease progression has occurred and the Investigator and the Sponsor Medical Monitor agree that continued treatment at the same or lower dose is in the best interest of the patient; otherwise discontinue the study drug.

6.5.2. Dose Modification Criteria for EO-3021

Dose modifications may occur during Part A (Dose Escalation) or Part B (Expansion). In Part A (Dose Escalation), any patient who was previously enrolled in a dose cohort that was subsequently determined to be above the MTD will be allowed to continue to receive EO-3021 at the MTD, if deemed medically appropriate by the Investigator and the Sponsor.

After Cycle 1 in Part A (Dose Escalation), if a dose reduction is recommended, then the dose selected should be the last highest dose tested that was considered to be tolerable in prior subjects receiving that dose. After Cycle 1 in Part B (Expansion), if a dose reduction is recommended, then the first dose reduction should be 25% of the RP2D and the next dose reduction, if needed, should be 50% of the RP2D. Up to two dose reductions are allowed.

In general, the dose modifications described in Table 4 for non-hematologic and Table 5 for hematologic toxicities should be applied to the dosing of EO-3021. Toxicities should be managed per institutional guidelines, as appropriate, and should include evaluation for all potential underlying causes. Appropriate subspeciality consultation should be sought, as clinically indicated.

Management and supportive care guidelines for selected toxicities are outlined in Section 6.5.2.1 (nausea and/or vomiting), Section 6.5.2.2 (infusion-related reactions), and Section 6.5.2.3 (ocular adverse events).

Table 4: Dose Modification Guidelines for Non-Hematologic Toxicities Considered Related to Study Treatment

CTCAE v5.0 Grade	Action and Dose Modification for EO-3021[b]
Grade 1	• Continue study treatment at current dose level • Monitor closely • Provide supportive care according to institutional standards
Grade 2	• Interrupt study treatment if clinically indicated • Monitor closely • Provide supportive care according to institutional standards • If the toxicity resolves to Grade ≤1 or the patient's baseline within 21 days, resume EO-3021 at current dose level • If the Grade 2 toxicity recurs, a dose reduction may be considered if medically appropriate in consultation with the Sponsor Medical Monitor • If the Grade 2 toxicity does not resolve to Grade ≤1 or the patient's baseline within 21 days, consider discontinuation of study treatment or further dose reduction
Grade 3 (does not meet DLT criteria)	• Interrupt study intervention if clinically indicated • Monitor closely • Provide supportive care according to institutional standards • The study treatment may be considered for a dose reduction upon recovery of the toxicity to Grade ≤1 or the patient's baseline within 21 days • If the Grade 3 toxicity recurs, either permanently discontinue study treatment or, if the

CTCAE v5.0 Grade	Action and Dose Modification for EO-3021[b]
	subject is clinically benefiting, consider continuation of study treatment at a further lower dose in consultation with the Sponsor Medical Monitor • If the Grade 3 toxicity does not resolve to Grade ≤1 or the patient's baseline within 21 days, discontinue study treatment unless the treating physician and the Medical Monitor agree that continued treatment at lower doses is in the best interest of the patient
Grade 3 (meets DLT criteria[a])	• Interrupt or discontinue study treatment as deemed medically appropriate • Monitor closely • Provide supportive care according to institutional standards • The study treatment may be considered for a dose reduction upon recovery of the toxicity to Grade ≤1 or the patient's baseline within 21 days, if deemed medically appropriate by the investigator and Sponsor Medical Monitor • If the Grade 3 toxicity recurs, either permanently discontinue study treatment or, if the subject is clinically benefiting, consider continuation of study treatment at a further lower dose in consultation with the Sponsor Medical Monitor • If the Grade 3 toxicity does not resolve to Grade ≤1 or the patient's baseline within 21 days, discontinue study treatment unless the treating physician and the Medical Monitor agree that continued treatment at lower doses is in the best interest of the patient
Grade 4	• Discontinue study treatment • Monitor closely • Provide supportive care according to institutional standards

CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose limiting criteria.
[a] DLT criteria and exceptions are described in Section 6.3.4.
[b] Any patients who require a treatment delay of more than 21 days due to treatment-related toxicity will be discontinued from study treatment, unless the treating physician and the Medical Monitor agree that continued treatment at lower doses is in the best interest of the patient.

Table 5: Dose Modification Guidelines Due to Hematologic Toxicities

Event per CTCAE v5.0	Action and Dose Modification for EO-3021[c]
Neutropenia	
ANC <1.0×10^9/L (Grade 3)	Hold dose until recovery to ≤Grade 2 (ANC ≥1.0 x 10^9/L)[a] • If resolved in ≤7 days, then resume without a dose reduction • If resolved in >7 days but ≤21 days, then resume dose at a 25% dose reduction
Recurrence of ANC <1.0×10^9/L (Grade 3)	Hold dose until recovery to ≤Grade 2 (ANC ≥1.0 x 10^9/L)[a] • If resolved in ≤7 days, then resume dose at a 25% dose reduction • If resolved in >7 days but ≤21 days, then resume dose at a 50% dose reduction
ANC <0.5 x 10^9/L (Grade 4)	Hold dose until recovery to ≤Grade 2 (ANC ≥1.0 x 10^9/L)[a] • If resolved in ≤7 days without use of G-CSF, then resume dose at a 25% dose reduction • If resolved in >7 days but ≤21 days and/or requires use of G-CSF, then resume dose at a 50% dose reduction
Recurrence of ANC <0.5 x 10^9/L (Grade 4)	Discontinue study treatment

Event per CTCAE v5.0	Action and Dose Modification for EO-3021[c]
Thrombocytopenia	
Platelets <50 x 10^9/L (Grade 3)	Hold dose until improvement to platelets ≥75 x 10^9/L[a] • If resolved in ≤7 days, then resume without a dose reduction[b] • If resolved in >7 days but ≤21 days, then resume dose at a 25% dose reduction[b]
Recurrence of Platelets <50 x 10^9/L (Grade 3)	Hold dose until improvement to platelets ≥75 x 10^9/L[a,b] • If resolved in ≤7 days, then resume dose at a 25% dose reduction • If resolved in >7 days but ≤21 days, then resume dose at a 50% dose reduction
Platelets <25 x 10^9/L (Grade 4)	Discontinue study treatment
Anemia	
Hemoglobin (Hgb) <80 g/L (Grade 3)	Hold dose and consider transfusion per institutional standards • If recovered to Grade ≤2 or the patient's baseline without transfusion, then resume at a 25% dose reduction. • If transfusion is required to recover to Grade ≤2, then resume at a 50% dose reduction.
Recurrence of Hgb <80 g/L (Grade 3)	Hold dose and consider transfusion per institutional standards • If recovered to Grade ≤2 or the patient's baseline without transfusion, then resume EO-3021 at a further 25% dose reduction • If transfusion is required to recover to Grade ≤2, consider discontinue study treatment
Life threatening consequences; urgent intervention indicated (Grade 4)	Discontinue study treatment

ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; G-CSF = granulocyte colony -stimulating factor; Hgb = hemoglobin

[a] Hold EO-3021 treatment; do at least weekly CBC with differential until toxicity resolves (ANC recovery ≥1.0 x 10^9/L).

[b] Re-treatment criteria = platelets ≥75 x 10^9/L.

[c] Any patients who require a treatment delay of more than 21 days due to treatment-related toxicity will be discontinued from study treatment, unless the treating physician and the Medical Monitor agree that continued treatment at lower doses is in the best interest of the patient.

6.5.2.1. Management of Nausea and/or Vomiting

Gastrointestinal toxicity of nausea/vomiting was dose limiting with EO-3021 in the first-in-human trial of EO-3021 "A Phase 1 Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetic Characteristics, Immunogenicity and Preliminary Efficacy of SYSA1801 Injection in Patients with CLDN18.2-expressing Advanced Solid Tumors" (Protocol No.: SYSA1801-CSP-001) being conducted by CSPC in China. Additionally, nausea and vomiting were the most frequently observed side effects in clinical trials of investigational agents targeting CLDN18.2 in patients with advanced gastric/GEJ and pancreatic adenocarcinoma (Sahin et al., 2018; Tureci et al., 2019). Based on nonclinical toxicology studies, the stomach was one of the main toxic target organs, which is not surprising given expression of CLD18.2 in normal gastric mucosa. Based on these clinical and nonclinical findings, it is recommended that patients receive optimal medical management of nausea and vomiting with initiation of treatment with EO-3021. Institutional guidelines may exist and should be consulted for recommended treatment; several major oncology organizations such as ASCO have also provided comprehensive guidelines for management of nausea and vomiting (Hesketh et al., 2020).

The recommended treatment regimens for the prevention and management of nausea/vomiting are outlined below. Patients may receive the recommended antiemetic treatment prior to EO-3021 dosing on Day 1 and to cover Days 2-4 of each Cycle starting with C1D1. Additional supportive medications as needed (PRN) should also be considered at the discretion of the treating physician. The choice of medications should be selected based on patient-centric factors such as response to prior antiemetics and include medications of different mechanisms of actions. Premedication for nausea/vomiting, which is a treatment before study drug administration, should be documented on the dose eCRF as well as any concomitant medications.

One of the following regimens, based on the ASCO guidelines for antiemetics in oncology (Hesketh et al., 2020) are acceptable for the prevention and management of nausea/vomiting in patients receiving EO-3021.

Regimen I: 5-HT$_3$ receptor antagonist + NK1-receptor antagonist + dexamethasone		
Drug class	Day 1	Days 2-4
5-HT$_3$ receptor antagonist **(select one)**	• Palonosetron 0.50 mg oral or 0.25 mg IV • Granisetron 2 mg oral or 1 mg or 0.01 mg/kg IV or 1 transdermal patch or 10 mg subcutaneous • Tropisetron 5 mg IV/PO • Ondansetron Single 24-mg dose administered by tablets, successive oral dissolving tablets, or oral dissolving film applications before the start of chemotherapy, or 8mg or 0.15 mg/kg IV • Dolasetron 100 mg oral ONLY • Tropisetron 5 mg oral or 5 mg IV • Ramosetron 0.3 mg IV	N/A
NK1-receptor antagonist **(select one)**	• Aprepitant 125 mg PO **or** 130 mg IV • Fosaprepitant 150 mg IV • Netupitant-palonosetron 300 mg netupitant/0.5 mg palonosetron oral in single capsule • Fosnetupitant-palonosetron 235 mg fosnetupitant/0.25 mg palonosetron IV • Rolapitant 180 mg PO	Aprepitant 80 mg PO once daily on Days 2-3 (if aprepitant on Day 1)
Dexamethasone	12 mg or 20 mg IV/PO	8 mg IV/PO once daily

Regimen II. 5-HT$_3$ receptor antagonist + dexamethasone + olanzapine		
Drug class	Day 1	Days 2-4
5-HT$_3$ receptor antagonist **(select one)**	• Palonosetron 0.50 mg oral or 0.25 mg IV • Granisetron 2 mg oral or 1 mg or 0.01 mg/kg IV or 1 transdermal patch or 10 mg subcutaneous • Tropisetron 5 mg IV/PO • Ondansetron Single 24-mg dose administered by tablets, successive oral dissolving tablets, or oral dissolving film applications before the start of chemotherapy, or 8mg or 0.15 mg/kg IV • Dolasetron 100 mg oral ONLY • Tropisetron 5 mg oral or 5 mg IV • Ramosetron 0.3 mg IV	N/A
Dexamethasone	12 mg or 20 mg IV/PO	N/A
Olanzapine	5 mg or 10 mg, PO, once	5 mg or 10 mg PO daily

Regimen III. 5-HT$_3$ receptor antagonist + NK1-receptor antagonist + dexamethasone + olanzapine		
Drug class	Day 1	Days 2-4
5-HT$_3$ receptor antagonist **(select one)**	• Palonosetron 0.50 mg oral or 0.25 mg IV • Granisetron 2 mg oral or 1 mg or 0.01 mg/kg IV or 1 transdermal patch or 10 mg subcutaneous • Tropisetron 5 mg IV/PO • Ondansetron Single 24-mg dose administered by tablets, successive oral dissolving tablets, or oral dissolving film applications before the start of chemotherapy, or 8mg or 0.15 mg/kg IV • Dolasetron 100 mg oral ONLY • Tropisetron 5 mg oral or 5 mg IV • Ramosetron 0.3 mg IV	N/A
NK1-receptor antagonist **(select one)**	• Aprepitant 125 mg PO **or** 130 mg IV • Fosaprepitant 150 mg IV • Netupitant-palonosetron 300 mg netupitant/0.5 mg palonosetron oral in single capsule • Fosnetupitant-palonosetron 235 mg fosnetupitant/0.25 mg palonosetron IV Rolapitant 180 mg PO	Aprepitant 80 mg PO once daily on Days 2-3 (if oral aprepitant on Day 1)
Dexamethasone	12 mg or 20 mg IV/PO	8 mg IV/PO once daily
Olanzapine	5 mg or 10 mg, PO, once	5 mg or 10 mg PO daily

6.5.2.2. Management of Infusion-related Reactions

As with any therapeutic antibodies, there is a possibility of infusion-related reactions and immune responses causing allergic or anaphylactic reactions following the administration of EO-3021. Patients receiving EO-3021 should be monitored by means of vital signs, physical examination, and signs and symptoms of infusion-related reaction including but not limited to: fever, chills, nausea, vomiting, headache, cough, dizziness, rash, and/or lower back pain usually of mild to moderate severity and may lead to shortness of breath and severe lowering of blood pressure. Infusion of EO-3021 will be slowed or interrupted in case of infusion-related reactions and/or hypersensitivity. The Investigator will manage infusion reaction-related AEs according to local standard procedure. In the absence of local standard procedures, the Investigator should consider treatment guidelines and dose reductions for infusion-related reactions shown in Table 6.

