
Investigator's Brochure

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C O N F I D E N T I A L

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SUMMARY OF CHANGES TO PREVIOUS EDITION

The significant changes since Edition 5.0 of the Investigator's Brochure are listed in the tables below. Minor editorial changes have also been made that are not included in the summary tables below.

Table 1 Substantial Changes (Edition 5.0 to Edition 6.0)

Section	Overview of change	Rationale for change
5.5 Emerging Safety Profile	Section updated to include new ADRs and to update CIOMS frequencies for all ADRs.	Sufficient evidence exists to update ADR information and provide CIOMS frequencies.
5.6 Summary of Risks	Recategorization of the following risks from potential to identified: - Pneumonitis/interstitial lung disease - Hepatic events - Diarrhea/colitis	To reflect the most recent clinical data for rilvegostomig.
5.6.3 Potential Risks Based on Clinical Data with Other Immune Checkpoint Inhibitors 5.6.8 Summary of Risks for Rilvegostomig	Recategorization of imAEs from important potential risk to potential risk.	To reflect the most recent clinical data for rilvegostomig.
5.7 Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions	Section updated to include the newly created RSI for rilvegostomig monotherapy. The following SARs for rilvegostomig are considered expected by the sponsor for the purpose of expedited reporting and identification of SUSARs: - Diarrhea - Hepatitis	Increased data availability supported the creation of RSI for rilvegostomig monotherapy.

CIOMS = Council for International Organizations of Medical Sciences.

Table 2 Other Changes (Edition 5.0 to Edition 6.0)

Section	Overview of change	Rationale for change
1 Summary 4 Nonclinical Studies	Nonclinical study numbers added where missing.	For consistency and accuracy.
1 Summary 6 Summary of Data and Guidance for the Investigators	Updated in line with changes in the main body of the IB.	To ensure consistency throughout the IB.
2.1.1 Rilvegostomig	Added Chariou et al 2024 reference to the background information.	To reflect the currently available data.

Section	Overview of change	Rationale for change
2.2 Rationale for Clinical Development	Updated nonclinical and clinical information to support rilvegostomig clinical development.	To reflect the currently available data.
3.2 Drug Product (Including Formulation and Dosage/Supply & Storage)	Added information about sc rilvegostomig and updated the dilution information for ivrilvegostomig.	To align with currently available drug products.
4.2 Nonclinical Pharmacokinetics 4.2.2 Single Dose sc or iv PK, PD, and Tolerability Study in the Non-human Primate (Study 8529365) 4.3.1 Single Dose iv PK and PD Study in the Cynomolgus Monkey (Study 8399632) 4.3.2 Single sc or iv Dose PK, PD and Tolerability Study in the Cynomolgus Monkey (Study 8529365) 4.3.8 Local Tolerance	Existing Sections 4.2 and 4.3.8 updated, and new Sections 4.2.2, 4.3.1, and 4.3.2 added to include data from Studies 8529365 and 8399632.	To reflect the currently available data.
5 Effects in Humans	Introductory text updated to reflect the latest available data (DCO 05 July 2025). Overview table of completed and ongoing clinical studies updated.	To align with the current clinical development program.
5.2.2 Preliminary Pharmacodynamic Analyses	Wording of Footnote b of Figure 38 updated from "20% increase referring to technical and biological variability based on double baseline" to "20% increase referring to technical and biological variability based on predose samples".	To clarify the approach taken.
5.2.5 Dosing Justification Conclusion	Editorial changes to align with the rilvegostomig CSP template.	To ensure consistency across documents.
5.3 Safety and Efficacy in Humans	Section updated to include introductory information for the safety data included in the IB. A table of studies providing data to the IB was added.	To reflect the most recent data.
5.3 Safety and Efficacy in Humans	Subheadings added: 5.3.1 Rilvegostomig Monotherapy 5.3.2 Rilvegostomig + Chemotherapy 5.3.3 Rilvegostomig + Antibody Drug Conjugates	To aid classification of the included clinical studies.

Section	Overview of change	Rationale for change
5.3 Safety and Efficacy in Humans	Exposure and safety data were added or updated as of 05 July 2025 for the ongoing studies. Efficacy data were added or updated, where available, for the ongoing studies.	To include the most recent data.
5.3.1.2 MAGELLAN (Cohort A5) 5.3.2.1 MAGELLAN (Cohort B5)	Monotherapy and combination therapy data in the MAGELLAN study were split.	To aid classification of the included cohorts.
5.6 Summary of Risks	Section updated to include further information about the included risks, including how patients should be monitored for those risks.	To clarify the approach that should be taken and to reflect the most recent data.
5.6.3 (Edition 5 numbering) Risks Based on Clinical Data	Section removed from the IB.	To streamline the document (risks are described in Section 5.6.1).
5.6.3 Potential Risks Based on Clinical Data with other Immune Checkpoint Inhibitors	List of known imAEs updated to remove the following: - Respiratory disorders: pneumonitis; interstitial lung disease - GI disorders: diarrhea; colitis - Hepatic disorders: elevation of ALT and/or AST; hepatitis	To reflect the most recent data and the recategorization of the imAEs as identified risks.
5.6.5 Potential Risks Related to TIGIT and PD-1 Inhibition Based on Literature Review	Section updated to remove TLS.	To reflect the most recent data.
5.6.6 Risks Common to Any Biologic	Subsection for Identified Risks was removed.	To reflect the most recent data and other changes in the IB.
7 References	New references added	To support newly added text.
Appendix A2 Summary of Nonclinical PK Appendix A3 Summary of Nonclinical Toxicity	Information regarding Study 8529365 added to summary tables.	To align with the addition in the main body.

Upon finalization of Investigator's Brochure Edition 6.0, data were identified that did not align with the rilvegostomig program criteria, prompting an update. Consequently, Investigator's Brochure Edition 6.1 supersedes Investigator's Brochure Edition 5.0.

Table 3 Other Changes (Edition 6.0 to Edition 6.1)

Section	Overview of change	Rationale for change
1 Summary 6 Summary of Data and Guidance for the Investigators	Updated in line with changes in the main body of the IB.	To ensure consistency throughout the IB.
5 Effects in Humans 5.3 Safety and Efficacy in Humans	Preliminary clinical data removed from the presented clinical data.	Streamlining clinical data to align with the rest of the IB and the program.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Definition
1L	first-line
ADA	antidrug antibody(ies)
ADC	antibody drug conjugate
ADCC	antibody-dependent cellular cytotoxicity
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	AUC from zero to infinity
AUC_{0-168h}	AUC from zero to 168 hours
AUC_{0-21d}	AUC from zero to 21 days
$AUC_{0-Day43}$	AUC from zero to Day 43
AUC_{τ} or AUC_r	AUC during one dosing interval
BTC	biliary tract cancer
C1q	complement component 1q
C3a	complement component 3a
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CHO	Chinese Hamster Ovary
CI	confidence interval
CL	clearance
C_{max}	maximum observed concentration
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor
CPS	combined positive score
CRS	cytokine release syndrome
CSP	Clinical Study Protocol
Dato-DXd	datopotamab deruxtecan
DCO	data cut-off
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

Abbreviation or special term	Definition
DoR	duration of response
EBV	Epstein-Barr Virus
EC ₅₀	half maximal effective concentration
ECG	electrocardiogram
Fab	fragment antigen-binding
Fc	fragment crystallizable
FcγR	Fc gamma receptor
FOLFOX	folinic acid + fluorouracil + oxaliplatin
FTIH	first-time-in-human
gCV	geometric coefficient of variance
GI	gastrointestinal
GLP	Good Laboratory Practice
HCC	hepatocellular carcinoma
HCl	hydrochloride
HER2	human epidermal growth factor receptor 2
HLA	human leukocyte antigen
HR	hazard ratio
HSCT	human stem cell transplantation
IB	Investigator's Brochure
IC	immunocomplex
ICD	immune complex disease
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICOS	inducible T-cell costimulatory
IFN-γ	Interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
ILD	interstitial lung disease
imAE	immune-mediated adverse event
IP	investigational product
IRR	infusion-related reaction
iv	intravenous
IVBP	intravenous bag protectant
mAb	monoclonal antibody
mPFS	median progression-free survival

Abbreviation or special term	Definition
NC	not calculable
NE	not evaluable
NFAT	nuclear factor of activated T cells
NK	natural killer
No.	number
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
NSG	non-obese diabetic/severe combined immunodeficiency (NOD-scid) IL-2 receptor gamma null, immunocompromised mice
OE21-10xGSV3	human Caucasian esophageal squamous cell carcinoma cell line engineered to express viral peptides
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC9-MART1	human lung adenocarcinoma cell line engineered to express a melanoma antigen
PD	pharmacodynamic(s)
PD-1	programmed cell death protein-1
PD-L1/2	programmed cell death-ligand 1/2
PFS	progression-free survival
PFS-6	6-month progression-free survival rate
PFS-12	12-month progression-free survival rate
PK	pharmacokinetics
PopPK	population pharmacokinetics
PR	partial response
PT	preferred term
QxW	every x weeks
RO	receptor occupancy
RSI	reference safety information
SAE	serious adverse event
SAR	serious adverse reaction
sc	subcutaneous
scFv	single chain variable fragment
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
t _{1/2}	elimination half-life

Abbreviation or special term	Definition
TCR	T-cell receptor
T-DXd	trastuzumab deruxtecan
TIGIT	T-cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif domains
TIM-3	T-cell immunoglobulin and mucin domain containing protein 3
TM	triple mutation
T _{max}	time to maximum concentration
TNF	tumor necrosis factor
TPS	tumor proportion score
TRAE	treatment-related adverse event
V _H	human immunoglobulin heavy chain variable region
V _L	human immunoglobulin light chain variable region
V _{ss}	steady-state volume of distribution
w/v	weight/volume
XELOX	oxaliplatin + capecitabine

1 SUMMARY

Rilvegostomig (AZD2936) is being developed by AstraZeneca for use in the treatment of cancer. Rilvegostomig is a monovalent, bispecific, humanized, IgG1 monoclonal antibody 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.

1.1 Nonclinical Overview

1.1.1 Nonclinical Pharmacology

Nonclinical pharmacology studies demonstrate that rilvegostomig can specifically bind human and cynomolgus monkey PD-1 and TIGIT, with a 21-fold increased intrinsic affinity to human TIGIT (15 pM) in comparison to human PD-1 (320 pM). Rilvegostomig inhibited TIGIT and PD-1 binding to their primary ligands, cluster of differentiation-155 and programmed cell death-ligand 1, respectively in a TIGIT and PD-1 dual reporter Jurkat cell assay, leading to an increased amount of luciferase driven by the NFAT-response element. Rilvegostomig promoted increased NFAT activity in the Jurkat reporter cell assay greater than bivalent anti-TIGIT or anti-PD-1 antibodies and led to similar levels of activity ($EC_{50} = 5.82$ nM) as the combination of bivalent anti-TIGIT and anti-PD-1 antibodies ($EC_{50} = 6.27$ nM). Furthermore, rilvegostomig triggered an increase in antigen-specific T-cell-mediated lysis of the human esophageal squamous carcinoma cell line, OE21, and enhanced IFN- γ release following co-culture with antigen expressing tumor cells over an isotype control and anti-PD-1 antibodies. The lytic activity and IFN- γ release elicited by rilvegostomig was similar to the combination of bivalent parental antibodies, indicating that the monovalent bispecific format of rilvegostomig mediated a similar amount of activity in vitro as compared to the combination, regardless of valency of the binding paratopes. In antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity assays, rilvegostomig did not demonstrate Fc-mediated effector functionality against a TIGIT and PD-1 expressing cell line at a greater level than an isotype control antibody.

The activity of rilvegostomig was also investigated in 2 human tumor xenograft mouse models (4 independent experiments in each model) using immunocompromised non-obese diabetic/severe combined immunodeficient/IL-2 receptor- γ null (NOD-*scid* IL2Rgamma^{null}, otherwise called 'NSG') mice. In these models, administration of rilvegostomig to animals significantly inhibited the growth of tumors as compared to the activity of its parental bivalent anti-PD-1 antibody, anti-TIGIT/anti-PD-1 combination, and an isotype control antibody. Information on the nonclinical pharmacology of rilvegostomig is presented in Section 4.1.

1.1.2 Nonclinical Pharmacokinetics

In the non-GLP single dose PK study evaluating single doses of rilvegostomig with and without treatment with abatacept (Study number 8399632), 8 female cynomolgus monkeys received a single iv dose at 5 or 100 mg/kg of rilvegostomig on study Day 1. An additional cohort of 4 female cynomolgus monkeys received a total of 5 weekly iv administrations of 10 mg/kg iv abatacept, from study Day -1 to study Day 28 and a single dose of 5 mg/kg of rilvegostomig on study Day 1. Exposure to rilvegostomig increased with the increase in dose level from 5 to 100 mg/kg. At 5 mg/kg rilvegostomig exposure was similar for up to 15 days postdose when rilvegostomig was dosed at 5 mg/kg alone or with abatacept. Higher CL was observed after 15 days post dose when rilvegostomig was dosed at 5 mg/kg alone than with abatacept. All 8 animals receiving 5 or 100 mg/kg of rilvegostomig alone showed evidence of immunogenicity (ADA) after a single dose of rilvegostomig.

In the GLP single dose PK study evaluating rilvegostomig administered iv or sc (Study 8529365), 5 groups of male cynomolgus monkeys, each consisting of 3 animals/group, were given one dose of vehicle control or rilvegostomig at a dose of 50, 100, or 200 mg/kg via sc injection or rilvegostomig at a dose of 200 mg/kg via manual iv slow bolus injection on Day 1 of the dosing phase. After sc injection administration, rilvegostomig was absorbed, with median T_{max} values of 72.0 hours on Day 1. After reaching C_{max} , concentrations declined, with mean $t_{1/2}$ values ranging from 1.42 to 2.29 days. The sc bioavailability was 67.1%. After iv bolus administration, rilvegostomig concentrations declined generally in a multi-exponential manner, with a mean $t_{1/2}$ value of 1.98 days.

In the GLP 1-month repeat-dose toxicity study (Study 20260563) of iv-administered rilvegostomig at 50, 100, and 200 mg/kg in cynomolgus monkeys with a 6-week treatment-free recovery period, the increases in rilvegostomig mean C_{max} and the AUC_{τ} values in the serum were proportional to the increase in dose level from 50 to 200 mg/kg/dose. There was 1.2 to 1.5-fold accumulation in C_{max} and 1.4 to 1.7-fold accumulation in AUC_{τ} observed after multiple weekly doses of rilvegostomig from 50 to 200 mg/kg in monkeys. The CL was similar across all dose groups.

Reduced PK exposure was observed for a total of 9 out of 26 monkeys dosed with rilvegostomig that developed high ADA, including 2 males and one female at 50 mg/kg, 2 males and one female at 100 mg/kg, and 3 males at 200 mg/kg. ADA was not noted in 10 control animals (5 males and 5 females).

In the GLP 3-month repeat-dose toxicity and toxicokinetics study (Study 8522498) of iv-administered rilvegostomig at 50, 100 and 200 mg/kg once weekly in cynomolgus monkeys, exposure, as assessed by rilvegostomig mean C_{max} and AUC_{0-168h} values, increased with the increase in dose level from 50 to 200 mg/kg/week. There were no sex differences in exposure. The increases in rilvegostomig mean C_{max} and AUC_{0-168h} values were generally dose

proportional. Rilvegostomig mean $C_{\max}$ and AUC_{0-168h} values were notably higher on Day 85 than on Day 1, indicating accumulation of rilvegostomig after multiple weekly iv bolus doses in monkeys. Mean accumulation ratio values ranged from 1.43 to 1.97 for $C_{\max}$ and from 2.14 to 2.67 for AUC_{0-168h} .

The overall incidence of ADA response to rilvegostomig across the study (including all sampling times) was 33% (2 out of 6) at 0 mg/kg/week, 100% (6 out of 6) at 50 mg/kg/week, 100% (6 out of 6) at 100 mg/kg/week, and 83% (5 out of 6) at 200 mg/kg/week. Animals that had ADA detected generally exhibited similar exposure to animals that were ADA negative.

1.1.3 Nonclinical Toxicology

Consistent with ICH S6 R(1) guidelines, a single species safety assessment package was conducted since the amino acid sequence homology and binding affinities for the PD-1 and TIGIT antigens had the greatest similarity between human and cynomolgus monkey when compared to other animal species. The cynomolgus monkey was therefore considered to be the only pharmacologically relevant species for nonclinical safety testing of rilvegostomig. In accordance with ICH S9 (June 2018, Q13), no studies assessing tissue cross-reactivity of rilvegostomig or the potential for reproductive toxicity have been conducted. Further, in accordance with ICH S6 R(1), there are no plans to conduct studies assessing genotoxicity.

In a single iv dose PK study (non-GLP) (Study 8399632), groups of 4 female cynomolgus monkeys were dosed with either a single 30-minute iv infusion of vehicle, 5 mg/kg or 100 mg/kg of rilvegostomig on Day 1, or dosed with abatacept on Days -1, 7, 14, 21, and 28 and a single dose of rilvegostomig (5 mg/kg) on Day 1. At 5 mg/kg, rilvegostomig exposure was similar for up to 15 days postdose when rilvegostomig was dosed at 5 mg/kg alone or with abatacept. Higher clearance was observed after 15 days postdose when rilvegostomig was dosed at 5 mg/kg alone than when dosed with abatacept.

In the single sc or iv dose PK, PD and tolerability study (Study 8529365), rilvegostomig dosed at up to 200 mg/kg sc or iv was well tolerated in male monkeys, with transient edema and erythema at the dose site and minimal transient increases in IL-6 noted. No rilvegostomig-related clinical observations, alterations in body weight or food consumption, or peripheral blood immunophenotyping effects were noted. The sc bioavailability was 67.1%, as assessed by $AUC_{0-Day43}$ values.

There were no adverse treatment-related findings in the 1-month repeat dose iv toxicity study (Study 20260563) with a 6-week assessment of recovery in the cynomolgus monkey following 5 repeated weekly administrations at doses up to and including 200 mg/kg/week by the iv route. Changes noted were reversible and associated with either the anticipated pharmacological activity of rilvegostomig on T cells or the immune response mounted by the animals to the humanized bispecific antibody. The changes noted in the spleen (increased

weight and mononuclear cell infiltration) and brain (mononuclear cell infiltration in choroid plexus) were indicative of an activation of the immune system, and most likely driven by the formation of immune complexes as a result of the ADA response by the monkey to this human bispecific protein. Mononuclear cell infiltrates in the brain are a known background change in cynomolgus monkeys and are also known to be associated with the immunogenicity of large molecule biologics. Thus, the NOAEL for this study is considered to be 200 mg/kg/week iv. At the NOAEL, mean $C_{\max}$ and AUC_{0-168h} values for males were 4440 $\mu\text{g/mL}$ and 348,000 $\text{h}\cdot\mu\text{g/mL}$, and for females 4790 $\mu\text{g/mL}$ and 278,000 $\text{h}\cdot\mu\text{g/mL}$, respectively, after 4 weeks of treatment.

In the GLP 3-month repeat dose iv toxicity study (Study 8522498), cynomolgus monkeys were administered rilvegostomig at 50, 100 or 200 mg/kg once weekly via iv (slow bolus) injection for at least 13 weeks (total of 14 doses). Findings observed in this study included increased lymphoid cellularity in the spleen and axillary and mesenteric lymph nodes and perivascular mononuclear cell infiltrates, perivascular mixed cell infiltrates, and/or intimal mixed cell infiltrates in the aorta and blood vessels of a range of tissues in animals dosed with ≥ 50 mg/kg/week. These findings were considered non-adverse and of the same nature as the findings observed in the 1-month study, indicative of an activation of the immune system, and most likely driven by the formation of immune complexes as a result of the ADA response by the monkey to this human bispecific protein. Perivascular lymphocytic infiltrates were observed in more tissues and at a higher level of severity in the brain in the 3-month study compared to the 1-month study, reflecting a broader/stronger inflammatory response due to extended dosing duration. Based on these results, the dose level of 200 mg/kg/week, the highest dose tested, was considered the NOAEL. This corresponded to sex combined mean $C_{\max}$ and AUC_{0-168h} values of 13,500 $\mu\text{g/mL}$ and 1,380,000 $\text{h}\cdot\mu\text{g/mL}$, respectively, on Day 85.

To assess the potential for cytokine release in humans, PBMCs were collected from 9 healthy donors (Study G-CY-0192). After stimulation, samples were collected and analyzed to measure concentrations of the cytokines IFN- γ , IL-2, IL-6, and TNF- α . Assessment was conducted on both immobilized and soluble cells at concentrations of rilvegostomig of 1 and 10 $\mu\text{g/mL}$.

Rilvegostomig, when presented in soluble phase to donor whole blood, did not induce IFN- γ , IL-2, IL-6, or TNF- α release at a statistically significantly greater level compared to human IgG1-TM isotype control. When presented immobilized on polypropylene plates to donor PBMCs, rilvegostomig induced IL-6 (1.1-fold) and TNF- α (2.8-fold) at a statistically significantly greater level compared to isotype control.

Due to the magnitude of response with positive controls known to induce cytokine release syndrome (TGN1412 and alemtuzumab), the observed changes with rilvegostomig are of small magnitude and are considered to be of low concern, and unlikely to translate into a

clinical AE. In the single sc or iv dose study in cynomolgus monkey (Study 8529365), the increases in IL-6 levels were transient and did not coincide with clinical observations indicating no impact on animal health. There were no rilvegostomig-related effects on cytokine release in the 1-month iv repeat dose study in cynomolgus monkey. Increase in IL-6 concentration was only observed in a low dose male animal in the 3-month iv repeat dose study with clinical signs considered related to an anaphylactoid-like reaction, likely as a secondary reaction to the presence of ADAs. No rilvegostomig-related changes in IL-6 or other cytokines were observed in other animals at the same or higher dose groups. The absence of adverse events observed in the in vivo animal studies with rilvegostomig is aligned with known clinical experience with anti-PD-1 and anti-TIGIT molecules tested in the clinic where no dose-limiting CRS were reported.

1.2 Clinical Overview

Clinical studies conducted to date on the rilvegostomig program (including combination studies with other molecules) are conducted in accordance with the study protocols, ICH guidelines, Good Clinical Practice principles, the Declaration of Helsinki, and applicable laws and regulations.

As of the DCO date (05 July 2025), approximately 1358 participants had been enrolled into the rilvegostomig clinical development program: approximately 201 have received rilvegostomig monotherapy, 219 received rilvegostomig in combination with ADCs, 83 received rilvegostomig in combination with chemotherapy, 75 received rilvegostomig in combination with other therapies, and 780 received study treatment that is blinded at the time of DCO.

At the time of preparation of this IB, there were 19 ongoing studies and 1 completed study with rilvegostomig. An overview of all completed and ongoing studies with rilvegostomig is presented in [Table 29](#). Data are available from the 7 studies listed below; unless otherwise specified, the DCO of 05 July 2025 applies to the clinical data for rilvegostomig included in this IB.

- ARTEMIDE-01 is an FTIH Phase I/II study in adult participants with advanced or metastatic NSCLC. A total of 199 NSCLC patients received rilvegostomig monotherapy: 83 CPI-experienced participants (Parts A and B); and 116 CPI-naïve participants (Parts C, D, and E). Across Parts A and B, a total of 15 participants received 70 or 210 mg rilvegostomig, 54 participants received 750 mg rilvegostomig, and 14 participants received 1500 mg rilvegostomig. Across Parts C, D, and E, a total of 86 participants received 750 mg rilvegostomig and 30 participants received 1500 mg rilvegostomig.
- MAGELLAN is a Phase Ib platform study in adult participants with Stage IV NSCLC. As of the final DCO date of 23 May 2023, a total of 7 participants received 1L rilvegostomig therapy (750 mg Q3W) across the 2 rilvegostomig cohorts: Cohort A5, rilvegostomig

monotherapy (2 participants) and Cohort B5, rilvegostomig + chemotherapy (5 participants).

- GEMINI-Gastric is a Phase II platform study in adult participants with HER2-negative, locally advanced unresectable or metastatic gastric cancer or gastroesophageal junction adenocarcinoma. A total of 40 participants received rilvegostomig combination therapy (750 mg Q3W) across 2 cohorts in Substudy 2: 27 participants received rilvegostomig + XELOX (capecitabine and oxaliplatin); and 13 participants received rilvegostomig + FOLFOX (5-fluorouracil, oxaliplatin, and leucovorin).
- GEMINI-Hepatobiliary is a Phase II platform study in adult participants with advanced hepatocellular carcinoma and BTC who have not received previous treatment for advanced/metastatic disease. A total of 30 participants have received rilvegostomig (750 mg Q3W) in combination with gemcitabine and cisplatin in Cohort 2A.
- TROPION-Lung04 is a Phase Ib platform study in adult participants with advanced or metastatic NSCLC, not previously treated. A total of 40 participants have received rilvegostomig (750 mg Q3W) + Dato-DXd in Cohort 5.
- TROPION-PanTumor03 is a Phase II platform study in adult participants with advanced/metastatic solid tumors. A total of 40 participants with advanced unresectable or metastatic urothelial cancer have received rilvegostomig (750 mg Q3W) + Dato-DXd in Cohort 6B.
- DESTINY-Gastric03 is a Phase Ib/II platform study in adult participants with HER2-expressing locally advanced or metastatic unresectable gastric cancer. A total of 60 participants have received rilvegostomig (750 mg Q3W) + T-DXd + fluoropyrimidine in Arms 4A and 4B.

The dosing regimen of rilvegostomig 750 mg Q3W is supported by the available target engagement, PK, PD, safety, and efficacy data for rilvegostomig in participants with NSCLC (see Section 5.2 for details):

- The rilvegostomig dose of 750 mg Q3W is the lowest predicted dose to achieve $\geq 90\%$ RO 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 PD analyses showed 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 PopPK 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 to 1500 mg Q3W evaluated in ARTEMIDE-01, there were no DLTs and all dose levels were well tolerated. Exposure-safety analysis suggested no relationship between the rate of maximum Grade 3 or 4 AEs or all grade TRAEs and rilvegostomig exposure (AUC_{0-21d}) at all 4 dose levels analyzed (rilvegostomig 70 to 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, demonstrated encouraging efficacy of rilvegostomig 750 mg Q3W in CPI-naïve NSCLC participants, with no further improvement observed at the 1500 mg Q3W dose.

In conclusion, the overall benefit/risk profile favors the choice of 750 mg Q3W as the recommended dose for rilvegostomig as a monotherapy or in combination with other agents, including in studies with registrational intent.

1.2.1 Clinical Pharmacokinetics

Preliminary PK data from ARTEMIDE-01, based on a bioanalytical DCO date of 21 March 2024, were evaluated using noncompartmental analysis in 182 participants who received rilvegostomig monotherapy at 70, 210, 750, and 1500 mg Q3W, in the dose escalation and expansion parts of ARTEMIDE-01.

Rilvegostomig systemic exposure across the dose range of 70 to 1500 mg increased in a near dose proportional manner. There was no target-mediated drug disposition observed at 70, 210, 750, and 1500 mg Q3W dose levels. Following a single dose iv administration, rilvegostomig levels declined in a bi-phasic manner with a mean terminal elimination half-life of about 8 to 10 days. See Section 5.1 for details.

1.2.2 Safety Summary

The risks identified for rilvegostomig as monotherapy are consistent with its mechanism of action, align with known risks of the therapeutic class, and are in line with current clinical understanding of immune checkpoint inhibition (Section 5.6). ADRs associated with rilvegostomig, as indicated by emerging clinical data, include rash, IRR, ILD/pneumonitis, hepatic events, and diarrhea or colitis. Potential risks include imAEs, abnormal laboratory findings, CRS, embryo-fetal toxicity, complications related to allogeneic HSCT, transplanted organ rejection, hypersensitivity reactions, and ICD.

1.2.2.1 Rilvegostomig Monotherapy

1.2.2.1.1 ARTEMIDE-01

- As of the DCO date (05 July 2025), out of 83 CPI-experienced participants, 4 participants, 11 participants, 54 participants, and 14 participants received 70, 210, 750, and 1500 mg rilvegostomig Q3W, respectively; and out of 116 CPI-naïve participants, 86 participants and 30 participants received 750 and 1500 mg rilvegostomig Q3W, respectively.
- A total of 75 CPI-experienced participants (90.4%) and 112 CPI-naïve participants (96.6%) had at least one AE, regardless of causality (see Section 5.3.1.1.2 for safety data).

- In the Combined 750 mg Cohort (those participants who received rilvegostomig 750 mg Q3W throughout the CPI-experienced and CPI-naïve cohorts [Parts A3, B, C, D1, and E]), 133 participants (95.0%) had at least one AE, regardless of causality.
- The most frequently reported AEs by PT in the Combined 750 mg Cohort were anemia (17.9%), and constipation and decreased appetite (16.4% each).
- In the Combined 750 mg Cohort, AEs (any grade) assessed by the investigator as possibly related to rilvegostomig occurred in 92 participants (65.7%), with the most frequently reported (> 5% of the total treatment group) being rash (10.7%), lipase increased and pruritus (7.9% each), and AST increased, constipation, decreased appetite, fatigue, hypercholesterolemia, hypothyroidism, and myalgia (5.7% each).
- A total of 47 participants (33.6%) in the Combined 750 mg Cohort reported AEs (regardless of causality) of maximum Grade 3 or 4 in severity, with the most frequently reported being anemia (5.0%). A total of 15 participants (10.7%) had maximum Grade 3 AEs assessed by the investigator as possibly related to rilvegostomig. There were no AEs of maximum Grade 4.
- SAEs were reported in 38 participants (27.1%) in the Combined 750 mg Cohort, with the most frequently reported being pneumonia (4.3%), dyspnea (2.9%), and anemia, COVID-19, diarrhea, pleural effusion, pneumothorax, pyrexia, and sepsis (1.4% each). Eight participants (5.7%) in the Combined 750 mg Cohort had SAEs assessed by the investigator as possibly related to rilvegostomig.
- In the Combined 750 mg Cohort, 3 participants (2.1%) had AEs with outcome of death, comprising pneumonia, sepsis, and ventricular arrhythmia (1 participant [0.7%] each). None of the events were considered possibly related to rilvegostomig based on investigator assessment.
- In the Combined 750 mg Cohort, 5 participants (3.6%) had AEs leading to permanent discontinuation of rilvegostomig; the events were myocarditis and limb injury (both Grade 1), pneumonitis (Grade 2), and hepatitis acute and immune-mediated hepatitis (both Grade 3). The events of hepatitis acute, immune-mediated hepatitis, myocarditis, and pneumonitis were assessed by the investigator as possibly related to rilvegostomig.

1.2.2.1.2 MAGELLAN (Cohort A5)

- As of the final DCO date (23 May 2023), 2 participants received rilvegostomig monotherapy (750 mg Q3W) in Cohort A5.
- Both participants (2; 100%) had at least one AE, regardless of causality (see Section 5.3.1.2.2 for safety data).
- AEs assessed by the investigator as possibly related to rilvegostomig, of any grade, occurred in both participants (2; 100%).
- One participant (50.0%) in Cohort A5 had maximum Grade 3 or 4 AEs comprising ALT increased (Grade 4) and AST increased (Grade 3), both assessed by the investigator as possibly related to rilvegostomig.
- Neither participant had an SAE.
- Neither participant had an AE with outcome of death.

- One AE of Grade 4 ALT increased led to permanent discontinuation of rilvegostomig, and was judged by the investigator to be possibly related to rilvegostomig.

1.2.2.2 Rilvegostomig + Chemotherapy

1.2.2.2.1 MAGELLAN (Cohort B5)

- As of the final DCO date (23 May 2023), 5 participants received rilvegostomig (750 mg Q3W) + chemotherapy in Cohort B5.
- Four participants (80.0%) had at least one AE, regardless of causality (see Section 5.3.2.1.2 for safety data).
- AEs assessed by the investigator as possibly related to rilvegostomig, of any grade, occurred in 1 participant (20.0%).
- No participants had maximum Grade 3 or 4 AEs.
- An SAE (pneumonia; Grade 2) was reported in 1 participant (20.0%) and was assessed by the investigator as unrelated to rilvegostomig.
- No participants had an AE with outcome of death.
- No participants had an AE leading to permanent discontinuation of rilvegostomig.

1.2.2.2.2 GEMINI-Gastric Substudy 2

- As of the DCO date (05 July 2025), a total of 40 participants have received rilvegostomig (750 mg Q3W) across 2 cohorts: 27 participants received rilvegostomig + XELOX and 13 participants received rilvegostomig + FOLFOX.
- All 40 participants (100%) had at least one AE, regardless of causality (see Section 5.3.2.2.2 for safety data).
- The most frequently reported AEs by PT were nausea (62.5%), neutrophil count decreased (50.0%), decreased appetite (42.5%), asthenia (37.5%), and anemia, lipase increased, and platelet count decreased (35.0% each).
- AEs (any grade) assessed by the investigator as possibly related to rilvegostomig occurred in 26 participants (65.0%), with the most frequently reported being AST increased and lipase increased (22.5% each), ALT increased (20.0%), and blood creatine phosphokinase increased (17.5%).
- A total of 23 participants (57.5%) across both dose cohorts had at least one AE of maximum Grade 3 or 4 in severity (regardless of causality), with the most frequently reported being neutropenia (15.0%), neutrophil count decreased (12.5%), anemia, asthenia, and lipase increased (7.5% each), and abdominal pain, ascites, blood creatine phosphokinase increased, intestinal obstruction, and upper GI hemorrhage (5.0% each). A total of 4 participants (10.0%) had maximum Grade 3 or 4 AEs assessed by the investigator as possibly related to rilvegostomig.
- SAEs were reported in 11 participants (27.5%), with the only reported SAEs occurring in more than 1 participant being intestinal obstruction and upper GI hemorrhage (2 participants [5.0%] each). In 1 participant (2.5%) each, the reported SAEs of platelet

count decreased and pneumonitis were assessed by the investigator as possibly related to rilvegostomig.

- No participants had an AE with outcome of death in the rilvegostomig arms of the study.
- Eleven participants (27.5%) had AEs leading to permanent discontinuation of study treatment.

1.2.2.2.3 GEMINI-Hepatobiliary (Cohort 2A)

- As of the DCO date (05 July 2025), a total of 30 participants had received rilvegostomig (750 mg Q3W) in combination with gemcitabine and cisplatin.
- All 30 participants (100%) had at least one AE, regardless of causality (see Section 5.3.2.3.2 for safety data).
- The most frequently reported AEs by PT were anemia (60.0%), neutrophil count decreased (50.0%), platelet count decreased (43.3%), pyrexia and white blood cell count decreased (33.3% each), and abdominal pain, nausea, and neutropenia (30.0% each).
- AEs (any grade) assessed by the investigator as possibly related to rilvegostomig occurred in 21 participants (70.0%), with the most frequently reported being ALT increased (20.0%) and rash (13.3%).
- A total of 27 participants (90.0%) had at least one AE (regardless of causality) that was maximum Grade 3 or 4 in severity, with the most frequently reported being neutrophil count decreased (43.3%), anemia and neutropenia (30.0% each), platelet count decreased (16.7%), white blood cell count decreased (13.3%), and cholangitis (6.7%). A total of 5 participants (16.7%) had maximum Grade 3 or 4 AEs assessed by the investigator as possibly related to rilvegostomig.
- SAEs (regardless of causality) were reported in 14 participants (46.7%), with the most frequently reported being cholangitis (13.3%), pyrexia (10.0%), and platelet count decreased (6.7%). Three participants (10.0%) had SAEs assessed by the investigator as possibly related to rilvegostomig.
- Two participants (6.7%) had an AE with outcome of death, with events assessed by the investigator as unrelated to rilvegostomig in both participants.
- Six participants (20.0%) had an AE leading to permanent discontinuation of rilvegostomig, in 1 participant an AE of hepatic function was assessed by the investigator as possibly related to rilvegostomig.

1.2.2.3 Rilvegostomig + Antibody Drug Conjugates

1.2.2.3.1 TROPION-Lung04 (Cohort 5)

- As of the DCO date (05 July 2025), a total of 40 participants had received rilvegostomig (750 mg Q3W) in combination with Dato-DXd (6 mg/kg).
- All 40 participants (100%) had at least one AE, regardless of causality (see Section 5.3.3.1.2 for safety data).
- The most frequently reported AEs by PT were stomatitis (55.0%), alopecia and nausea (45.0% each), and rash (32.5%).

- AEs (any grade) assessed by the investigator as possibly related to rilvegostomig occurred in 34 participants (85.0%), with the most frequently reported being rash (27.5%), pneumonitis and stomatitis (25.0% each), and alopecia (22.5%).
- A total of 25 participants (62.5%) had at least one AE (regardless of causality) that was maximum Grade 3 or 4 in severity, with the most frequently reported being pneumonia and pneumonitis (10.0% each). Ten participants (25.0%) had maximum Grade 3 or 4 AEs assessed by the investigator as possibly related to rilvegostomig.
- SAEs (regardless of causality) were reported in 23 participants (57.5%), with the most frequently reported being pneumonia and pneumonitis (12.5% each). Six participants (15.0%) had SAEs assessed by the investigator as possibly related to rilvegostomig.
- Seven participants (17.5%) had an AE with outcome of death, with events assessed by the investigator as possibly related to rilvegostomig in 1 participant (2.5%; pneumonitis).
- Seventeen participants (42.5%) had an AE leading to permanent discontinuation of study treatment. In 9 participants (22.5%) the events leading to discontinuation were assessed as being possibly related to rilvegostomig by the investigator.

1.2.2.3.2 TROPION-PanTumor03 (Cohort 6B)

- As of the DCO date (05 July 2025), a total of 40 participants had received rilvegostomig (750 mg Q3W) in combination with Dato-DXd (6 mg/kg).
- All 40 participants (100%) had at least one AE, regardless of causality (see Section 5.3.3.2.2 for safety data).
- The most frequently reported AEs by PT were stomatitis (45.0%), nausea (30.0%), and amylase increased, constipation, and decreased appetite (27.5% each).
- AEs (any grade) assessed by the investigator as possibly related to rilvegostomig occurred in 33 participants (82.5%), with the most frequently reported being asthenia (25.0%), nausea, pruritus, and rash (17.5% each), and fatigue and stomatitis (15.0% each).
- A total of 14 participants (35.0%) had at least one AE (regardless of causality) that was maximum Grade 3 or 4 in severity, with the most frequently reported being amylase increased (15.0%). Eight participants (20.0%) had maximum Grade 3 or 4 AEs assessed by the investigator as possibly related to rilvegostomig.
- SAEs (regardless of causality) were reported in 10 participants (25.0%), with no events reported in more than 1 participant. Two participants (5.0%) had SAEs assessed by the investigator as possibly related to rilvegostomig.
- Two participants (5.0%) had an AE with outcome of death, with neither event related to rilvegostomig.
- Seven participants (17.5%) had an AE leading to permanent discontinuation of study treatment. AEs reported in 3 participants (7.5%) were considered to be possibly related to rilvegostomig by the investigator.

1.2.2.3.3 DESTINY-Gastric03 (Arms 4A and 4B)

- As of the DCO date (05 July 2025), a total of 60 participants had received rilvegostomig (750 mg Q3W) in combination with T-DXd (5.4 mg/kg) and fluoropyrimidine.

