
Clinical Study Protocol

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Phase III, Randomized, Open-label, Global, Multicenter Study of Rilvegostomig or Durvalumab in Combination With Chemotherapy as a First-line Treatment for Patients With Advanced Biliary Tract Cancer (ARTEMIDE-Biliary02)

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Study Phase: Phase III

Acronym: ARTEMIDE-Biliary02

Study Clinical Lead Name and Contact Information will be provided separately.

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LIST OF ABBREVIATIONS

Abbreviations and special terms are written in full below and the list is considered ‘first use’.

Abbreviation or special term	Explanation
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
anti-HBc	hepatitis B core antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase/transaminase
AUC	area under the curve
AxMP	auxiliary medicinal product
BICR	Blinded Independent Central Review
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BTC	biliary tract cancer
C	Cycle
CA-19-9	cancer antigen 19-9
CD	cluster of differentiation
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
C _{max}	maximum observed concentration
CMH	Cochran–Mantel–Haenszel
CMV	cytomegalovirus
COA	clinical outcome assessment
COVID-19	Coronavirus disease 2019
CPI	checkpoint inhibitor
CPS	combined positive score
CR	complete response
CrCL	calculated creatinine clearance
CRF	Case Report Form
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation or special term	Explanation
ctDNA	circulating tumor DNA
CTIS	Clinical Trial Information System (EU)
CV	cardiovascular
CYP	cytochrome P450
D	Day
DCO	data cut-off
DES	data entry site
DMC	Data Monitoring Committee
DoR	duration of response
DUS	disease under study
EBV	Epstein–Barr virus
eCCA	extra-hepatic cholangiocarcinoma
ECG	electrocardiogram
ECHO	echocardiogram
eCOA	electronic clinical outcome assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EORTC IL	European Organization for Research and Treatment of Cancer Item Library
EoT	end-of-treatment
EQ-5D-5L	EuroQoL 5-dimension, 5-level health state descriptive system
EQ-VAS	EuroQol-visual analogue scale
EU	European Union
EU CT	European Union Clinical Trial
FA	final analysis
Fab	fragment antigen-binding
FAS	Full Analysis Set
Fc	fragment crystallizable
FDA	United States Food and Drug Administration
FDG-PET	¹⁸ F-fluoro-deoxyglucose positron emission tomography
FFPE	formalin fixed paraffin embedded
FGFR2	fibroblast growth factor receptor 2
FOCBP	female of childbearing potential
FOLFOX	folinic acid (leucovorin or calcium folinate), fluorouracil (5-FU), and oxaliplatin
GBC	gallbladder cancer
GCP	Good Clinical Practice

Abbreviation or special term	Explanation
G-CSF	granulocyte colony stimulating factor
GEJ	gastroesophageal junction
GemCis	gemcitabine and cisplatin
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GHS	Global Health Status
HAV	hepatitis A virus
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCP	healthcare provider
HCV	hepatitis C virus
HDV	hepatitis D virus
HER2	human epidermal growth factor receptor 2
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HOSPAD	Hospital Admission (form)
HR	hazard ratio
HRT	hormone replacement therapy
HSV	herpes simplex virus
IA	interim analysis
IB	Investigator's Brochure
iCCA	intra-hepatic cholangiocarcinoma
ICF	Informed Consent Form
ICH	International Council for Harmonization
iCRO	imaging Contract Research Organization
IDH1	isocitrate dehydrogenase 1
IEC	Independent Ethics Committee
IFN- γ	interferon gamma
IgG	immunoglobulin G
IgM	immunoglobulin M
IHC	immunohistochemistry
IL	Item Library
imAE	immune-mediated adverse event
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board

Abbreviation or special term	Explanation
IRR	infusion-related reaction
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	intent-to-treat
iv/IV	intravenous
IVD	in vitro diagnostic
KRAS	kirsten rat sarcoma viral oncogene homologue
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTP	multiple testing procedure
MUGA	multigated acquisition
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NED	no evidence of disease
NK	natural killer
NL	new lesion
NSCLC	non-small cell lung cancer
NTL	non-target lesion
NTRK	neurotrophic tyrosine receptor kinase
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-2	programmed cell death protein 2
PD-L1	programmed cell death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PFS2	time to second progression or death
PGI-C	Patients' Global Impression of Change
PGI-S	Patients' Global Impression of Severity
PGI-TT	Patients' Global Impression of Treatment Tolerability
PK	pharmacokinetic(s)

Abbreviation or special term	Explanation
PR	partial response
PRO	patient-reported outcome
PROMIS SF-PF 8c	Patient-Reported Outcomes Measurement Information System Short Form – Physical Function 8c
PT	prothrombin time
PTT	partial thromboplastin time
QxW	every x weeks
QC	quality control
QLQ-C30	30-item core quality of life questionnaire
QoL	quality of life
QTcF	QT interval corrected by Fridericia's formula
RANKL	receptor activator of nuclear factor- κ B ligand
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RNA	ribonucleic acid
RoW	rest of the world
RPM	remote patient monitoring
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SoC	standard of care
SPECT	single photon emission computed tomography
SpO ₂	peripheral capillary oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TAP	tumor area positivity
TBL	total bilirubin
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TgAb	anti-thyroglobulin antibody
TIGIT	T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain
TIL	tumor-infiltrating lymphocyte
TL	target lesion
TMG	Toxicity Management Guideline
TPOAb	anti-thyroid peroxidase antibody
TPS	tumor proportion score

Abbreviation or special term	Explanation
TRAb	anti-thyrotropin receptor antibody
TSH	thyroid-stimulating hormone
TTD	time-to-treatment discontinuation
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
WHO	World Health Organization
WMA	World Medical Association
XELOX	capecitabine and oxaliplatin

1 **PROTOCOL SUMMARY**

1.1 **Synopsis**

Protocol Title: Phase III, Randomized, Open-label, Global, Multicenter Study of Rilvegostomig or Durvalumab in Combination With Chemotherapy as a First-line Treatment for Patients With Advanced Biliary Tract Cancer (ARTEMIDE-Biliary02)

Brief Title: A Global Phase III Study of Rilvegostomig Plus Chemotherapy for First-line Treatment of Advanced BTC

Regulatory Agency Identifier Number(s):

Registry

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US Investigational New Drug Number 170039

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Rationale:

BTC is a heterogenous malignancy that arises from the bile duct or gallbladder and can be divided by anatomical subtype into iCCA, eCCA, and GBC. The 5-year OS rates are poor for patients with unresectable (locally advanced or metastatic) BTC (3% to 9%; [American Cancer Society 2025](#)). BTC is a rare disease, accounting for 0.7% of all malignant tumors, and 3% of all gastrointestinal malignancies, in adults. The incidence of BTC varies widely globally with country level variation driven by different causative etiologies such as hepatitis B, hepatitis C, gallstones, endemic liver flukes, obesity and non-alcoholic fatty liver disease ([Baria et al 2022](#)). Both incidence and mortality are increasing, predominantly due to a rise in iCCA ([Lamarca et al 2020](#)).

The majority (approximately 80%) of BTC patients present with advanced (unresectable or metastatic) disease ([Shroff et al 2019](#)). BTC is characterized by many molecular alterations of differing mechanisms ([Banales et al 2020](#)), including mutations in *IDH1*, *KRAS* and *BRAF* genes, translocations in *FGFR2* and *NTRK*, *HER2* amplification and MSI ([Abou-Alfa et al 2020a](#), [Abou-Alfa et al 2020b](#), [Drilon et al 2018](#), [Farha et al 2023](#), [Kehmann et al 2024](#), [Lamarca et al 2022](#), [Le et al 2017](#), [Subbiah et al 2020](#)). BTC exhibits immunogenic features and expression of the immune checkpoint molecules in the tumor microenvironment ([Oh et al 2022a](#)).

Nonclinical studies have demonstrated that both PD-1 and TIGIT are key inhibitors of antitumor responses that can hinder multiple steps of the cancer immunity cycle ([Iwai et al 2002](#), [Johnston et al 2014](#)). Emerging clinical data suggest that dual blockade of the converging ([Sundstrom et al 2025](#)), immunosuppressive PD-1 and TIGIT pathways may

extend the clinical benefit of immune checkpoint inhibition. TIGIT has also been found to be over-expressed in cholangiocarcinoma relative to normal tissue ([Wen et al 2021](#)).

Despite advances in the first-line treatment of BTC, OS remains poor and there is a high unmet need to improve outcomes. In TOPAZ-1 the addition of durvalumab to GemCis significantly improved OS vs chemotherapy alone (HR 0.80 [95% CI: 0.66, 0.97], median OS 12.9 months [95% CI: 11.6, 14.1] vs 11.3 months [95% CI: 10.1, 12.5], $p = 0.021$) ([Oh et al 2022b](#)). However, despite this improvement, the 3-year OS was only 14.6% vs 6.9% in the experimental and control arms respectively ([Oh et al 2025](#)). In TOPAZ-1 and KEYNOTE-966 (pembrolizumab plus GemCis vs GemCis in first-line BTC), approximately 50% of patients who discontinued the current SoC did not receive any additional lines of treatment ([Oh et al 2022a](#), [Kelley et al 2023](#)). Due to the poor survival post first-line progression, improved therapies in the first-line setting are needed.

The bispecific format of rilvegostomig allows targeting of the converging, immunosuppressive PD-1 and TIGIT pathways within one molecule. The use of an anti-TIGIT/anti-PD-1 monovalent bispecific antibody is an innovative approach for targeting both TIGIT and PD-1 receptors at the same time. This approach has some potential advantages compared to the administration of 2 separate anti-TIGIT and anti-PD-1/PD-L1 antibodies. Along with a decrease in burden of drug delivery (1 vs 2 infusions), there is a certainty of equal biodistribution of a single molecule targeting both receptors. The cooperative binding of both receptors has the potential to elicit novel biological effect(s) that may not be achieved by a combination of monospecific antibodies ([Chariou et al 2024](#), [Dovedi et al 2021](#), [Lee et al 2022](#)), as suggested by encouraging antitumor activity for rilvegostomig in nonclinical models showing significant immune activation and tumor growth inhibition over controls and compared to a combination of 2 parental anti-TIGIT and anti-PD-1 antibodies ([Chariou et al 2024](#), [Lee et al 2022](#)).

Supportive preliminary efficacy and safety data has been observed in Cohort 2A of GEMINI-Hepatobiliary Phase II platform study (NCT05775159). This cohort investigates rilvegostomig in combination with GemCis in first-line BTC. As of the DCO date of 04 November 2024, a total of 30 participants have received rilvegostomig therapy (750 mg Q3W) with median follow-up of 6.9 months. The 6-month PFS rate was 73% (95% CI: 53.3 to 85.5), median PFS 8.31 months (95% CI: 6.74 to 9.63). These efficacy data compared favorably to historical benchmark data from TOPAZ-1 and KEYNOTE-966 ([Zhou et al 2025](#)).

The safety profile of rilvegostomig in combination with GemCis was tolerable and no new safety signals were observed in GEMINI-Hepatobiliary Cohort 2A when compared to TOPAZ-1 data. As of 04 November 2024, all participants in GEMINI-Hepatobiliary Cohort 2A had at least one AE. Four participants (13.3%) had a Grade ≥ 3 AE considered related to rilvegostomig and there were no fatal AEs related to study treatment. One (3.3%)

participant had an AE leading to rilvegostomig discontinuation ([Zhou et al 2025](#)).

This trial hypothesizes that the combination of rilvegostomig (a bispecific antibody inhibiting both PD-1 and TIGIT) plus chemotherapy will improve treatment efficacy in patients with advanced BTC in the first-line setting over durvalumab plus chemotherapy with a comparably tolerable safety profile.

Objectives, Endpoints and Estimands:

Objectives	Estimands descriptions/Endpoints
Primary	
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of OS in the PD-L1 $\geq 1\%$ population.	OS is defined as time from randomization until the date of death due to any cause. The analysis will include all randomized participants in the PD-L1 $\geq 1\%$ population. All deaths will be included, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the HR of OS.
Key secondary	
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of OS in the ITT population.	OS is defined as time from randomization until the date of death due to any cause. The analysis will include all randomized participants. All deaths will be included, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the HR of OS.
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of PFS in the PD-L1 $\geq 1\%$ population.	PFS is defined as the time from randomization until radiological progression per RECIST 1.1 as assessed by Investigator, or death due to any cause (in the absence of progression), whichever occurs first. The analysis will include all randomized participants in the PD-L1 $\geq 1\%$ population. All events will be included regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to radiographic progression per RECIST 1.1. However, if the participant progresses or dies immediately after 2 or more consecutive missed visits, the participant will be censored at the time of the latest evaluable assessment prior to the 2 missed visits. PFS will also be assessed by BICR for supplementary/sensitivity analysis. The measure of interest is the HR of PFS.
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of PFS in the ITT population.	PFS is defined as the time from randomization until radiological progression per RECIST 1.1 as assessed by Investigator, or death due to any cause (in the absence of progression), whichever occurs first. The analysis will include all randomized participants. All events will be included regardless of whether the

Objectives	Estimands descriptions/Endpoints
	participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to radiographic progression per RECIST 1.1. However, if the participant progresses or dies immediately after 2 or more consecutive missed visits, the participant will be censored at the time of the latest evaluable assessment prior to the 2 missed visits. PFS will also be assessed by BICR for supplementary/sensitivity analysis. The measure of interest is the HR of PFS.
Secondary	
To characterize and compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of ORR in the PD-L1 $\geq 1\%$ population.	ORR is defined as the proportion of participants who have a confirmed CR or confirmed PR, as determined by Investigator assessments using RECIST 1.1. The analyses will include all randomized participants in the PD-L1 $\geq 1\%$ population. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who discontinue treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR analysis. The measure of interest is the difference of the ORR.
To characterize and compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of ORR in the ITT population.	ORR is defined as the proportion of participants who have a confirmed CR or confirmed PR, as determined by Investigator assessments using RECIST 1.1. The analyses will include all randomized participants. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who discontinue treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR analysis. The measure of interest is the difference of the ORR.
To characterize and compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of DoR in the PD-L1 $\geq 1\%$ population.	DoR is defined as the time from the date of first documented response until the date of documented progression per Investigator assessments using RECIST 1.1 or death due to any cause (in the absence of progression), whichever occurs first. The analyses will include all randomized participants who have a confirmed response in the PD-L1 $\geq 1\%$ population. The end of response coincides with the date of progression or death from any cause used for the PFS endpoint. The measure of interest is the median of DoR.
To characterize and compare the efficacy of rilvegostomig plus chemotherapy relative to	DoR is defined as the time from the date of first documented response until the date of documented progression per Investigator assessments using

Objectives	Estimands descriptions/Endpoints
durvalumab plus chemotherapy by assessment of DoR in the ITT population.	RECIST 1.1 or death due to any cause (in the absence of progression), whichever occurs first. The analyses will include all randomized participants who have a confirmed response. The end of response coincides with the date of progression or death from any cause used for the PFS endpoint. The measure of interest is the median of DoR.
To compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of PFS2 in the PD-L1 $\geq 1\%$ population.	PFS2 is defined as the time from randomization until the earliest of the progression event (following the initial Investigator-assessed progression event), after the start of the first subsequent therapy, or death from any cause, whichever occurs first. The date of the second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice. The analyses will include all randomized participants in the PD-L1 $\geq 1\%$ population. All events will be included, regardless of whether the participant withdraws from subsequent therapy and regardless of missed visits. The measure of interest is the HR of PFS2.
To compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of PFS2 in the ITT population.	PFS2 is defined as the time from randomization until the earliest of the progression event (following the initial Investigator-assessed progression event), after the start of the first subsequent therapy, or death from any cause, whichever occurs first. The date of the second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice. The analyses will include all randomized participants. All events will be included, regardless of whether the participant withdraws from subsequent therapy and regardless of missed visits. The measure of interest is the HR of PFS2.
To assess the safety and tolerability of rilvegostomig plus chemotherapy compared to durvalumab plus chemotherapy.	Safety and tolerability will be evaluated in terms of AEs (graded by CTCAE v5.0), clinical laboratory assessments, vital signs, physical examination, and ECOG performance status. These analyses will include all randomized participants who received at least one dose of study intervention (safety analysis set).
To assess the PK of rilvegostomig.	Concentration of rilvegostomig in serum and PK parameters (such as peak and trough concentration, as data allow; sparse sampling will be performed).
To investigate the immunogenicity of rilvegostomig.	Presence of ADAs, titer, and neutralizing antibodies for rilvegostomig.
To assess patient-reported BTC symptoms.	Proportion of participants with maintained or improved pain as measured by the EORTC IL445 and EORTC IL446. The analysis will include all randomized participants. The measure of interest will be the proportion of participants with maintained or improved pain.

Objectives	Estimands descriptions/Endpoints
To assess patient-reported GHS/QoL.	Proportion of participants with maintained or improved GHS/QoL as measured by the EORTC IL172. The analysis will include all randomized participants. The measure of interest is the proportion of participants with maintained or improved GHS/QoL.

For Tertiary/Exploratory objectives and estimands descriptions/endpoints, see Section 3 of the full CSP.

Overall Design Synopsis:

Brief Summary:

The purpose of ARTEMIDE-Biliary02 is to assess the efficacy and safety of rilvegostomig in combination with chemotherapy compared with durvalumab in combination with chemotherapy as first-line treatment in participants with advanced (unresectable or metastatic) BTC.

This study will be conducted in approximately 185 sites across 20 countries.

Participants must have advanced BTC with tumors of primary tumor type of iCCA, eCCA or GBC.

Disclosure Statement: This is a Phase III, two-arm, randomized, open-label, multicenter, global study, assessing the efficacy and safety of rilvegostomig in combination with gemcitabine and cisplatin chemotherapy compared with durvalumab in combination with gemcitabine and cisplatin chemotherapy in participants with advanced BTC.

Participant Population:

The target population of interest in this study is participants with advanced (unresectable or metastatic) BTC. Participants must not have received prior therapy in the advanced setting, and must not have received prior immunotherapy.

Number of Participants:

Approximately 1572 participants will be screened to achieve approximately 1100 participants randomized into the study.

Note: ‘Screened’ means a participant’s, or their legally authorized representative’s (where allowed per local regulations), agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomized/assigned in the study, are considered ‘screen failures’, unless otherwise specified by the protocol.

Recruitment of participants with GBC will be capped at approximately 25% of the total randomized participants. Recruitment of participants with PD-L1 $\geq 1\%$ will include a minimum of 825 randomized participants.

Study Arms and Duration:

Participants will be randomized in a 1:1 ratio to one of the following intervention arms:

- **Experimental arm:** Rilvegostomig in combination with gemcitabine plus cisplatin. Participants will receive rilvegostomig 750 mg IV Q3W on D1 of each cycle starting on C1D1 in combination with chemotherapy for up to 8 cycles, after which participants will receive rilvegostomig 750 mg IV Q3W as a single-agent, until disease progression or unacceptable toxicity. Gemcitabine 1000 mg/m² IV Q3W plus cisplatin 25 mg/m² IV Q3W will be administered on D1 and D8 of each cycle starting on C1D1 for up to 8 cycles.
- **Control arm:** Durvalumab in combination with gemcitabine plus cisplatin. Participants will receive durvalumab 1500 mg IV Q3W on D1 of each cycle starting on C1D1 in combination with chemotherapy for up to 8 cycles, after which participants will receive durvalumab 1500 mg IV Q4W as a single-agent, until disease progression or unacceptable toxicity. Gemcitabine 1000 mg/m² IV Q3W plus cisplatin 25 mg/m² IV Q3W will be administered on D1 and D8 of each cycle starting on C1D1 for up to 8 cycles.

Randomization will be stratified by PD-L1 expression (TAP $< 1\%$ vs $\geq 1\%$), disease status (initially unresectable vs recurrent), primary tumor location (iCCA vs eCCA vs GBC), and geographical region (Asia vs RoW).

Participants will be prospectively tested for PD-L1 expression for stratification. Participants must have a tumor sample available for PD-L1 IHC testing performed by a central reference laboratory during the screening period. PD-L1 status is required prior to randomization. PD-L1 expression will be determined using the investigational VENTANA PD-L1 (SP263) CDx assay.

Participants in both experimental and control arms will continue to receive study intervention (rilvegostomig or durvalumab) until RECIST 1.1-defined radiological progression as assessed by the Investigator, unacceptable toxicity, the participant requests to stop the study treatment, or until any other intervention discontinuation criterion are met (see Section 7.1).

Following Investigator-assessed RECIST 1.1-defined disease progression, due to the potential pseudo-progression observed in participants treated with immunotherapies, participants may continue to receive rilvegostomig or durvalumab until confirmed with a subsequent scan (performed at least 4 weeks later, but no later than the next scheduled imaging visit) as long as

they continue to show clinical benefit (see Section 6.1.5). If disease progression is confirmed by this second scan, the participant must discontinue study treatment.

Participants receiving cisplatin should receive pretreatment hydration and antiemetics as for highly emetic regimens. Please refer to prescribing information for guidance.

Follow-up of Participants Post Discontinuation of Study Intervention:

After study intervention discontinuation, all participants will undergo an EoT visit (30 [+ 7] days after their last dose of all study interventions) and will be followed up for safety assessments 90 ($\pm$ 7) days after their last dose of study intervention (ie, the safety follow-up visit).

Every effort should be made to perform the D30 (EoT) and D90 (safety follow-up) visits within the correct time window in relation to last dose of study intervention. However, if the decision to discontinue all study interventions is made after D30 but before D90 after last study intervention, the D30 (EoT) visit should be conducted within 7 days of the decision to discontinue all study interventions. If the decision to discontinue all study interventions is made after D90 after last study intervention, then a D30 (EoT) visit should be conducted within 7 days of the decision to discontinue and the D90 (safety follow-up) visit can be omitted.

Participants who have discontinued study intervention in the absence of RECIST 1.1-defined radiological progression by Investigator assessment will be followed up with tumor assessments according to the SoA (Section 1.3) until RECIST 1.1-defined disease progression (plus an additional follow-up scan) or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

In addition, all participants will be followed up for survival status every 12 weeks ($\pm$ 14 days) from the safety follow-up visit until death, withdrawal of consent, or the end of the study, as per the SoA.

Data Monitoring Committee

A DMC has been appointed for this study. The DMC comprises a group of independent experts who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to AstraZeneca to continue, amend, or stop the study based on safety findings, efficacy, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

The DMC will convene and meet initially once at least 40 participants (approximately 20 participants per study arm) have received treatment and have had at least 6 weeks of

follow-up or once at least 6 months has elapsed from the first randomized participant, whichever occurs first. This will be considered the DCO date for the first DMC meeting. The DMC will review unblinded safety data and make recommendations to continue, amend, or stop the study based on safety findings. The DMC will meet approximately every 6 months thereafter.

For any interim efficacy analysis, the DMC will review unblinded efficacy data and inform AstraZeneca whether the interim boundaries specified in Section 9.5 are met. Full details of the DMC procedures, processes, and interim analyses can be found in the DMC Charter.

Statistical Methods

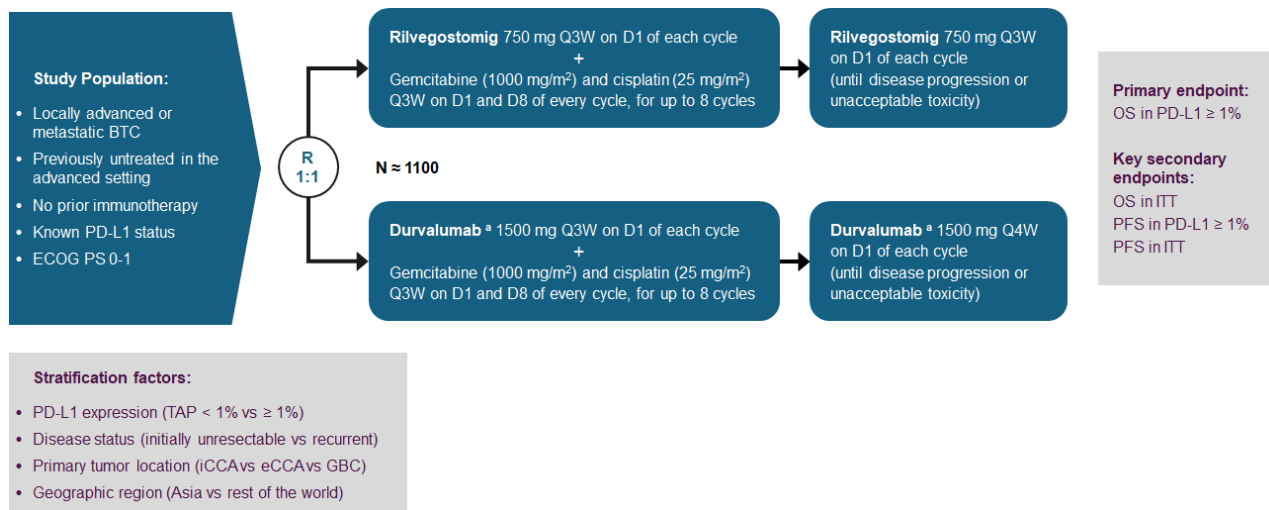
For the primary endpoint of OS in the PD-L1 $\geq 1\%$ population, there are two IAs and one FA, which are planned to occur when approximately 258, 532 and 620 OS events have been observed (IA1, IA2, and FA, respectively) in the PD-L1 $\geq 1\%$ population. IA1 is a (non-binding) futility analysis, while IA2 and FA are superiority analyses. It is expected the analyses will be performed approximately 21, 35, and 43 months after the first participant is randomized into the study. The OS superiority of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy will be assessed using a stratified log-rank test adjusting for the 3 stratification factors (disease status, primary tumor location, and geographical region). A stratified Cox proportional hazards model will be used to estimate the HR and associated 95% CI. To address the multiplicity issue caused by the evaluation of treatment effect at several analysis timepoints, Lan-DeMets (Lan and DeMets 1983) spending function to approximate O'Brien-Fleming boundaries is implemented. If the superiority IA/FA of OS are performed at exactly 532 events (IA2), and 620 events (FA), the study will have approximately 94% overall power to demonstrate a statistically significant OS difference with a 2-sided 5% alpha and a target average HR = 0.75 at the FA.

OS in the ITT population, PFS in the PD-L1 $\geq 1\%$ population, and PFS in the ITT population are included as key secondary endpoints in the prespecified MTP. An alpha-recycling strategy will be applied in order to preserve the overall type I error rate (family-wise error rate) at the 2-sided 5% level in the strong sense. See Section 3 and Section 9.1 of the full CSP for further details.

Other endpoints, including other efficacy, COA, safety, PK, and immunogenicity data, are described in the full CSP and will be further detailed in the SAP if needed.

1.2 Schema

Figure 1 Study Design



^a Durvalumab is administered Q3W on Day 1 of each cycle in combination with chemotherapy for up to 8 cycles, followed by Q4W on Day 1 of each cycle as a single-agent. If weight falls to ≤ 30 kg, the participant should receive weight-based dosing of 20 mg/kg of durvalumab (for full details, see Section 6.6).

1.3 Schedule of Activities

The procedures for this study are presented in the SoA (Table 1 and Table 2). Procedures and/or assessments are required from screening until data collection ends (inclusive of follow-up periods).

Table 1 Schedule of Activities: Intervention Period

Procedure	Screening ^a	Intervention period 1 cycle = 21 days (during chemotherapy)																	Details in protocol Section or Appendix
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9+ 1 cycle = 21 days for rilvegostomig and 28 days for durvalumab	
Day	D-28 to D1	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	
Window (±days)	NA	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Informed consent: main study ^b	X																		Section 5.1 and Appendix A
Informed consent, Genomics Initiative optional consent (optional) ^c	X																		Section 8.7
Study Procedures and Safety Assessments																			
Inclusion and exclusion criteria	X	X ^d																	Sections 5.1 and 5.2
Randomization		X ^e																	Section 6.3
Past/current medical conditions and surgical history	X	X ^d																	Sections 5.1 and 5.2
ECOG performance status	X	X ^d	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	Sections 5.1 and 8.3.5.3
Demography	X																		Section 5.1

Table 1 Schedule of Activities: Intervention Period

Procedure	Screening ^a	Intervention period 1 cycle = 21 days (during chemotherapy)																	Details in protocol Section or Appendix
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9+ 1 cycle = 21 days for rilvegostomig and 28 days for durvalumab	
Day	D-28 to D1	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	
Window (±days)	NA	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Full physical examination	X	X ^d																	Section 8.3.1
Targeted physical examination		X		X		X		X		X		X		X		X		X	Section 8.3.1
Height	X																		Section 8.3.1
Weight	X	X ^{d, f}		X ^f		X ^f		X ^f		X ^f		X ^f		X ^f		X ^f		X ^f	Section 8.3.1
Vital signs, including pulse oximetry (SpO ₂) ^h	X	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	Section 8.3.2
12-lead ECG ⁱ	X	X ^d	As clinically indicated																Section 8.3.3
LVEF by ECHO/MUGA	X	As clinically indicated																	Section 8.3.5.2
AE review	X	←=====→ At every visit and may be conducted by phone if not tied to a visit																	Sections 6.6 and 8.4
Concomitant medication review	X	←=====→ At every visit and may be conducted by phone if not tied to a visit																	Sections 5.2 and 6.9

Table 1 Schedule of Activities: Intervention Period

Procedure	Screening ^a	Intervention period 1 cycle = 21 days (during chemotherapy)																	Details in protocol Section or Appendix
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9+ 1 cycle = 21 days for rilvegostomig and 28 days for durvalumab	
Day	D-28 to D1	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	
Window (±days)	NA	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Laboratory Assessments																			
Highly sensitive serum OR urine pregnancy test (FOCBP only)	X (Serum only)	X		X		X		X		X		X		X		X		X	Sections 5.1, 5.2, and 8.3.4
Tuberculosis testing (per local practice)	X	Per local practice																	Sections 5.2 and 8.3.4
Hepatitis B and C testing ^j	X	X ^k		X ^k		X ^k		X ^k		X ^k		X ^k		X ^k		X ^k		X ^k	Sections 5.2 and 8.3.4.1
HIV testing (as per local regulations)	X	Viral RNA load and CD4+ count is recommended only for participants with HIV infection at screening																	Sections 5.2 and 8.3.4
Hematology ^l	X	X ^d	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	Sections 5.1 and 8.3.4
Clinical chemistry ^l	X	X ^d	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	X ^g	X	Sections 5.1 and 8.3.4
Coagulation	X	X ^d	As clinically indicated																Section 8.3.4

Table 1 Schedule of Activities: Intervention Period

Procedure	Screening ^a	Intervention period 1 cycle = 21 days (during chemotherapy)																	Details in protocol Section or Appendix
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9+ 1 cycle = 21 days for rilvegostomig and 28 days for durvalumab	
Day	D-28 to D1	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	
Window (±days)	NA	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Thyroid function test	X	X ^d		X		X		X		X		X		X		X		X	Sections 8.3.4
Troponin	X	X ^d		X		X		X						X				C10D1, C13D1 and on D1 every 3 cycles thereafter until the end- of-study intervention	Section 8.3.4
Creatine phosphokinase	X	X ^d		X		X		X		As clinically indicated									Section 8.3.4
CA-19-9 and CEA (serum) ^m		X		X		X		X		X		X		X		X		X	Section 8.3.5.1
Urinalysis	X	As clinically indicated																	Sections 8.3.4

Table 1 Schedule of Activities: Intervention Period

Procedure	Screening ^a	Intervention period 1 cycle = 21 days (during chemotherapy)																	Details in protocol Section or Appendix
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9+ 1 cycle = 21 days for rilvegostomig and 28 days for durvalumab	
Day	D-28 to D1	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	
Window (±days)	NA	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Pharmacokinetic Testing																			
Pre-dose blood sample for rilvegostomig PK testing (≤ 2 hours prior to the start of IMP infusion)		X		X				X				X						C10D1, C14D1	Section 8.5.1
Post-dose blood sample for rilvegostomig PK testing (≤ 15 minutes after the end of IMP infusion)		X						X											Section 8.5.1
Immunogenicity Testing																			
Pre-dose blood sample for rilvegostomig immunogenicity testing (≤ 2 hours prior to the start of IMP infusion)		X		X				X				X						C10D1, C14D1	Section 8.9
Biomarker Assessments																			
Mandatory screening tumor sample ⁿ (archival or newly acquired biopsy)	X																		Section 8.8

Table 1 Schedule of Activities: Intervention Period

Procedure	Screening ^a	Intervention period 1 cycle = 21 days (during chemotherapy)																	Details in protocol Section or Appendix
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9+ 1 cycle = 21 days for rilvegostomig and 28 days for durvalumab	
Day	D-28 to D1	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	
Window (±days)	NA	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Plasma for ctDNA ^{o, p}		X ^q				X						X						At PD	Section 8.8
PBMC for immune profiling ^{o, p}		X	X (optional)	X		X				X									Section 8.8
Whole blood for RNA analysis ^{o, p}		X	X (optional)	X		X													Section 8.8
Serum for biomarker analysis ^{o, p}		X	X (optional)	X		X													Section 8.8
Optional on-study tumor sample ^p		C3D1 and/or at PD																	Section 8.8
Genomics Initiative (optional), exploratory genomics and multi-omics sample ^{o, p, r}		X																	Section 8.7 and Appendix D

Table 1 Schedule of Activities: Intervention Period

Procedure	Screening ^a	Intervention period 1 cycle = 21 days (during chemotherapy)																	Details in protocol Section or Appendix	
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9+ 1 cycle = 21 days for rilvegostomig and 28 days for durvalumab		
Day	D-28 to D1	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1		
Window (±days)	NA	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Imaging and Efficacy Assessments																				
Tumor imaging (RECIST 1.1) ^s	X	Every 6 weeks (± 7 days) up to Week 24 then Every 8 weeks (± 7 days) up to Week 56 and Every 12 weeks (± 7 days) thereafter relative to the date of randomization until RECIST 1.1-defined radiological disease progression plus an additional follow-up scan at least 4 weeks later, but no later than when the next scheduled imaging visit would have occurred																	Section 8.2.1 and Appendix F	
Clinical Outcome Assessment ^t and Medical Resource Utilization																				
COA training and setup		X																	Section 8.2.5.9	
EORTC IL445		X	Every week for the first 9 weeks, then every 3 weeks until Week 24; then every 4 weeks until PD																	Section 8.2.5
EORTC IL446, EORTC IL172, PROMIS PF-SF 8c-7 day, PGI-S		X	Every 3 weeks until Week 24; then every 4 weeks until PD																	Section 8.2.5
EORTC IL444, PGI-TT ^u		X	Every week for the first 9 weeks, then every 3 weeks until Week 24; then every 4 weeks until EoT																	Section 8.2.5
PGI-C			Every 3 weeks until Week 24; then every 4 weeks until PD																	Section 8.2.5
EQ-5D-5L		X	Every 6 weeks until Week 24; then every 8 weeks until PD																	Section 8.2.5

Table 1 Schedule of Activities: Intervention Period

Procedure	Screening ^a	Intervention period 1 cycle = 21 days (during chemotherapy)																	Details in protocol Section or Appendix
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9+ 1 cycle = 21 days for rilvegostomig and 28 days for durvalumab	
Day	D-28 to D1	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	
Window (±days)	NA	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Digestive symptoms tracker		Daily tracker completion from C1D1 until EoT included																	Section 8.2.5.8
HOSPAD review ^v		←=====→ At every visit																	Section 8.10
Study Intervention Administration																			
Rilvegostomig ^{w, x}		X		X		X		X		X		X		X		X		X Q3W	Section 6
Durvalumab ^{w, x}		X		X		X		X		X		X		X		X		X Q4W	Section 6
Gemcitabine ^y		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 6
Cisplatin ^y		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 6

- ^a Up to 28 days before randomization. It is strongly recommended that screening assessments be conducted as close as possible to Day 1.
- ^b Written (or electronic) informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.
- ^c A signed informed consent indicating whether or not the participant agrees to the optional genomics initiative samples and analysis must be obtained. This activity/these samples will not be conducted/collected where not allowed per local regulations (eg, in China).
- ^d If screening assessments have been performed within 3 days prior to starting study intervention, they do not have to be repeated at C1D1 if the participant's condition has not changed. The results of safety laboratory tests (clinical chemistry and hematology) performed within 3 days prior to C1D1 must be checked to confirm eligibility prior to randomization.
- ^e Every effort should be made to start treatment within 3 business days of randomization.
- ^f If participant weight falls to ≤ 30 kg, the participant should receive weight-based dosing equivalent to 20 mg/kg of durvalumab (for full details, see Section 6.6). No adjustment is needed for participants receiving rilvegostomig.
- ^g Assessment required only whilst the participant is receiving gemcitabine/cisplatin.
- ^h Vital signs to be taken before blood collection for laboratory tests. Post-dose vital signs are required for rilvegostomig and durvalumab at C1D1.
- ⁱ Triplicate ECGs will be taken at screening.