Table 6: Treatment Guidelines and Dose Modifications for Suspected Infusion-related Reactions

Toxicity Grade per CTCAE v5.0	Action for EO-3021 Dose
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Consider slowing infusion rate by 50%, or per institutional guidelines based on patient tolerance • Monitor patient every 15 minutes for worsening of condition
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	• Stop infusion • Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 500-650 mg orally, and oxygen • Resume infusion at 50% of the prior rate once infusion reaction has resolved, or per institutional guidelines based on patient tolerance • Monitor patient every 15 minutes for worsening of condition • For all subsequent infusions, premedicate with dexamethasone 10 mg orally or IV
Grade 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	• Stop infusion and disconnect infusion tubing from patient • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary • No further treatment with EO-3021 will be permitted
Grade 4 Life-threatening consequences; urgent intervention indicated	• Stop infusion and disconnect infusion tubing from patient • Administer epinephrine, bronchodilators, or oxygen as indicated for bronchospasm • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV • Consider hospital admission for observation • No further treatment with EO-3021 will be permitted

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAIDS = non-steroidal anti-inflammatory drugs

6.5.2.3. Management of Ocular Adverse Events

For monitoring risk of keratopathy, ophthalmic exams including slit lamp examination, optical coherence tomography (OCT), and visual acuity, will be performed prior to initiation of drug, during treatment and end of treatment. Patients are to be advised to use preservative-free lubricant eye drops and avoid contact lenses unless directed by an ophthalmologist.

Use Table 7 for management of corneal adverse reactions, based on both corneal examination findings and changes in best-corrected visual acuity (BCVA):

Table 7: Dose Reductions for Ocular Adverse Events

Toxicity Grade per NCI-CTCAE v5.0	Action for EO-3021 Dose
Grade 2 Corneal examination findings: Moderate superficial keratopathy[a] and/or Change in visual acuity: Decline from baseline of 3 lines or less or BCVA 20/40 and better	• Withhold drug until improvement in both corneal examination findings and change in BCVA to Grade 1 or better • Resume at same dose • If recurrence of Grade 2, resume at reduced dose
Grade 3 Corneal examination finding(s): Severe superficial keratopathy[b] and/or Change in visual acuity: Decline from baseline by more than 3 lines or BCVA worse than 20/40 up to 20/200	• Withhold drug until improvement in both corneal examination findings and change in BCVA to Grade 1 or better • Resume at reduced dose (reduce dose by 25%) • If recurrence of Grade 3, discontinue study treatment
Grade 4 Corneal examination finding(s): Corneal epithelial defect[c] and/or Change in visual acuity: BCVA worse than 20/200:	• Consider permanent discontinuation of drug. If continuing treatment, withhold drug until improvement in both corneal examination findings and change in BCVA to Grade 1 or better • Resume at reduced dose (reduce dose by 50%) • If recurrence of Grade 3 or higher, discontinue study treatment

BCVA = best-corrected visual acuity; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

[a] Moderate superficial keratopathy with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.

[b] Severe superficial keratopathy with or without diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.

[c] Corneal epithelial defect such as corneal perforation.

6.5.3. Dose Modification Criteria for Ramucirumab (CYRAMZA)

Reduce dose, withhold dose, or discontinue ramucirumab (CYRAMZA) to manage adverse reactions as described in Table 8. The dose of ramucirumab is 10 mg/kg IV Q3W in combination with EO-3021. Ramucirumab may be dose reduced to 8 mg/kg IV Q3W for the first dose reduction and to 6 mg/kg IV Q3W if a second dose reduction is needed. Patients must discontinue ramucirumab if more than 2 dose reductions are required. The patient may continue to receive EO-3021 as monotherapy if, in the Investigator's and Sponsor's opinions, the patient may continue to derive clinical benefit.

All dose modifications and the rationale for the dose modification must be documented in the eCRF.

Table 8: Dosage Modifications for Ramucirumab (CYRAMZA)

Adverse Reaction	Severity	Dosage Modification
Hemorrhage	Grade 3 or 4	Permanently discontinue CYRAMZA
Gastrointestinal Perforation	All Grades	Permanently discontinue CYRAMZA

Adverse Reaction	Severity	Dosage Modification
Wound Healing Complications	All Grades	• Withhold CYRAMZA for 28 days prior to elective surgery. Resume CYRAMZA no sooner than 2 weeks after surgery and until adequate wound healing. • The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.
Hypertension	Severe hypertension (Grade 3)	Withhold CYRAMZA until controlled with medical management
	Severe hypertension that cannot be controlled with antihypertensive therapy (Grade 3 and/or 4)	Permanently discontinue CYRAMZA
Infusion-Related Reaction (IRR)	Grade 1 or 2 IRR	Reduce the infusion rate of CYRAMZA by 50%
	Grade 3 or 4 IRR	Permanently discontinue CYRAMZA
Posterior Reversible Encephalopathy Syndrome (PRES)	All Grades	Permanently discontinue CYRAMZA
Proteinuria	First occurrence of increased urine protein levels greater than or equal to 2 g per 24 hours	• Withhold CYRAMZA until urine protein level is less than 2 g per 24 hours. • Resume CYRAMZA at a reduced dose: o Reduce 10 mg/kg dose to 8 mg/kg
	Reoccurrence of urine protein level greater than 2 g per 24 hours following initial dose reduction	• Withhold CYRAMZA until urine protein level is less than 2 g per 24 hours. • Resume CYRAMZA at a reduced dose: o Reduce 8 mg/kg dose to 6 mg/kg
	Urine protein level greater than 3 g per 24 hours or in the setting of nephrotic syndrome	Permanently discontinue CYRAMZA

Discontinuation of ramucirumab:

Any patient who experiences signs of hepatic encephalopathy or other serious signs of liver impairment such as hepatorenal syndrome must be permanently discontinued from ramucirumab therapy.

Patients with unresected primary tumors (or local recurrence) who develop Grade 3 and 4 venous thromboembolism may also receive anticoagulation and continue ramucirumab therapy provided that the tumor does not confer an excessive bleeding risk, in the opinion of the patient's physician.

Grade 3 and 4 arterial thromboembolic events, or any PE/DVT occurring or worsening during anticoagulant therapy, require permanent discontinuation of ramucirumab therapy. Any venous or arterial event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the serious adverse event (SAE) mechanism.

The patient will have ramucirumab permanently discontinued if the protein level is >3 g/24 hours, if there is a third occurrence of >2 g/24 hours, or if the protein level does not return to <2 g/24 hours within 2 weeks.

Ramucirumab should be permanently discontinued in the event of a gastrointestinal perforation or fistula formation.

6.5.4. Dose Interruption, Delay, or Discontinuation Criteria for Dostarlimab (JEMPERLI)

Dostarlimab dose reductions are not permitted. Dostarlimab Dose Modification and Toxicity Management Guidelines for Suspected Drug related Immune-mediated AEs (imAEs) are included in Appendix D. Treatment may be interrupted, delayed, or discontinued due to toxicity. The maximum duration of the combination of dostarlimab and EO-3021 is 3 years from the date of therapy start. If EO-3021 is discontinued, then dostarlimab should also be discontinued. The patient may continue to receive EO-3021 as monotherapy if, in the Investigator's and Sponsor's opinions, the patient may continue to derive clinical benefit.

Study intervention interruption is defined as stopping the study intervention administration before completion of the infusion, including both cases in which the infusion is resumed and completed on the same day and cases in which administration is not resumed that day.

Study intervention delay is defined as withholding study intervention administration for longer than the regularly scheduled study intervention dosing interval. Patients with dose delays of ≥12 weeks or those where events do not return to baseline or Grade ≤1 (see Appendix D), should permanently discontinue study intervention unless the investigator and medical monitor agree there is strong evidence supporting continued treatment.

All dose modifications and the rationale for the dose modification must be documented in the eCRF.

Safety management guidelines, including dose modifications algorithms, for ICI related imAE are provided in Section 6.5.4.1.

6.5.4.1. Dose Modifications for Immune Checkpoint Inhibitor (ICI) Immune-mediated Adverse Events

An imAE is defined as an AE of any organ that is associated with study intervention exposure, is of unknown etiology, and is consistent with an immune-related mechanism. Special attention should be paid to AEs that may be suggestive of potential imAEs. Onset of imAEs can occur after the first dose, later after several doses have been administered, or several months after the last dose of immunotherapy treatment (Ramos-Casals, 2020).

Organs most frequently affected by ICI imAEs include the endocrine glands, skin, and liver. Less frequently affected systems include the GI tract, nervous, cardiovascular, pulmonary, musculoskeletal, ocular, and hematologic systems. Lower grade imAEs are usually treated symptomatically and do not require dose delays or discontinuation. Higher grade and persistent lower grade imAEs typically necessitate interrupting or discontinuing study intervention and administration of systemic steroids or other immunosuppressive agents (such as tumor necrosis factor [TNF] blockers) if systemic steroids are not effective, or with hormone replacement or anti-thyroid therapy.

Early recognition of drug-related imAEs and initiation of treatment are critical in mitigating severity and reducing the risk of complications, because the majority of imAEs are reversible with the use of steroids and other immune suppressants or therapies (Pardoll, 2012; Weber, 2012). If a

drug-related imAE is suspected, the patient should return to the study site as soon as possible instead of waiting for their next scheduled visit. Patients who experience a new or worsening imAE should be contacted and/or evaluated at the study site more frequently. A thorough evaluation should be conducted to rule out neoplastic, infectious, metabolic, toxin-related, or other etiologies before diagnosing a drug-related imAE. Serological, immunological, and histological (i.e., via a biopsy) data should be considered to support the diagnosis of an immune-related toxicity. Consultation with an appropriate medical specialist should be considered when investigating a possible imAE.

Details relating to specific subtypes of imAEs suspected to be related to ICI administration with corresponding dose modification and general management guidelines are presented in Appendix D and Appendix E (Liver safety: requirements and guidelines). All AEs are to be graded according to NCI-CTCAE v5 (US Department of Health and Human Services, 2017) unless otherwise specified.

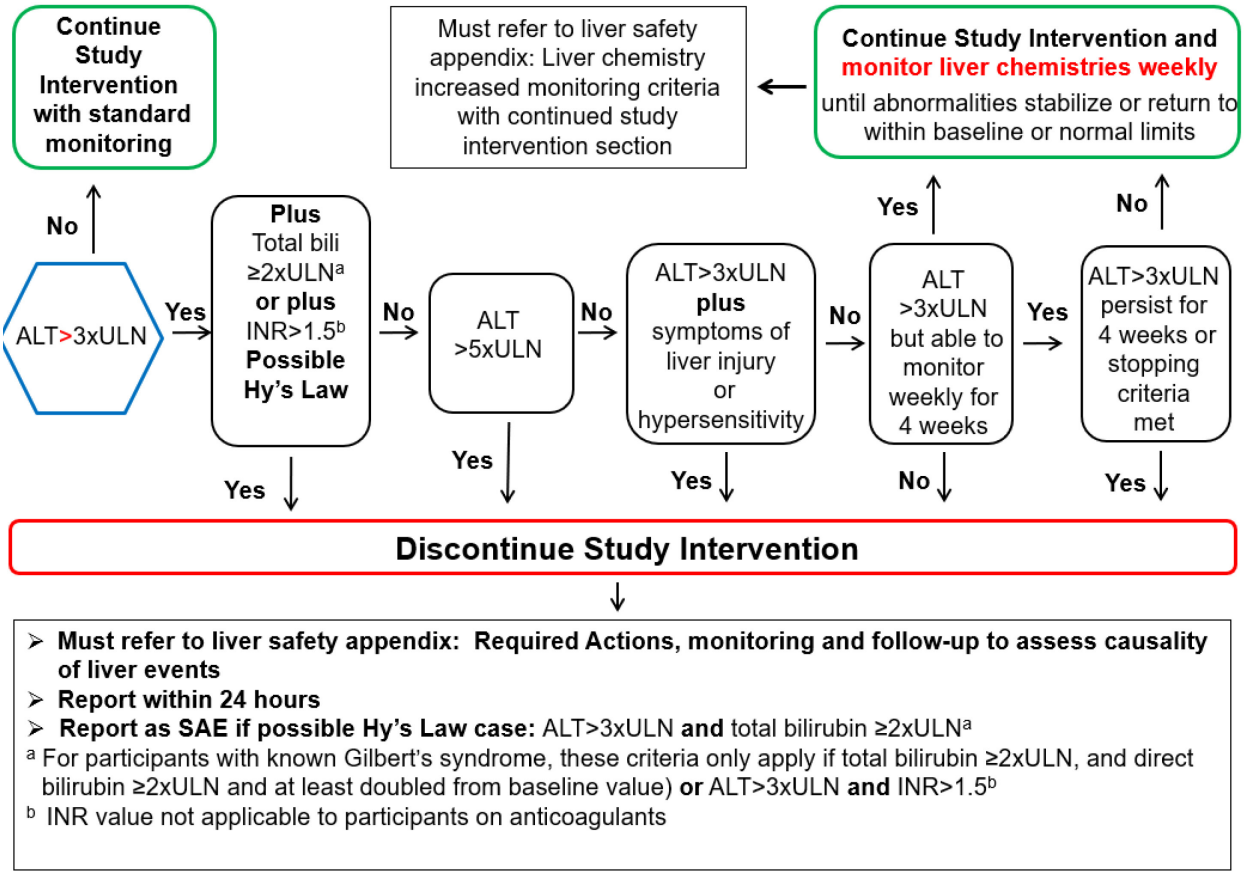
Institutional management guidelines, the Society for Immunotherapy of Cancer clinical practice guideline on immune checkpoint-inhibitor-related AEs (Naidoo, 2023), the National Comprehensive Cancer Network clinical practice guideline for management of imAEs (NCCN, 2023), the European Society for Medical Oncology clinical practice guideline for management of toxicities from immunotherapy (Haanen, 2022) and/or the American Society of Clinical Oncology guideline on management of immune-related adverse events in patients treated with ICI therapy (ASCO, 2021) may be consulted and used to supplement the algorithms provided below in Appendix D.

6.5.4.1.1. Liver Event Stopping Criteria for Dostarlimab Arm

Discontinuation of study intervention for abnormal liver tests is required by the investigator when:

- a patient meets 1 of the conditions outlined in Figure 5
- a patient has abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the patient

Figure 5: Liver Event Study Intervention Stopping Criteria and Liver Event Increased Monitoring Criteria with Continued Study Intervention



ALT = alanine aminotransferase; INR = international normalized ratio; SAE = serious adverse event; Total bili = total bilirubin; ULN = upper limit of normal

Refer to Appendix E for required liver safety actions, monitoring, and follow up to assess the causality of liver events.

Patients who do not meet protocol-specified liver event stopping criteria but meet protocol-defined increased monitoring criteria may continue to receive study intervention with increased (i.e., weekly) liver chemistry monitoring. Refer to Appendix E for details regarding required increased monitoring of liver chemistry with continued study intervention.

In cases where the investigator is directed to discontinue study intervention permanently, these instructions are mandatory; some exceptions may be permitted after consultation with the sponsor if the dose modification/treatment guidelines differ from the institutional or professional society guidance. The medical monitor can be contacted if there are additional questions about drug-related imAE management.