- A total of 54 participants (90.0%) had at least one AE, regardless of causality (see Section 5.3.3.3.2 for safety data).
- The most frequently reported AEs by PT were nausea (50.0%), anemia (35.0%), and diarrhea (31.7%).
- AEs (any grade) assessed by the investigator as possibly related to rilvegostomig occurred in 33 participants (55.0%), with the most frequently reported being nausea (21.7%), diarrhea (13.3%), and AST increased and decreased appetite (11.7% each).
- A total of 20 participants (33.3%) had at least one AE (regardless of causality) that was maximum Grade 3 or 4 in severity, with the most frequently reported being neutrophil count decreased (8.3%) and decreased appetite (5.0%). Nine participants (15.0%) had maximum Grade 3 or 4 AEs assessed by the investigator as possibly related to rilvegostomig.
- SAEs (regardless of causality) were reported in 15 participants (25.0%), with the most frequently reported being decreased appetite, febrile neutropenia, and upper GI hemorrhage (3.3% each). Five participants (8.3%) had SAEs assessed by the investigator as possibly related to rilvegostomig.
- One participant (1.7%) had an AE with outcome of death, the event was not related to rilvegostomig.
- Five participants (8.3%) had an AE leading to permanent discontinuation of study treatment. Four events in 1 participant (1.7%) each were considered to be possibly related to rilvegostomig by the investigator.

1.2.3 Efficacy Summary

1.2.3.1 Rilvegostomig Monotherapy

1.2.3.1.1 ARTEMIDE-01 CPI-naïve Cohorts

As of 21 April 2025, 65 participants were enrolled in Cohorts C and D1 (750 mg). PD-L1 was assessed locally for eligibility and then reviewed centrally, retrospectively.

- In CPI-naïve participants with PD-L1 TPS $\geq 50\%$, by local assay, ORR was 61.8%, PFS-12 was 55.5%, and mPFS was 12.3 months (only local available); by central assay, ORR was 68.2% and PFS-12 was 63.6%.
- In CPI-naïve participants with PD-L1 TPS 1% to 49%, by local assay, ORR was 29.0%, PFS-12 was 27.2%, and mPFS was 6.1 months (only local available); by central assay, ORR was 34.8% and PFS-12 was 30.4%.
- Response was ongoing in 16 responders (53.3%).
- Rilvegostomig led to higher T-effector activation and T-cell clonal expansion versus a historical anti-PD-L1 cohort.

1.2.3.2 Rilvegostomig + Chemotherapy

1.2.3.2.1 GEMINI-Gastric Substudy 2

In GEMINI-Gastric Substudy 2, preliminary efficacy data are available based on the DCO date of 04 July 2024 (Section [5.3.2.2.3](#)).

- Confirmed ORR was 62.5% among 40 evaluable participants, 81.3% in participants with PD-L1 CPS ≥ 5 , and 50.0% in participants with PD-L1 CPS < 5 .
- All participants had disease control (complete response, partial response, or stable disease); none had primary progressive disease.
- Median PFS in response evaluable participants was 8.3 months, 7.1 months in participants with a PD-L1 CPS < 5 and 11.1 months in participants with a PD-L1 CPS ≥ 5 after a median follow-up for PFS of 7.4 months.

1.2.3.2.2 GEMINI-Hepatobiliary (Cohort 2A)

In GEMINI-Hepatobiliary Cohort 2A, efficacy data are available based on the DCO date of 04 November 2024 (Section [5.3.2.3.3](#)).

- Confirmed ORR was 31% among 29 evaluable participants.
- 62.1% participants had stable disease as best overall response.
- The PFS-6 was 73.0% and the mPFS was 8.3 months after a median follow-up of 6.9 months.

1.2.3.3 Rilvegostomig + Antibody Drug Conjugates

1.2.3.3.1 TROPION-Lung04 (Cohort 5)

Overall, 40 participants (Cohort 5A, n = 20; Cohort 5B, n = 20) had received Dato-DXd + rilvegostomig at DCO (24 October 2024). Median follow-up was 5.60 months (range: 0.1 to 18.3 months).

- Confirmed ORR was 57.7% (95% CI: 40.9, 73.0).
- Disease control rate (defined as patients with CR + PR + stable disease; stable disease includes unconfirmed CR/PR or stable disease ≥ 5 weeks) was 95.0% (95% CI: 83.1, 99.4).

1.2.3.3.2 TROPION-PanTumor03 (Cohort 6B)

As of 17 February 2025, a total of 40 participants (cisplatin ineligible n = 22; platinum treated n = 18) had received Dato-DXd + rilvegostomig. Median follow-up in cisplatin ineligible participants was 6.6 months (range: 1.0 to 15.3 months) and in platinum treated participants was 6.1 months (range: 1.2 to 13.6 months).

- Confirmed ORR in cisplatin ineligible participants was 68.2% (95% CI: 45.1, 86.1) and in platinum treated participants was 33.3% (95% CI: 13.3, 59.0).
- Median DoR was not calculable as the data were immature at the DCO.
- Disease control rate (defined as patients with CR + PR + stable disease; stable disease includes unconfirmed CR/PR or stable disease ≥ 5 weeks) was 95.5% (95% CI: 83.44, 99.52) for cisplatin ineligible participants and 83.3% (95% CI: 66.56, 93.71) for platinum treated participants.

2 INTRODUCTION

2.1 Background Information on the Product

2.1.1 Rilvegostomig

Rilvegostomig (AZD2936) is a monovalent, bispecific, humanized, IgG1 mAb engineered with a Fc domain that carries a TM (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 (Section 4.1.1). Dual blockade of TIGIT and PD-1 by rilvegostomig is expected to restore anti-tumor 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 versus 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 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](#)).

2.1.2 Biology of PD-1 and TIGIT

TIGIT and PD-1 are surface receptors predominately expressed on tumor infiltrating T cells that, upon binding to their cognate ligands, negatively regulate T-cell activity.

PD-1

The PD-1 receptor was one of the first co-inhibitory cell surface molecules identified to regulate T-cell activation and function ([Freeman et al 2000](#), [Hui et al 2017](#), [Latchman et al 2001](#)). PD-1 is transiently upregulated upon TCR stimulation, with the highest cell surface expression observed on T cells due to chronic antigen exposure ([Wherry and Kurachi 2015](#)). The PD-1 receptor mediates inhibitory effects on T-cell activation upon engagement with its ligands, PD-L1 or PD-L2 ([Freeman et al 2000](#), [Hui et al 2017](#), [Latchman et al 2001](#)). Agents that competitively inhibit the PD-1/PD-L1 pathway have demonstrated improved clinical activity in a wide range of cancers relative to the previous standard of care and have led to several regulatory approvals by the Food and Drug Administration and/or the European Medicines Agency for the treatment of various malignancies ([Chai et al 2020](#)). For the treatment of NSCLC, anti-PD-1/PD-L1 agents are approved for 1L therapy as monotherapy or

in combination with platinum-containing therapy, or as second-line treatment after platinum-containing therapy (NCCN 2020). While PD-1/PD-L1 targeting strategies have yielded a breakthrough in cancer therapeutics, the majority of patients progress after initial response to anti-PD-1/PD-L1 antibody therapy suggesting that additional immune therapies are required to further improve patient outcome (Bai et al 2017).

TIGIT

TIGIT (also called WUCAM, Vstm3, VSIG9) is a receptor of the Ig superfamily, which plays a critical role in limiting T-cell and NK-cell effector functions. TIGIT is highly expressed on T cells within human tumors and is strongly correlated with CD8⁺ T-cell infiltration and PD-1 expression (Johnston et al 2014). TIGIT 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, Stanitsky 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: TIGIT may either act by interfering with CD226 co-stimulation and/or by directly delivering inhibitory signals to the effector cells (Chauvin and Zarour 2020). In addition to conventional T cells, TIGIT is also expressed by the majority of regulatory T cells in humans and modulates the immunosuppressive function and stability of regulatory T cells (Joller et al 2014, Lucca et al 2019).

Blockade of both PD-1 and TIGIT enhances proliferation and function of tumor antigen-specific CD8⁺ T cells and tumor-infiltrating lymphocytes isolated from patients with melanoma as compared with single blockade (Chauvin et al 2015, Inozume et al 2016). In mouse tumor models, dual PD-1/TIGIT blockade potently increases tumor antigen-specific CD8⁺ T-cell expansion and function in vitro and promotes tumor rejection (Johnston et al 2014). These findings support development of dual PD-1/TIGIT blockade in patients with cancer.

2.2 Rationale for Clinical Development

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 (Manieri et al 2017). Although anti-TIGIT monotherapy showed promising antitumor effects in animal tumor models and human

xenograft tumor models, blockade of TIGIT was not the primary reason for these antitumor effects. Instead, the effects in animal models were attributed to the functional Fc region in the anti-TIGIT antibody, which enables FcγR binding and leads to monocyte activation, dendritic cell antigen presentation, and/or intratumoral regulatory T cell depletion by NK cells ([Waight et al 2018](#)). By contrast, in humans, anti-TIGIT monotherapy is not efficacious ([Kim et al 2023](#), [Niu et al 2022](#)), suggesting that the Fc-mediated effects observed in animal studies do not translate to human efficacy. There is compelling evidence from nonclinical studies and ongoing clinical studies that blockade of PD-1/PD-L1 is key to unleashing the efficacy of anti-TIGIT and generating a synergistic antitumor effect ([Sundstrom et al 2025](#)).

Recent randomized Phase I and Phase II studies in NSCLC, gastric cancer and HCC suggest that anti-TIGIT agents combined with anti-PD-1/PD-L1 therapies may advance antitumor activity versus standard immunotherapy alone ([Cho et al 2022](#), [Johnson et al 2022](#), [Cheng et al 2022](#), [Wu et al 2023](#), [Janjigian et al 2023](#), [Finn et al 2023](#), [Rivera Herrero et al 2024](#)). This has led to the advancement of several monoclonal anti-TIGIT antibodies. However, results from Phase II and Phase III studies have been variable. These outcomes reflect the complex biology of the TIGIT pathway and underscore the need for careful patient selection and choice of target disease. Ongoing research is focused on refining the understanding of optimal combinations, dosing strategies, and biomarkers that may identify patients most likely to benefit from TIGIT-targeted therapies.

A distinct feature of the functional Fc region is that it promotes FcγR binding and can mediate additional effector functions beyond TIGIT blockade. While this may enhance antitumor activity, it also introduces the risk of depleting T cells and NK cells targeted for activation ([Sundstrom et al 2025](#)).

Fc-reduced anti-TIGIT molecules, such as rilvegostomig, are designed with limited FcγR engagement to minimize the risk of depleting activated T cells and NK cells, while preserving immune function and improving safety. This selective Fc modification distinguishes these molecules from Fc-active TIGIT antibodies by reducing unwanted effector activity, which is an important advantage when balancing antitumor efficacy with immune cell preservation. Notably, only Fc-silent and Fc-reduced antibodies (including rilvegostomig) currently remain in ongoing Phase III development.

Rilvegostomig is a bispecific mAb designed to target both TIGIT and PD-1 receptors at the same time, in a coordinated fashion (Section [2.1.1](#)). 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 (see Section [4.1.2](#)).

In clinical studies evaluating rilvegostomig, encouraging preliminary efficacy data have been observed in the following participant groups:

- Participants with CPI-naïve NSCLC in ARTEMIDE-01 (Section 5.3.1.1.3).
- Participants with 1L gastric cancer in GEMINI-Gastric Substudy 2 (Section 5.3.2.2.3).
- Participants with advanced BTC in GEMINI-Hepatobiliary Cohort 2A (Section 5.3.2.3.3).
- Participants with advanced/metastatic NSCLC in TROPION-Lung04 Cohort 5 (Section 5.3.3.1.3).
- Participants with advanced unresectable or metastatic urothelial cancer in TROPION-PanTumor03 Cohort 6B (Section 5.3.3.2.3).

As of 05 July 2025, 116 CPI-naïve participants have been treated with rilvegostomig monotherapy in ARTEMIDE-01, 34 participants in Part C (PD-L1 TPS $\geq$ 1%; 750 mg Q3W) and 61 participants in Part D (PD-L1 TPS $\geq$ 50%; 31 participants at 750 mg Q3W [Cohort D1] and 30 participants at 1500 mg Q3W [Cohort D2]), and 21 participants in Part E (PD-L1 TPS $\geq$ 1%; 750 mg Q3W) (see Section 5.3.1.1.1). In participants with PD-L1 TPS $\geq$ 50% (Cohorts C and D1), ORR was 61.8% (21 of 34 participants) based on local assay results and 68.2% (15 of 22 participants) based on retrospective central assay results (see Section 5.3.1.1.3).

Rilvegostomig exhibited a favorable safety profile in participants with NSCLC who received rilvegostomig 750 mg Q3W throughout the CPI-experienced and CPI-naïve cohorts in ARTEMIDE-01, with low rates of maximum Grade 3 or 4 AEs (any: 33.6%; possibly related to rilvegostomig as assessed by the investigator: 10.7%) and of AEs leading to treatment discontinuation (any: 3.6%; possibly related to rilvegostomig as assessed by the investigator: 2.9%) (see Section 5.3.1.1.2).

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.

3 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATIONS

3.1 Drug Substance

Rilvegostomig is a monovalent, bispecific, humanized, IgG1 TM mAb with an overall molecular weight of approximately 149 kDa. Rilvegostomig is expressed by a clonal production CHO cell line. The manufacturing of clinical supplies is conducted in accordance with current Good Manufacturing Practices.

3.2 Drug Product (Including Formulation and Dosage/Supply & Storage)

Rilvegostomig is supplied as a liquid product for iv or sc administration.

Intravenous rilvegostomig is supplied as a sterile concentrate for solution for infusion product in a 20R glass vial. Intravenous rilvegostomig is stored at 2 to 8 °C (36 to 46 °F). Intravenous rilvegostomig is diluted into 0.9% saline or 5% dextrose for iv infusion. Intravenous rilvegostomig is formulated at 50 mg/mL in 20 mM L-histidine/L-histidine-HCl, 240 mM sucrose, 0.04% (w/v) poloxamer 188, pH 6.0. The vial contains 750 mg (label claim) of active IP.

Subcutaneous rilvegostomig is supplied as a sterile solution for injection product in a 10R glass vial. Subcutaneous rilvegostomig is stored at 2 to 8 °C (36 to 46 °F). Subcutaneous rilvegostomig is not diluted prior to sc injection. Subcutaneous rilvegostomig is formulated at 200 mg/mL in 20 mM L-histidine/ L-histidine-HCl, 210 mM arginine-HCl, 0.04% (w/v) poloxamer 188, pH 6.0. The vial contains 750 mg (label claim) of active IP.

Information for proper handling and preparation of the IPs is provided in the clinical study protocol(s).

4 NONCLINICAL STUDIES

4.1 Nonclinical Pharmacology

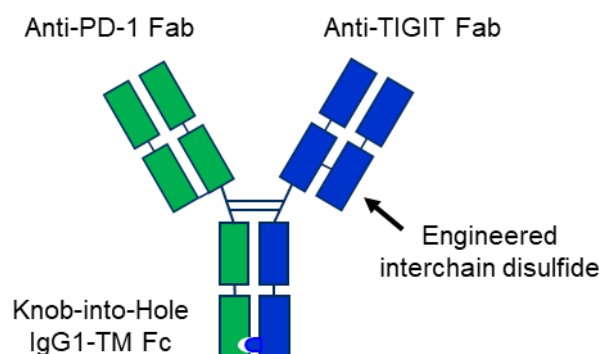
4.1.1 Primary Pharmacology: In Vitro Studies

4.1.1.1 Generation of a Monovalent Bispecific Antibody Rilvegostomig Targeting PD-1 and TIGIT Receptors

Rilvegostomig was constructed on the backbone of the DuetMab molecule ([Mazor et al 2015](#)) and is comprised of the variable domains of the anti-human PD-1 LO115 mAb and the anti-human TIGIT COM902 mAb, the derivation of which can be found in Pharmacology Report ONC2936-0002, see [Figure 1](#). The V_H gene of the anti-PD-1 LO115 mAb (AstraZeneca IND 144833, Pharmacology Report ONC5752-0001) was inserted into a human gamma-1 constant heavy chain carrying the 'Hole' mutations (T366S, L368A, and Y407V),

while the V_L gene of LO115 was inserted in frame into a human Kappa constant domain designed to pair with the 'Hole' heavy chain. The V_H gene of the optimized anti-TIGIT COM902 was inserted into a human gamma-1 constant heavy chain carrying the "Knob" mutation (T366W) and the alternative interchain cysteine mutations (F126C and C219V). The V_L gene of the optimized COM902 was inserted in frame into a human Lambda constant domain carrying the corresponding alternative interchain cysteine mutations (S121C and C214V) designed to pair with the "Knob" heavy chain. In addition, 2 residues in the CH3 domains of "Knob" and "Hole" heavy chains were mutated to cysteine (S354C in "Knob" and Y349C in "Hole") to form a stabilizing disulfide bridge. The Fc domain was further engineered to carry the TMs (L234F, L235E and P331S) designed to reduce the ability to trigger Fc-mediated immune effector functions such as CDC, ADCC, and antibody-dependent cell-mediated phagocytosis (Oganesyan et al 2008). Amino acid residues are numbered by Kabat numbering system. The assembled monovalent bispecific DuetMab antibody was designated as rilvegostomig. The variable domains of the 2 parental mAbs; LO115 and COM902 were cloned onto the backbone of a human IgG1 TM isotype and the resulting antibodies were used as control articles.

Figure 1 Schematic Diagram of Rilvegostomig



Shown are the anti-TIGIT and anti-PD-1 Fabs, engineered interchain disulfide in the anti-TIGIT CH1-CL interface, and knob-into-hole IgG1-TM (L234F/L235E/P331S) Fc domain of rilvegostomig.

4.1.1.2 Sequence Homology Comparison of Human PD-1 and TIGIT Proteins with Orthologs in Cynomolgus Monkey, Rhesus Monkey, Rat and Mouse

Amino acid sequences for human PD-1 and TIGIT were identified and aligned to orthologs in cynomolgus monkey, rhesus monkey, mouse, and rat (Pharmacology Report ONC2936-0001). Percentage identity was calculated based on the results of these alignments. PD-1 is well conserved among non-human primates and human PD-1 shares 95% and 96% sequence identity with cynomolgus monkey and rhesus monkey PD-1, respectively (Table 4). Rodent species are less conserved; mouse and rat PD-1 share 59% and 60% homology with human PD-1, respectively.

The amino acid sequence of TIGIT is conserved among non-human primates, with an 87% identity between human TIGIT and cynomolgus or rhesus monkey TIGIT (Table 5). Sequence homology is reduced upon comparison to rodent species; human TIGIT shares 59% and 57% identity between mouse and rat TIGIT, respectively.

High amino acid sequence identity in PD-1 and TIGIT across human and non-human primates suggests that rilvegostomig is likely to bind to cynomolgus monkey and rhesus monkey PD-1 and TIGIT. In contrast, the amino acid identity comparison between human, mouse, and rat PD-1 and TIGIT is considerably lower, indicating that binding of rilvegostomig to murine or rat PD-1 or TIGIT is less likely.

Table 4 PD-1 Ortholog Percentage Identity Matrix

	hPD-1	cyPD-1	rhPD-1	mPD-1	rPD-1
hPD-1	100	95	96	59	60
cyPD-1		100	98	60	62
rhPD-1			100	60	63
mPD-1				100	86
rPD-1					100

Black fill used to prevent duplication of values per species comparison.

cy = cynomolgus monkey; h = human; m = mouse; r = rat; rh = rhesus monkey.

Table 5 TIGIT Ortholog Percentage Identity

	hTIGIT	cyTIGIT	rhTIGIT	mTIGIT	rTIGIT
hTIGIT	100	87	87	59	57
cyTIGIT		100	100	59	58
rhTIGIT			100	59	58
mTIGIT				100	85
rTIGIT					100

Black fill used to prevent duplication of values per species comparison.

cy = cynomolgus monkey; h = human; m = mouse; r = rat; rh = rhesus monkey.

4.1.1.3 Binding Affinities of Rilvegostomig for Recombinant PD-1 and TIGIT Antigens

The intrinsic binding kinetics of rilvegostomig for recombinant human, cynomolgus monkey, and murine PD-1 and TIGIT antigens were determined by surface plasmon resonance on a Biacore T200 instrument (Pharmacology Report ONC2936-0002). The association rate constant, disassociation rate constant, and dissociation constant are shown in Table 6. The PD-1 arm of rilvegostomig maintains the binding properties of parental anti-PD-1 IgG and binds human and cynomolgus monkey PD-1 with an affinity of 0.32 nM and 0.34 nM, respectively. Consistent with the binding properties of parental anti-PD-1 IgG, rilvegostomig

exhibits only residual binding to the murine ortholog of PD-1 with an affinity of 950 nM. The TIGIT arm of rilvegostomig maintains the binding properties of parental anti-TIGIT IgG and binds human, cynomolgus monkey and murine TIGIT with an affinity of 15 pM, 41.1 nM and 2.9 nM. Evaluating the differential binding affinities of rilvegostomig to PD-1 and TIGIT antigens demonstrated a 21-fold increased intrinsic affinity to human TIGIT in comparison to human PD-1.

Table 6 Kinetics of Rilvegostomig to PD-1 and TIGIT Antigens

Antibody	Antigen	$K_{on} (M^{-1} s^{-1})$	$K_{off} (s^{-1})$	$K_D (nM)$
Rilvegostomig	Human PD-1	1.80×10^5	5.81×10^{-5}	0.32
	Cynomolgus monkey PD-1	1.53×10^5	5.17×10^{-5}	0.34
	Mouse PD-1	6.31×10^4	6.00×10^{-2}	950
	Human TIGIT	4.37×10^6	6.57×10^{-5}	0.015
	Cynomolgus monkey TIGIT	9.99×10^5	4.11×10^{-2}	41.1
	Mouse TIGIT	2.17×10^6	6.31×10^{-3}	2.9
Anti-PD-1 IgG	Human PD-1	3.02×10^5	2.37×10^{-4}	0.79
	Cynomolgus monkey PD-1	3.46×10^5	2.38×10^{-4}	0.69
	Mouse PD-1	1.49×10^5	6.65×10^{-2}	447
Anti-TIGIT IgG	Human TIGIT	4.86×10^6	3.94×10^{-5}	0.008
	Cynomolgus monkey TIGIT	3.56×10^6	4.94×10^{-2}	13.6
	Mouse TIGIT	8.68×10^6	7.29×10^{-3}	0.84

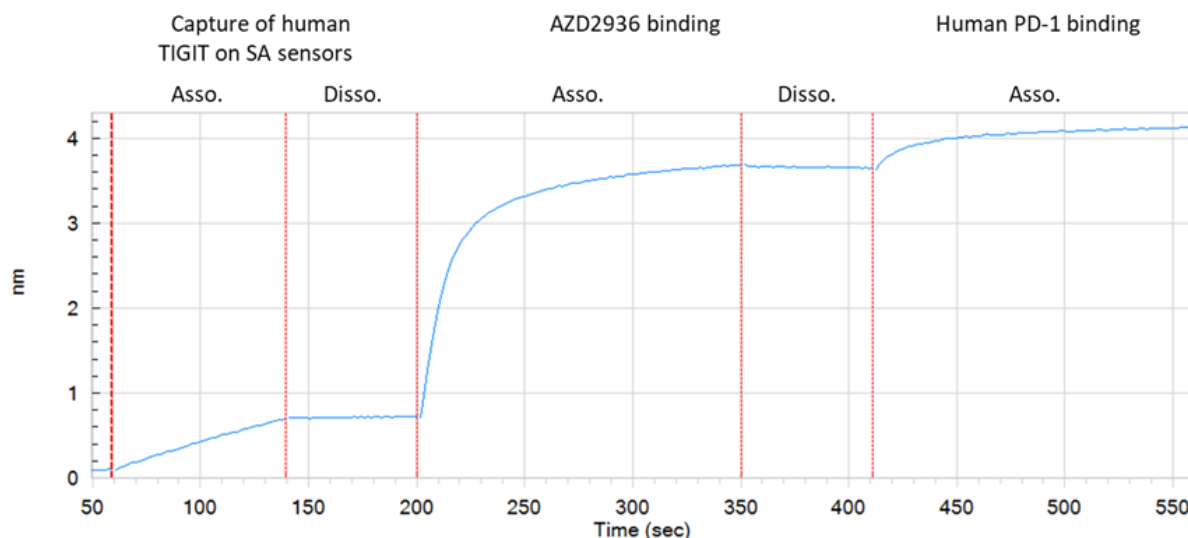
Kinetic measurements to soluble monomeric forms of PD-1 and TIGIT antigens were performed using a Biacore instrument. K_D were calculated as the ratio of k_{off}/k_{on} from a non-linear fit of the data.

K_{on} = association rate constant; K_{off} = dissociation rate constant; K_D = dissociation constant.

4.1.1.4 Rilvegostomig Concurrently Binds to PD-1 and TIGIT

The ability of rilvegostomig to concurrently bind recombinant human and cynomolgus monkey PD-1 and TIGIT proteins was determined by Octet analysis (Pharmacology Report ONC2936-0002). Rilvegostomig demonstrated simultaneous binding to human PD-1 and human TIGIT antigens (Figure 2). Furthermore, rilvegostomig demonstrated simultaneous binding to cynomolgus monkey PD-1 and cynomolgus monkey TIGIT antigens (Figure 3).

Figure 2 Concurrent Binding of Rilvegostomig to Human PD-1 and TIGIT Proteins Determined by Octet



Simultaneous binding using antigen capture format. Sensors loaded with human TIGIT antigen were exposed to successive association and dissociation interactions first with rilvegostomig then with human PD-1. Asso = association; AZD2936 = rilvegostomig; Disso = dissociation; SA = streptavidin.

Figure 3 Concurrent Binding of Rilvegostomig to Cynomolgus Monkey PD-1 and TIGIT Proteins Determined by Octet



Simultaneous binding using antigen capture format. Sensors loaded with cynomolgus monkey PD-1 antigen were exposed to successive association and dissociation interactions first with rilvegostomig then with cynomolgus monkey TIGIT.

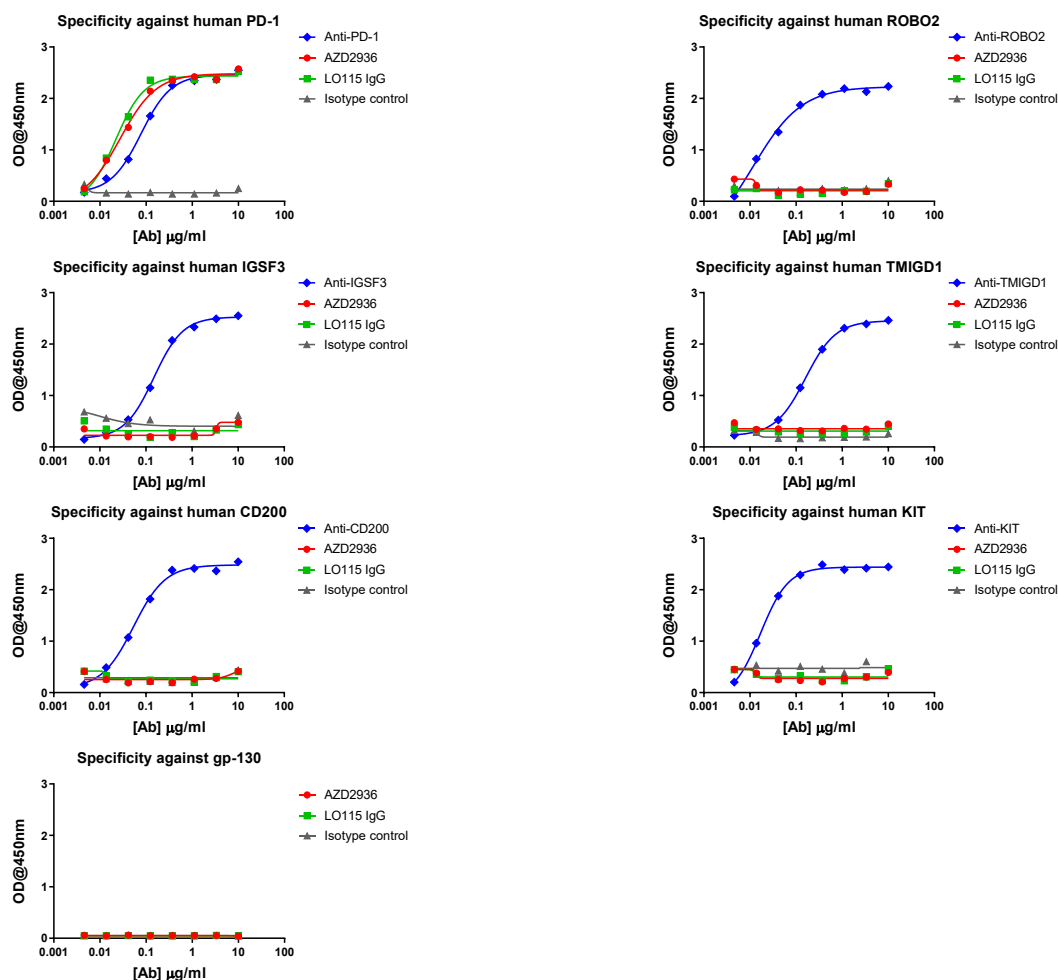
Asso = association; AZD2936 = rilvegostomig; Disso = dissociation; NI-NTA = nickel-nitrilotriacetate.

4.1.1.5 Specificity of Rilvegostomig to PD-1 and TIGIT

To minimize off-target effects, the specificity of rilvegostomig for PD-1 and TIGIT was evaluated alongside endogenous related proteins exhibiting > 25% sequence identity to PD-1

or TIGIT (Pharmacology Report ONC2936-0002). As shown in [Figure 4](#), rilvegostomig specifically binds to human PD-1 antigen and exhibits no off-target binding to endogenous related human proteins. Similarly, rilvegostomig specifically binds to human TIGIT antigen and exhibits no off-target binding to endogenous related human proteins ([Figure 5](#)).

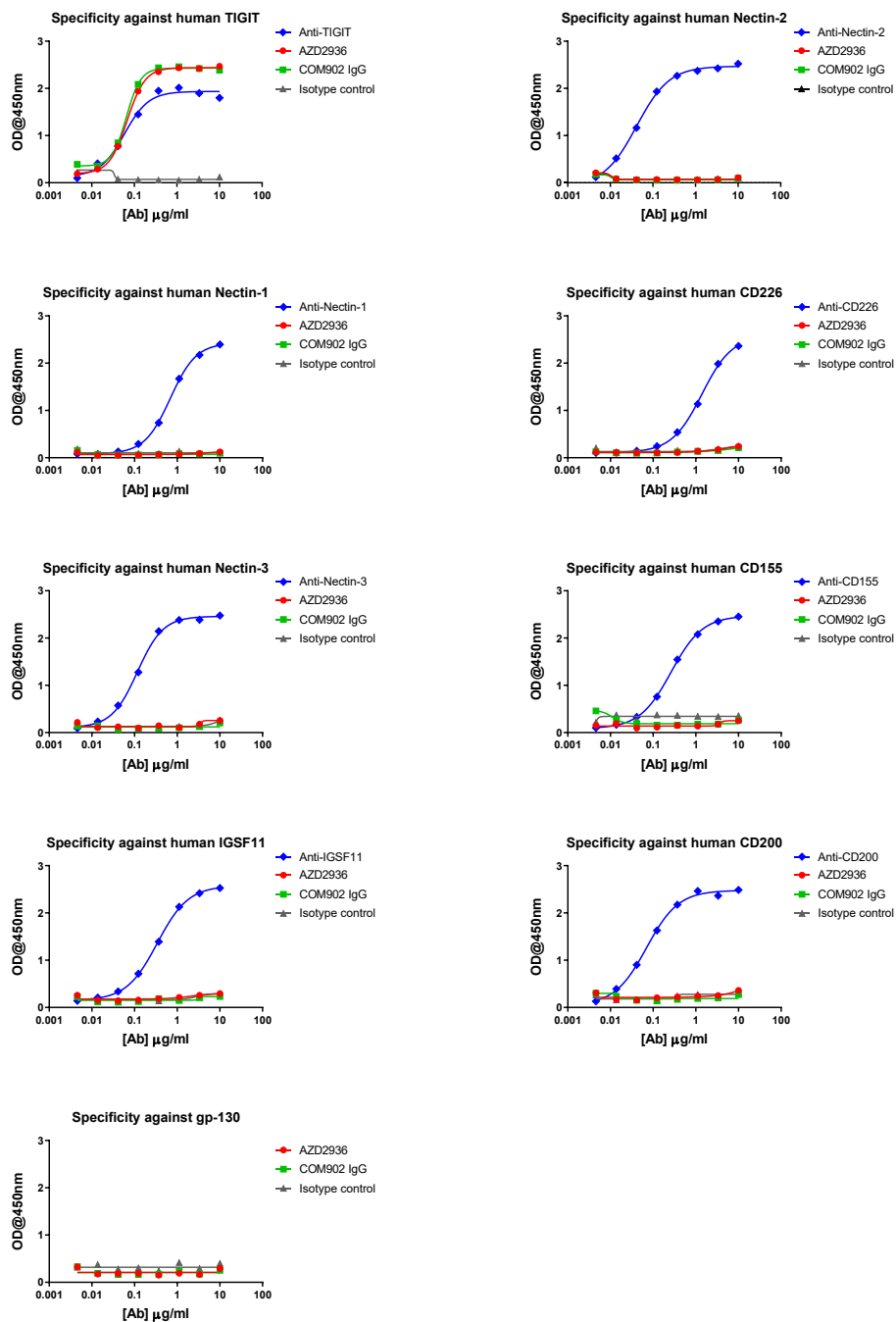
Figure 4 Selective Binding of Rilvegostomig to Human PD-1 over Endogenous Related Proteins Determined by ELISA



Plates were coated with recombinant human proteins exhibiting > 25% sequence identity to human PD-1 extracellular domain. The human gp-130 protein was used as a negative control protein. Test and control article antibodies were detected with HRP-conjugated species-specific secondary antibody. The ELISA was developed using the chromogenic HRP substrate TMB. Assay plates were read at 450 nm.

Ab = antibody; AZD2936 = rilvegostomig; ELISA = enzyme linked immunosorbent assay; gp-130 = glycoprotein 130; HRP = horseradish peroxidase; IGSF3 = immunoglobulin superfamily member 3; KIT = tyrosine-protein kinase KIT; OD = optical density; ROBO2 = roundabout guidance receptor 2; TMB = 3,3',5'-Tetramethylbenzidine; TMIGD1 = transmembrane and immunoglobulin domain containing 1.

Figure 5 Selective Binding of Rilvegostomig to Human TIGIT over Endogenous Related Proteins Determined by ELISA



Plates were coated with recombinant human proteins exhibiting > 25% sequence identity to human TIGIT extracellular domain. The human gp-130 protein was used as a negative control protein. Test and control article antibodies were detected with HRP-conjugated species-specific secondary antibody. The ELISA was developed using the chromogenic HRP substrate TMB. Assay plates were read at 450 nm.

Ab = antibody; AZD2936 = rilvegostomig; ELISA = enzyme linked immunosorbent assay; gp-130 = glycoprotein 130; HRP = horseradish peroxidase; IGSF11 = immunoglobulin superfamily member 11; OD = optical density; TMB = 3,3',5'-Tetramethylbenzidine.

4.1.1.6 Cellular Binding of Rilvegostomig to Human PD-1 and TIGIT Receptors on Jurkat Cell Lines

Cellular based equilibrium binding assays were performed to measure the apparent affinity of rilvegostomig binding to human PD-1 and TIGIT receptors expressed on the cell surface of engineered cell lines (Pharmacology Report ONC2936-0003). For this purpose, Jurkat cell lines were engineered to express human PD-1 and/or TIGIT receptors. To determine if these cellular subsets were relevant for evaluation of rilvegostomig binding, cell surface receptor densities of human PD-1 and TIGIT were quantified. As shown in [Table 7](#), PD-1 receptor density on the single-positive Jurkat PD-1⁺TIGIT⁻ cells was determined at 11,700 (SD ± 6690) receptors/cell and TIGIT receptor density on the single-positive Jurkat PD-1⁻TIGIT⁺ cells was determined at 147,000 (SD ± 91,500) receptors/cell. PD-1 and TIGIT receptor densities on the double-positive Jurkat PD-1⁺TIGIT⁺ cells were 621,000 (SD ± 210,000) and 149,000 (SD ± 89,100), exhibiting a 4.17:1 excess of PD-1 receptor over TIGIT receptor.

Table 7 PD-1 and TIGIT Receptor Density on Engineered Jurkat Cell lines, n = 4

Cell line	PD-1 (receptors/cell, mean ± SD)	TIGIT (receptors/cell, mean ± SD)	PD-1/TIGIT (ratio)
Jurkat PD-1 ⁺ TIGIT ⁻	11,700 (± 6690)	ND	ND
Jurkat PD-1 ⁻ TIGIT ⁺	ND	147,000 (± 91,500)	ND
Jurkat PD-1 ⁺ TIGIT ⁺	621,000 (± 210,000)	149,000 (± 89,100)	4.17

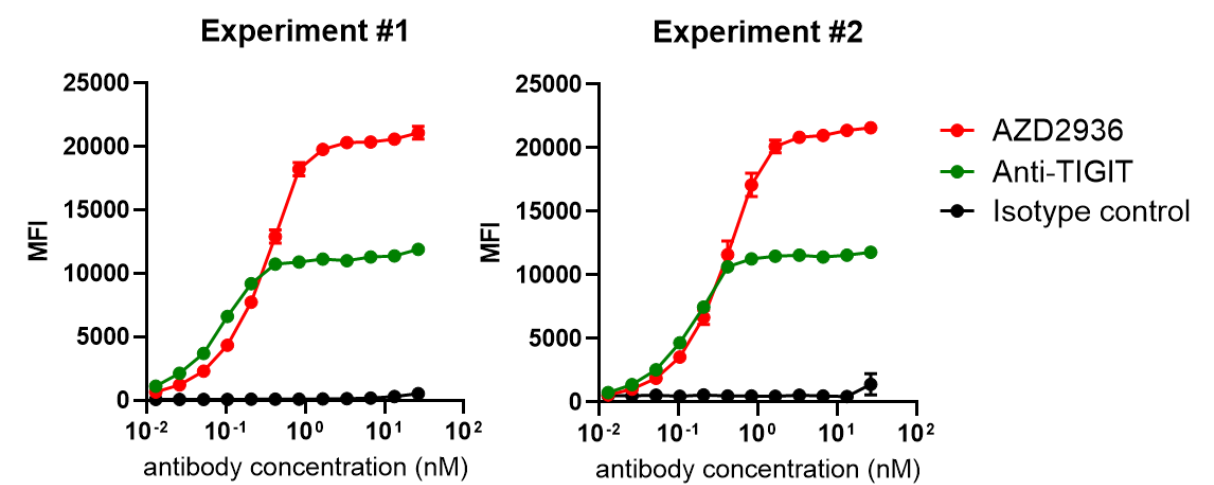
ND = not determined.