- j If known history of HBV infection or positive for anti-HBc total and/or HBsAg at screening, then HBV DNA test required at screening. If known history of HCV infection or positive HCV antibody, then HCV RNA test required at screening. For details on the hepatitis B testing (specific tests to be performed and frequency) refer to Section 8.3.4.1. HAV should be tested if clinically indicated. Testing for anti-HDV antibodies is required during screening for any participant positive for anti-HBc total or HBsAg at screening. HDV RNA should be tested if anti-HDV is positive.
- k Routine testing for HBV DNA on Day 1 of each cycle is only required for participants who test positive for anti-HBc or HBsAg at screening. Routine testing for HCV RNA on Day 1 of each cycle is only required for participants who test positive for anti-HCV antibody at screening.
- l At a minimum, laboratory results for hematology, creatinine, electrolytes, and liver function tests must be reviewed prior to every dosing. Refer to Section 8.3.4 for details.
- m To be performed on D1 of each cycle whilst receiving study intervention and then performed to coincide with imaging visits.
- n The mandatory screening tumor tissue sample should either be newly acquired or archival (≤ 12 months old prior to screening). This sample will be used for mandatory PD-L1 testing to determine eligibility and stratification as well as for other biomarker research as described in Section 8.8. A valid centrally tested PD-L1 result is mandatory prior to randomization. Please refer to the Laboratory Manual and Pathology Manual for further information on the collection, processing, handling and shipment of samples.
- o All blood samples will be collected 'pre-dose' within 2 hours prior to dosing.
- p In China, plasma for ctDNA to be collected at C1D1 and EoT/PD, and PBMC for immune profiling to be collected at C1D1 and C2D1 upon local regulatory approval. Whole blood for RNA analysis, serum for biomarker analysis, optional on-study tumor sample and Genomics Initiative exploratory samples will **not** be collected in China and will only be collected in other countries where locally applicable/permissible (see Section 8.8 for further details).
- q Buffy coat (white blood cells) will be collected at C1D1 during plasma processing for ctDNA.
- r The samples for the Optional Genomics Initiative will be obtained at Day 1 pre-dose. If, for any reason, the samples are not drawn at Day 1, it may be taken at any visit until the last study visit. Two samples should be collected per participant for genetics during the study.
- s The schedule of assessments must be followed regardless of any delay in study treatment.
- t Refer to site training material for the window of completion information. The data collected contain generated data from the questionnaires, device and metadata. To be conducted for eligible participants only (ie, excluding screening failures) once the participant has been randomized or assigned to study intervention and prior to the first dose of study intervention and any other study procedures. The provisioned device should be fully charged, and checked that it is fully functioning, prior to the participant's first dosing visit. The site should ensure the participant is trained and understands how to use the COA device prior to the first use. As feasible and unless otherwise indicated, site staff should ensure questionnaires are completed prior to intervention administration and other study procedures, such as collection of laboratory samples and/or discussion of disease progression, to further minimize bias.
- u If a participant progresses, but does not end treatment, the EORTC IL444 and PGI-TT will continue to be collected per the SoA until 12 weeks after progression or EoT, whichever comes first.
- v At each scheduled visit, sites are to review if a hospital admission has been made since the last visit; if it has, then HOSPAD is completed. This module should be completed whenever the participant has attended or been admitted to the hospital (ie, each hospital admission, outpatient, or emergency room attendance encountered). It excludes routine study-related follow-up clinic visits.
- w Immunotherapy (either rilvegostomig or durvalumab according to treatment arm) should be administered prior to intravenous chemotherapy on Day 1 of cycles when both are being administered (see Section 6.1.4).
- x If durvalumab or rilvegostomig is discontinued due to toxicity possibly related to durvalumab or rilvegostomig, treatment with gemcitabine/cisplatin may be continued per Investigator judgement until 8 cycles of chemotherapy are completed. See Section 7.1 for further details.
- y If gemcitabine and cisplatin are both discontinued before cycle 8 due to toxicity possibly related to chemotherapy, treatment with rilvegostomig or durvalumab may continue per Investigator judgement and in accordance with TMGs or local prescribing information as appropriate. In such cases, for participants in the control arm, durvalumab as a single-agent will be administered Q4W. See Section 7.1 for further details.

Note: All assessments on treatment days are to be performed prior to study intervention administration, unless otherwise indicated. Data collection following study analysis until the end of the study is described in Section 8.

Table 2 Schedule of Activities: Post-intervention Period

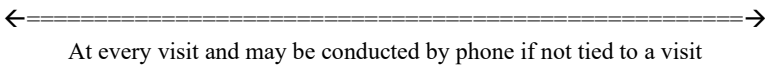
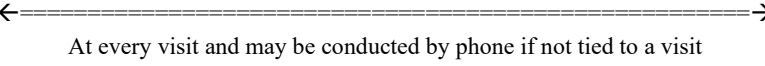
Procedure	Post-intervention period			Details in protocol Section or Appendix
	End-of-treatment ^a	Follow-up		
		Safety	Survival ^b	
Day	D30 post last dose of study treatment	D90 post last dose of study treatment	Q12W	
Window (±days)	+7	±7	±14	
Study procedures and safety assessments				
ECOG performance status	X	X		Sections 5.1 and 8.3.5.3
Targeted physical examination	X	X		Section 8.3.1
Weight	X	X		Section 8.3.1
Vital signs, including pulse oximetry (SpO ₂)	X	X		Section 8.3.2
12-lead ECG ^c	As clinically indicated			Section 8.3.3
LVEF by ECHO/MUGA	X	As clinically indicated		Section 8.3.5.2
AE review				Sections 6.6 and 8.4
Concomitant medication review				Sections 5.2 and 6.9
Subsequent anticancer therapy use (including surgery and radiation therapy)	X	X	X	Section 7.1.1
Laboratory Assessments				
Highly sensitive serum OR urine pregnancy test (FOCBP only)	X Pregnancy test must be performed monthly for 60 days after last dose of rilvegostomig, or 90 days after the last dose of durvalumab, or for 6 months after the last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is longer			Sections 5.1, 5.2, and 8.3.4
Tuberculosis testing	Per local practice			Sections 5.2 and 8.3.4
Hepatitis B and C testing ^d	As clinically indicated			Sections 5.2 and 8.3.4.1

Table 2 Schedule of Activities: Post-intervention Period

Procedure	Post-intervention period			Details in protocol Section or Appendix
	End-of-treatment ^a	Follow-up		
		Safety	Survival ^b	
Day	D30 post last dose of study treatment	D90 post last dose of study treatment	Q12W	
Window (±days)	+7	±7	±14	
HIV screening (as per local regulations)	Viral RNA load and CD4+ count is recommended only for participants with HIV infection at screening			Sections 5.2 and 8.3.4
Hematology	X	X		Sections 5.1 and 8.3.4
Clinical chemistry	X	X		Sections 5.1 and 8.3.4
Coagulation	As clinically indicated			Section 8.3.4
Thyroid function test	X	X		Sections 8.3.4
Troponin	As clinically indicated			Section 8.3.4
Creatine phosphokinase	As clinically indicated			Section 8.3.4
Urinalysis	X			Sections 5.1 and 8.3.4
Pharmacokinetic Testing				
Blood sample for rilvegostomig PK testing ^c	X	X		Section 8.5.1
Immunogenicity Testing				
Blood sample for rilvegostomig immunogenicity testing	X	X		Section 8.9
Biomarker Assessments				
Plasma for ctDNA	X (PD)			Section 8.8

Table 2 Schedule of Activities: Post-intervention Period

Procedure	Post-intervention period			Details in protocol Section or Appendix
	End-of-treatment ^a	Follow-up		
		Safety	Survival ^b	
Day	D30 post last dose of study treatment	D90 post last dose of study treatment	Q12W	
Window (±days)	+7	±7	±14	
Imaging and efficacy assessments				
Tumor imaging (RECIST 1.1) ^f	Every 6 weeks (± 7 days) up to Week 24 then Every 8 weeks (± 7 days) up to Week 56 and Every 12 weeks (± 7 days) thereafter relative to the date of randomization until RECIST 1.1-defined radiological disease progression plus an additional follow-up scan at least 4 weeks later, but no later than when the next scheduled imaging visit would have occurred			Section 8.2.1 and Appendix F
PFS2			X	Sections 7.1.2 and 8.2.3
Survival status	X	X	X	Sections 7.1.3 and 8.2.4
Clinical Outcome Assessment ^g and Medical Resource Utilization				
EORTC IL445, EORTC IL446, PGI-S, PGI-C, EORTC IL172, PROMIS PF-SF 8c-7 day, EQ-5D-5L	X	After progression, every 4 weeks for 3 timepoints		Section 8.2.5
EORTC IL444, PGI-TT	X			Section 8.2.5
Digestive symptoms tracker	X			
HOSPAD review ^h	X	X		Section 8.10

^a If the reason for discontinuation is PD, the decision to discontinue study intervention and the EoT assessments can be conducted at the same visit. Every effort should be made to perform the D30 (EoT) visit and D90 safety follow-up visit within the correct time window in relation to last dose of study intervention. However, if the decision to discontinue all study interventions is made after D30 but before D90 after last study intervention, the D30 (EoT) visit should be conducted within 7 days of the decision to discontinue all study interventions. If the decision to discontinue all study interventions is made after D90 after last study intervention, then a D30 (EoT) visit should be conducted within 7 days of the decision to discontinue and the D90 (safety follow-up) visit can be omitted.

^b Survival follow-up will be conducted Q12W ± 14 days from the safety follow-up visit until end-of-study or death.

^c Single ECG only. Triplicate ECGs should only be conducted if clinically significant abnormalities are observed by single ECG.

^d Testing for HBV DNA and/or HCV RNA in the post-intervention period is only required as clinically indicated for participants who test positive for anti-HBc or HBsAg, or anti-HCV antibody at screening. For details on the hepatitis B testing (specific tests to be performed and frequency) refer to Section 8.3.4.1.

^e PK samples must be timed from end of rilvegostomig dosing.

^f The schedule of assessments must be followed regardless of any delay in study treatment.

- ^g Refer to site training material for the window of completion information. The data collected contain generated data from the questionnaires, device and metadata. The site should ensure the participant is trained and understands how to use the COA device prior to the first use. As feasible and unless otherwise indicated, site staff should ensure questionnaires are completed prior other study procedures, such as collection of laboratory samples and/or discussion of disease progression, to further minimize bias.
- ^h At each scheduled visit, sites are to review if a hospital admission has been made since the last visit; if it has, then HOSPAD is completed. This module should be completed whenever the participant has attended or been admitted to the hospital (ie, each hospital admission, outpatient, or emergency room attendance encountered). It excludes routine study-related follow-up clinic visits.

2 INTRODUCTION

2.1 Study Rationale

The purpose of this Phase III trial is to evaluate the efficacy and safety of rilvegostomig in combination with chemotherapy compared with durvalumab in combination with chemotherapy as first-line treatment in participants with advanced (unresectable or metastatic) BTC. Outcomes of participants treated with rilvegostomig plus chemotherapy will be compared to those from participants receiving durvalumab plus chemotherapy (see Section 4.2 for scientific rationale).

Despite advances in the first-line treatment of BTC, OS remains poor and there is a high unmet need to improve outcomes. In TOPAZ-1 the addition of durvalumab to GemCis significantly improved OS vs chemotherapy alone (HR 0.80 [95% CI: 0.66, 0.97], median OS 12.9 months [95% CI: 11.6, 14.1] vs 11.3 months [95% CI: 10.1, 12.5], $p = 0.021$) (Oh et al 2022b). However, despite this improvement, the 3-year OS was only 14.6% vs 6.9% in the experimental and control arms respectively (Oh et al 2025). In TOPAZ-1 and KEYNOTE-966 (pembrolizumab plus GemCis vs GemCis in first-line BTC), approximately 50% of patients who discontinued the current SoC did not receive any additional lines of treatment (Oh et al 2022a, Kelley et al 2023). Due to the poor survival post first-line progression, improved therapies in the first-line setting are needed.

Emerging clinical data suggest that dual blockade of the converging (Sundstrom et al 2025) immunosuppressive PD-1 and TIGIT pathways may extend the clinical benefit of immune checkpoint inhibition. TIGIT has also been found to be over-expressed in cholangiocarcinoma relative to normal tissue (Wen et al 2021).

The bispecific format of rilvegostomig allows targeting of the converging immunosuppressive PD-1 and TIGIT pathways within one molecule. The use of an anti-TIGIT/anti-PD-1 monovalent bispecific antibody is an innovative approach for targeting both TIGIT and PD-1 receptors at the same time. This approach has some potential advantages compared to the administration of 2 separate anti-TIGIT and anti-PD-1/PD-L1 antibodies. Along with a decrease in burden of drug delivery (1 vs 2 infusions), there is a certainty of equal biodistribution of a single molecule targeting both receptors. The cooperative binding of both receptors has the potential to elicit novel biological effect(s) that may not be achieved by a combination of monospecific antibodies (Chariou et al 2024, Dovedi et al 2021, Lee et al 2022), as suggested by encouraging antitumor activity for rilvegostomig in nonclinical models showing significant immune activation and tumor growth inhibition over controls and compared to a combination of 2 parental anti-TIGIT and anti-PD-1 antibodies (Chariou et al 2024, Lee et al 2022).

As described in Section 2.2.3, preliminary efficacy and safety data are available from the BTC

substudy (Cohort 2A) of the Phase II GEMINI-Hepatobiliary platform study investigating rilvegostomig in combination with GemCis in first-line BTC (NCT05775159). Efficacy data compared favorably to historical benchmark data from TOPAZ-1 and KEYNOTE-966, and the safety profile of rilvegostomig in combination with GemCis was tolerable and no new safety signals were observed when compared to TOPAZ-1 data ([Zhou et al 2025](#)).

The Phase III ARTEMIDE-Biliary02 trial hypothesizes that the combination of rilvegostomig (a bispecific antibody inhibiting both PD-1 and TIGIT) plus chemotherapy will improve treatment efficacy in patients with advanced BTC in the first-line setting over durvalumab plus chemotherapy with a comparably tolerable safety profile.

2.2 Background

2.2.1 Disease Background and Current Treatment Landscape

BTC is a heterogeneous malignancy that arises from the bile duct or gallbladder and can be divided by anatomical subtype into iCCA, eCCA, and GBC. The 5-year OS rates are poor for patients with unresectable (locally advanced or metastatic) BTC (3% to 9%; [American Cancer Society 2025](#)). BTC is a rare disease, accounting for 0.7% of all malignant tumors, and 3% of all gastrointestinal malignancies, in adults. The incidence of BTC varies widely globally, with country level variation driven by different causative etiologies such as hepatitis B, hepatitis C, gallstones, endemic liver flukes, obesity and non-alcoholic fatty liver disease ([Baria et al 2022](#)). Both incidence and mortality are increasing, predominantly due to a rise in iCCA ([Lamarca et al 2020](#)).

Worldwide, there were an estimated 210,878 new cases of BTC and estimated 173,974 deaths from BTC in 2017 ([Ouyang et al 2021](#)). Countries in the Asia-Pacific region and South America have higher incidence rates of BTC (Asia-Pacific 1.12 to 9 cases per 100,000 person-years; South America 2.73 to 12.42 cases per 100,000 person-years) than European and North American countries (Europe 2.00 to 3.59 cases per 100,000 person-years; North America 2.33 to 2.35 cases per 100,000 person-years).

In the US, there were an estimated 12,610 new cases of BTC and an estimated 4,400 deaths from BTC in 2025 ([American Cancer Society 2025](#)).

There is a lack of published data on the annual incident cases of BTC and mortality from BTC in Europe in aggregate. However, some country level data are available. In Germany, there were an estimated 5,109 new cases of BTC and an estimated 3,722 deaths from BTC in 2019 ([Zentrum 2019](#)). In the United Kingdom, there were an estimated 2,187 new cases of BTC and 2,700 deaths from BTC in 2017 ([Genus et al 2019](#)).

The majority (approximately 80%) of BTC patients present with advanced (unresectable or metastatic) disease ([Shroff et al 2019](#)). BTC is characterized by many molecular alterations of

differing mechanisms (Banales et al 2020), including mutations in *IDH1*, *KRAS*, and *BRAF* genes, translocations in *FGFR2* and *NTRK*, *HER2* amplification, and MSI (Abou-Alfa et al 2020a, Abou-Alfa et al 2020b, Drilon et al 2018, Farha et al 2023, Kehmann et al 2024, Lamarca et al 2022, Le et al 2017, Subbiah et al 2020). BTC exhibits immunogenic features and expression of the immune checkpoint molecules in the tumor microenvironment (Oh et al 2022a).

In the setting of advanced disease, the ABC-02 trial established the combination of gemcitabine and cisplatin in first-line BTC, demonstrating a survival advantage over gemcitabine alone (Valle et al 2010). More recently the addition of immunotherapy to the chemotherapy backbone of gemcitabine and cisplatin has demonstrated survival benefit compared to gemcitabine and cisplatin alone (Kelley et al 2023, Oh et al 2022b). Based on the results of the TOPAZ-1 study, durvalumab in combination with gemcitabine and cisplatin is a recommended first-line treatment for patients with advanced BTC, irrespective of primary tumor subtype, molecular alterations, or PD-L1 status (Oh et al 2022b). TOPAZ-1 was a randomized, double blind, global, Phase III study that evaluated the efficacy and safety of adding the PD-L1 inhibitor durvalumab to SoC chemotherapy (gemcitabine and cisplatin) in first-line advanced BTC. The addition of durvalumab to gemcitabine and cisplatin significantly improved OS and PFS vs chemotherapy alone. At the IA DCO: (11 August 2021), the addition of durvalumab to GemCis showed significantly improved OS (61.9% OS maturity; HR 0.80 [95% CI: 0.66, 0.97], $p = 0.021$) and PFS (PFS; HR 0.75 [95% CI: 0.63, 0.89], $p = 0.001$) vs chemotherapy alone (Oh et al 2022b). OS was reassessed with an additional 6 months of follow-up (median follow-up 23.4 months), and the treatment effect was consistent with the IA (DCO: 25 February 2022; 77% maturity; HR 0.76 [95% CI: 0.64, 0.91]) (Oh et al 2022c).

In TOPAZ-1, treatment benefit was observed regardless of PD-L1 expression (in TAP $\geq 1\%$ HR 0.79 [95% CI: 0.61, 1.0] and in TAP $< 1\%$ HR 0.86 [95% CI: 0.60, 1.23]) (Oh et al 2024). PD-L1 expression was available in 608 patients (biomarker evaluable population) and 66.1% ($n=402/608$) had a TAP score of $\geq 1\%$. Durvalumab plus chemotherapy demonstrated a manageable and tolerable safety profile.

More recently, the role of immunotherapy in improving OS in the first-line advanced BTC setting was further confirmed in KEYNOTE-966 using GemCis in combination with pembrolizumab (OS HR 0.83, and median OS 12.7 vs 10.9 months) (Kelley et al 2023). Consistent with TOPAZ-1, treatment benefit was observed regardless of PD-L1 expression (OS HR 0.85 [95% CI: 0.72, 1.00] in PD-L1 $\geq 1\%$, and HR 0.84 [95% CI: 0.62, 1.14] in PD-L1 $< 1\%$).

Durvalumab in combination with GemCis is now considered a SoC in advanced BTC; pembrolizumab in combination with GemCis is also a recommended option in current

treatment guidelines ([NCCN Guidelines 2025](#), [Benson et al 2023](#), [Vogel et al 2023](#)).

The following baseline clinico-pathological characteristics/factors could be clinically relevant to the target study population of interest for this study:

- *Disease status (initially unresectable vs recurrent)*: Impacts prognosis and treatment efficacy for anti-PD-1/PD-L1 immunotherapy in first-line BTC. In TOPAZ-1, the OS HR was 0.56 (95% CI: 0.32, 0.96) and 0.84 (95% CI: 0.69, 1.03) for patients with recurrent and initially unresectable disease, respectively, and prevalence was 19% and 81%, respectively ([Oh et al 2022a](#)).
- *PD-L1 expression (TAP < 1% vs ≥ 1%)*: PD-L1 expression level is a predictive biomarker of immunotherapy efficacy in multiple tumor types ([Lu et al 2019](#)). However, in BTC, the TOPAZ-1 and KEYNOTE-966 studies did not demonstrate a significant association between PD-L1 expression and treatment efficacy. The prevalence of PD-L1 ≥ 1% cases was 66% in TOPAZ-1 (SP263 RPA assay) and 77% in KEYNOTE-996 (22C3 pharmDx IUO assay), based on the biomarker-evaluable population. Emerging efficacy data from the BTC substudy (Cohort 2A: rilvegostomig plus GemCis in first-line BTC) of the GEMINI-Hepatobiliary study suggest a trend towards improved PFS in PD-L1 ≥ 1% patients.
- *Primary tumor location (iCCA vs eCCA vs GBC)*: Disease biology differs by BTC subtype and impacts prognosis and potentially immunotherapy efficacy. In TOPAZ-1, OS HR by BTC subtype was 0.94 (95% CI: 0.65, 1.37) for GBC, 0.76 (95% CI: 0.58, 0.98) for iCCA, and 0.76 (95% CI: 0.49, 1.19) for eCCA. The prevalence of iCCA, eCCA, and GBC in the setting of first-line BTC is approximately 55% to 60%, 18% to 20%, and 20% to 25%, respectively ([Oh et al 2022a](#)).
- *Geographic region (Asia vs RoW)*: Disease biology, medical care, and prognosis are known to vary by region. In TOPAZ-1, the OS HR was 0.72 (95% CI: 0.56, 0.94) for Asia and 0.89 (95% CI: 0.66, 1.19) for RoW ([Oh et al 2022a](#)). In KEYNOTE-966, the OS HR was 0.88 (95% CI: 0.72, 1.08) for Asia and 0.80 (95% CI: 0.67, 0.96) for RoW ([Kelley et al 2023](#)).
- *Performance status – ECOG (0 vs 1)*: Performance status is an indicator of overall patient condition and has potential to impact study results. In TOPAZ-1, the OS HR was 0.90 (95% CI: 0.68, 1.20) for ECOG performance status at baseline 0 and 0.72 (95% CI: 0.56, 0.94) for ECOG performance status at baseline 1 ([Oh et al 2022a](#)). In KEYNOTE-966, the OS HR was 0.87 (95% CI: 0.71, 1.07) and 0.84 (95% CI: 0.70, 1.00) for ECOG 0 and 1 respectively ([Kelley et al 2023](#)). The prevalence of ECOG 0 was 49% and 46% in TOPAZ-1 46% and KEYNOTE-966, respectively, vs 51% and 54% for ECOG 1.
- *Disease distribution (locally advanced vs metastatic)*: Impacts prognosis and potentially treatment efficacy. In KEYNOTE-966, the OS HR was 0.69 (95% CI: 0.45, 1.06) for locally advanced and 0.85 (95% CI: 0.74, 0.98) for metastatic disease. In TOPAZ-1, the

OS HR was 0.49 (95% CI: 0.26, 0.88) for locally advanced and 0.83 (95% CI: 0.68, 1.02) for metastatic disease. The prevalence of locally advanced disease was 14% in TOPAZ-1 and 12% in KEYNOTE-966 (Oh et al 2022a, Kelley et al 2023).

- *Age (< 65 vs ≥ 65 years)*: Has potential to impact treatment tolerability and efficacy. TOPAZ-1 showed no difference between < 65 and ≥ 65 years subgroups with OS HR of 0.80 (95% CI: 0.61, 1.04) and 0.79 (95% CI: 0.60, 1.04) respectively. KEYNOTE-966 showed improved trend in ≥ 65 years with 0.79 (95% CI: 0.5, 0.97) vs 0.88 (95% CI: 0.73, 1.05) in < 65 years subgroup. The prevalence of ≥ 65 years subgroups was 47% in both TOPAZ-1 and KEYNOTE-966 studies (Oh et al 2022a, Kelley et al 2023).

These may be recorded in IRT/RTSM and could be included as part of routine monitoring throughout enrollment of the study. Unexpected variations could be evaluated by AstraZeneca (see [Appendix A](#)).

2.2.2 TIGIT in Cancer Immunotherapy

The TIGIT receptor is a member of the immunoglobulin superfamily, which plays a critical role in limiting T cell and NK cell effector functions. It participates in a complex regulatory network involving multiple immune receptors (eg, CD96/TACTILE, CD112R/PVRIG), one competing costimulatory receptor (CD226/DNAM 1), and multiple ligands (eg, CD155 [PVR/NECL 5], CD112 [Nectin 2/PVRL2]) (Bottino et al 2003, Levin et al 2011, Stanietsky et al 2009, Yu et al 2009). Several mechanisms of action have been proposed for TIGIT-mediated inhibition of effector T cells and NK cells, including by interfering with CD226 co-stimulation and/or by directly delivering inhibitory signals to the effector cells (Chauvin and Zarour 2020). Nonclinical studies have demonstrated that TIGIT is a key inhibitor of antitumor responses that can hinder multiple steps of the cancer immunity cycle (Iwai et al 2002, Johnston et al 2014). Both PD-1 and TIGIT are inhibitory immune checkpoints with a component of their downstream signaling converging on the same immunosuppressive pathway (Sundstrom et al 2025). Therefore, combination therapies targeting PD-1/PD-L1 and TIGIT at the same time are being investigated as a way to increase the depth and durability of an antitumor immune response in multiple tumor types.

2.2.2.1 Dual Inhibition of TIGIT and PD-1 as a Therapeutic Target

Emerging clinical data in gastrointestinal cancer studies suggest that dual blockade of the converging, immunosuppressive PD-1 and TIGIT pathways may extend the clinical benefit of immune checkpoint inhibition.

Arm A1 of the EDGE-Gastric Phase II open-label non-randomized study investigates domvanalimab (Fc-silent anti-TIGIT mAb) plus zimberelimab (anti-PD-1 mAb) plus FOLFOX chemotherapy in first-line HER2-negative gastric/GEJ/esophageal adenocarcinoma (Rha et al 2024). At the DCO date of 12 March 2024 and median time on treatment of 11.4 months, the ORR was 59% and median PFS was 12.9 months (95% CI: 9.8,13.8) in the

ITT population ($n = 41$), while in participants with PD-L1 TAP $\geq 5\%$ ($n = 16$), the ORR was 69% and median PFS was 13.8 months (95% CI: 11.3, NE). The regimen was well tolerated with no new safety signals (TEAEs Grade ≥ 3 : 73% [related to domvanalimab or zimberelimab: 15%]; serious TEAEs: 37% [related to any study drug: 5%]).

Promising efficacy data have also been observed in HCC in the MORPHEUS-liver Phase Ib-II study. The addition of tiragolumab (Fc active anti-TIGIT mAb) to atezolizumab (anti-PD-L1 mAb) plus bevacizumab (anti-VEGF-A mAb) improved both ORR (42.5% vs 11.1%) and median PFS (11.1 months vs 4.2 months, HR 0.42) compared to atezolizumab plus bevacizumab alone in unresectable HCC ([Finn et al 2025](#)). Validation of these data in ongoing Phase III studies is awaited (NCT05568095, NCT05904886).

2.2.3 Rilvegostomig

Rilvegostomig (AZD2936) is being developed by AstraZeneca for use in the treatment of cancer. Rilvegostomig is a monovalent, bispecific, humanized, IgG1 mAb engineered with an Fc domain that carries a triple mutation (L234F/L235E/P331S) designed to reduce Fc-mediated effector functions. Rilvegostomig contains 2 distinct paratopes that bind to and inhibit human TIGIT and PD-1 from binding to their respective ligands. Rilvegostomig is comprised of 2 Fab arms that contain variable domains of the anti-TIGIT COM902 antibody and anti-PD-1 LO115 antibody. Dual blockade of TIGIT and PD-1 by rilvegostomig is expected to restore antitumor activity of dysfunctional T cells and NK cells.

The use of an anti-TIGIT/anti-PD-1 monovalent bispecific antibody is an innovative approach for targeting both TIGIT and PD-1 receptors at the same time. This approach has some potential advantages compared to the administration of 2 separate anti-TIGIT and anti-PD-1/PD-L1 antibodies. Along with a decrease in burden of drug delivery (1 vs 2 infusions), there is a certainty of equal biodistribution of a single molecule targeting both receptors. The cooperative binding of both receptors has the potential to elicit novel biological effect(s) that may not be achieved by a combination of monospecific antibodies ([Chariou et al 2024](#), [Dovedi et al 2021](#), [Lee et al 2022](#)), as suggested by encouraging antitumor activity for rilvegostomig in nonclinical models showing significant immune activation and tumor growth inhibition over controls and compared to a combination of 2 parental anti-TIGIT and anti-PD-1 antibodies ([Chariou et al 2024](#), [Lee et al 2022](#)).

The introduction of anti-PD-1/PD-L1 therapies has fundamentally altered treatment paradigms for a number of tumor types, but for most patients, responses remain of limited duration and a proportion of patients do not respond to these therapies at all.

Dual inhibition of the immunosuppressive PD-1 and TIGIT axes is currently being explored as a way of generating a stronger immune response compared to that generated by inhibition of PD-1/PD-L1 alone, and to extend the benefit of immune checkpoint blockade.

Nonclinical studies demonstrate that TIGIT is a key inhibitor of antitumor responses and can hinder multiple steps of the cancer immunity cycle ([Johnston et al 2014](#)). The evaluation of rilvegostomig within nonclinical in vitro and in vivo assays demonstrates that rilvegostomig can significantly enhance antigen-specific, T-cell-mediated lysis of human tumor cell lines and increase IFN- γ release over the activity of a bivalent anti-PD-1 antibody. In vivo nonclinical data also suggest that coordinated inhibition of both targets by rilvegostomig may confer improved activity compared to the coadministration of anti-PD-1 and anti-TIGIT antibodies.