6.6. Duration of Therapy

Patients will receive multiple cycles of EO-3021 (monotherapy), EO-3021 in combination with ramucirumab, or EO-3021 in combination with dostarlimab until disease progression,

unacceptable toxicity, or criteria for discontinuation of study treatment and/or withdrawal from the study are met (Section 6.8.1). The maximum duration of dostarlimab in combination with EO-3021 is 3 years from the date of therapy start.

6.7. Concomitant and Prohibited Medications

Standard supportive medications may be used in accordance with institutional guidelines and Investigator discretion. These may include hematopoietic growth factors to treat neutropenia and transfusions for thrombocytopenia or anemia in accordance with ASCO Guidelines, anti-emetics, anti-diarrheals, antibiotics, antipyretics, and corticosteroids (up to 10 mg per day prednisone or equivalent, unless a compelling clinical rationale for a higher dose is articulated by the Investigator and approved by the Sponsor's Medical Monitor; permitted corticosteroid uses include topical/cutaneous, ophthalmic, nasal and inhalational steroids, as well as short courses to treat asthma, chronic obstructive pulmonary disease, or other non-cancer related conditions). Additionally, while participating in the study, patients should use preservative-free lubricant eye drops and avoid contact lenses unless directed by an ophthalmologist.

All concomitant medications, including transfusions of blood products, will be recorded on the appropriate page of the case report form. Concomitant therapy (non-investigational products) includes any prescription medication, over-the-counter preparation, herbal therapy, or radiotherapy used by a patient between the 28 days preceding study treatment initiation and the study treatment discontinuation visit. After the End of Treatment Visit, only anti-cancer therapies will be collected in addition to survival information.

The following therapies are **not** permitted while on study treatment:

- Other anti-neoplastic therapy, including cytotoxics, targeted agents, endocrine therapy, or other antibodies (Excludes use of agents such as zoledronic acid or RANKL for bone metastases initiated at least 14 days prior to C1D1)
- Any other investigational therapy

6.7.1. Concurrent Palliative Radiotherapy and Elective Procedures

Palliative radiotherapy to specific sites of disease (e.g., bone metastasis) is permitted if considered medically necessary by the treating physician and with approval from the Sponsor Medical Monitor. Palliative radiotherapy should not be administered on the same week as EO-3021 treatment and there should be at least 7-14 days before the next dose of EO-3021 (monotherapy or combination). In general, target lesions should not be irradiated without discussion with the Sponsor and may be reason for the patient to be removed from study for progressive disease. Irradiated lesions will be considered not evaluable for response but can still be used to assess disease progression. The intensities, number, and dates of doses received for allowed palliative radiotherapy should be recorded on the appropriate eCRF.

Although EO-3021 is not expected to significantly affect wound healing, any unusual findings should be recorded as potential AEs. In the event that elective procedures, including surgery, are necessary during study participation, EO-3021 (monotherapy or combination) should not be administered at least 7-14 days before and after surgery. Ramucirumab, a VEGFR2 antagonist, has the potential to adversely affect wound healing; in the event that elective procedures, including

surgery, are necessary during study participation, ramucirumab (Arm A2 and Arm B2) should not be administered for 28 days before and at least 14 days after surgery (CYRAMZA, 2022).

6.7.2. Prohibited Medications

MMAE is substrate for CYP3A and P-glycoprotein, therefore, strong inhibitors and strong inducers of CYP3A and P-glycoprotein are prohibited on the study. If concomitant use of strong CYP3A/P-glycoprotein inhibitors/inducers is unavoidable, consider delaying EO-3021 treatment until the strong CYP3A/P-glycoprotein inhibitors/inducers have cleared from circulation (approximately 5 elimination half-lives of the inhibitors/inducers) when possible. If a strong CYP3A/P-glycoprotein inhibitors/inducers is co-administered and EO-3021 treatment cannot be delayed, patients should be closely monitored for adverse reactions.

Examples of strong CYP3A inhibitors and inducers are included, but not limited, to those provided in Table 9. For an expanded list of fruit juices that are strong CYP3A inhibitors, please see Petric et al, 2020.

Table 9: Examples of Strong CYP3A Inhibitors and Inducers

Strong CYP3A Inhibitors[a]	**Strong CYP3A Inducers[b]**
Boceprevir, clarithromycin, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, fruit juice[c] (e.g. grapefruit, pomegranate, Seville orange), idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole	Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

AUC = area under the concentration time curve, CYP = cytochrome P450
[a] Strong inhibitors are drugs that increase the AUC of sensitive index substrates ≥5-fold.
[b] Strong inducers are drugs that decrease the AUC of sensitive index substrates by ≥80%.
[c] See Petric et al, 2020 for an expanded list of fruit juices that are strong CYP3A inhibitors.
Source: US Food and Drug Administration. Drug Development and Drug Interactions. Table of Substrates, Inhibitors and Inducers.

6.8. Study Termination and Patient Discontinuation

6.8.1. Patient Discontinuation from Study Treatment

Patients can be discontinued from study treatment for any of the following reasons:

- Disease progression (as assessed using RECIST v1.1). Note: Patients with disease progression per RECIST v1.1 who, in both the Investigator's and Sponsor's opinions, may continue to derive clinical benefit, and who meet the criteria listed in Section 6.8.2, may be allowed to continue treatment with written approval from the Sponsor.
- Irreversible or intolerable toxicity thought to be related to drug toxicity;
- Conditions requiring therapeutic intervention(s) not permitted by the protocol;
- Significant intercurrent illness precluding continued study participation, or the inability of the patient to comply with study requirements for any reason;

- Patient requests to discontinue treatment (withdrawal of consent) or is lost to follow up. This category does not apply if the underlying reason for the patient request in any way relates to toxicity or perceived toxicity;
- Pregnancy.

Note: In Arm A2 and Arm B2 (combination with ramucirumab) and Arm A3 and B3 (combination with dostarlimab), patients must discontinue from study treatment if EO-3021 is discontinued for any reason.

After discontinuation from protocol treatment, patients must be followed for AEs for at least 28 days from the last dose of study treatment. Every effort should be made to follow patients after withdrawal from study; where the cause of study withdrawal relates to drug toxicity, every effort should be made to follow the patient until the toxicity has resolved.

6.8.2. Study Treatment Beyond Progression

As noted in Section 6.8.1, patients with disease progression per RECIST v1.1 who, in the Investigator's and Sponsor's opinions, may continue to derive clinical benefit, may be eligible to continue in the study if they meet the criteria outlined below:

- absence of clinical symptoms or signs indicating clinically significant disease progression;
- no decline in ECOG performance status;
- absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention;
- no significant, unacceptable, or irreversible toxicities related to the trial treatment;
- have written approval of the Sponsor;
- have signed an ICF agreeing to continue treatment; and
- no other treatment discontinuation criteria are met.

Patients must permanently discontinue treatment if subsequent imaging demonstrates further disease progression of ≥10% in the target lesions, unequivocal progression in non-target lesions, and/or the appearance of new lesions.

6.8.3. Site and Study Termination

This study may be terminated at the discretion of the Sponsor or any regulatory agency. Any site may elect to discontinue patient enrollment or withdraw their participation from the study for any reason. In these circumstances, every effort will be made by the site to provide all outstanding data for patients previously enrolled. Conditions that may warrant termination of the study include, but are not limited to the following:

- Emergence of an unexpected, serious, or unacceptable risk to the patients in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the investigational product.

In addition, the Investigator or Sponsor has the right to discontinue a site at any time during the study for medical or administrative reasons, such as the following:

- Unsatisfactory enrollment
- Good Clinical Practice (GCP) noncompliance such as inaccurate or incomplete data collection, falsification of records, failure to adhere to the study protocol.

6.9. Accountability of Study Drug

The investigator and investigational site staff are responsible for maintaining an accurate inventory and accounting of study drug. A record of all vials of study drug received and administered is maintained on an investigational drug inventory form provided by the Sponsor or an equivalent drug inventory form. The following information will be recorded:

- Date, quantity, and lot number(s) of study drug received
- Date, quantity, and lot number(s) of study drug dispensed from the pharmacy per patient
- Date, quantity, and lot number(s) of study drug administered to each patient
- Date, quantity, and lot number(s) of study drug destroyed (if prepared and dispensed, but not administered for any reason, the study drug may not be returned to inventory)
- Date, quantity, and lot number(s) of study drug returned to sponsor, if applicable

Each shipment of study drug contains an invoice describing the amount of drug shipped to the investigational site. The information on the invoice is verified against the actual amount received, after which the investigator or designee will place the invoice in the investigator's file. The Sponsor's monitor will reconcile the information on the investigational drug inventory form with the actual amount of study drug remaining at each site on a routine basis. At the conclusion of the study, the monitor will either package and ship all unused vials of the study drug back to Sponsor for destruction or document the destruction, in accordance with local regulations and institutional policy. Following use, empty vials of study drug may be destroyed according to local regulatory and environmental requirements. A record of any such destruction will be placed in the investigator's file.

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1. Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study are shown in Appendix C.

7.2. Screening Assessments

After written informed consent is completed, the following information is collected, and procedures are performed for each patient during screening. Unless otherwise specified, screening procedures are to be completed within 28 days of C1D1. If the date for a screening procedure falls out of the specified window, the procedure must be repeated prior to C1D1.

- Part B (Expansion) all arms: Prospective central testing of FFPE block or a minimum of 6 unstained slides of tumor tissue from a biopsy obtained within 6 months of enrollment must be available to submit for central review. (Note: If the patient received any CLDN18.2 directed therapy after the date of the archival biopsy a new biopsy should be performed and FFPE block or 6 unstained slides must be available for prospective central review.)
- Patient inclusion/exclusion criteria review
- Medical history (including medical/surgical/cancer histories and demographics)
- Physical examination (comprehensive exam at screening, including body systems: general, head, eyes, ears, nose, and throat (HEENT), respiratory, cardiovascular, abdomen, extremities, neurologic, and psychiatric)
- Vital signs including height (at screening only), weight, blood pressure (BP) in seated position, heart rate (HR), respiratory rate (RR), temperature, and oxygen saturation (SpO_2)
- ECOG performance status
- AE assessment (Section 11.3)
- Concomitant medication review (including any prescription medications, over-the-counter preparations, herbal/vitamin supplements used by a patient between the 28 days preceding study treatment initiation)
- Ophthalmic examination, to include OCT, slit lamp examination, and visual acuity exam
- 12- lead electrocardiogram in ECG (triplicate) after the subject has been supine for at least 5 minutes
- Chemistry (Comprehensive metabolic profile [CMP] to include sodium, potassium, chloride, blood urea nitrogen [BUN], creatinine, glucose [non-fasting], albumin, total protein, calcium, magnesium, phosphorus, uric acid, and LFTs [ALT, AST, total and direct bilirubin, alkaline phosphatase])
- Complete blood count (CBC) with differential including hemoglobin, hematocrit, platelets, white blood counts (WBC) including absolute counts for neutrophils, lymphocytes, and monocytes
- Tumor markers: only in patients with tumors where monitoring of tumor markers is clinically relevant (i.e., CA19-9, CEA, etc.)
- Coagulation profile to include prothrombin time (PT)/INR and aPTT and/or partial thromboplastin time (PTT)
- Urinalysis (reflex with microscopic examination as appropriate)
    - For Arms A2 and B2 (combination with ramucirumab), if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to allow participation in Arms A2 and B2)
- Assessment for HIV or active Hepatitis B or C infection if clinically indicated or required by local regulations within 3 months prior to C1D1.

  - For Arms A3 and B3 (combination with dostarlimab), the presence of HBsAg will be assessed. Patients with a negative HBsAg and positive Hepatitis B core antibody result are eligible only if HBV DNA is negative.

- Serum or urine pregnancy test for women of childbearing potential. If urine test is positive or cannot be confirmed as negative, a serum test is required
- Baseline disease assessment by CT with contrast (preferred) or MRI scan [chest, abdomen, pelvis is required at a minimum with scans of additional regions (such as of the neck or extremities etc.) to be included as appropriate based on presence of disease or symptoms]. Scans performed prior to consent, but within 28 days of C1D1, may fulfill the baseline disease assessment requirement, provided the same modality will be used for on-study assessments.
- Part A, Dose Escalation: Confirmation of available archival tumor tissue obtained within the last 24 months
- Part A, Dose Escalation: Fresh tumor tissue biopsy, if determined to be safe by the Investigator. A tumor biopsy obtained prior to consent but no more than 3 months prior to C1D1 without any intervening treatment between the biopsy and C1D1 may be used to fulfill the fresh tumor tissue requirement with Sponsor approval.

7.3. Study Treatment Assessments

Refer to the Schedule of Assessments for assessment cadence and windows (Appendix C).