Binding of rilvegostomig was evaluated alongside parental bivalent mAbs, and detected on 3 Jurkat cell lines engineered to express human PD-1 and/or human TIGIT receptors. Rilvegostomig bound to Jurkat PD-1⁻TIGIT⁺ cells in a concentration-dependent manner and maintained the cellular binding properties of the parental anti-TIGIT mAb to TIGIT receptors ([Figure 6](#)). Compared to the bivalent anti-TIGIT antibody, rilvegostomig demonstrated increased (2.85-fold) binding EC₅₀ values ([Table 8](#)) and increased maximal binding ([Figure 6](#)). Rilvegostomig bound to Jurkat PD-1⁺TIGIT⁻ cells in a concentration-dependent manner. Compared to the bivalent anti-PD-1 antibody for binding on the PD-1⁺TIGIT⁻ Jurkat cells, rilvegostomig demonstrated increased (4.82-fold) binding EC₅₀ values ([Table 9](#)) and increased maximal binding ([Figure 7](#)). These results demonstrated that monovalent binding is sufficient for the engagement of TIGIT or PD-1 on the Jurkat cells.

The cellular binding properties of rilvegostomig to the Jurkat cell lines expressing either PD-1 (PD-1⁺TIGIT⁻) or TIGIT (PD-1⁻TIGIT⁺) or both receptors (PD-1⁺TIGIT⁺) were determined by a flow cytometry binding assay. As shown in [Figure 7](#), rilvegostomig bound to all 3 types of Jurkat cells with similar cellular binding properties. To evaluate the difference in rilvegostomig binding affinity between the 3 cell lines, EC₅₀ values were determined [Table 10](#).

The mean EC₅₀ of rilvegostomig to the PD-1 single expressing cell line was 0.797 nM. The mean EC₅₀ of rilvegostomig to the TIGIT⁺PD-1⁺ dual expressing cell line was 0.632 nM. Binding to the cell line engineered to express TIGIT only receptors yielded the lowest mean EC₅₀ value at 0.314 nM, demonstrating that rilvegostomig has an approximately 2-fold increased binding affinity to human TIGIT single expressing cells, compared to PD-1 single or PD-1⁺TIGIT⁺ double positive cell lines.

Figure 6 Cellular Binding of Rilvegostomig to Human TIGIT Receptors on Engineered Jurkat PD-1⁻TIGIT⁺ Cells



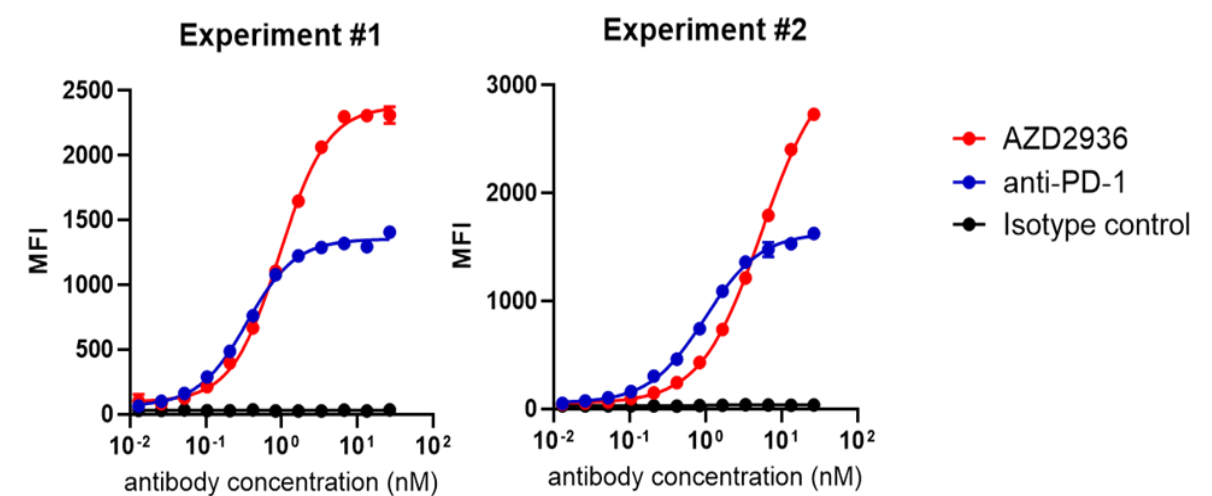
Cellular binding to human TIGIT single expressing cell line: Jurkat PD-1⁻TIGIT⁺. Test and control article antibodies were detected with fluorescently conjugated goat anti-human IgG secondary antibody and evaluated by flow cytometry.
AZD2936 = rilvegostomig; MFI = geometric mean fluorescence intensity.

Table 8 Rilvegostomig and Anti-TIGIT Binding Activity on TIGIT⁺ Jurkat Cells

	Experiment No. 1	Experiment No. 2	Mean EC ₅₀ (nM)	Fold Change vs anti-TIGIT
	EC ₅₀ (nM)	EC ₅₀ (nM)		
Rilvegostomig	0.303	0.375	0.339	2.85
Anti-TIGIT	0.092	0.147	0.119	1.00

EC₅₀ was derived from the mean values taken from 3 replicates.

Figure 7 Cellular Binding of Rilvegostomig to Human PD-1 Receptors on Engineered Jurkat PD-1⁺TIGIT⁻ cells



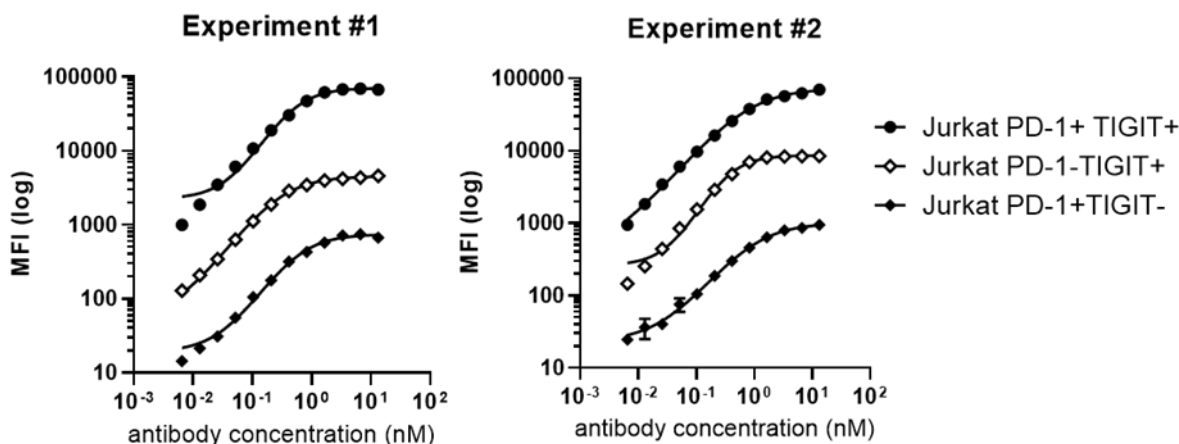
Cellular binding to human PD-1 single expressing cell line: Jurkat PD-1⁺TIGIT⁻. Test and control article antibodies were detected with fluorescently conjugated goat anti-human IgG secondary antibody and evaluated by flow cytometry.
AZD2936 = rilvegostomig; MFI = geometric mean fluorescence intensity.

Table 9 Rilvegostomig and anti-PD-1 Binding Activity on PD-1⁺ Jurkat Cells

	Experiment No. 1	Experiment No. 2	Mean EC ₅₀ (nM)	Fold Change vs anti-PD-1
	EC ₅₀ (nM)	EC ₅₀ (nM)		
Rilvegostomig	0.944	5.49	3.22	4.82
Anti-PD-1	0.349	0.985	0.667	1.00

EC₅₀ was derived from the mean values taken from 3 replicates.

Figure 8 Cellular Binding of Rilvegostomig to Human PD-1 and TIGIT Receptors on Engineered PD-1⁺TIGIT⁻, PD-1⁻TIGIT⁺ and PD-1⁺TIGIT⁺ Jurkat Cells



Cellular binding to human single expressing cell lines: Jurkat PD-1⁻TIGIT⁺ and Jurkat PD-1⁺TIGIT⁻ or human double expressing cell line: Jurkat PD-1⁺TIGIT⁺. Test and control article antibodies were detected with fluorescently conjugated goat anti-human IgG secondary antibody and evaluated by flow cytometry. MFI = geometric mean fluorescence intensity.

Table 10 Rilvegostomig Binding Activity on PD-1⁺TIGIT⁻, PD-1⁻TIGIT⁺ and PD-1⁺TIGIT⁺ Jurkat Cells

	Experiment No. 1	Experiment No. 2	Mean EC ₅₀ (nM)
	EC ₅₀ (nM)	EC ₅₀ (nM)	
PD-1 ⁺ TIGIT ⁺ Jurkat	0.495	0.769	0.632
PD-1 ⁻ TIGIT ⁺ Jurkat	0.282	0.346	0.314
PD-1 ⁺ TIGIT ⁻ Jurkat	0.584	1.01	0.797

EC₅₀ was derived from the mean values taken from 3 replicates.

4.1.1.7 Cellular Binding of Rilvegostomig to Cynomolgus Monkey PD-1 and TIGIT Receptors on Engineered Jurkat Cell Lines

Flow cytometry based cell binding assays were performed to evaluate binding of rilvegostomig to cynomolgus monkey PD-1 and TIGIT receptors (Pharmacology Report ONC2936-0003). For this purpose, Jurkat cell lines were engineered to express cynomolgus monkey PD-1 and/or cynomolgus monkey TIGIT receptors. To determine if these cellular subsets were relevant for evaluation of rilvegostomig binding, cell surface receptor densities of cynomolgus monkey PD-1 and TIGIT were quantified. As shown in Table 11, TIGIT receptor density on the single-positive Jurkat PD-1⁻TIGIT⁺ cells was determined at 31,300 (SD ± 7680) receptors/cell. PD-1 and TIGIT receptor densities on the double-positive Jurkat PD-1⁺TIGIT⁺ cells were 7640 (SD ± 662) and 27,200 (SD ± 3300), exhibiting an approximate 0.28:1 deficiency of PD-1 receptor to TIGIT receptor.

Table 11 PD-1 and TIGIT Receptor Density on Engineered Jurkat Cell lines, n = 3

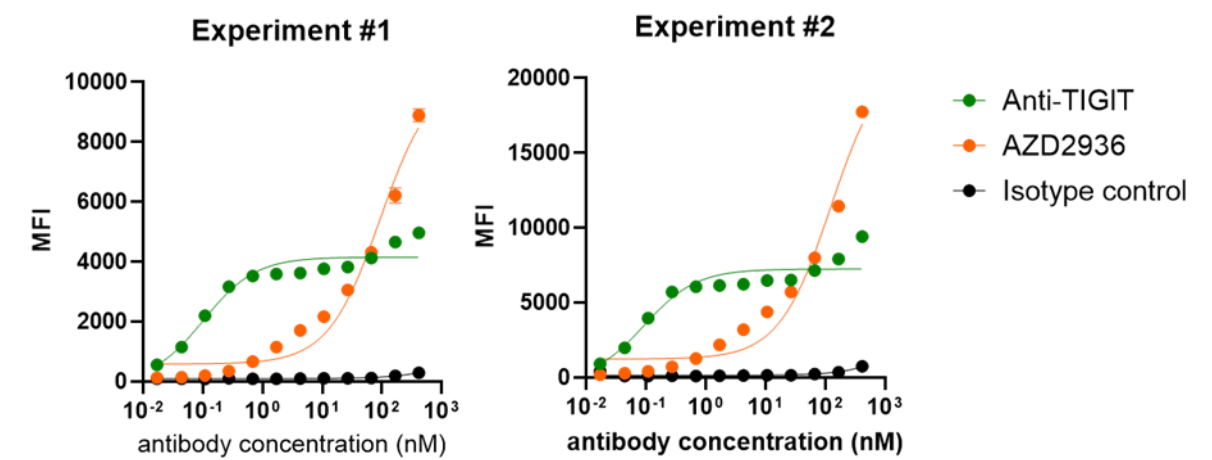
Cell line	PD-1 (receptors/cell, mean $\pm$ SD)	TIGIT (receptors/cell, mean $\pm$ SD)	PD-1/TIGIT (ratio)
Jurkat PD-1 ⁻ TIGIT ⁺	ND	31,300 ($\pm$ 7680)	ND
Jurkat PD-1 ⁺ TIGIT ⁺	7640 ($\pm$ 662)	27,200 ($\pm$ 3300)	0.28

ND = not determined.

As shown in [Figure 9](#), both rilvegostomig and anti-TIGIT bound to cynomolgus monkey TIGIT expressing Jurkat cells in a concentration-dependent manner and rilvegostomig has increased maximal binding than anti-TIGIT. Rilvegostomig demonstrated 1102-fold increased binding EC₅₀ values (108 nM) compared to the bivalent anti-TIGIT (EC₅₀ 0.099 nM) ([Table 12](#)), indicating rilvegostomig has reduced binding properties than anti-TIGIT mAb.

The cellular binding properties of rilvegostomig, the parental anti-PD-1 antibody, the parental anti-TIGIT antibody, or the combination of parental antibodies to the Jurkat cell line expressing cynomolgus monkey PD-1 and TIGIT receptors were determined by flow cytometry. In this assay, all test articles other than the isotype control mAb bound to the Jurkat cells in a concentration-dependent manner ([Figure 10](#)). The EC₅₀ values obtained by the anti-TIGIT or anti-PD-1 antibody for Jurkat cynomolgus monkey PD-1⁺TIGIT⁺ cells were determined at 0.157 nM and 6.66 nM, respectively [Table 13](#). The EC₅₀ value of rilvegostomig bound to the same cells was determined at 20.9 nM, which was 19.5-fold higher than the EC₅₀ values generated by the combination of anti-PD-1 and anti-TIGIT antibodies (1.07 nM) ([Table 13](#)), demonstrating that rilvegostomig has reduced binding properties than the combination of anti-PD-1 and anti-TIGIT antibodies.

Figure 9 Cellular Binding of Rilvegostomig to Cynomolgus Monkey TIGIT Receptors on Engineered Jurkat Cells



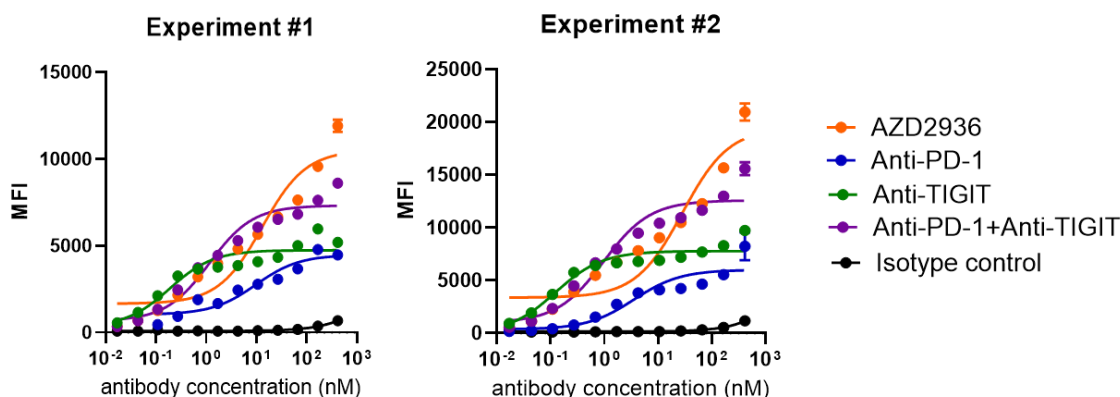
Cellular binding to Jurkat cynomolgus monkey TIGIT single expressing cell line. Test and control article antibodies were detected with fluorescently conjugated goat anti-human IgG secondary antibody and evaluated by flow cytometry.
AZD2936 = rilvegostomig; MFI = geometric mean fluorescence intensity.

Table 12 Rilvegostomig and Anti-TIGIT Binding Activity on Jurkat Cell lines Engineered to Express Cynomolgus Monkey TIGIT

	Experiment No. 1	Experiment No. 2	Mean EC ₅₀ (nM)	Fold Change vs anti-TIGIT
	EC ₅₀ (nM)	EC ₅₀ (nM)		
Rilvegostomig	93	124	108	1102
Anti-TIGIT	0.103	0.094	0.099	1.00

EC₅₀ was derived from the mean values taken from 3 replicates.

Figure 10 Cellular Binding of Rilvegostomig to Cynomolgus Monkey PD-1 and TIGIT Receptors on Engineered Jurkat Cells



Cellular binding to Jurkat cynomolgus monkey PD-1 and TIGIT double expressing cell line. Test and control article antibodies were detected with fluorescently conjugated goat anti-human IgG secondary antibody and evaluated by flow cytometry.

AZD2936 = rilvegostomig; MFI = geometric mean fluorescence intensity.

Table 13 Rilvegostomig Binding Activity on Jurkat Cell lines Engineered to Express Cynomolgus Monkey PD-1 and TIGIT

	Experiment No. 1	Experiment No. 2	Mean EC ₅₀ (nM)	Fold Change vs anti-PD-1 plus anti-TIGIT
	EC ₅₀ (nM)	EC ₅₀ (nM)		
Rilvegostomig	13.1	28.6	20.9	19.5
Anti-PD-1 plus anti-TIGIT	1.16	0.971	1.07	1.00
Anti-PD-1	9.76	3.55	6.66	6.22
Anti-TIGIT	0.189	0.124	0.157	0.147

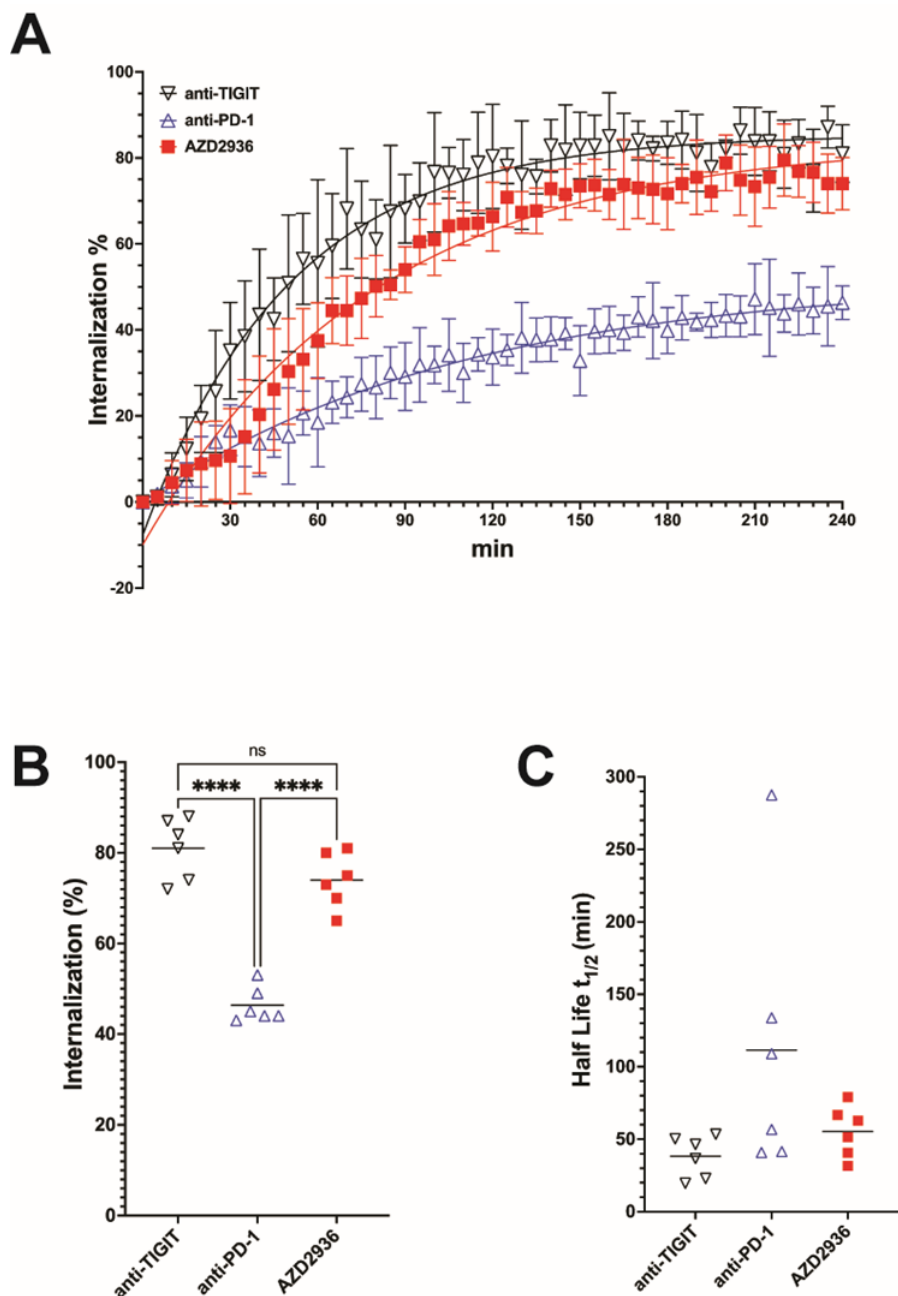
EC₅₀ was derived from the mean values taken from 3 replicates.

4.1.1.8 Internalization of Rilvegostomig into Primary Human CD8⁺ T Cells

The internalization properties of rilvegostomig and parental monospecific bivalent antibodies into stimulated primary human CD8⁺ T cells were evaluated using a quantitative live cell imaging assay (Pharmacology Report ONC2936-0004). Cells were imaged with a confocal fluorescence imager over a 4-hour incubation period at 37 °C. Rilvegostomig and the parental monospecific bivalent antibodies were directly conjugated with a fluorescent dye and added to the cells at 10 µg/mL. Rilvegostomig internalization showed a statistically significant difference in internalization percentage after 4 hours compared to the control anti-PD-1 mAb, but not different compared to the control anti-TIGIT mAb (Figure 11). Measurement of internalization kinetics across all 6 donors showed internalization half-life of 55.4 (SD ± 16.03) minutes, 111.6 (SD ± 85.99) minutes, and 38.3 (SD ± 13.08) minutes for the rilvegostomig, anti-PD-1 mAb, and anti-TIGIT mAb, respectively. These data indicate that

rilvegostomig efficiently internalized into activated primary human CD8⁺ T cells at an intermediate rate between that measured for the parental anti-PD-1 mAb and the parental anti-TIGIT mAb.

Figure 11 Live Cell Imaging Quantification of Rilvegostomig Internalization



Internalization properties of rilvegostomig and its parental monovalent mAbs into primary human CD8⁺ T cells were characterized by quantitative live cell imaging of images captured over a 240 minute time course. Test and control articles were administered to the cells at 10 μ g/mL. (A) Each point represents mean internalization percentage $\pm$ standard deviation of 6 donors at 5 minute intervals for 240 minutes. (B) Internalization percentage after 4 hours and (C) The predicted half-life from 6 donors is shown. These values were derived using the Dissociation – One phase exponential decay equation. Statistical differences are shown in (B) and there are no differences between groups in (C). Horizontal bars indicate intragroup arithmetic mean; Statistic significance was evaluated by one-way ANOVA, Tukey's multiple comparison test.

****, $p < 0.0001$.

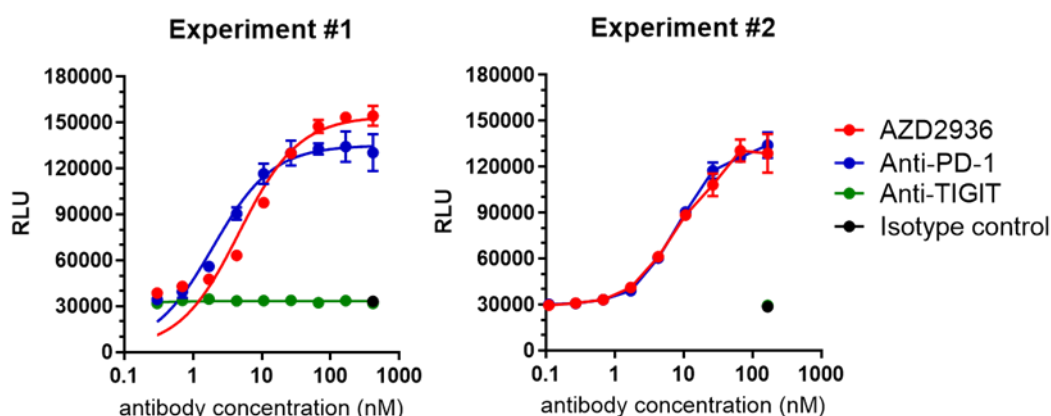
ANOVA = analysis of variance; AZD2936 = rilvegostomig; min = minutes; ns = not significant.

4.1.1.9 In Vitro Blocking Activity of Rilvegostomig in Assays Using Jurkat T Cells Engineered to Express Human PD-1 and/or TIGIT

To assess the ability of rilvegostomig to block PD-1/PD-L1 and/or TIGIT/CD155 interactions, two-cell co-culture bioactivity assays were utilized using CHO-K1 cells genetically engineered to express the anti-CD3 scFv of OKT3, PD-L1 and CD155 and Jurkat NFAT-luciferase reporter T cells genetically engineered to express human PD-1, human TIGIT or both antigens (Pharmacology Report ONC2936-0005). In the assay, luciferase activity under the control of NFAT response elements was measured in response to stimulation by OKT3. NFAT signaling occurs downstream of the TCR signaling, and has been reported to correlate with other measures of T-cell activation, such as proliferation and cytokine release. Full blockade of PD-1/PD-L1 and/or TIGIT/CD155 interactions facilitated maximum TCR agonism and subsequent luciferase activity.

The activity of rilvegostomig to block PD-1/PD-L1 interactions was tested in the two-cell co-culture assay with CHO-K1 OKT3 PD-L1 CD155 cells and PD-1⁺TIGIT⁻ Jurkat T cell NFAT-luciferase reporter cells. Rilvegostomig showed a concentration-dependent activity in 2 duplicate experiments with a mean EC₅₀ of 4.26 nM (EC₅₀ of 4.70 and 3.83 nM from Experiment No. 1 and No. 2, respectively) (Figure 12 and Table 14). In the same assay, the mean EC₅₀ of anti-PD-1 were 3.03 nM (EC₅₀ of 1.93 and 4.14 nM from Experiment No. 1 and No. 2, respectively). Neither anti-TIGIT antibody nor isotype control antibody showed activity in this assay.

Figure 12 Bioactivity of Rilvegostomig in Human PD-1⁺TIGIT⁻ Jurkat T cell NFAT-Luciferase Reporter Two-cell Co-culture Assays



Concentration-dependent activity of rilvegostomig, anti-PD-1, anti-TIGIT, or isotype control antibodies to enhance TCR-depending signaling through blockade of PD-1/PD-L1 interactions in a two-cell co-culture bioactivity assay with CHO-K1 OKT3 PD-L1 CD155 cells and a PD-1⁺TIGIT⁻ Jurkat T cell NFAT-luciferase reporter cell line. Activity is expressed in RLU. Luciferase activity was detected after 6 hours at 37 °C. Bio-Glo solution was added to plates and incubated for 10 minutes on a shaker at room temperature prior to measuring luminescence with a SpectraMax M5 plate reader. Reporter activity measured in 2 separate experiments. Data reported as mean +/- SD. AZD2936 = rilvegostomig; RLU = relative light unit.

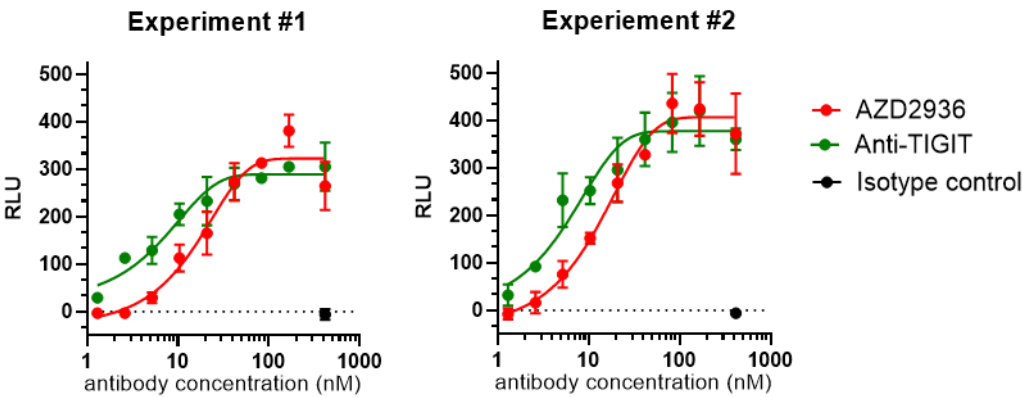
Table 14 **Bioactivity of Rilvegostomig and Anti-PD-1 Antibody in Human PD-1⁺TIGIT⁻ Jurkat T Cell NFAT-Luciferase Reporter Two-cell Co-culture Assays**

	Experiment No. 1	Experiment No. 2	Mean EC ₅₀ (nM)	Fold change of mean EC ₅₀ vs anti-PD-1
	EC ₅₀ (nM)	EC ₅₀ (nM)		
Rilvegostomig	4.70	3.83	4.26	1.40
Anti-PD-1	1.93	4.14	3.03	1.00

EC₅₀ was derived from the mean values taken from 3 replicates.

The activity of rilvegostomig to block TIGIT/CD155 interactions was tested utilizing an assay kit supplied by Promega (Madison, WI). In this assay, CD155 aAPC/CHO-K1 cells were co-cultured with Jurkat PD-1⁻TIGIT⁺ NFAT-luciferase reporter cells and the luciferase activities induced post the treatment of rilvegostomig, anti-TIGIT mAb, and an isotype control mAb were compared. In this assay, rilvegostomig showed increased activity over the isotype control antibody with a mean EC₅₀ of 15.3 nM from 2 experiments (EC₅₀ of 17.0 nM and 13.7 nM in Experiment No. 1 and No. 2, respectively) (Figure 13 and Table 15). In the same experiment, treatment of anti-TIGIT resulted in a mean EC₅₀ of 2.22 nM from 2 experiments (EC₅₀ of 1.59 and 2.85 nM in Experiment No. 1 and No. 2, respectively).

Figure 13 **Bioactivity of Rilvegostomig in Human PD-1⁻TIGIT⁺ Jurkat T Cell NFAT-Luciferase Reporter Two-cell Co-culture Assays**



The TIGIT/CD155 blockade bioassay supplied by Promega was utilized to assess the concentration-dependent activity of rilvegostomig and anti-TIGIT to enhance TCR-depending signaling through blockade of TIGIT/CD155. CD155 aAPC/CHO-K1 Cells from Promega were co-cultured with pre-seeded Jurkat PD-1⁻TIGIT⁺ cells (Promega) in the presence of either rilvegostomig, anti-TIGIT, or Isotype control antibody for 6 hours at 37 °C. Bio-Glo Reagent was added and plates were incubated with shaking for 5 to 10 minutes at room temperature prior to measuring luminescence with an Envision 2103 multilabel plate reader. Rilvegostomig, anti-TIGIT, and isotype control were assessed in individual wells on duplicate plates. Reporter activity measured in 2 separate experiments. Data reported as mean +/- SD. AZD2936 = rilvegostomig; RLU = relative light unit.

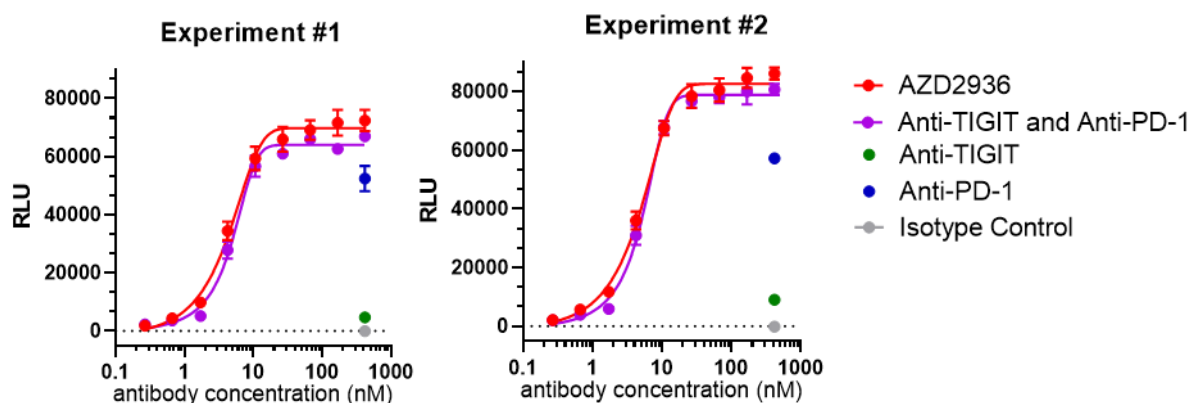
Table 15 Bioactivity of Rilvegostomig and Anti-TIGIT Antibodies in Human PD-1⁺TIGIT⁺ Jurkat T Cell NFAT-Luciferase Reporter Two-cell Co-culture Assays

	Experiment No. 1	Experiment No. 2	Mean EC ₅₀ (nM)	Fold change of mean EC ₅₀ vs anti-TIGIT
	EC ₅₀ (nM)	EC ₅₀ (nM)		
Rilvegostomig	17.0	13.7	15.3	6.89
Anti-TIGIT	1.59	2.85	2.22	1.00

EC₅₀ was derived from the mean values taken from 3 replicates.

The activity of rilvegostomig to block PD-1/PD-L1 and TIGIT/CD155 interactions in an assay was tested with CHO-K1 OKT3 PD-L1 CD155 cells and PD-1⁺TIGIT⁺ Jurkat T cell NFAT-luciferase reporter cells. Rilvegostomig showed activity in 2 duplicate experiments with a mean EC₅₀ of 5.82 nM (EC₅₀ of 5.57 and 6.07 nM in 2 separate experiments) (Figure 14 and Table 16). In the same experiments, the combination of anti-TIGIT and anti-PD-1 resulted in a mean EC₅₀ of 6.27 nM (EC₅₀ of 6.09 and 6.45 nM in 2 experiments). Therefore, rilvegostomig demonstrated equivalent activity to that of anti-TIGIT and anti-PD-1 combined.

Figure 14 Bioactivity of Rilvegostomig in human PD-1⁺TIGIT⁺ Jurkat T cell NFAT-Luciferase Reporter Two-cell Co-culture Assays



Concentration-dependent activity of rilvegostomig, anti-PD-1, anti-TIGIT, combination of anti-PD-1 and anti-TIGIT or isotype control antibodies to enhance TCR-depending signaling through blockade of PD-1/PD-L1 and CD155/TIGIT interactions in a two-cell co-culture bioactivity assay with CHO-K1 OKT3 PD-L1 CD155 cells and a human PD-1⁺TIGIT⁺ Jurkat T cell NFAT-luciferase reporter cell line. Cells were incubated for 6 hours at 37 °C followed by 15 minutes at room temperature. After adding Bright-Glo solution for 5 minutes, luminescence was assessed on a SpectraMax M5 plate reader. Rilvegostomig, anti-TIGIT, anti-PD-1, and the anti-PD-1 and anti-TIGIT antibody combination were conducted in triplicate wells, shown as mean +/- SD. AZD2936 = rilvegostomig; RLU = relative light unit.

Table 16 Bioactivity of Rilvegostomig and the Combination of Anti-PD-1 and Anti-TIGIT Antibodies in Human PD-1⁺TIGIT⁺ Jurkat T Cell NFAT-Luciferase Reporter Two-cell Co-culture Assays

	Experiment No. 1	Experiment No. 2	Mean EC ₅₀ (nM)	Fold change of mean EC ₅₀ vs anti-TIGIT and anti-PD-1 combination
	EC ₅₀ (nM)	EC ₅₀ (nM)		
Rilvegostomig	5.57	6.07	5.82	0.93
Combination of Anti-TIGIT and Anti-PD-1 antibodies	6.09	6.45	6.27	1.00

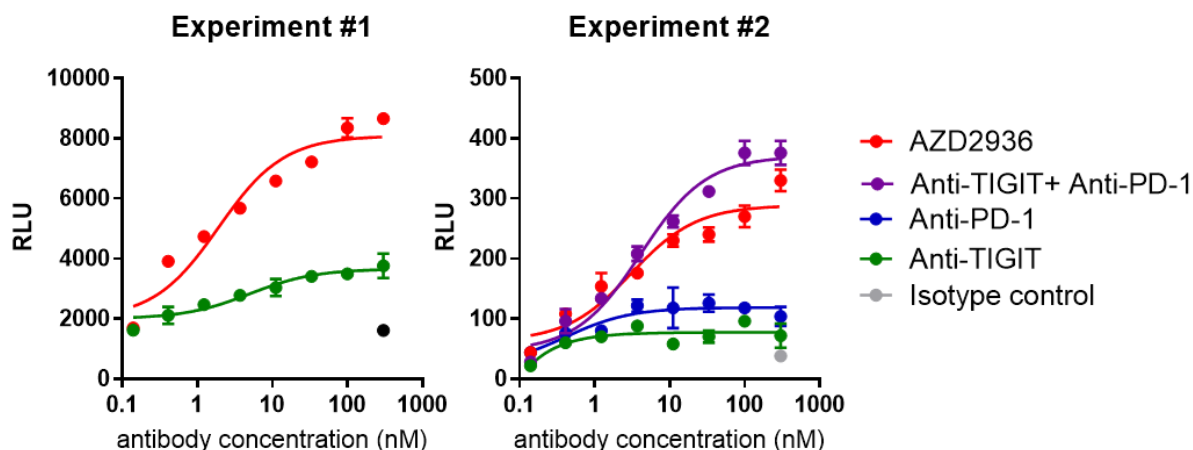
EC₅₀ was derived from the mean values taken from 3 replicates.

4.1.1.10 In Vitro Blocking Activity of Rilvegostomig in Assays Using Jurkat T cells Engineered to Express Cynomolgus Monkey PD-1 and/or TIGIT

To assess the ability of rilvegostomig to block cynomolgus monkey PD-1 and/or TIGIT, two-cell co-culture bioactivity assays were utilized using CHO-K1 cells genetically engineered to express the anti-CD3 scFv of OKT3, PD-L1 and CD155 and Jurkat NFAT-luciferase reporter T cells genetically engineered to express cynomolgus monkey TIGIT and PD-1 (Pharmacology Report ONC2936-0005).

Rilvegostomig showed activity in the Jurkat cynomolgus monkey PD-1 TIGIT dual luciferase reporter assay. In 2 separate experiments, the EC₅₀ for rilvegostomig was 1.93 and 3.09 nM (Figure 15 and Table 17). EC₅₀ of anti-PD-1 and anti-TIGIT combination was 4.13 nM. Neither anti-PD-1 nor anti-TIGIT antibody showed measurable activity in this reporter assay. Therefore, rilvegostomig demonstrated equivalent activity to that of the combination of anti-TIGIT and anti-PD-1 to block the negative signaling effects through cynomolgus monkey PD-1 and TIGIT in the Jurkat reporter cells.

Figure 15 Bioactivity of Rilvegostomig in Cynomolgus Monkey PD-1⁺TIGIT⁺ Jurkat T cell NFAT-Luciferase Reporter Two-cell Co-Culture Assays



Concentration-dependent activity of rilvegostomig, anti-PD-1, anti-TIGIT, combination of anti-PD-1 and anti-TIGIT or isotype control antibodies to enhance TCR-depending signaling through blockade of PD-1/PD-L1 and CD155/TIGIT interactions in a two-cell co-culture bioactivity assay with CHO-K1 OKT3 PD-L1 CD155 cells and a cynomolgus monkey PD-1⁺TIGIT⁺ Jurkat T cell NFAT-luciferase reporter cell line. Cell were incubated for 6 hours at 37 °C followed by 15 minutes at room temperature. After adding Bright-Glo solution for 5 minutes, luminescence was assessed on a SpectraMax M5 plate reader. Rilvegostomig, anti-TIGIT, anti-PD-1 and the anti-PD-1 and anti-TIGIT antibody combination were conducted in duplicate wells, shown as mean +/- SD.