In clinical studies evaluating rilvegostomig, encouraging preliminary efficacy has been observed in participants with CPI-naïve advanced NSCLC in the ARTEMIDE-01 study, in combinations with GemCis in the first-line setting of BTC in the GEMINI-Hepatobiliary study, and in combination with chemotherapy in the first-line setting of gastric cancer in the GEMINI-Gastric study.

ARTEMIDE-01 is a first-time-in-human Phase I/II study of rilvegostomig in adult participants with advanced or metastatic NSCLC. As of 07 July 2024, 95 CPI-naïve participants have been treated with rilvegostomig monotherapy in ARTEMIDE-01, 34 participants in Part C (PD-L1 $\geq 1\%$; 750 mg Q3W) and 61 participants in Part D (PD-L1 $\geq 50\%$; 31 participants at 750 mg Q3W [Cohort D1] and 30 participants at 1500 mg Q3W [Cohort D2]). For 62 cross-evaluable participants treated with 750 mg Q3W rilvegostomig in either Part C or Part D, ORR was 41.9% (26 participants) after ≥ 18 weeks of rilvegostomig treatment.

Rilvegostomig exhibited a favorable safety profile in CPI-naïve participants with NSCLC in ARTEMIDE-01, with low rates of Grade 3 or 4 AEs (any: 34.7%; possibly related to rilvegostomig: 10.5%) and of AEs leading to treatment discontinuation (any: 5.3%; possibly related to rilvegostomig: 4.2%).

Supportive preliminary efficacy and safety data have been observed in Cohort 2A of GEMINI Hepatobiliary Phase II platform study ([Zhou et al 2025](#)). As of the DCO date of 04 November 2024, a total of 30 participants have received rilvegostomig therapy (750 mg Q3W) in combination with GemCis with median follow-up of 6.9 months. The 6-month PFS rate was 73% (95% CI: 53.3 to 85.5) and the median PFS was 8.31 months (95% CI: 6.74 to 9.63). The ORR rate was 38.9% in PD-L1 TAP $\geq 1\%$ and 25% in PD-L1 TAP $< 1\%$ subgroups, respectively, and 31% overall in ORR response-evaluable participants (95% CI: 15.3 to 50.8). Subgroup analyses showed median PFS was 9.43 months in participants with PD-L1 TAP $\geq 1\%$ and 6.90 months in participants with PD-L1 TAP $< 1\%$. Note the following caveats: PFS maturity was lower in the PD-L1 TAP $\geq 1\%$ subgroup (61.1% vs 66.7%), and sample size was small in the PD-L1 TAP $< 1\%$ subgroup (TAP $< 1\%$, n = 9; TAP $\geq 1\%$, n = 18; TAP not evaluable, n = 3).

These efficacy data compared favorably to historical benchmark data from TOPAZ-1 (median PFS 7.2 month; 95% CI: 6.7, 7.4) and KEYNOTE-966 (median PFS 6.5 months, 95% CI: 5.7, 6.9).

The safety profile of rilvegostomig in combination with GemCis was tolerable and no new safety signals were observed when compared to TOPAZ-1 data. As of 04 November 2024, all participants in Cohort 2A of the GEMINI-Hepatobiliary study had at least one AE. Grade ≥ 3 AEs considered related to rilvegostomig were reported in 4 participants (13.3%), corresponding to one event each of anemia, blood ALP increased, lipase increased, and pneumonitis. There were no fatal AEs considered related to study treatment. Only one (3.3%) participant had an AE leading to rilvegostomig discontinuation. The most common treatment-related AEs were hematological: anemia in 53.3% patients followed by platelet count decreased in 43.3% patients. The most common rilvegostomig-related AEs were ALP increased (20.0%) and rash (13.3%).

The ongoing Phase II GEMINI-Gastric study (Substudy 2), in participants with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma, provides additional supportive safety and efficacy data for rilvegostomig in combination with chemotherapy (XELOX or FOLFOX). As of the DCO date of 04 July 2024, confirmed ORR was 62.5% among 40 evaluable participants, and 81.3% in participants with PD-L1 CPS ≥ 5 and 50.0% in participants with PD-L1 CPS < 5 (including local PD-L1 results). All participants had disease control (CR or PR, or SD); none had primary PD. The median PFS was 8.3 months (95% CI: 7.0, 9.9) in response-evaluable participants, 7.1 months (95% CI: 6.1, 8.8) in participants with a PD-L1 CPS < 5 , and 11.1 months (95% CI: 5.6, NC) in participants with a PD-L1 CPS ≥ 5 , after a median (range) follow-up for PFS of 7.4 (1.4 to 15.2) months.

Among the 40 participants who received rilvegostomig in combination with chemotherapy (XELOX or FOLFOX), all participants reported at least one AE. Grade ≥ 3 AEs considered related to rilvegostomig were reported in 4 participants (10.0%), corresponding to lipase increased (2 participants), and blood ALP increased, platelet count decreased and pneumonitis (one participant each). Only one participant had an AE leading to rilvegostomig discontinuation (upper respiratory tract infection, not considered related to rilvegostomig). AEs (any grade) considered possibly related to rilvegostomig by the Investigator occurred in 25 participants (62.5%). The most frequently reported rilvegostomig-related AEs were AST increased and lipase increased (9 participants [22.5%] each), ALT increased (8 participants [20.0%]), and blood creatine phosphokinase increased (7 participants [17.5%]). As of the DCO date, there were no deaths in the rilvegostomig plus chemotherapy cohorts of GEMINI-Gastric Substudy 2.

Taken together, both nonclinical and emerging clinical data demonstrate the potential of rilvegostomig to induce a strong antitumor immune response via coordinated inhibition of

PD-1 and TIGIT while maintaining a favorable safety profile largely in line with expectations for anti-PD-1 monotherapy.

Refer to the rilvegostomig IB for detailed background information on rilvegostomig.

2.2.4 Durvalumab

Durvalumab is a human mAb of the IgG1 kappa subclass that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca for use in the treatment of cancer. The proposed mechanism of action for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN- γ (Stewart et al 2015). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the participant's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular-cytotoxicity and complement-dependent cytotoxicity.

Durvalumab is an established product that has received global marketing authorization in various indications. Evidence for the efficacy and safety of durvalumab in combination with gemcitabine and cisplatin in first-line advanced BTC has been reported in the Phase III TOPAZ-1 study (Oh et al 2022a, Oh et al 2024).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of rilvegostomig may be found in the IB. Similar information for durvalumab, gemcitabine and cisplatin can be found in their respective local Prescribing Information (SmPC or USPI).

2.3.1 Risk Assessment

2.3.1.1 Risks of Rilvegostomig

Identified Risks:

The following are identified risks for rilvegostomig monotherapy:

- Infusion-related reactions: The majority of the IRRs were low-grade, manageable, and reversible
- Rash: The majority of the rash events (including rash maculopapular) were low-grade and resolved with treatment

Important Potential Risks:

Important potential risks are based on the clinical experience with marketed antibodies directed against PD-1 or PD-L1 used as monotherapy or in combination therapy. The potential risks are associated with imAEs which can affect every organ system and are most commonly observed in the skin, gastrointestinal tract, lung, endocrine, and musculoskeletal system. The imAEs are events (excluding infusion-related/hypersensitivity/anaphylactic reaction) consistent with an immune-mediated mechanism (mediated by a person's immune system and resemble autoimmune responses) that require treatment with systemic corticosteroids, other immunosuppressants, or endocrine therapy. The imAEs are well characterized, and various internationally recognized management guidelines are available for the treatment of patients experiencing such events ([Brahmer et al 2021](#), [Haanen et al 2022](#), [Schneider et al 2021](#), [Thompson et al 2024](#)) (see Section 6.6.1 and the TMG Annex for further details). The majority of imAEs are low-grade, monitorable, manageable, and reversible with immunosuppressive treatment. Safety information from competitor studies with TIGIT-blocking antibodies as a monotherapy or in combination with antibodies against PD-1 or PD-L1 also included immune-mediated events ([Kim et al 2023](#)).

Known imAEs with PD-1 inhibitors include, but are not limited to, those listed below. Of all the potential risks (described in full in the rilvegostomig IB), imAEs are considered to be important potential risks for rilvegostomig.

- Respiratory disorders: pneumonitis; interstitial lung disease
- Gastrointestinal disorders: diarrhea; colitis, including intestinal perforation and ileus
- Endocrinopathies: hypothyroidism; hyperthyroidism; hypophysitis; adrenal insufficiency; Type 1 diabetes mellitus
- Hepatic disorders: elevation of ALT and/or AST; hepatitis
- Renal disorders: nephritis; elevation of blood creatinine
- Cardiac disorders: myocarditis
- Pancreatic disorders: elevation of lipase and amylase, pancreatitis
- Skin disorders: pruritus; dermatitis, including lichenoid; vitiligo; psoriasis exacerbation; alopecia; serious exfoliative skin disorders: bullous pemphigoid, Stevens Johnson syndrome, and toxic epidermal necrolysis; xerostomia and oral lichenoid reactions
- Encephalitis
- Other: myositis/polymyositis; rhabdomyolysis; uveitis; iritis; arthritis; Guillain-Barré syndrome; myasthenia gravis; vasculitis; hemolytic anemia; aplastic anemia; hemophagocytic lymphohistiocytosis; sarcoidosis

Potential Risks:

Potential risks for rilvegostomig are listed below:

- Abnormal investigations: including elevation of triglycerides and cholesterol; hyperkalemia and hyponatremia
- Immune reactivity (ADA Formation; Immune Complex Disease)
- Hypersensitivity reactions including severe allergy and anaphylaxis
- Cytokine release syndrome
- Embryo-fetal toxicity
- Tumor lysis syndrome
- Complications of allogeneic hematopoietic stem cell transplantation (graft vs host disease), and rejection of transplanted organs

No additional potential risks have been identified based on preclinical data.

2.3.1.2 Risks of Rilvegostomig plus Gemcitabine/Cisplatin

Gemcitabine/cisplatin and rilvegostomig do not share a common pharmacological mechanism of action by which an increase in the rates or severity of adverse effects would be expected.

Safety data regarding the combination of gemcitabine/cisplatin and rilvegostomig are available from the GEMINI-Hepatobiliary Substudy 2 (DCO date of 04 November 2024), as reported in Section 2.2.3, and are summarized here.

GEMINI-Hepatobiliary Substudy 2: Among the 30 participants treated with rilvegostomig (750 mg Q3W) + gemcitabine (1000 mg/m² D1 and D8) and cisplatin (25 mg/m² D1 and D8) Q3W for up to 8 cycles, the median number of cycles of rilvegostomig received was 10.5 (range 2 to 16), 4 participants (13.3%) experienced an AE of Grade ≥ 3 that was assessed as possibly related to rilvegostomig. By preferred term these were anemia, blood ALP increased, lipase increased, and pneumonitis (n = 1 each). Rilvegostomig AESIs were reported in 18 participants (60%). No participants reported an AE leading to permanent discontinuation of rilvegostomig and there were no deaths assessed as related to rilvegostomig or chemotherapy.

2.3.1.3 Risks of Approved Agents

Please refer to the respective local Prescribing Information (SmPC or USPI) for the risks associated with durvalumab, gemcitabine, and cisplatin.

2.3.2 Benefit Assessment

Data from the TOPAZ-1 and KEYNOTE-966 trials established the value of PD-(L)1 blockade

in combination with chemotherapy for the first-line treatment of locally advanced, unresectable or metastatic BTC. Nonclinical studies have demonstrated that TIGIT is a key inhibitor of antitumor responses that can hinder multiple steps of the cancer immunity cycle (Johnston et al 2014). Therefore, TIGIT blockade in combination with anti-PD-1 therapy has the potential to improve clinical response over anti-PD-1 therapy alone. Rilvegostomig has shown encouraging preclinical activity including tumor growth inhibition greater than or equal to combinations of monoclonal anti-PD-L1 and anti-TIGIT antibodies (Lee et al 2022). TIGIT has also been found to be over-expressed in cholangiocarcinoma relative to normal tissue (Wen et al 2021). Preliminary data from Cohort 2A of GEMINI-Hepatobiliary Phase II study further demonstrated promising efficacy in this disease setting (Zhou et al 2025).

2.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to participants in this study, the potential risks identified in association with rilvegostomig in combination with gemcitabine and cisplatin are justified by the anticipated benefits that may be afforded to participants with advanced BTC.

The study design aims to minimize potential risks to participants in the study based on the protocol inclusion and exclusion criteria (Section 5), safety monitoring (including review of all available safety, PK, and other relevant data [Section 9.6]), and TMGs (see TMG Annex). Specific intensive safety monitoring is in place (Section 1.3 and Section 8.3.4).

More detailed information about the known and expected benefits and risks of rilvegostomig and chemotherapy (gemcitabine and cisplatin) may be found in the current IB and local prescribing information, respectively.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 3 Objectives and Endpoints

Objectives	Estimands descriptions/Endpoints
Primary	
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of OS in the PD-L1 $\geq 1\%$ population.	OS is defined as time from randomization until the date of death due to any cause. The analysis will include all randomized participants in the PD-L1 $\geq 1\%$ population. All deaths will be included, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the HR of OS.
Key secondary	
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of OS in the ITT population.	OS is defined as time from randomization until the date of death due to any cause. The analysis will include all randomized participants. All deaths will be included, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the HR of OS.
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of PFS in the PD-L1 $\geq 1\%$ population.	PFS is defined as the time from randomization until radiological progression per RECIST 1.1 as assessed by Investigator, or death due to any cause (in the absence of progression), whichever occurs first. The analysis will include all randomized participants in the PD-L1 $\geq 1\%$ population. All events will be included regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to radiographic progression per RECIST 1.1. However, if the participant progresses or dies immediately after 2 or more consecutive missed visits, the participant will be censored at the time of the latest evaluable assessment prior to the 2 missed visits. PFS will also be assessed by BICR for supplementary/sensitivity analysis. The measures of interest is the HR of PFS.

Table 3 Objectives and Endpoints

Objectives	Estimands descriptions/Endpoints
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of PFS in the ITT population.	PFS is defined as the time from randomization until radiological progression per RECIST 1.1 as assessed by Investigator, or death due to any cause (in the absence of progression), whichever occurs first. The analysis will include all randomized participants. All events will be included regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to radiographic progression per RECIST 1.1. However, if the participant progresses or dies immediately after 2 or more consecutive missed visits, the participant will be censored at the time of the latest evaluable assessment prior to the 2 missed visits. PFS will also be assessed by BICR for supplementary/sensitivity analysis. The measures of interest is the HR of PFS.
Secondary	
To characterize and compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of ORR in the PD-L1 $\geq 1\%$ population.	ORR is defined as the proportion of participants who have a confirmed CR or confirmed PR, as determined by Investigator assessments using RECIST 1.1. The analyses will include all randomized participants in the PD-L1 $\geq 1\%$ population. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who discontinue treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR analysis. The measure of interest is the difference of the ORR.
To characterize and compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of ORR in the ITT population.	ORR is defined as the proportion of participants who have a confirmed CR or confirmed PR, as determined by Investigator assessments using RECIST 1.1. The analyses will include all randomized participants. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who discontinue treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR analysis. The measure of interest is the difference of the ORR.

Table 3 Objectives and Endpoints

Objectives	Estimands descriptions/Endpoints
To characterize and compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of DoR in the PD-L1 $\geq 1\%$ population.	DoR is defined as the time from the date of first documented response until the date of documented progression per Investigator assessments using RECIST 1.1 or death due to any cause (in the absence of progression), whichever occurs first. The analyses will include all randomized participants who have a confirmed response in the PD-L1 $\geq 1\%$ population. The end of response coincides with the date of progression or death from any cause used for the PFS endpoint. The measure of interest is the median of DoR.
To characterize and compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of DoR in the ITT population.	DoR is defined as the time from the date of first documented response until the date of documented progression per Investigator assessments using RECIST 1.1 or death due to any cause (in the absence of progression), whichever occurs first. The analyses will include all randomized participants who have a confirmed response. The end of response coincides with the date of progression or death from any cause used for the PFS endpoint. The measure of interest is the median of DoR.
To compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of PFS2 in the PD-L1 $\geq 1\%$ population.	PFS2 is defined as the time from randomization until the earliest of the progression event (following the initial Investigator-assessed progression event), after the start of the first subsequent therapy, or death from any cause, whichever occurs first. The date of the second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice. The analyses will include all randomized participants in the PD-L1 $\geq 1\%$ population. All events will be included, regardless of whether the participant withdraws from subsequent therapy and regardless of missed visits. The measure of interest is the HR of PFS2.
To compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of PFS2 in the ITT population.	PFS2 is defined as the time from randomization until the earliest of the progression event (following the initial Investigator-assessed progression event), after the start of the first subsequent therapy, or death from any cause, whichever occurs first. The date of the second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice. The analyses will include all randomized participants. All events will be included, regardless of whether the participant withdraws from subsequent therapy and regardless of missed visits. The measure of interest is the HR of PFS2.

Table 3 Objectives and Endpoints

Objectives	Estimands descriptions/Endpoints
To assess the safety and tolerability of rilvegostomig plus chemotherapy compared to durvalumab plus chemotherapy.	Safety and tolerability will be evaluated in terms of AEs (graded by CTCAE v5.0), clinical laboratory assessments, vital signs, physical examination, and ECOG performance status. These analyses will include all randomized participants who received at least one dose of study intervention (safety analysis set).
To assess the PK of rilvegostomig.	Concentration of rilvegostomig in serum and PK parameters (such as peak and trough concentration, as data allow; sparse sampling will be performed).
To investigate the immunogenicity of rilvegostomig.	Presence of ADAs, titer, and neutralizing antibodies for rilvegostomig.
To assess patient-reported BTC symptoms.	Proportion of participants with maintained or improved pain as measured by the EORTC IL445 and EORTC IL446. The analysis will include all randomized participants. The measure of interest will be the proportion of participants with maintained or improved pain.
To assess patient-reported GHS/QoL.	Proportion of participants with maintained or improved GHS/QoL as measured by the EORTC IL172. The analysis will include all randomized participants. The measure of interest is the proportion of participants with maintained or improved GHS/QoL.

Table 3 Objectives and Endpoints

Objectives	Estimands descriptions/Endpoints
Tertiary/Exploratory	
To collect and assess blood and tumor samples for biomarker analysis in participants treated with rilvegostomig plus chemotherapy compared to durvalumab plus chemotherapy.	Assessment of tumor, immune, and/or other cell/biological component associated biomarkers (markers, signatures and/or profiles) in peripheral blood (whole blood, serum, and plasma) and tumor samples (or images) at baseline, on treatment, and at progression as evaluated by, but not limited to, the presence of, profile of, or changes in DNA, RNA, protein, analyte, and/or imaging measurements using different analytical methods including computer-aided and artificial intelligence, and in relation with participants baseline characteristics, clinical outcomes/endpoints and/or other clinical or molecular assessments. Assessments may include but are not limited to: • Presence of, or changes in phenotype or expression of immune and tumor marker/profile (activated T cells, immune cell receptor repertoires, HLA allotypes, IFN-γ, CD8, etc). • Presence/profile of, or changes in ctDNA mutation(s)/genomic alteration(s), and tumor mutation burden, from plasma and tumor samples. • Biomarker expression and/or spatial distribution in the tumor microenvironment (eg, CD8, TIGIT, PD-L1) as measured by IHC and other assays/analytical methods (eg, digital pathology, artificial intelligence).
To assess patient-reported BTC symptoms.	Change from baseline and TTD of BTC symptom subscales as measured by the EORTC IL445 and EORTC IL446. The analysis will include all randomized participants. The measure of interest is mean and mean change from baseline and HR of TTD of symptom subscales measured by the EORTC IL445 and EORTC IL446.
To describe patient-reported treatment-related symptoms and tolerability.	Patient-reported tolerability will be described among participants, as treated, using the following outcomes: • Symptomatic AEs: Proportion of participants experiencing different levels of symptomatic AEs as measured by the EORTC IL445 and EORTC IL444. • Overall side effect bother: Proportion of participants reporting overall side effect bother on the PGI-TT. The analysis will include all dosed participants. The measure of interest is the proportion of participants reporting different levels of AEs and overall tolerability.
To assess patient-reported physical functioning.	Change from baseline and TTD of physical functioning as measured by the PROMIS PF-SF 8c-7 day. The analysis will include all randomized participants. The measure of interest is the mean and mean change from baseline and HR of TTD in physical functioning.

Table 3 Objectives and Endpoints

Objectives	Estimands descriptions/Endpoints
To assess patient-reported functioning.	Change from baseline of social, role, cognitive, and emotional functioning as measured by the EORTC IL172. The analysis will include all randomized participants. The measure of interest is the mean and mean change from baseline of functioning.
To assess the impact of treatment and disease on health state in participants.	VAS score and its change from baseline and 5-dimension scores over time as measured by the EQ-5D-5L. The analysis will include all randomized participants. The measure of interest is the mean and mean change from baseline of VAS score and proportion of participants reporting different levels of each 5-dimension score.
To explore the impact of treatment and disease on health care resource use in all randomized participants.	Number and type of hospitalizations and procedures, and length of stay, as captured by the Concomitant Procedure, SAE reporting forms and HOSPAD.
To describe prevalence, severity, impact, and prophylactic or palliative treatment of patient-reported gastrointestinal symptoms.	Descriptive summary of the proportion of participants reporting each symptom, levels of severity, levels of change of severity, and ADL impact, adherence with prophylactic or palliative treatment over time. The Safety Analysis Set will be used.
To explore how multi-omics variations, including genetics, may affect clinical parameters, risk and prognosis of diseases and the response to medications as detailed in Appendix D Optional Genomics Initiative. Note: The samples are taken from consented participants for DNA isolation, blood derivatives, and storage. Results will not be reported in the CSR.	Exploratory endpoints are related to the data generated from multi-omics analysis, including genetics which may be part or all of the participant's genetic information.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase III, two-arm, randomized, open-label, multicenter, global study, assessing the efficacy and safety of rilvegostomig in combination with gemcitabine and cisplatin chemotherapy compared with durvalumab in combination with gemcitabine and cisplatin chemotherapy in participants with advanced BTC.

Refer to the Study Schema ([Figure 1](#)) and SoA ([Table 1](#) and [Table 2](#)) for the overall design and required assessments. Day 1 is defined as the first day of study treatment.

This study will be conducted in approximately 185 sites across 20 countries.

Approximately 1100 participants will be randomized in a 1:1 ratio to one of the following intervention arms:

- **Experimental arm:** Rilvegostomig in combination with gemcitabine plus cisplatin. Participants will receive rilvegostomig 750 mg IV Q3W on D1 of each cycle starting on C1D1 in combination with chemotherapy for up to 8 cycles, after which participants will receive rilvegostomig 750 mg IV Q3W as a single-agent, until disease progression or unacceptable toxicity. Gemcitabine 1000 mg/m² IV Q3W plus cisplatin 25 mg/m² IV Q3W will be administered on D1 and D8 of each cycle starting on C1D1 for up to 8 cycles.
- **Control arm:** Durvalumab in combination with gemcitabine plus cisplatin. Participants will receive durvalumab 1500 mg IV Q3W on D1 of each cycle starting on C1D1 in combination with chemotherapy for up to 8 cycles, after which participants will receive durvalumab 1500 mg IV Q4W as a single-agent, until disease progression or unacceptable toxicity. Gemcitabine 1000 mg/m² IV Q3W plus cisplatin 25 mg/m² IV Q3W will be administered on D1 and D8 of each cycle starting on C1D1 for up to 8 cycles.

Recruitment of participants with GBC will be capped at approximately 25% of the total randomized participants. Recruitment of participants with PD-L1 $\geq 1\%$ will be at a minimum of 825 randomized participants.

Randomization will be stratified by PD-L1 expression (TAP $< 1\%$ vs $\geq 1\%$), disease status (initially unresectable vs recurrent), primary tumor location (iCCA vs eCCA vs GBC), and geographical region (Asia vs RoW).

Participants will be prospectively tested for PD-L1 expression for stratification. Participants must have a tumor sample available for PD-L1 IHC testing performed by a central reference laboratory during the screening period. PD-L1 status is required prior to randomization. PD-L1 expression will be determined using the investigational VENTANA PD-L1 (SP263) CDx assay.

Participants in both experimental and control arms will continue to receive study intervention (rilvegostomig or durvalumab) until RECIST 1.1-defined radiological progression as assessed by the Investigator, unacceptable toxicity, the participant requests to stop the study treatment, or until any other intervention discontinuation criteria are met (see Section 7.1).

A DMC, comprised of independent experts, will review unblinded safety and efficacy data (see Section 9.6).

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Primary and Key Secondary Endpoints

OS in the PD-L1 $\geq 1\%$ population is the primary endpoint and the study is designed to investigate the safety and efficacy of rilvegostomig in combination with gemcitabine and cisplatin compared with durvalumab in combination with gemcitabine and cisplatin chemotherapy. The study will be considered positive in the primary PD-L1 $\geq 1\%$ population if the OS endpoint (Experimental Arm vs Control Arm) is statistically significant. Additional details on planned analyses can be found in Section 9.4.2.

OS in the ITT population is a key secondary endpoint in the study to investigate the safety and efficacy of rilvegostomig in combination with gemcitabine and cisplatin compared with durvalumab in combination with gemcitabine and cisplatin chemotherapy in all randomized participants. The study will be considered positive in the ITT population if the OS endpoint (Experimental Arm vs Control Arm) analysis is statistically significant. Additional details on planned analyses can be found in Section 9.4.2.

OS is considered the most appropriate endpoint in randomized controlled oncology clinical studies for registration (EMA 2023, FDA 2018). OS has distinct advantages as it is easily and precisely measured without bias, and most relevant to participants (Driscoll and Rixe 2009). Randomization will minimize the effect of known and unknown differences by providing a direct outcome comparison. For CPIs, OS is an appropriate endpoint as it enables capture of long-term OS benefit.

PFS in the PD-L1 $\geq 1\%$ population and PFS in the ITT population are key secondary endpoints in the study. PFS is considered to be an appropriate regulatory efficacy endpoint in cancer trials in general, and it can represent direct clinical benefit in patients with locally advanced or metastatic disease in the first-line setting, when the observed magnitude of effect is substantial and taken together with the tolerability of the treatment and other relevant factors. PFS can reflect tumor growth and be assessed before the determination of an OS benefit, and its determination is not confounded by subsequent therapy (EMA 2023, FDA 2018).

4.2.2 Rationale for Selection of Control Arm

The control arm in this study is durvalumab plus gemcitabine and cisplatin which is a current SoC in first-line BTC (NCCN Guidelines 2025, Benson et al 2023, Vogel et al 2023). This regimen was selected based on the results of the TOPAZ-1 study, which demonstrated that durvalumab in combination with gemcitabine and cisplatin as first-line treatment for patients with advanced BTC resulted in a statistically significant improvement in OS and PFS compared to chemotherapy alone, irrespective of primary tumor subtype, molecular alterations, or PD-L1 status (Oh et al 2022b, Oh et al 2022c). TOPAZ-1 study efficacy and

safety results have been validated in a real-world setting by global research ([Rimini et al 2023](#), [Mitzlaff et al 2024](#), [Muddu et al 2024](#), [Olkus et al 2024](#), [Reimann et al 2024](#), [Rimini et al 2024a](#), [Rimini et al 2024b](#), [Lo Prinzi et al 2025](#), [Shionoya et al 2025](#), [Zheng et al 2025](#)). See Section 2.2.1 for further details.

4.2.3 Rationale for Stratification Factors

Participants will be stratified according to PD-L1 expression (TAP < 1% vs $\geq$ 1%), disease status (initially unresectable vs recurrent), primary tumor location (iCCA vs eCCA vs GBC), and geographical region (Asia vs RoW) to ensure that there is a balanced distribution of these important prognostic/predictive factors between treatment arms (for further details see Section 2.2.1).

4.2.4 Open-label Design

The dosing frequency of rilvegostomig and durvalumab differs after the chemotherapy combination period. Rilvegostomig is dosed at a fixed Q3W interval throughout the treatment period (in combination with chemotherapy for up to 8 cycles and then as a single-agent) whilst durvalumab is dosed Q3W in combination with chemotherapy for up to 8 cycles followed by Q4W as a single-agent. This difference in dosing frequency makes it infeasible to maintain double-blinding throughout the study. Therefore, the study has an open-label design. Potential bias from lack of Investigator blinding is minimized by use of OS as primary and key secondary endpoints, which are not impacted by assessment bias. Randomization is employed to address any possible selection bias.

4.3 Justification for Dose

4.3.1 Rilvegostomig Dose and Treatment Regimen

The rilvegostomig dosing regimen selected for ARTEMIDE-Biliary02 is 750 mg Q3W, which is supported by the available target engagement, PK, pharmacodynamic, safety, and efficacy data for rilvegostomig, as summarized below:

- The rilvegostomig dose of 750 mg Q3W is the lowest predicted dosage to achieve $\geq$ 90% receptor occupancy in both the periphery and tumor microenvironment for both PD-1 and TIGIT in more than 90% of patients across a broad spectrum of analysis conditions.
- Preliminary pharmacodynamic analyses show that the rilvegostomig 750 mg dose was associated with a robust and higher level of T-cell clonal expansion in CPI-naïve NSCLC participants, as well as a higher level of activated CD8 T cells among responders. These observed levels are higher as compared to historical data available for the anti-PD-L1 durvalumab ([Antonia et al 2019](#), [McCoon et al 2021](#)).
- Interim population PK analyses indicated that intrinsic and extrinsic factors do not have a clinically relevant impact on the rilvegostomig PK parameters evaluated, supporting the proposed fixed dosing of rilvegostomig.

- Across the dose levels of 70 mg to 1500 mg Q3W evaluated in the ARTEMIDE-01 study (NCT04995523) in adult participants with advanced or metastatic NSCLC, there were no dose-limiting toxicities and all dose levels were well tolerated. Exposure-safety analysis suggested no relationship between the rate of Grade ≥ 3 treatment-emergent AEs or all-grade treatment-related AEs and rilvegostomig exposure (AUC_{0-21d}) at all 4 dose levels analyzed (rilvegostomig 70, 210, 750, and 1500 mg Q3W).
- Preliminary ORR data from ARTEMIDE-01, as well as exposure-response analysis comparing administration of rilvegostomig 750 mg Q3W with 1500 mg Q3W, demonstrate encouraging efficacy of rilvegostomig 750 mg Q3W in CPI-naïve NSCLC participants, with no further improvement observed at the 1500 mg Q3W dosage.

In conclusion, the overall benefit/risk profile favors the choice of 750 mg Q3W as the recommended dosage for rilvegostomig in this study.

4.3.2 Durvalumab, Gemcitabine and Cisplatin and Dose Justification

The dose of durvalumab will follow the approved local label for advanced BTC, based on the TOPAZ-1 study as follows:

Durvalumab dose for patients with body weight > 30 kg:

- 1500 mg in combination with gemcitabine and cisplatin chemotherapy Q3W for up to 8 cycles followed by 1500 mg Q4W as a single-agent until radiological progression or any other discontinuation criteria are met.

Weight based durvalumab dosing is required if body weight falls to ≤ 30 kg^a:

- 20 mg/kg in combination with gemcitabine and cisplatin chemotherapy Q3W for up to 8 cycles followed by 20 mg/kg Q4W as a single-agent until progression or any other discontinuation criteria are met.

^a Weight-based dosing is required until weight increases to greater than 30 kg. Note: For participants in Europe and UK, weight-based dosing of durvalumab 20 mg/kg is required for participants who weigh ≤ 36 kg until weight increases to > 36 kg.

The doses of gemcitabine plus cisplatin proposed in this study are derived from the Phase III TOPAZ-1 study. The specific dosages are noted below and in Section 6.1.1.

Gemcitabine will be dosed at 1000 mg/m^2 , cisplatin will be dosed at 25 mg/m^2 . Gemcitabine and cisplatin will be administered for up to 8 cycles Q3W, on Day 1 and Day 8 of each cycle, as tolerated and per local guidelines. The doses of gemcitabine and cisplatin are further

supported by the ABC-01 study which established gemcitabine-cisplatin as a first-line treatment in BTC ([Valle et al 2010](#)).

4.4 End-of-study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally.

A participant is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA (including OS determination).

As this study is event driven, the accrual of the predetermined number of events included in the study endpoints will determine the duration of the data collection phase of the study. There will be a final DCO, defined by the time of the OS FA, which will take place approximately 43 months after the first participant is randomized, which is expected to be after the primary endpoint of OS in the PD-L1 $\geq 1\%$ population reaches approximately 75% maturity of events across both treatment arms (see Section [9.2](#)). At this time, the clinical database will close to new data.

Should the study meet the primary endpoint at any of the prescribed interim analyses, additional data cuts may be needed per local health authority requirements.

See Section [6.7](#) for details on participant management following the final DCO, as well as following study completion.

4.5 Study Stopping Rules

If the study Investigators, study medical monitor, DMC or regulatory authorities discover conditions arising during the study that indicate that the participants' safety and/or scientific value of the study and/or quality of the IMP have been compromised, the study should be halted or the study center's participation should be terminated.

If the Sponsor decides to stop data collection, participants ongoing with study treatment deriving clinical benefit from their assigned treatment may be allowed to continue treatment.

5 STUDY POPULATION

The target population of interest in this study is participants with advanced (unresectable or metastatic) BTC, who have not received prior systemic therapy in the advanced setting and must not have received prior immunotherapy.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Participants who do not meet the eligibility criteria requirements are screen failures; refer to Section 5.4.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

- 1 Participant must be ≥ 18 years at the time of signing the informed consent.