7.3.1. Cycle 1 (Days 1, 2, 3, 5, 8, and 15)

- Review of patient inclusion/exclusion criteria (Day 1 only)
- Physical examination (comprehensive on C1D1, then problem/symptom focused at C1D8, C1D15). Body systems for comprehensive exam should include the following: general, HEENT, respiratory, cardiovascular, abdomen, extremities, neurologic, and psychiatric.
- Vital signs (Days 1, 8, 15) including weight, BP in seated position, HR, RR, temperature, and SpO_2
- ECOG performance status (Day 1 only)
- AE assessment (Section 11.3)
- Concomitant medication review (including any prescription medications, over-the-counter preparations, herbal/vitamin supplements, and transfusions)
- 12-lead ECG in triplicate after the patient has been supine for at least 5 minutes
- Chemistry (CMP), including sodium, potassium, chloride, BUN, creatinine, glucose (non-fasting), albumin, total protein, calcium, magnesium, phosphorus, uric acid, and LFTs (ALT, AST, total and direct bilirubin, alkaline phosphatase) (Days 1, 8, 15 only)
- CBC with differential including hemoglobin, hematocrit, platelets, WBCs including absolute counts for neutrophils, lymphocytes, and monocytes (Days 1, 8, 15 only)

- Tumor markers: only in patients with tumors where monitoring of tumor markers is clinically relevant (Day 1 only)
- Coagulation profile to include PT/INR and aPTT (and/or PTT) (Day 1 only)
- Urinalysis (reflex with microscopic examination as appropriate) (Day 1 only)
    - For Arms A2 and B2 (combination with ramucirumab), if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to receive ramucirumab)
- Serum or urine pregnancy test for women of childbearing potential. If urine test is positive or cannot be confirmed as negative (Day 1 only)
- Study treatment (EO-3021 alone or in combination with ramucirumab or dostarlimab) administration (Day 1 only)
- DLT assessment, with a minimum observation period of 21 days from first dose of study drug
- PK assessment (Section 7.7)
- ADA/neutralizing antibodies (nAb) assessment (Section 7.8) (Day 1 only)

7.3.2. Cycles 2 and Beyond (on Day 1 of every cycle unless otherwise noted)

- Physical examination (Limited/problem/symptom focused physical examinations to include at a minimum HEENT, cardiovascular, respiratory, and abdomen)
- Vital signs including weight, BP in seated position, HR, RR, temperature, and SpO_2
- ECOG performance status
- AE assessment (Section 11.3)
- Concomitant medication review (including any prescription medications, over-the-counter preparations, herbal/vitamin supplements, and transfusions)
- Ophthalmic examination, including slit lamp examination performed at the end of Cycle 2 and every other cycle thereafter. Additional exams should be guided by specific ocular signs and symptoms as clinically indicated.
- 12-lead electrocardiogram in ECG (triplicate) after the patient has been supine for at least 5 minutes, collected pre-dose on D1 of each cycle through Cycle 5, then pre-dose D1 of every other cycle starting with Cycle 7
- Chemistry (CMP), including sodium, potassium, chloride, BUN, creatinine, glucose (non-fasting), albumin, total protein, calcium, magnesium, phosphorus, uric acid, and LFTs (ALT, AST, total and direct bilirubin, alkaline phosphatase)
- CBC with differential including hemoglobin, hematocrit, platelets, WBCs including absolute counts for neutrophils, lymphocytes, and monocytes
- Tumor markers: only in patients with tumors where monitoring of tumor markers is clinically relevant (i.e., CA19-9, CEA, etc.) (Day 1 only)

- Coagulation profile to include PT/INR and aPTT (or PTT) (Day 1 of every other cycle starting with Cycle 3; additional testing may be performed as clinically indicated)
- Urinalysis (reflex with microscopic examination as appropriate)
    - For Arms A2 and B2 (combination with ramucirumab), if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to receive ramucirumab)
- Serum or urine pregnancy test for women of childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum test is required.
- Study treatment (EO-3021 alone or in combination with ramucirumab or dostarlimab) administration (Day 1 Q3W)
- PK assessment (Section 7.7)
- ADA/nAb assessment (Section 7.8) collected pre-dose on Day 1 of every other cycle e.g., C1, C3, C5, etc. Ad hoc samples can be collected at the Investigator or Sponsor's discretion.
- Disease assessment per RECIST v1.1. Scans (CT with contrast or MRI) every 6 weeks from C1D1 for the first 12 months. After 12 months, imaging studies will be conducted every 12 weeks. Scans should still be performed following the outlined schedule even if doses are delayed/interrupted/missed. The same imaging modality should be used throughout the study.

7.4. End of Treatment Visit (within 28 ±3 Days of Last Dose)

Patients are permitted to continue study treatment (EO-3021 alone or in combination with ramucirumab or dostarlimab) until disease progression, unacceptable toxicity, or other discontinuation criteria are met (Section 6.8.1). The maximum duration of dostarlimab in combination with EO-3021 is 3 years from the date of therapy start.

If treatment is discontinued because of toxicity or for any other reason(s) at a scheduled treatment visit and no study treatment is administered, that visit may fulfill the End-of-Treatment (EOT) Visit.

After withdrawal from or completion of protocol treatment, patients must be followed for AEs/SAEs for 28 days after the last dose of study treatment or initiation of the next anti-cancer treatment, whichever occurs first. After this period, investigators are only required to report AEs/SAEs that they become aware of and are thought to be possibility related to study treatment.

The following end-of-treatment visit procedures will be performed:

- Physical examination (comprehensive exam including body systems: general, HEENT, respiratory, cardiovascular, abdomen, extremities, neurologic, and psychiatric)
- Vital signs including weight, BP in seated position, HR, RR, temperature, and SpO_2
- ECOG performance status
- AE assessment (Section 11.3)

- Concomitant medication review (including any prescription medications, over-the-counter preparations, herbal/vitamin supplements, and transfusions)
- Ophthalmic examination, including OCT, slit lamp examination, and visual acuity exam
- 12-lead Electrocardiogram in ECG (triplicate) after the patient has been supine for at least 5 minutes
- Chemistry (CMP), including sodium, potassium, chloride, BUN, creatinine, glucose (non-fasting), albumin, total protein, calcium, magnesium, phosphorus, uric acid, and LFTs (ALT, AST, total and direct bilirubin, alkaline phosphatase)
- CBC with differential including hemoglobin, hematocrit, platelets, WBCs including absolute counts for neutrophils, lymphocytes, and monocytes
- Tumor markers: only in patients with tumors where monitoring of tumor markers is clinically relevant (i.e., CA19-9, CEA, etc.)
- Coagulation profile to include PT/INR and aPTT (and/or PTT)
- Urinalysis (reflex with microscopic examination as appropriate)
- Serum or urine pregnancy test for women of childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum test is required.
- Optional fresh tumor tissue biopsy, if determined to be safe by the Investigator
- PK assessment (Section 7.7)
- ADA/nAb assessment (Section 7.7)
- Disease assessment by CT with contrast or MRI scan. If a patient discontinues study treatment for reasons other than disease progression (e.g., due to toxicities) tumor assessments with imaging will continue until initiation of next anti-cancer therapy, death, or withdrawal of consent, whichever occurs first.

7.5. Long-term Follow-up (Every 3 Months ±28 Days from Last Treatment)

Once off study treatment, survival data will be collected via written communication (e.g., telephone, email, electronic medical record) or clinic visits every 3 months (±28 days) from the date of last treatment until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor. Survival follow-up should include collection of any new anti-cancer therapies and procedures taken after the EOT visit. Patients who discontinue study treatment for reasons other than disease progression including due to toxicities will continue to receive tumor assessments until initiation of next anti-cancer therapy, death, or withdrawal of consent, whichever occurs first. Attempts should be made to obtain any death information available via public records.

7.6. Correlative Studies

Prospective documentation of CLDN18.2 is not a requirement for participation in the dose escalation arms. The expression level of CLDN18.2 will be determined retrospectively using an IHC assay in a central laboratory and analyzed for the ability to predict or correlate with tumor response to EO-3021 as monotherapy and in combination. Enrolling tumors with a broad range of

CLDN18.2 expression will support correlative analysis of clinical outcomes with varying CLDN18.2 expression in order to potentially establish a more defined cut-off that is clinically meaningful to predict and enrich for efficacy.

As the data around CLDN18.2 as a predictive biomarker for EO-3021 monotherapy matures, the Sponsor plans to implement a prospective CLDN18.2 biomarker selection strategy to identify and enroll patients who would derive the greater benefit from EO-3021 as monotherapy or in combination with ramucirumab or dostarlimab in the expansion arms.

For patients with tumors where monitoring of tumor markers is clinically relevant (i.e., CA19-9, CEA, etc.) tumor marker values will be collected in the eCRF. Baseline PD-L1 status will be collected in the eCRF.

Remaining tumor tissue after conducting the above studies may be used by the Sponsor for further analysis of other biomarkers that may be mechanistically linked to EO-3021 activity and resistance. At the time of informed consent, patients will be able to refuse storage of these remaining samples.

Directions for processing and shipping the samples are outlined in the Laboratory Manual.

7.7. Pharmacokinetic and ADA Assessments

The plasma PK parameters (including C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, T_{max}, $t_{1/2}$, etc.) of EO-3021, total antibody (including EO-3021, i.e., the intact ADC and dissociated antibody), and free MMAE, as well as the development of ADA following administration will be assessed by analysis of blood samples. For ADA positive samples, further determination of neutralizing activity (i.e., measurement of neutralizing antibodies, nAb) will be considered based on the results of the study.

PK and ADA/nAb samples are to be collected, handled, and processed in accordance with the instructions provided in the Laboratory Manual. Blood samples should be collected at prescribed time points and the actual sampling time recorded in the eCRF.

Unscheduled samples for assessment of PK and/or ADA/nAb may be drawn at any time during the study at the Investigator or Sponsor's discretion.

7.8. Adverse Events of Special Interest

Relevant Information regarding the Adverse Events of Special Interest (AESIs) specified below for the EO-3021 clinical program regardless of seriousness will be collected through the targeted questionnaires built within the applicable eCRF in the clinical study database. All AESIs should be reported within 24 hours following the SAE reporting guidelines.

Ocular adverse events

Ocular adverse events including corneal epitheliopathy, keratopathy and keratitis is considered to be an important potential risk based on nonclinical data, literature, and available safety information for drugs of similar class (e.g., ADCs). While the target antigen, CLDN18.2, has not been reported to be expressed in normal ocular tissues, off-target toxicity can result from exposure of ocular tissues to the MMAE payload. EO-3021 is produced using a highly selective and site-directed conjugation technique, and the concentration of free MMAE toxin component in blood is very low, at picogram levels. The mechanism leading to ocular adverse events caused by this product needs further study. In the repeat-dose toxicity study of EO-3021 and MMAE in rats, the eye was

evaluated as a target organ for toxicity. Single cell necrosis/increased mitotic figures in the cornea were observed in the EO-3021 rats treated at ≥10 mg/kg. These microscopic findings were not observed in the MMAE small molecule treatment group; however, eye discharge was observed in one of the moribund animals. Referring to the experience of marketed products, the clinical study of EO-3021 specifies in the study protocol: ophthalmological examination should be performed regularly; prophylactic use of preservative-free eye drops with the effects of ocular lubrication and protection is recommended from the first dose through the entire period of the study medication. After an ocular adverse event occurs, symptomatic treatment should be performed according to the advice of the ophthalmologist, ophthalmic examinations should be performed regularly, and EO-3021 should be temporarily discontinued until improvement or recovery according to the intensity.

Interstitial lung disease/pneumonitis

Interstitial lung disease (ILD)/pneumonitis is considered to be an important potential risk based on literature and available safety information for drugs of similar class (e.g., ADCs). Expression of the target antigen, CLDN18.2, is restricted to normal gastric mucosa. EO-3021 was purposely designed to specifically target CLDN18.2 and not CLDN18.1, the expression of the latter can be found in normal lung tissue. Nevertheless, ILD/pneumonitis should be ruled out if a patient develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever. If ILD/pneumonitis is suspected, treatment with EO-3021 should be interrupted pending further evaluation. Evaluations should include high resolution CT, pulmonologist consultation, pulmonary function tests and pulse oximetry (SpO_2), arterial blood gases if clinically indicated, and one blood sample collection for PK and exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible. As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines (Kubo et al., 2013).

8. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using RECIST v1.1 as outlined in Appendix B.

Appropriate imaging studies are conducted every 6 weeks ±7 days for the first 12 months. After 12 months, imaging studies are conducted every 12 weeks (±7 days). Patients who discontinue study treatment for reasons other than disease progression including due to toxicities will continue to receive tumor assessments following the outlined schedule until initiation of next anti-cancer therapy, death, or withdrawal of consent, whichever occurs first. Scans should still be performed following the outlined schedule even if doses are delayed/interrupted/missed. The same imaging modality should be used throughout the study. Confirmation of response (by repeat scans after 4 weeks) is required for trials in which response rate is the primary endpoint.

9. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

9.1. Study Treatments

Investigational Product	Dosage Form and Strength	Manufacturer
EO-3021 Infusion	Solution for Infusion / 10.0 mg/mL	CSPC Megalith Biopharmaceutical Co., Ltd.
Ramucirumab Infusion	Solution for Infusion / 10.0 mg/mL	Eli Lilly and Company
Dostarlimab	Solution for Infusion / 50.0 mg/mL	GlaxoSmithKline LLC

9.1.1. Labelling, Packaging, and Supply

EO-3021 Solution for Infusion is supplied to the pharmacy at the clinical trial site by the CRO in vials (of 7.5 mL each vial contains 75 mg EO-3021 drug substance). The immediate packaging will contain a statement to conform with FDA Investigational New Drug (IND) requirements as follows: Caution: New Drug - Limited by Federal (or US) law to investigational use. The batch number of the study drug dispensed to the patient should be entered on the eCRF, if applicable.

Storage conditions for EO-3021 are included on the investigational product label and in the Pharmacy Manual.

Eli Lilly and Company is providing the sponsor commercially labeled drug product vials: CYRAMZA® (ramucirumab) injection, for intravenous use. GlaxoSmithKline is providing the sponsor dostarlimab-gxly drug product in the form of unlabeled vials.

Ramucirumab and dostarlimab will be supplied to the pharmacy at the clinical trial site by the CRO and should be stored, prepared, and administered per the label (CYRAMZA, 2022 and JEMPERLI, 2024; respectively). Refer to the Pharmacy Manual for information regarding packaging and labeling.

All study drugs must be kept in a secure place under appropriate storage conditions.

9.1.2. Preparation and Administration of Study Treatment

The Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site. All study drug inventories must be made available for inspection by the Sponsor or its representatives and regulatory agency inspectors upon request.

All CRO Drug Accountability Record Form(s) will be completed by the site and sent to the CRO Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact the CRO regarding disposal of any study drug.

9.1.2.1. EO-3021

Administration of EO-3021 may require multiple vials, all of which should originate from the same lot number. Any vials or preparations are for single use only. Visually inspect the drug product before preparation. Discard the vial if visible particles are observed. Based on the calculated amount needed for the given dose, EO-3021 drug product is withdrawn from the vial under aseptic conditions and diluted in 0.9% sodium chloride injection solution to obtain a solution in the range of 0.3-2.0 mg/mL in an infusion bag. Further instructions are provided in the Pharmacy Manual.

EO-3021 is administered by IV infusion once every 21 days (±3 days). Patients should receive EO-3021 infused over 90 to 120 (±10) minutes for the first dose in C1D1. In the absence of infusion reactions, subsequent infusion time may gradually be decreased to 60 to 90 (±10) minutes, as tolerated. EO-3021 should not be administered as a bolus or a push.

9.1.2.2. Ramucirumab

Administration of CYRAMZA (ramucirumab) may require multiple vials, all of which should originate from the same lot number. Any vials or preparations are for single use only. Visually inspect the drug product before preparation for particulate matter or discoloration. Discard the vial if visible particles or discolorations are identified. Based on the calculated amount needed for the given dose, CYRAMZA (ramucirumab) is withdrawn from the vial under aseptic conditions and diluted in 0.9% sodium chloride injection solution in an intravenous infusion container to a final volume of 250 mL. Do not use dextrose containing solutions. Further instructions are provided in the Pharmacy Manual.