AZD2936 = rilvegostomig; RLU = relative light unit.

Table 17 Bioactivity of Rilvegostomig and the Combination of Anti-PD-1 and Anti-TIGIT Antibodies in Cynomolgus Monkey PD1⁺TIGIT⁺ Jurkat T cell NFAT-luciferase Reporter Two-culture Assays

	Experiment No. 1	Experiment No. 2	Mean EC ₅₀ (nM)	Fold change of mean EC ₅₀ vs anti-TIGIT and anti-PD-1 combination
	EC ₅₀ (nM)	EC ₅₀ (nM)		
Rilvegostomig	1.93	3.09	2.51	0.608
Combination of Anti-TIGIT and Anti-PD-1 antibodies	ND	4.13	4.13	1.00

EC₅₀ was derived from the mean values taken from 2 replicates.

4.1.1.11 Activity of Rilvegostomig on Human Peripheral Blood Mononuclear Cells in a T Cell-Mediated Tumor Cell Line Lysis Assay

To assess the ability of rilvegostomig to modulate T-cell cytolytic activity, an assay to evaluate T-cell mediated lysis of a human tumor cell line was established (Pharmacology Report ONC2936-0006). For this purpose, an HLA-A*02:01 positive human esophageal squamous cell carcinoma cell line, OE21, was engineered to express 6 viral antigen peptides known to bind HLA-A*2:01 (OE21-10xGSV3). The 67 viral peptides utilized were human

EBV LMP2356-364 peptide (amino acid sequence of CLGGLLTMV), LMP2426-434 (amino acid sequence of CLGGLLTMV), BMLF1280-288 (amino acid sequence GLCTLVAML); Influenza M158-66 (amino acid sequence GILGFVFTL), Influenza A PA46-54 (amino acid sequence FMYSDFHFI); and CMV pp65495-503 (amino acid sequence NLVPMVATV). This engineered cell line was used as the target cell within the assay.

Human leukocyte antigen A locus*02:01 positive healthy donor PBMC known to be reactive to EBV BMLF1280-288 peptide (GLCTLVAML) and CMV pp65495-503 peptide (NLVPMVATV) were stimulated in vitro in the presence of 1 µg/mL peptide and 55 IU/mL IL-2 for 7 days, subsequently stained with fluorescently conjugated CD3, CD8, CD25, and TIM-3 antibodies and evaluated by flow cytometry for binding. The donors were identified as EBV BMLF1280-288 peptide or CMV pp65495-503 reactive if > 10% CD3+CD8+ T cells stain positively for both CD25 and TIM-3. These EBV or CMV reactive T cells were used as the effector population within the co-culture assay. Tumor cell lysis was evaluated utilizing the Agilent xCELLigence real time cell analysis platform, whereby loss of cellular impedance was used as a surrogate for tumor cell death (Oberg et al 2014).

Anti-PD-1, anti-TIGIT, a combination of anti-PD-1 and anti-TIGIT, and rilvegostomig showed activity in the co-culture assay in 5 independent experiments using antigen-specific T cells enriched from different donor PBMC. Figure 16 shows the normalized cell index for one representative donor at the time T cells were added, until the experiment was terminated 5 days later. Compared to tumor cells only (red), there is a decrease in normalized cell index over time with T-cell containing groups (Figure 16A). Area under the concentration-time curve for normalized cell index over time was calculated for each well. An average of all wells containing T cells plus 0.2 nM isotype control antibody (green) represents the baseline of tumor cell killing, and each AUC value for treatment was compared so that the fold increase in cytotoxicity over control antibody could be determined (Figure 16B). Comparing the treatments to anti-PD-1, there was an increase in cytotoxicity when anti-TIGIT, a combination of anti-PD-1 and anti-TIGIT, or rilvegostomig was used. However, cytotoxicity elicited by rilvegostomig was not significantly different than the combination of the 2 bivalent antibodies (anti-PD-1 and anti-TIGIT).

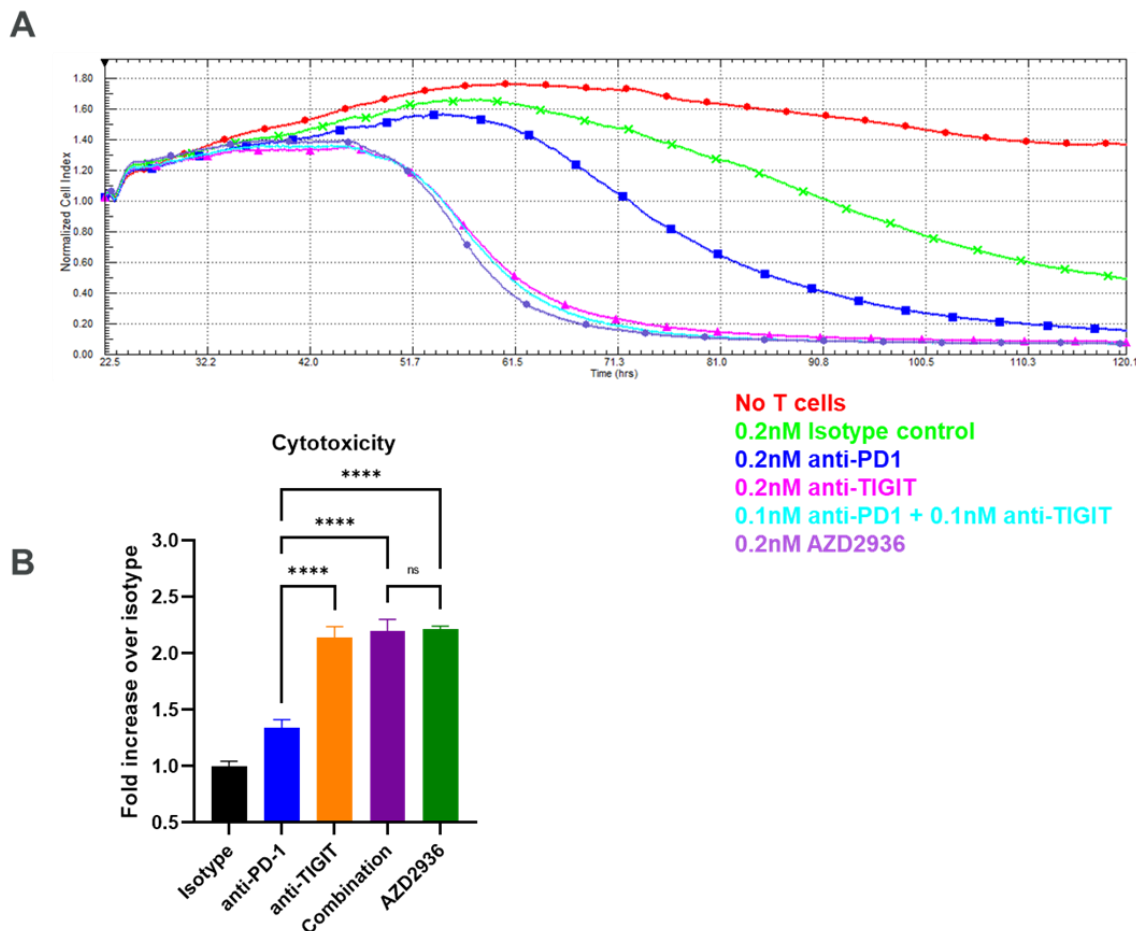
The data for PBMC from 5 donors are compiled in Figure 17, and show that anti-TIGIT (1.41-fold increase), a combination of anti-PD-1 and anti-TIGIT (1.54-fold increase), or rilvegostomig (1.52-fold increase) significantly increases T-cell-mediated tumor cell line cytotoxicity over anti-PD-1 alone, across multiple PBMC donors with different peptide reactivities.

A concentration titration of antibodies from 10 nM to 0.1 pM showed the arithmetic mean EC₅₀ for rilvegostomig was 21.9 ± 3.4 pM (SD) and 163 ± 70.6 pM (SD) for anti-PD-1,

yielding a 7.44-fold increase in potency of rilvegostomig in comparison to anti-PD-1 (Figure 18).

Upon antigen recognition, CD8⁺ T cells secrete IFN- γ , a cytokine which further promotes anti-tumor immunity and CD8⁺ T-cell cytotoxic effects (Bhat et al 2017). Thus, IFN- γ release was evaluated following peptide-specific CD8⁺ T cell co-culture with OE21-10xGSV3 cells. In co-cultures of T cells isolated and expanded from the PBMC of 4 healthy donors, rilvegostomig induced a statistically significantly increased amount of IFN- γ in the supernatant of co-cultures with tumor cells compared to isotype control and anti-PD-1 (Figure 19). Rilvegostomig was not significantly different than the combination of anti-PD-1 and anti-TIGIT antibodies or anti-TIGIT only treatment.

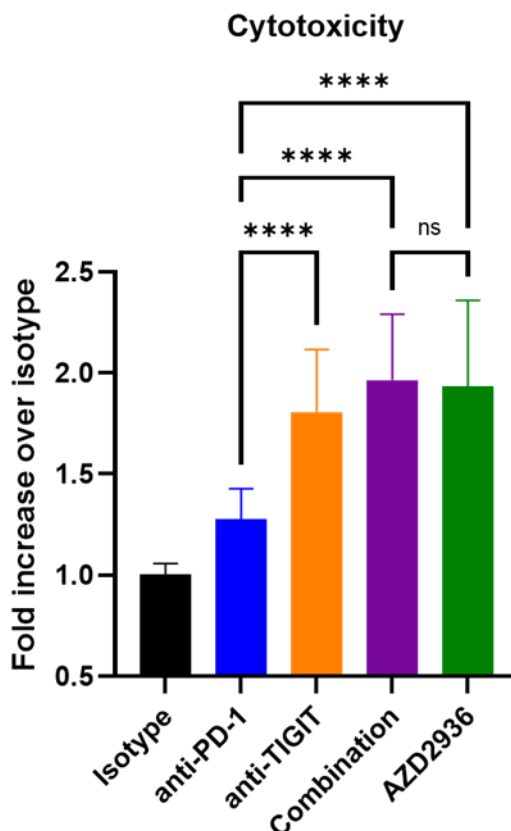
Figure 16 Real-Time Cytolytic Activity and Fold-increase of Cytolytic Activity of Rilvegostomig as Compared to Anti-PD-1



(A) Cytolytic activity (RTCA Pro Software) and (B) quantitation of cytolytic activity from one representative donor tested in the antigen-specific T cell and tumor cell co-culture xCELLigence RTCA assay. Primary human PBMC from donor 109 expanded with the CMV peptide were co-cultured with 0.2 nM isotype control, 0.2 nM anti-PD-1, 0.2 nM anti-TIGIT, 0.1 nM anti-PD-1 + 0.1 nM anti-TIGIT, or 0.2 nM rilvegostomig and OE21-10xGSV3 tumor cells. (A) Cellular impedance changes over time were utilized as a surrogate marker of tumor cell death. (B) AUC of normalized cell index over time was calculated as fold increase over the isotype control antibody (mean = 1). Data of one representative donor are shown. Horizontal bars indicate intragroup arithmetic mean value. Statistical significance was calculated with one-way ANOVA with Tukey's multiple comparisons. ****, $p < 0.0001$.

ANOVA = analysis of variance; AZD2936 = rilvegostomig; ns = not significant; RTCA = real time cell analysis.

Figure 17 **Activity of Rilvegostomig in an In Vitro Antigen-specific T-Cell Cytotoxicity Assay Against Human Tumor Cells**

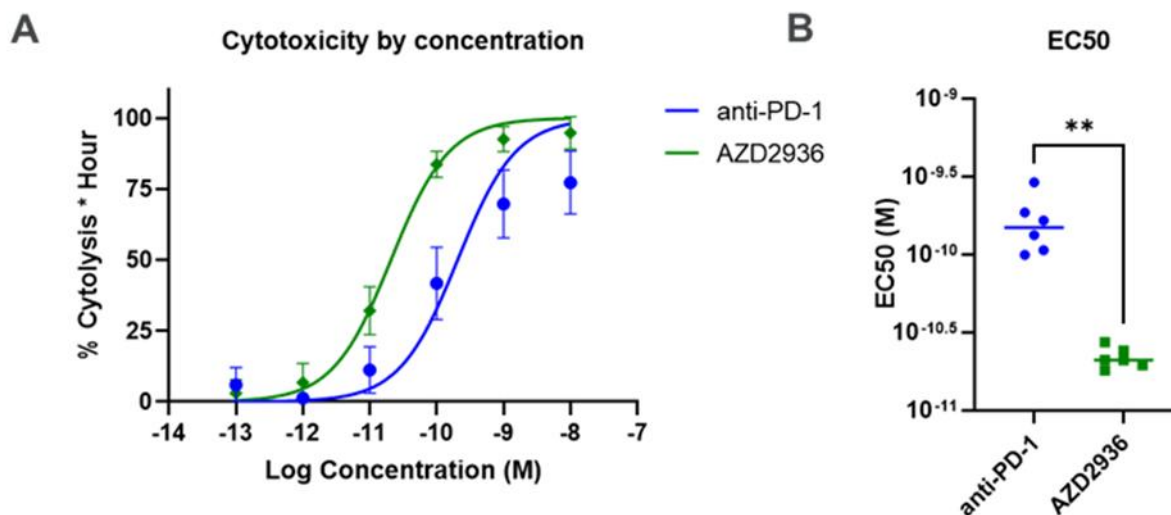


Primary human PBMC expanded with the EBV or CMV peptide were co-cultured with test/control articles (0.2 nM isotype control, 0.2 nM anti-PD-1, 0.2 nM anti-TIGIT, 0.1 nM anti-PD-1 + 0.1 nM anti-TIGIT, or 0.2 nM rilvegostomig) and OE21-10xGSV3 tumor cells. Cellular impedance changes over time were utilized as a surrogate marker of tumor cell death. AUC of normalized cell index over time was calculated as fold increase over the isotype control antibody (mean = 1). The data were generated from 5 different donors. Statistical significance was calculated using one-way ANOVA and Tukey's multiple comparison test. Horizontal bars represent intragroup arithmetic mean value.

****, $p < 0.0001$.

ANOVA = analysis of variance; AZD2936 = rilvegostomig; ns = not significant.

Figure 18 Comparison of Log Transformed EC_{50} Values of Cytolytic Activity for Rilvegostomig versus Anti-PD-1

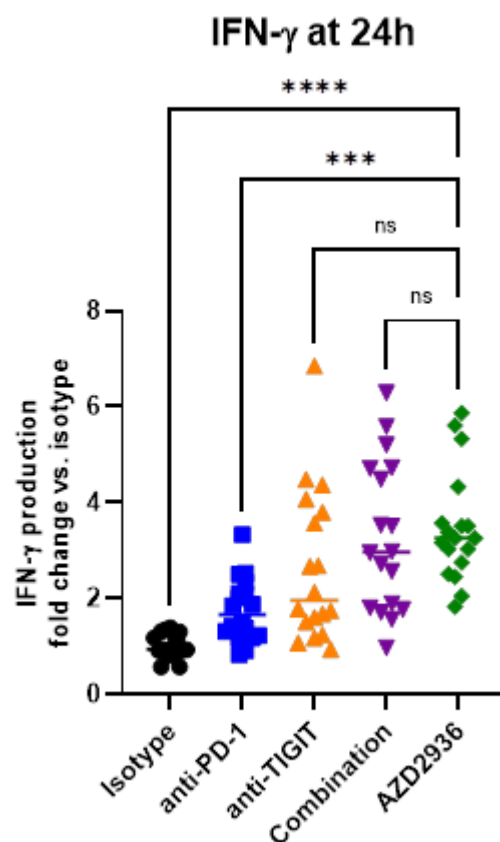


Primary human PBMC expanded with the CMV peptide were co-cultured with rilvegostomig or anti-PD-1 and OE21-10xGSV3 tumor cells. Test and control article concentration started at 10 nM with a 10-fold serial dilution for 6 points. Cellular impedance changes over time were utilized as a surrogate marker of tumor cell death. (A) EC_{50} values were determined from cytolytic AUC plot (Cytolysis*Hours). EC_{50} values were log-transformed and plotted in the graph above. Group means were compared using 2-sided unpaired student's t-test. Error bars depict SD. (B) rilvegostomig treatment group induced a significantly ($p = 0.0044$) reduced average EC_{50} value compared to the anti-PD-1 group. Data of one representative donor are shown; however similar EC_{50} values were determined from 3 independent experiments utilizing 3 donors. Horizontal bars indicate intragroup arithmetic mean EC_{50} values.

**, $p < 0.005$

AZD2936 = rilvegostomig.

Figure 19 **Fold-increase of Human IFN- γ Released from a T Cell and Human Tumor cells Co-culture Assay in Response to Rilvegostomig and Other Antibodies**



Primary human PBMC expanded with the EBV or CMV peptide were co-cultured with test and control articles (0.2 nM isotype control, 0.2 nM anti-PD-1, 0.2 nM anti-TIGIT, 0.1 nM anti-PD-1 + 0.1 nM anti-TIGIT, or 0.2 nM rilvegostomig) and OE21-10xGSV3 tumor cells. The concentration of IFN- γ of the T cell and tumor cell co-culture assay was measured from supernatants collected 24 hours after T cell addition. The concentration of IFN- γ was determined using Mesoscale Discovery multi-spot ELISA for human IFN- γ . Fold change of all values compared to an average for the isotype control are reported. (A) The data represent 4 distinct donors. Statistical significance was calculated using one-way ANOVA and Tukey's multiple comparison test. Horizontal lines represent intragroup arithmetic mean values.

, $p < 0.001$, *, $p < 0.0001$.

ANOVA = analysis of variance; AZD2936 = rilvegostomig; ELISA = enzyme linked immunosorbent assay; ns = not significant.

4.1.1.12 Characterization of Effector Function for Rilvegostomig

Therapeutic antibodies rely on 2 types of functionalities to exert clinical efficacy: target specific binding by the Fab domain and immune-mediated effector functions via interaction of the Fc domain ([Wang et al 2008](#)). When IgG antibodies bind cell surface antigens via their Fab domains, the Fc portion of the antibodies can bind to C1q, the first member of the antibody triggered classical complement pathway, or it can engage with FcγRs expressed on NK and other myeloid cells.

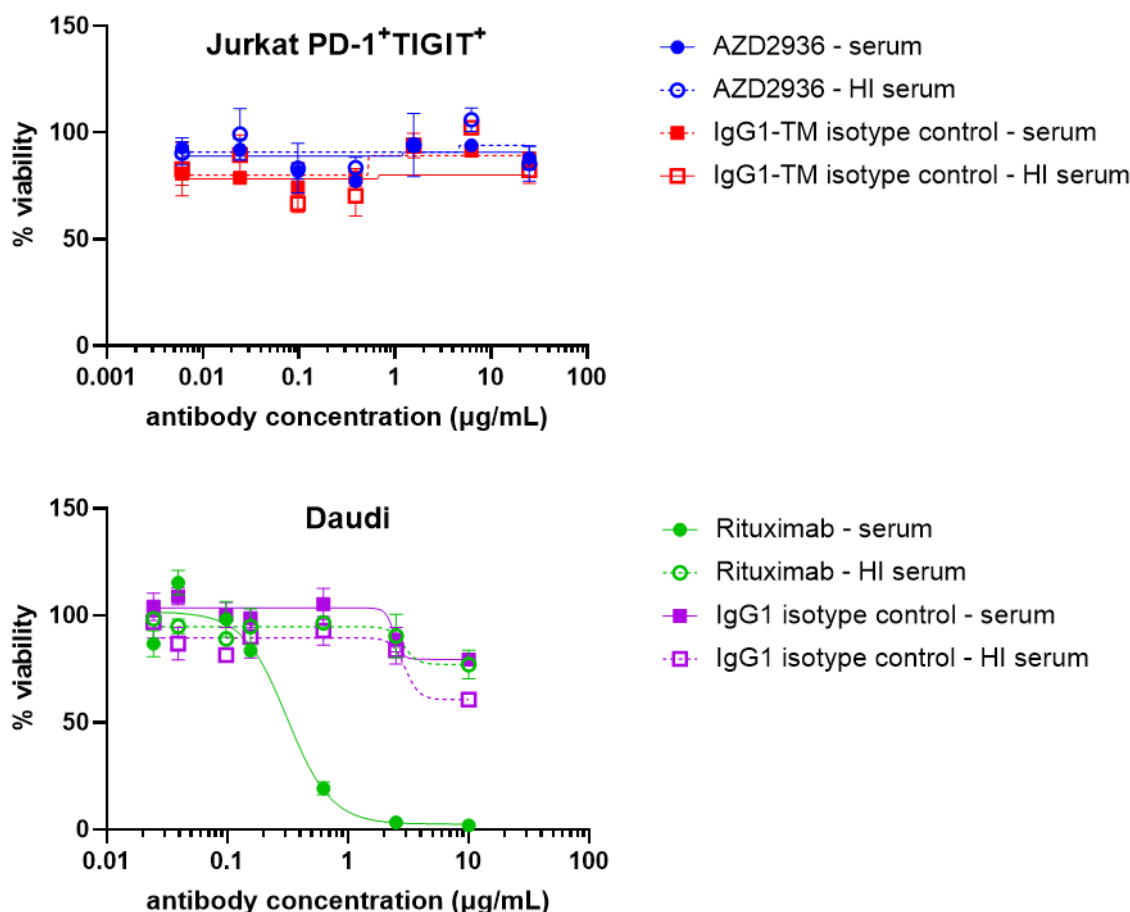
The interaction with C1q initiates the complement cascade, resulting in the formation of membrane attack complex that kills the target cell by disrupting its cell membrane, a process described as CDC ([Wang et al 2008](#)). The interaction of the Fc domain with FcγRIIIa induces cross-linking of the FcγRs, which triggers the release of cytotoxic granules containing perforin and granzymes, leading to the death of the target cell, a process called ADCC ([Nimmerjahn and Ravetch 2008](#)).

Rilvegostomig is a humanized monovalent bispecific antibody engineered to have mutations within its Fc domain to diminish Fc-mediated effector functionality ([Oganesyan et al 2008](#)). The potential of rilvegostomig to initiate CDC and ADCC activity was evaluated utilizing a Jurkat cell line engineered to express TIGIT and PD-1 (Pharmacology Report ONC2936-0008).

As shown in [Figure 20](#), rilvegostomig did not trigger CDC. Conversely, rituximab, an anti-CD20 antibody known to have CDC activity, demonstrated concentration-dependent effects on CD20-expressing Daudi cells in the presence of the same human serum used in the assay with rilvegostomig, but not in the presence of heat-inactivated serum.

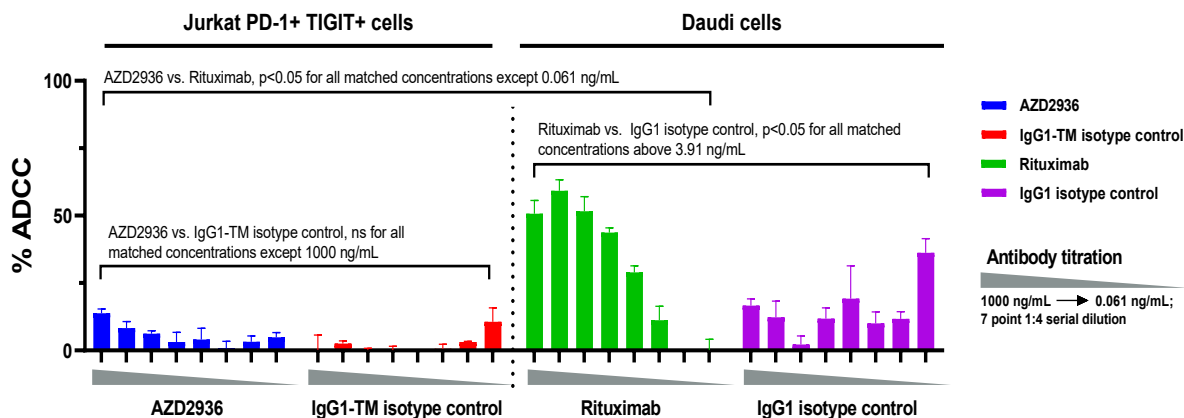
Antibody-dependent cellular cytotoxicity activity was evaluated utilizing PBMC from healthy donors as the effector cells and a PD-1 and TIGIT expressing Jurkat cell line as the target cell. In this assay, rilvegostomig demonstrated similar activity as the isotype control samples, and yielded a statistically significant reduction in ADCC activity compared to the positive control, rituximab using CD20-expressing Daudi cells as the target cell, at all matched concentrations above 0.061 ng/mL ([Figure 21](#)). The results of this study show rilvegostomig did not trigger ADCC or CDC against a PD-1 and TIGIT expressing Jurkat cell line.

Figure 20 Measurement of CDC Activity Mediated Against Target Cell Lines by Rilvegostomig and Control Articles



The percentage of live, (top) PD-1 and TIGIT expressing Jurkat or (bottom) Daudi following incubation with rilvegostomig, IgG1-TM isotype control, rituximab, or IgG1 isotype control, together with complement containing human serum or heat-inactivated human serum was estimated by addition of Cell-Titer Glo. Cell-Titer Glo produces a luminescent signal proportional to the number of live cells in each well. Neither rilvegostomig nor isotype control IgG1-TM, had any effect on the percentage of viable cells present. Addition of rituximab resulted in a concentration-dependent decrease in viability. Conversely, IgG1 isotype control did not have any effect on percentage of viable cells. No sample using heat-inactivated serum resulted in a dose-dependent decrease in viability, confirming that cell death is mediated by CDC. Error bars represent SD (n = 2). AZD2936 = rilvegostomig; HI = heat inactivated.

Figure 21 Measurement of ADCC Activity Mediated against Target Cell Lines by Rilvegostomig and Control Articles



Specific killing of Jurkat cells expressing PD-1 and TIGIT or Daudi cells by primary human PBMC. Dose-dependent ADCC is mediated by Rituximab but not IgG1 isotype control, rilvegostomig, or IgG1-TM isotype control. Error bars represent SD (n = 2). AZD2936 = rilvegostomig; ns = not significant.

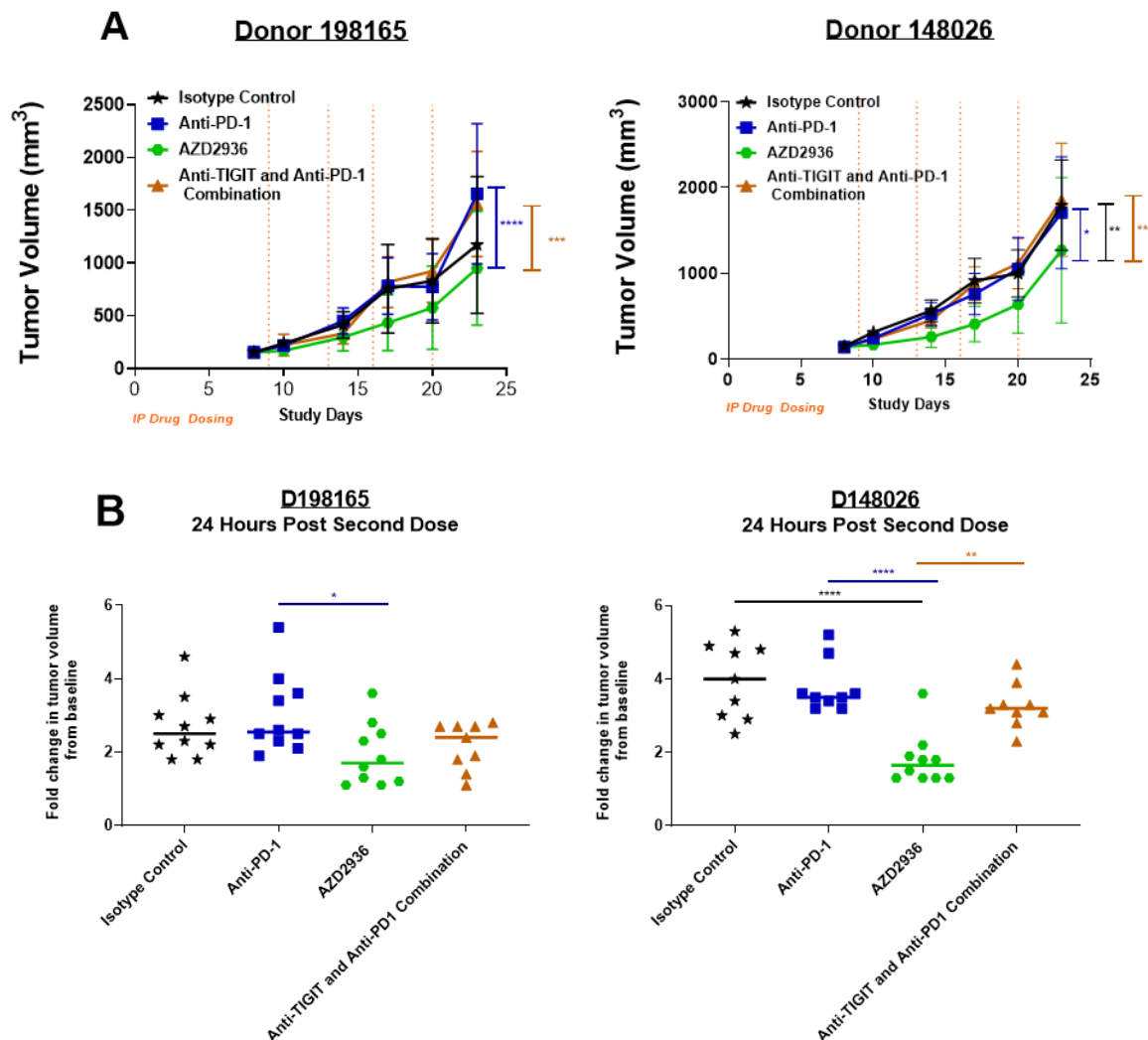
4.1.2 Primary Pharmacology: In Vivo Studies

The activity of rilvegostomig was investigated in human tumor xenograft mouse models using immunodeficient NSG mice (Pharmacology Report ONC2936-0007). Animals were inoculated subcutaneously with human cancerous cell lines engineered to express peptide antigens presented by HLA-A*2:01. One model utilized OE21-10xGSV3, an esophageal carcinoma cell line engineered to express viral peptides as described in the in vitro tumor cell lysis assay (Pharmacology Report ONC2936-0006). Another model utilized PC9-MART1, a lung adenocarcinoma cell line engineered to express a melanoma antigen-1. Tumor cell lines were injected in the flank of mice by subcutaneous injection and after tumors grew in volume to approximately 200 mm³, each mouse received an iv injection of human T cells specific for antigens expressed by the tumor cell lines. Mice were dosed with 10 mg/kg of rilvegostomig, the isotype control, or anti-PD-1 by intraperitoneal injection. Mice receiving the combination of anti-TIGIT and anti-PD-1 antibodies received 5 mg/kg of each antibody by intraperitoneal injection. Animals received the first dose of the test and control articles within 24 hours after randomization, and were subsequently administered 3 additional doses of the test and control articles (Figure 22 and Figure 24).

Intraperitoneal administration of rilvegostomig to animals significantly inhibited the growth of tumors as compared to the activity of its parental bivalent anti-PD-1 antibody (anti-PD-1), anti-TIGIT and anti-PD-1 combination and a bivalent isotype control antibody targeting an irrelevant antigen, R347 (Isotype Control) as shown in Figure 22 and Figure 24. Rilvegostomig treatment significantly enhanced survival of mice compared to mice treated with anti-PD-1, anti-TIGIT, and anti-PD-1 combination and Isotype Control (Figure 23).

Rilvegostomig treatment of mice significantly increased the amount of human IFN- γ detected in the serum and tumor lysate as compared to Isotype Control treated mice (Figure 25 and Figure 26). Rilvegostomig treatment inhibited tumor growth for the entire duration of the studies and in 2 xenograft mouse models utilizing T cells with different antigen specificities Figure 22 and Figure 24. Antitumor activity of rilvegostomig occurred utilizing tumor-specific T cells derived from 2 independent, healthy donors each for the OE21-10xGSV3 and the PC9-MART-1 models.

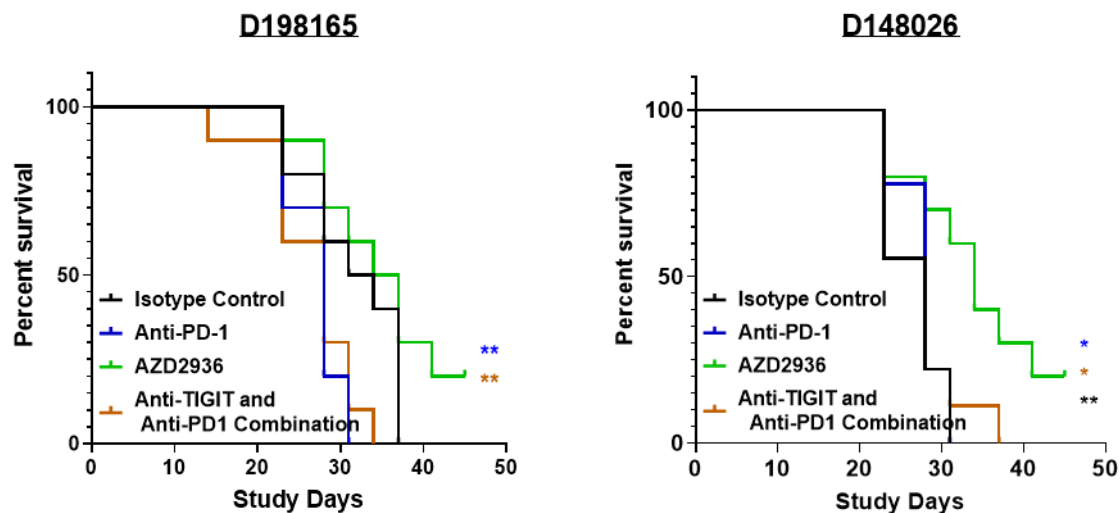
Figure 22 Effect of Rilvegostomig on Growth of OE21-10xGSV3 Cells in a Mouse Xenograft Model



Ten NSG mice in each group were engrafted sc on Day 1 with 2×10^6 OE21-10xGSV3 cells. Tumor antigen-specific CD8⁺ T cells originating from the PBMC of 2 different healthy donors (D198165 and D148026) were administered iv on Day 7. Mice were randomized by tumor volume on Day 8. Test and control articles were administered IP on Day 9, 13, 16, and 20. Mice were dosed at 10 mg/kg for rilvegostomig, anti-PD-1 or the isotype control single agent treatment groups; mice receiving combination therapy received 5 mg/kg of anti-PD-1 mAb and 5 mg/kg of anti-TIGIT mAb. (A) Tumor growth curves for both donors showing comparisons between rilvegostomig-treated, anti-PD-1, anti-TIGIT and anti-PD-1 combination or Isotype Control-treated animals. Intergroup differences were analyzed for statistical significance by a 2-way ANOVA, assuming sphericity (equal variability of differences), Tukeys multiple comparison test. (B) Fold-change from baseline measurements were calculated for each group. Each symbol represents the fold-change in tumor volume from baseline to 24 hours after the second dose (Day 14) of test or control articles. A comparison between the fold-change of rilvegostomig-treated and anti-PD-1 or Isotype Control-treated animals was made, and intergroup differences were analyzed for statistical significance by a one-way ANOVA, Tukeys multiple comparison test. The horizontal bars represents the intragroup arithmetic mean fold-change. ****, $p < 0.0001$; ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

ANOVA = analysis of variance; AZD2936 = rilvegostomig; D198165 = individual healthy donor; D148026 = individual healthy donor; IP = intraperitoneal.

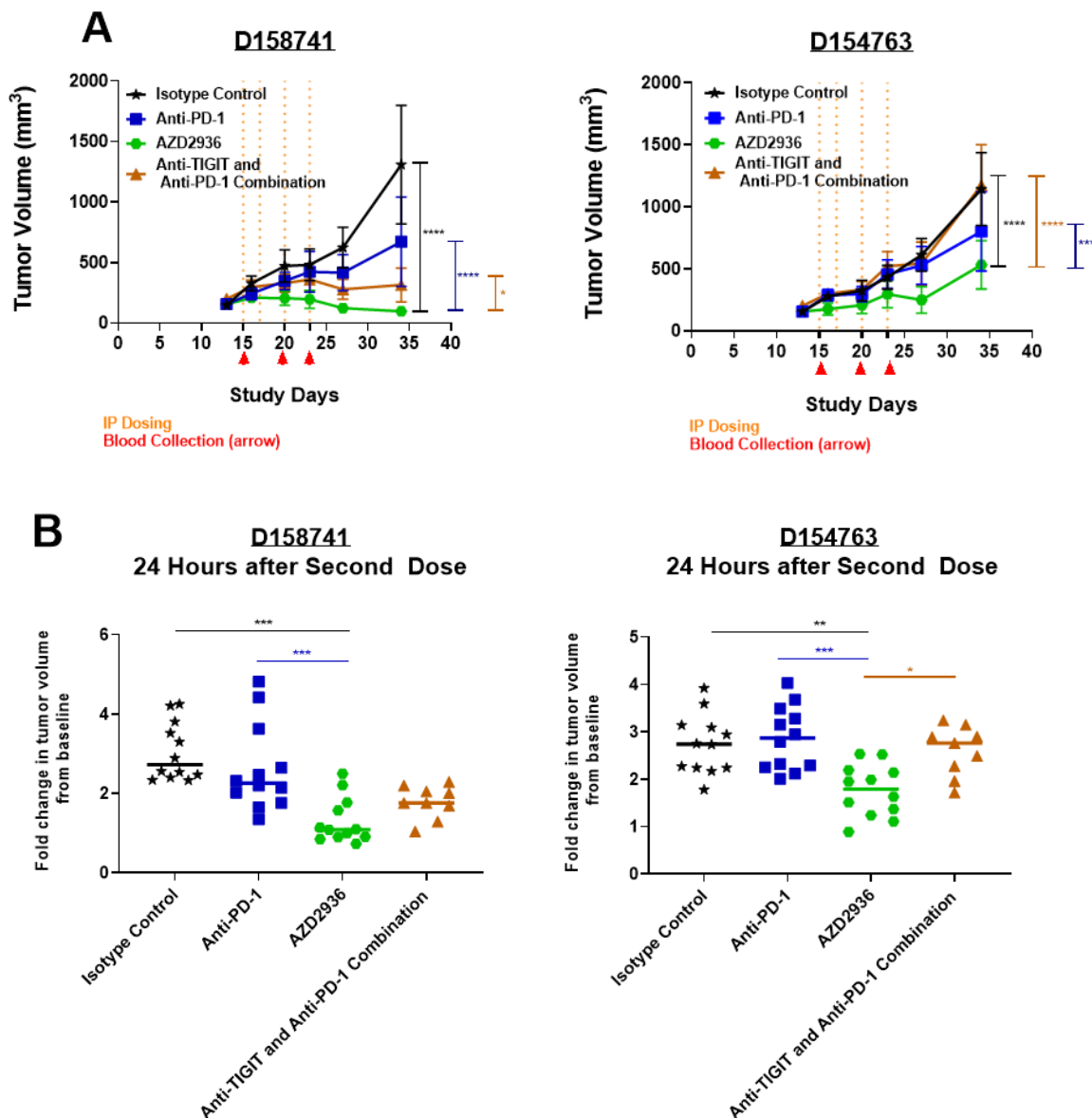
Figure 23 Rilvegostomig Effect on Mouse Survival in OE21-10xGSV3 Mouse Xenograft Model



Ten NSG mice in each group were engrafted sc on Day 1 with 2×10^6 OE21-10xGSV3 cells. Tumor antigen-specific CD8⁺ T cells originating from the PBMC of 2 different healthy donors (D198165 and D148026) were administered iv on Day 7. Mice were randomized by tumor volume on Day 8. Test and control articles were administered IP on Day 9, 13, 16, and 20. Mice were dosed at 10 mg/kg for rilvegostomig, anti-PD-1 or the isotype control single agent treatment groups; mice receiving combination therapy received 5 mg/kg of anti-PD-1 mAb and 5 mg/kg of anti-TIGIT mAb. When a tumor burden limit of 2000 mm³ was reached mice were humanely euthanized. A comparison between the survival curves of rilvegostomig-treated and anti-PD-1 or anti-TIGIT and anti-PD-1 combination-treated animals was made. Intergroup differences were analyzed by Kaplan-Meier survival curves and a Log-rank (Mantel-Cox) test performed to evaluate statistical significance between 2 groups. *, $p < 0.05$; **, $p < 0.01$.