Type of Participant and Disease Characteristics

- 2 Histologically confirmed adenocarcinoma of the biliary tract, including cholangiocarcinoma (iCCA or eCCA) and gallbladder carcinoma.
- 3 Participants with mixed-type histology are eligible if adenocarcinoma or adenosquamous carcinoma is predominant.
- 4 Unresectable locally advanced or metastatic BTC, previously untreated in the advanced disease setting
- 5 ECOG performance status of 0 or 1, with no deterioration over the previous 2 weeks prior to baseline at screening and prior to randomization.
- 6 Minimum life expectancy of 12 weeks.
- 7 Provision of an acceptable tumor sample that is ≤ 12 months old, as defined in the Pathology Manual and Laboratory Manual and summarized in Section 8.8 to confirm PD-L1 expression status using the VENTANA PD-L1 (SP263) CDx Assay at a Sponsor-designated centralized test laboratory prior to randomization. Participants with unknown PD-L1 status are not eligible for the study.
Note: If PD-L1 status has already been assessed using the same VENTANA PD-L1 (SP263) CDx Assay in the same test laboratory as part of screening for another AstraZeneca study, this test result may be used if the sample requirements are met.
An FFPE tumor block is the preferred sample type. If a block cannot be submitted, then newly cut tissue sections on unstained slides should be provided.
- 8 At least one measurable lesion not previously irradiated that qualifies as a RECIST 1.1 TL at baseline and can be accurately measured as ≥ 10 mm in longest diameter (except

lymph nodes, which must have short axis ≥ 15 mm) with CT (preferable) or MRI and is suitable for accurate repeated measurements. In cases where there is only one potential TL that fulfills the criteria above but had been previously irradiated (external beam radiotherapy only), the lesion must show radiographic evidence of subsequent growth to qualify as a measurable TL.

- 9 Adequate organ and bone marrow function as defined in [Table 4](#):

Table 4 Criteria for Adequate Organ and Bone Marrow Function

Type	Parameter	Value
Hematological	Hemoglobin	≥ 9.0 g/dL (5.59 mmol/L) with no blood transfusions (packed red blood cells) or growth factor support within 14 days prior to first dose.
	Absolute neutrophil count	$\geq 1.5 \times 10^9/L$ (1,500 per mm^3) in the absence of growth factor support within 14 days prior to first dose.
	Platelet count	$\geq 100 \times 10^9/L$ (100,000 per mm^3) with no platelet transfusions or growth factor support within 14 days prior to first dose.
Hepatic	TBL	$\leq 2.0 \times ULN$ in the absence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia). Any clinically significant biliary obstruction should be resolved before randomization.
		$\leq 3 \times ULN$ for participants with documented Gilbert's syndrome (unconjugated hyperbilirubinemia).
	ALT and AST	$\leq 3 \times ULN$ $\leq 5 \times ULN$ for participants with liver metastasis.
Renal	Calculated CrCL by Cockcroft-Gault ^a or measured renal function ^b	≥ 50 mL/min
Coagulation	INR/PT and either partial thromboplastin or aPTT	$\leq 1.5 \times ULN$

^a Calculated CrCL determined by Cockcroft Gault (using actual body weight).

^b Measured renal function per local guidelines and may include CrCL by 24-hour urine collection or nuclear medicine GFR (eg, Cr-EDTA).

Cockcroft-Gault formula:

Males:

$$CrCL (mL/min) = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$CrCL (mL/min) = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

Weight

10 Minimum body weight of 30 kg.

Sex and Contraceptive/Barrier Requirements

11 Contraceptive use by participants or participant partners should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Refer to [Appendix G](#) for further details.

(a) Male participants who are sexually active with a female partner of childbearing potential:

- Must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) from enrollment and throughout study, until at least 60 days after the last dose of rilvegostomig, or 90 days after last dose of durvalumab, or 6 months after last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is longer. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.
- In addition, female partners of childbearing potential of male participants must use a highly effective method of contraception (see [Table 18](#)) from enrollment until at least 60 days after the last dose of rilvegostomig, or 90 days after last dose of durvalumab, or 6 months after last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is longer.

(b) Female participants of childbearing potential:

- See [Appendix G](#) for definition of female of childbearing potential (FOCBP).
- Females receiving HRT and whose menopausal status is in doubt will be required to use one of the contraception methods outlined for FOCBP if they wish to continue using HRT during the study. Otherwise, HRT must be discontinued to allow confirmation of postmenopausal status prior to randomization; see [Appendix G](#) for further details.
- Must use at least one highly effective form of contraception from enrollment throughout study and until at least 60 days after last dose of rilvegostomig, or 90 days after last dose of durvalumab, or 6 months after last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is longer.
- In addition, non-sterilized male partners of FOCBP participants enrolled in this study must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) from enrollment until at least 60 days after the last dose of rilvegostomig, or 90 days after last dose of durvalumab, or

6 months after last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is longer.

- All FOCBP must have a negative serum pregnancy test result at screening.

Informed Consent

- 12 Capable of giving signed informed consent as described in [Appendix A](#) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
- 13 Provision of signed and dated written Optional Genomics Initiative Research Information and Consent Form prior to collection of samples for optional genomics initiative research that supports the Genomic Initiative (see [Appendix D 2](#)).

Other Inclusion Criteria

- 14 All races, gender and ethnic groups are eligible for this study.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

- 1 Ampullary carcinoma.
- 2 Known medical contraindication to gemcitabine or cisplatin chemotherapy.
- 3 Active or ongoing interstitial lung disease/pneumonitis (of any grade), serious chronic gastrointestinal conditions associated with diarrhea, or active non-infectious skin disease (including any grade rash, urticaria, dermatitis, ulceration, or psoriasis) requiring systemic treatment.
- 4 Any severe or uncontrolled systemic diseases which, in the Investigator's opinion, makes it undesirable for the participant to participate in the study or that would jeopardize compliance with the protocol, including psychiatric illness/social situations and substance abuse.
- 5 History of organ transplant or allogeneic stem cell transplant.
- 6 History of another primary malignancy except for malignancy treated with curative intent with no known active disease for 2 years prior to randomization and of low potential risk for recurrence. Exceptions include adequately resected non-melanoma skin cancer and curatively treated in situ disease.
- 7 Brain metastases unless asymptomatic, stable, and not requiring steroids or anticonvulsants for at least 7 days prior to randomization. A minimum of 2 weeks must have elapsed between the end of brain radiotherapy and randomization. A minimum of 4 weeks must have elapsed from the completion of neurosurgery and randomization.

- Participants must have recovered from the acute toxic effect of radiotherapy (eg, dizziness and signs of increased intracranial pressure) or surgery prior to randomization.
- 8 Spinal cord compression unless the participant received adequate local treatment (surgery and/or radiotherapy) and all of the following conditions are met:
 - (a) Participants must have stable neurological status for at least 2 weeks after completion of local treatment and randomization.
 - (b) At least 4 weeks must have elapsed from the completion of surgery (if performed) and randomization.
 - (c) At least 7 days have elapsed after completion of steroids prior to randomization.
 - 9 Leptomeningeal carcinomatosis.
 - 10 Persistent toxicities (CTCAE $\geq$ Grade 2) caused by previous anticancer therapy, excluding alopecia.
 - Participants who have the following chronic, stable Grade 2 toxicities (defined as no worsening to $>$ Grade 2 for at least 3 months prior to randomization and managed with SoC treatment) which the Investigator deems related to previous anticancer therapy can be included:
 - (a) Fatigue
 - (b) Vitiligo
 - (c) Endocrine disorders that are controlled with replacement hormone therapy.
 - 11 Evidence of any of the following infections:
 - (a) Known active hepatitis A or acute hepatitis B infection (anti-HBc IgM positive).
 - (b) Chronic hepatitis B infection defined as either positive HBsAg regardless of HBV DNA level, or positive anti-HBc with detectable HBV DNA (≥ 10 IU/mL or above the limit of detection per local laboratory), unless all of the following are met:
 - Received antiviral therapy for a minimum of 14 days prior to randomization AND
 - There is evidence of HBV stabilization or signs of viral response (eg, reduction of HBV DNA levels) prior to randomization. Participants must remain on antiviral therapy for the study duration and for 6 months after the last dose of study treatment.
 - (c) Co-infection with HBV and HDV (HBV infection indicated by the presence of HBsAg or anti-HBc with detectable HBV DNA [≥ 10 IU/mL or above the limit of detection per local laboratory] and HDV by the presence of anti-HDV antibodies).
 - (d) Co-infection with HBV and HCV (HBV infection indicated by the presence of HBsAg or anti-HBc with detectable HBV DNA [≥ 10 IU/mL or above the limit of detection per local laboratory] and HCV by presence of anti-HCV antibodies).

- (e) Active hepatitis C infection defined as: anti-HCV positive with detectable HCV RNA.
 - Participants who are anti-HCV positive with undetectable HCV RNA can be included.
 - (f) Known HIV infection that is not well controlled. All of the following criteria are required to define an HIV infection that is well controlled: undetectable viral RNA load for 6 months, CD4+ count of ≥ 350 cells/ μ L, no history of AIDS-defining opportunistic infection within the past 12 months, and stable for at least 4 weeks on the same anti-HIV medications and have an HIV viral load < 400 copies/mL. If an HIV infection meets the above criteria, monitoring of viral RNA load and CD4+ count is recommended.
 - (g) Active tuberculosis infection (clinical evaluation that may include clinical history, physical examination and radiographic findings, or tuberculosis testing in line with local practice).
 - (h) Any other active or uncontrolled infection requiring systemic treatment that has not resolved by the time of randomization.
- 12 History of any of the following cardiac conditions:
- (a) Clinically significant arrhythmias, including those that are symptomatic or uncontrolled.
 - (b) Symptomatic congestive heart failure (as defined by New York Heart Association class ≥ 3).
 - (c) Myocardial infarction within the past 6 months
 - (d) Mean resting corrected QT interval > 470 ms, obtained from triplicate ECGs performed at screening.
 - (e) Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives.
- 13 Active or prior documented autoimmune disorders or inflammatory disorders (including, but not limited to, inflammatory bowel disease, systemic lupus erythematosus, Graves' disease) requiring chronic treatment with steroids or other immunosuppressive treatment.
- The following participants can be included:
 - Participants with vitiligo or alopecia
 - Participants with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
 - Participants with any chronic skin condition that does not require systemic therapy
 - Participants without active disease in the last 5 years
 - Participants with coeliac disease controlled by diet alone

Prior/Concomitant Therapy

- 14 Any prior systemic therapy received for unresectable locally advanced or metastatic BTC.
Note: Prior treatment in the curative intent setting (including surgery, radiation or systemic therapy) is permissible provided > 3 months (90 days) have elapsed between the between the end of curative intent treatment and the diagnosis of recurrence. If the curative intent treatment included gemcitabine or cisplatin a minimum of 6 months (180 days) must have elapsed between the end of curative intent treatment and diagnosis of recurrence. If the curative intent treatment included immunotherapy the participant is excluded (see exclusion criterion 15).
- 15 Any prior exposure to an anti-PD-1, anti-PD-L1, anti-TIGIT or anti-CTLA-4 therapy, or any other anticancer therapy targeting immune-regulatory receptors or mechanisms, including therapeutic anticancer vaccines.
- 16 Herbal or natural products intended as treatment or prophylaxis for any type of cancer that may interfere with the activity of the study intervention are excluded, see Appendix H 2.
- 17 Any concurrent chemotherapy, radiotherapy, immunotherapy, investigational, biologic, or hormonal therapy for cancer treatment other than those under investigation in this study. Concurrent use of bisphosphonates or hormonal therapy (eg, insulin for diabetes, HRT, gonadotropin-releasing hormone analogs) for non-cancer-related conditions is allowed.
- 18 Received prior radiotherapy for metastatic or recurrent disease within 2 weeks prior to randomization. Ongoing radiation toxicities should resolve to Grade 1 or baseline prior to randomization.
- 19 Current or prior use of immunosuppressive medication within 14 days prior to randomization. The following are exceptions to this criterion (see Appendix H 2):
 - (a) Intranasal, inhaled, topical steroids, or local steroid injections (eg, intraarticular injection).
 - (b) Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication), or a single dose for palliative purpose (eg, pain control).
 - (c) Systemic corticosteroids at physiological doses not to exceed 10 mg/day of prednisone or 2 mg/day of dexamethasone or equivalent.
- 20 Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 4 weeks prior to randomization or an anticipated need for major surgery during the study.
- 21 Receipt of live attenuated vaccine within 30 days prior to randomization.
Note: Participants, if enrolled, should not receive live vaccine while receiving study intervention and for up to 30 days after the last dose of study intervention (see Appendix H 2).

Prior/Concurrent Clinical Study Experience

- 22 Participation in another clinical study with a study intervention or investigational medicinal device administered in the last 6 months prior to randomization or concurrent enrollment in another clinical study (unless the study is observational or non-interventional, or the participant is in the follow-up period of an interventional study).

Note: Participants who entered screening in another clinical study with a study intervention or investigational medicinal device but did not receive any study interventions can be included.

- 23 Prior randomization in another rilvegostomig study regardless of treatment arm.
- 24 Participants with a known hypersensitivity to any study intervention or any of the excipients of the products.

Other Exclusions

- 25 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
- 26 Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.
- 27 Previous enrollment in the present study. Note: participants may be rescreened once; for details see Section 5.4.
- 28 For females only – currently pregnant (confirmed with positive pregnancy test) or who are planning to become pregnant.

5.3 Lifestyle Considerations

The following restrictions apply while the participant is receiving study intervention and for the specified times before and after:

- Participants and partners of participants must follow the contraception requirements outlined in [Appendix G](#).
- Participants should not donate blood or blood components, ova, or sperm while participating in this study and until at least 60 days after last dose of rilvegostomig, or 90 days last dose of durvalumab, or 6 months after last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is longer.
- Investigators will advise participants to consider the preservation of ova and/or sperm prior to enrollment in this study due to the possibility of irreversible infertility caused by study treatments.
- Female participants should refrain from active breastfeeding from screening throughout the study and until at least 60 days after last dose of rilvegostomig, or 90 days last dose of

durvalumab, or 6 months after last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is longer.

Restrictions relating to concomitant therapies are described in Appendix [H 2](#).

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, Informed Consent date, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreening is only allowed once per participant, but participants cannot be re-randomized. Rescreened participants should be assigned the same participant number (ie, E-code) as for the initial screening. However, rescreening must be documented so that any effect on study results can be assessed. All assessments, with the exception of PD-L1 testing (if a valid result was obtained), must be repeated for rescreening unless they were carried out within 28 days of randomization.

All screen failure participants should have the reason for study withdrawal recorded as “screen failure” (ie, participant does not meet the required inclusion/exclusion criteria) in the eCRF. This reason for study withdrawal is only valid for screen failures (ie, participants who are not randomized).

Participant enrollment and randomization is described in Section [6.3](#).

5.5 Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

Not applicable.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified medicinal products (classified as IMPs and AxMPs), medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

AstraZeneca will supply rilvegostomig and durvalumab.

Chemotherapy (gemcitabine and cisplatin) will be supplied locally wherever possible.

Details of all study interventions are presented in [Table 5](#). Dose modifications are described in [Section 6.6](#).

Table 5 Study-specific Treatments

Study intervention	Rilvegostomig	Comparator INN	Chemotherapy		Rescue medication	
Arm	Experimental	Control	Experimental, Control	Experimental, Control	NA	NA
Intervention name	Rilvegostomig	Durvalumab	Gemcitabine	Cisplatin	Mycophenolate mofetil	Infliximab
Type	Biologic	Biologic	Drug	Drug	Drug	Biologic
Dosage form	Concentrate for solution for infusion.	Concentrate for solution for infusion.	Concentrate for solution for infusion.	Concentrate for solution for infusion.	Capsule	Powder for concentrate for solution for infusion.
Unit dose strength(s)	750 mg	500 mg	Variable	Variable	250 mg	100 mg
Dosage level(s) and regimen	One IV infusion Q3W on Day 1 of each 21-day cycle.	During chemotherapy combination: One IV infusion of 1500 mg Q3W on Day 1 of each 21-day cycle in combination with chemotherapy for up to 8 cycles. After chemotherapy combination: One 1500 mg IV infusion Q4W on Day 1 of each 28-day cycle as a single-agent. 20 mg/kg in participants who weigh ≤ 30 kg ^a (or per country Prescribing Information).	One IV infusion of 1000 mg/m ² Q3W on D1 and D8 of each 21-day cycle, for up to 8 cycles.	One IV infusion of 25 mg/m ² Q3W on D1 and D8 of each 21-day cycle, for up to 8 cycles.	Max daily dose 3 g. See Section 6.10 for further details.	5 mg/kg. See Section 6.10 for further details.

Study intervention	Rilvegostomig	Comparator INN	Chemotherapy		Rescue medication	
Route of administration	IV infusion	IV infusion	IV infusion	IV infusion	Oral	IV infusion
Use	Experimental	Active comparator	Standard chemotherapy	Standard chemotherapy	Rescue medication	Rescue medication
IMP or AxMP	IMP	IMP	IMP	IMP	AxMP	AxMP
Sourcing	Provided centrally by Sponsor.	Provided centrally by Sponsor.	Provided locally by the study site, subsidiary, or designee or, if not available locally, centrally by AstraZeneca.	Provided locally by the study site, subsidiary, or designee or, if not available locally, centrally by AstraZeneca.	Provided locally by the study site, subsidiary, or designee or, if not available locally, centrally by AstraZeneca (see Section 6.10).	Provided locally by the study site, subsidiary, or designee or, if not available locally, centrally by AstraZeneca (see Section 6.10).
Packaging and labeling	Rilvegostomig will be provided as a vial in a carton. ^b Each vial and carton will be labeled as required per country requirement.	Durvalumab will be provided in vials in a carton. Each vial and carton will be labeled as required per country requirement. ^{c, d}	Labels will be prepared in accordance with local regulatory guidelines. Label text will be in the local language. ^d	Labels will be prepared in accordance with local regulatory guidelines. Label text will be in the local language. ^d	Labels will be prepared in accordance with local regulatory guidelines. Label text will be in the local language. ^{d, e}	Labels will be prepared in accordance with local regulatory guidelines. Label text will be in the local language. ^d
Current/former name(s) or alias(es)	AZD2936	IMFINZI	Not applicable	Not applicable	NA	NA

^a For participants in Europe and UK, durvalumab dose is 20 mg/kg for participants who weigh ≤ 36 kg until weight increases to > 36 kg.

^b Label text for rilvegostomig may show “AZD2936” depending on the agreed product name used in the respective approved study master label document.

^c Label text for durvalumab may show “MEDI4736” depending on the agreed product name used in the respective approved study master label document. All naming conventions for these compounds are correct during this transitional period.

^d Refer to the local label(s) or national guidance with regard to warnings, precautions, and contraindications.

^e Label text for mycophenolate mofetil may show as “mycophenolate”.

6.1.1 Rilvegostomig

Rilvegostomig will be supplied by AstraZeneca as a sterile concentrate for solution for infusion and is formulated at 50 mg/mL in 20 mM L-histidine/L-histidine-HCl monohydrate, 240 mM sucrose, 0.04% (w/v) poloxamer 188, pH 6.0. The vial contains 750 mg (label claim) of active IP.

6.1.2 Durvalumab

Durvalumab will be supplied by AstraZeneca as a concentrate for solution for infusion and is formulated at 50 mg/mL durvalumab in 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The vial contains 500 mg of durvalumab in a label claim volume of 10 mL.

6.1.3 Gemcitabine and Cisplatin

Gemcitabine and cisplatin will be locally sourced and administered according to prescribing information or treatment guidance in general use by the investigating site. Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply these products, and they will be labeled with local language-translated text in accordance with regulatory guidelines.

Refer to the gemcitabine and cisplatin local labels or national guidance with regard to warnings, precautions, and contraindications.

6.1.4 Rilvegostomig or Durvalumab Plus Chemotherapy

6.1.4.1 Experimental Arm: Rilvegostomig in Combination with Gemcitabine plus Cisplatin

Participants will receive rilvegostomig 750 mg IV Q3W on D1 of each cycle starting on C1D1; rilvegostomig will be administered until disease progression or unacceptable toxicity. Gemcitabine 1000 mg/m² IV Q3W plus cisplatin 25 mg/m² IV Q3W will be administered on D1 and D8 of each cycle starting on C1D1 for up to 8 cycles ([Figure 2](#)).

6.1.4.2 Control Arm: Durvalumab in Combination with Gemcitabine plus Cisplatin

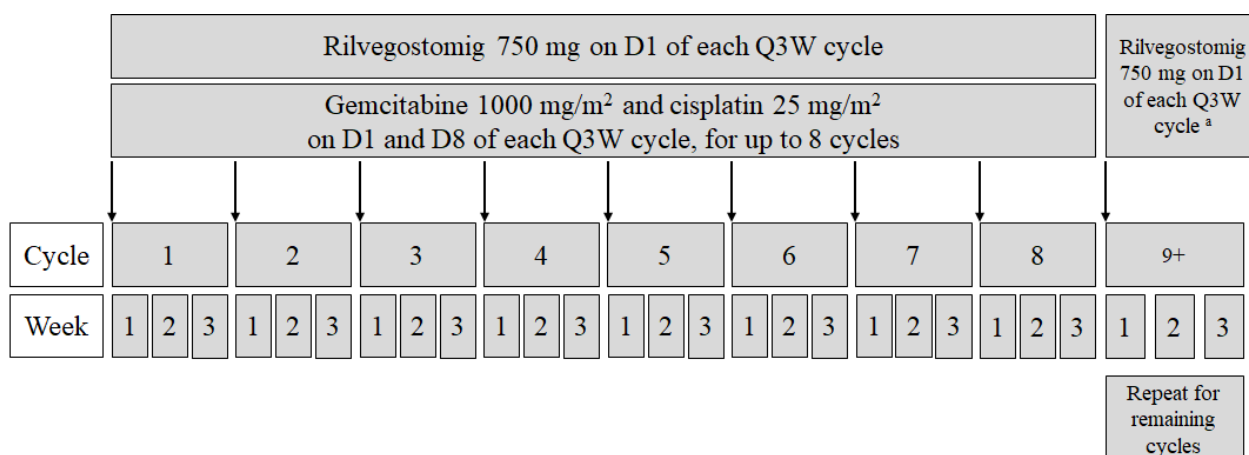
Participants will receive durvalumab 1500 mg IV Q3W on D1 of each cycle starting on C1D1, in combination with chemotherapy for up to 8 cycles after which participants will receive durvalumab 1500 mg IV Q4W as a single-agent until disease progression or unacceptable toxicity. Gemcitabine 1000 mg/m² IV Q3W plus cisplatin 25 mg/m² IV Q3W will be administered on D1 and D8 of each cycle starting on C1D1 for up to 8 cycles ([Figure 2](#)).

The order of administration is:

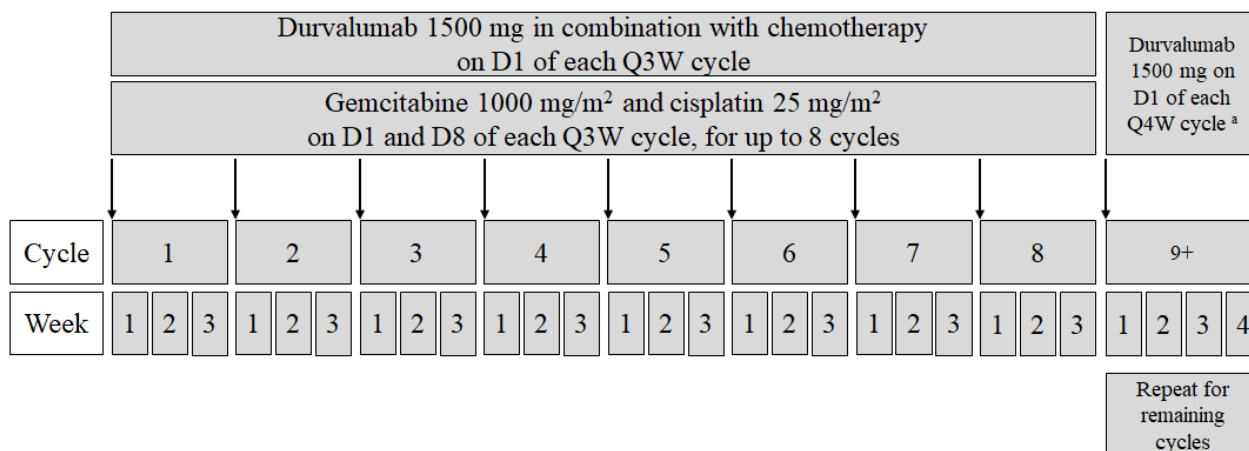
- 1) Rilvegostomig or durvalumab (according to treatment arm) is given first, followed by an observation period lasting a minimum of 30 minutes. If no infusion reactions occur during the first 2 cycles, the observation period may be shortened or omitted at the Investigator's discretion;
- 2) Followed by chemotherapy (gemcitabine and cisplatin).

Figure 2 Dosing Schedule

Experimental arm:



Control arm:



^a From Cycle 9 onwards, rilvegostomig or durvalumab will be administered until disease progression or unacceptable toxicity or any other treatment discontinuation criteria is met (see Section 7.1).

Note: For participants who discontinue gemcitabine or cisplatin before completion of Cycle 8, treatment with rilvegostomig or durvalumab may continue as a single-agent at the Investigator's discretion provided other discontinuation criteria have not been met. In such cases, rilvegostomig Q3W or durvalumab Q4W will be administered. See also Sections 6.6 and 7.1.

6.1.5 Duration of Treatment

Participants in the experimental arm will receive rilvegostomig 750 mg Q3W in combination with chemotherapy for up to 8 cycles followed by rilvegostomig 750 mg Q3W as a single-agent until RECIST 1.1-defined radiological progression as assessed by the Investigator, unacceptable toxicity, or until any other intervention discontinuation criterion is met (see Section 7.1 for the study discontinuation criteria).

Participants in the control arm will receive durvalumab 1500 mg Q3W in combination with chemotherapy for up to 8 cycles followed by durvalumab 1500 mg Q4W as a single-agent, until RECIST 1.1-defined radiological progression as assessed by the Investigator, unacceptable toxicity, or until any other intervention discontinuation criterion is met (see Section 7.1 for the study discontinuation criteria).

6.1.6 Treatment Through Progression

Following Investigator-assessed RECIST 1.1-defined disease progression, due to the potential pseudo-progression observed in participants treated with immunotherapies, participants may continue to receive study intervention until a subsequent scan is performed at least 4 weeks later, but no later than the next scheduled imaging visit, as long as they are continuing to show clinical benefit, as judged by the Investigator, and they are not meeting any other discontinuation criteria. If PD is confirmed at this subsequent scan, the participant must discontinue all study interventions; otherwise, participants may continue to receive study interventions.

Crossover within the study is not permitted.

6.2 Preparation, Handling, Storage, and Accountability

- The Investigator or designee (eg, unblinded pharmacist) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorization is provided for on-site destruction or removal of the IMP reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures provided in the Pharmacy Manual; release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by AstraZeneca (or designated party).
- Only participants randomized may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

- The Investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.2.1 Storage of Rilvegostomig and Durvalumab

Rilvegostomig and durvalumab vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The Investigator, or an approved representative (eg, pharmacist), will ensure that rilvegostomig and durvalumab is stored in a secured area, in refrigerated temperatures (2°C to 8°C [36°F to 46°F]) and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

Rilvegostomig and durvalumab must be kept in their original packaging until time of preparation to prevent prolonged light exposure.

6.2.2 Dose Preparation

6.2.2.1 Rilvegostomig

The dose of rilvegostomig for administration must be prepared by the pharmacy staff members (or an appropriate designee trained in study drug preparation), using aseptic technique in compliance with local regulations and site requirements.

The IV bag size used to prepare the dose(s) should not exceed 250 mL.

The total time from needle puncture of the rilvegostomig vial to the start of administration must not exceed 24 hours. Of this time, not more than 4 hours may be at room temperature, with the remaining time at 2°C to 8°C (36°F to 46°F), otherwise a new dose must be prepared from new vials.

Refer to the Pharmacy Manual for detailed information on dose preparation and handling procedures for rilvegostomig.

6.2.2.2 Durvalumab

Doses of durvalumab for administration must be prepared by the pharmacy staff members (or an appropriate designee trained in study drug preparation), using aseptic technique in compliance with local regulations and site requirements.

The total time from needle puncture of the durvalumab vial to the start of administration must not exceed 24 hours. Of this time, not more than 4 hours may be at room temperature, with the remaining time at 2°C to 8°C (36°F to 46°F), otherwise a new dose must be prepared from new vials.

Refer to the Pharmacy Manual for detailed information on dose preparation and handling procedures for durvalumab.

6.2.3 Dose Administration

The first day of dosing is considered Cycle 1 Day 1. Administration of study intervention in each cycle must not proceed until medical history, physical examination, and safety assessments including ECG (if clinically indicated) and laboratory tests confirm safety of administration.

Vital signs should be obtained within 30 minutes prior to start of iv administration of each study intervention.

6.2.3.1 Rilvegostomig

Rilvegostomig will be administered using an IV bag containing 0.9% sodium chloride or 5% dextrose for injection through an IV administration set, using local practices. Do not shake the prepared IV bag.

The infusion must be administered with a 0.2- or 0.22-µm filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing.

Rilvegostomig infusion time is a minimum of 60 minutes (up to a total of 90 minutes). In case of interruptions, the total allowed infusion time must not exceed 4 hours with the IV bag kept at room temperature, otherwise a new dose must be prepared from new vials to complete the dose.

Do not co-administer other drugs through the same infusion line.

After the content of the IV bag is administered, the IV line will be promptly flushed with a volume of 0.9% sodium chloride or 5% dextrose for injection equal to the IV line volume, at the same rate as infusion according to local practices, to ensure the full dose is administered. Infusion time does not include the final flush time.

The total infusion time recorded in the EDC system reflects when the infusion IV bag is empty; the infusion time does not include the post-infusion flush. Pharmacokinetic samples collected as a C_{max} (peak) concentration after an infusion are to be collected 15 minutes following the completion of the post-infusion flush.

6.2.3.2 Durvalumab

Durvalumab will be administered using an IV bag containing 0.9% sodium chloride for injection or 5% dextrose for injection through an IV administration set, using local practices. Do not shake the prepared IV bag.

The infusion will be administered through an IV administration set with a 0.2- or 0.22- μ m filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing.

The durvalumab infusion time is 1 hour ($\pm$ 10 minutes); however, if there are interruptions, the total allowed time must not exceed 8 hours with the infusion bag maintained at room temperature, otherwise a new dose must be prepared from new vials.

Do not co-administer other drugs through the same infusion line.

After the content of the IV bag is administered, the IV line will be promptly flushed with a volume of 0.9% sodium chloride for injection or 5% dextrose for injection equal to the IV line volume, at the same rate as infusion according to local practices, to ensure the full dose is administered. Infusion time does not include the final flush time.

An observation period of at least 1 hour is recommended after the first infusion of durvalumab. If no infusion reaction has occurred with the initial infusion of durvalumab, and at the discretion of the Investigator, this observation period may be shortened or eliminated. Other study interventions should not be co-administered with durvalumab through the same infusion line.

6.2.3.3 Gemcitabine and Cisplatin

Chemotherapy (gemcitabine and cisplatin) will either be locally sourced by the study site, or if not available locally centrally supplied by AstraZeneca and will be prepared and administered according to Prescribing Information or treatment guidance in general use by the investigating site. Under certain circumstances, when local sourcing by the study site is not feasible, AstraZeneca will centrally supply the study intervention, which will be labeled with local language translated text in accordance with regulatory guidelines. Accountability and storage requirements, as specified in Section 6.2, apply for any study intervention.

6.3 Assignment to Study Intervention

Before study initiation, login instructions for the IRT and/or login information and instructions for the RTSM will be provided to each site.

Participant details will be recorded in the IRT/RTSM per country regulations.

At screening/baseline (Days -28 to -1), the Investigators or suitably trained delegate will:

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the participant. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization.
- Obtain a unique 7-digit enrollment code (E-code), through the IRT/RTSM in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the participant enrollment code at the center). This number is the participant's unique identifier and is used to identify the participant on the eCRFs.
- Obtain sample and send for centralized PD-L1 testing. Obtaining the tumor sample should be given the highest priority and, as such, the sample may be obtained and sent for central testing as early as possible during the 28-day screening window (after obtaining signed informed consent) in order to permit analysis prior to randomization. Screening procedures may be obtained while PD-L1 status/expression is being assessed.
- Determine participant eligibility (see Sections 5.1 and 5.2).
- Obtain signed informed consent for the optional genetic research component of the study. Participants who decide not to sign the optional genetic research ICF (but have provided consent to participate in the study) remain eligible for study enrollment and all other study procedures.

Investigators should keep a record (ie, the participant screening log) of all participants who enter screening.

If the participant is ineligible and not randomized, the IRT/RTSM should be accessed to terminate the participant in the system.

Participants will begin treatment on Cycle 1, Day 1. Participants must not be randomized and treated unless all eligibility criteria have been met.

If a participant withdraws from the study, then his/her enrollment/randomization code cannot be reused. Withdrawn participants will not be replaced.