Ramucirumab is administered by IV infusion once every 21 days (±3 days). Patients should receive ramucirumab infused over 60 (±10) minutes, subsequent infusion time may gradually be decreased to 30 (±10) minutes as tolerated by the patient. Ramucirumab should not be administered as a bolus or a push. Flush the line with sterile 0.9% sodium chloride injection solution at the end of the infusion.

9.1.2.3. Dostarlimab

Administration of JEMPERLI (dostarlimab) may require multiple vials, all of which should originate from the same lot number. Any vials or preparations are for single use only. Visually inspect the drug product before preparation for particulate matter or discoloration. The solution is clear to slightly opalescent, colorless to yellow. Discard the vial if solution discoloration or visible particles are observed. Based on the calculated amount needed for the given dose, JEMPERLI (dostarlimab) is withdrawn from the vial under aseptic conditions and diluted in 0.9% sodium chloride injection solution to obtain a solution with a final concentration between 2.0-10.0 mg/mL in an infusion bag. Further instructions are provided in the Pharmacy Manual.

Dostarlimab is administered by IV infusion once every 21 days (±3 days). Patients should receive dostarlimab infused over 30 (±10) minutes. Dostarlimab should not be administered as a bolus or a push.

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

The statistical analyses for this study will be descriptive. Data collected will be presented using summary tables, figures, and individual patient data listings. 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 patients in each category will be presented.

In general, all analyses will be presented by study part (Part A or Part B), Arm (e.g. A1, A2, B1, etc.) and by dose levels in Part A or by randomized arm in Arm B1. Pooled safety analyses across

phase and dose will also be performed for all patients treated by EO-3021 monotherapy, EO-3021 in combination with ramucirumab, EO-3021 in combination with dostarlimab, and potentially all EO-3021 treated patients as appropriate.

A statistical analysis plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology, including methods to handle missing data, and to address all study objectives.

10.2. Analysis Populations

- Safety Analysis Population includes all patients receiving at least one dose of study treatment.
- DLT Evaluable Population includes all patients who receive at least one dose of EO-3021 and complete the DLT observation period or experience DLT(s) within the DLT observation period.
- Efficacy Evaluable Population includes all patients who receive at least one dose of EO-3021, have baseline measurable disease and at least one post baseline imaging assessment.
- PK Analysis Population will include all patients in the Safety Analysis Population who have at least one evaluable PK assessment.
- ADA Analysis Population will include all patients in the Safety Analysis Population who have at least one valid ADA result.

Each analysis population may be further grouped by study part, arm, by dose in Part A (Dose Escalation), and by arm in Arm B1.

10.3. Determination of Sample Size

10.3.1. Dose Escalation (Part A)

The sample size during Part A (Dose Escalation) will follow the BOIN design for Arm A1 (monotherapy) and traditional 3+3 design for Arm A2 (combination with ramucirumab) and Arm A3 (combination with dostarlimab). Approximately 70 patients are expected (approximately 30 patients in Arm A1, 20 patients in Arm A2, and 20 patients in Arm A3). The actual sample size (including backfills) will depend on the number of DLTs observed and the number of doses explored.

10.3.2. Expansion (Part B)

For the Part B (Expansion), approximately 120 patients will be treated at the RP2D, including approximately 80 patients in Arm B1 (monotherapy) and 20 patients each in Arm B2 (combination with ramucirumab) and Arm B3 (combination with dostarlimab).

For Arm B1, the sample size is not powered based on hypothesis testing between the 2 randomized arms. It is based on practical considerations to enable the dose selection for future trials based on the totality of data involving efficacy, safety, and tolerability. With 40 patients per arm, the 95% exact Clopper-Pearson confidence intervals for ORR are calculated for the various assumed response rates (Table 10).

Table 10: ORR and 95% Confidence Intervals Based on N=40 or 20

ORR (95% CI) N=40	ORR (95% CI) N=20
10% (3%, 24%)	10% (1%, 32%)
20% (9%, 36%)	20 % (6%, 44%)
30% (17%, 47%)	30% (12%, 54%)
40% (25%, 57%)	40% (19%, 64%)
50% (34%, 66%)	50 % (27%, 73%)

CI = confidence interval; ORR = objective response rate

For Arms B2 and B3, 20 patients are planned for each cohort. With 20 patients per cohort, the 95% exact Clopper-Pearson confidence intervals for ORR are calculated for the various assumed response rates (Table 10).

10.4. Analysis Methods

10.4.1. Disposition

The number and percent of patients who have consented, treated, discontinued (including reasons for discontinuation), and completed the study will be summarized. The number of patients for each analysis population defined in Section 10.2 will be tabulated.

10.4.2. Demographics and Baseline Characteristics

Summary statistics will be provided for demographic variables (age, sex, race, ethnicity) and baseline disease characteristics (e.g., ECOG performance status). Relevant biomarker, medical history, and prior anti-cancer treatments will also be summarized.

10.4.3. Efficacy Analysis

The primary analysis for efficacy will be based on the Efficacy Evaluable Population in Part B (Expansion) by Arm and by Arm (Arm B1 only). Sensitivity analysis may be performed based on the Full Analysis Population if it is sufficiently different from the Efficacy Evaluable Population. In addition, patients in Part A (Dose Escalation) with the same type of disease and receiving the same dose as in Part B (Expansion) may be pooled into the expansion cohort in Part B (Expansion) for a sensitivity analysis.

Best Overall Response (BOR) will be summarized based on the response assessments from all visits (scheduled or unscheduled) for each patient. The BOR is defined as the best response per RECIST v1.1 in the order of CR, PR, SD, PD, non-evaluable (NE). A patient will be considered as NE for response per RECIST v1.1 at a protocol specified time point if no imaging/measurement is done or only a subset of lesion measurements is made. Confirmation scans per RECIST v1.1 must be done at least 28 days after the initial response. SD measurements must have met the SD criteria at least once after study entry at a minimum interval of 35 days.

Overall Response Rate is defined as the proportion of patients with measurable disease at baseline who achieve a CR or PR (confirmed CR or a PR) per RECIST v1.1. The estimate of ORR will be accompanied by the Clopper-Pearson 95% confidence intervals (CIs).

Duration of Response (DOR) is defined as the time from the first occurrence of a response (CR or PR) until the date of PD per RECIST v1.1 or death, whichever is earlier. It is calculated among

responders (confirmed CR or PR). The Kaplan-Meier methodology will be used to estimate DOR. Patients who continue to respond at the time of the analysis will be censored at the last assessment of response. The median DOR, if estimable, and the 95% CI will be provided. The proportion of patients continuing to respond at 3 months and 6 months from the date of the first response and the 95% CI will be provided.

Disease Control Rate (DCR) is defined as the proportion of patients with measurable disease at baseline who achieve a CR, PR, or SD per RECIST v1.1. DCR will be analyzed similarly as the ORR.

Progression-free Survival (PFS) is measured from the date of first study treatment dose (or from the date of randomization in Arm B1) until the first date when PD is objectively documented per RECIST v1.1 or death from any cause, whichever is earlier. Patients without PD or death will be censored at the last available tumor assessment. Details of the PFS and DOR censoring rule will be specified in the SAP. PFS will be analyzed using the Kaplan-Meier methodology. The median PFS, if estimable, and the 95% CI will be provided. The proportion of patients who are progression-free at landmark times (e.g., 3 months, 6 months) from the date of the first dose and the 95% CI will be provided.

Overall survival is measured from the date of first study treatment dose (or from the date of randomization in Arm B1) until death. Patients who are alive will be censored at the last known alive date. OS will be analyzed similarly as the PFS using the Kaplan-Meier methodology.

10.4.4. Safety Analysis

Safety analyses will be based on the Safety Analysis Population. Patient incidence of all TEAEs, SAEs, and treatment-related AEs will be tabulated by SOC and preferred term per Medical Dictionary for Regulatory Activities (MedDRA). All AEs are graded according to NCI-CTCAE Version 5.0. AEs by worst grade and AEs leading to treatment discontinuation will also be summarized. Other safety endpoints including laboratory results, vital signs, and ECG findings will be summarized for all patients in the Safety Analysis Population.

Concomitant medications will be coded using the World Health Organization-Drug Dictionary and they will be listed and summarized by dose level.

In Part A (Dose Escalation), DLTs, if any, will be summarized based on the DLT analysis set. At the end of Part A (Dose Escalation), isotonic regression will be used to estimate the MTD.

Duration of study treatment, number of doses administered, cumulative amount of dose, and relative dose intensity will be summarized by each study drug (EO-3021, ramucirumab, dostarlimab). For the combination treatment, the total duration of all study treatment will also be calculated. In addition, any modifications to the planned dose including treatment discontinuation will be summarized along with the corresponding reasons for each study drug.

10.4.5. Pharmacokinetics

Plasma concentrations of EO-3021 will be used to calculate the PK parameters. Parameters evaluated will include plasma concentration-time profiles and C_{max}, T_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$, and $t_{1/2}$ etc. Besides EO-3021, total antibody (including EO-3021, i.e., the intact ADC and dissociated antibody), and free MMAE will be analyzed. Evaluation of ADA and nAb levels in appropriate patients will also be presented. These parameters will be listed by individual patient and

summarized by descriptive statistics (means, medians, ranges, standard deviations, and coefficient of variation as appropriate, by treatment group/cohort).

If potential interactions are suspected, plasma concentrations of ramicurimab or dostarlimab may be evaluated.

Additional details will be provided in a separate PK/ADA analysis plan.

10.5. Planned Analyses

10.5.1. Final Analysis

The final analysis of the study will occur when either:

- The last patient completes treatment with a minimum of 12-month follow up, **or**
- 3 years following the enrollment of the first patient

10.5.2. Interim Analysis

In Part A, analyses will be performed for dose escalation/de-escalation decisions at each dose level within each Arm (A1, A2, and A3) per the study design.

In Arm B1, an interim futility analysis will be performed after 20 patients have been randomized in the biomarker-selected population in each arm. A Bayesian futility assessment based on a beta-binomial model will be used in each arm. The prior distribution is assumed to be a beta distribution, beta (0.5, 0.5). If the posterior probability is at least 70% that the ORR is less than 15% in an arm, it may be considered futile to continue the arm. Specifically, if 2 or less patients respond at the interim, the futility boundary is crossed. No formal interim analysis is planned in Arm B2 or Arm B3. However, the Bayesian framework will be considered as a monitoring tool. The details will be specified in the SAP and the SRC charter.

Unplanned interim analysis for regulatory interaction or publication purposes may be performed.

10.6. Stopping Rules

In Part A (Dose Escalation), DLTs will be monitored to guide the dose escalation/de-escalation decisions following the BOIN design per Table 2 in Section 6.3. Regular safety reviews will be conducted by the Sponsor's SRC following the SRC charter.

During Part B (Expansion), evaluations of all Grade 4 or higher treatment-related adverse events (TRAE) rate will be conducted to assess if the unacceptable toxicity threshold has been reached. If this threshold is met (i.e., TRAE Grade 4 >20%), enrollment to expansion will be halted pending review of safety data.

In Arm B1, an interim futility analysis will be performed after 20 patients have been randomized in each arm. Specifically, if 2 or less patients respond at the interim, the futility boundary is crossed.

The study will enroll patients with advanced/metastatic gastric/GEJ adenocarcinoma or advanced solid tumors that are likely to express CLDN18.2. Expression of CLDN18.2 is not a requirement for enrollment into the study; however, the number of patients with tumors that do not expression

CLDN18.2 (e.g., no tumor cells show staining of CLDN18.2 by IHC) and objective responses will be assessed periodically to determine benefit/risk.

After reviewing the cumulative data, the SRC may recommend one of the following actions:

- Terminate the study
- Amend the protocol to potentially improve the benefit/risk for patients (e.g., increase safety monitoring, modify dose/schedule, mandate premedication, biomarker selection, etc.)
- Continue dose expansion without any changes

11. SAFETY REPORTING AND ASSESSMENT

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs, measurement of protocol-specified hematology, clinical chemistry, and UA variables, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug. Adverse events will be coded using the latest MedDRA dictionary. Severity will be graded according to the NCI-CTCAE Version 5.0.

The Investigator is responsible for recognizing and reporting AEs to the CRO Safety Department. It is the Sponsor's responsibility to ensure the reporting of relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRB/EC according to the policies of that IRB/EC.

The Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and does not necessarily have to have a causal relationship with this treatment. An AE can therebefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgement about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, dose or including overdose.

11.1.2. Serious Adverse Event

A SAE is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization of at least 24-hours or prolongation of existing hospitalization

  - For the purpose of this protocol, any hospital admission will be considered an inpatient hospitalization, regardless of duration. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalizations for a procedure scheduled before study enrollment (first dose of study drug) or elective procedures schedule during the study. However, unexpected complications that occur during elective surgery should be recorded as AEs and assessed for seriousness.

- Results in persistent or significant incapacity or disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
  - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AE, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea that persists for several hours may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF screen and SAEs on the SAE Report Form.

All SAEs occurring from the time that written informed consent has been obtained through the EOT Follow-up Visit (within 28 days after the last dose of study drug administration or initiation of alternative anticancer treatment, whichever occurs first) must be reported to the Sponsor CRO within 24 hours of the knowledge of the occurrence. After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies). Additionally, all SAEs that the Investigator considers possibility related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor.

An event attributed to disease progression must be reported as an SAE if it meets any of the SAE reporting criteria listed in this section. If death due to disease progression occurs within 28 days after the last dose of study drug, the event term should be listed as "malignant neoplasm progression" with the outcome of death.

11.1.3. Adverse Event of Special Interest

An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate.

11.1.4. Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the Investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes a SAE or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the Investigator's assessment of causality (i.e., the relationship to the study treatment). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. AEs will be graded according to the NCI-CTCAE v5.0, and changes will be documented.

Wherever possible, constellation of symptoms representing a recognized syndrome will be collected uniquely and will not be recorded as the separate component symptoms. For example, a patient displaying "flu like symptoms" will have the AE "flu like symptoms" reported but will not have each symptom listed. In this example, the symptoms of pyrexia/fever/asthenia/myalgia would not be reported individually.