AZD2936 = rilvegostomig; D198165 = individual healthy donor; D148026 = individual healthy donor; IP = intraperitoneal.

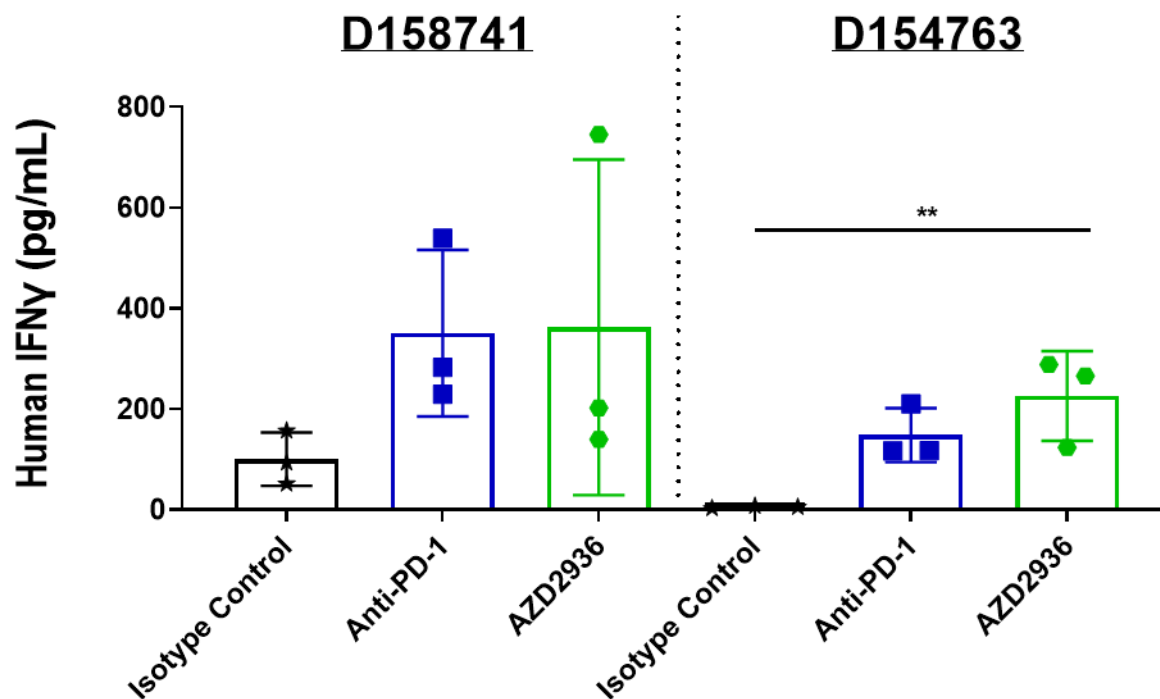
Figure 24 Effect of Rilvegostomig on Growth of PC9-MART1 Cells in a Mouse Xenograft Model



Twelve NSG mice in each group were engrafted sc on Day 1 with 3×10^6 PC9-MART1 cells. Tumor antigen-specific CD8⁺ T cells originating from the PBMC of 2 different healthy donors (D158741 and D154763) were administered iv on Day 14. Mice were randomized by tumor volume the day prior (Day 13). Test and control articles were administered IP on Day 15, 17, 20, and 23. Mice were dosed at 10 mg/kg for rilvegostomig, anti-PD-1 or the isotype control single agent treatment groups; mice receiving combination therapy received 5 mg/kg of anti-PD-1 mAb and 5 mg/kg of anti-TIGIT mAb. (A) Tumor growth curves for both donors showing comparisons between rilvegostomig-treated, anti-PD-1, anti-TIGIT and anti-PD-1 combination or Isotype Control-treated animals. Intergroup differences were analyzed for statistical significance by a 2-way ANOVA, assuming sphericity (equal variability of differences), Tukeys multiple comparison test. (B) Fold-change from baseline measurements was calculated for each group. Each symbol represents the fold-change in tumor volume from baseline to 24 hours after the second dose (Day 18) of test or control articles. A comparison between the fold-change of rilvegostomig-treated and anti-PD-1 or Isotype Control-treated animals was made, and intergroup differences were analyzed for statistical significance by a one-way ANOVA, Tukeys multiple comparison test.

The horizontal bars represent the intragroup arithmetic mean fold-change. Significant p-values are presented in the figures as *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; ****, $p < 0.0001$. ANOVA = analysis of variance; AZD2936 = rilvegostomig; D158741 = individual healthy donor; D154763 = individual healthy donor; IP = intraperitoneal.

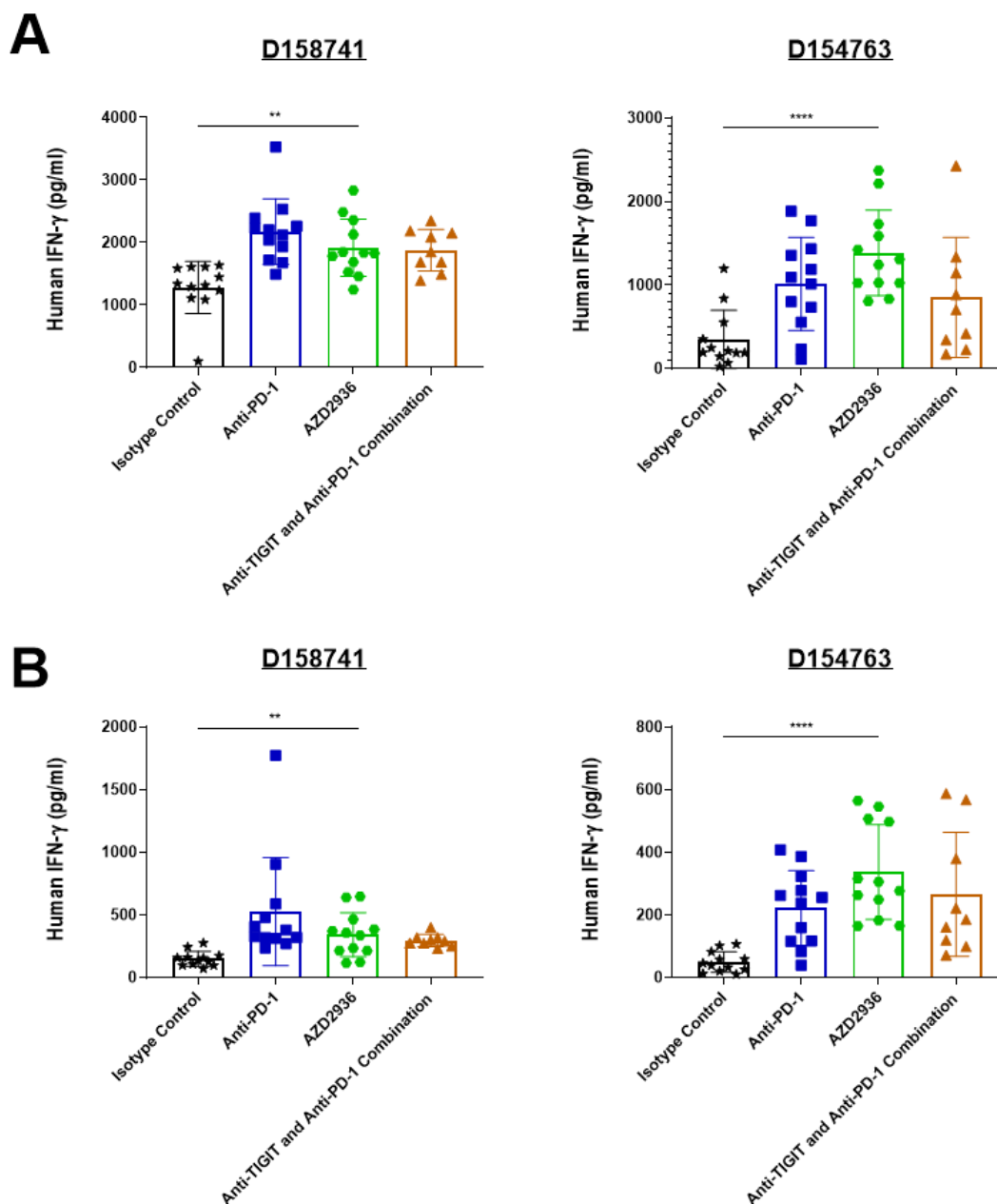
Figure 25 **Effect of Rilvegostomig on the Amount of Human Interferon Gamma in PC9-MART1 Tumors in a Mouse Xenograft Model**



Twelve NSG mice in each group were engrafted sc on Day 1 with 3×10^6 PC9-MART1 cells. Tumor antigen-specific CD8⁺ T cells originating from the PBMC of 2 different healthy donors (D158741 and D154763) were administered iv on Day 14. Mice were randomized by tumor volume the day prior (Day 13). Test and control articles were administered at 10 mg/kg IP on Day 15, 17, 20, and 23. The day after the last dose, 3 tumors were harvested from Isotype control, anti-PD-1, and rilvegostomig treatment groups from both donors (D158741 and D154763). The supernatant of dissociated tumors was collected from pelleted cell suspensions and analyzed for concentrations of human IFN- γ . Human IFN- γ cytokine concentrations are plotted for tumors from both donors. Comparisons between rilvegostomig-treated, anti-PD-1, or Isotype Control-treated animals was made, and intergroup differences were analyzed for statistical significance by a one-way ANOVA. Significant p-values are presented in the figures as **, $p < 0.01$.

ANOVA = analysis of variance; AZD2936 = rilvegostomig; D158741 = individual healthy donor; D154763 = individual healthy donor; IP = intraperitoneal.

Figure 26 Effect of Rilvegostomig on Human Interferon Gamma Serum Concentrations in a Mouse Xenograft Model



Twelve NSG mice in each group were engrafted sc on Day 1 with 3×10^6 PC9-MART1 cells. Tumor antigen-specific CD8⁺ T cells originating from the PBMC of 2 different healthy donors (D158741 and D154763) were administered iv on Day 14. Mice were randomized by tumor volume the day prior (Day 13). Test and control articles were administered IP on Day 15, 17, 20, and 23. Mice were dosed at 10 mg/kg for rilvegostomig, anti-PD-1 or the isotype control single agent treatment groups; mice receiving combination therapy received 5 mg/kg of anti-PD-1 mAb and 5 mg/kg of anti-TIGIT mAb. (A) Three days after the second dose (Day 20) and (B) immediately after the fourth dose (Day 23) mouse plasma was collected from all mice on study. Human IFN- γ concentrations in mouse plasma were plotted for both donors. Comparisons between rilvegostomig-treated, anti-PD-1, anti-TIGIT, and anti-PD-1 combination or Isotype Control-treated animals

were made, and intergroup differences were analyzed for statistical significance by an unpaired t-test. Significant p-values are presented in the figures as **, $p < 0.01$; ****, $p < 0.0001$.
AZD2936 = rilvegostomig; D158741 = individual healthy donor; D154763 = individual healthy donor;
IP = intraperitoneal.

4.1.3 Secondary Pharmacology

Secondary pharmacology studies for rilvegostomig were not conducted.

4.1.4 Safety Pharmacology

In accordance with ICH S6(R1), ICH S7A, and ICH S9, no standalone safety pharmacology studies were conducted with rilvegostomig. Safety pharmacology parameters including neurological (assessed by neurobehavioral observations), cardiovascular parameters (electrocardiogram; including heart rate, wave form morphology, heart rate, RR interval, PR interval, QRS duration, QT interval, or QTc interval [derived using Bazett's formula]) and blood pressure (as assessed using a pressure cuff), and respiration rate were evaluated following administration of rilvegostomig in the GLP 1-month and 3-month repeat-dose iv toxicity studies in cynomolgus monkeys (Study 20260563 and Study 8522498).

There were no rilvegostomig-treatment related effects on cardiovascular, neurological or respiratory end points.

4.2 Nonclinical Pharmacokinetics

The PK package of rilvegostomig consisted of: (1) a non-GLP single dose PK study of iv-administered rilvegostomig in cynomolgus monkeys, (2) a GLP single dose PK study of iv- and sc-administered rilvegostomig in cynomolgus monkeys, (3) a GLP 1-month repeat-dose toxicity study of iv-administered rilvegostomig in cynomolgus monkeys with a 6-week treatment-free recovery period, and (4) a GLP 3-month repeat-dose toxicity study of rilvegostomig administered once weekly to cynomolgus monkeys via iv slow bolus injection for at least 13 weeks.

4.2.1 Single Dose PK Study (non-GLP) (Study 8399632)

The objective of this study was to evaluate the PK of rilvegostomig in 12 female cynomolgus monkeys following a single 30-minute iv infusion at 5 or 100 mg/kg rilvegostomig with or without abatacept. Groups of 4 female cynomolgus monkeys were dosed with either a single 30-minute iv infusion of 5 mg/kg or 100 mg/kg of rilvegostomig on Day 1, or dosed with abatacept on Days -1, 7, 14, 21, and 28 and a single dose of rilvegostomig (vehicle or 5 mg/kg) on Day 1 ([Table 18](#)).

Table 18 Study Design ^a (8399632)

Group no.	Test material	Dose level (mg/kg)	Dose volume (mL/kg)	No. of females
1 ^b	Control/Vehicle	0	5	2
2 ^b	Rilvegostomig	5	5	4
3	Rilvegostomig	5	5	4
5	Rilvegostomig	100	5	4

^a All animals were dosed on Day 1 and released to colony on Day 36. Group 4 is for the parental drug and is not included in the table.

^b Animals in Groups 1, and 2 (not Groups 3 or 5) were administered abatacept intravenously as a 30-minute infusion (10 mg/kg, 2 mg/mL, 5 mL/kg) on Days -1, 7, 14, 21, and 28 (5 total doses/animal).

Exposure to rilvegostomig increased with the increase in dose level from 5 to 100 mg/kg. At 5 mg/kg rilvegostomig exposure was similar for up to 15 days postdose when rilvegostomig was dosed at 5 mg/kg alone or with abatacept. Higher CL was observed after 15 days post dose when rilvegostomig was dosed at 5 mg/kg alone than with abatacept. All 8 animals receiving 5 or 100 mg/kg of rilvegostomig alone showed evidence of immunogenicity (ADA) after a single dose of rilvegostomig.

In group 2, following rilvegostomig at 5 mg/kg with abatacept, the mean $C_{\max}$ and AUC_{∞} values were 91.6 µg/mL and 574 µg·day/mL. The $t_{1/2}$, CL and V_{ss} were calculated to 14.2 days, 217 mL/day and 3330 mL, respectively.

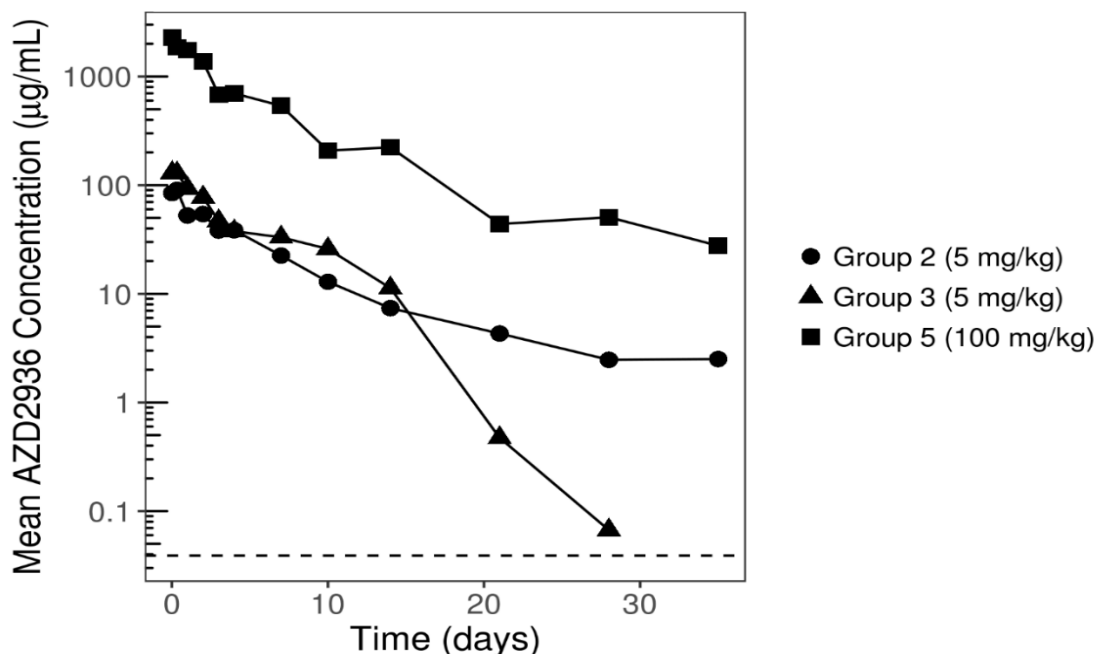
In groups 3 and 5, following a single iv dose of 5 or 100 mg/kg rilvegostomig alone, mean $C_{\max}$ values were 150 and 2690 µg/mL, respectively. The mean AUC_{∞} values were 616 and 12,000 µg·day/mL, respectively (Table 19). The ADA caused an increase in CL after Day 10 in all 8 female monkeys administered 5 or 100 mg/kg rilvegostomig (Figure 27). In group 3, the mean $t_{1/2}$ was calculated to be 1.43 days. The mean CL and V_{ss} were calculated to be 251 mL/day and 1164 mL, respectively (Table 19). In group 5, the $t_{1/2}$ was calculated to be 4.35 days. The mean CL and V_{ss} were calculated to be 262 mL/day and 1614 mL, respectively (Table 19).

Table 19 Summary of Mean PK Parameters of Rilvegostomig after a Single iv Dose (8399632)

Group	Dose level (mg/kg/dose)		C _{max} (µg/mL)	AUC _∞ (µg·day/mL)	V _{ss} (mL)	CL (mL/day)	t _{1/2} (day)
2	5	N	4	1	1	1	1
		Mean	91.6	574	3330	217	14.2
		SD	10.6	NA	NA	NA	NA
3	5	N	4	4	4	4	4
		Mean	150	616	1164	251	1.43
		SD	27.0	118	51.6	48.6	0.427
5	100	N	4	2	2	2	2
		Mean	2690	12000	1614	262	4.35
		SD	1110	NA	NA	NA	NA

The ADA caused an increase in CL after Day 10 in all 8 female monkeys. Animals in Groups 1, and 2 (not Groups 3, or 5) were administered abatacept intravenously as a 30-minute infusion (10 mg/kg, 2 mg/mL, 5 mL/kg) on Days -1, 7, 14, 21, and 28 (5 total doses/animal).
N = number of monkeys; NA = not applicable.

Figure 27 Mean Concentrations of Rilvegostomig in Serum of Female Cynomolgus Monkeys



Animals in Groups 1, and 2 (not Groups 3, or 5) were administered abatacept intravenously as a 30-minute infusion (10 mg/kg, 2 mg/mL, 5 mL/kg) on Days -1, 7, 14, 21, and 28 (5 total doses/animal). The black dashed line represents the limit of quantitation (0.039 µg/mL) of the bioassay for measuring rilvegostomig. AZD2936 = rilvegostomig.

4.2.2 Single Dose sc or iv PK, PD, and Tolerability Study in the Non-human Primate (Study 8529365)

This study evaluated the PK and PD profiles and tolerability of rilvegostomig after single dose by sc or iv injection to male cynomolgus monkeys followed by a 6-week observation period. Five groups of male cynomolgus monkeys, each consisting of 3 animals/group, were given 1 dose of vehicle control article or rilvegostomig at a dose of 50, 100, or 200 mg/kg via sc injection (Groups 1 through 4) or rilvegostomig at a dose of 200 mg/kg via manual iv slow bolus injection (Group 5) on Day 1 of the dosing phase. The injection volume was 1 mL/kg (Groups 1 through 4) or 5 mL/kg (Group 5). At initiation of dosing, animals were 44 to 54 months old, and body weights ranged from 2.6 to 4.9 kg.

Systemic exposures (C_{max} and $AUC_{0-Day43}$) to rilvegostomig following a single sc injection were dose proportional from 50 to 200 mg/kg, with mean C_{max} values ranging from 578 to 2480 µg/mL and mean $AUC_{0-Day43}$ values ranging from 7000 to 25,100 day*µg/mL. The profiles are shown in Figure 28 and Figure 29. Systemic exposure to rilvegostomig for animals dosed with 200 mg/kg was higher for animals dosed via iv bolus injection, compared with those dosed via sc injection, with C_{max} and $AUC_{0-Day43}$ values of 8610 µg/mL and 37,400 day*µg/mL, respectively; $AUC_{0-Day43}$ values for animals dosed with 200 mg/kg sc were 0.671-fold lower than those for animals dosed with 200 mg/kg iv. The iv profile is

shown in [Figure 29](#). The PK parameters for sc or iv administration are summarized in [Table 20](#).

Animals given any dose of rilvegostomig tested positive for ADAs during the dosing phase. The exposure for animals dosed with 200 mg/kg sc appeared to be impacted by ADA presence, as rilvegostomig concentrations declined quicker compared to animals dosed with 50 or 100 mg/kg sc.

Table 20 Summary PK of Rilvegostomig Following a Single sc or iv Dose Administration

Parameter	50 mg/kg (sc)	100 mg/kg (sc)	200 mg/kg (sc)	200 mg/kg (iv)
Median T _{max} (h)	72.0	72.0	72.0	0.500
Mean C _{max} (µg/mL) ± SD (n = 3)	578 ± 65.1	1390 ± 90.7	2480 ± 234	8610 ± 300
Mean AUC _{0-Day43} (day*µg/mL) ± SD (n = 3)	7000 ± 395	17,200 ± 4870	25,100 ± 5970	37,400 ± 5760

Figure 28 Mean (+ SD) Concentrations (ng/mL) of Rilvegostomig in Male Monkey Serum Following a Single Dose sc Injection Administration: Day 1

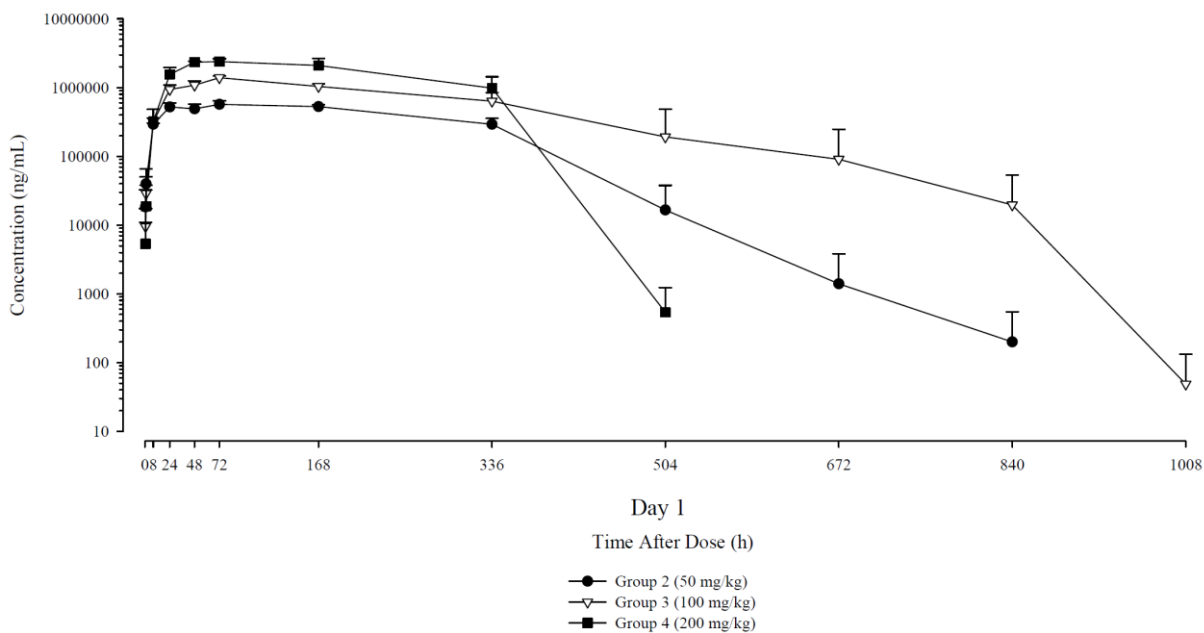
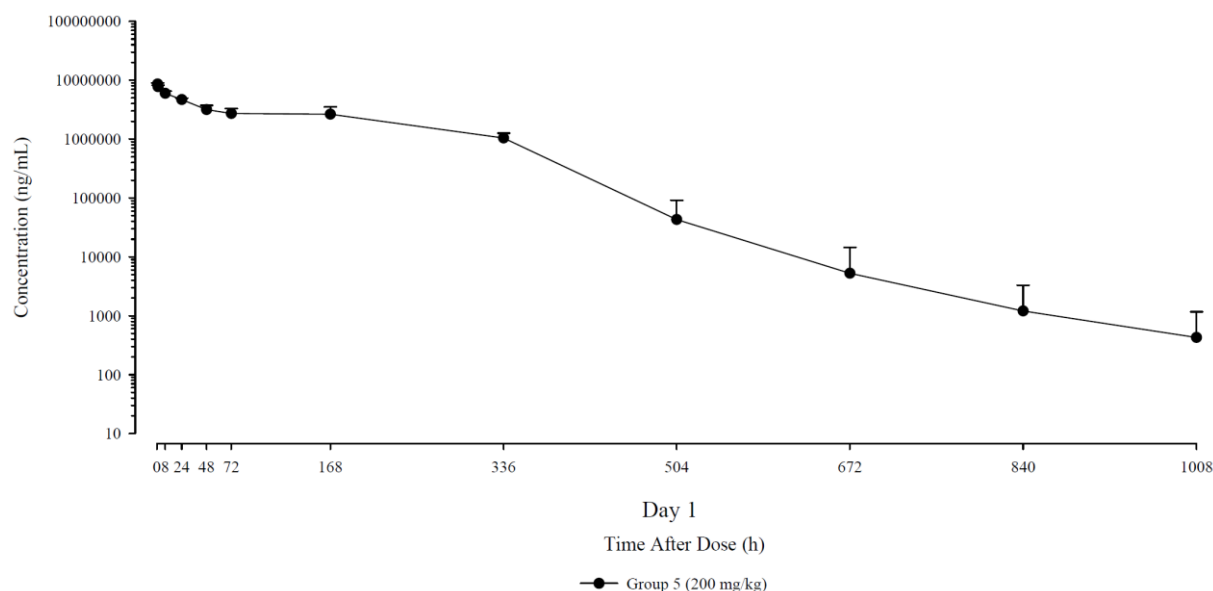


Figure 29 Mean (+ SD) Rilvegostomig Dose Normalized C_{max} and $AUC_{0-Day43}$ Relationships in Male Monkey Serum Following a Single Dose sc Injection Administration



4.2.3 Repeat Dose PK in a 1-Month Repeat Dose Toxicity Study in the Cynomolgus Monkey (GLP) (Study 20260563)

The objective of this study phase of the toxicology study was to evaluate the serum PK of rilvegostomig in male and female cynomolgus monkeys when given once weekly for 1 month (on Days 1, 8, 15, 22, and 29) by an iv bolus injection at 50, 100, and 200 mg/kg with a 6-week recovery (Table 21). Blood samples (approximately 1.0 mL) were collected from monkeys via venipuncture on Days 1, 8, 15, 22, and 29 of the dosing phase and on Days 41, 55, and 70 during the recovery phase. Additional blood samples (approximately 1.0 mL) were collected from monkeys via venipuncture at week -1 (Day -5), and at predose on Days 8, 15, 29 and on Day 36 of the dosing phase for all animals, and on Day 70 of the recovery phase for animals in the recovery study for evaluation of ADA.

Table 21 Study Design (20260563)

Group no.	Test material	Dose level (mg/kg/week)	Dose volume (mL/kg) ^a	Dose concentration (mg/mL)	No. of animals ^b			
					Main study		Recovery study	
					Males	Females	Males	Females
1	Vehicle	0	5	0	3	3	2	2
2	Rilvegostomig	50	5	10	4	4	0	0
3	Rilvegostomig	100	5	20	4	4	0	0
4	Rilvegostomig	200	5	40	3	3	2	2

^a Based on the most recent body weight measurement.

^b Main study animals were euthanized on Day 36. Recovery animals were euthanized on Day 71.

All serum concentration values of rilvegostomig in the vehicle control group were below the lower limit of quantitation. Exposure to rilvegostomig, as assessed by mean $C_{\max}$ and AUC_{τ} values, increased in the serum with the increase in dose level from 50 to 200 mg/kg/dose (Table 22 and Table 23). The increases in rilvegostomig mean $C_{\max}$ and AUC_{τ} values were proportional to the doses. There is no obvious sex difference in the exposure of rilvegostomig in monkeys. Accumulation of rilvegostomig was observed after multiple weekly doses of 50, 100, or 200 mg/kg/day in monkeys (Table 23). Mean serum concentration-time profiles by doses are shown in Figure 30.

Overall, animals in the vehicle control group did not screen positive for ADA. Reduced PK exposure was observed for a total of 9 monkeys that developed high ADA starting on Day 15 after 2 weekly doses, including 2 males and one female at 50 mg/kg, 2 males and one females at 100 mg/kg, and 3 females at 200 mg/kg. In addition, the signal to background ratios of ADA for these 9 animals were markedly higher than the other 17 animals with ADA positive results, with signals more than 1000-fold higher than the background level in 4 of the 9 animals.

In the other 17 monkeys administered rilvegostomig whose PK exposures were not impacted by ADA, this reduced PK exposure was not observed and any positive ADA results in the 17 monkeys did not produce reduced PK exposure.

The mean CL, V_{ss} , and $t_{1/2}$ were similar across all dose groups on both Day 1 and Day 29. On Day 1, the $t_{1/2}$ values at 50, 100, and 200 mg/kg were calculated to be from 4.6 to 6.8 days. The mean CL were calculated to be from 26.7 to 35.6 mL/day. The mean V_{ss} were calculated to be from 198 to 246 mL (Table 22). On Day 29, the mean terminal $t_{1/2}$ values at 50, 100, and 200 mg/kg were calculated to be from 7.1 to 9.9 days. The mean CL were calculated to be from 15.3 to 18.5 mL/day. The mean V_{ss} were calculated to be from 156 to 237 mL (Table 23).

As a result, animals with positive ADA results and impacted exposure were excluded from descriptive statistics and PK interpretation beginning on Day 15 after 2 weekly doses. In all instances, at least 2 animals/sex/group were included in descriptive statistics, ensuring a sufficient number of animals for the interpretation of results. Therefore, these events did not impact the overall inferences and conclusions drawn from the PK analysis for this study.

Table 22 Summary of Mean Rilvegostomig PK Parameters in Cynomolgus Monkey Serum Following Once Weekly iv Dosing after Day 1 (20260563)

Group	Dose level (mg/kg/dose)		C _{max} (µg/mL)	AUC _τ (µg·day/mL)	V _{ss} (mL)	CL (mL/day)	t _{1/2} (day)
2	50	N	8	8	8	8	8
		Mean	1081	2817	198	30.0	4.6
		SD	111	493	65.2	5.7	1.5
3	100	N	8	8	8	8	8
		Mean	1968	5460	246	26.7	6.8
		SD	451	918	45.2	6.1	2.6
4	200	N	10	10	10	10	10
		Mean	3563	9958	232	35.6	4.7
		SD	646	2239	56.9	10.0	1.2

N = number of monkeys.

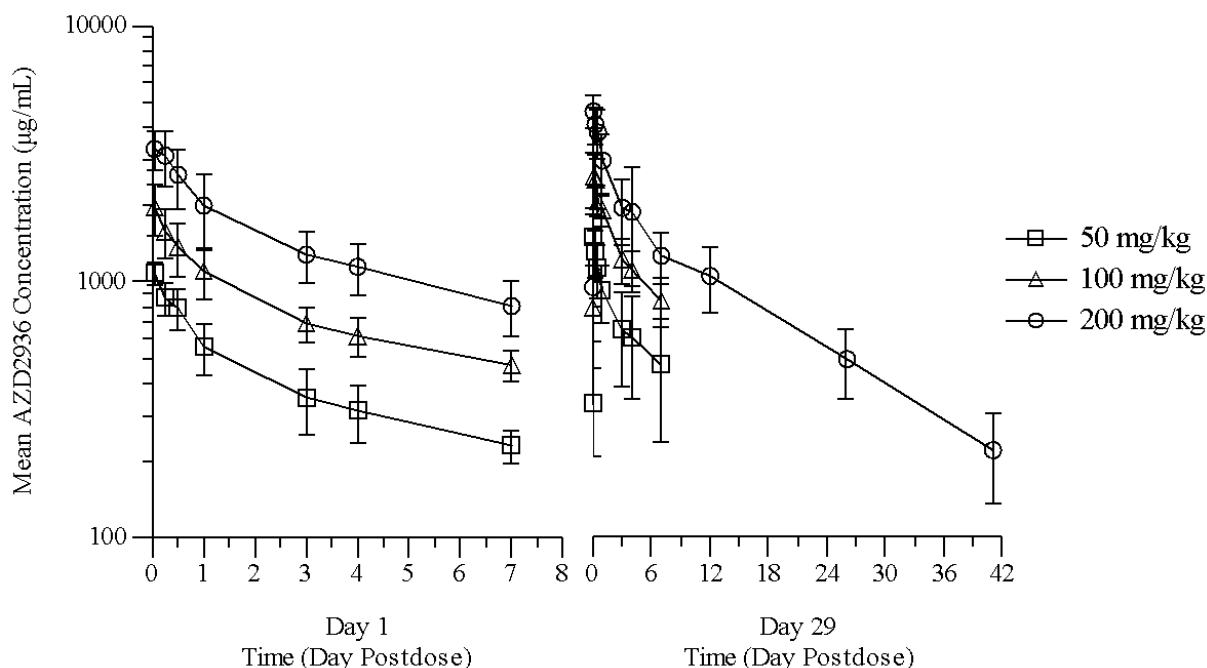
Table 23 Summary of Mean Rilvegostomig PK Parameters in Cynomolgus Monkey Serum Following Once Weekly iv Dosing after Day 29 (20260563)

Group	Dose level (mg/kg/dose)		C _{max} (µg/mL)	AUC _τ (µg·day/mL)	V _{ss} (mL)	CL (mL/day)	t _{1/2} (day)	AR of C _{max}	AR of AUC _τ
2	50	N	5	5	5	5	5	5	5
		Mean	1488	4930	164	15.3	8.0	1.3	1.5
		SD	348	1717	53.9	6.9	1.9	0.28	0.40
3	100	N	5	5	5	5	5	5	5
		Mean	2797	9329	156	15.5	7.1	1.5	1.7
		SD	596	1334	38.9	2.4	2.0	0.26	0.26
4	200	N	7	7	7	7	7	7	7
		Mean	4637	15115	237	18.5	9.9	1.2	1.4
		SD	624	4140	66.7	7.7	3.8	0.26	0.29

Animals with reduced exposure and positive ADA results were excluded from descriptive statistics starting on Day 15.

AR = Accumulation Ratio; N = number of monkeys.

Figure 30 Mean ($\pm$ SD) Concentrations (μ g/mL) of Rilvegostomig in Combined Male and Female Monkey Serum following Once Weekly iv Administration: Days 1 and 29



Animals with reduced exposure and positive ADA results were excluded from graphical analysis starting on Day 15.
AZD2936 = rilvegostomig.

4.2.4 Repeat Dose Toxicity and Toxicokinetics in a 3-month Study in Cynomolgus Monkeys (GLP) (Study 8522498)

The objective of this study was to determine the toxicokinetics of rilvegostomig when administered once weekly to cynomolgus monkeys via iv slow bolus injection for at least 13 weeks (14 total doses). Groups of 3 male and 3 female monkeys were dosed with rilvegostomig at 50, 100 or 200 mg (Table 24).

Blood samples were collected from all animals on Days 1 and 85 predose and at approximately 1, 6, 12, 24, 72, 96, and 168 hours postdose. Blood samples were also collected from all animals on Days 22 and 50 predose and at approximately 24 hours postdose.

Blood samples were collected from all animals for ADA analysis once during the predose phase and predose on Days 22 and 85 during the dosing phase.

Table 24 Study Design (8522498)

Group	Dose level ^b (mg/kg/week)	Dose concentration ^b (mg/mL)	No. of animals	
			Males	Females
1 (Control) ^a	0	0	3	3
2 (Low)	50	10	3	3
3 (Intermediate)	100	20	3	3
4 (High)	200	40	3	3

^a Group 1 was administered vehicle control only.

^b Animals were dosed at a volume of 5 mL/kg.

All animals dosed with rilvegostomig demonstrated exposure at all time points on Days 1 and 85 (Table 25 and Figure 31). Exposure, as assessed by rilvegostomig mean $C_{\max}$ and AUC_{0-168h} values, increased with the increase in dose level from 50 to 200 mg/kg/week. There were no sex differences in exposure. The increases in rilvegostomig mean $C_{\max}$ and AUC_{0-168h} values were generally dose proportional. Rilvegostomig mean $C_{\max}$ and AUC_{0-168h} values were notably higher on Day 85 than on Day 1, indicating accumulation of rilvegostomig after multiple weekly iv bolus doses in monkeys. Mean accumulation ratio values ranged from 1.43 to 1.97 for $C_{\max}$ and from 2.14 to 2.67 for AUC_{0-168h} .

Due to the inability to characterize the elimination phase, AUC_{∞} , $t_{1/2}$, CL, and V_{ss} could not be calculated on Day 1, and $t_{1/2}$ and V_{ss} could not be calculated on Day 85 for all dose groups. On Day 85, mean CL values ranged from 0.148 to 0.165 mL/h/kg and appeared to be dose-independent. Mean concentration values for rilvegostomig were measurable at all time points on Days 1 and 85.