Methods for Assigning Treatment Groups

At randomization, once the participant is confirmed to be eligible for study entry, all participants will be centrally assigned to randomized study intervention using a randomization scheme in the IRT/RTSM.

The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers. One randomization

list will be produced for each of the randomization strata. A blocked randomization will be generated. All sites will use the same central list in order to minimize any imbalance in the number of participants assigned to each treatment arm.

Randomization codes will be assigned strictly sequentially, within each stratum, as participants become eligible for randomization. The IRT/RTSM will provide the kit identification number to be allocated to the participant at the randomization visit and subsequent treatment visits.

Study intervention will be dispensed at the study visits summarized in SoA (Section 1.3).

Returned study intervention should not be re-dispensed to the participants.

Procedures for Handling Incorrectly Randomized Participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Participants who are enrolled but subsequently found not to meet all the eligibility criteria must not be randomized or started on study intervention and must be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the Study Clinical Lead immediately, and a discussion should occur between the Study Clinical Lead and the Investigator regarding whether to continue or discontinue the participant from treatment. The Study Clinical Lead must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant. This participant remains in the FAS analysis set, and is expected to participate in study follow-up.

6.4 Blinding

This is an open-label study for the personnel at study sites; however, the study will be conducted as ‘sponsor-blind’ and the specific treatment to be taken by a participant will be assigned using an IRT/RTSM (see Section 6.3 for details). To maintain the integrity of the study, AstraZeneca personnel directly involved in the study conduct will not undertake or have access to efficacy data aggregated by treatment arm prior to the primary or final data readout for the primary endpoint (see Section 9.5 for further details). Before the first patient is randomized, a Study Integrity Plan will be generated, in which data access levels for relevant AstraZeneca personnel will be prespecified.

6.5 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention(s) under the direction of the Investigator or designee. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF.

The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The Investigational Product Storage Manager is responsible for managing the study intervention from receipt by the study site until the destruction or return of all unused study intervention.

6.6 Dose Modification

All dose reductions and delays (including any missed doses), and the reasons for the reductions/delays are to be recorded in the eCRF. Dose delays are permitted for chemotherapy, rilvegostomig, and durvalumab. Dose reduction of rilvegostomig and durvalumab are not permitted. Dose modification for gemcitabine/cisplatin should follow the local guidance.

If a participant's weight falls to ≤ 30 kg:

- No dose adjustment of rilvegostomig is necessary.
- Weight-based dosing is required for durvalumab which is equivalent to 20 mg/kg until weight increases to greater than 30 kg. Note: For participants in Europe and UK, durvalumab dose is 20 mg/kg for participants who weigh ≤ 36 kg until weight increases to > 36 kg.

In the event of a rilvegostomig dose delay occurring prior to completion of PK blood sampling in the study, Investigators should contact the Study Clinical Lead for guidance regarding scheduling of these procedures.

6.6.1 Dose Modification for Rilvegostomig

TMGs have been developed to assist Investigators with the recognition and management of toxicities associated with rilvegostomig treatment.

These TMGs are applicable to the management of participants receiving rilvegostomig as specified in this protocol. The TMGs provide information for the management of immune-mediated reactions, IRRs, and non-immune-mediated reactions that may be observed with monotherapy or combination CPI regimens, with specific instructions for CPI-specific dose modifications (ie, withholding or discontinuation) and study interventions. The TMGs apply to toxicities considered causally related to rilvegostomig by the reporting Investigator and are provided as a separate Annex (TMG Annex) and maintained within the Site Master File.

Dosing of rilvegostomig may be delayed (interrupted) per the TMGs; however, dose reduction is not permitted.

- Dosing may be delayed for a maximum of 3 consecutive cycles (84 days from the last infusion date) to allow for resolution of toxicity and tapering of steroids. If it is not possible for a participant to restart treatment within this time frame, treatment with rilvegostomig should be discontinued permanently.
- Dosing delays lasting longer than 3 consecutive cycles (84 days from the last infusion date) for non-drug-related reasons may be allowed after consultation with the Study Clinical Lead.

Dosing of rilvegostomig may be resumed once toxicity has resolved (to Grade ≤ 1 if not stated otherwise in the TMGs).

- If dosing of rilvegostomig is delayed due to toxicity possibly related to rilvegostomig while the participant is receiving rilvegostomig in combination with chemotherapy, chemotherapy may still be administered as scheduled. Every effort should be made to ensure participants receive all scheduled cycles of chemotherapy, if conditions allow. When it is feasible to restart dosing, rilvegostomig should be administered at the next planned treatment visit with other planned study intervention(s).
- If dosing of rilvegostomig is delayed due to treatment-related toxicity while the participant is receiving rilvegostomig only, dosing should be restarted as soon as feasible once toxicity has resolved.
- If dosing is delayed for reasons other than treatment-related toxicity while the participant is receiving rilvegostomig only, it should resume as soon as feasible.
- Every effort should be made to allow synchronized administration of all study interventions.

The dosing interval of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of radiological and COA assessments. Consecutive doses of rilvegostomig must not be given less than 15 days apart.

6.6.2 Dose Modification for Durvalumab

Dose delays (interruptions) are permitted for durvalumab; however, dose reduction is not permitted. Dose modifications (interruptions) for durvalumab related AEs should follow local prescribing information.

- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
- Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) and PRO assessments. Subsequent time between 2 consecutive doses cannot be less than 21 days.

However, a window of ± 3 days is allowed around dosing visits, and during administration of the chemotherapy combination a minimum of 18 days is permissible between 2 consecutive doses.

6.6.3 Dose Modification for Chemotherapy

Chemotherapy-related toxicities and necessary dose modifications should be managed according to local Prescribing Information and clinical practice. However, if chemotherapy is delayed by at least one week while rilvegostomig or durvalumab is administered, once safe to resume, chemotherapy should be resumed at the following cycle.

Chemotherapy should be administered in combination with rilvegostomig or durvalumab during the first 8 cycles. In the event that chemotherapy is delayed due to toxicity but rilvegostomig or durvalumab is administered as scheduled, it is permitted to receive chemotherapy beyond Cycle 8 of rilvegostomig or durvalumab, provided the total number of chemotherapy cycles does not exceed 8. After Cycle 8 of durvalumab, dosing of durvalumab is adjusted to Q4W but chemotherapy cycles should always be Q3W.

6.7 Continued Access to Study Intervention After the End of the Study

As described in Section 4.4, the study will remain open until all participants have discontinued study intervention and completed their last expected visit/contact.

After the final DCO for this study, AstraZeneca will continue to supply rilvegostomig and durvalumab to participants who were randomized to receive rilvegostomig or durvalumab until PD occurs as judged by the Investigator or until meeting any other discontinuation criteria as defined in Section 7.1, where permitted under local laws and regulations.

Participants should be followed according to the institution's SoC assessments. No further data collection is required, except for non-serious AEs, SAEs, and special situations (ie, pregnancy, overdoses, medication error, drug abuse, and drug misuse) until the end of post-study access or until consent has been withdrawn (see Section 8.4.12).

Participants who discontinue from the study, should continue appropriate treatment at the discretion of the Investigator.

AstraZeneca will continue to supply rilvegostomig or durvalumab in the continued access phase of this study while, in the opinion of the Investigator, the participant is benefiting.

In the event product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the participant(s) to alternative supply, where possible.

In the event a roll-over or safety extension study is available, participant(s) currently receiving treatment with rilvegostomig may then be transitioned to such a study, and the current study may reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would be eligible to move to such a study would be given a new informed consent, as applicable.

In the event that AstraZeneca terminates further development of the study intervention, AstraZeneca will continue to supply study intervention where possible, however the supply may become unavailable. AstraZeneca will notify Investigators in advance if supply of study intervention must be discontinued.

6.8 Treatment of Overdose

For this study, any dose of study intervention exceeding that specified in the protocol will be considered an overdose.

For durvalumab and chemotherapy (gemcitabine and cisplatin), refer to the local Prescribing Information for treatment of cases of overdose.

In cases of known or suspected overdose, symptomatic treatment and monitoring of vital functions should be performed according to routine clinical practice. Immediate discontinuations of the study intervention should be performed, and appropriate symptomatic therapy should be instituted.

In the event of an overdose, the Investigator should:

- Evaluate the participant to determine, in consultation with the Study Clinical Lead, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Refer to Section 8.4.16 for details of AE/SAE reporting related to overdose.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Prior and Concomitant Therapy

Any prior/concomitant treatment, procedure, or other medication considered necessary by the Investigator for the participant's safety and wellbeing (including vaccines, over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant (except for screen failures) is receiving at the time of screening or receives during the study, including the 90 ($\pm$ 7) day follow-up period following the last dose of study intervention, must be recorded in the eCRF along with:

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

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded.

Participants must be instructed not to take any medications, including over-the-counter products, and/or complimentary alternative medicines/herbal products without first consulting with the Investigator.

Prohibited and permitted/supportive concomitant medications/therapies are described in more detail in Appendix [H 2](#).

Guidance regarding potential interactions with concomitant medications is provided in Appendix [H 1](#).

The Study Clinical Lead should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Drug-drug Interactions

As rilvegostomig is a mAb and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that rilvegostomig will induce or inhibit the major drug metabolizing CYP pathways. As a result, there are no expected PK drug-drug interactions. Based on the mechanism of action of rilvegostomig, significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected.

Guidance regarding potential interactions with concomitant medications is provided in Appendix [H 1](#).

6.9.2 Premedication

Participants receiving cisplatin should receive pretreatment hydration and antiemetics as for highly emetic regimens. Adequate hydration and urinary output should be checked following the infusion of cisplatin. Please refer to prescribing information for guidance.

6.10 Rescue Medicine

Rescue medication will be sourced locally and will be provided by the study site. The following rescue medications are required to be available at the site:

- Infliximab/infliximab biosimilar (eg, for colitis).
- Mycophenolate (eg, for hepatitis).

Note that the above rescue medications are defined in this study as AxMPs (see [Table 5](#)).

Under certain circumstances when local sourcing by the study site is not feasible or if infliximab or mycophenolate are not approved locally for management of immunotherapy-related toxicities, AstraZeneca will centrally supply the required rescue medications, which will be labeled with local language translated text in accordance with regulatory guidelines. Accountability and storage requirements, as specified in [Section 6.2](#), apply for any study intervention. If required to manage an imAE, then the IRT/RTSM will allocate the specific medication either by a kit or another identification number, to the pharmacist for a specific participant at the time of the event.

As a result of imAEs that could potentially be experienced by participants on rilvegostomig or durvalumab, appropriate treatment (eg, steroids and specific immunosuppressant rescue medications) must be made readily available to this participant population.

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are handled as part of [Appendix A](#).

7.1 Discontinuation of Study Intervention

Note that discontinuation from study intervention is not the same thing as a discontinuation or withdrawal from the study (see [Section 7.2](#)).

If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study.

The Investigator should instruct the participant to contact the site before or at the time of study intervention is stopped. A participant that decides to discontinue study intervention must always be asked about the reason(s) and the presence of any AEs. The reason for

discontinuation should be documented in the source document and the appropriate section of the eCRF.

Participants who have permanently discontinued from further receipt of study intervention will need to be discontinued from the IRT/RTSM. All study intervention should be returned by the participant at their next on-site study visit or unscheduled visit.

Participants must be discontinued from study intervention in the following situations:

- RECIST 1.1-defined radiological progression (refer to Section 8.2.1 and Appendix F), except for participants who receive treatment through progression (see Section 6.1.6).
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation defined in the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6) or as defined in the local Prescribing Information for durvalumab and chemotherapy (gemcitabine and cisplatin).
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment. A participant who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.2).
- Severe non-compliance with the protocol, as judged by the Investigator or AstraZeneca.
- Pregnancy or intent to become pregnant.
- Initiation of subsequent anticancer therapy, including another investigational agent.

If a participant discontinues treatment with one or both chemotherapy agents (gemcitabine and cisplatin) due to toxicity or other reasons, they may continue with rilvegostomig or durvalumab as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria. The maximum number of cycles of chemotherapy is 8.

If a participant discontinues treatment with the immunotherapy agents (rilvegostomig or durvalumab) due to toxicity or other reasons, they may continue with chemotherapy (gemcitabine and cisplatin) as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria, for up to a maximum of 8 cycles.

See the SoA (Section 1.3) for data to be collected at the time of discontinuation of all study interventions and follow-up and for any further evaluations that need to be completed.

7.1.1 Follow-up of Participants Post Discontinuation of Study Intervention

Participants who have discontinued all study interventions will be followed up by an EoT visit at 30-days (+ 7 days) and safety visit at 90 ($\pm$ 7) days after their last dose of study intervention. Additional assessments to be performed at the time of the 90-day ($\pm$ 7 days) safety follow-up visit are detailed in the SoA (Section 1.3). Every effort should be made to perform the 30-day (EoT) visit and 90-day safety follow-up visit within the correct time window in relation to last dose of study intervention. However, if the decision to discontinue all study interventions is made after D30 but before D90 after last study intervention dose, the D30 (EoT) visit should be conducted within 7 days of the decision to discontinue all study interventions. If the decision to discontinue all study interventions is made after D90 after last study intervention, then a D30 (EoT) visit should be conducted within 7 days of the decision to discontinue and the D90 (safety follow-up) visit can be omitted.

Participants who have discontinued study intervention prior to objective RECIST 1.1-defined radiological progression will be followed up with tumor assessments according to the SoA until RECIST 1.1-defined disease progression (plus an additional follow-up scan to be conducted at least 4 weeks later and no later than the next scheduled imaging visit) or death, regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

Subsequent anticancer therapy (including surgery and radiation therapy) will be assessed and recorded from the EoT with study intervention through the safety and survival follow-up period or until death for participants who have discontinued study intervention, including at PD.

7.1.2 Follow-up of Participants to PFS2

Following the initial RECIST 1.1-defined radiological progression by Investigator assessment, participants will have their subsequent progression status recorded every 12 weeks ($\pm$ 7 days) to assess PFS2. Assessments will be performed according to the local practice, and formal RECIST 1.1 measurements will not be collected for assessment of PFS2. See Section 8.2.3 for additional information.

7.1.3 Follow-up for Survival

Participants will be followed up for survival status as indicated in the SoA (Section 1.3) until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the participant or the participant's family, or by contact with the participant's current physician. Additional assessments, including subsequent anticancer therapy, are to be recorded at the time of survival follow-up and are detailed in the SoA.

7.2 Participant Discontinuation/Withdrawal From the Study

Discontinuation of the participant from the study by the Investigator:

- A participant may be discontinued from the study at any time at the discretion of the Investigator for behavioral, or compliance reasons.
- At the time of discontinuing from the study, if the participant has not been discontinued from the study intervention, see Section 7.1.

Voluntary withdrawal from the study by the participant:

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason) without any implication on participant's rights.
- A participant who wishes to withdraw from the study must be informed by the Investigator about modified follow-up options to ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact at 30 days [+ 7 days] after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records).
- At the time of discontinuing from the study, if possible, an EoT visit should be conducted, as shown in the SoA.
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, AstraZeneca may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented, unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the Investigator and the Investigator must inform the Local and Global Study Team. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and no contact has been established by the time the study is completed, such that there is insufficient information to determine the participant's status at that time. Participants who have been contacted, including telephone contact, and decline to continue participation in the study, should be documented as "withdrawal of consent" rather than "lost to follow-up."

Investigators should document attempts to re-establish contact with missing participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the protocol.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counseled on the importance of maintaining the assigned visit schedule and ascertain whether the participant should or wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, texts, emails, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study/been lost to follow-up.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant during survival follow-up within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

In order to support key efficacy endpoints of PFS, PFS2, and OS analyses, the survival status of all participants in the FAS and the Safety Analysis Set should be re-checked; this includes those participants who withdrew consent or are classified as "lost to follow-up".

- Lost to follow-up – Site personnel should check hospital records and a publicly available death registry (if available), as well as checking with the participants' current physician, to obtain a current survival status (the applicable eCRF modules will be updated).
- In the event that the participant has actively withdrawn consent to the processing of their personal data, the survival status of the participant can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Requirements for data collection following study analysis until the end of the study are described below. Protocol waivers or exemptions are not allowed.
- Urgent safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Instructions for the collection and handling of Human Biological Samples will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on handling of Human Biological Samples see [Appendix C](#).

The participant will be required to collect some data using a digital application. The data to be collected are COAs: PROs and gastrointestinal symptoms.

- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by AstraZeneca or the Investigator, as per local health authority/ethics requirements.
- Planned timepoints for all assessments are provided in the SoA.

Data Collection Following Study Analysis Until the End of the Study

Following the DCO for the final OS analysis (DCO3), tumor assessments per the SoA will be discontinued and tumor assessments will be performed according to local practice. Participants will continue with all other assessments as indicated in the SoA.

For SAE and AE reporting and laboratory assessment collection after FA, see Section [8.4.12](#).

After the final DCO and database closure, only non-serious AEs, SAEs, and special situations

(pregnancy, overdose, medication error, drug abuse, and drug misuse) will be collected and reported for participants continuing to receive IMP/study intervention(s) (see Section 8.4.12).

8.1 Administrative Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3).

The Investigator will ensure that data are recorded on the eCRFs. The Rave Web Based Data Capture system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

8.2 Efficacy Assessments

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

8.2.1 Imaging Tumor Assessments

Tumor assessments use images from CT (preferred) or MRI, with iv contrast, of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis, collected during screening/baseline and at regular (follow-up) intervals during study intervention. Any other areas of disease involvement should be additionally imaged at screening based on known metastasis sites or by the signs and symptoms of individual participants. Participants with known brain metastasis should have a brain MRI (preferred) at screening and repeated imaging as part of their follow-up tumor assessments. The use of PET scans is described in [Appendix F](#).

The imaging modality used for baseline tumor assessment, CT (preferred) or MRI, should be kept the same consistently at each subsequent follow-up assessment throughout the study if possible. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoA) relative to randomization.

Screening/baseline imaging should be performed no more than 28 days prior to randomization and ideally should be performed as close as possible to and prior to the start of study intervention. An already existing scan performed as SoC will be acceptable as baseline, if performed within 28 days prior to randomization and is consistent with the required modalities (see [Appendix F](#)).

Tumor imaging continues every 6 weeks (± 7 days) up to Week 24, then every 8 weeks (± 7 days) up to Week 56, and then every 12 weeks (± 7 days) thereafter relative to the date of randomization until RECIST 1.1-defined radiological disease progression, plus an additional

follow-up scan at least 4 weeks later, and no later than the next scheduled imaging visit even if the participant discontinues or delays study intervention. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit.

The RECIST 1.1 assessments of baseline images identify TLs (defined as measurable) and NTLs. On-study images are evaluated for TLs and NTLs chosen at baseline, and for NLs when they appear. This allows determination of follow-up TL response, NTL response, the presence of unequivocal NLs, and overall time point responses (CR, PR, SD, PD, or NE).

8.2.2 Central Reading of Scans

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed iCRO for QC, and storage. Digital copies of all original scans should be stored at the Investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged.

A BICR of images will be performed at the discretion of AstraZeneca to enable a supplementary/sensitivity analysis of RECIST 1.1 tumor assessments. Results of these independent reviews will not be communicated to Investigators, and results of Investigator tumor assessments will not be shared with the central reviewers.

Further details of the BICR will be documented in an Independent Review Charter.

8.2.3 Time to Second Progression or Death

Following first objective progression participants will have their subsequent progression status recorded every 12 weeks ($\pm$ 14 days) according to local standard practice by the Investigator until the second progression event has occurred after the start of a subsequent anticancer therapy.

Assessments Prior to Start of Subsequent Anticancer Therapy

If at the subsequent progression assessment, the subsequent anticancer therapy has not started, subsequent progression is assessed in relation to the first objective RECIST 1.1 progression. In addition, the reasons for not starting a subsequent anticancer therapy are recorded.

Assessments After Start of Subsequent Anticancer Therapy

If at the PFS2 assessment, the subsequent anticancer therapy has started, then second progression is assessed in relation to the last tumor assessment prior to starting the subsequent anticancer therapy.

The Investigator opinion of progression status (PD, non-PD) will be recorded, and if PD is recorded, then the type of progression is also recorded.

8.2.4 Overall Survival

Assessments for survival will be conducted every 12 weeks $\pm$ 14 days following objective PD or treatment discontinuation. Survival information may be obtained via telephone contact with the participant, participant's family, by contact with the participant's current physician, or local death registries, as described in Section 7.1.3.

Note: Survival calls will be made following the DCO date for the analysis (these contacts should generally occur within 7 days of the DCO date). If participants are confirmed to be alive or if the death date is after the DCO date, then these participants will be censored at the date of DCO.

8.2.5 Clinical Outcome Assessments

A COA is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit.

PRO assessment is one type of COA and is a general term referring to all outcomes and symptoms that are directly reported by the participant. PROs have become important in evaluating the efficacy and tolerability of study interventions in clinical studies and will aid in understanding of the benefit/risk evaluation ([Kluetz et al 2018](#)).

In addition, PROs could be applied to inform participants' health status with regards to symptoms including their occurrence and evolution over time. This information, as available to Investigators and their representative(s), can support remote monitoring of participants for selected symptoms.

The following PRO instruments will be administered in this study:

- EORTC IL446
- EORTC IL445
- EORTC IL444
- PGI-TT
- PROMIS Physical Function – Short Form 8c-7 day
- EORTC IL172
- PGI-S
- PGI-C
- EQ-5D-5L

COA instruments will be administered according to the SoA regardless of any delay in study treatment (see Section 1.3). The COA instruments will be completed by participants if a

linguistically validated version is available in their language for the country in which they reside.

8.2.5.1 EORTC IL446, EORTC IL445, and EORTC IL444: Selected Items From the EORTC QLQ-BIL21 and IL

The EORTC QLQ-BIL21 was developed and validated specifically for cholangiocarcinoma (Friend et al 2011; Kaupp-Roberts et al 2016). It consists of 21 items, which are grouped into 9 multi-item or single-item scales measuring eating problems, jaundice, tiredness, pain, anxiety, treatment side effects, drainage bags/tubes, and weight loss.

The EORTC IL is an online platform comprised of more than 900 individual items from over 60 EORTC questionnaires. Selecting items from EORTC IL offers new opportunities to leverage existing EORTC items for capturing additional symptoms that are relevant to a given study, as the static questionnaires might not always be sufficient to meet the demands of quickly evolving treatment modalities.

The EORTC requirements dictate that any unique combination of items included within a single form must be designated as a separate and unique instrument. Therefore, select short forms with overlapping items are assigned a unique EORTC identifier.

The EORTC IL446 will be used to assess disease-related symptoms. The EORTC IL446 contains items from the eating problems, jaundice, tiredness, pain, and drainage bags/tubes subscales of the EORTC QLQ-BIL21.

The EORTC IL445 will be used to measure both disease- and treatment-related symptoms. It contains items from the pain and jaundice subscales, as well as other items from the EORTC IL (constipation, diarrhea, vomiting, nausea).

Treatment-related symptoms will also be assessed using the IL444. The pre-selected items assessing treatment-related symptoms in IL444 will include the following: shortness of breath, lack of appetite, tiredness, cough, rash, and fever/chills.

8.2.5.2 PGI-TT

The PGI-TT item is included to assess how a participant perceives the overall burden of treatment-related side effects of cancer treatment over the past 7 days. Participants will be asked to choose the response that best describes the level of burden by the side effect of their cancer treatment over the past week. The response options are: “not at all”, “a little bit”, “somewhat”, “quite a bit”, and “very much”. This item is included to aid in the interpretation of other PRO measures and to evaluate the overall impact of treatment-related side effects.

8.2.5.3 PROMIS Physical Function – Short Form 8c-7 day

The PROMIS Physical Function item bank (PROMIS®) is an assessment tool that was designed using well-specified instrument development protocols with an item bank that allows for assessment across a wide range of activities and levels of ability.

The PROMIS Physical Function v2.0 – Short Form 8c-7 day (PROMIS PF-SF 8c-7 day) is currently under qualification as an indicator of treatment benefit in physical function among adults with advanced or metastatic cancer and will provide the primary support for the assessment of physical function in the current study. Data from PROMIS PF-SF 8c-7 day will capture participants' perceived ability to perform specific activities.

8.2.5.4 EORTC IL172: Selected Items From the EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC QoL Group 1993. It consists of 30 item and measures symptoms, functioning, and GHS/QoL ([Aronson et al 1993](#)) for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), a 2-item global QoL scale, 5 single items assessing additional symptoms commonly reported by cancer participants (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and one item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this participant population when paired with items from the EORTC QLQ-BIL21 ([Friend et al 2011](#), [Kaupp-Roberts et al 2016](#)).

The current study will include subscales of the EORTC QLQ-C30. EORTC IL172 includes the following subscales: role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), social functioning (2 items), and GHS (2 items). This modular approach is to reduce redundancy across PROs, therefore, reducing participant burden. Subscales will be used in their entirety in order to maintain scoring conventions. Financial difficulties will not be included due to the lack of relevance in a study setting. Items assessing symptoms will also not be assessed due to irrelevance or duplicate information being collected in another questionnaire.

8.2.5.5 PGI-S

The PGI-S item is a single-item questionnaire assessing how a participant perceives the overall severity of cancer symptoms over the past 7 days. The response options are: “None”, “Mild”, “Moderate”, and “Severe”. This item is included to aid in the interpretation of other PRO measures and to evaluate the overall impact of treatment on the global severity of cancer symptoms.

8.2.5.6 PGI-C

The PGI-C is a single-item questionnaire assessing how a participant perceives overall change in health status since the start of study intervention. The response options are “Much better”,

“Moderately better”, “A little better”, “About the same”, “A little worse”, “Moderately worse”, and “Much worse”.

8.2.5.7 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility.

The EQ-5D-5L, developed by the EuroQoL Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status used for economic appraisal (EuroQol 2019). The EQ-5D-5L questionnaire is comprised of 6 questions that cover 5 dimensions of health (eg, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Respondents also assess their health today using the EQ-VAS, which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

8.2.5.8 Remote Monitoring of Digestive Signs and Symptoms

The RPM digital solution is comprised of connected participant- and HCP-interfaces, to support exchange of specific patient generated data between the participant and the Investigator(s) or delegate(s) to inform HCP monitoring of onset and worsening of selected symptoms or signs associated with selected AESI(s). Collection of measurements such as digestive signs and symptoms takes place outside of a clinical setting, such as at home, which reduces participant burden. Investigator delegates include any HCP with access to the HCP-interfaces including nurse collaborator.

These digital solution(s) will be available according to local regulations pertaining to digital health technology facilitating exchange of information between participant and/or caregiver and health care provider(s).

Participants are provided with a tracker that includes instructions to recognize symptoms and/or signs relevant to AESI(s) and their worsening. To minimize burden, the solution uses a gated approach to data acquisition with participants providing more details only when symptoms are reported to occur: for asymptomatic participants, providing data will require less than one minute as only questions on symptom occurrence and use of concomitant medication(s) and/or prophylactic/preventative strategies (when relevant) are surfaced. For participants who are reporting any of the cardinal symptoms of interest, additional questions to capture contextual information such as symptom severity could be surfaced for a completion time of less than a few minutes.

Participants are reminded to contact their care providers when changes in health status are occurring or if they have any questions.

Investigator(s) or delegate(s) can access and view the data for all participants via a web portal at any time or when notified via email according to a pre-defined data event such as symptoms

occurring or worsening. In the occurrence of a data event, the Investigator or delegates will be invited to review and acknowledge the data. They may then elect to contact their patient to obtain more information concerning the participant's data and may discuss options for treatment or mitigation of symptoms consistent with the clinical protocol or SoC.

The Investigator(s) or delegate(s) must manage symptoms and signs according to relevant TMGs and are expected to follow existing processes for AE information collection, assessment, and if required, reporting, consistent with the conduct of a clinical trial for an IMP. The data collected by the RPM solution(s) can be used to trigger a clinical evaluation for the purpose of AE elicitation but in itself does not constitute an AE that needs to be reported as an AE. Of note, the solutions for RPM do not replace or amend standard AE collection or SAE reporting by the Investigator as per protocol.

Metadata to inform usage of the solution will be collected and analyzed alongside data captured in the RPM module and relevant clinical data to optimize the module.

8.2.5.8.1 Digestive Symptoms

The Digestive digital solution enables Investigator(s) and delegate(s) to remotely view selected signs and symptoms consistent with selected gastrointestinal AESI(s) reported by participants when outside of a medical facility.

8.2.5.8.1.1 Digestive Symptom Tracker

On a daily basis (until end-of-study treatment), participants report whether they have any of the following digestive symptom(s): nausea, vomiting, diarrhea, constipation, change in appetite, or signs consistent with dehydration. The interface captures contextual information such as frequency, additional signs (eg, color of vomit), or use of concomitant medication(s).

To encourage use of the solution, participants are reminded of information consistent with the ICF (eg, GI symptoms could occur as the result of the treatment or the tumor) and provided with publicly available knowledge on coping strategies such as dietary or behavioral changes to help with their symptoms. Representative examples include consuming sufficient fluid volumes in response to experience with repeated vomiting or diarrhea, or to avoid oral intake for several hours after vomiting.

8.2.5.8.1.2 HCP Web Portal

Investigators and delegates will be notified via email or in-app that the participant reported the following data event(s):

- Onset or worsening of diarrhea, and/or vomiting, and/or an impact of constipation

The Investigators or delegates are encouraged to review the data at the earliest opportunity and at the latest within 5 calendar days of the notification.

8.2.5.9 Administration of Electronic Clinical Outcome Assessments

Baseline COA questions should be completed after informed consent and before the first dose of study intervention. COA questionnaires completed at sites should be completed prior to treatment administration performed at the site and ideally before any discussions of health status to avoid biasing the participant's responses to the questions. As feasible, site staff should also ensure COA questionnaires are completed prior to other study procedures, such as collection of laboratory samples, to further minimize bias.

Each site must allocate the responsibility for the administration of the eCOA instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent.

A web back-up may be available to answer the questionnaires if there are technical problems with the device or if preferred by the participant.

COA questionnaires will be self-administered electronically at home by the participants using handheld devices at the time points indicated in the SoA. The device may either belong to the participant ("bring your own device") or be provisioned for the study by AstraZeneca. Participants should complete the eCOAs prior to or at the site if the assessment time point coincides with a scheduled site visit. Alerts will remind participants when eCOAs should be completed. Participants should be instructed to bring the device to all visits.

The amount of time needed to complete questionnaires at each time point will vary based on the specific questionnaires being administered. During the first 9 weeks, participants will need approximately 2 to 10 minutes per week for questionnaire completion. For subsequent timepoints, approximately 10 minutes will be required for questionnaire completion per cycle.

The RPM(s) should not take more than 2 to 3 minutes daily. However, the participant should take their own time to complete these.

The below instructions should be followed when collecting COA data:

- The research nurse or appointed site staff should explain to participants the value and relevance of these data so they are motivated to comply with questionnaire completion. The participant should be informed that these questions are being asked to find out, directly from them, how they feel.
- It is vital that the eCOA reporting is initiated at C1D1, as specified in the SoA to capture the effect of study intervention. The eCOA device must be charged and fully functional at the beginning of the baseline visit to ensure that the COAs can be completed at the start of the visit.
- Every effort should be made to ensure participants complete the baseline questionnaires before revealing the treatment arm allocated to the participants.

- The participant should bring the eCOA device to each site visit so the research nurse or appointed site staff can check if there are available COA questionnaires to be completed and that the device is functioning properly.
- If questionnaires are completed at the site, the device should be handed back to the research nurse or appointed staff nurse, who should check that all questionnaires were completed.
- COA questionnaires should be completed by the participant in a quiet and private location.
- The participant should be given sufficient time to complete the COA questionnaires at their own speed.
- When each instrument is due to be completed, the following order must be observed. This order will be pre-programmed into the eCOA schedule. Not all COA questionnaires will be administered at every time point. Please refer to the SoA (Section 1.3):
 - EORTC IL446
 - EORTC IL445
 - EORTC IL444
 - PGI-TT
 - PROMIS Physical Function – Short Form 8c-7 day
 - EORTC IL172
 - PGI-S
 - PGI-C
 - EQ-5D-5L
- The research nurse or appointed site staff should stress that the data are not routinely reviewed in real time by study staff. Therefore, if the participant has any medical problems, they should discuss them with the doctor or research nurse separately from the eCOA assessment.
- The research nurse or appointed site staff must train the participant on how to use the eCOA device using the materials and training provided by the eCOA vendor.
- The research nurse or appointed site staff must provide guidance on who to call if there are problems with the device(s) when the participant is completing the eCOA at home.
- If technical or other device-related issues prohibit completion on the eCOA device, an appropriate backup option may be considered with prior approval from AstraZeneca.
- The research nurse or appointed site staff must remind participants that there are no right or wrong answers and avoid introducing bias by not clarifying items.
- The participant should be instructed not to receive help from relatives, friends, or clinic staff when answering the COA questions. If individuals are not able to complete the

eCOAs independently, they can receive help with the manual actions (including navigation and use of the device), but they must select their answers themselves.