If the AE is serious, it should be reported immediately to the nominated CRO Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms, changes in physical examination, hypersensitivity, and other measurements that occur will be reported as AEs and recorded on the relevant eCRF screen. Laboratory data will be separately graded, coded, and analyzed according to the NCI-CTCAE system. The consistent grading of laboratory data in this manner provides a greater level of transparency to abnormalities and renders reporting of laboratory anomalies as AEs duplicative and redundant.

Test findings will be reported as an AE if the test result requires an adjustment in the study drug(s) or discontinuation of treatment; and/or test findings require additional testing or surgical intervention; a test result or finding is associated with accompanying symptoms; or a test result is considered to be an AE by the Investigator.

Reporting Period for Adverse Events

All AEs regardless of seriousness or relationship to EO-3021, ramucirumab, or dostarlimab treatment (called study treatment), spanning from the start of study treatment, until 28 days after discontinuation or completion of study treatment or initiation of alternative anticancer treatment, whichever occurs first, as defined by the study for that patient, are to be recorded on the

corresponding screen(s) included in the eCRF. After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies).

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the Investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF screen.

After 28 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the Investigator as treatment related are to be reported.

11.1.5. Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

> **RELATED:** There is a plausible temporal relationship between the onset of the AE and administration of the study medication (EO-3021, ramucirumab, or dostarlimab), and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **UNRELATED:** Evidence exists that the AE has an etiology other than the study drug(s) (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed two days after first dose of study drug).

11.2. Serious Adverse Event Reporting by Investigators

AEs classified by the treating Investigator as serious require expeditious handling and reporting to the Sponsor in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from consent through 28 days following the last dose of study drug or initiation of alternative anticancer treatment, whichever occurs first. and must be reported to the Sponsor as SAEs in the EDC system and followed until resolution (with autopsy report if applicable). After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies). Additionally, all SAEs that the Investigator considers possibility related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor. **The Sponsor**

must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.

To report an SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the internet, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available. Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Safety Contact Information:

Medpace Clinical Safety

Medpace SAE Hotline

Telephone: +1-800-730-5779, dial "3" or +1-513-579-9911, dial "3"

Fax: +1-866-336-5320 or +1-513-579-0444

Email: medpace-safetynotification@medpace.com

Follow-up information for SAEs and information on nonserious AEs that become serious should also be reported to the CRO Safety Department as soon as it is available; these reports should be submitted using the CRO SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

11.3. Recording of Adverse Events and Serious Adverse Events

Monitoring for and recording of AEs and SAEs is conducted throughout the study and 28 days after the last dose of study treatment or initiation of alternative anticancer treatment, whichever occurs first. After this period, investigators are only required to report AE and SAEs that they become aware of them and are thought to be related to EO-3021. After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies). All SAEs should be reported to the Sponsor or designee within 24 hours of investigator awareness.

11.3.1. Diagnosis Versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or eCRF). If a diagnosis is subsequently established, it should be reported as

follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes) in and of itself, if documented by use of appropriate method (e.g., as per RECIST v1.1 for solid tumors), should not be reported as an SAE. An event attributed to disease progression must be reported as an SAE if it meets any of the SAE reporting criteria listed in Section 11.1.2 (e.g., hospitalization). If death due to disease progression occurs within 28 days after the last dose of study drug, the event term should be listed as "malignant neoplasm progression" with the outcome of death.

11.3.2. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation timepoints, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3. Deaths

Deaths that occur during the protocol-specified AE reporting period that are assessed by the Investigator solely attributable to progression of disease will be recorded on the "Study Discontinuation" eCRF screen. All other on-study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the CRO Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and AE screen of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event screen. During poststudy survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" eCRF screen.

11.3.4. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities are not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility

- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a preplanned surgical or medical procedure (one that was planned prior to entry in the study) does not require reporting as a SAE to the CRO Safety Department.

11.3.5. Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History of the eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.6. New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least 1 of the seriousness criteria (Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.7. Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If the patient or partner of a patient participating in the study becomes pregnant while on study, the Investigator should report the pregnancy to the Sponsor's clinical safety representative within 24 hours of being notified. The Sponsor's safety representative will then forward the Pregnancy form to the Investigator for completion as outlined in the Study Manual.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed. The investigator should inform the patient of the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. The Sponsor will collect information on the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

In the event of a pregnancy occurring in the partner of a male patient participating in the study, the pregnant partner should be requested to report the pregnancy to the investigator, who in turn should report it to the Sponsor. The partner should also be informed of the risks of continuing with the pregnancy, and the possible effects on the fetus.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A

Pregnancy Form should also have been previously completed and will need to be updated to reflect the outcome of the pregnancy.

11.3.8. Adverse Events of Special Interest (AESIs)

Adverse events of ocular toxicities (e.g., corneal epitheliopathy, keratopathy, keratitis) and ILD/pneumonitis are required to be reported as AESIs within 24 hours of knowledge of the event to the sponsor representative as an SAE using the eCRF. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

11.3.9. EO-3021 Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF system. Any accidental or intentional overdose with the study treatment, even if not fulfilling a seriousness criterion, is to be reported to the CRO Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting. For definition purposes, a drug overdose is considered to be a dose of study drug that is greater than 15% over the theoretical protocol specified dose for the patient considering any toxicities that may have warranted dose reduction.

For information on how to manage an overdose of EO-3021, see the IB.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Monitoring

Site monitoring shall be conducted to ensure that patient protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet Sponsor, GCP/ICH and, when appropriate, regulatory guidelines. Overall study monitoring will be conducted through a combination of on-site visit and centralized monitoring. A clinical monitor will make regularly scheduled trips to the investigational site to review the progress of the study, study data and site processes. At each visit, the monitor will review various aspects of the study including, but not limited to: screening and enrollment logs; compliance with the protocol and study manuals and with the principles of GCP; completion of CRFs; source data verification; study drug accountability and storage; facilities and staff.

The actual frequency of monitoring trips will depend on the enrollment rate and performance at each site. The investigator will allow Elevation Oncology, and/or its representatives or designees, access to all pertinent medical records, as required by federal regulations, in order to allow for the verification of all data gathered in the eCRFs and for the review of the data collection process.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the study, make necessary corrections to CRF entries, respond to data clarification requests and respond to any other study-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct which require further information or action will be discussed within the

study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other study-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

In accordance with Health Insurance Portability and Accountability Act (HIPAA) and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

12.2. Audits and Inspections

At any time during the course of the study, representatives of the FDA and/or other regulatory agencies may review the conduct or results of the study at the investigational site. The Investigator will permit study-related quality audits and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB/EC of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, CRFs). The Investigator will ensure the capability for review of applicable study-related facilities. The Investigator will ensure that the auditor or inspector or any other compliance or quality assurance reviewer is given access to all study-related documents and study-related facilities.

The investigator must promptly inform Elevation Oncology of any audit requests by health authorities and will provide Elevation Oncology with the results of any such audits and with copies of any regulatory documents related to such audits.

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of GCP outlined in the ICH R2 Tripartite Guideline and Code of Federal Regulations (CFR) Title 21 Part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

13.1. Institutional Review Board Approval

The clinical study protocol, ICF, patient information sheet (PIS), IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Investigator payments) and compensation available to the patients and documentation evidencing the PI's qualifications should be submitted to the IRB/EC for ethical review and approval if required by local regulations, prior to the study start.

The PI/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB/EC study review. The PI/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB/EC.

Safety updates for EO-3021, will be prepared by the Sponsor or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB/EC.

The study will not be initiated until there is approval of the protocol, informed consent document and any other material used to inform the patient about the nature of the study by the local IRB or EC. The IRB or EC should be duly constituted according to local regulatory requirements. Approval must be in the form of a letter signed by the Chairperson of the IRB/EC or the Chairperson's designee, must be on IRB/EC stationery and must include the protocol by name and/or by designated number. If an investigator is a member of the IRB/EC, the approval letter must stipulate that the Investigator did not participate in the final vote, although the investigator may participate in the discussion of the study. The investigator will also inform the IRB/EC of any SAE that the Sponsor reports to regulatory authorities, will report on the progress of the study at least yearly (or more frequently if required by local regulation or guidance) and will provide to the IRB/EC a final summary of the results of the study at the conclusion of the study.

13.2. Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3. Informed Consent

No study related procedures will be performed until a patient or a patient's legal representative has given written informed consent. The Sponsor will provide to the investigator a sample informed consent document that includes all the requirements for informed consent according to the ICH GCP, U.S. FDA guidelines (21 CFR 50) and/or local regulatory guidelines. However, it is up to the investigator to provide a final informed consent that may include additional elements required by the investigator's institution. Changes to the Sponsor's sample informed consent should receive approval from the Sponsor or the Sponsor's representative prior to use in the study. The informed consent document must clearly describe the potential risks and benefits of the study, and each prospective participant must be given adequate time to discuss the study with the Investigator or site staff and to decide whether or not to participate. Each patient who agrees to participate in the study and who signs the ICF will be given a copy of the signed, dated, and witnessed document. The provision of informed consent must be documented in the medical record.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

If an amendment to the protocol substantially alters the study design or the potential risks to the patient, the patient's consent to continue participation in the study should be obtained.

13.4. Confidentiality

13.4.1. Patient Confidentiality

It is the responsibility of the investigator to ensure that the confidentiality of all patients participating in the study and all of their medical information is maintained. Case report forms,

and other documents submitted to the Sponsor must never contain the name of a study patient. All patients in the study will be identified by a unique identifier which will be used on all eCRFs and any other material submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. All CRFs, and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the study. Patients will be informed of their rights within the ICF/PIS.

Confidentiality of patient's personal data will be protected in accordance with the HIPAA of 1996 and any applicable local regulations. HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization from the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR, it is a requirement that the Investigator and institution permit authorized representatives of Sponsor, the regulatory authorities, and the IRB/EC direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF system or other documents submitted to the Sponsor. Patient names or addresses will not be entered in the eCRF database system. No material bearing a patient's name will be kept on file by Sponsor.

13.4.2. Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the CRO database and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub-Investigator, the CRO shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.5. Financial Information

The finances for this clinical study will be subject to a separate written agreement between the Sponsor and applicable parties. Any Investigator financial disclosures applicable to 21CFR Part 54 shall be appropriately provided.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1. Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

The protocol will only be amended by the Sponsor and requires approval of the IRB/EC. Changes to the protocol must be in the form of a written amendment; changes other than those of a simple administrative nature (e.g., a new telephone number for a medical monitor) must be submitted by the investigator to the local IRB/EC and such amendments will only be implemented after approval of the requisite IRB/EC. All amendments will also be submitted to the FDA and/or local regulatory authorities by the Sponsor. Protocol changes to eliminate an immediate hazard to a study patient may be implemented by the investigator immediately. The investigator must then immediately inform their IRB/EC and the Sponsor will immediately notify applicable regulatory authorities.

14.2. Documentation Required to Initiate the Study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to the CRO. Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signed Investigator Protocol Agreement and contract
- A copy of the official IRB/EC approval of the study, and the IRB/EC members list, or the multiple project assurance number from the US Federal Wide Assurance program where applicable
- Current (i.e., updated no more than 24 months prior) Curricula Vita for the Investigator and any sub-Investigator(s) who will be involved in the study
- A copy of the current medical license for the Investigator and each sub-Investigator
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator) or equivalent form, appropriately completed and signed
- A copy of the IRB/EC-approved ICF (and PIS, if applicable) containing permission for audit by representatives of CRO, the Sponsor, the IRB, and the FDA and other regulatory agencies (as applicable)

- Financial disclosure forms for all Investigators listed on Form FDA 1572
- Site qualification reports, where applicable
- Verification of Investigator acceptability from local and/or national debarment list(s)
- Any other material provided to potential study participants with information about the study (e.g., advertisements)

14.3. Study Documentation and Storage

The Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Investigator and each study staff member are responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or investigator study file (ISF) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Investigator name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation/records of IRB activities as per 21 CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records [e.g., eCRFs, medical records]), all original, signed ICFs, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Sponsor or its representatives will notify the Investigator(s)/ institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor or its representative throughout the study and will be transferred to the Sponsor at the conclusion of the study.

14.4. Data Collection

The study eCRF is the primary data collection instrument for the study. Electronic case report forms (eCRF) will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, and year of birth will identify the patient in the eCRF system. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to the CRO and replaced instead with the patient number and patient's initials. The Investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested by the eCRF system must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will electronically sign and date the patient eCRF indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Investigator, once all data for that patient is final.

15. PUBLICATION POLICY

Elevation Oncology, as the Sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between the Investigator and Elevation Oncology personnel. Authorship will be established prior to the writing of the manuscript in alignment with International Committee of Medical Journal Editors (ICMJE) authorship recommendations. No manuscripts or presentations regarding this study will be submitted for publication without written authorization from Elevation Oncology.

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17. APPENDICES

Appendix A. Guidelines for Women of Childbearing Potential and Fertile Male Patients

EO-3021 is an anti-CLDN18.2 antibody conjugated to a cytotoxic payload (MMAE). Based on its mechanism of action, dostarlimab can cause fetal harm when administered to a pregnant woman. The teratogenicity of ramucirumab is not known.

Female Patients:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 6 months (or longer as required by local regulations including 6 months plus 5 half-lives for female patients in South Korea) after stopping treatment with EO-3021.

All women of childbearing potential must use highly effective methods of contraception for a period of 6 months after the last EO-3021 infusion. Highly effective contraception methods include the following:

1. Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are NOT acceptable methods of contraception.
2. Female sterilization (has had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
3. Male partner sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
4. Use of oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
5. Use of IUDs are not acceptable due to increased risks of infection and bleeding in this population. However, IUD inserted prior to consent may remain in place, and a second method of contraception is mandated.
6. In case of use of oral contraception, women must be stable on the same pill for a minimum of 3 months before taking study treatment.

Women who are not of reproductive potential (defined as postmenopausal for at least 12 consecutive months [i.e., have had no menses without an alternative medical cause] or have undergone hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) are eligible without requiring the use of contraception.

Unacceptable Contraception Methods for women of childbearing potential include:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding

- Fertility awareness
- Withdrawal
- Cervical shield

Male Patients:

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus spermicidal agent during the study treatment period and for 3 months after the last dose of study drug (or longer as required by local regulations including 3 months plus 5 half-lives for male patients in South Korea), and should not father a child during this period.

Male patients must also refrain from donating sperm during for the same time period.