The overall incidence of ADA response to rilvegostomig across the study (including all sampling times) was 33% (2 out of 6) at 0 mg/kg/week (control group), 100% (6 out of 6) at 50 mg/kg/week, 100% (6 out of 6) at 100 mg/kg/week, and 83% (5 out of 6) at 200 mg/kg/week. Animals first screened positive for ADA during the predose phase in the 100 and 200 mg/kg/week dose groups and on Day 22 of the dosing phase for the 0 and 50 mg/kg/week dose groups. Animals that had ADA detected generally exhibited similar exposure to animals that were ADA negative, with the exception of one Group 2 male (50 mg/kg/week). Due to the widespread presence of ADA and the general lack of impact on exposure in ADA positive animals, all animals were included in descriptive statistics and toxicokinetic analysis, except for this Group 2 male, which was excluded.

Table 25 Summary of the Rilvegostomig Mean Toxicokinetic Parameters in Cynomolgus Monkey Serum (8522498)

Interval (Day)	Dose group	Dose level (mg/kg/week)	Sex	C ₀ (µg/mL)	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-168h} (h*µg/mL)
1	2	50	M	1590	1490	1.00	107000
			F	2080	1890	1.00	150000
			M/F	1840	1690	1.00	128000
	3	100	M	3300	3150	1.10	229000
			F	3810	3720	1.00	286000
			M/F	3550	3440	1.05	257000
	4	200	M	10600	10100	1.00	603000
			F	9330	9020	1.00	685000
			M/F	9950	9540	1.00	644000
85	2	50	M	2940 ^a	2920 ^a	1.00 ^a	271000 ^a
			F	3140	3460	6.00	393000
			M/F	3060	3240	1.00	344000
	3	100	M	6270	6160	1.00	586000
			F	7030	6950	1.00	772000
			M/F	6650	6560	1.00	679000
	4	200	M	13300	13100	1.00	1270000
			F	14100	14000	1.15	1490000
			M/F	13700	13500	1.00	1380000

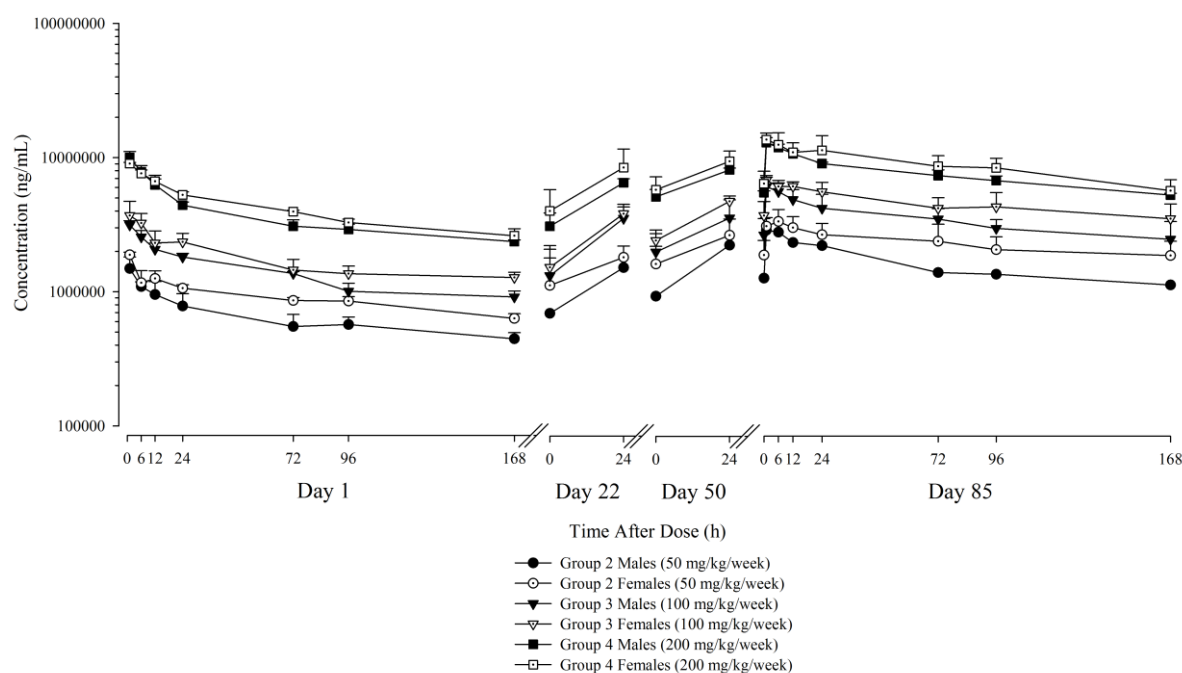
^a Not a true mean or median (n = 2).

Toxicokinetics units were converted from ng/mL to µg/mL.

Median values are presented for T_{max}.

C₀ = initial concentration; F = female; M = male.

Figure 31 Mean (+ SD) Concentrations (ng/mL) of Rilvegostomig in Male and Female Monkey Serum following Once Weekly iv Bolus Administration (Days 1, 22, 50, and 85; Study 8522498)



4.3 Toxicology

4.3.1 Single Dose iv PK and PD Study in the Cynomolgus Monkey (Study 8399632)

In the single iv dose study, groups of 4 female cynomolgus monkeys were dosed with either a single 30-minute iv infusion of vehicle, 5 mg/kg or 100 mg/kg of rilvegostomig on Day 1, or dosed with abatacept on Days -1, 7, 14, 21, and 28 with a single dose of rilvegostomig (5 mg/kg or 100 mg/kg) on Day 1. The aim of the study was to investigate systemic exposure/PK profiles in the absence of “clearing” ADAs. Blood was collected at various time points following dosing for the following assessments; PK/PD markers, ADA and immunogenicity.

A single dose of 100 mg/kg iv was well tolerated. Exposure to rilvegostomig in female monkeys increased with the increase in dose level from 5 to 100 mg/kg. At 5 mg/kg rilvegostomig exposure was similar for up to 15 days postdose when rilvegostomig was dosed at 5 mg/kg alone or with abatacept. Higher systemic clearance was observed after 15 days postdose when rilvegostomig was dosed at 5 mg/kg alone than with abatacept indicating pre-treatment with abatacept minimized the effects of ADAs on systemic exposure.

4.3.2 Single sc or iv Dose PK, PD and Tolerability Study in the Cynomolgus Monkey (Study 8529365)

In the single sc or iv dose study, groups of 3 male monkeys received a single dose of rilvegostomig sc at 0 [vehicle (20 mM histidine, 210 mM arginine, 0.04% poloxamer 188, pH 6.0)], 50, 100 or 200 mg/kg on Day 1. An additional group of 3 male monkeys received a single dose of rilvegostomig by iv bolus injection at 200 mg/kg on Day 1. The aim of the study was to evaluate the PK, PD profiles and tolerability of rilvegostomig to support sc dosing in patients. Injection volume was 1 mL/kg for sc administration and 5 mL/kg for iv administration. All animals were returned to the stock colony after the last blood sample was collected (Day 43).

A single dose sc administration of rilvegostomig resulted in dose proportional exposure from 50 to 200 mg/kg. Both sc and iv administrations were associated with the induction of ADA. After a single sc injection of rilvegostomig at 50, 100, or 200 mg/kg, ADA positivity was noted in all animals on Days 15, 29, and 43. After a single iv bolus administration of rilvegostomig at 200 mg/kg, ADA positivity was noted in all animals on Days 15, 29, and 43. The effect of ADA induction on rilvegostomig exposure could not be determined for individual animals. However, exposure for animals dosed with 200 mg/kg sc appeared to be impacted by ADA presence, as rilvegostomig concentrations declined quicker compared to animals dosed with 50 or 100 mg/kg sc. Bioavailability of sc administered rilvegostomig was 67.1%, as assessed by AUC_{0-Day43} values.

Rilvegostomig administered at dose levels of up to 200 mg/kg sc or at 200 mg/kg iv was well tolerated in male monkeys. No rilvegostomig-related clinical observations, alterations in body weight or food consumption, or peripheral blood immunophenotyping effects were noted. Rilvegostomig-related dermal observations included edema and erythema at the sc or iv dose site for animals dosed with 200 mg/kg sc or iv. Edema and erythema were mild in severity for animals dosed with 200 mg/kg sc and resolved within 1 day. For animals dosed with 200 mg/kg iv, edema and erythema generally persisted for a longer duration but resolved by Day 6 for all animals. Increases in IL-6 level above the lower limit of quantitation and control values were noted at 6 hours postdose on Day 1 in animals administered rilvegostomig (1 to 2 animals at each dose level). Given the timing and magnitude of increases, they were considered related to rilvegostomig. However, the increases in IL-6 levels were transient and did not coincide with clinical observations indicating no impact on animal health. The dose level of 200 mg/kg sc resulted in a C_{max} value of 2480 µg/mL and an AUC_{0-Day43} value of 25,100 day*µg/mL, which was 0.671-fold lower than for animals dosed with 200 mg/kg iv.

4.3.3 1-Month Intravenous Toxicity Study with 6-Week Assessment of Recovery in the Cynomolgus Monkey (Study 20260563)

The aim of this study was to evaluate the systemic and local potential toxicity of rilvegostomig upon repeated iv bolus injection once weekly for 1 month (on Days 1, 8, 15, 22,

and 29) to cynomolgus monkeys. In addition, the reversibility of any potential rilvegostomig-mediated toxicity was evaluated after a 6-week recovery period. The toxicokinetic characteristics of rilvegostomig were also determined.

Groups of 3 or 4 male and 3 or 4 female monkeys received 5 doses of rilvegostomig by iv bolus injection at 0 (vehicle - 20 mM Histidine/Histidine-HCl, 240 mM Sucrose, 0.02% polysorbate-80, pH 6.0), 50, 100 or 200 mg/kg at weekly intervals (dosing on Days 1, 8, 15, 22 and 29). Injection volume was 5 mL/kg. Scheduled necropsies were conducted 7 days after the final dose (Day 36). Two additional groups of 2 male and 2 female monkeys were dosed with vehicle or 200 mg/kg as above but were retained for an additional 6-week recovery period with scheduled necropsies 42 days after the last dose (Day 71).

There were no rilvegostomig-related clinical signs or effects on survival, body weights, food consumption, ophthalmology, neurology, quantitative or qualitative electro-cardiology, vital signs (blood pressure, heart rate or respiratory rate), coagulation parameters, urinalysis or urine chemistry parameters, or systemic cytokine release.

Systemic exposures (mean $C_{\max}$ and mean AUC_{0-168h}) were approximately dose proportional after a single dose on Day 1 and after repeat dosing on Day 29 (following 5 administrations of rilvegostomig), consistent with linear kinetics, and without any apparent differences in exposure between male and female animals. Following the final dose administration, mean, combined sex, $C_{\max}$ values were 1190, 2470, and 4620 $\mu\text{g/mL}$, and mean, combined sex, AUC values were 84200, 156000 and 313000 $\text{h} \cdot \mu\text{g/mL}$ at 50, 100 and 200 mg/kg/week, respectively. In terms of mean AUC_{0-168h} , there was some variability compared to after a single dose. This variability can be explained by the presence of ADA that reduced exposure of rilvegostomig in 3/8, 3/8 and 3/10 animals in the 50, 100 and 200 mg/kg/week dose groups, respectively.

Injection site observations (edema, ranging from grade 1 to mild-moderate) were noted in some animals across control and treated groups, but due to the increased occurrences in 2 animals, one each at 100 and 200 mg/kg/week, a treatment-related effect cannot be ruled out. However, there were no microscopic correlates to this observation.

The administration of rilvegostomig by iv bolus injection once weekly for 1-month (5 administrations) was associated with reversible changes in hematology and clinical chemistry parameters. Changes in hematology parameters were limited to females at 200 mg/kg/week and were transient on Day 15. These changes consisted of minimal decreases in the red blood cell mass (red blood cell count, hemoglobin, and hematocrit) with minimally increased reticulocytes (the expected bone marrow response to the decreased red blood cell mass), and minimal increases monocytes and large unstained cells. No changes were observed on Day 70 in animals administered 200 mg/kg/week following a 6-week recovery. rilvegostomig-related changes in clinical chemistry parameters were observed in one or more

animals at all dose levels, except in males at 200 mg/kg/week, and were consistent with an acute phase response, first noted on Day 15 (mildly decreased albumin and mildly increased C-reactive protein, minimally increased globulin and mildly decreased cholesterol) and then on Day 31 (minimally to mildly decreased albumin, minimally to mildly increased globulin and minimally increased C-reactive protein). All changes fully recovered by Day 70 in animals administered 200 mg/kg/week following a 6-week recovery period.

Rilvegostomig exposure resulted in transient, dose-independent T-cell population changes along with transient increases in activation markers that are consistent with the proposed mechanism of activation for rilvegostomig. For example, animals administered 200 mg/kg/week expressed increases in T-cytotoxic lymphocyte absolute counts on Day 4 that generally returned to the level of baseline or below on Day 9, with recovery animals expressing increases on Day 70.

Evidence of activation of the complement system by rilvegostomig was noted by measurement of dose-independent, small-magnitude increases in C3a levels across all treatment groups between Day 8 predose and Day 36 that peaked between Day 15 predose and Day 22 predose before trending or returning to baseline by Day 36. Rilvegostomig-related increases were not observed in plasma C3a concentrations in the recovery animals at Day 70.

At terminal necropsy, increased spleen weights were noted in both sexes (males more pronounced changes than females), at all dose levels of rilvegostomig and with macroscopic enlargement of the spleen in one male at 200 mg/kg/week. These changes were not observed at the end of the recovery phase on Day 71.

Microscopic changes associated with administration of rilvegostomig were observed at dose levels ≥ 50 mg/kg/week in the spleen and brain. In the spleen, minimal to mild increased lymphoid cellularity was observed and correlated with increases in spleen weights. In the brain, minimal to mild mononuclear cell infiltrates were observed within the choroid plexus and/or within the meninges/parenchyma. By the end of the recovery phase on Day 71, there were no microscopic changes noted within the spleen, indicating complete recovery. Within the brain, minimal mononuclear cell infiltrates were observed within the choroid plexus and/or within the meninges/parenchyma at 200 mg/kg/week and were considered partially recovered based upon the minimal severity. These reversible changes were considered likely indicative of an activated immune system and associated with the ADA response noted in all rilvegostomig-treated animals.

Non-adverse treatment-related changes were minimal, recoverable and associated with the anticipated pharmacological activity of rilvegostomig or an immune response by the animals to the humanized antibody, as shown in [Table 26](#).

Table 26 Findings in the 1-month Repeat Dose Toxicity Study in Cynomolgus Monkeys

Findings	Dose level findings noted	Comments
<u>Hematology</u> - Decreased red cell mass (red blood cell count, hemoglobin, and hematocrit) with minimally increased reticulocytes - Increases in monocytes and large unstained cells on Day 15.	200 mg/kg/wk - females only	- Minimal change, and the expected bone marrow response to the decreased RBC mass - On Day 31, these values approximated baseline and/or controls and no changes were observed on Day 70 following a 6-week recovery - Non-adverse
<u>Clinical chemistry</u> - Decreased albumin - Increased C-reactive protein - Minimally increased globulin - Mildly decreased cholesterol	≥ 50 mg/kg/wk - noted in one or more animals	- Consistent with a minimal to mild acute phase response - All changes fully recovered by Day 31 and Day 70, following the 6-week treatment-free period - Non-adverse
<u>Organ weights</u> Spleen: Increased absolute weight, and relative to body weight and brain weight	≥ 50 mg/kg/wk - noted in all rilvegostomig-dosed animals; increases greater in males vs females	- Reversible increases in spleen weight are associated with increased lymphoid cellularity and likely associated with ADA response - Non-adverse
<u>Histopathology</u> - Spleen: increased cellularity - Brain: Minimal to mild mononuclear cell infiltrates within the choroid plexus and/or within the meninges/parenchyma of the brain.	≥ 50 mg/kg/wk - noted in all rilvegostomig dosed animals; increases greater in males vs females	- Reversible and associated with ADA response - Brain findings may also be exacerbation of a background finding in cynomolgus monkeys due to immune activation - Non-adverse
<u>Immunophenotyping</u> - Transient, dose-independent decreases (some of which attained statistical significance) in total T lymphocyte absolute counts were noted in some animals across all dose groups - Similar trends, some of which reached statistical significance, were noted, such as a decrease in T helper lymphocytes and a transient increase in regulatory T lymphocytes and cytotoxic T lymphocytes.	≥ 50 mg/kg/wk - noted in all rilvegostomig dosed animals; increases greater in males vs females	- Changes in T-cell populations consistent with mechanism of action of rilvegostomig, minor and reversible - Non-adverse

RBC = red blood cells; wk = week.

In conclusion, administration of rilvegostomig by repeated iv bolus injection once weekly for one month (on Days 1, 8, 15, 22, and 29) was well tolerated in cynomolgus monkeys at levels of 0, 50, 100, or 200 mg/kg/week. Rilvegostomig-related changes in hematology (at 200 mg/kg/week only), clinical chemistry, and complement C3a were generally minimal, and reversible either at the end of the dosing period or after the 6-week recovery period. Minimal changes in T-cell populations were expected based on the pharmacology of the test article and were also generally reversible. At the end of the dosing phase, administration of rilvegostomig was associated with increased spleen weights at all doses, with macroscopic enlargement of the spleen observed in one male at 200 mg/kg/week. These changes were not observed at the end of the recovery phase on Day 71. Microscopically, target organ effects associated with administration of rilvegostomig were observed at doses $\geq$ 50 mg/kg/week in the spleen and brain, which recovered completely for the spleen, and partially recovered for the brain infiltrates and were considered consistent with activation of the immune system and associated with the ADA response of the cynomolgus monkey to the humanized bispecific rilvegostomig ([Butt et al 2014](#), [Chamanza et al 2010](#), [Naylor et al 2019](#), [Sato et al 2012](#)).

Based on these results, the NOAEL level was considered to be 200 mg/kg/week. At the NOAEL, on Day 29 the mean $C_{\max}$ and AUC_{0-168h} values for males were 4440 $\mu\text{g/mL}$ and 348,000 $\text{h}\cdot\mu\text{g/mL}$, and for females 4790 $\mu\text{g/mL}$ and 278,000 $\text{h}\cdot\mu\text{g/mL}$, respectively, after 4 weeks of treatment.

4.3.4 3-Month Intravenous Toxicity Study in the Cynomolgus Monkey (Study 8522498)

The objective of this study was to further characterize the toxicity and determine the toxicokinetics of rilvegostomig, when administered once weekly to cynomolgus monkeys via iv slow bolus injection for at least 13 weeks (14 total doses). Toxicokinetics results can be found in Section [4.2.4](#).

Four groups of cynomolgus monkeys, each consisting of 3 males and 3 females, were administered 14 doses of either vehicle (20 mM histidine, 240 mM sucrose, 0.04% poloxamer 188, pH 6.0) or rilvegostomig at doses of 50, 100, or 200 mg/kg/week at weekly intervals (Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, and 92). At initiation of dosing, animals were 3 to 5 years of age, and body weight ranged from 2.4 to 3.7 kg for males and from 2.0 to 5.0 kg for females. The injection volume was 5 mL/kg. Scheduled necropsies were conducted 3 days after the final dose (Day 95).

No rilvegostomig-related clinical observations, changes in mean body weight, respiratory rate effects, blood pressure effects, or ECG effects were noted. No rilvegostomig-related neurobehavioral, dermal, or ophthalmic observations were noted. All animals survived to the terminal necropsy.

One male dosed with 50 mg/kg/week was noted with clinical observations of emesis/vomitus, excess salivation, pale pink gums, and tachycardia on Day 29 after dosing, and this animal was treated with diphenhydramine, ondansetron, and cerenia as needed. From Week 8, the animal was noted with thrombocytopenia, an increase in IL-6 concentration, mildly decreased red cell mass, and evidence of transient muscle perturbation (increases in AST, ALT, and creatine kinase). These findings showed reversibility by Day 71, and collectively were considered related to an anaphylactoid-like reaction, likely as a secondary reaction to the presence of ADA. This immune response correlated with rilvegostomig concentration values below the lower limit of quantitation of the assay, resulting in this animal being excluded from the toxicokinetic evaluation from Day 22.

No other rilvegostomig-related changes were noted in IL-6, IL-2, IFN- γ , TNF- α values or clinical pathology test results in animals dosed with up to and including 200 mg/kg/week.

Marginal, non-dose dependent increases in C3a were noted on Day 15 in animals administered up to 200 mg/kg/week, compared with predose phase values. These changes were noted in the majority of animals administered 100 or 200 mg/kg/week but only select animals administered 50 mg/kg/week. Increases in C3a levels resolved by Day 78 of the study in all animals. No rilvegostomig-related changes were noted in the levels of CH50 in animals dosed up to and including 200 mg/kg/week.

No changes in T cells, helper T cells, cytotoxic T cells, regulatory T cells, CD25⁺ T-cell subsets, CD69⁺ T-cell subsets, CD127⁺ T-cell subsets, or NK cells were noted in animals dosed with up to and including 200 mg/kg/week.

Rilvegostomig-related findings were noted in the spleen, lymph nodes (axillary and mesenteric), aorta, brain (choroid plexus and meninges), colon, epididymis, heart, kidney, stomach, connective tissues (eye, testes, and sciatic nerve), spinal cord (meninges), tongue, rectum, and/or injection site.

Minimally to markedly increased lymphoid cellularity of the spleen was noted in animals dosed with ≥ 50 mg/kg/week and was noted in 1 or 2 males and females in all groups given rilvegostomig, except for females dosed with 200 mg/kg/week. Increased lymphoid cellularity included variably enlarged follicles, germinal centers, and/or periarterial lymphoid sheaths and correlated with increased splenic weights and subgross enlargement. Additionally, minimally to slightly increased lymphoid cellularity of the axillary lymph nodes was noted in males dosed with ≥ 100 mg/kg/week and females dosed with ≥ 50 mg/kg/week.

Rilvegostomig-related, slightly increased lymphoid cellularity of the mesenteric lymph nodes was noted in males dosed with 200 mg/kg/week. Increased lymphoid cellularity in the axillary and mesenteric lymph nodes correlated with subgross enlargement and a generalized increase in size and cellularity of the paracortex and, to a lesser extent, the cortex. Treatment-related findings of perivascular mononuclear cell infiltrates, perivascular mixed cell infiltrates, and/or

intimal mixed cell infiltrates were noted in the aorta and blood vessels of the brain (choroid plexus and meninges), colon, epididymis, heart, kidney, stomach, connective tissue (eye, testes, and sciatic nerve), spinal cord (meninges), tongue, rectum and/or injection site of both sexes dosed with ≥ 50 mg/kg/week.

The incidence and/or severity of the rilvegostomig-related findings generally had no relationship to dose or sex. All rilvegostomig-related findings were considered non-adverse (Table 27).

Table 27 Findings in the 3-Month Repeat Dose Toxicity Study in Cynomolgus Monkeys

Findings	Dose level findings noted	Comments
<u>Clinical observation</u> Emesis/vomitus, excess salivation, pale pink gums, and tachycardia on Day 29 after dosing.	One male (Animal P0102) at 50 mg/kg/week	This animal was treated with diphenhydramine, ondansetron, and cerenia as needed.
<u>Hematology, clinical chemistry, cytokine</u> - Mildly decreased red cell mass (ie, decreased red blood cell count, hemoglobin concentration, and hematocrit) on Days 51, 57, and 63. - Transiently, markedly decreased platelet count on Day 51 and evidence of a transient muscle perturbation (markedly increased creatine kinase activity and minimally increased AST and ALT activities) on Day 57. - Increase in IL-6 above the LLOQ and controls at 6 hours postdose on Days 15 and 57.	One male (Animal P0102) at 50 mg/kg/week	- All clinical pathology effects resolved/trended toward baseline predose phase values on or before Day 71. - Collectively, the findings from this animal were considered related to an anaphylactoid-like reaction, likely as a secondary reaction to the presence of ADA. - This immune response correlated with rilvegostomig concentration values below the LLOQ of the assay, resulting in this animal being excluded from the toxicokinetic evaluation from Day 22.
<u>Complement</u> Marginal (approximately 1.5-2-fold), non-dose dependent increases in C3a on Day 15.	≥ 50 mg/kg/week	- These changes were noted in the majority of animals administered 100 or 200 mg/kg/week but only select animals administered 50 mg/kg/week. - Increases in C3a levels resolved by Day 78 in all animals.
<u>Organ weights</u> Spleen: Increased absolute weight, and weight relative to body weight and brain weight.	≥ 100 mg/kg/week; statistically significant for males dosed with 200 mg/kg/week	Increases in spleen weight correlated with increased lymphoid cellularity.

Table 27 Findings in the 3-Month Repeat Dose Toxicity Study in Cynomolgus Monkeys

Findings	Dose level findings noted	Comments
<u>Histopathology</u> - Spleen: increased lymphoid cellularity. - Lymph nodes (axillary and mesenteric): increased lymphoid cellularity. - Aorta and blood vessels of the brain (choroid plexus and meninges), colon, epididymis, heart, kidney, stomach, connective tissue (eye, testes, and sciatic nerve), spinal cord (meninges), tongue, rectum and/or injection site: perivascular mononuclear cell infiltrates, perivascular mixed cell infiltrates, and/or intimal mixed cell infiltrates.	≥ 50 mg/kg/wk	- The incidence and/or severity generally had no relationship to dose or sex. - The findings were consistent with secondary immunological reaction to biotherapeutics.

LLOQ = lower limit of quantification.

In conclusion, once weekly administration of rilvegostomig to cynomolgus monkeys via iv slow bolus injection at the dose levels of 50, 100, or 200 mg/kg/week for 13 weeks was tolerated. Treatment-related clinical observations and changes in hematology and clinical chemistry parameters and IL-6 in one male dosed at 50 mg/kg/week were considered related to an anaphylactoid-like reaction, likely as a secondary reaction to the presence of ADA to rilvegostomig. Marginal, non-dose dependent increases in complement C3a noted on Day 15 in all rilvegostomig dose groups resolved by Day 78 in all animals. Rilvegostomig-related, non-adverse microscopic findings were observed in both sexes dosed with ≥ 50 mg/kg/week. Increased lymphoid cellularity in the spleen correlated with increased splenic weights for both sexes dosed with ≥ 100 mg/kg/week. Based on these findings, the dose level of 200 mg/kg/week, the highest dose tested, is considered the NOAEL. This corresponded to sex combined, mean $C_{\max}$ and AUC_{0-168h} values of 13,500 $\mu\text{g/mL}$ and 1,380,000 $\text{h} \cdot \mu\text{g/mL}$, respectively, on Day 85 (see Section 4.2.4).

4.3.5 Genotoxicity

In accordance with ICH S6 (R1), no genotoxicity testing has been conducted with rilvegostomig and is not planned because it is not applicable to biotechnology-derived large protein products. Rilvegostomig is a large protein molecule that is not expected to cross the nuclear or mitochondrial membranes to interact directly with DNA or other chromosomal materials.

4.3.6 Carcinogenicity

In accordance with ICH S6 (R1) and ICH S9 guidance, carcinogenicity studies have not been performed and are not planned for rilvegostomig, given the characteristics of this product and the intended clinical use in patients with advanced cancer.

4.3.7 Reproductive and Development Toxicity

Reproductive and developmental toxicity studies with rilvegostomig have not been conducted and are not planned. A weight of evidence approach will be applied to risk assessment for women of childbearing potential and embryo-fetal development. PD-L1 is present in the placenta throughout gestation and upregulated significantly during the fourth month of pregnancy in humans ([Holets et al 2006](#)). Blockade of PD-L1 signaling in murine models of pregnancy has been shown to disrupt tolerance to the fetus and to increase fetal loss ([Zhang et al 2015](#)). Given the known roles of PD-1/PD-L1 and TIGIT in pregnancy and development ([Zhang and Sun 2020](#)), and real world clinical evidence from anti-PD-1/PD-L1 and anti-TIGIT CPIs, the risk of embryo-fetal toxicity can be assumed for rilvegostomig without the need to conduct an in vivo reproductive assessment.

4.3.8 Local Tolerance

No dedicated studies assessing local tolerance of rilvegostomig were performed. Local tolerance was assessed as part of the 1-month and 3-month repeated dose toxicology studies in cynomolgus monkeys. No effects on local tolerance were observed in the 1-month study. In the 3-month study, rilvegostomig-related findings at the iv injection site were limited to minimal mixed cell infiltrate in animals dosed with ≥ 50 mg/kg/week. The findings were considered non-adverse due to the low level of severity.

Local tolerance at the sc or iv injection sites was also assessed by dermal Draize evaluation following a single sc or iv dose administration with rilvegostomig up to Day 43 after dosing (Study 8529365). Edema and erythema observed at the sc or iv dose site were transient, of low level of severity, and were therefore considered not adverse.

4.3.9 Other Toxicity Studies

4.3.9.1 Assessment of the Potential for Cytokine Release in Human PBMCs

The objective of this study (Study G-CY-0192) was to perform analysis of the potential for rilvegostomig to elicit cytokine release responses, in human isolated PBMCs, collected from 9 healthy donors. Peripheral blood mononuclear cells were incubated in duplicate at 37 °C for 24 hours (nominal). After stimulation, samples were centrifuged and supernatant was collected and stored frozen (-70 °C nominal) prior to analysis by Luminex to measure concentrations of the cytokines IFN- γ , IL-2, IL-6, and TNF- α . Assessment was conducted on both immobilized (maximum saturation on plate) antibodies at concentrations of

rilvegostomig at 10 µg/mL and soluble antibodies at concentrations of rilvegostomig at 1 and 10 µg/mL.

Rilvegostomig, when presented in soluble phase to donor whole blood, did not induce IFN-γ, IL-2, IL-6, or TNF-α release at a statistically significantly greater level compared to human IgG1-TM isotype control. When presented immobilized on polypropylene plates to donor PBMCs, rilvegostomig induced IL-6 (1.1-fold) and TNF-α (2.8-fold) at a statistically significantly greater level compared to isotype control ([Table 28](#)).

In comparison with the magnitude of difference with agents known to induce CRS, (positive controls TGN1412 and Alemtuzumab) the observed changes with rilvegostomig are considered to be of low concern; in particular, for IL-6, a minimal change noticed only in the immobilized assay (1.1-fold) is unlikely to translate into a clinical AE. These findings are also aligned with known clinical experience with anti-PD-1 and anti-TIGIT mAbs tested in the clinic where no dose-limiting CRS was reported ([Ahn et al 2020](#), [Bendell et al 2020](#), [Niu et al 2020](#), [Rodriguez-Abreu et al 2020](#), [Sheng et al 2017](#), [Spain et al 2016](#)).

Table 28 **Immobilized CRA**

Fold-shift (median conc)	IFN-γ	IL-2	IL-6	TNF-α
Rilvegostomig vs IgG1-TM isoct	1.0	1.0	1.1	2.8
OKT3 vs IgG1 isoct	106.0	9.5	15.1	6.5
TGN1412 analog vs IgG4P isoct	13.6	70.4	27.6	49.3

Conc = concentration; CRA = cytokine release assay; isoct = isotype control.

5 EFFECTS IN HUMANS

As of the DCO date (05 July 2025), approximately 1358 participants had been enrolled into the rilvegostomig clinical development program: approximately 201 have received rilvegostomig monotherapy, 219 received rilvegostomig in combination with ADCs, 83 received rilvegostomig in combination with chemotherapy, 75 received rilvegostomig in combination with other therapies, and 780 received study treatment that is blinded at the time of DCO.

Clinical data are presented for one completed study (MAGELLAN [Cohorts A5 and B5]) and for the ongoing ARTEMIDE-01, GEMINI-Gastric Substudy 2, GEMINI-Hepatobiliary (Cohort 2A), TROPION-Lung04 (Cohort 5), TROPION-PanTumor03 (Cohort 6B), and DESTINY-Gastric03 (Arms 4A and 4B) studies. Data for the other 13 ongoing studies are not included in this IB. Data are presented from AstraZeneca-sponsored studies, which have read out and for which the data have been published. These include studies with interim or final analyses.

An overview of completed and ongoing studies with rilvegostomig is presented in [Table 29](#).

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
Completed studies				
MAGELLAN (D933IC00001) NCT03819465	Phase Ib, open-label, multicenter platform study to evaluate the efficacy and safety of durvalumab and/or novel oncology therapies, with or without chemotherapy	Adults with Stage IV NSCLC, not previously treated <u>Cohort A5:</u> PD-L1 TC $\geq$ 50% <u>Cohort B5:</u> Non-squamous NSCLC PD-L1 TC < 50%	<u>Cohort A5:</u> Rilvegostomig 750 mg Q3W iv <u>Cohort B5:</u> Rilvegostomig 750 mg Q3W iv + cisplatin (75 mg/m ²) or carboplatin (AUC5 or AUC6) Q3W iv for 4 cycles + pemetrexed 500 mg/m ² Q3W iv for 4 cycles (maintenance therapy with pemetrexed 500 mg/m ² Q3W allowed after 4 cycles)	<u>Cohort A5:</u> 30/2 ^b <u>Cohort B5:</u> 60/5 ^b

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
Ongoing studies with data presented in this IB				
ARTEMIDE-01 (D7020C00001) NCT04995523	Phase I/II, FTIH, multi-part, open-label, dose escalation and dose expansion study to evaluate the efficacy, safety, PK, and pharmacodynamics of rilvegostomig monotherapy	Adults with advanced/metastatic NSCLC <u>Part A and B:</u> Previously treated with 1 CPI (CPI-experienced) and other therapies. PD-L1 TPS $\geq$ 1% <u>Part C:</u> No prior treatment with any CPI (CPI-naïve), 1 prior line of chemotherapy permitted. PD-L1 TPS $\geq$ 1% <u>Part D:</u> No prior treatment with any CPI (CPI-naïve), 1 prior line of chemotherapy permitted. PD-L1 TPS $\geq$ 50% <u>Part E:</u> Squamous NSCLC only. No prior treatment for metastatic NSCLC. PD-L1 TPS $\geq$ 1%.	<u>Part A Dose Escalation:</u> Rilvegostomig 70, 210, 750, or 1500 mg, Japan safety cohort (750 mg); all Q3W iv <u>Part B Dose Expansion:</u> Rilvegostomig 750 mg Q3W iv <u>Part C Dose Expansion and Part C China Safety Cohort:</u> Rilvegostomig 750 mg Q3W iv <u>Part D Dose Expansion:</u> Rilvegostomig 750 mg or 1500 mg Q3W iv <u>Part E Dose Expansion:</u> Rilvegostomig 750 mg Q3W iv	Planned <u>Part A:</u> up to approx. 72 (3-12 per dose level cohort) <u>Part B:</u> up to approx. 30 Treated Cohort A1 + A2: 15; Cohort A3 + B: 54; Cohort A4: 14 <u>Part C:</u> up to approx. 30/34 <u>Part D:</u> approx. 60 (30 per dose)/61 (750 mg: 31 participants; 1500 mg: 30 participants) <u>Part E:</u> approx. 20-30/21

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
GEMINI-Gastric (D7986C00001) NCT05702229	Phase II, open-label, multi-drug, multicenter platform study to evaluate the efficacy, safety, PK, tolerability, and immunogenicity of novel combination therapies	Adults with HER2 negative, locally advanced unresectable or metastatic gastric cancer or gastroesophageal junction adenocarcinoma, not previously treated	<u>Substudy 2:</u> Rilvegostomig 750 mg Q3W iv + XELOX (capecitabine 1000 mg/m² D1-D14 + oxaliplatin 130 mg/m² D1 Q3W iv) or rilvegostomig 750 mg Q3W iv + FOLFOX (5-FU 400 mg/m² iv, oxaliplatin 85 mg/m², leucovorin 400 mg/m², D1; 5-FU 1200 mg/m² iv over 24 h D1-D2 Q2W) <u>Substudy 4:</u> Rilvegostomig 750 mg Q3W iv + AZD0901 2.2 or 1.8 mg/kg Q3W iv + 5-FU (800 mg/m²/day, D1-D5 Q3W) or capecitabine Q3W (1000 mg/m² BID, D1-D14 Q3W)	<u>Substudy 2:</u> 40/40 <u>Substudy 4:</u> 40/45
GEMINI-Hepatobiliary (D7987C00001) NCT05775159	Phase II, open-label, multi-drug, multicenter platform study to determine the efficacy and safety of novel immunomodulators as monotherapy and in combination with anticancer agents	<u>HCC Substudy 1:</u> Adults with advanced HCC who have not received previous treatment for advanced/metastatic disease <u>BTC Substudy 2:</u> Adults with advanced BTC who have not received previous treatment for advanced/metastatic disease	<u>Substudy 1; Cohort 1D:</u> Volrustomig (1500 mg on Cycle 1, then maintenance dose of 750 mg), Q12W + rilvegostomig 750 mg Q3W from Cycle 2 + bevacizumab 15 mg/kg Q3W from Cycle 2 <u>Substudy 1; Cohort 1E:</u> Rilvegostomig 750 mg Q3W + bevacizumab 15 mg/kg, Q3W <u>Substudy 2; Cohort 2A:</u> Rilvegostomig 750 mg Q3W iv for up to 2 years + gemcitabine 1000 mg/m² + cisplatin 25 mg/m² on D1 and D8 Q3W from Cycle 1 for up to 8 cycles	<u>Substudy 1; Cohort 1D:</u> up to 60/36 <u>Substudy 1; Cohort 1E:</u> up to 60/39 <u>Substudy 2; Cohort 2A:</u> 30/30

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
Tropion-Lung04 (D926FC00001) NCT04612751	Phase Ib, open-label, multicenter platform study to determine the efficacy, safety, and tolerability of Dato-DXd in combination with immunotherapy	Adults with advanced/metastatic NSCLC, not previously treated <u>Cohort 5 (Part 1 and 2):</u> Part 1 and 2A: PD-L1 TPS $\geq$ 50% Part 2B: PD-L1 TPS < 50% (< 1% in at least 6 participants) Part 2 will recruit participants with non-squamous histology NSCLC only. ^c <u>Cohort 6:</u> PD-L1 TPS $\geq$ 50% <u>Cohort 7 and 8:</u> PD-L1 TPS < 50%	<u>Cohort 5 (Part 1 and 2):</u> Rilvegostomig 750 mg Q3W iv + Dato-DXd 6 mg/kg Q3W iv <u>Cohort 6:</u> Rilvegostomig 750 mg Q3W iv + Dato-DXd 4 mg/kg Q3W iv or Rilvegostomig (dose TBD) + Dato-DXd 6 mg/kg Q3W iv <u>Cohort 7:</u> Rilvegostomig 750 mg Q3W iv + Dato-DXd 6 mg/kg + Carboplatin AUC5 Q3W iv for 4 cycles <u>Cohort 8:</u> Rilvegostomig 750 mg Q3W iv + Dato-DXd 4 mg/kg Q3W iv + Carboplatin AUC5 Q3W iv for 4 cycles or Rilvegostomig (dose TBD) + Dato-DXd 6 mg/kg Q3W iv + Carboplatin AUC5 Q3W iv for 4 cycles	<u>Cohort 5:</u> 40/40

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
Tropion-PanTumor03 (D926UC00001) NCT05489211	Phase II, open-label, multicenter platform study to determine the efficacy and safety of Dato-DXd as monotherapy and in combination with anticancer agents	<u>Urothelial Cancer Substudy 6:</u> Adults with advanced unresectable or metastatic urothelial cancer, previously treated with a platinum-based chemotherapy or ineligible to receive cisplatin-based chemotherapy and not previously treated	<u>Cohort 6B:</u> Rilvegostomig 750 mg Q3W iv + Dato-DXd 6 mg/kg Q3W iv	<u>Cohort 6B:</u> 40/40