- Participants should be instructed to bring visual aids for reading (eg, glasses or contact lenses) to the baseline visit and all subsequent visits. If visual aids are not available at the visit, COA questionnaires may be completed after the visit during the available window.
- If the participant is unable to complete the COAs (eg, being blind, illiterate, not fluent in the available language), that participant is exempted from completing COAs but may still participate in the study. If the eCOA system is not ready, the participant is exempt from completing the COAs during that time only. When the COAs are available, the participant is required to complete them. If the participant cannot complete the COAs due to reasons other than being blind, illiterate, not fluent in the available language, or eCOA system is not ready, the AstraZeneca study team must be contacted to determine if they can be exempted. Participants exempted in this regard should be flagged appropriately by the site staff in the source documents and in the designated eCRF.
- Questions must not be translated from an available language in the device into the language the participant speaks.
- Reminders should be provided to participants, as needed to ensure compliance with the assessment schedules.
- The research nurse or appointed site staff should monitor compliance since minimizing missing data is a key aspect of study success.
- The research nurse or appointed site staff will review the completion status of questionnaires throughout the study and during site visits, and document the reason(s) why a participant could not complete assessments, in the source documents and in the designated eCRF. If the site receives an email notification regarding the participant's compliance, or if compliance is observed to be below the acceptable threshold, appropriate action will be taken (eg, discussion with participant to improve compliance, a check in call from the site to ask the participant if they have any difficulties in completing questionnaires on schedule, etc). A solution to enhance/resolve compliance should be discussed with the participant. Discussions and compliance review should be reflected in source documents.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.3).

8.3.1 Physical Examinations

A full physical examination will be performed and include assessments of the following: general appearance, respiratory, cardiovascular system, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including

spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, hematologic/lymphatic, and neurological systems.

Targeted physical examinations are to be used by the Investigator on the basis of clinical observations and symptomatology. A targeted physical examination will include, at a minimum, assessments of skin, lungs, cardiovascular system, and abdomen (liver and spleen). Additional assessments are performed by the Investigator on the basis of clinical observations and symptomatology.

Physical examination, as well as assessment of height and weight, will be performed at timelines as specified in the SoA. Investigators should pay particular attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.4.4 for details.

8.3.2 Vital Signs

Vital signs (temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry) will be measured according to the SoA and should be obtained within 30 minutes prior to start of iv administration of study intervention. Post-dose vital signs for rilvegostomig or durvalumab should be collected at Cycle 1 Day 1 within 30 minutes from the end of the infusion and at additional timepoints if clinically indicated. For subsequent cycles, post-dose vitals can be collected as clinically indicated. For gemcitabine/cisplatin, post-dose vital signs can be collected per local practice.

Temperature should be measured using the same method throughout the study.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse measurement and 3 blood pressure measurements (if the first blood pressure measurement is within a clinically acceptable range, the second and third blood pressure measurements are not mandatory; otherwise, if clinically indicated, 3 consecutive blood pressure readings will be recorded at intervals of at least one minute). The average of the 3 blood pressure readings will be recorded in the eCRF.

Situations in which vital sign results should be reported as AEs are described in Section 8.4.4.

For any AEs of infusion reactions, the vital signs values should be entered into the eCRF.

8.3.3 Electrocardiograms

Single 12-lead ECG will be performed at timelines as specified in the SoA. If an ECG was conducted within 3 calendar days prior to dosing, then it does not need to be repeated pre-dose on Day 1 of the cycle if the participant's condition has not changed. Post-dose ECGs can be carried out as clinically indicated. All ECG recordings are made after the participant has been resting semi-supine for at least 5 minutes and recorded while the participant remains in that position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Note: For sites that do not have access to ECG machines that automatically calculate the QTcF interval, manual calculations are permitted.

All ECGs should be assessed by the Investigator as to whether they are clinically significantly abnormal. Any clinically significant abnormalities detected require triplicate ECG results. If triplicate ECGs are required, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes.

Situations in which ECG results should be reported as AEs are described in Section [8.4.4](#).

8.3.4 Clinical Safety Laboratory Tests

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA. If the samples were collected within 3 calendar days prior to dosing, then the tests do not need to be repeated pre-dose on Day 1 of the cycle if the participant's condition has not changed. The same method should be used to calculate the renal function from screening throughout the study.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

Prior to dosing at each cycle, all available safety laboratory results should be reviewed. At a minimum, the Investigator must review:

- Hematology
- Creatinine and electrolytes (calcium, magnesium, sodium, phosphate/phosphorus, and potassium)
- Liver function (AST, ALT, ALP, and TBL)

All safety laboratory tests will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Every effort should be made to obtain and provide the corresponding laboratory reference ranges.

The laboratory variables to be measured are listed in [Table 6](#), [Table 7](#), [Table 8](#), and [Table 9](#).

Other safety laboratory tests include assessment for pregnancy (serum at screening; serum or urine at other time points). Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test).

Abnormal clinically significant laboratory result should be repeated as soon as possible (preferably within 72 hours).

Table 6 Hematology/Hemostasis (Whole Blood)

White blood cells	Hemoglobin
Absolute (or differential, %) lymphocyte count	Hematocrit
Absolute (or differential, %) monocyte count	Mean corpuscular volume
Absolute (or differential, %) neutrophil count	Platelet count
Absolute (or differential, %) eosinophil count	

Table 7 Clinical Chemistry (Serum or Plasma)

Calcium (total or ionized)	Aspartate aminotransferase (AST)
Magnesium	Alanine aminotransferase (ALT)
Creatinine	Alkaline phosphatase (ALP)
Sodium	Albumin
Blood urea nitrogen or urea	Total protein
Glucose	Phosphate or phosphorous
Potassium	Troponin T or I a
Total bilirubin (TBL)	Creatine phosphokinase
Amylase	Gamma-glutamyl transpeptidase
Lipase	Lactate dehydrogenase (LDH)
Chloride	

^a Standard or high sensitivity assay.

Note: Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.

If TBL is $\geq 2 \times$ ULN, indirect bilirubin should be assessed unless previously documented Gilbert's disease.

Note: In case a participant shows an AST **or** ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN, see [Appendix E](#) for Hy's Law guidance and further instructions.

Table 8 Urinalysis

Color	Glucose
Appearance	Ketones
Specific gravity	Blood
pH	Bilirubin
Total protein or albumin	Urinalysis (dipstick acceptable). Urine high-power field microscopy or digital flow morphology is to be assessed if other urinalysis measurements are abnormal or if clinically indicated.

Table 9 Other Safety Tests

Coagulation tests: At screening and then as clinically indicated. PTT (or aPTT), INR. PT and fibrinogen (both optional).
HIV tests: At screening (<i>as per applicable local regulations</i>). HIV-1 or HIV-2 antibodies; HIV PCR. Participants with HIV infection at screening: viral RNA load and CD4+ count as clinically indicated
Tuberculosis tests: At screening and, if required per local practice, throughout treatment and safety follow-up periods.
Thyroid function tests: TSH will be measured at screening and before each cycle. Free T4 (optional: free T3) should only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
Other tests to be performed as clinically indicated: - Ferritin and iron studies - Glycated hemoglobin - Uric acid - Anti-thyroid antibodies (anti-TPOAb, TRAb, and TgAb)

The Investigator should assess the available results with regard to clinically relevant abnormalities in documentation. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.4.4.

In case a participant shows an **AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN** please refer to [Appendix E](#), for further instructions.

All participants with CTCAE Grade 3 or 4 laboratory values at the time of completion or discontinuation from study intervention must be followed and have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.3.4.1 Hepatitis Testing

At screening, all participants will be evaluated for hepatitis B and C by evaluation of:

- Hepatitis B virus surface antigen (HBsAg)
- Hepatitis B virus core antibodies (anti-HBc)
- Anti-hepatitis B surface antibodies (HBsAb)
- Anti-HCV antibody
- Quantitative HBV DNA (if HBsAg or anti-HBc positive)
- Quantitative HCV RNA (if anti-HCV antibody positive)

Anti-hepatitis D antibodies are required during screening for any participant who tests positive for HBsAg or anti-HBc. HDV RNA should be measured if anti-HDV positive.

After screening, additional viral studies are required on D1 of each cycle as specified in the SoA ([Table 1](#)) under the following circumstances:

- Quantitative HBV DNA – Required for participants who test positive for HBsAg or anti-HBc at screening.
- Quantitative HCV RNA – Required for participants who test positive for anti-HCV antibody at screening.

All participants with HBV infection, as indicated by the presence of HBsAg regardless of HBV DNA level or anti-HBc with detectable HBV DNA (≥ 10 IU/mL or above the limit of detection per local lab standard) must remain on antiviral therapy for the study duration and for 6 months after the last dose of study intervention.

Participants with active HCV infection (as characterized by the presence of detectable HCV RNA and anti-HCV antibody [anti-HCV]) at screening are not eligible.

8.3.5 Other Safety Assessments

8.3.5.1 Disease-specific Tumor Marker Samples

As part of routine safety blood samples, CA-19-9 and CEA will be assessed at the timepoints specified in the SoA ([Table 1](#) and [Table 2](#)). Cancer antigen-19-9 and CEA assessments should only be performed at the specified timepoints. Review of CA-19-9 and CEA outside of the specified timepoints should be avoided, and if additional assessments are performed, results

must be recorded in RAVE.

A rise in CA-19-9 or CEA alone is not sufficient to declare progression and discontinue study intervention. Progression events should be determined by Investigator-assessed radiological evidence per RECIST 1.1.

Further assessment of CA-19-9 and CEA after radiological progression will be at the discretion of the Investigator according to local clinical practice.

8.3.5.2 Echocardiogram/Multigated Acquisition Scan

An ECHO or MUGA scan to assess LVEF will be performed at the visits as shown in SoA. The modality of the cardiac function assessments must be consistent for a given participant (ie, if ECHO is used for the screening assessment for a given participant, then ECHO should also be used for subsequent scans for that participant). The participants should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken (ie, accurate to 1% and not estimated to 5%).

If a participant has had an ECHO or MUGA performed within 4 weeks prior to treatment discontinuation, the discontinuation visit ECHO/MUGA scan is not required unless clinically indicated. If a participant has any clinically significant decrease in LVEF (greater than 10 percentage points to below 50%), there should be follow-up within 4 weeks until resolution.

Situations in which ECHO or MUGA results should be reported as AEs are described in Section [8.4.4](#).

8.3.5.3 ECOG Performance Status

ECOG performance status will be assessed at the times specified in the SoA based on the following:

- 0 Fully active; able to carry out all usual activities without restrictions.
- 1 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work).
- 2 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.
- 3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
- 4 Completely disabled; unable to carry out any self-care and totally confined to bed or chair.
- 5 Dead.

Any significant change from baseline or screening must be reported as an AE.

8.4 AEs, SAEs, and Other Safety Reporting

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in [Appendix B](#).

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorized representative) will notify the Investigator or designees of symptoms. These must then be assessed by the Investigator and if considered an AE it will be reported by the Investigator.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

AE Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum CTCAE grade or changes in CTCAE grade
- Whether the AE is serious or not (see [Appendix B 2](#) for definition of SAEs)
- Investigator causality rating against the IMP/study intervention(s) (yes or no)
- Action taken with regard to IMP/study intervention(s)
- AE caused participant's withdrawal from the study (yes or no)
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE description
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

The grading scales found in the revised NCI CTCAE version 5.0 will be utilized for all events unless otherwise stated in the TMGs. This version will be used for the duration of the study. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the NCI CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (<http://ctep.cancer.gov>).

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected from the time of signature of the ICF and throughout the treatment period until the safety follow-up period is completed (90 [$\pm$ 7 days] days post last dose of study treatment). Collection and reporting of AEs and SAEs after the final DCO is described in Section [8.4.12](#).

If the Investigator becomes aware of an SAE with a suspected causal relationship to the IMP/study intervention(s) that occurs after the end of the clinical study in a treated participant, the Investigator shall, without undue delay, report the SAE to AstraZeneca, as described in Section [8.4.13](#).

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.3 Causality Collection

The Investigator should assess causal relationship between IMP/study intervention(s) and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP/study intervention(s)?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in [Appendix B](#).

8.4.4 AEs Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs (temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry), physical examination, ECGs, ECHO/MUGA scans, ECOG performance status should only be reported as AEs if they meet any of the following:

- Fulfill any of the SAE criteria
- Are the reason for discontinuation of the IMP/study intervention(s)
- Are clinically relevant as judged by the Investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required or other action was taken with the IMP/study intervention(s), eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia vs low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the DUS. Please refer to Section [8.4.8](#).

The results from the protocol-mandated laboratory tests and vital signs will be summarized in the CSR.

8.4.5 AEs Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to [Appendix E](#) for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.4.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the IMP is being studied. It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as AEs during the study.

8.4.8 Disease Under Study

Symptoms of DUS are those which might be expected to occur as a direct result of advanced BTC. Events which are unequivocally due to DUS should not be reported as AEs during the study unless they meet SAE criteria or lead to discontinuation of the IMP/study intervention(s).

8.4.9 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria (eg, important medical event). New primary cancers are those that are not the primary reason for the administration of study intervention and are identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.4.10 Deaths

All deaths that occur during the study intervention period, or within the protocol-defined follow-up period after the administration of the last dose of study intervention, must be reported as follows:

- Death clearly resulting from PD should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to PD under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a

cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined follow-up period after the administration of the last dose of study intervention should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined follow-up period and the event is considered to be due to a late-onset toxicity to study intervention, then it should also be reported as an SAE.

8.4.11 Adverse Events of Special Interest

AESIs will be collected and reported for the experimental arm and the control arm using the events defined for rilvegostomig, as per Section 8.4.11.1.

AESIs are events of scientific and medical interest specific to the further understanding of rilvegostomig safety profile and require close monitoring. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.4.13.

8.4.11.1 Adverse Events of Special Interest for Rilvegostomig

The AESIs for rilvegostomig include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or HRT. Additionally, IRRs, and events of similar presentation, are considered AESIs for rilvegostomig. These AESIs are being closely monitored in clinical studies with rilvegostomig.

An imAE is defined as an AESI that is associated with drug exposure, is consistent with an immune-mediated mechanism of action, and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

ImAEs that may be observed with rilvegostomig (based on the available preclinical and clinical data, review of the cumulative literature, reported toxicities for the same class of agents, and biological plausibility) and are considered AESIs for this study include, but are not limited to, the following medical concepts or terms:

- Respiratory disorders: pneumonitis; interstitial lung disease
- Gastrointestinal disorders: diarrhea; colitis, including intestinal perforation and ileus

- Endocrinopathies: hypothyroidism; hyperthyroidism; hypophysitis; adrenal insufficiency; Type 1 diabetes mellitus
- Hepatic disorders: ALT/AST increased; hepatitis
- Renal disorders: nephritis; blood creatinine increased
- Cardiac disorders: myocarditis
- Skin disorders: rash; pruritus; dermatitis, including lichenoid; vitiligo; psoriasis exacerbation; serious exfoliative skin disorders: bullous pemphigoid, Stevens-Johnson syndrome, and toxic epidermal necrolysis; xerostomia and oral lichenoid reactions
- Encephalitis
- Other: myositis/polymyositis; rhabdomyolysis; uveitis; iritis; arthritis; Guillain-Barré syndrome; myasthenia gravis; vasculitis; pancreatitis; hemolytic anemia; aplastic anemia; hemophagocytic lymphohistiocytosis; and sarcoidosis

Other AEs which are considered to be AESIs with rilvegostomig include, but are not limited to:

- IRRs; hypersensitivity including anaphylactic/anaphylactoid and other allergic reactions.
- Immune complex disease; where the participant forms antibodies to rilvegostomig. Symptoms may include aching joints, rash, fever, nephritis, or vasculitis.
- Cytokine release syndrome; tumor lysis syndrome.

More detailed guidelines on the evaluation and treatment of these risks are described in the TMGs (see TMG Annex and Section 6.6). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the IMP/study regimen by the reporting Investigator.

For management of toxicities due to chemotherapy agents, please refer to the local approved regulatory Prescribing Information or manage in accordance with institutional guidelines.

AESIs are detailed in the IB, Section 5.6.4.

8.4.12 Safety Data to be Collected Following the Final Data Cut-off of the Study

For participants continuing to receive IMP/study intervention(s) after the final DCO, AEs, SAEs, and special situations (ie, pregnancy, overdoses, medication error, drug abuse, and drug misuse) will be collected and reported. In addition, it is recommended that Investigators monitor the participant's safety laboratory results periodically during treatment with IMP/study intervention(s) in order to manage AEs, consistent with the dose modification

guidelines for management of study intervention-related toxicities (see Section 6.6). All data after the final DCO and database closure will be recorded in the participant notes but, with the exception of AEs, SAEs, and special situations, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants still receiving IMP/study intervention(s) (or within the 90 [± 7] days following the last dose of IMP/study intervention[s]) after the final DCO must be reported as detailed in Section 8.4.13.

8.4.13 Reporting of SAEs

All SAEs must be reported, whether or not considered causally related to the IMP/study intervention(s). All SAEs will be recorded in the eCRF during study conduct. After study completion, when EDC is closed and SAE needs to be reported, paper SAE form should be used.

If any SAE occurs during the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety DES **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports the SAE via secure method to the appropriate AstraZeneca representative.

When the EDC is temporarily not accessible, the AstraZeneca Study Representative should confirm that the Investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

For further guidance on the definition of an SAE, see [Appendix B](#).

For regulatory reporting requirements for SAEs, see [Appendix A 1](#).

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca IMP/study intervention(s) and AstraZeneca active comparator.

8.4.14 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following the first date of study intervention, including pregnancy in the partners of male participants, should be reported to AstraZeneca except if the pregnancy is discovered before the study participant has received any study intervention.

8.4.14.1 Maternal Exposure

If a participant becomes pregnant during the study, the IMP/study intervention(s) should be discontinued immediately and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. All pregnancies should be collected and provided to the AstraZeneca DES via PREGREP module in the eCRF. If an AE/SAE is associated with the pregnancy, AE/SAE eCRF modules should also be completed and sent to AstraZeneca DES. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study. The paper based PREGOUT form should be used to report the outcome of the pregnancy.

If any pregnancy occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives immediately but no later than **24 hours** after he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca DES **within one or 5 calendar days** for pregnancies associated with SAEs (see Section 8.4.13) and **within 30 days** for all other pregnancies.

8.4.14.2 Paternal Exposure

Non-sterilized male participants who intend to be sexually active with a female partner of childbearing potential should refrain from fathering a child or donating or banking sperm for the duration of the study (from the time of screening) and for 60 days after last dose of rilvegostomig, or 90 days after last dose of durvalumab, or 6 months after last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is the longest.

Pregnancy of the participant's partner is not considered to be an AE. However, all pregnancies occurring from the date of the first dose of study intervention until 60 days after last dose of rilvegostomig, or 90 days after last dose of durvalumab, or 6 months after last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is the longest, should be followed up and the outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) documented in the medical record and provided to the AstraZeneca Patient Safety DES. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the participant's partner. The local study team should adopt the Master Pregnant Partner Form in line with local procedures/requirements and submit it to the relevant Regulatory Authority/IRBs/IECs prior to use.

8.4.15 Medication Error, Drug Abuse, and Drug Misuse

8.4.15.1 Timelines

Medication error, Drug Abuse, and Drug Misuse alone are not AE/SAE. All Medication Errors/Drug Abuse/Drug Misuse are to be collected for IMPs and AstraZeneca AxMPs and provided to AstraZeneca DES via the respective Medication Error eCRF module or Drug Abuse/Drug Misuse paper CRF forms. If an AE/SAE is associated with the Medication Error/Drug Abuse/Drug Misuse, the AE/SAE eCRF modules should also be completed and sent to AstraZeneca DES.

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to AstraZeneca DES within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or drug misuse (see Section [8.4.13](#)) and **within 30 days** for all other events.

8.4.15.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca AxMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix [B 4](#).

8.4.15.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca AxMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix [B 4](#).

8.4.15.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca AxMP for medicinal purposes outside of the authorized product information, or unauthorized IMPs or AstraZeneca AxMP, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix [B 4](#).

8.4.16 Reporting of Overdose

Refer to Section [6.8](#) for definition and treatment of overdose.

Overdose alone is not an AE/SAE. All overdoses are collected for IMPs and AstraZeneca AxMPs and provided to AstraZeneca DES via the Overdose eCRF module. If an AE/SAE is associated with the overdose, AE/SAE eCRF modules should also be completed and sent to AstraZeneca DES. An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP or AstraZeneca AxMP occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to AstraZeneca DES within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with overdose (see Section [8.4.13](#)) and **within 30 days** for all other overdoses.

For participants receiving chemotherapy (gemcitabine/cisplatin), if any overdose is associated with an AE or SAE, record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

8.4.17 Adverse Device Effects and Device Deficiencies

Not applicable.

8.5 Pharmacokinetics

- Whole blood samples will be collected for measurement of serum concentrations of rilvegostomig as specified in the SoA (Section 1.3).
- Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and AstraZeneca, eg, for urgent safety reasons, and this may be reflected as a protocol deviation.
- The timing of sampling may be altered during the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Samples collected for analyses of rilvegostomig serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.
- For storage, re-use, and destruction of samples for PK see [Appendix C](#).
- Pharmacokinetics samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier).
- Additional analyses may be conducted on the anonymized, pooled, or individual PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Samples collected from participants in China will be destroyed or repatriated within one year of the CSR.

8.5.1 Collection of Samples for Pharmacokinetics

Blood samples will be collected for measurement at timepoints specified in the SoA ([Table 1](#)). Pharmacokinetic samples collected as a $C_{\max}$ (peak) concentration after an infusion are to be collected within 15 minutes following the end of IMP infusion (infusion time does not include the final flush time).

8.5.2 Determination of Drug Concentration

Samples for determination of drug concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.6 Pharmacodynamics

8.6.1 Collection of Samples for Pharmacodynamics

Biological samples collected for exploratory biomarkers (see SoA [Section 1.3] and Section 8.8) can be used for pharmacodynamic assessments to evaluate biological changes associated with study intervention and in association with PK parameters.

For storage, re-use, and destruction of samples for pharmacodynamics see [Appendix C](#).

Samples collected from participants in China will be destroyed or repatriated within one year of the CSR.

8.7 Optional Genomics Initiative

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA and is subject to participant agreement in the optional Genomics Initiative research information ICF.

Blood samples for DNA and blood derivatives isolation will be collected from participants who have consented to participate in the genomic and multi-omics analysis component of the study. Participation is optional. Participants who do not wish to participate in genomic and multi-omics research may still participate in the study.

Healthy volunteers samples will not be collected for the optional Genomics Initiative sample.

See [Appendix D](#) for information regarding the Genomics Initiative genomic and multi-omics samples. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices of this protocol or in the Laboratory Manual.

Note: This sample will not be collected in China and will only be collected in other countries where locally applicable/permissible.

8.8 Biomarkers

8.8.1 Mandatory Biomarker Sample Collection

Samples for biomarker research are required and will be collected from all screened participants in this study as specified in the SoA (Section 1.3).

By consenting to participate in the study, the participant consents to the mandatory research components of the study and collection and use of donated biological samples as described here within the scope of the protocol-defined objectives (see Section 3).

In regions where permitted, samples may be retained to allow for specific analysis to meet requests by Regulatory Authorities for the development of the companion diagnostic and further support the regulatory filing if needed.

8.8.1.1 Tumor Samples

Provision of FFPE tumor tissue sample (≤ 12 months old prior to screening) is mandatory for participant eligibility to study entry and for exploratory biomarker analyses as described below. Note, if participant has been rescreened, the tumor sample should be obtained ≤ 12 months prior to the rescreening date, unless a valid PD-L1 result was obtained during the initial screening. The mandatory tumor sample must be obtained following signature of informed consent during the screening window, in order to complete analysis prior to randomization.

An FFPE block is the preferred sample type. If the block cannot be submitted, then newly cut tissue sections on unstained slides should be provided. Details for tumor sample collection, sample criteria (including tumor content, quality, volumes, storage and processing) and shipment of tumor samples are presented in the Pathology Manual and Laboratory Manual.

Samples should be collected via core needle biopsy, excisional or incisional biopsy. Acceptable sample types are detailed in the Pathology Manual. The mandatory screening tumor biopsy obtained from either primary or metastatic lesions are acceptable and must not be taken from a previously irradiated lesion. Collection of tumor cells from fluid such as ascites or pleural effusion is not permitted. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component and not decalcified. Tumor lesions used for new biopsies should not be the same lesions used as RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy; in this instance excisional/incisional biopsy is not allowed. For participants with a single tumor lesion, the screening biopsy must be collected prior to screening imaging for baseline tumor assessment, allowing approximately 2 weeks before baseline imaging scans are acquired.

Unstained tumor slides collected from participants in China will be destroyed or repatriated within one year of the CSR. Storage and retention of stained tumor slides from participants in China will follow China local regulations. Human Genetic Resources approval will be followed for China sample collection and usage.

For further details on Handling of Human Biological Samples, including storage, re-use and destruction, refer to [Appendix C](#) and the Laboratory Manual.

8.8.1.1.1 PD-L1 Expression Assessment

Tumor samples will be tested for PD-L1 expression for eligibility and stratification using the investigational VENTANA PD-L1 (SP263) CDx assay, as described in the protocol-defined objectives. Central PD-L1 results obtained during screening from another AstraZeneca study

may be used for this study (provided the testing was performed with the same VENTANA PD-L1 (SP263) CDx assay testing platform, same test laboratory, and scoring manual using prospective central test, and tumor sample tested meets the study requirements).

In the case of histopathology, tissue sections and stained tumor specimens may be imaged (digitized) for QC monitoring purposes.

Where applicable, investigational use of the PD-L1 assay will comply with the European In Vitro Diagnostic Regulation 2017/746.

Refer to the Clinical Performance Study Plan for detailed sample testing and diagnostic device information.

8.8.1.1.2 TIGIT Expression Assessment

Leftover mandatory tumor tissue collected at screening from each participant will be tested for TIGIT expression per the protocol-defined objectives (see Section 3).

In the case of histopathology, tissue sections and stained tumor specimens of TIGIT expression may be imaged (digitized). Digital images will be treated as data. In China, remaining mandatory tumor samples will be used for these analyses only after Human Genetics Resources approval.

8.8.1.1.3 Exploratory Biomarker Analysis

Mandatory tumor samples collected at screening including the remaining tumor samples following completion of PD-L1 testing, and TIGIT testing, may be evaluated for exploratory biomarker analysis as measured by DNA, RNA, protein, and/or digital image measures (digital pathology). These exploratory biomarkers may include but are not be limited to the presence or quantification of mutation profile, tumor mutational burden, immune cell receptor repertoire, gene/RNA or protein expression, markers of tumor, immune and tumor microenvironment and their spatial distribution (eg, CD8, TILs, IFN- γ as measured by IHC or other assays/analytical methods including computer-aided, artificial intelligence) and in association with clinical outcomes/endpoints, participants baseline characteristics or other clinical/molecular assessments. Biomarker analyses may further validate and/or characterize mechanism of action or sensitivity/resistance to therapy, guide identification of participants who are most likely to benefit of therapy, and/or enable the development of methods for predicting outcomes and diagnostics. In the case of histopathology, tissue sections and stained tumor specimens may be imaged (digitized). These images may be used to investigate an association with observed clinical responses or survival and in development of methods for predicting outcomes and diagnostics. Digital images will be treated as data. Image data collection and usage in China will follow local regulation such as Human Genetic Resources approval.

These samples will be evaluated for exploratory biomarker analysis for participants in China upon China local regulatory approval.

These samples, with the exception of TIGIT testing, will not be evaluated for exploratory biomarker analysis for participants in Brazil.

Results of exploratory biomarker analyses may be reported as an addendum to CSR or separately in a scientific report or publication.

The results of biomarker analyses may be pooled with biomarker data from other studies to evaluate biological responses across indications and to compare biological effects across cancer types and in monotherapy and combination settings.

8.8.1.2 Blood Samples

Blood samples for exploratory biomarkers are required and will be collected from all participants as specified in the SoA (Section 1.3). Samples may be tested to assess, but not be limited to, presence of, or changes in immune, tumor, and/or cell/biological component associated biomarkers (markers, signatures, profiles, etc) as evaluated by DNA, RNA, protein, and/or analyte measurements (single, multiplexed, or multi-omics assays using different analytical methods including computer-aided, artificial intelligence) in relation with participants baseline characteristics, clinical outcomes/endpoints, and/or other molecular, clinical, and PK assessments. Biomarker analyses may further validate and/or characterize mechanism of action or sensitivity/resistance to therapy, may guide identification of participants who are most likely to benefit of therapy, and/or enable the development of methods for predicting outcomes and diagnostics. Results of exploratory biomarker analyses may be pooled with biomarker data from other studies to evaluate and compare, but not limited to, biological effects across cancer types and in monotherapy and combination settings.

Results of biomarker analyses may be reported as an addendum to the CSR or separately in a scientific report or publication.

For storage, re-use, and destruction of biomarker samples see [Appendix C](#) and the Laboratory Manual.

Plasma for ctDNA

Whole blood to extract plasma will be collected and may be used to generate ctDNA for DNA sequencing for exploratory biomarker analysis that may include but is not limited to presence/quantification of, profile of, or changes in ctDNA, mutation/genetic alterations, methylome profile and tumor mutational burden. In addition, buffy coat (white blood cells) will be collected from the pretreatment whole blood sample (C1D1) and may be used for DNA

sequencing to aid somatic variant calling and tumor mutational analysis of plasma ctDNA and tumor tissue samples.

These samples will only be collected at C1D1 and EoT/PD for exploratory biomarker analysis for participants in China upon China local regulatory approval.

These samples will not be collected for exploratory biomarker analysis for participants in Brazil.

PBMC for Immune Profiling

PBMC may be used for exploratory biomarker analysis including but not limited to presence/quantification of, profile of, or changes in immune cell receptor repertoire (eg, T-cell receptor sequencing), HLA allotyping, immune phenotype as measured by flow cytometry or single cell sequencing.

These samples will only be collected at C1D1 and C2D1 for exploratory biomarker analysis for participants in China upon China local regulatory approval.

These samples will not be collected for exploratory biomarker analysis for participants in Brazil.

Whole Blood for RNA Analysis

Whole blood for RNA analysis may be used for exploratory biomarker analysis including but not limited to baseline level or changes in specific RNA/gene expression or signature/profile analysis (CD8, effector T-cell signature, etc).

These samples will not be evaluated for exploratory biomarker analysis for participants in China or Brazil.

Serum and Plasma for Biomarker Analysis

Serum from whole blood and plasma samples (derived from PBMC processing or leftover from plasma for ctDNA) may be evaluated for exploratory biomarker analysis including but not limited to presence/quantification of, profile of, or changes in circulating markers or analytes (cytokines, chemokines, lipidome, metabolomics, etc).

These samples will not be evaluated for exploratory biomarker analysis for participants in China or Brazil.

8.8.2 Optional Biomarker Sample Collection

Collection of optional samples for biomarker research is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement to optional consent that does not affect a participant's wish and right to be in the study. Participants will not be excluded from the study

if either consent to the collection of these samples is not given or, if consented, the samples are not collected.

Optional Tumor Samples

Optional tumor samples may be collected at C3D1 and at disease progression as specified in the SoA and should be taken prior to dosing with study intervention. If clinically feasible, at each newly acquired tumor sample time point, up to 4 core image-guided needle biopsies should be collected from lesions with significant soft tumor tissue component and should not be the same lesions used as RECIST 1.1 TLs; in this instance, only core needle (not excisional/incisional) biopsy is allowed. Fine needle aspirates tumor samples are not acceptable. Optional tumor samples may be evaluated for exploratory biomarker analyses by DNA, RNA, protein, and/or digital image measures (eg, digital pathology, computer-aided, AI) including, but may not be limited to the presence or quantification of mutation profile, tumor mutational burden, immune cell receptor repertoire, gene/RNA or protein expression, markers of tumor, immune and tumor microenvironment and their special distribution (eg, CD8, TILs, IFN- γ as measured by IHC or other assays/analytical methods) and in association with clinical outcomes/endpoints, participants baseline characteristics or other clinical/molecular assessments. This sample might enable the identification biomarkers of response and resistance to treatments.

Results of exploratory biomarker analyses may be pooled with biomarker data from other studies to evaluate and compare biological effects across cancer types and in monotherapy and combination settings.

This sample will not be collected for participants from China or Brazil.

For further details on Handling of Human Biological Samples, including storage, re-use and destruction, refer to [Appendix C](#) and the Laboratory Manual.

8.8.3 Other Study-related Biomarker Research

Residual blood collected as mandatory and tumor samples collected as mandatory (at screening) and as optional (C3D1 and at PD) may be used for future biomarker research outside the scope of the protocol-defined objectives (per Section 3, Section 8.8.1, and Section 8.8.2), only where participants provided their consent for optional future research (see informed consent process in [Appendix A](#)). Results of future biomarker research may be pooled with biomarker data from other studies to evaluate and compare biological effects across cancer types and in monotherapy and combination settings. Participants will not be excluded from the study if consent to the use of these samples for future research is not given.

The use of residual biological samples for future research are not applicable for participants from China or Brazil.

For storage, re-use, and destruction of biomarker samples see [Appendix C](#) and the Laboratory Manual.

8.9 Immunogenicity Assessments

- Blood samples for determination of ADA in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. If required, the baseline samples may also be used for additional method validation activities (eg, cut points). Full details of the methods used will be described in a separate report.
- ADA samples may also be further tested for characterization of the ADA response.
- Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.
- For storage, re-use, and destruction of ADA samples see and [Appendix C](#).
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years from last subject last visit. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.
- Samples collected from participants in China will be destroyed or repatriated within one year of CSR.