Reporting of Unintended Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the CRO Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the completion of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the Investigator to the **CRO Safety Department**. Pregnancy follow-up should be recorded in the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Appendix B. Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Definitions

Response and progression will be evaluated in this trial using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT by computerized tomography (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10- to <15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of ≥15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.
Non-Target Lesions:	**All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.**

Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per protocol screening requirements.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, a CT scan is preferable.
Conventional CT and MRI:	CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).
Ultrasound:	When the primary trial endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Response Criteria

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<10 mm short axis).
Stable Disease (SD):	Persistence of one or more non-target lesions and/or persistence of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the subject also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

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

Confirmation of response (by repeat scans after 4 weeks) is required for trials in which response rate is the primary endpoint but is not required in randomized trials or trials with primary survival endpoints (i.e., where response is not a primary endpoint).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the eCRF.

Appendix C. Schedule of Assessments

Study Procedures	PRETREATMENT	TREATMENT (21-day cycles)							POST TREATMENT	
	Screening[a]	Cycle 1 (21-day Cycle)						Cycle 2 and beyond (21-day Cycle)	EOT[c] (within 28 ±3 days of last dose)	Long-term Follow-up[d] (every 3 months ±28 days)
		D1[b]	D2	D3	D5 (± 1 day)	D8 (± 1 day)	D15 (± 1 day)	D1 (±3 days)		
CLINICAL ASSESSEMENTS										
Informed Consent[e]	X									
Archival Tumor Tissue Collection[f]	X									
Fresh Tumor Tissue Biopsy[f]	X								X[f]	
Patient Inclusion/Exclusion Criteria	X	X								
Medical/Surgical/Cancer History and Demographics	X									
Physical Examination[g]	X	X				X	X	X	X	
Vital Signs[h]	X	X[h]				X	X	X[h]	X	
ECOG PS	X	X						X	X	
Adverse Event Assessment[i]	X									
Concomitant Medication Review[j]	X									
Ophthalmic Examination[k]	X							X	X	
CLINICAL LABORATORY ASSESSMENTS										
Triplicate ECG[l]	X	X[b]	X		X	X	X	X	X	
Chemistry (CMP)[m]	X	X[b]				X	X	X	X	
CBC with Differential[n]	X	X[b]				X	X	X	X	
Thyroid Stimulating Hormone (TSH) (Arms A3 and B3 [combination with dostarlimab] only)	X	X[b]						X	X	
Tumor Marker[o]	X	X[b]						X	X	
Coagulation profile: PT/INR/aPTT[p]	X	X[b]						X	X	
Urinalysis[q]	X	X[b]						X	X	
Serum or urine Pregnancy Test[r]	X	X[b]						X	X	
PK Assessment[s]		X	X		X	X	X	X	X	
ADA/nAb Assessment[t]		X						X	X	
STUDY DRUG ADMINSTRATION										
EO-3021 infusion[u]		X						X		

Study Procedures	PRETREATMENT	TREATMENT (21-day cycles)							POST TREATMENT	
	Screening[a]	Cycle 1 (21-day Cycle)						Cycle 2 and beyond (21-day Cycle)	EOT[c] (within 28 ±3 days of last dose)	Long-term Follow-up[d] (every 3 months ±28 days)
		D1[b]	D2	D3	D5 (± 1 day)	D8 (± 1 day)	D15 (± 1 day)	D1 (±3 days)		
Ramucirumab infusion[v]		X						X		
Dostarlimab infusion[w]		X						X		
DLT Assessment[x]		X								
TUMOR ASSESSMENT (±7 days)										
CT/MRI scan[y]	X							X[y]	X	X[z]
SURVIVAL FOLLOW UP										
Overall Survival Reporting[d]										X

ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; C1D8 = Cycle 1 Day 8; C1D15 = Cycle 1 Day 15; CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computed tomography; DLT = dose limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = end of treatment; HEENT = head, eyes, ears, nose, and throat; HR = heart rate; INR = international normalized ratio; LFT = liver function test; MRI = magnetic resonance imaging; nAb = neutralizing antibodies; OCT = optical coherence tomography; PK = pharmacokinetic; PS = performance status; PT = prothrombin time; PTT = partial thromboplastin time; RR = respiratory rate; SAE = serious adverse event; SpO_2 = oxygen saturation; TSH = thyroid-stimulating hormone; WBC = white blood cells

[a] Unless otherwise specified, all screening procedures must be performed within 28 days of C1D1.

[b] If screening laboratory tests are completed within 3 days prior to C1D1, pre-dose laboratory tests on C1D1 do not need to be repeated. Laboratory tests (not inclusive of PK/ADA/nAb) for D1 of each cycle may be completed within 3 days prior to the dosing visit.

[c] EOT visit: In clinic visit to occur 28 (±3) days after last dose of study drug. If treatment is discontinued because of toxicity or for any other reason(s) at a scheduled treatment visit and no study treatment is administered, that visit may fulfill the EOT visit. If a patient discontinues EO-3021 due to RECIST progression, imaging studies at EOT visit are not required.

[d] Long term follow-up to be every 3 months (±28 days) from the date of last treatment until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor. May be conducted in person or via telephone/email/electronic medical record. Survival follow-up should include collection of any new anti-cancer therapies and procedures taken after EOT visit. Attempts should be made to obtain any death information available via public records.

[e] Must be signed prior to any protocol-specific procedures.

[f] Patients enrolled to Part A (all arms): A fresh tumor biopsy should be performed during the screening period if determined to be medically feasible by the Investigator. In addition to obtaining a fresh tumor tissue biopsy, an archival tumor tissue sample (collected within the past 24 months) should be provided to the central laboratory for retrospective testing. Patients enrolled to Part B (all arms): Prospective central testing for CLDN18.2 is required for patients enrolled in Part B (all arms). After signing informed consent, a FFPE block or a minimum of 6 unstained slides of tumor tissue from a biopsy obtained within 6 months of enrollment should be provided to central laboratory for prospective testing. If the patient received prior CLDN18.2 direct therapy after the date of the archival sample, a fresh tissue biopsy must be performed. For all patients (Part A and Part B) a fresh tissue biopsy at EOT is recommended to explore mechanisms of resistance.

[g] Comprehensive physical examination should be performed at the screening visit and on C1D1. Body systems should include: general, HEENT, respiratory, cardiovascular, abdomen, extremities, neurologic, and psychiatric. Limited/problem/symptom focused physical examinations to include at a minimum HEENT, cardiovascular, respiratory, and abdomen should be performed at C1D8, C1D15 and Day 1 of each cycle starting at Cycle 2. Physical exam for C1D1 may be completed within 3 days prior to the visit.

[h] Vital signs include the following: height (at screening only), weight (dosing is based on patient's body weight on Day 1 of each cycle (or at each dosing day if change in body weight is > 10% or if required by institutional policy), BP in seated position, HR, RR, oral temperature, and SpO_2. For C1D1, BP in a seated position, HR, RR, temperature, and SpO_2 will be collected pre-dose (within 10 minutes prior), every 30 mins during infusion, end of infusion EOI within 10 minutes after), and 1-hour post-EOI (±10 minutes). For all subsequent cycles, vital signs will be collected pre-dose (within 10 minutes prior) and EOI within 10 minutes after).

[i] Monitor and record AEs and SAEs throughout the study and 28 days after the last dose of study treatment or initiation of alternative anticancer treatment, whichever occurs first. After this period, investigators are only required to report SAEs that they become aware of and are thought to be related to EO-3021. Record all AEs, regardless of relationship to study treatment, that occur after initiation of first study treatment until EOT. After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies). All SAEs should be reported to the Sponsor or designee within 24 hours of investigator awareness.

[j] Record all concomitant medications including any prescription medications, over-the-counter preparations, herbal/vitamin supplements, and transfusions received by patients from 7 days preceding C1D1 through the EOT or start of a new anticancer treatment.

[k] Ophthalmic examination will be performed at screening, during treatment (performed at end of Cycle 2 and every other cycle thereafter) and at EOT and will include OCT, slit lamp examination, and visual acuity exam. Additional exams should be guided by specific ocular signs and symptoms as clinically indicated. Ophthalmic exams conducted within a ± 7-day window are acceptable.

[l] After the patient has been supine for at least 5 minutes, triplicate 12-lead ECGs will be collected as closely together as possible but within 30 minutes pre-dose and 30 minutes (±10 minutes) post dose on C1D1. ECG on Days 2, 5, 8, and 15 to coincide with PK sampling (±1 hour). ECG to be pre-dose on Day 1 of each cycle through Cycle 5, then pre-dose Day 1 of every other cycle starting with Cycle 7.

[m] CMP to include sodium, potassium, chloride, BUN, creatinine, glucose (non-fasting), albumin, total protein, calcium, magnesium, phosphorus, uric acid, and LFTs (ALT, AST, total and direct bilirubin, alkaline phosphatase)

[n] CBC with differential including hemoglobin, hematocrit, platelets, WBCs including absolute counts for neutrophils, lymphocytes, and monocytes.

[o] Only in patients with tumors where monitoring of tumor markers is clinically relevant (e.g., CA19-9, CEA, etc.).

[p] Coagulation profile to include PT/INR and aPTT (or PTT) on Day 1 of every other cycle starting with Cycle 3; additional testing may be performed as clinically indicated.

[q] Dipstick urinalysis with reflex to urinalysis with microscopic examination as clinically indicated. At Screening and prior to each dose, for Arms A2 and B2 (Combination of EO-3021 plus ramucirumab), the patient's urinary protein must be ≤1+ on dipstick or routine urinalysis; if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must be performed and must demonstrate <1000 mg of protein in 24 hours to allow participation in Arms A2 and B2.

[r] A pregnancy test should only be performed for women of childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required.

[s] PK blood sample collection on C1 pre-dose (within 30 minutes prior), and at end of infusion (within 10 minutes) and post-infusion at 1 hour (±10 min), 2 hours (±10 min), and 4 hours (±10 min). D2 at 24 hours post infusion (±2 hr.), D5 at 96 hours post infusion (± 1 day), D8 at 168 hours (±1 day) post infusion and D15 at 336 hours (±1 day) post infusion. Cycles 2-4: D1 pre-dose (within1 hr. prior) and within 10 mins after end of infusion. Cycle 5 and beyond, PK samples will be collected every other cycle (Cycle 5, 7, 9, 11, etc.) on D1 pre-dose (within 1 hr. prior) and within 10 min after end of infusion.

[t] ADA/nAb blood samples will be collected pre-dose (within 30 min prior) on Day 1 of every other cycle (Cycle 1, 3, 5, etc.) and at EOT. Ad hoc ADA samples can be collected at the Investigator or Sponsor's discretion.

[u] Study drug administration intravenously once every 3 weeks (3QW) ± 3 days. Laboratory assessments should be reviewed prior to treatment.

[v] Ramucirumab will be administered to patients enrolled to Arms A2 and B2 at 10 mg/kg IV Q3W ± 3 days. Ramucirumab will be administered after EO-3021. Laboratory assessments should be reviewed prior to treatment.

[w] Dostarlimab will be administered to patients enrolled in Arms A3 and B3 at 500 mg IV Q3W ± 3 days. Dostarlimab will be administered after EO-3021. Laboratory assessments should be reviewed prior to treatment.

[x] DLT assessment to be performed throughout Cycle 1 with a minimum observation period of 21 days from first dose of study drug.

[y] Imaging (CT with contrast or MRI) of the chest, abdomen, pelvis is required at a minimum throughout the study with scans of additional regions (such as of the neck or extremities etc.) to be included as appropriate based on presence of disease or symptoms. The same imaging modality should be used throughout the study. Imaging studies must be performed every 6 weeks (±7 days) from C1D1 for the first 12 months. After 12 months, imaging studies may be conducted every 12 weeks (±7 days). Scans should be performed following the outlined schedule even if doses are delayed/interrupted/missed. Confirmation of response (by repeat scans after 4 weeks) is required.

[z] If a patient discontinues study treatment for reasons other than disease progression (e.g., due to toxicities) tumor assessments with imaging will continue until initiation of next anti-cancer therapy, death, or withdrawal of consent, whichever occurs first.

Appendix D. Immune Checkpoint Inhibitor Dose Modification and Toxicity Management Guidelines for Suspected Drug related Immune-mediated AEs (imAEs)

Adverse Reaction	Toxicity grade or conditions (NCI-CTCAE v5)	Action Taken with Study Intervention	imAE management with corticosteroids and/or other therapies	Monitoring and follow-up
General instructions: This table provides guidelines for dose modifications / dose discontinuations for adverse events that are suspected to be imAEs related to the ICI. Corticosteroid taper should be initiated upon AE improving to Grade ≤1 and continue to taper over at least 4 weeks. For situations where study intervention has been withheld, administration can be resumed after the imAE has been reduced to Grade ≤1 and corticosteroid has been tapered. Study intervention should be permanently discontinued if the imAE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg/day prednisone, or equivalent, within 12 weeks. For severe and life-threatening imAEs, IV corticosteroid should be initiated first, followed by oral steroid. Other immunosuppressive treatment should be initiated if imAEs cannot be controlled by corticosteroids.				
Adrenal insufficiency	Grade 2, 3, or 4	Hold until administration of HRT results in return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade ≤1. For recurrent or worsening Grade ≥2 adrenal insufficiency while adequate HRT is continuing, permanently discontinue study intervention.	Start treatment with corticosteroids before other HRT to avoid adrenal crisis (hydrocortisone, slowly titrating doses down according to symptoms OR prednisone and fludrocortisone, titrating up or down based on BP, other symptoms, and laboratory assessments); participants with severe symptoms may require additional fluids (e.g., saline >2 L).	• Monitor for cortisol level (AM), comprehensive metabolic panel (Na, K, CO_2, glucose), and renin. • Ensure adequate endocrine evaluation (e.g., endocrine consultation).
AST/ALT elevation, increased bilirubin, or hepatitis	Grade 2 with AST or ALT >3 to 5×ULN or total bilirubin >1.5 to 3×ULN	• Withhold. Restart when toxicity resolves to Grade ≤1. Inform Sponsor Medical Monitor before resuming dose	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg methylprednisolone or equivalent) followed by taper.	• Inform Sponsor Medical Monitor • Monitor with LFTs (consider weekly or more frequently until liver enzyme value[s] return to baseline or are stable). • Ensure adequate hepatology evaluation (e.g., hepatologist consultation). • See Appendix E for liver chemistry monitoring guidance.