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
DESTINY-Gastric03 (D967LC00001) NCT04379596	Phase Ib/II, open-label, dose escalation and dose expansion, multicenter platform study to determine the safety, PK, immunogenicity, tolerability, and antitumor activity of T-DXd monotherapy and in combination	Adults with HER2-expressing locally advanced or metastatic, unresectable GC <u>Arm 4A:</u> HER2-positive (IHC 3+ or IHC 2+/ISH-positive) <u>Arm 4B:</u> HER2-low (IHC 2+/ISH-negative or IHC 1+)	<u>Arm 4A and 4B:</u> Rilvegostomig 750 mg Q3W iv + T-DXd 5.4 mg/kg Q3W iv + fluoropyrimidine (capecitabine 750 mg/m ² , BID, D1-D14 or 5-FU 600 mg/m ² /day continuous infusion D1-D5)	<u>Arms 4A and 4B:</u> 60/60
Ongoing studies with no data presented in this IB				
ARTEMIDE-Biliary01 (D7025C00001) NCT06109779	Phase III, randomized, double-blind, placebo-controlled, multicenter study to determine the efficacy and tolerability of rilvegostomig in combination with chemotherapy	Adults with BTC after macroscopically complete resection with curative intent	Rilvegostomig 750 mg (or matching placebo) Q3W iv + chemotherapy (8 cycles with capecitabine or gemcitabine/cisplatin, or 4 cycles with tegafur/gimeracil/oteracil) for up to 6 months, followed by rilvegostomig 750 mg (or matching placebo) as monotherapy Q3W for a maximum of 12 months in total, or until investigator-assessed radiological recurrence guided by RECIST 1.1.	750/578

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
ARTEMIDE-Gastric01 (D702AC00001) NCT06764875	Phase III, randomized, multicenter study to assess the efficacy and safety of rilvegostomig in combination with fluoropyrimidine and T-DXd	Adults with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma with PD-L1 CPS $\geq$ 1	<u>Arm A:</u> Rilvegostomig 750 mg Q3W iv + T-DXd 5.4 mg/kg Q3W iv + fluoropyrimidine (capecitabine 750 mg/m², BID for D1-D14 Q3W PO or 5-FU: 600 mg/m²/day continuous infusion D1-D5 Q3W iv) <u>Arm C:</u> Rilvegostomig 750 mg Q3W iv + trastuzumab 8 mg/kg loading dose, then 6 mg/kg Q3W iv + either FP (cisplatin 80 mg/m² iv + 5-FU 800 mg/m²/day continuous infusion D1-D5 Q3W iv) or CAPOX (capecitabine 1000 mg/m² BID D1-D14 Q3W PO + oxaliplatin 130 mg/m² Q3W iv)	840/9
ARTEMIDE-HCC01 (D7029C00001) NCT06921785	Phase III, randomized, open-label, sponsor-blinded, 3-arm, multicenter, global study assessing the efficacy and safety of rilvegostomig in combination with bevacizumab with or without tremelimumab	Adult participants with advanced HCC who are not amenable to curative therapy or locoregional therapy	<u>Arm A:</u> Rilvegostomig 750 mg Q3W iv + tremelimumab 300 mg $\times$ 2 doses Q12W iv + bevacizumab 15 mg/kg Q3W iv <u>Arm B:</u> Rilvegostomig 750 mg Q3W iv + bevacizumab 15 mg/kg Q3W iv	800/10

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
ARTEMIDE-Lung02 (D702BC00001) NCT06692738	Phase III, 2-arm, randomized, double-blind, global, multicenter study assessing the efficacy and safety of rilvegostomig compared to pembrolizumab, both in combination with platinum-based doublet chemotherapy	Adults with squamous metastatic NSCLC whose tumors express PD-L1 (TC ≥ 1%), not previously treated	<u>Arm A:</u> Rilvegostomig 750 mg Q3W iv + carboplatin AUC6 Q3W iv + paclitaxel 200 mg/m ² Q3W iv or nab-paclitaxel 100 mg/m ² iv D1, D8, and D15 of each cycle for 4 cycles followed by rilvegostomig 750 mg Q3W iv	880/36
ARTEMIDE-Lung03 (D702FC00001) NCT06627647	Phase III, 2-arm, randomized, double-blind, global, multicenter study assessing the efficacy and safety of rilvegostomig in combination with cisplatin or carboplatin and pemetrexed	Adults with non-squamous metastatic NSCLC whose tumors express PD-L1 (TC ≥ 1%) without known actionable genomic mutations (including but not limited to <i>EGFR</i> , <i>ALK</i> , and <i>ROS1</i>), not previously treated	<u>Arm A:</u> Rilvegostomig 750 mg Q3W iv + cisplatin 75 mg/m ² Q3W iv + pemetrexed 500 mg/m ² Q3W iv or carboplatin AUC6 Q3W iv + pemetrexed 500 mg/m ² Q3W iv for 4 cycles followed by rilvegostomig 750 mg Q3W iv + pemetrexed 500 mg/m ² Q3W iv	878/43

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
ARTEMIDE-Lung04 (D702GC00001) NCT06868277	Phase III, 2-arm, randomized, double-blind, multicenter, global study assessing the efficacy and safety of rilvegostomig or pembrolizumab monotherapy	Adults with squamous or non-squamous metastatic NSCLC whose tumors express PD-L1 (TC $\geq 50\%$) without known actionable genomic mutations (including but not limited to <i>EGFR</i> , <i>ALK</i> , and <i>ROS1</i>), not previously treated	<u>Arm A:</u> Rilvegostomig 750 mg Q3W iv	830/0 ^d
BLUESTAR (D6900C00001) NCT05123482	Phase I/IIa, open-label, multicenter study to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary antitumor activity of AZD8205 as a monotherapy and in combination with other anticancer agents	Adults with B7-H4 expressing advanced solid tumors (breast, ovarian, endometrial, biliary tract, and squamous NSCLC)	<u>Substudy 2 (Part A dose escalation):</u> Rilvegostomig 750 mg Q3W iv + AZD8205 (starting dose 1.6 mg/kg Q3W iv)	<u>Substudy 2:</u> 36/10

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
DESTINY-BTC01 (D781PC00001) NCT06467357	Phase III, randomized, open label, global, multicenter study to evaluate the efficacy and safety of T-DXd with rilvegostomig or T-DXd monotherapy	Adults with previously untreated, unresectable, locally advanced or metastatic, HER2-expressing (IHC 3+ or IHC 2+) BTC	<u>Safety run-in and Arm A:</u> Rilvegostomig 750 mg Q3W iv + T-DXd 5.4 mg/kg Q3W iv	<u>Safety run-in:</u> 23/23 <u>Arm A:</u> 200/0
DESTINY-Endometrial01 (D781DC00001) NCT06989112	Phase III, open-label, sponsor-blinded, randomized, controlled, multicenter, 3-arm study assessing the efficacy and safety of 1L T-DXd + rilvegostomig or T-DXd + pembrolizumab	Adults with HER2-expressing (IHC 3+/2+), pMMR, primary advanced (Stage III/IV) or first recurrent EC	<u>Arm A:</u> Rilvegostomig 750 mg Q3W iv + T-DXd 5.4 mg/kg Q3W iv	600/1

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
DESTINY-Lung03 (D967YC00001) NCT04686305	Phase Ib, open-label, multicenter, dose escalation study to evaluate the safety, tolerability and RP2D of T-DXd and immunotherapy with and without chemotherapy agents	Adults with non-squamous HER2-OE metastatic NSCLC	<u>Part 4 (Arm 4A):</u> Rilvegostomig 750 mg Q3W iv + T-DXd 5.4 mg/kg Q3W iv <u>Part 4 (Arm 4B):</u> Rilvegostomig 750 mg Q3W iv + T-DXd 5.4 mg/kg Q3W iv + carboplatin AUC5 Q3W iv (up to 4 cycles)	<u>Part 4:</u> 80/17
NeoCOAST-2 (D9077C00001) NCT05061550	Phase II, open-label, multi-arm, multicenter, randomized, neoadjuvant and adjuvant study	Adult patients with resectable early-stage NSCLC (Stage II to IIIB)	<u>Arm 6:</u> Neoadjuvant: rilvegostomig 750 mg Q3W iv + platinum doublet chemotherapy Q3W for 4 cycles Adjuvant: rilvegostomig 750 mg Q3W iv for 16 cycles <u>Arm 7:</u> Neoadjuvant: rilvegostomig 750 mg Q3W iv + Dato-DXd 6 mg/kg Q3W + single agent platinum chemotherapy Q3W for 4 cycles Adjuvant: rilvegostomig 750 mg Q3W iv for 16 cycles	<u>Arm 6:</u> 70/8 <u>Arm 7:</u> 70/8

Table 29 Overview of Completed and Ongoing Clinical Studies with Rilvegostomig (DCO date: 05 July 2025)

Study ID	Study description	Study population	Intervention regimen	Number of participants planned/treated ^a
Tropion-Lung10 (D7632C00001) NCT06357533	Phase III, randomized, open-label study to determine the efficacy and safety of Dato-DXd in combination with rilvegostomig or rilvegostomig monotherapy	Participants with previously untreated, locally-advanced or metastatic NSCLC with PD-L1 TC $\geq$ 50% without actionable genomic alterations	<u>Arm 1:</u> Rilvegostomig 750 mg + Dato-DXd 6.0 mg/kg Q3W iv <u>Arm 2:</u> Rilvegostomig 750 mg Q3W iv	675/76
TROPION-Lung12 (D926TC00001) NCT06564844	Phase III, randomized, open-label, multicenter, global study assessing the efficacy and safety of adjuvant Dato-DXd in combination with rilvegostomig compared with SoC	Adult patients with Stage I adenocarcinoma NSCLC who are ctDNA-positive or have at least one high-risk pathological feature, after complete surgical resection (R0)	<u>Arm 1:</u> Rilvegostomig 750 mg Q3W iv + Dato-DXd 6 mg/kg Q3W iv for 4 cycles followed by rilvegostomig 750 mg Q3W iv <u>Arm 2:</u> Rilvegostomig 750 mg Q3W iv	660/4

^a Data are based on the DCO date of 05 July 2025.

^b Recruitment into the rilvegostomig arms was terminated early due to a change in the clinical development strategy and not as a result of any safety concerns.

^c This change was made following a protocol amendment and therefore some participants in Part 2 have squamous NSCLC.

^d As of the DCO date of 05 July 2025, the study had achieved FSI, but no participants had been treated.

5-FU = 5-fluorouracil; approx = approximate(ly); BID = twice daily; CAPOX = capecitabine and oxaliplatin; ctDNA = circulating tumor deoxyribonucleic acid; D = day; EC = endometrial cancer; FP = 5-fluorouracil and cisplatin; FSI = first subject in; GC = gastric cancer; GEJ = gastroesophageal junction; HER2-OE = human epidermal growth factor receptor 2 over-expressing; ID = identification; ISH = in situ hybridization; N = number; pMMR = mismatch repair proficient; PO = oral; RECIST = Response Evaluation Criteria in Solid Tumors; SoC = standard of care; TBD = to be determined; TC = tumor cells.

5.1 Pharmacokinetics and Drug Metabolism in Humans

5.1.1 Pharmacokinetics

Preliminary PK data from ARTEMIDE-01, based on a bioanalytical DCO date of 21 March 2024, were evaluated using noncompartmental analysis in 182 participants who received rilvegostomig monotherapy at 70, 210, 750, and 1500 mg Q3W, in the dose escalation and expansion parts of ARTEMIDE-01. A summary of the Cycle 1 PK parameters following a single dose of rilvegostomig is shown in [Table 30](#). Geometric mean ($\pm$ % gCV) serum concentration-time profiles stratified by dose cohorts are presented in [Figure 32](#).

Rilvegostomig systemic exposure across the 70 to 1500 mg dose range increased in a near dose proportional manner. There was no target-mediated drug disposition observed at 70, 210, 750, and 1500 mg Q3W dose levels. Following a single dose iv administration, rilvegostomig levels declined in a bi-phasic manner with a mean terminal elimination half-life of about 8 to 10 days.

There was a minimal accumulation in steady-state after multiple dosing of rilvegostomig based on comparison of $C_{\max}$ at Cycle 1 and Cycle 4 (accumulation ratio: 1.07 and 1.17 for 750 mg and 1500 mg, respectively).

Table 30 Summary of Cycle 1 PK Parameters Following a Single iv Administration of Rilvegostomig

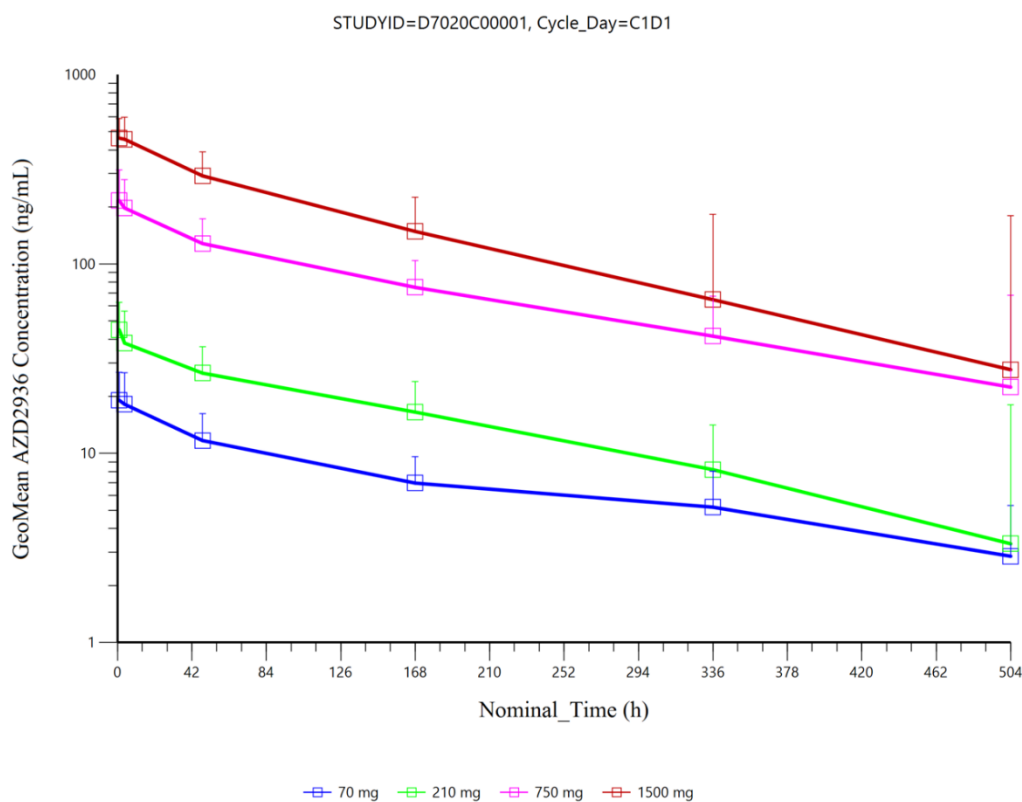
Parameters (unit)	Summary statistics	70 mg	210 mg	750 mg	1500 mg
$C_{\max}$ ($\mu\text{g/mL}$)	n	4	11	122	45
	Geomean	20.3	46.6	222	469
	% gCV	35.3	36.0	29.8	25.2
AUC_{last} ($\text{day} \cdot \mu\text{g/mL}$)	n	4	11	122	45
	Geomean	102	290	1509	2887
	% gCV	65.7	38.3	32.6	34.9
AUC_{tau} ($\text{day} \cdot \mu\text{g/mL}$)	n	3	11	106	38
	Geomean	126	300	1597	3093
	% gCV	48.2	36.2	27.9	33.4
$t_{\max}$ (h)	n	4	11	122	45
	Median	1	1	1	1
	(Min, Max)	(1, 4)	(1, 4)	(1, 4)	(1, 4)

Table 30 Summary of Cycle 1 PK Parameters Following a Single iv Administration of Rilvegostomig

Parameters (unit)	Summary statistics	70 mg	210 mg	750 mg	1500 mg
$t_{1/2}$ (day)	n	3	11	102	37
	Geomean	7.93	7.61	9.13	7.43
	% gCV	30.6	56.5	53.6	78.3

AUC_{last} = area under serum concentration-time curve from zero to the last quantifiable concentration;
Geomean = geometric mean; Max = maximum; Min = minimum; n = number of participants included per category.

Figure 32 Geometric Mean ($\pm$ gSD) Rilvegostomig Serum Concentration-time Profile Following iv Administration of Rilvegostomig



PK data up to 21 days (504 hours) post first dose are presented. One participant who received 70 mg rilvegostomig and 2 participants who received 750 mg rilvegostomig had BLQ values at 504 h postdose; to calculate the geometric mean these BLQ values were set to 0.02 $\mu\text{g/mL}$ (LLOQ).
AZD2936 = rilvegostomig; BLQ = below the limit of quantification; gSD = geometric standard deviation; LLOQ = lower limit of quantitation.

5.1.2 Immunogenicity

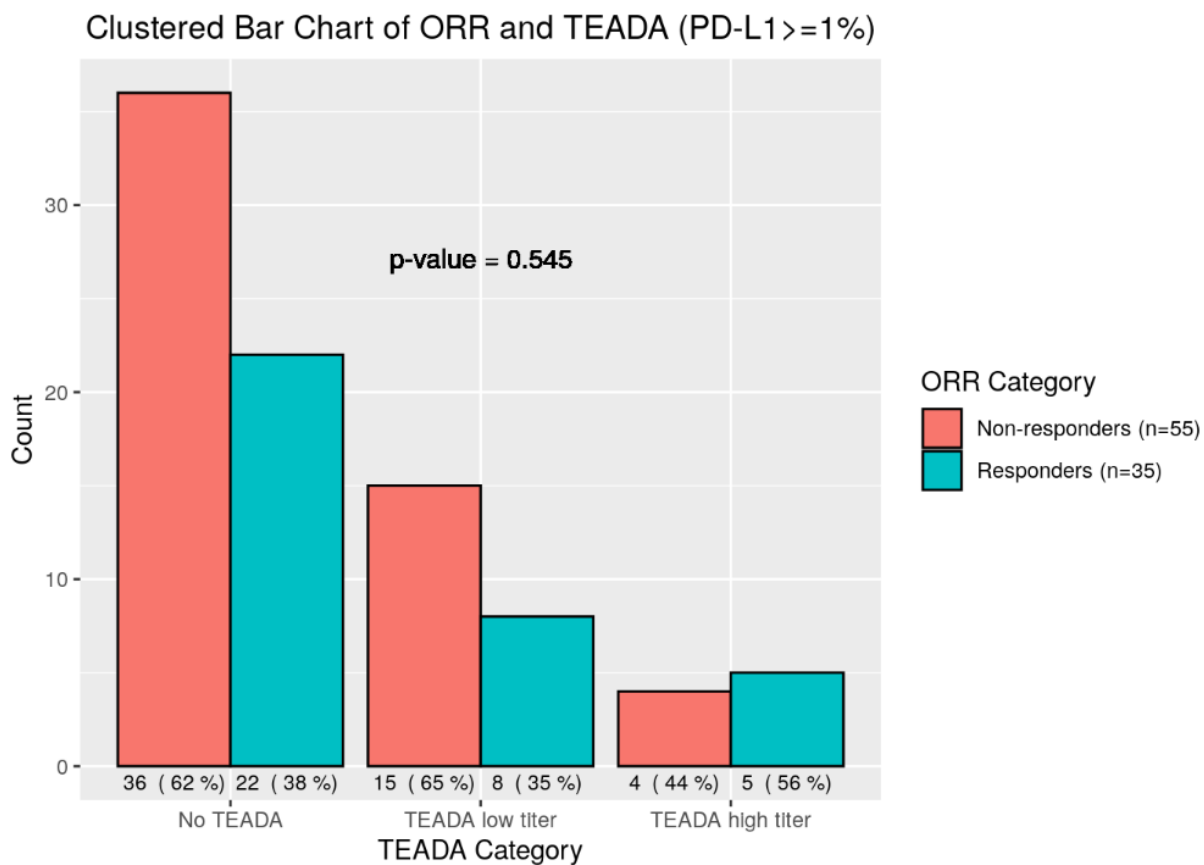
Based on a bioanalytical DCO date of 21 March 2024, a total of 177 participants in dose escalation and expansion cohorts in ARTEMIDE-01 had at least one available ADA result. ADA incidence is defined as the proportion of ADA evaluable participants who were either treatment-induced ADA positive (with ADA positive result at post-baseline, and negative or missing result at baseline) or treatment-boosted ADA positive (with baseline positive ADA titer boosted to ≥ 4 -fold after treatment). ADA incidence was 38.1% (45 of 118 participants) at the 750 mg dose level and 34.1% (15 of 44 participants) at the 1500 mg dose level (Table 31). Upon preliminary evaluation, the impact of treatment-emergent ADA on PK was significant for participants with high ADA titers (≥ 2560 ; 11.9% [21 of 177 participants]; 41.8% decrease in steady-state AUC compared to ADA negative), however there was no clinically meaningful impact of treatment-emergent ADA on efficacy (Figure 33) or safety (Figure 34).

Table 31 Summary of Antidrug Antibody Response to Rilvegostomig by Dose Groups (Immunogenicity Analysis Set)

	70 mg (N = 4)	210 mg (N = 11)	750 mg (N = 118)	1500 mg (N = 44)
ADA incidence	3 (75%)	5 (45.5%)	45 (38.1%)	15 (34.1%)
Min	160	160	40	80
Q1	160	320	320	320
Median	160	480	640	1280
Q3	327680	1280	2560	5120
Max	327680	20480	327680	327680

max = maximum; min = minimum; Q = quartile of ADA titer.

Figure 33 **Number (%) of Responders in Each Treatment-emergent ADA Category in Parts C and D of ARTEMIDE-01**

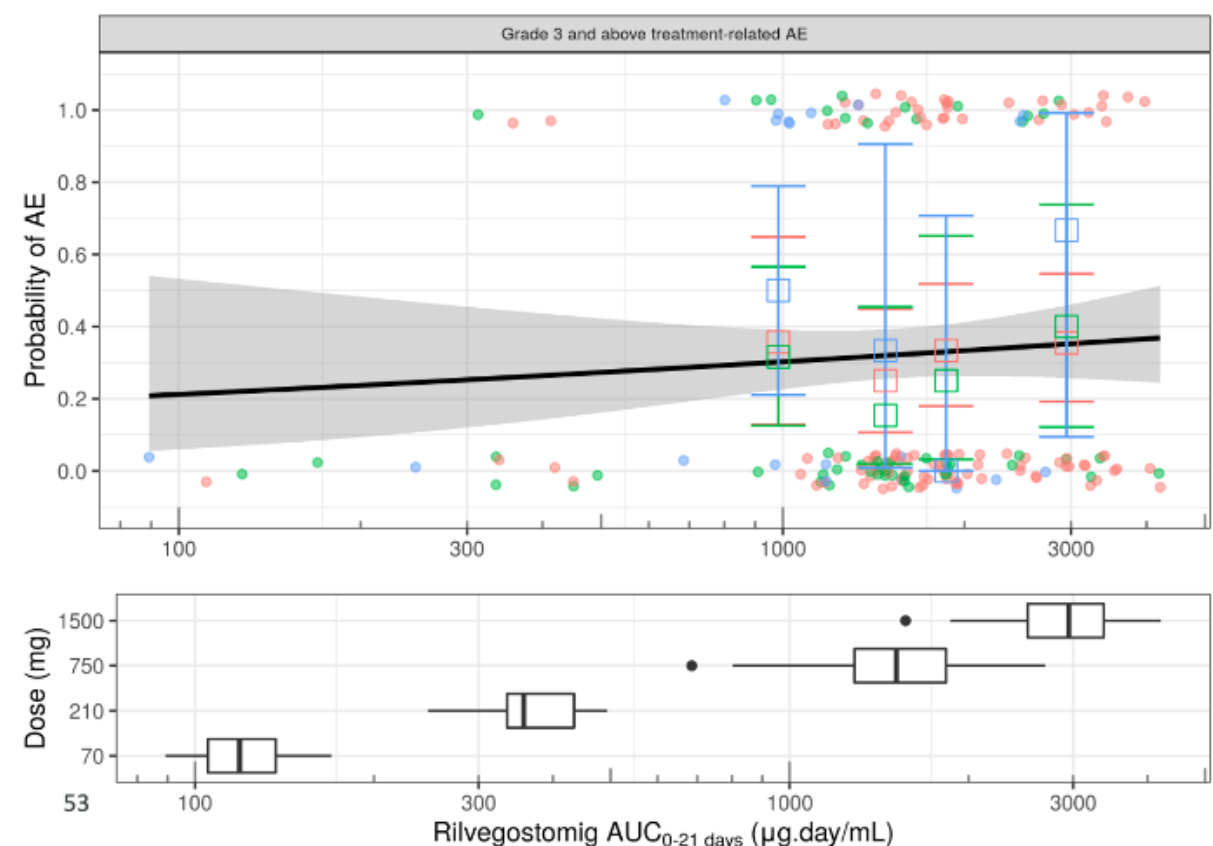


Participants with confirmed complete response or partial response were classed as responders. Non-responders were those participants who were not responders (stable disease, progressive disease or not evaluable).

Low titer: ADA titer < 2560. High titer: ADA titer ≥ 2560.

TEADA = treatment-emergent antidrug antibody.

Figure 34 Grade 3 and Above Treatment-related AEs by Rilvegostomig AUC_{0-21d} Quartiles and Treatment-emergent ADA Categories in Parts A to D of ARTEMIDE-01



Lower panel shows AUC_{0-21d} by dose group (70, 210, 750 and 1500 mg Q3W).
Red = TEADA negative; green = TEADA positive, low titer (< 2560); blue = TEADA positive, high titer (≥ 2560).
TEADA = treatment-emergent antidrug antibody.

5.1.3 Drug Interaction

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 cytochrome P450 pathways. As a result, there are no expected PK drug-drug interactions. Based on the mechanism of action of rilvegostomig, significant PD drug interactions with the commonly administered concomitant medications are not expected.

5.2 Justification for Rilvegostomig Dose and Treatment Regimen

Rilvegostomig 750 mg Q3W was selected as the recommended dosing regimen for use as a monotherapy or in combination with other agents based on preliminary PK and RO data, and emerging clinical safety and efficacy data from the ARTEMIDE-01 study of rilvegostomig in

NSCLC at the time of Phase III program initiation. Clinical pharmacology analyses (see Section 5.2.1), in conjunction with clinical safety and efficacy data from ARTEMIDE-01 (see Section 5.3.1.1), support a favorable overall benefit/risk profile for rilvegostomig 750 mg Q3W as the recommended dose. The available data, as of the DCO date, supportive of the recommended rilvegostomig dose are summarized below.

5.2.1 Preliminary Target Engagement Analyses

Similar to the known mechanism of action of approved anti-PD-1 or anti-PD-L1 therapies, the biological activity of rilvegostomig (dual PD-1/TIGIT blockade) is expected to occur in the tumor and, minimally, in the periphery. In the absence of paired pre- and on-treatment tumor biopsies, intratumoral RO modeling was used to predict the optimal rilvegostomig dose that would achieve intratumoral PD-1 and TIGIT RO saturation. In addition, observed peripheral blood RO was analyzed to further support expected rilvegostomig target engagement.

5.2.1.1 Intratumoral Receptor Occupancy Modeling

Using PK/PD modeling to predict intratumoral RO, rilvegostomig 750 mg Q3W was the lowest dose predicted to achieve $\geq 90\%$ RO in the tumor microenvironment for both PD-1 and TIGIT in most participants across a broad spectrum of analysis conditions (Figure 35 and Table 32).

Figure 35 Predicted PD-1 and TIGIT Receptor Occupancy (%) in Tumor Microenvironment

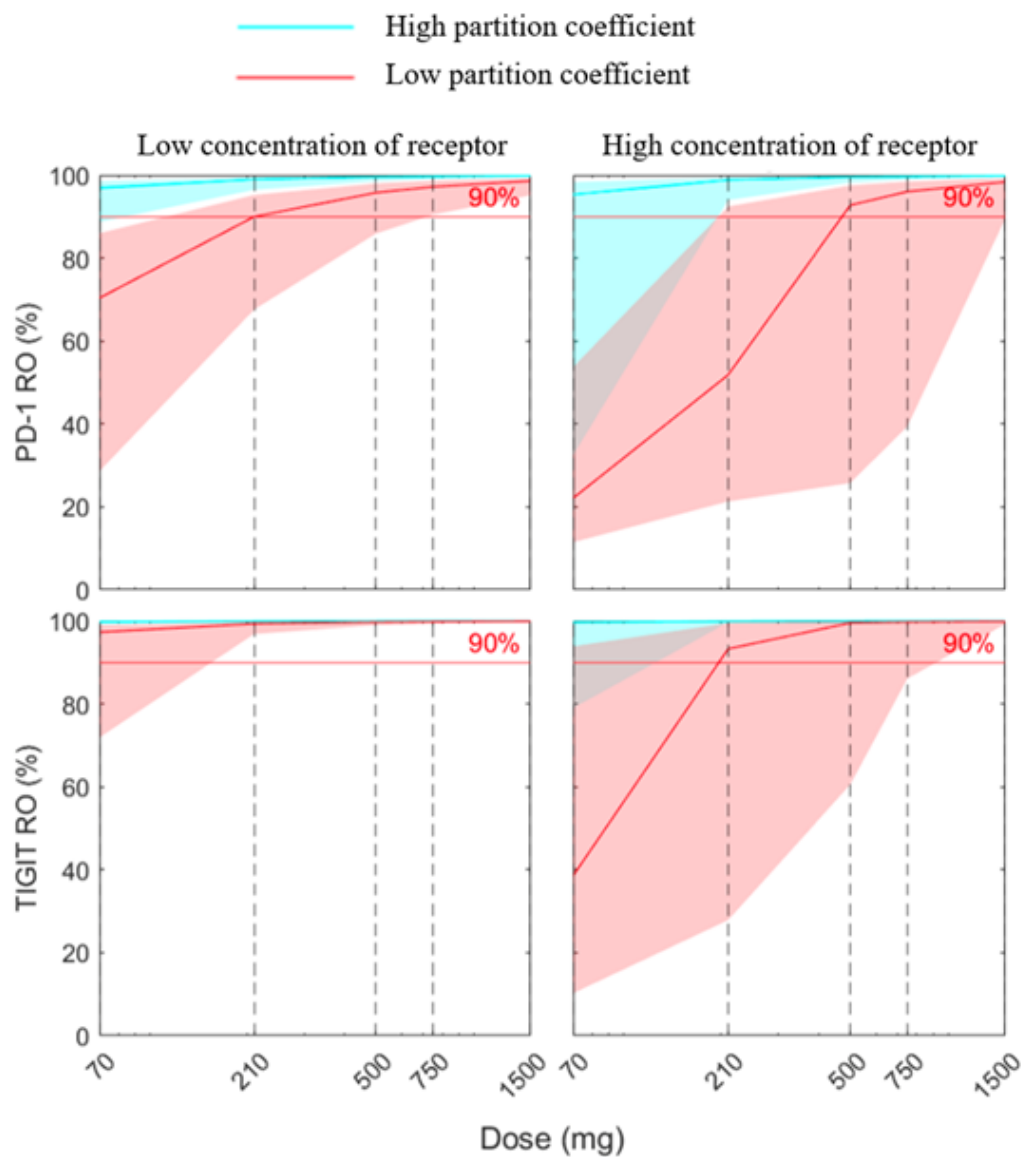


Table 32 Predicted Percentage of Patients with $\geq 90\%$ Receptor Occupancy in Tumor

Rilvegostomig dose	70 mg	210 mg	750 mg	1500 mg
High PC, low CR				
PD-1 % RO $> 90\%$	$\geq 90\%$	$\geq 90\%$	$\geq 90\%$	$\geq 90\%$
TIGIT % RO $> 90\%$	$\geq 90\%$	$\geq 90\%$	$\geq 90\%$	$\geq 90\%$
High PC, high CR				
PD-1 % RO $> 90\%$	74.2%	$\geq 90\%$	$\geq 90\%$	$\geq 90\%$

Table 32 Predicted Percentage of Patients with $\geq 90\%$ Receptor Occupancy in Tumor

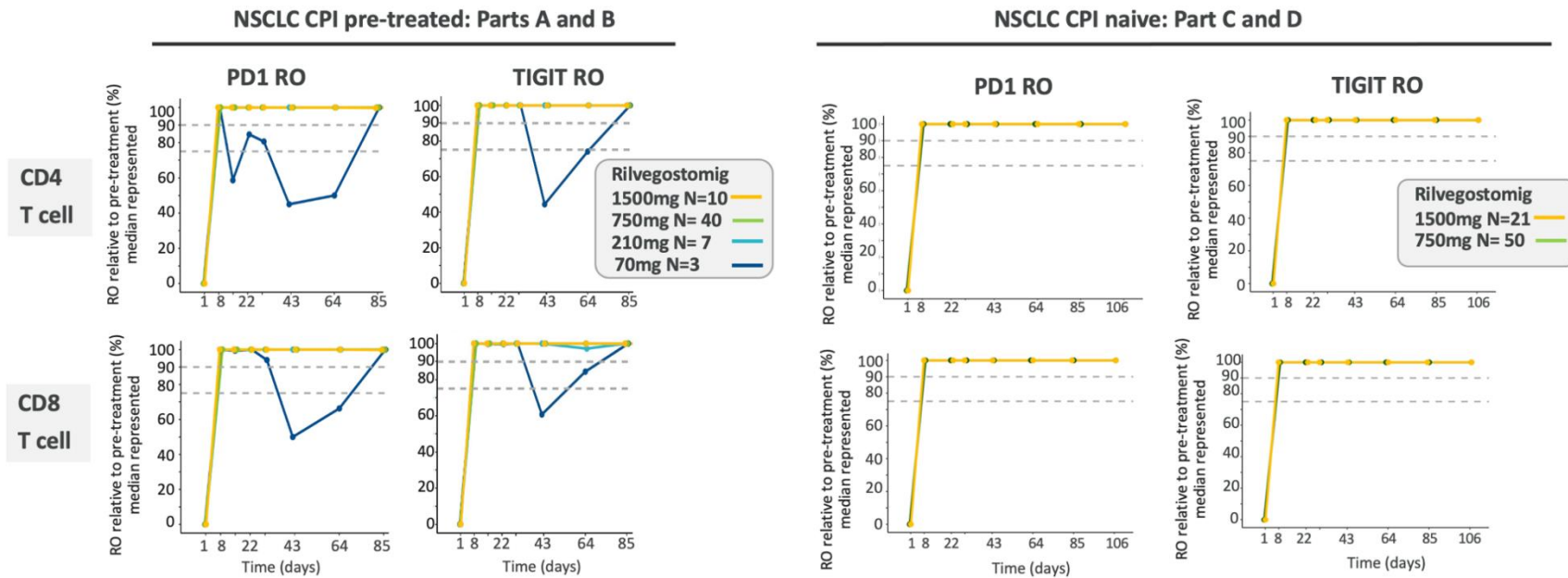
Rilvegostomig dose	70 mg	210 mg	750 mg	1500 mg
TIGIT % RO > 90%	$\geq 90\%$	$\geq 90\%$	$\geq 90\%$	$\geq 90\%$
Low PC, low CR				
PD-1 % RO > 90%	< 1%	49.5%	$\geq 90\%$	$\geq 90\%$
TIGIT % RO > 90%	86.6%	$\geq 90\%$	$\geq 90\%$	$\geq 90\%$
Low PC, high CR				
PD-1 % RO > 90%	< 1%	9.7%	78.5%	$\geq 90\%$
TIGIT % RO > 90%	8.2%	54.1%	$\geq 90\%$	$\geq 90\%$

CR = concentration of receptor; PC = partition coefficient.

5.2.1.2 Observed Peripheral Receptor Occupancy

Based on the available and evaluable peripheral RO data for both PD-1 and TIGIT as measured by flow cytometry in peripheral blood samples from ARTEMIDE-01, the rilvegostomig 750 mg and 1500 mg Q3W doses achieved sustained > 90% PD-1 and TIGIT RO in CPI-experienced and CPI-naïve participants with NSCLC ([Figure 36](#)).

Figure 36 PD-1 and TIGIT RO in Peripheral Blood, as Measured by Flow Cytometry (ARTEMIDE-01)



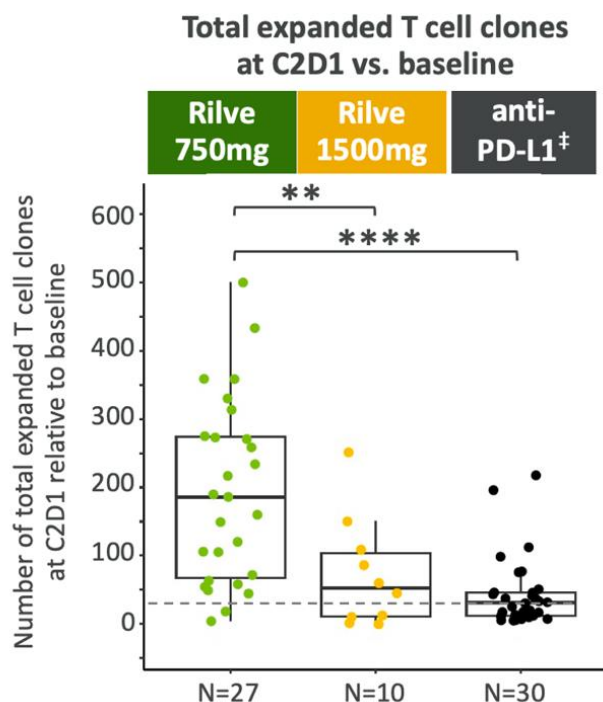
Data shown are for all available and evaluable blood samples for RO analysis by flow cytometry from participants in Parts A to D of the study as of 03 July 2024.

Gray dashed lines represent 90% and 75% RO.

5.2.2 Preliminary Pharmacodynamic Analyses

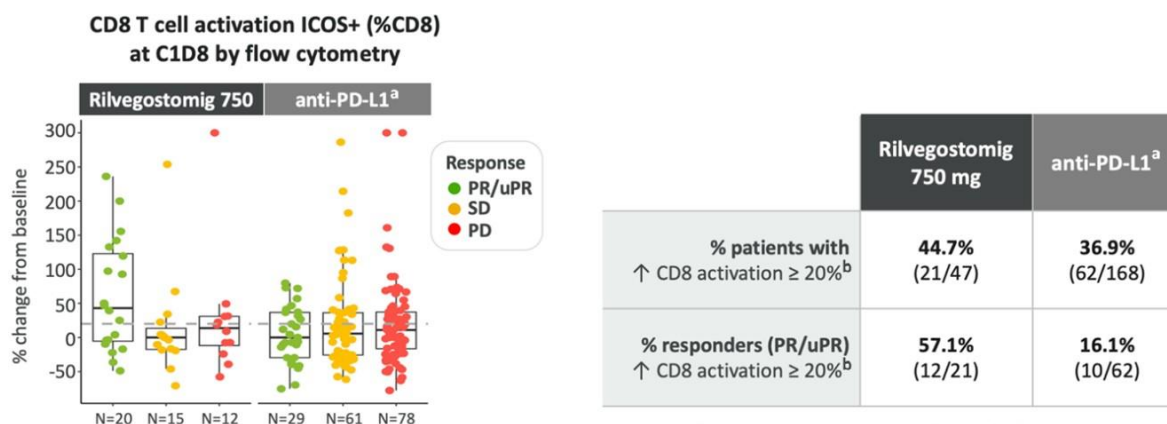
Preliminary PD analysis, as measured by T-cell receptor sequencing to rilvegostomig, showed a robust and higher level of clonal expansion at Cycle 2 Day 1 relative to baseline in CPI-naïve NSCLC participants compared to historical data observed with PD-L1 antibody durvalumab (McCoon et al 2021). In addition, a higher number of expanded T-cell clones was observed with rilvegostomig at 750 mg versus 1500 mg, further supporting 750 mg as the recommended Phase II and Phase III dose (Figure 37). Moreover, as analyzed by flow cytometry, rilvegostomig showed a higher level of activated CD8 T cells at Cycle 1 Day 8 (% of CD8⁺ICOS⁺ out of total CD8) associated with response (partial response/unconfirmed partial response), compared to historical data with anti-PD-L1 durvalumab in CPI-naïve 1L NSCLC (Antonia et al 2019). The potentiation of T-cell activation above anti-PD-1/PD-L1 alone further supports rilvegostomig cooperative targeting and blockade of the 2 convergent pathways, PD-1 and TIGIT (Figure 38).