8.9.1 Collection of Samples for Immunogenicity Assessments

Blood samples will be collected for measurement ADAs for rilvegostomig at the timepoints specified in the SoA ([Table 1](#)).

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the eCRF by the Investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected will be used to inform economic evaluations for payers and will include:

- Non-study-related unplanned and planned hospitalizations
- Duration of hospitalization
- Concomitant procedures such as surgery

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared and signed before the first participant is randomized to ensure approval before review of any potential treatment-revealing data. The SAP will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

The hypothesis of the primary endpoint with regards to the efficacy is:

- H_{01} : No OS difference between rilvegostomig plus chemotherapy and durvalumab plus chemotherapy in the $PD-L1 \geq 1\%$ population.
- H_{11} : OS difference between rilvegostomig plus chemotherapy and durvalumab plus chemotherapy in the $PD-L1 \geq 1\%$ population.

In addition, the hypotheses of interest with regards to the key secondary endpoint are:

- H_{02} : No OS difference between rilvegostomig plus chemotherapy and durvalumab plus chemotherapy in the ITT population.
- H_{12} : OS difference between rilvegostomig plus chemotherapy and durvalumab plus chemotherapy in the ITT population.
- H_{03} : No PFS difference between rilvegostomig plus chemotherapy and durvalumab plus chemotherapy in $PD-L1 \geq 1\%$ population.
- H_{13} : PFS difference between rilvegostomig plus chemotherapy and durvalumab plus chemotherapy in $PD-L1 \geq 1\%$ population.
- H_{04} : No PFS difference between rilvegostomig plus chemotherapy and durvalumab plus chemotherapy in the ITT population.
- H_{14} : PFS difference between rilvegostomig plus chemotherapy and durvalumab plus chemotherapy in the ITT population.

Multiplicity

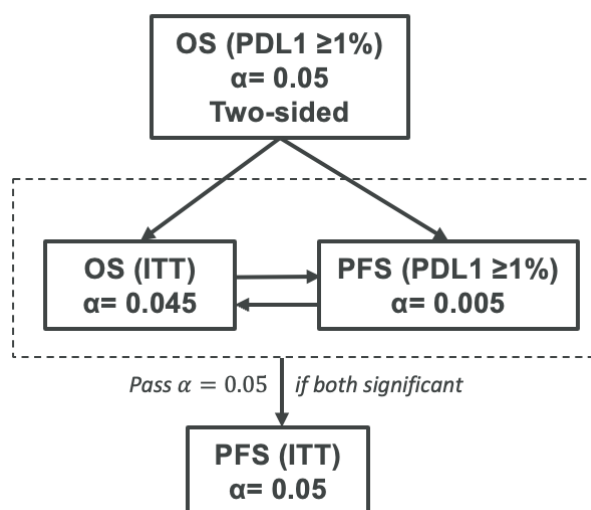
The MTP will define which significance levels should be applied to the interpretation of the raw p-values for the primary endpoint of OS in the $PD-L1 \geq 1\%$ population and the key secondary endpoints (OS in the ITT population, PFS in the $PD-L1 \geq 1\%$ population, and PFS in the ITT population) intended for label claims.

Hypotheses will be tested using an MTP with a graphic approach and alpha-recycling strategy (Burman et al 2009). With this approach, hypotheses will be tested in a pre-defined order:

- 1 Initially, $\alpha = 0.05$ (2-sided) is allocated to the primary endpoint of OS (PD-L1 $\geq 1\%$), which will be tested first.
- 2 When OS (PD-L1 $\geq 1\%$) is statistically significant, $\alpha = 0.045$ and $\alpha = 0.005$ will then be allocated to test the key secondary endpoints of OS (ITT) and PFS (PD-L1 $\geq 1\%$), respectively.
- 3 If PFS (PD-L1 $\geq 1\%$) is statistically significant while OS (ITT) is not, $\alpha = 0.005$ will be passed from PFS (PD-L1 $\geq 1\%$) to test OS (ITT) at $\alpha = 0.05$ level; Conversely, if OS (ITT) is statistically significant while PFS (PD-L1 $\geq 1\%$) is not, $\alpha = 0.045$ will be passed from OS (ITT) to test PFS (PD-L1 $\geq 1\%$) at $\alpha = 0.05$ level.
- 4 When both PFS (PD-L1 $\geq 1\%$) and OS (ITT) are statistically significant, $\alpha = 0.05$ will then be passed to test the key secondary endpoint of PFS (ITT).

To preserve the overall type 1 error (family-wise error rate) in the strong sense, an MTP including the primary and key secondary endpoints will be implemented. The MTP will be fully specified in the SAP. The MTP for the primary and key secondary endpoints is illustrated in Figure 3.

Figure 3 Multiple Testing Procedure



To ensure the strong control of overall family-wise error rate throughout multiple looks (interim and final analyses), the Multiple Testing in Group Sequential Trials Using Graphical Approaches (Maurer and Bretz 2013) will be applied, using the Lan-DeMets approach with the O'Brien-Fleming boundary for interim and final superiority boundaries. See further details

of the prespecified interim analyses in Section 9.5.

9.2 Sample Size Determination

Approximately 1572 patients will be screened to achieve 1100 randomized participants (1:1 to each arm). Based on a projected 75% prevalence of PD-L1 $\geq 1\%$, a minimum of 825 participants with PD-L1 $\geq 1\%$ will be enrolled to adequately power the primary endpoint. There is no planned cap on enrollment by PD-L1 status; thus, the total sample size may slightly exceed 1100. The expected recruitment period is approximately 21 months.

Note: ‘Screened’ means a participant’s, or their legally acceptable representative’s (where allowed per local regulations), agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomized/assigned in the study, are considered ‘screen failures’, unless otherwise specified by the protocol.

This study is sized to characterize the OS benefit of rilvegostomig plus chemotherapy vs durvalumab plus chemotherapy in both the PD-L1 $\geq 1\%$ and ITT populations. The study will be deemed positive for the primary population (PD-L1 $\geq 1\%$) if the OS analysis in this population is statistically significant; it will be further considered positive for the ITT population if statistical significance is also achieved in the OS analysis for ITT.

See Table 10 for a summary of the sample size and power calculations for the study.

Table 10 Summary of Sample Size and Power Calculation

Endpoint	Primary OS (in PD-L1 $\geq 1\%$)	Key secondary OS (in ITT)	Key secondary PFS (in PD-L1 $\geq 1\%$)	Key secondary PFS (in ITT)
Sample size	825	1100	825	1100
Effect size	Average HR = 0.75	Average HR = 0.78	Average HR = 0.75	Average HR = 0.78
Events (maturity)	620 OS (75%)	839 OS (76%)	729 (88%)	978 (89%)
Cumulative power (2-sided alpha)	94% ($\alpha = 0.05$)	94% ($\alpha = 0.045$) 95% ($\alpha = 0.05$)	86% ($\alpha = 0.005$) $\geq 95\%$ ($\alpha = 0.05$)	$\geq 95\%$ ($\alpha = 0.05$)
Looks (superiority)	2	2	2	2
Projected duration	43 months	43 months	43 months	43 months
Drop-out rate	5% annually	5% annually	10% annually	10% annually

OS in PD-L1 $\geq 1\%$ Population

The FA will be performed when approximately 620 OS events have occurred across experimental and control arms (75% maturity). For 75% maturity, 825 PD-L1 $\geq 1\%$

participants are to be randomized. A piecewise exponential survival distribution is assumed for the control arm with median OS = 13.3 months, where the hazard rate is 0.0521 (median = 13.3 months) before Month 13.3, and 0.0693 (median = 10 months) after Month 13.3. For the experimental arm (as compared to the control arm), a HR of 0.9 is assumed before Month 5, followed by a smaller HR thereafter (HR = 0.695). This results in an average HR of 0.75 at the FA, which is expected to occur around 43 months after the first participant is randomized. The study will have 94% cumulative power to demonstrate statistical significance at the 5% level (using a 2-sided test), allowing 1 interim analysis to be conducted once all participants are randomized and at an information fraction of approximately 86% of the target events (per the O'Brien and Fleming approach [[Lan and DeMets 1983](#)]). The smallest treatment difference that could be statistically significant at the FA is a HR of approximately 0.85, allowing for 1 interim analysis. With an approximately 21-month non-linear recruitment period and an exponential drop-out rate of 5% for both arms in the first 12 months, it is anticipated that these analyses will be performed 35 and 43 months after the first participant has been randomized.

OS in the ITT Population

The FA will be performed when approximately 839 OS events (projected) have occurred across experimental and control arms (76% maturity). For 76% maturity, 1100 participants are to be randomized (ITT). A piecewise exponential survival distribution is assumed for control arm with median OS = 12.8 months, where the hazard rate is 0.0542 (median = 12.8 months) before Month 12.8, and 0.0693 (median = 10 months) after Month 12.8. For the experimental arm (as compared to the control arm), a HR of 0.9 is assumed before Month 5, followed by a smaller HR thereafter (HR = 0.734). This results in an average HR of 0.78 at the FA, which is expected to occur around 43 months after the first participant is randomized. The study will have 94% cumulative power to demonstrate statistical significance at the 4.5% level (using a 2-sided test), or 95% power at the 5% level, allowing 1 interim analysis to be conducted once all participants are randomized and at an information fraction of approximately 86% of the target events (per the O'Brien and Fleming approach [[Lan and DeMets 1983](#)]). The smallest treatment difference that could be statistically significant at the FA is a HR of approximately 0.87, allowing for 1 interim analysis. With an approximately 21-month non-linear recruitment period and an exponential drop-out rate of 5% for both arms in the first 12 months, it is anticipated that these analyses will be performed 35 and 43 months after the first participant has been randomized.

See [Table 11](#) for a summary of the distribution assumptions for the OS endpoints.

Table 11 Overall Survival Distribution Assumptions

Starting at time (month)	Experimental arm hazard rate	Control arm hazard rate	Hazard ratio (experimental arm vs control arm)
OS in PD-L1 $\geq$ 1% population			
0	0.0469	0.0521	0.9
5	0.0362	0.0521	0.695
13.3	0.0482	0.0693	0.695
OS in ITT population			
0	0.0488	0.0542	0.9
5	0.0398	0.0542	0.734
12.8	0.0509	0.0693	0.734

PFS in PD-L1 $\geq$ 1% population

The FA will be performed when approximately 729 PFS events (projected) have occurred across experimental and control arms (88% maturity). For 88% maturity, 825 PD-L1 $\geq$ 1% participants are to be randomized. A piecewise exponential survival distribution is assumed for control arm with median PFS = 7.2 months, where the hazard rate is 0.0963 (median = 7.2 months) before Month 7.2, and 0.1386 (median = 5 months) after Month 7.2. For the experimental arm (as compared to the control arm), a HR of 0.9 is assumed before Month 3, followed by a smaller HR thereafter (HR = 0.697). This results in an average HR of 0.75 at the FA, which is expected to occur around 43 months after the first participant is randomized. The study will have 86% cumulative power to demonstrate statistical significance at the 0.5% level (using a 2-sided test), or $\geq$ 95% power at the 5% level, allowing 1 interim analysis to be conducted once all participants are randomized and at an information fraction of approximately 94% of the target events (per the O'Brien and Fleming approach [Lan and DeMets 1983]). The smallest treatment difference that could be statistically significant at the FA is a HR of approximately 0.86, allowing for 1 interim analysis. With an approximately 21-month non-linear recruitment period and an exponential drop-out rate of 10% for both arms in the first 12 months, it is anticipated that these analyses will be performed 35 and 43 months after the first participant has been randomized.

PFS in the ITT population

The FA will be performed when approximately 978 PFS events (projected) have occurred across experimental and control arms (89% maturity). For 89% maturity, 1100 participants are to be randomized (ITT). A piecewise exponential survival distribution is assumed for control arm with median PFS = 7.2 months, where the hazard rate is 0.0963 (median = 7.2 months) before Month 7.2, and 0.1386 (median = 5 months) after Month 7.2. For the experimental arm

(as compared to the control arm), a HR of 0.9 is assumed before Month 3, followed by a smaller HR thereafter (HR = 0.737). This results in an average HR of 0.78 at the FA, which is expected to occur around 43 months after the first participant is randomized. The study will have $\geq 95\%$ power at the 5% level, allowing 1 interim analysis to be conducted once all participants are randomized and at an information fraction of approximately 94% of the target events (per the O'Brien and Fleming approach [Lan and DeMets 1983]). The smallest treatment difference that could be statistically significant at the FA is a HR of approximately 0.88, allowing for 1 interim analysis. With an approximately 21-month non-linear recruitment period and an exponential drop-out rate of 10% for both arms in the first 12 months, it is anticipated that these analyses will be performed 35 and 43 months after the first participant has been randomized.

9.3 Populations for Analyses

The populations for analysis are defined in [Table 12](#).

Table 12 Populations for Analysis

Population/analysis set	Description
Screened	All participants who sign the ICF.
FAS (ITT)	All participants who are randomized in the study. The FAS will be used for all the efficacy analyses including PROs. Treatment groups will be compared on the basis of randomized study intervention, regardless of the treatment actually received. Participants who were randomized but did not subsequently receive study intervention are included in the analysis in the treatment group to which they were randomized.
PD-L1 $\geq 1\%$	All PD-L1 $\geq 1\%$ participants who are randomized in the study. The PD-L1 $\geq 1\%$ analysis set will be used for all the efficacy analyses including PROs. Treatment groups will be compared on the basis of randomized study intervention, regardless of the treatment actually received. Participants who were randomized but did not subsequently receive study intervention are included in the analysis in the treatment group to which they were randomized.
Safety	The safety analysis set consists of all randomized participants who received any amount of any study treatment. Safety data will be summarized using the safety analysis set according to the actual treatment received.
PK	The PK analysis set consists of all participants who received at least one dose of study intervention for whom there is at least one reportable PK concentration.
ADA evaluable	All participants in the safety analysis set who received at least one dose of rilvegostomig with a reportable ADA result at any time, either baseline or post-baseline, according to the actual treatment received.

9.4 Statistical Analyses

9.4.1 General Considerations

The below general principles will be followed:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum. For log-transformed data it is more appropriate to present geometric mean, CV, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group. Overall totals will be calculated for baseline summaries only.
- In general, for efficacy the last observed measurement prior to randomization will be considered the baseline measurement. For RECIST 1.1 tumor assessment, baseline must be no more than 28 days before the date of randomization. If a baseline radiological tumor assessment is performed more than 28 days before randomization, then it will be reported as a protocol deviation, but will still be included as baseline.
- In general, stratified analyses (eg, stratified log-rank test, stratified Cox proportional hazards model, CMH test) for efficacy endpoints in PD-L1 $\geq 1\%$ population will use 3 stratification factors (dropping PD-L1 status); while the stratified analyses for efficacy endpoints in the ITT population will use 3 stratification factors (dropping region).
- The method for handling missing data, whenever applicable, will be detailed in the SAP.

Depending on the extent of any impact, summaries of data relating to civil crisis, natural disaster, or public health crisis may be generated. More details will be provided in the SAP.

9.4.2 Efficacy

9.4.2.1 Calculation or Derivation of Tumor Response Variables

Investigator RECIST 1.1-based Assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a participant discontinues study intervention or receives another anticancer therapy.

At each visit, participants will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, PD, or NE depending on the status of their disease compared with baseline and previous assessments. The tumor response endpoints (PFS, ORR, best observed response, and DoR) will then be derived from the scan dates and overall visit responses.

BICR

A BICR of radiological scans will be performed on all participants as a sensitivity analysis to confirm the robustness of the Investigator-assessed PFS, ORR, and DoR endpoints.

All images will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each participant, the BICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). If a participant has had a tumor assessment that cannot be evaluated, then the participant will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints (eg, PFS, ORR, DoR) will then be derived from the scan dates and overall visit responses.

Further details of the BICR will be documented in an Independent Review Charter.

9.4.2.2 Primary Endpoint

9.4.2.2.1 Overall Survival in the PD-L1 $\geq$ 1% Population

OS is defined as the time from the date of randomization until death due to any cause. The analysis will include all randomized participants as randomized. All deaths will be included, regardless of whether the participant withdraws from therapy or receives another anticancer therapy.

Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Analysis Methods

OS in the PD-L1 $\geq$ 1% population will be analyzed using a log-rank test stratified by disease status, primary tumor location, and geographical region. The HR together with its 95% CI and p-value will be presented (a HR less than one will favor the experimental arm). The HR and CI will be estimated from a stratified Cox proportional hazards model (with ties = Efron), and the CI will be calculated using a profile likelihood approach. If there are insufficient events per strata, the strata will be pooled following a pooling strategy that will be prespecified in the SAP.

The stratification variables will be defined according to data from the IRT.

Kaplan-Meier plots of OS will be presented by treatment group. Summaries of the number and percentage of participants experiencing an OS event will be provided along with median OS for each treatment. The proportion of participants alive at 6-monthly intervals from randomization will be summarized by treatment group.

As a lack of proportionality is expected, a three-component stratified MaxCombo test may be conducted as a supplementary analysis, using the same stratification factors as the primary analysis. Further supplementary and sensitivity analyses to explore the robustness of the primary OS endpoint will be documented in the SAP.

Subgroup Analysis

Subgroup analyses will be conducted, comparing OS (PD-L1 $\geq 1\%$ population) between rilvegostomig plus chemotherapy and durvalumab plus chemotherapy. Details of subgroup analyses will be provided in the SAP.

9.4.2.3 Key Secondary Endpoints

9.4.2.3.1 Overall Survival in the ITT Population

OS in the ITT population will follow the same definitions for survival and censoring rules as for OS in the PD-L1 $\geq 1\%$ population.

Analysis Methods

OS in the ITT population and in the PD-L1 $\geq 1\%$ population will be analyzed using the same methodology. The effect of rilvegostomig plus chemotherapy vs durvalumab plus chemotherapy will be analyzed using a stratified log-rank test, and estimated by the HR together with its corresponding CI. Kaplan-Meier plots will be presented by treatment group. The stratification factors for OS (ITT) are PD-L1 status, disease status, and primary tumor location.

Subgroup Analysis

Subgroup analyses will be conducted, comparing OS (ITT) between rilvegostomig plus chemotherapy and durvalumab plus chemotherapy. Details of subgroup analyses will be provided in the SAP.

9.4.2.3.2 Progression-free Survival in PD-L1 $\geq 1\%$ Population and in ITT Population

PFS will be defined as the time from the date of randomization until the date of objective disease progression per RECIST 1.1 as assessed by the Investigator at the local site or death (by any cause in the absence of progression) (ie, date of event or censoring – date of randomization + 1). The analysis will include all randomized participants. All events will be included regardless of whether the participant withdraws from therapy, receives another anticancer therapy or clinically progresses prior to RECIST 1.1 progression.

Participants who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the participant progresses or dies immediately after 2 or more consecutive missed

visits, the participant will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. (Note: NE visit is not considered as missed visit).

If the participant has no evaluable visits or does not have baseline data, they will be censored at Day 1, unless they die within 2 visits of baseline (12 weeks plus one week allowing for a late assessment within the visit window).

The PFS time will always be derived based on scan/assessment dates and not visit dates.

RECIST 1.1 assessments/scans contributing toward a particular visit may be performed on different dates. The following rules will be applied:

- For Investigator assessments, the date of progression will be determined based on the earliest RECIST 1.1 assessment/scan dates of the component that indicates progression.
- For BICR assessments, the date of progression will be determined based on the earliest dates of the component that triggered the progression on the first set of scans that indicates progression for the adjudicated reviewer selecting PD, or of either reviewer where both reviewers select PD as a time point response, and there is no adjudication for central review (BICR) data.
- When censoring a participant for PFS, the participant will be censored at the latest scan dates contributing to a particular overall visit assessment.

Analysis Methods

The key secondary PFS will be based on the Investigator-recorded assessment of disease progression by RECIST 1.1.

PFS will be analyzed using the same methodology specified for OS (see Section 9.4.2.2.1 and Section 9.4.2.3.1). The effect of rilvegostomig plus chemotherapy vs durvalumab plus chemotherapy will be analyzed using a stratified log-rank test, and estimated by the HR together with its corresponding CI. Kaplan-Meier plots will be presented by treatment group. The stratification factors for PFS (PD-L1 $\geq 1\%$) are disease status, primary tumor location, and geographical region. The stratification factors for PFS (ITT) are PD-L1 status, disease status, and primary tumor location.

PFS as defined by BICR assessment will be conducted as a supplementary/sensitivity analysis. Further supplementary and sensitivity analyses to explore the robustness of the key secondary PFS endpoint will be documented in the SAP.

Subgroup Analysis

Subgroup analyses will be conducted, comparing PFS between rilvegostomig plus chemotherapy and durvalumab plus chemotherapy.

9.4.2.4 Secondary Endpoints

9.4.2.4.1 Objective Response Rate

ORR is defined as the proportion of participants who have a confirmed CR or confirmed PR, as determined by the Investigator at local site per RECIST 1.1.

The analysis will include all randomized participants as randomized with measurable disease at baseline.

Data obtained from randomization up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Participants who discontinue randomized treatment without progression, receive a subsequent anticancer therapy and then respond will be included as non-responders in the ORR (note that for this analysis palliative radiotherapy is not considered a subsequent anticancer therapy). Participants without an evaluable post-baseline assessment will be included as non-responders. Participants without a baseline assessment will also be included as non-responders unless the participant has a CR at the first post-baseline assessment that is confirmed at the next assessment (confirmed response).

ORR is based on the Investigator at local site data and using all scans regardless of whether they were scheduled or not.

Analysis Methods

ORR will be analyzed in PD-L1 $\geq 1\%$ population and ITT population, using the CMH test stratified using the same stratification factors as the primary and key secondary endpoints in the corresponding population. The p-value from the CMH test is presented along with the stratified relative risk (rilvegostomig plus chemotherapy vs durvalumab plus chemotherapy) and common risk difference expressed as a percentage and corresponding 95% CI using the Miettinen-Nurminen approach ([Miettinen and Nurminen 1985](#)).

The analyses of ORR outlined based on Investigator assessment will be repeated based on the BICR assessment as a supplementary/sensitivity analysis.

9.4.2.4.2 Duration of Response

DoR will be defined as the time from the date of first documented confirmed response until the date of the first documentation of objective disease progression per RECIST 1.1 as assessed by Investigator and derived from the raw tumor data or death by any cause in the absence of disease progression (ie, date of PFS event - date of first response + 1).

The analysis will include all randomized participants who have a confirmed response, as randomized. All events will be included regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1

progression.

Analysis Methods

DoR will be analyzed by summary statistics. Kaplan-Meier estimates will be presented graphically by treatment arm.

The analyses of DoR outlined based on Investigator assessment will be repeated based on the BICR assessment as a supplementary/sensitivity analysis.

9.4.2.4.3 Time to Second Progression or Death

PFS2 will be defined as the time from randomization to the earliest of progression event (following the initial Investigator-assessed objective progression) after first subsequent therapy, or death from any cause, whichever occurs first (ie, date of PFS2 event or censoring – date of randomization + 1), where the first objective progression includes progression occurring after 2 missed visits. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice.

The comparison will include all randomized participants. All events will be included, regardless of whether the participant withdraws from subsequent therapy and regardless of missed visits.

Analysis Methods

PFS2 will be analyzed in PD-L1 $\geq 1\%$ population and ITT population, using the same methodology specified for PFS. The effect of rilvegostomig plus chemotherapy vs durvalumab plus chemotherapy will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment group.

9.4.2.4.4 Clinical Outcome Assessments

All COA efficacy analyses will be based on FAS or a subset of FAS, if not otherwise stated. Tolerability-related analyses will use the safety analysis set.

COA endpoints will be scored according to the relevant scoring manuals.

Full detail of COA endpoint derivation will be documented in the SAP along with the analysis methodology.

9.4.2.4.5 ECOG Performance Status

Full details of the analysis of ECOG performance status will be provided in the SAP.

9.4.2.4.6 Medical Resource Utilization and Health Economics

Full details of the analysis of endpoints to assess the potential impact of the disease and

treatment on health care resource use will be provided in the SAP.

9.4.2.5 Tertiary/Exploratory Endpoint(s)

Full details of the analysis of exploratory endpoints will be provided in the SAP.

Data collected from the digital solution for remote monitoring of digestive symptoms, including usage data, will be analyzed to evaluate the performance of the solution including engagement, validity and utility and inform future technology and analytical improvement. A digital analysis plan will be developed to include the details for data access, data transfer, and data analysis.

9.4.3 Safety

Safety analyses will be performed using the safety analysis set. Safety data will be presented using descriptive statistics and will not be formally tested, unless otherwise specified.

Baseline

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of study intervention. Details are described in the SAP.

9.4.3.1 Adverse Events

AEs will be coded using the most recent version of MedDRA released for execution at AstraZeneca/designee.

AEs will be presented for each treatment arm by System Organ Class and/or Preferred Term covering number and percentage of participants reporting at least one event and number of events where appropriate.

Treatment-emergent AEs and post-treatment AEs will be presented separately. The following AEs are considered treatment-emergent:

- AEs with an onset date on or after first dose of study treatment and within 90 days after last dose of study treatment or up to the day prior to start of subsequent therapy, whichever comes first.
- Worsening of pre-existing AEs on or after first dose of study treatment and within 90 days after last dose of study treatment or up to the day prior to start of subsequent therapy, whichever comes first.

An overview of AEs will be presented for each treatment arm for the number and percentage of participants with any AE, AEs with outcome of death, SAEs, AEs leading to discontinuation of study intervention, AEs leading to study intervention dose interruptions, and AEs leading to study intervention dose reduction as well as the number of individual occurrences in those categories.

Separate AE tables will be provided taking into consideration relationship as assessed by the Investigator, common terminology criteria grading, seriousness, death, and events leading to discontinuation of study intervention as well as other action taken related to study intervention, AESIs, and other significant AEs.

An additional table will present the number and percentage of participants with most common AEs. Most common (eg, frequency of $> x\%$, $\geq x\%$) will be defined in the SAP.

Key participant information will be presented for participants with AEs with outcome of death, SAEs, and AEs leading to discontinuation of study intervention.

An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

9.4.3.2 Other Safety Endpoint(s)

Other safety data will be assessed in terms of physical examinations, clinical chemistry, hematology, urinalysis, laboratory findings, vital signs, and ECGs. Exposure to study treatment will be summarized. Time on study, dose interruption, dose delays and dose reductions will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.4.4 Other Analyses

9.4.4.1 Pharmacokinetics and Pharmacodynamics

Details of PK, population PK, pharmacodynamic, PK/pharmacodynamic relationships, and/or exposure-response/safety analyses will be described in the SAP. If performed, population PK analysis and pharmacodynamic analyses will be presented separately from the main CSR (if applicable).

Only participants who received at least one dose of rilvegostomig and provided at least one post-treatment sample will be evaluated. Participants with major protocol deviations including changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PK may be excluded from the PK analysis set.

9.4.4.2 Biomarkers

Biomarker status will be assessed for participants in each cohort according to pre-specified criteria that may be detailed in the SAP. Biomarker exploratory analyses may be described in a separate analysis plan and may be reported outside the CSR in a separate report. The results of this biomarker assessment will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker assessment may be pooled with biomarker data from other studies to generate hypotheses to be tested in future research.

9.4.4.3 Optional Exploratory Genetic Sample

Data will be reported outside the CSR (please see [Appendix D](#)).

9.4.4.4 Immunogenicity Data

Full details of the analysis of immunogenicity data will be provided in the SAP.

9.5 Interim Analyses

There are 3 planned DCOs for this study:

- **DCO1:** Futility IA of OS in the PD-L1 $\geq 1\%$ population. This will occur when approximately 258 OS events in the PD-L1 $\geq 1\%$ population have been reached across both treatment arms.
- **DCO2:** Superiority IA of OS and PFS in the PD-L1 $\geq 1\%$ and ITT populations. This will occur when approximately 532 OS events in the PD-L1 $\geq 1\%$ population have been reached across both treatment arms.
- **DCO3:** FA of OS and PFS in the PD-L1 $\geq 1\%$ and ITT populations. This will occur when approximately 620 OS events in the PD-L1 $\geq 1\%$ population have been reached across both treatment arms.

Futility Interim Analysis (DCO1)

This study will include a single IA for futility on the primary endpoint of OS in the PD-L1 $\geq 1\%$ population. The IA will occur when approximately 258 OS events have occurred (41% maturity) across the treatment and control arms. It is anticipated that this analysis will be performed approximately 21 months after the first participant is randomized. At the planned DCO, an observed HR greater than 1.00 for OS (PD-L1 $\geq 1\%$) is expected to result in a recommendation to stop the study for futility.

If in truth, there is no difference between the treatment and control arms (HR = 1), there is a 50% probability that this study will stop early for futility. If the true OS average HR is 0.75, there is a 3% probability that this study will be terminated incorrectly for futility.

Details of this analysis will be included in the SAP and DMC Charter. Futility in this study will be considered non-binding. A DMC will review the futility outcomes and provide a recommendation for whether the study should continue.

Superiority Interim and Final Analyses (DCO2 and DCO3)

DCO2 will be an IA and DCO3 will be the FA. The analysis DCOs will occur after recruitment is completed and at the prespecified total number of OS events, whichever is later.

At DCO2, a superiority IA will be performed for OS in both the PD-L1 $\geq 1\%$ and ITT

populations. This will be triggered by approximately 532 OS events in $PD-L1 \geq 1\%$, at an information fraction of approximately 86% of the final number of OS events, and it is projected to observe 721 OS events in ITT. At the same DCO, PFS will also be analyzed in both the $PD-L1 \geq 1\%$ and ITT populations.

The study will use the method of Multiple Testing in Group Sequential Trials Using Graphical Approaches ([Maurer and Bretz 2013](#)) for alpha spending with multiple hypotheses and IA. The overall alpha allocation and recycling among hypotheses will follow the MTP described in [Figure 3](#). Given the overall alpha level by the MTP, the Lan-DeMets spending function that approximates an O'Brien and Fleming approach ([Lan and DeMets 1983](#)) will be used for alpha spending across the IAs and FA for each endpoint (OS and PFS). Note: that the actual alpha spent will be adjusted according to the observed event numbers and information fractions.

The criterion for superiority is a statistically significant improvement in OS at the IA or FA. Detailed operating characteristics for the IA and FA for each endpoint (OS and PFS) are provided in [Table 13](#). If the interim results do not meet the criterion of stopping for superiority, then follow-up will continue until the FA. If an endpoint is tested significant at the interim, it will be considered the primary analysis for that endpoint (ie, not expected to be formally tested again thereafter).

For the IA, the DMC will review unblinded interim data and advise whether the interim boundaries (demonstrated in [Table 13](#)) are met.

Table 13 **Planned Superiority Interim and Final Analyses**

	Interim analysis (superiority) at Month ~35						Final analysis at Month ~43					
Endpoint	OS (PD-L1 ≥ 1%)	OS (ITT)		PFS (PD-L1 ≥ 1%)		PFS (ITT)	OS (PD-L1 ≥ 1%)	OS (ITT)		PFS (PD-L1 ≥ 1%)		PFS (ITT)
Events (maturity)	532 (65%)	721 (65%)		685 (83%)		921 (84%)	620 (75%)	839 (76%)		729 (88%)		978 (89%)
Information fraction	0.86	0.86		0.94		0.94	1	1		1		1
Alpha	0.05	0.045	0.05	0.005	0.05	0.05	0.05	0.045	0.05	0.005	0.05	0.05
P-value boundary	0.0310	0.0276	0.0312	0.0036	0.0416	0.0418	0.0412	0.0372	0.0412	0.0040	0.0392	0.0392
Power	85%	84%	86%	81%	≥ 95%	≥ 95%	94%	94%	95%	86%	≥ 95%	≥ 95%
HR boundary	0.83	0.85	0.85	0.8	0.86	0.87	0.85	0.87	0.87	0.81	0.86	0.88

The observed number of events may not match the planned number of events; the critical boundaries will be updated based on the actual number of observed events using the prespecified α -spending functions. Different alpha levels depend on whether the alpha can be recycled.

9.6 Data Monitoring Committee

For details on the DMC, refer to Appendix [A 6](#).

A DMC comprised of independent experts will be convened and will meet on a regular basis (as outlined in the DMC Charter) to review safety data and make recommendations to continue, amend, or stop the study based on safety findings, efficacy, or for futility. The DMC will review unblinded safety data.

The DMC will convene and meet initially once at least 40 participants (approximately 20 participants per study arm) have received treatment and have had at least 6 weeks of follow-up, or once at least 6 months has elapsed from the first randomized participant, whichever occurs first. This will be considered the DCO date for the first DMC meeting. The DMC will meet approximately every 6 months thereafter.

In addition, the DMC will review efficacy data. For the IA (DCO1 and DCO2), the DMC will review unblinded efficacy data and inform AstraZeneca whether the futility criteria or superiority interim boundaries specified in Section [9.5](#) are met.

Full details of the DMC procedures, processes, and interim analyses can be found in the DMC Charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH GCP Guidelines
 - Applicable laws and regulations
- The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research, ISO-14155 for clinical device (if applicable), European In Vitro Diagnostic Regulation 2017/746 for in vitro diagnostic medical device research (in countries where applicable) and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All

Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), European In Vitro Diagnostic Regulation 2017/746 for in vitro diagnostic medical device research (in countries where applicable), and all other applicable local regulations.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

A ‘Serious Breach’ means any deviation of the approved version of the protocol or Good Clinical Practice (GCP) that is likely to affect the safety, rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial.