Adverse Reaction	Toxicity grade or conditions (NCI-CTCAE v5)	Action Taken with Study Intervention	imAE management with corticosteroids and/or other therapies	Monitoring and follow-up
	Grade 3 with AST or ALT >5×ULN up to 8×ULN	• Discontinue[a]. See Appendix E for liver chemistry stopping criteria and monitoring guidance, and for liver rechallenge process and criteria.	Administer corticosteroids (initial dose of 1 to 2 mg/kg methylprednisolone or equivalent) followed by taper.	• Strongly recommend specialist hepatology evaluation • See Appendix E for liver chemistry monitoring guidance
AST/ALT elevation, increased bilirubin, or hepatitis (cont)	Grade 3 (AST or ALT >8×ULN up to 20×ULN) or total bilirubin > 3×ULN (up to 10×ULN)	• Permanently discontinue. See Appendix E for liver chemistry stopping criteria and monitoring guidance.	Administer corticosteroids (initial dose of 1 to 2 mg/kg methylprednisolone or equivalent) followed by taper	• Inform Sponsor Medical Monitor • See Appendix E for liver chemistry monitoring guidance. • Strongly recommend specialist hepatology evaluation
	Grade 4 (AST or ALT > 20×ULN or total bilirubin > 10×ULN)	• Permanently discontinue. See Appendix E for liver chemistry stopping criteria and monitoring guidance.	Administer corticosteroids (initial dose of 2 mg/kg methylprednisolone or equivalent), followed by taper.	• Inform Sponsor Medical Monitor • See Appendix E for liver chemistry monitoring guidance. • Specialist hepatology evaluation is recommended.
Diarrhea/colitis	Grade 2 or 3	• Restart when toxicity resolved to Grade ≤1.	Administer corticosteroids (initial dose of 1 to 2 mg/kg methylprednisolone or equivalent) followed by taper.	• Monitor participants for signs and symptoms of enterocolitis (e.g., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (e.g., peritoneal signs and ileus). • Participants with Grade ≥2 diarrhea where colitis is suspected should consider GI consultation and an endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

Adverse Reaction	**Toxicity grade or conditions (NCI-CTCAE v5)**	**Action Taken with Study Intervention**	**imAE management with corticosteroids and/or other therapies**	**Monitoring and follow-up**
Severe neurologic events (myasthenic syndrome/ myasthenia gravis, Guillain Barré syndrome, transverse myelitis)	Grade 2, 3, or 4	Permanently discontinue.	• Consider high dose corticosteroids and other therapies as needed. It is highly recommended that investigators discuss any AEs with the sponsor before using infliximab.	• Ensure adequate evaluation (e.g., neurology consultation). • Consider MRI of brain and/or spine depending on symptoms. • Consider inpatient management as clinically indicated.
Hemophagocytic lymphohistiocytosis (HLH)	Suspected HLH	Withhold	Obtain specialist opinion for diagnosis and management	Obtain specialist opinion for monitoring and follow-up
	Confirmed	Permanently discontinue.	Obtain specialist opinion for management	Obtain specialist opinion for monitoring and follow-up
Hyperthyroidism	Grade 3 or 4	Hold until return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade ≤1.	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate.	• Monitor for signs and symptoms of thyroid disorders. • Ensure adequate evaluation (e.g., endocrine consultation).
Hypophysitis	Grade 3 or 4	For Grade 3 or 4, hold until administration of HRT results in return to adequate hormone levels based on laboratory values and restart when toxicity resolves to Grade ≤1. For recurrence or worsening of Grade ≥2 hypophysitis after steroid taper has been completed and participant is on adequate HRT, permanently discontinue.	Administer corticosteroids and initiate HRT as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). • Ensure adequate evaluation (e.g., endocrine consultation).

Adverse Reaction	**Toxicity grade or conditions (NCI-CTCAE v5)**	**Action Taken with Study Intervention**	**imAE management with corticosteroids and/or other therapies**	**Monitoring and follow-up**
Hypothyroidism	Grade 3 or 4	Hold until administration of HRT results in return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade ≤1.	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per SOC.	• Monitor for signs and symptoms of thyroid disorders. • Monitor thyroid function tests. • Ensure adequate evaluation (e.g., endocrine consultation). • Exclude concomitant adrenal insufficiency (AM cortisol level).
Encephalitis	Any grade	Permanently discontinue.	• Consider IV acyclovir until PCR results obtained. • Trial with methylprednisolone; if severe, treatment with methylprednisolone. • If positive for autoimmune encephalopathy antibody or no improvement after 7 to 14 days, consider rituximab.	• Ensure adequate evaluation to confirm etiology and/or exclude other causes. • Obtain specialist neurology consultation
Myocarditis	Any grade	Permanently discontinue.	• Administer high dose corticosteroids (1 g/day of IV methylprednisolone) for 3 to 5 days, if responding and stable, switch to oral prednisone taper over 6 to 12 weeks based on clinical response and improvement in cardiac biomarkers. • If no improvement in 24-48 hours, consider adding other potent immunosuppressive agents.	• Ensure adequate evaluation (e.g., urgent cardiology consultation) to confirm etiology and/or exclude other causes.

Adverse Reaction	**Toxicity grade or conditions (NCI-CTCAE v5)**	**Action Taken with Study Intervention**	**imAE management with corticosteroids and/or other therapies**	**Monitoring and follow-up**
Pneumonitis (adverse event of special interest for EO-3021)	Grade 2	Restart dosing when toxicity resolves to Grade ≤1. If Grade ≥2 recurs, permanently discontinue.	Administer corticosteroids (initial dose of 1 to 2 mg/kg methylprednisolone or equivalent) followed by taper on improvement to Grade ≤1.	• Monitor participants for signs and symptoms of pneumonitis. • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Ensure adequate evaluation (e.g. specialist pulmonologist / respiratory opinion) • Add prophylactic antibiotics for opportunistic infections (e.g. PJP).
Exfoliative dermatologic conditions (e.g. SJS, TEN, DRESS)	Suspected DRESS, SJS, or TEN	Withhold.	• Treat with high potency topical steroids to affected areas. • Treat with prednisone.	Ensure adequate evaluation (e.g., urgent dermatology consultation) to confirm etiology and/or exclude other causes.
	Confirmed DRESS, SJS, or TEN	Permanently discontinue.	Administer 1 to 2 mg/kg/day IV methylprednisolone; taper steroid when dermatitis is controlled.	
Recurrence of suspected drug related imAEs after resolution to ≤Grade 1	Grade 1 or 2	Withhold (except for pneumonitis, see above).	Based on severity of AEs, administer appropriate treatment until symptoms improve to Grade ≤2.	Ensure adequate evaluation (e.g., specialist opinion)
	Grade 3 or 4	Permanently discontinue.		Ensure adequate evaluation (e.g. specialist opinion)
Renal failure or nephritis	Grade 2	Restart dosing when toxicity resolves to Grade ≤1.	Start treatment with prednisone; if persistent Grade 2 beyond 1 week, prednisone/methylprednisolone.	• Monitor participants for signs and symptoms, including monitoring of creatinine and urine protein every 3 to 7 days. • Ensure adequate evaluation (e.g., nephrology consultation) to confirm etiology and/or exclude other causes.

Adverse Reaction	**Toxicity grade or conditions (NCI-CTCAE v5)**	**Action Taken with Study Intervention**	**imAE management with corticosteroids and/or other therapies**	**Monitoring and follow-up**
	≥ Grade 3	Permanently discontinue.	• Start treatment with prednisone/methylprednisolone. • Consider adding 1 of the following after 1 week of steroids: azathioprine, cyclosporine, cyclophosphamide, infliximab, mycophenolate.	• Ensure adequate evaluation (e.g., nephrology consultation, renal biopsy) to confirm etiology and/or exclude other causes. • Consider inpatient care.
T1DM or hyperglycemia	Grade 3 to 4 hyperglycemia or T1DM (associated with metabolic acidosis or ketonuria)	Restart in appropriately managed clinically and metabolically stable participants; insulin replacement therapy is required.	• Initiate insulin replacement therapy for participants with T1DM.	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes. • Ensure adequate evaluation (e.g. specialist consultation)
Uveitis	Grade 2	Withhold.	• Urgent ophthalmology consultation. • Administer treatment with ophthalmic and systemic prednisone/methylprednisolone.	• Ensure adequate evaluation (e.g., urgent ophthalmology consultation)
	Grade 3 or 4	Permanently discontinue.		
Other suspected drug related imAEs	Based on severity and type of reaction (Grade 2 or 3)	Restart dosing when toxicity resolves to Grade ≤1.	Based on severity of AE, administer corticosteroids. When controlled, taper steroid.	• Ensure adequate evaluation (including specialist consultation) to confirm etiology and exclude other causes.
	Grade 4 or recurrent Grade 3	Permanently discontinue.		

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; DRESS = drug reaction with eosinophilia and systemic symptoms; GI = gastrointestinal; HLH = hemophagocytic lymphohistiocytosis; HRT = hormone replacement therapy; ICI = immune checkpoint inhibitor; imAE = immune-mediated adverse event; IV = intravenous; LFT = liver function test; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PCR = polymerase chain reaction; PJP= Pneumocystis jiroveci pneumonia; SJS=Stevens-Johnson syndrome; SOC = standard of care; T1DM= Type 1 diabetes mellitus; TEN=toxic epidermal necrolysis; ULN=upper limit of normal

Appendix E. Liver Chemistry Monitoring Guidance for Dostarlimab

Level 1 Monitoring

If a participant develops elevations in liver enzyme parameters as defined in Table 11, an increased frequency of liver chemistry monitoring (i.e., at weekly intervals) will apply.

Table 11: Liver Event Increased Monitoring Criteria (Level 1 Liver Monitoring)

Criteria	Actions
ALT >3x ULN and ≥1.5x baseline value and not meeting any Level 2 monitoring criteria, without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks	• Notify the Elevation Oncology medical monitor within 24 hours of learning of the abnormality to discuss participant safety. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin, and INR) until they stabilize (i.e., ALT or AST ≤3x ULN and <1.5x baseline value, and no increases in total bilirubin or INR) or return to within baseline or normal limits. • If, during monitoring, ALT increases to >5x ULN and ≥2x baseline value or remains >3x ULN and ≥1.5x baseline value for ≥4 weeks, or if total bilirubin increases to ≥2x ULN, refer to Level 2 monitoring guidance (Table 12). • If Level 2 monitoring criteria are not met after 4 weeks of monitoring but any of the monitored liver chemistry values (ALT, AST, alkaline phosphatase, total bilirubin, or INR) remain abnormal/above baseline, monitor the participant twice monthly until value(s) stabilize or return to within baseline or normal limits. Alternatively, the monitoring can return to standard per protocol (if applicable) or stopped when the investigator and medical monitor agree that values are stable or no longer significantly abnormal; this may require local investigation of potential causes for liver chemistry abnormality.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GSK = GlaxoSmithKline; INR = international normalized ratio; ULN = upper limit of normal.

Level 2 Monitoring

If a participant develops elevations in liver enzyme parameters as defined in Table 12, increased frequency of liver chemistry monitoring (i.e., twice weekly) will apply.

Table 12: Liver Event Increased Monitoring Criteria (Level 2 Liver Monitoring)

Parameter	Criteria
ALT absolute	Both ALT >5x ULN and ≥2x baseline value
ALT increase	Both ALT >3x ULN and ≥1.5x baseline value that persists for 4 weeks
Bilirubin[a,b]	ALT >3x ULN and total bilirubin ≥2x ULN (for participants with known Gilbert's syndrome, these criteria only apply if total bilirubin ≥2x ULN and direct bilirubin ≥2x ULN and ≥2x baseline value)
INR[b]	ALT >3x ULN and INR >1.5
Symptomatic[c]	Both ALT >3x ULN and ≥1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions, Monitoring and Follow-up to Assess Causality for Liver Event	
Actions and Monitoring	**Follow-up to Assess Causality of Liver Event**
• Report the event to Elevation Oncology within 24 hours • Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[b] • Perform liver event follow-up to assess causality of liver event • Monitor the participant liver chemistries (see MONITORING) MONITORING: If ALT >3x ULN *and* total bilirubin ≥2x ULN or INR >1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up to assess liver event causality within 24 hours • Monitor participants twice weekly until liver chemistries reduce to ≤3x ULN for ALT, <2x ULN for total bilirubin, or ≤1.5 for INR or return to or remain within baseline or normal limits • A specialist or hepatology consultation is recommended For all other criteria (total bilirubin <2x ULN and INR ≤1.5): • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up to assess causality of liver event within 24-72 hours	• Viral serology[d] • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins • Serum CPK, LDH, GGT, GLDH, and serum albumin • Fractionate bilirubin, if total bilirubin ≥2x ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury or hypersensitivity on adverse event form • Record use of concomitant medications on the concomitant medications eCRF including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications • Record alcohol use in narrative if serious adverse event If ALT >3x ULN *and* total bilirubin ≥2x ULN or INR >1.5, obtain the following in addition to the assessments listed above: • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury • Liver imaging (ultrasound, MRI, or CT) to evaluate liver disease; complete liver imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: ○ When serology raises the possibility of AIH

• Monitor participant weekly until liver chemistries reduce to ≤3x ULN and <1.5x baseline value for ALT or return to or remain within baseline or normal limits	○ When suspected DILI progresses or fails to resolve on withdrawal of study intervention ○ In participants with acute or chronic atypical presentation.

AIH = autoimmune hepatitis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; CT = computed tomography; DILI = drug-induced liver injury; eCRF = electronic case report form; GGT = gamma glutamyl transferase; GLDH = glutamate dehydrogenase; GSK = GlaxoSmithKline; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV= hepatitis B virus; HCV = hepatitis C virus; HDV= hepatitis D virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PK = pharmacokinetic(s); RNA = ribonucleic acid; SAE = serious adverse event; ULN = upper limit of normal.

a. Serum bilirubin fractionation should be performed if testing is available. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

b. All events of ALT >3x ULN and total bilirubin ≥2x ULN (for participants with known Gilbert's syndrome, these criteria only apply if total bilirubin ≥2x ULN and direct bilirubin ≥2x ULN and ≥2x baseline value) or ALT >3x ULN and INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE [(excluding studies of hepatic impairment or cirrhosis)]; the INR threshold value stated will not apply to participants receiving anticoagulants.

c. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash, or eosinophilia).

d. Includes: Hepatitis A IgM antibody; HBsAg and HBcAb (IgM); HCV RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody, and RNA PCR test. HBV DNA quantification, and HDV antibody should be measured if participant is known to be HBsAg and/or HBcAb-positive prior to onset of the liver event or is subsequently found to be HBsAg-positive on investigation following the liver event. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of HDV RNA virus (where needed and if this is feasible).