All parties (Sponsor, Service Provider, Investigator Site Staff) involved in the conduct of the clinical trial:

- are responsible for promptly identifying and documenting any actual or potential serious breach.
- should have a process in place to ensure that they are able to identify the occurrence of a (actual/potential) serious breach.
- should report to AstraZeneca (or delegated party) without delay, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

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

A 3 Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study including the risks and benefits, to the participant (or their legally authorized representative if applicable per local regulation) and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants (or their legally authorized representative if applicable per local regulation) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant (or the participant's legally authorized representative if applicable per local regulation).

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional Human Biological Samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use, and may withdraw their consent at any time and for any reason during the retention period.

A 4 Recruitment Strategy

Patients are expected to be recruited through clinical chart review, existing patient lists, referrals, advertisement, etc. Details of recruitment strategy and tools will be provided in a separate document.

A 5 Data Protection

- Participants will be assigned a unique identifier by Trusted Third Party contracted by the Sponsor or by a Principal Investigator. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that their personal study-related and coded (pseudonymized) data will be used by AstraZeneca in accordance with local data protection law. The purposes of use and the level of disclosure and use of their data (including the legal basis AstraZeneca relies upon processing their data, where required) must also be explained to the participant in the informed consent.
- The participants must be informed that their medical records may be examined by Quality Assurance auditors or other authorized personnel appointed by AstraZeneca, who are independent of the staff involved in the study in accordance with current Quality Assurance Standard Operating Procedures and Quality Assurance Audit Schedule; by appropriate IRB/IEC members; and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected and used to develop the drug/investigational product, get permission to introduce and keep it on the market, monitor its safety and get it reimbursed eg, by governments eg, throughout the drug development program, which includes related research activities necessary for this drug development program, including to: understand how the study drug(s) and similar drugs work in the body (eg, evaluate the study drug mode of action, alone or in combination with other study drugs); better understand the studied disease and associated health problems; develop diagnostic tests for the disease; learn from past studies to plan new studies or improve scientific analysis methods; publish research results in scientific journals or use them for educational purposes. AstraZeneca will only collect and use the minimum amount of personal data to support the research and safety monitoring activities within the drug development program and will not make personal data available to anyone (including internal staff) who is not authorized or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be further pseudonymized and/or anonymized.
- Appropriate safeguards will be implemented to protect coded data during and after the study that include:
 - Access to the coded data will be restricted and monitored, and limited to specific individuals subject to confidentiality obligations (including the obligation to not attempt to re-identify individuals/decode the clinical data).
 - The coded data will be protected with security measures to avoid data alteration, loss, and unauthorized accesses and further de-identification techniques may be applied; as well as other high-standard technical security means such as encryption.
 - A data protection impact assessment (DPIA), where required, will apply to identify and mitigate privacy risks, if any, associated with each scientific research.
 - The coded data will not be shared for direct marketing purposes or other purposes that are not legal duties or are not related to scientific research purposes of the

study. In particular, it will not be used to make decisions about future services available to the participant, such as insurance.

- Participants are also protected legally by the following means, if the coded data will be shared with third parties – other companies within the Sponsor group; Service providers; Research partners, who may be located in countries which do not offer the same level of protection as the participants country for which the participant will be informed in the ICF:
 - Within the Sponsor group, the participants' coded data are protected by Binding Corporate Rules (BCR). More information about the Sponsor's BCR are provided here: www.astrazenecabindingcorporaterules.com, or by other contractual arrangements as may be required under local law.
 - In all other cases, the participants' coded data is protected by contractual arrangements, Codes of Conduct, or certifications that set the rules for personal data protection to those available in the participant's country or other alternatives set forth in the law, as well as any supplementary technical and organizational measures that may results out of conducted transfer impact assessments, where required.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller¹ for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that Investigators that work with AstraZeneca have controls in place to protect participant data privacy.

¹ The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission.

The Investigator should have a process in place to ensure that:

- Allow site staff or service providers delegated by the Investigator/institution to identify the occurrence of (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- Have taken all necessary steps to avoid personal data breaches and
- Have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- Where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- Where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal Data Breach to participants:

- Notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.

- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

Unless previously specified, the biomarker data will have unknown clinical significance and AstraZeneca will not provide biomarker assessment results to participants, their family members, any insurance company, any employer, a clinical study Investigator, a general physician, or any other third party, unless required to do so by law.

The participant's samples will not be used for any purpose other than those described in the study protocol.

A 6 Committees Structure

A Trial Steering Committee that includes Principal Investigators for this study and that may include Principal Investigators from the other pivotal studies will provide:

- Advice on any aspect of the study design or conduct based on requests from AstraZeneca
- Review relevant research (completed, ongoing, and pending) which may impact upon the study, assure consistency across the entire rilvegostomig pivotal program, and to support the study team with interpretation of study outcomes.

A Steering Committee Charter will define the primary responsibilities of the steering committee, its members, and the purpose and timing of meetings.

A DMC will be established in order to assess the progress of the clinical study at regular intervals. This will include reviewing unblinded safety and tolerability data.

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by

AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the protocol and letters to Investigators.

A 7 Dissemination of Clinical Study Data

Study overall results, both technical and written in lay language (Trial Results Summary, also known as Lay Language Summary of overall study results), will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, to ensure scientific integrity, completeness, robustness, and reliability of data published results.

A description of this clinical study will be available on www.astrazenecaclinicaltrials.com, <http://www.clinicaltrials.gov> and <https://euclinicaltrials.eu/> as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 8 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined in the Quality Risk Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Oversight Plan(s).

- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform source data verification for sample of sites, participants and data, which will be selected in a risk-based fashion as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorized site personnel are verifiable from source documents.
- Study monitors will perform ongoing source data review as per the Monitoring Plan(s) to confirm that data in source are accurate and complete; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 9 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in source data acknowledgment or monitoring guidelines. All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 10 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants (first site activated).

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 11 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to AstraZeneca

before submission. This allows AstraZeneca to protect proprietary information and to provide comments.

- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of AEs

An AE is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a patient or clinical study participant administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of SAEs

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-SAE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (ie, it is *not* the tumor for which entry into the study is a criterion and that is being treated by the study intervention and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter’s transformation of B-cell chronic lymphocytic leukemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumor.

Life-threatening

‘Life-threatening’ means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the medicinal product would result in the participant’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Important medical events:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization

- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

The grading scales found in the revised NCI CTCAE version 5.0 will be utilized for all events, unless otherwise stated in the TMGs. This version will be used for the duration of the study. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (<http://ctep.cancer.gov>). The applicable version of CTCAE should be described clearly.

B 3 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the medicinal product.

- Time Course. Exposure to suspect drug. Has the participant received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of ‘related’ is made if following a review of the relevant data, there is evidence for a ‘reasonable possibility’ of a causal relationship for the individual case. The expression ‘reasonable possibility’ of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as ‘not related’.

Causal relationship in cases where the DUS has deteriorated due to lack of effect should be classified as ‘no reasonable possibility’.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca AxMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant

- Drug not administered as indicated, eg, wrong route, or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca AxMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study).
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca AxMP for medicinal purposes outside of the authorized product information, or

for unauthorized IMPs or AstraZeneca AxMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected human biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing and tracking information related to the samples whilst at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used, disposed of or until further shipment, and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca team for the remainder of the sample life cycle.

All appropriately consented samples will be retained for up to a maximum of 15 years from last subject last visit.

Samples collected from participants in China will be destroyed or repatriated within one year of the CSR.

If required, AstraZeneca will ensure that remaining human biological tissue samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Human Biological Samples

If a participant withdraws consent specifically to the subsequent use of donated human biological samples, applicable samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research. The participant will be presented with the option to opt out of the subsequent use of the donated samples during the withdrawal process. If the participant decides to opt out, then the donated samples will be disposed of. If the participant withdraws consent without opting out for the subsequent use of the donated samples, then the samples will be used per protocol.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures the participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

C 3 International Air Transport Association Guidance Document 62nd Edition

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

The International Air Transport Association (IATA) (<https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx>) classifies infectious substances into 3 categories: Category A, Category B, or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN 3373 and IATA 650

Exempt Substances are substances which do not contain infectious substances, or substances which are unlikely to cause disease in humans or animals, are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
(<https://www.iata.org/contentassets/b08040a138dc4442a4f066e6fb99fe2a/dgr-66-en-pi650.pdf>).
- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content.

Appendix D Optional Genomics Initiative Research

D 1 Use/Analysis of DNA and Blood Derivatives

- AstraZeneca intends to collect and store DNA and blood derivatives (such as plasma and serum) for genomic and comprehensive omics characterization research (such as protein, nucleotides, and other entities in circulation), which may include metabolomic, proteomic and lipidomic analysis, to explore how genomic and time-point omics variations may affect clinical parameters, risk and prognosis of diseases, and the response to medicinal product.
- This genomic and multi-omics research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care, and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA and multi-omics analysis from consenting participants.
- This optional genomic and multi-omics research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of these genetic and multi-omics analyses may be reported in a separate study summary.
- AstraZeneca will store the DNA and blood derivative samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Multi-omics Research Plan and Procedures

Selection of Multi-omics Research Population

All participants will be asked to participate in this genomic and multi-omics research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genomic and multi-omics research, participants must fulfill all of the inclusion criteria described in the main body of the protocol and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

Exclusion from this genomic and multi-omics research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant

- Transfusion of non -leukocyte depleted blood or blood component within 120 days of genetic sample collection
- Healthy volunteer's samples will not be collected for the Genomics Initiative.

Withdrawal of Consent for Multi-omics Research

- Participants may withdraw from this genomic and multi-omics research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main protocol.

Collection of Samples for Multi-omics Research

- The blood samples for this genomic and multi-omics research will be obtained from the participants pre-dose at the first dosing visit. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the samples are not drawn at the first dosing visit, it may be taken at any visit until the last study visit
- During this study, only one sample should be collected for each of the analyses listed; ie, one for genetics and one for multi-omics research.

Coding and Storage of DNA and Multi-omics Samples

The processes adopted for the coding and storage of samples for genomic and multi-omics analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years from the date of last subject last visit, after which they will be destroyed. DNA and blood derivatives are a finite resource that will be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

- An additional second code will be assigned to the samples either before or at the time of sample processing, replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca analysis laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA or blood derivatives).
- The link between the participant enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant samples for analysis, facilitate correlation of genotypic, or multi-omics results with

clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genomics, and multi-omics research component, are outlined in [Appendix A](#).

Informed Consent

- The genomic and multi-omics component of this study are optional and the participant may participate in other components of the main study without participating in this multi-omics component. To participate in the genomic and multi-omics component of the study the participant must sign and date both the consent form for the main study and the Optional Genomics Initiative Research Information and Consent Form. Copies of both signed and dated consent forms must be given to the participant and the originals filed at the study center. The Principal Investigator(s) is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdraw from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual sequencing, genotype, or multi-omics results to participants, any insurance company, any employer, their family members, or general physician unless required to do so by law. Extra precautions are taken to preserve confidentiality and prevent genomic and multi-omics data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a participant's identity and also have access to his or her genomic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genomic files would remain physically separate.

Data Management

- Any genomic or multi-omics data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genomics and multi-omics research with other researchers, such as hospitals, academic organizations, or drug- or health-related companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related

research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.

- Some or all of the clinical datasets from the main study may be merged with the multi-omics data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law cases and Hy's Law cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the study the Investigator should remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential Hy's Law criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, potential Hy's Law criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the IMP.

The Investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law

AST or ALT $\geq 3 \times \text{ULN}$ **together with** TBL $\geq 2 \times \text{ULN}$ at any point during the study following the start of study intervention irrespective of an increase in ALP.

Hy's Law

AST or ALT $\geq 3 \times \text{ULN}$ **together with** TBL $\geq 2 \times \text{ULN}$, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For potential Hy's Law and Hy's Law the elevation in transaminases must precede or be

coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- $ALT \geq 3 \times ULN$
- $AST \geq 3 \times ULN$
- $TBL \geq 2 \times ULN$

Local Laboratories Being Used:

The Investigator will without delay review each new laboratory report and, if the identification criteria are met, will:

- Notify the AstraZeneca representative.
- Determine whether the participant meets potential Hy's Law criteria (see Appendix [E 2](#) for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet potential Hy's Law criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet potential Hy's Law criteria the Investigator will:

- Determine whether potential Hy's Law criteria were met at any study visit prior to starting study intervention (see Appendix [E 6](#))
- Notify the AstraZeneca representative who will then inform the central Study Team.

- Within one day of potential Hy's Law criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the protocol process for SAE reporting.
- For participants who met potential Hy's Law criteria prior to starting IMP, the Investigator is not required to submit a potential Hy's Law SAE unless there is a significant change[#] in the participant's condition.
- The Study Clinical Lead will contact the Investigator, to provide guidance, discuss, and agree an approach for the study participant's follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
 - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
 - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Clinical Lead.
 - Complete the 3 Liver eCRF Modules as information becomes available.

[#] A **'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Clinical Lead if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this appendix should be followed for all cases where potential Hy's Law criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the Study Clinical Lead will contact the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than drug-induced liver injury caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date potential Hy's Law criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a

determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: Update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term, causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
 - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
 - As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to protocol process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following protocol process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions Required When Potential Hy's Law Criteria are met Before and After Starting Study Intervention

This appendix is applicable to participants with liver metastases who meet potential Hy's Law criteria on study intervention, having previously met potential Hy's Law criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of potential Hy's Law criteria being met the Investigator will determine if there has been a **significant change** in the participant's condition compared with the last visit where potential Hy's Law criteria were met

- If there is no significant change no action is required.
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix E 4.2.

E 7 **Actions Required for Repeat Episodes of Potential Hy's Law**

This section is applicable when a participant meets potential Hy's Law criteria on study intervention and has already met potential Hy's Law criteria at a previous on-study intervention visit (refer to Appendix E 6).

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of potential Hy's Law is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of potential Hy's Law criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of potential Hy's Law criteria being met found to be the DUS, eg, chronic or progressing malignant disease, severe infection, or liver disease or did the participant meet potential Hy's Law criteria prior to starting study intervention and at their first on-study intervention visit as described in Appendix E 6?

If **No**: Follow the process described in Appendix E 4.2 for reporting potential Hy's Law as an SAE

If **Yes**: Determine if there has been a significant change[#] in the participant's condition compared with when potential Hy's Law criteria were previously met:

- If there is no significant change no action is required.
- If there is a significant change[#] follow the process described in Appendix E 4.2 for reporting potential Hy's Law as an SAE.

[#] A '**significant**' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Clinical Lead if there is any uncertainty.

E 8 Laboratory Tests

Hy's Law Laboratory Kit

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HbsAg IgM and IgG anti-HBc HBV DNA ^a IgM and IgG anti-HCV HCV RNA ^b IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgG anti-HSV, and HSV 1 /2 IgM testing or HSV PCR ^c IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) ^d
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin ^d Transferrin saturation

^a HBV DNA is only recommended when IgG anti-HBc is positive.

^b HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

^c HSV 1 /2 IgM testing or HSV 1 /2 PCR testing depending on region.

^d CD-transferrin and transferrin are not available in China.

Appendix F Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

F 1 Introduction

This appendix details the implementation of RECIST 1.1 guidelines ([Eisenhauer et al 2009](#)). Investigator assessments will use the RECIST 1.1 guidelines described in this appendix.

F 2 Imaging Modalities and Acquisition Specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of TLs, NTLs, and NLs is provided in [Table 14](#).

Table 14 Summary of Imaging Modalities for Tumor Assessment

Target lesions	Non-target lesions	New lesions
CT MRI	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy/SPECT) ¹⁸ F-fluoro-deoxyglucose-PET/CT	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy) ¹⁸ F-fluoro-deoxyglucose-PET/CT

F 2.1 Computed Tomography and Magnetic Resonance Imaging

CT with iv contrast is the preferred imaging modality (although MRI with iv contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumor assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumor assessor (eg, radiologist), and method of tumor assessment (eg, RECIST 1.1) are used consistently for each participant throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumor assessment schedule as closely as possible (refer to the SoA), and this on-study imaging schedule **MUST** be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artefacts (eg, heart, major blood

vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

The most critical CT and MRI image acquisition parameters for optimal tumor evaluation are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest-abdomen (-pelvis). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants. Because a lesion later identified in a body part not scanned at baseline would be considered as a NL representing PD, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumor burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these time points are specified in the SoA. Examples include the following:

- Intravenous contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) and pelvis.
- Non-contrast CT of chest and iv contrast-enhanced abdomen (including the entire liver and both adrenal glands) and pelvis.
- Intravenous contrast-enhanced MRI (preferred) or CT of the brain.

For chest-abdomen-pelvis imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when participants have sensitivity to IV contrast or have compromised renal function:

- 1 Chest-abdomen-pelvis CT with iv CT contrast (most preferred).
- 2 Chest CT without iv-contrast + abdomen-pelvis MRI with iv MRI contrast, if CT iv contrast (iodine based) is medically contraindicated at any time during the study.
- 3 Chest-abdomen-pelvis CT without iv contrast, if both iv CT and MRI contrast are medically contraindicated or the participant has compromised renal function.

- 4 Chest-abdomen-pelvis MRI with iv MRI contrast, if CT cannot be performed at any time during the study.

b. Intravenous contrast administration: Optimal visualization and measurement of metastases in solid tumors require consistent administration (dose and rate) of iv contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given participant. Oral contrast is recommended to help visualize and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤ 5 mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. However, a slice thickness of ≤ 3 mm is preferred. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses > 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

F 2.2 Chest X-ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

F 2.3 Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

F 2.4 Isotopic Bone Scan

Isotopic bone scans (Scintigraphy/SPECT) may be used as a method of assessment to identify the presence of bone lesions at any visit.

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as TLs if measurable (soft tissue component of the bone lesion) or NTLs if unmeasurable and followed by the same method per baseline assessment (CT, MRI, or X-ray). For lesions identified by bone scan at baseline that cannot be confirmed by these methods, they can be recorded as NTLs.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits as clinically indicated. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

F 2.5 ¹⁸F-Fluoro-deoxyglucose-PET/CT

This section describes the use of ¹⁸F-fluoro-deoxyglucose PET (FDG-PET), but the same applies for dual modality scans like FDG-PET/CT or FDG-PET/MRI.

FDG-PET may be used as a method of assessment to identify the presence of lesions at any visit.

Lesions identified on a FDG-PET at baseline and confirmed by CT or MRI at baseline should be recorded as TLs if measurable or NTLs if unmeasurable and followed by the same method per baseline assessment (CT, MRI). For lesions identified by FDG-PET scan at baseline that cannot be confirmed by these methods, they can be recorded as NTL.

FDG-PET/CT scans may be used as a method for identifying new lesions for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive ¹⁸F-Fluoro-deoxyglucose uptake² not present on baseline or prior FDG-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the FDG-PET scan. The PET portion of the PET/CT introduces additional data that may bias an Investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior FDG-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

At present, low-dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with iv contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not

² A positive FDG-PET scan lesion should be reported only when an uptake (eg, standard uptake value) greater than twice that of the surrounding tissue or liver is observed.

routinely or serially performed. The same rules apply to MRI if a FDG-PET/MRI is performed.

F 2.6 Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

F 2.7 Other Tumor Assessments

F 2.7.1 Clinical Examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

F 2.7.2 Endoscopy and Laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

F 2.7.3 Histology, Cytology, and Tumor Markers

Histological or cytological examination of the tumor biopsy samples cannot be used on their own to provide a tumor response assessment. Histological or cytological examination of the tumor biopsy samples can, however, be used to support radiological findings to confirm tumor response assessment as per RECIST 1.1 to differentiate between PR and CR in cases with residual benign lesions.

Results of cytological examination for confirming the neoplastic origin of any effusion (eg, ascites, pericardial effusion, or pleural effusion) that appears or worsens during the study can be used in the tumor response assessment as per RECIST 1.1 to confirm progression in case of SD, PR, or CR.

Tumor markers alone cannot be used to assess tumor response if markers are initially high. However, they must be normal to determine CR or as indicated in the CSP.

F 3 Measurability of Tumor Lesions at Baseline

F 3.1 RECIST 1.1 Measurable Lesions at Baseline

A tumor lesion that can be accurately measured at baseline as ≥ 10 mm in the longest diameter

for non-nodal lesions or ≥ 15 mm in short axis³ diameter for lymph node lesions using intravenous contrast-enhanced CT or MRI with slice thickness < 5 mm and that is suitable for accurate repeated measurements. If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

F 3.2 Non-measurable Lesions at Baseline

- Truly non-measurable lesions include the following:
 - Bone lesions (see exception below for soft tissue component).
 - Leptomeningeal disease.
 - Ascites, pleural effusion, or pericardial effusion.
 - Inflammatory breast disease.
 - Lymphangitic involvement of skin or lung.
- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis diameter at baseline).⁴
- Previously irradiated lesions.⁵
- Brain metastasis.

F 3.3 Special Considerations Regarding Lesion Measurability at Baseline

- Bone lesions:
 - Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
 - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability.
 - Blastic lesions are considered non-measurable.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if

³ The short axis is defined as the longest in-plane axis perpendicular to the long axis.

⁴ Lymph nodes with < 10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

⁵ Localized post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment. However, lesions that have demonstrated significant growth beyond their initial post-radiation size and show no evidence of scarring, fibrosis, or necrosis may be considered measurable and included in assessments if no other lesions without prior intervention are available.

non-cystic lesions are present in the same participant, these should be selected over cystic lesions as TLs.

F 3.4 RECIST 1.1 TL Selection at Baseline

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TLs at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimeters. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

F 3.4.1 Special Cases for TL Assessment at Baseline

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumor lesions selected for newly acquired screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a NL.

F 3.5 RECIST 1.1 NTL Selection at Baseline

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

F 4 Evaluation of Tumor Response and Progression

F 4.1 RECIST 1.1 TL Assessment at Follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimeters. The sum of the diameters for all TLs at each follow-up visit will be compared with the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression).

F 4.1.1 Special Cases for TL Assessment at Follow-up

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. The choice of “Too large to measure” in the CRF will trigger an overall visit response of PD.
- When a TL has had any intervention (eg, definitive radiotherapy, embolization, surgery, transarterial chemoembolization, etc) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 CRF for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Response definitions per RECIST 1.1 for evaluation of TLs are provided in [Table 15](#).

Table 15 **RECIST 1.1 Evaluation of Target Lesions**

CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir). This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
NE	Only relevant if any of the TLs at follow-up were not assessed or NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
Not applicable	Only relevant if no TLs present at baseline.

F 4.2 RECIST 1.1 NTL Assessment at Follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the Investigator.

To achieve “unequivocal progression” on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD, CR, or PR in TLs, the overall tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest “increase” in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD, CR, or PR of target disease will therefore be extremely rare.

Response definitions per RECIST 1.1 for evaluation of NTLs are provided in [Table 16](#).

Table 16 **RECIST 1.1 Evaluation of Non-target Lesions**

CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/non-PD	Persistence of one or more NTLs.
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.

NE	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For participants without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable	Only relevant if no NTLs present at baseline.

F 4.3 RECIST 1.1 NL Identification at Follow-up

All NLs (equivocal NLs and unequivocal NLs) must be recorded. Details, including the imaging modality, the date of scan, the location, and the NL status (equivocal/unequivocal) will also be recorded in the CRF. The presence of one or more new unequivocal lesions is assessed as progression. The finding of a NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If a NL is equivocal, for example because of its small size, it does not indicate progression, and the treatment and tumor assessments should be continued. If an equivocal NL becomes unequivocal at a later visit, then the progression date should be declared using the date of the initial scan when the equivocal NL first appeared.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a NL and will indicate PD.

F 4.4 RECIST 1.1 Evaluation of Overall Visit Response at Follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in [Table 17](#).

Table 17 RECIST 1.1 Overall Visit Response

Target lesions	Non-target lesions	New unequivocal lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE or NA	No	PR
SD	Non-PD or NE or NA	No	SD
NE	Non-PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Non-CR/Non-PD for overall response if only NTL (no TLs) are present at baseline.

Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For participants with TLs (at baseline): CR, PR, SD, PD, or NE.

F 4.5 Study-specific Scans Subsequent to Investigator-assessed RECIST 1.1-defined Progression

A follow-up scan is requested at least 4 weeks after a RECIST 1.1-defined radiological progression and no longer than the next regularly scheduled imaging visit, regardless of whether participant has stopped study intervention and/or started a subsequent anticancer therapy. The follow-up scans provide additional information to mitigate potential informative censoring events by BICR-associated study endpoints. Investigators should assess these scans following the same RECIST guidelines described above and as a standard follow-up visit.

F 4.6 Evaluation of Scans Subsequent to RECIST 1.1-defined Progression

The follow-up scans after a RECIST 1.1-defined radiological progression provide additional information to the Investigator for participant management and further treatment decisions, and since the published RECIST 1.1 criteria ([Eisenhauer et al 2009](#)) do not provide guidance on how to assess scans acquired after RECIST 1.1-defined disease progression, supplemental instructions for Investigators on how to evaluate these follow-up scans are provided below. An immediate prior RECIST 1.1-defined radiologic disease progression would be considered confirmed if any of the following criteria are met in the subsequent follow-up scan:

- $\geq 20\%$ increase and at least a 5 mm increase in the sum of diameters of TLs compared with the nadir sum of diameters at 2 consecutive visits.
- Significant progression (worsening) of NTLs at the follow-up scan time point compared with the immediate prior time point.
- Significant progression (worsening) of previously NLs (pre-existing NLs) at the follow-up scan time point compared with the immediate prior time point.
- Additional brand-new unequivocal lesions at the follow-up scan time point.

F 5 References

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-47.

Appendix G Contraception Requirements

Contraception requirements for this study are as follows.

G 1 Female Participants

Females not of childbearing potential are defined as females who are either permanently sterilized (ie, hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrheic for 12 months prior to planned randomization without an alternative medical cause. The following age-specific requirements apply:

- Females < 50 years old are considered postmenopausal if they have been amenorrheic for 12 months or more prior to randomization following cessation of exogenous hormonal treatment and follicle-stimulating hormone levels in the postmenopausal range.
- Females $\geq$ 50 years old are considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment, or had radiation-induced menopause with last menses > 1 year ago, or had chemotherapy-induced menopause with last menses > 1 year ago.

Females of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a non-sterilized male partner must use at least one highly effective method of contraception from enrollment throughout study and until at least 60 days after the last dose of rilvegostomig, or 90 days after the last dose of durvalumab, or 6 months after the last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is longer. (Table 18). A highly effective method of contraception is defined as one that has a failure rate of < 1% per year when used consistently and correctly. Cessation of contraception after this time should be discussed with a responsible physician.

Females on HRT and whose menopausal status is in doubt will be required to use one of the contraception methods outlined for females of childbearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status prior to randomization. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their postmenopausal status, they can resume use of HRT during the study without use of a contraceptive method.

In addition, non-sterilized male partners of FOCBP participants enrolled in this study must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of enrollment of their female partner, throughout their participation in the study, and until 60 days after their female partners last dose of rilvegostomig, or 90 days after the last dose of durvalumab, or 6 months after their last dose of chemotherapy (unless

local Prescribing Information requires a longer duration), whichever is longer. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together. Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments).

G 2 Male Participants with a Female Partner of Childbearing Potential

Non-sterilized male participants (including males sterilized by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with a FOCBP must be using an acceptable method of contraception, such as male condom plus spermicide (condom alone in countries where spermicides are not approved), from enrollment throughout the study until at least 60 days after the last dose of rilvegostomig, or 90 days after the last dose of durvalumab, or 6 months after the last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is longer, to avoid conception during treatment.

Periodic abstinence (eg, calendar, ovulation symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP/study intervention, and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together. Male participants should refrain from sperm donation or banking throughout this period.

Vasectomized males are considered fertile if there was no medical assessment of the surgical success and should still use a male condom plus spermicide as indicated above during the clinical study.

Even if the female partner is pregnant, male participants should still use a condom plus spermicide (where approved), as indicated above during the clinical study, if there is a concern about damaging the developing fetus from drug in ejaculate.

In addition, female partners (of childbearing potential) of male participants enrolled in this study must use a highly effective method of contraception ([Table 18](#)) from the time of study enrollment of their male partner, throughout their participation in the study, and until at least 60 days after their male partners last dose of rilvegostomig, or 90 days after the last dose of durvalumab, or 6 months after their last dose of chemotherapy (unless local Prescribing Information requires a longer duration), whichever is longer.

G 3 Highly Effective Methods of Contraception

A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly, see [Table 18](#). Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 18 Highly Effective Methods of Contraception (< 1% Failure Rate)

Non-hormonal methods	Hormonal methods
- Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) - Vasectomized sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) - Bilateral tubal occlusion - Intrauterine device (provided coils are copper-banded)	- Injection: Medroxyprogesterone injection (eg, Depo-Provera[®]) ^a - Levonorgestrel-releasing intrauterine system (eg, Mirena[®]) ^a - Implants: Etonogestrel-releasing implants (eg, Implanon[®] or Nexplanon[®]) - Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing[®]) - Combined pill: Normal and low dose combined oral contraceptive pill ^b - Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Xulane[®], Ortho Evra[®]) - Mini pill: Progesterone-based oral contraceptive pill using desogestrel: Cerazette[®] is currently the only highly effective progesterone-based pill ^b

^a Hormonal methods not prone to drug-drug interactions.

^b In line with the Clinical Trial Facilitation Group guidance on the recommendations related to contraception and pregnancy testing in clinical studies, oral contraceptives are only highly effective when associated with inhibition of ovulation.

Appendix H Concomitant Medications

H 1 Guidance Regarding Potential Interactions with Concomitant Medications

The use of any natural/herbal products or other “folk remedies” should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

H 2 Prohibited and Permitted Concomitant Medications/Therapies

Prohibited and permitted/supportive concomitant medications/therapies are described in [Table 19](#) and [Table 20](#). Refer also to the dose modification guidelines for management of study-intervention-related toxicities in Section [6.6](#).

Table 19 Prohibited Medications/Therapies

Prohibited medication/class of drug/therapy	Usage
Any investigational therapy, including anticancer therapy, other than those under investigation in this study	Must not be given concomitantly while the participant is on study intervention
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Must not be given concomitantly while the participant is on study intervention. (Concurrent use of bisphosphonates or hormonal therapy [eg, insulin for diabetes, HRT, gonadotropin-releasing hormone analogs] for non-cancer-related conditions is acceptable. Local treatment of isolated lesions, excluding TLs, for palliative intent is acceptable [eg, by local surgery or radiotherapy].)
Vaccines	• Live attenuated vaccines should not be given within 30 days prior to the first dose through 30 days after the last dose of study intervention. • COVID-19 vaccination should not be given for 72 hours prior to administration of the first dose of study intervention.

Table 19 Prohibited Medications/Therapies

Prohibited medication/class of drug/therapy	Usage
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or 2 mg/day of dexamethasone or equivalent, methotrexate, azathioprine, and tumor necrosis factor- α blockers	Should not be given concomitantly or used for premedication prior to the immunotherapy infusions. The following are allowed exceptions (see also Section 6.10 regarding rescue medicine): • Use of immunosuppressive medications for the management of IMP-related AEs (refer to TMG Annex). • Premedication before chemotherapy per product Prescribing Information and/or SoC. • Premedication for management of recurrent Grade 1 or Grade 2 IRRs after C1D1 such as a combination of acetaminophen, H1 blocker and H2 blocker, is advised. If necessary, a steroid premedication may be added. • However, steroids should not be used as routine premedication. for Grade 1 or 2 IRRs (refer to TMGs). • Use in participants with contrast allergies. • Inhaled, topical, and intranasal corticosteroids. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy-related events experienced by the participant (eg, chronic obstructive pulmonary disease, radiation, nausea).
EGFR tyrosine kinase inhibitor	Should not be given concomitantly. Should be used with caution during the 90 days post last dose of study intervention.
Prophylactic use of any premedication for rilvegostomig in participants without prior IRR	Should not be given. Note: For participants that have previously experienced an IRR, refer to TMGs.
Herbal and natural remedies that may interfere with the activity of the study intervention	Must not be given concomitantly

Table 20 Supportive Medications/Therapies

Supportive medication/class of drug/therapy	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate AE management, prophylactic or supportive care, except for those medications identified as “prohibited,” as listed above	To be administered as prescribed by the Investigator except for those medications identified as “prohibited,” as listed in Table 19
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc]) except for those medications identified as “prohibited,” as listed above	Should be used, when necessary, for all participants except for those medications identified as “prohibited,” as listed in Table 19

Table 20 Supportive Medications/Therapies

Supportive medication/class of drug/therapy	Usage
Bone-modifying agents (bisphosphonates, RANKL inhibitors) used to prevent skeletal-related events and for management of osteoporosis	Permitted
Inactivated viruses, such as those in the influenza vaccine or authorized inactivated COVID-19 vaccines, based on local Prescribing Information	Permitted
Premedication for management of diarrhea, nausea, and vomiting	Permitted after but not before the first dose of study intervention
Blood transfusions	Permitted at any time after C1D1
Erythropoietin	Permitted at any time after C1D1
G-CSF	Permitted
Megestrol acetate	Permitted for appetite stimulation
Required for management of other medical conditions	As required except for those identified as “prohibited,” as listed in Table 19

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