Figure 37 T cell Clonal Expansion at Cycle 2 Day 1 in NSCLC CPI-naïve Participants Treated With Rilvegostomig at 750 mg and 1500 mg vs Anti-PD-L1



Data shown for rilvegostomig are for all available and evaluable blood samples for pharmacodynamic analysis as measured by TCR sequencing from participants in Parts C and D of the ARTEMIDE-01 study as of July 2024. T-cell clonal expansion observed following durvalumab derived from Study 22 (McCoon et al 2021). The gray dashed line represents median of total number of expanded clones following treatment with durvalumab (McCoon et al 2021). Statistics: Wilcoxon test, ** and **** represent p-value equal or lower than 0.01 and 0.0001, respectively. C2D1 = Cycle 2 Day 1; Rilve = rilvegostomig.

Figure 38 CD8 T-cell Activation ICOS⁺ (% CD8) at Cycle 1 Day 8 in CPI-naïve Participants With NSCLC Treated With Rilvegostomig at 750 mg vs Anti-PD-L1



^a Anti-PD-L1 data are from Study CP1108 (Antonia et al 2019).

^b 20% increase referring to technical and biological variability based on predose samples.

Data shown for rilvegostomig are for all available and evaluable blood samples for pharmacodynamic analysis as measured by flow cytometry from participants in Parts C and D1 of the ARTEMIDE-01 study as of July 2024. 1L+ = first-line and greater; C1D8 = Cycle 1 Day 8; ICOS⁺ = inducible T-cell costimulatory positive; PD = progressive disease; uPR = unconfirmed partial response.

5.2.3 Preliminary Population PK Analysis

Based on the available PK data from the ongoing ARTEMIDE-01 study as of the DCO date, rilvegostomig PK exposure (C_{max} , AUC_{0-21d}) increased in an approximately dose proportional manner over the dose range of 70 to 1500 mg in the first dosing cycle. PK data from a total of 177 participants (DCO date of 07 July 2024) following 70, 210, 750, and 1500 mg Q3W doses of rilvegostomig from ARTEMIDE-01 were used to build the interim PopPK model. The impact of intrinsic and extrinsic factors (demographics, smoking, and other disease-related factors) on rilvegostomig PK were evaluated and none were found to be clinically relevant covariates impacting PK parameters, supporting the proposed fixed dosing of rilvegostomig.

As of the DCO date, the interim PopPK model indicated a moderate impact of body weight and treatment-emergent ADA on the PK of rilvegostomig. Treatment-emergent ADA (with high titers of ≥ 2560) had a significant impact on PK but no impact on efficacy or safety (Section 5.1.2). The PopPK model will continue to be updated by the Sponsor as further data from the ongoing and planned rilvegostomig studies become available.

5.2.4 Preliminary Exposure-response Analyses

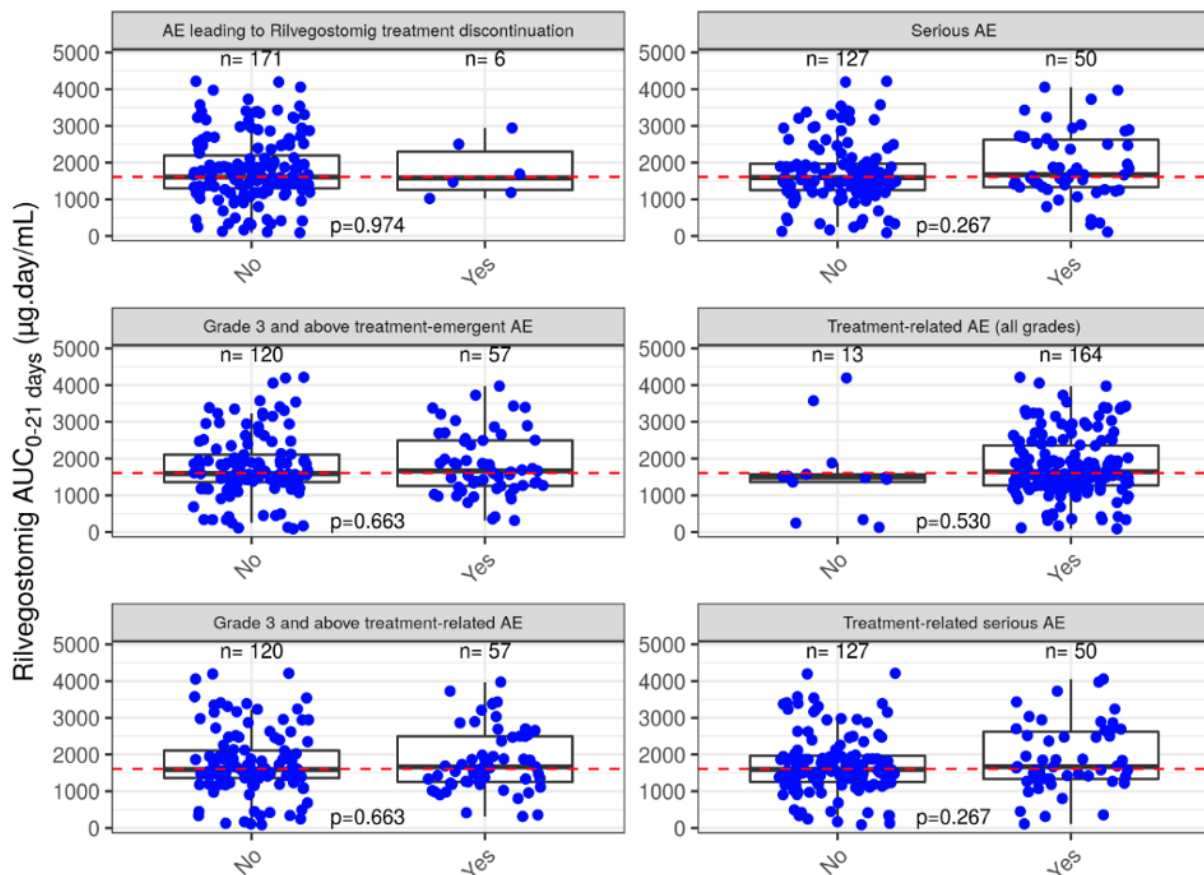
The exposure metrics used for exposure-response analyses (efficacy and safety) were C_{max} , minimum concentration, and AUC after first dosing (Cycle 1) and steady-state.

5.2.4.1 Exposure-response for Safety

Preliminary exposure-response for safety analyses were conducted using data from both CPI-experienced and CPI-naïve participants with NSCLC from the ongoing ARTEMIDE-01 study (DCO date of 07 July 2024). Specifically, the Sponsor included preliminary safety data from Parts A through D ($n = 177$ [total exposure-safety analysis set]), as well as additional analysis using CPI-naïve participants only (Parts C and D, $n = 63$, PD-L1 $\geq 50\%$ [CPI-naïve exposure-safety analysis set]) (see Section 5.3.1.1.2 for full safety results). Six safety endpoints were evaluated: Grade ≥ 3 AEs, all grade TRAEs, Grade ≥ 3 TRAEs, SAEs, treatment-related SAEs, and AEs leading to treatment discontinuation. Grade ≥ 3 AEs and all-grade TRAEs have been selected as representative plots, taking into consideration the scarcity of event frequency for other safety endpoints. AUC_{0-21d} was selected as the representative exposure metric, but the results were consistent across all 6 exposure metrics.

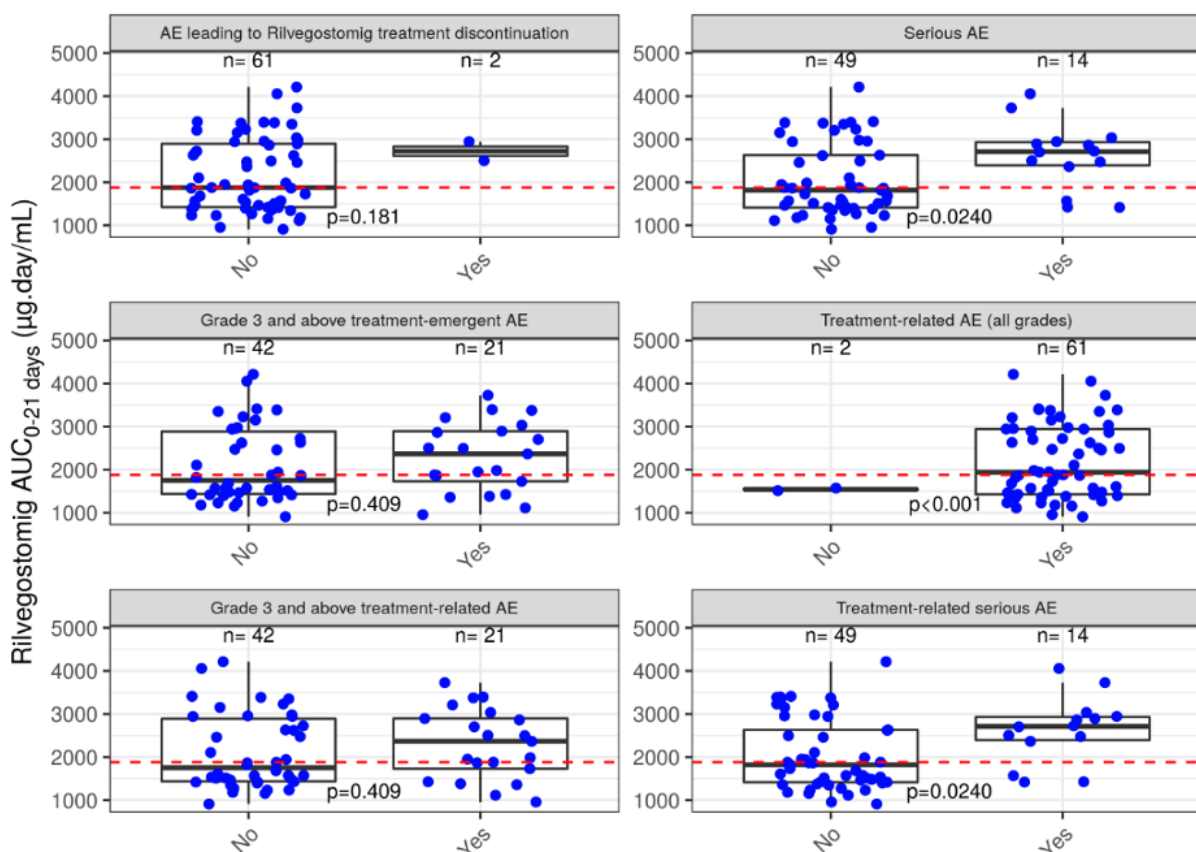
The exposure-response for safety analysis suggested no relationship between the rate of Grade ≥ 3 AEs or all-grade TRAEs and rilvegostomig exposure (AUC_{0-21d}) from all 4 dose levels in CPI-experienced and CPI-naïve participants (70 to 1500 mg Q3W; Parts A to D; Figure 39), as well as the 2 dose levels in CPI-naïve participants (750 and 1500 mg; Parts C and D; Figure 40). Logistic regression between rilvegostomig exposure (AUC_{0-21d}) and Grade ≥ 3 AEs or all grade TRAEs from all 4 dose levels (70 to 1500 mg Q3W) also showed no significant trends (Figure 41; $p = 0.662$ and $p = 0.381$, respectively).

Figure 39 Comparison of Exposures for CPI-experienced and CPI-naïve Participants with NSCLC Treated with Rilvegostomig Monotherapy With and Without AEs (ARTEMIDE-01; Total Exposure-safety Analysis Set)



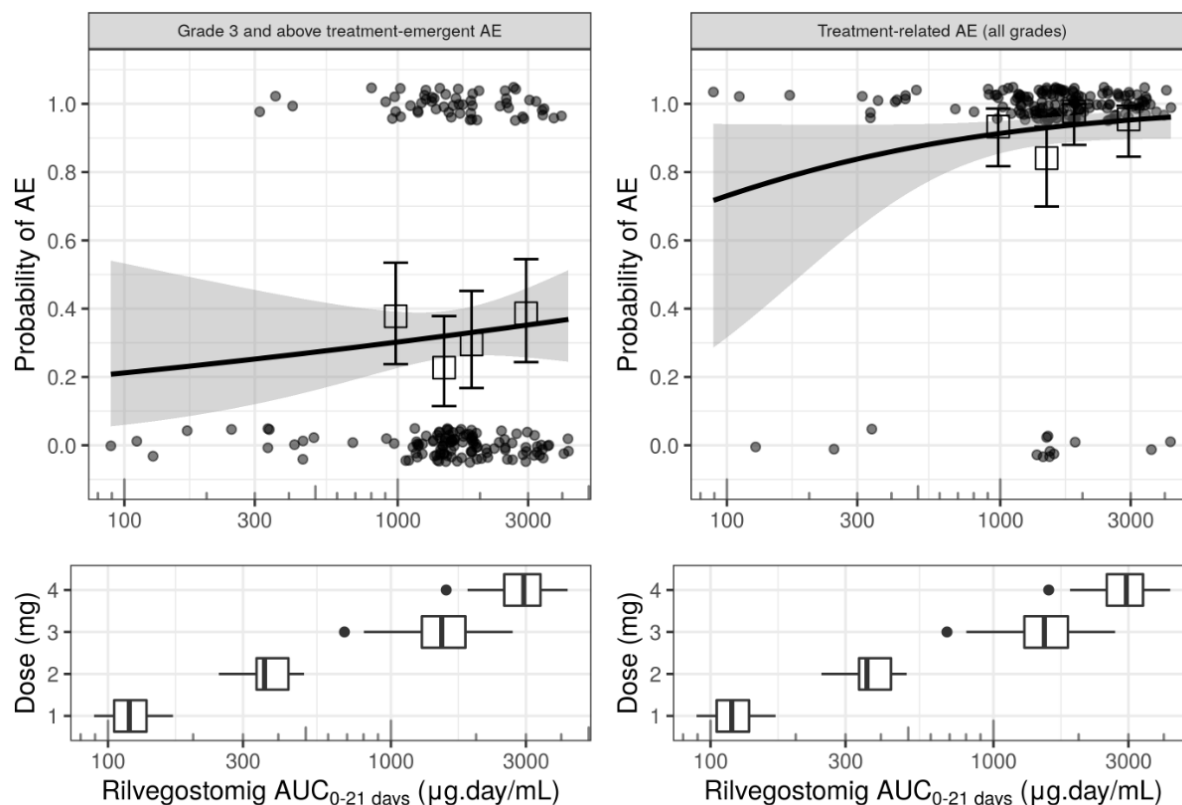
Total exposure-safety analysis set: All dosed participants (as of 07 July 2024) who have at least one measurable PK concentration after first dose and safety records in Parts A to D (CPI-experienced and CPI-naïve participants treated with 70 to 1500 mg rilvegostomig Q3W). The box represents the IQR (25th percentile and 75th percentile). The horizontal line inside the box is the median of the data. The whiskers represent 1.5 times the IQR. The dashed red horizontal line represents the median value of PK exposure in the population. IQR = interquartile range; n = number of participants per treatment group.

Figure 40 Comparison of Exposures for CPI-naïve Participants With NSCLC Treated With Rilvegostomig Monotherapy With and Without AEs (ARTEMIDE-01; CPI-naïve Exposure-safety Analysis Set)



CPI-naïve exposure-safety analysis set: All dosed participants (as of 07 July 2024) who have at least one measurable PK concentration after first dose and safety records in Parts C and D (CPI-naïve participants treated with 750 and 1500 mg rilvegostomig Q3W). The box represents the IQR (25th percentile and 75th percentile). The horizontal line inside the box is the median of the data. The whiskers represent 1.5 times the IQR. The dashed red horizontal line represents the median value of PK exposure in the population. IQR = interquartile range; n = number of participants per treatment group.

Figure 41 **Logistic Regression Between Probability of Grade ≥ 3 Treatment-emergent AEs (Left) or All Grade TRAEs (Right) and Rilvegostomig PK Exposure (AUC_{0-21d}) for CPI-experienced and CPI-naïve Participants with NSCLC Treated with Rilvegostomig Monotherapy (ARTEMIDE-01; Total Exposure-safety Analysis Set)**



Total exposure-safety analysis set: All dosed participants (as of 07 July 2024) who have at least one measurable PK concentration after first dose and safety records in Parts A to D (CPI-experienced and CPI-naïve participants treated with 70 to 1500 mg rilvegostomig Q3W).

Upper panels: The gray solid circles reflect the observed events. The black solid circles are the observed probability of AEs, and the error bars are the standard errors for quartiles of PK exposures (plotted at the median value within each quartile). The black lines are the logistic regression between two variables and the gray area represents the associated 95% CI.

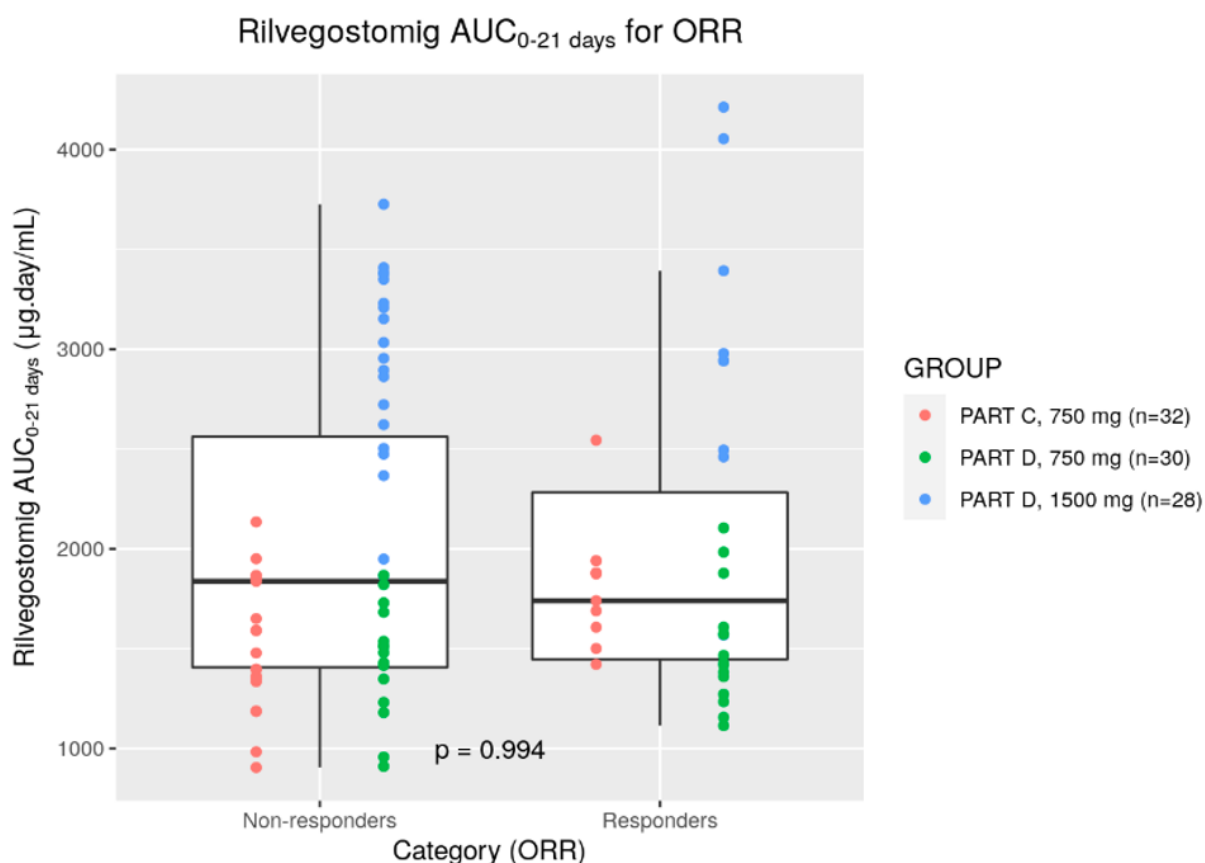
Lower panels: The box represents the IQR (25th percentile and 75th percentile). The vertical line inside the box is the median of the data. The whiskers represent 1.5 times the IQR. IQR = interquartile range.

5.2.4.2 Exposure-response for Efficacy

Preliminary exposure-response for efficacy analyses were conducted using data from CPI-naïve participants with NSCLC from the ongoing ARTEMIDE-01 study (DCO date of 07 July 2024). Specifically, the Sponsor included preliminary efficacy data from Part C (750 mg, n = 32 [CPI-naïve exposure-efficacy analysis set]) and Part D (750 mg, n = 30; 1500 mg, n = 28) (see Section 5.3.1.1.3 for full efficacy results).

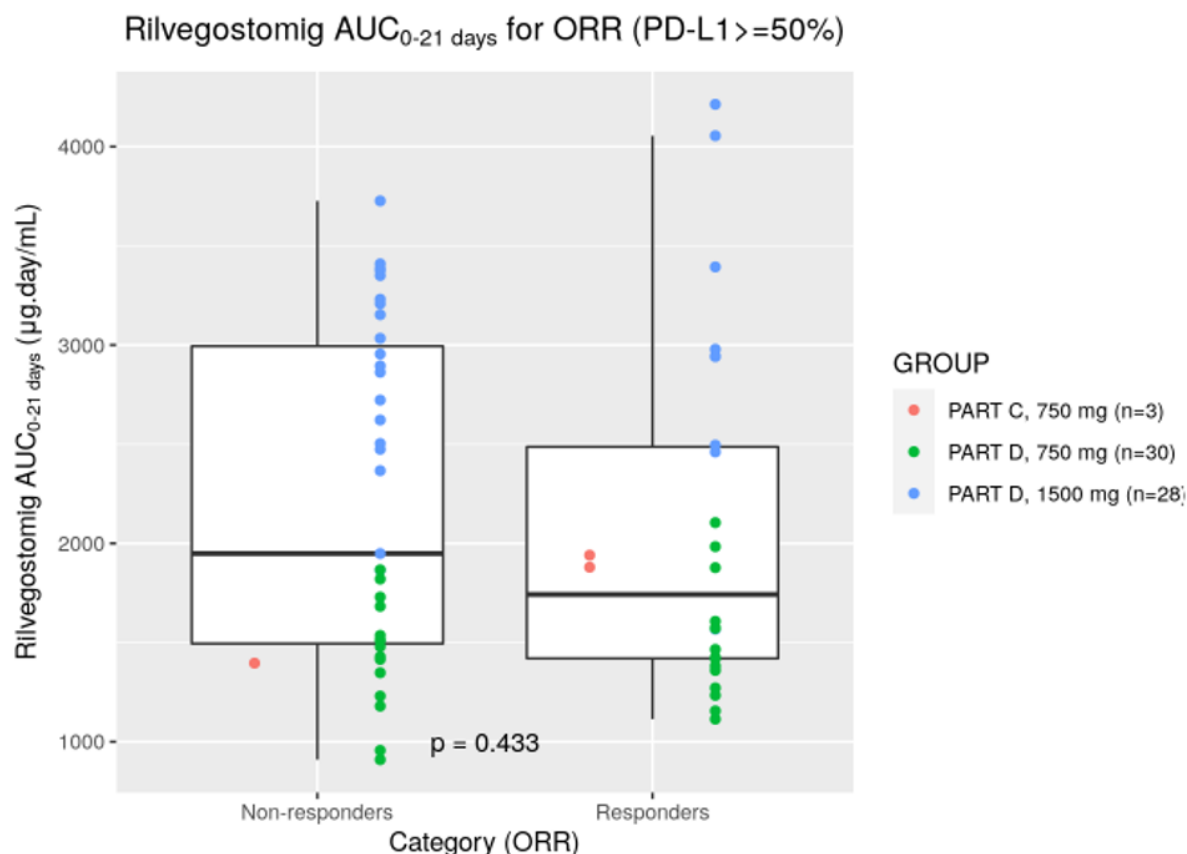
The exposure-response analysis for efficacy evaluated the relationship between rilvegostomig AUC_{0-21d} with confirmed objective response, which suggests that there is no relationship between exposure of rilvegostomig across the 750 to 1500 mg dose levels and objective response in CPI-naïve participants with NSCLC (Figure 42). This observation was further confirmed in participants whose tumors express PD-L1 TPS $\geq 50\%$ ($n = 61$; Figure 43).

Figure 42 Probability of Confirmed Responses for CPI-naïve Participants with NSCLC and PD-L1 TPS $\geq 1\%$ Treated with Rilvegostomig Monotherapy (ARTEMIDE-01; CPI-naïve Exposure-efficacy Analysis Set)



CPI-naïve exposure-efficacy analysis set: All dosed participants (as of 07 July 2024) who have at least one measurable PK concentration after first dose and efficacy records in Parts C and D (CPI-naïve participants treated with 750 and 1500 mg rilvegostomig Q3W). The box represents the IQR (25th percentile and 75th percentile). The horizontal line inside the box is the median of the data. The whiskers represent 1.5 times the IQR. Non responders = participants with stable disease or progressive disease. Responders = participants who achieved either a complete response or partial response. IQR = interquartile range; n = number of participants per treatment group.

Figure 43 Probability of Confirmed Responses for CPI-naïve Participants with NSCLC and PD-L1 TPS $\geq 50\%$ Treated with Rilvegostomig Monotherapy (ARTEMIDE-01; CPI-naïve Exposure-efficacy Analysis Set)



CPI-naïve exposure-efficacy analysis set: All dosed participants (as of 7 July 2024) who have at least one measurable PK concentration after first dose and efficacy records in Parts C and D (CPI-naïve participants treated with 750 and 1500 mg rilvegostomig Q3W). The box represents the IQR (25th percentile and 75th percentile). The horizontal line inside the box is the median of the data. The whiskers represent 1.5 times the IQR. Non responders = participants with stable disease or progressive disease. Responders = participants who achieved either a complete response or partial response.

IQR = interquartile range; n = number of participants per treatment group.

5.2.5 Dosing Justification Conclusion

The dosing regimen of rilvegostomig 750 mg Q3W is supported by the available target engagement, PK, PD, safety, and efficacy data for rilvegostomig in participants with NSCLC, as summarized below:

- The rilvegostomig dose of 750 mg Q3W is the lowest predicted dose to achieve $\geq 90\%$ RO 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 PD 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 PopPK 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 to 1500 mg Q3W evaluated in the ARTEMIDE-01 study, there were no DLTs (see Section 5.3.1.1.2 for full safety results) and all dose levels were well tolerated. Exposure-safety analysis suggested no relationship between the rate of Grade ≥ 3 or 4 AEs or all grade TRAEs and rilvegostomig exposure (AUC_{0-21d}) at all 4 dose levels analyzed (rilvegostomig 70 to 1500 mg Q3W).
- Preliminary ORR data from ARTEMIDE-01 (see Section 5.3.1.1.3 for full efficacy results), 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 dose for rilvegostomig as monotherapy or in combination with other agents, including in studies with registrational intent.

5.3 Safety and Efficacy in Humans

As of the date of this document, data are available from the studies in Table 33. Safety data are based on the DCO date of 05 July 2025 for all studies except MAGELLAN which has a DCO of 23 May 2023.

All AE summaries are based on treatment-emergent AEs, and severity is based on maximum Common Terminology Criteria for AEs grade by event. The reported causal relationship to IP is according to investigator assessment and does not necessarily reflect the Sponsor's position. Data from the ongoing studies are preliminary and subject to change due to ongoing data querying and SAE reconciliation.

The AESIs presented in this IB are defined as AEs that include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism that may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with rilvegostomig monotherapy and combination therapy.

Table 33 Studies Providing Data to the IB

Study and included groups	Study design	Efficacy DCO dates ^a	Section
Rilvegostomig Monotherapy			
ARTEMIDE-01	Phase I/II, FTIH, multi-part, open-label, dose escalation and dose expansion study to evaluate the safety, PK, pharmacodynamics, and efficacy of rilvegostomig as a monotherapy in adult participants with advanced or metastatic NSCLC	21 April 2025	5.3.1.1
Rilvegostomig Monotherapy and Rilvegostomig + Chemotherapy			
MAGELLAN Cohort A5 monotherapy Cohort B5 combination	Phase Ib, open-label, multicenter platform study to determine the efficacy and safety of durvalumab and/or novel oncology therapies with or without chemotherapy as 1L treatment for adult participants with Stage IV NSCLC	NA	5.3.1.2 and 5.3.2.1
Rilvegostomig + Chemotherapy			
GEMINI-Gastric Substudy 2	Phase II, open-label, multi-drug, multicenter platform study to evaluate the efficacy, safety, tolerability, PK, and immunogenicity of novel combination therapies in adult participants with locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma, not previously treated	04 July 2024	5.3.2.2
GEMINI-Hepatobiliary Cohort 2A	Phase II, open-label, multi-drug, multicenter, platform study evaluating the efficacy and safety of novel immunomodulators as monotherapy and in combination with anticancer agents in adult participants with advanced HCC or BTC who have not received previous treatment for advanced/metastatic disease	04 November 2024	5.3.2.3
Rilvegostomig + ADCs			
TROPION-Lung04 Cohort 5	Phase Ib, open-label, multicenter platform study to determine the efficacy, safety, and tolerability of Dato-DXd in combination with immunotherapy as 1L treatment in adult participants advanced/metastatic NSCLC	24 October 2024	5.3.3.1
TROPION-PanTumor03 Cohort 6B	Phase II, open-label, multicenter platform study to determine the efficacy and safety of Dato-DXd as monotherapy and in combination with anticancer agents in adult participants with advanced unresectable or metastatic solid tumors (Cohort 6B: advanced unresectable or metastatic urothelial cancer)	17 February 2025	5.3.3.2

Table 33 **Studies Providing Data to the IB**

Study and included groups	Study design	Efficacy DCO dates ^a	Section
DESTINY-Gastric03 Arms 4A and 4B	Phase Ib/II, open-label, dose escalation and dose expansion, multicenter platform study to determine the safety, PK, immunogenicity, tolerability, and antitumor activity of T-DXd monotherapy and in combination in adult participants with HER2-expressing locally advanced or metastatic, unresectable GC	NA	5.3.3.3

^a The DCO date for the safety data for all studies is 05 July 2025.
GC = gastric cancer; NA = not applicable.

5.3.1 Rilvegostomig Monotherapy

5.3.1.1 ARTEMIDE-01

5.3.1.1.1 Exposure in ARTEMIDE-01

As of the DCO date of 05 July 2025, 199 participants had received rilvegostomig in ARTEMIDE-01: 83 CPI-experienced participants (Parts A and B) and 116 CPI-naïve participants (Parts C, D, and E). In Parts A and B, 4 participants, 11 participants, 54 participants, and 14 participants received 70, 210, 750, and 1500 mg rilvegostomig, respectively. In Parts C, D, and E, 86 participants received 750 mg rilvegostomig and 30 participants received 1500 mg.

Across the CPI-experienced cohort, the median duration of exposure was 12.43 weeks. Across the CPI-naïve cohort, the median duration of exposure was 27.93 weeks. For exposure details of individual cohorts, see [Table 34](#) and [Table 35](#).

Table 34 Duration of Rilvegostomig Exposure in CPI-experienced Participants with NSCLC (ARTEMIDE-01; Safety Analysis Set)

	A1 + A2 70 and 210 mg N = 15	A3 + B 750 mg N = 54	A4 1500 mg N = 14	Total A + B Any dose N = 83
Rilvegostomig total treatment duration (weeks)^a				
Mean (SD)	25.93 (34.570)	28.64 (30.213)	29.06 (34.673)	28.22 (31.398)
Median	10.00	17.21	11.57	12.43
Min, Max	1.7, 108.0	3.0, 118.3	2.3, 116.0	1.7, 118.3

^a Total exposure (weeks) of IP = (min (last dose date where dose > 0 mg + 20, date of death, date of DCO) – first dose date + 1) / 7.

Part A1 = rilvegostomig 210 mg Q3W 2L+ CPI-experienced. Part A2 = rilvegostomig 70 mg Q3W 2L+ CPI-experienced. Part A3 + B = rilvegostomig 750 mg Q3W 2L+ CPI-experienced. Part A4 = rilvegostomig 1500 mg Q3W 2L+ CPI-experienced.

2L+ = second line or beyond; max = maximum; min = minimum; N = number of participants per treatment group.

Table 35 **Duration of Rilvegostomig Exposure in CPI-naïve Participants with NSCLC (ARTEMIDE-01; Safety Analysis Set)**

	C 750 mg N = 34	D1 750 mg N = 31	D2 1500 mg N = 30	E 750 mg N = 21^b	Total C + D + E Any dose N = 116
Rilvegostomig total treatment duration (weeks)^a					
Mean (SD)	41.83 (31.424)	58.91 (31.879)	38.42 (33.689)	16.27 (8.819)	40.89 (32.378)
Median	30.00	71.71	22.64	15.71	27.93
Min, Max	3.0, 104.3	3.0, 105.0	3.0, 112.4	1.3, 30.4	1.3, 112.4

^a Total exposure (weeks) of IP = (min (last dose date where dose > 0 mg + 20, date of death, date of DCO) – first dose date + 1) / 7.

^b The reduced duration of exposure in Part E is attributable to participant recruitment occurring nearer to the DCO date, resulting in a shorter time that participants have spent in the study.

Part C = rilvegostomig 750 mg Q3W 2L+ CPI-naïve. Part D1 = rilvegostomig 750 mg Q3W 2L CPI-naïve. Part D2 = rilvegostomig 1500 mg Q3W 2L CPI-naïve. Part E = rilvegostomig 750 mg Q3W 2L CPI-naïve. 2L = second line; 2L+ = second line or beyond; max = maximum; min = minimum; N = number of participants per treatment group.

5.3.1.1.2 Safety in ARTEMIDE-01

Overview of Adverse Events

An overall summary of AEs across all rilvegostomig dosing cohorts (as of the DCO date of 05 July 2025) is presented in [Table 36](#) and [Table 37](#). The safety analysis set is defined as all participants who received at least 1 dose of rilvegostomig. Throughout this IB, safety data for ARTEMIDE-01 are described for those participants who received rilvegostomig 750 mg Q3W throughout the CPI-experienced and CPI-naïve cohorts (Parts A3, B, C, D1, and E); this group is referred to as the Combined 750 mg Cohort.

Overall, in CPI-experienced and CPI-naïve participants the safety profile of rilvegostomig was similar across dose levels and all the dose levels evaluated have been well tolerated ([Table 36](#) and [Table 37](#)).

Among the 140 participants in the Combined 750 mg Cohort ([Table 37](#)), a total of 133 participants (95.0%) had at least one AE, and 92 participants (65.7%) had an AE that was considered by the investigator to be possibly related to rilvegostomig treatment.

Forty-seven participants (33.6%) had maximum Grade 3 or 4 AEs; 15 participants (10.7%) had Grade 3 and 4 AEs that were assessed by the investigator as possibly related to rilvegostomig (all of which were Grade 3). SAEs were reported in 38 participants (27.1%), with SAEs assessed by the investigator as possibly related to rilvegostomig in 8 participants (5.7%). Three participants (2.1%) had SAEs resulting in death, however, no fatal SAEs were assessed as possibly related to rilvegostomig. Four participants (2.9%) had an AE leading to discontinuation of rilvegostomig that was assessed by the investigator as possibly related to rilvegostomig, and 19 participants (13.6%) had an AE that led to dose interruption of

rilvegostomig that was assessed by the investigator as possibly related to rilvegostomig. AEs assessed by the investigator as possibly related to rilvegostomig were reported in 63 participants (45.0%). ImAEs were reported in 33 participants (23.6%) and were assessed by the investigator as possibly related to rilvegostomig in 32 participants (22.9%).

Table 36 Overall Summary of AEs in CPI-experienced Participants with NSCLC (ARTEMIDE-01; Safety Analysis Set)

Participants with ^a	A1 + A2 70 and 210 mg N = 15 n (%)	A3 + B 750 mg N = 54 n (%)	A4 1500 mg N = 14 n (%)	Total A + B Any dose N = 83 n (%)
Any AE	12 (80.0)	51 (94.4)	12 (85.7)	75 (90.4)
Any AE possibly related to rilvegostomig ^b	5 (33.3)	33 (61.1)	8 (57.1)	46 (55.4)
Any AE of maximum CTCAE Grade 3 or Grade 4	3 (20.0)	17 (31.5)	4 (28.6)	24 (28.9)
Any AE of maximum CTCAE Grade 3 or Grade 4, possibly related to rilvegostomig ^b	0	5 (9.3)	2 (14.3)	7 (8.4)
Any AE leading to discontinuation of rilvegostomig	0	2 (3.7)	0	2 (2.4)
Any AE leading to discontinuation of rilvegostomig, possibly related to rilvegostomig ^b	0	2 (3.7)	0	2 (2.4)
Any AE leading to dose interruption of rilvegostomig	4 (26.7)	11 (20.4)	6 (42.9)	21 (25.3)
Any AE leading to dose interruption of rilvegostomig, possibly related to rilvegostomig ^b	1 (6.7)	6 (11.1)	3 (21.4)	10 (12.0)
Any SAE ^c	4 (26.7)	18 (33.3)	6 (42.9)	28 (33.7)
Any SAE possibly related to rilvegostomig ^{b,c}	0	4 (7.4)	2 (14.3)	6 (7.2)
Any SAE with outcome = death	1 (6.7)	0	2 (14.3)	3 (3.6)
Any SAE with outcome = death, possibly related to rilvegostomig ^b	0	0	0	0
Any SAE leading to discontinuation of treatment	0	1 (1.9)	0	1 (1.2)
Any SAE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	0	1 (1.9)	0	1 (1.2)
Any AE of special interest to treatment	6 (40.0)	33 (61.1)	11 (78.6)	50 (60.2)
Any AE of special interest to treatment, possibly related to rilvegostomig ^b	5 (33.3)	22 (40.7)	8 (57.1)	35 (42.2)
Any imAE	0	2 (3.7)	2 (14.3)	4 (4.8)
Any imAE, possibly related to rilvegostomig ^b	0	2 (3.7)	2 (14.3)	4 (4.8)

^a Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

^b As assessed by the investigator. Missing responses are counted as related.

^c Seriousness, as assessed by investigator.

Part A1 = rilvegostomig 210 mg Q3W 2L+ CPI-experienced. Part A2 = rilvegostomig 70 mg Q3W 2L+ CPI-experienced. Part A3 + B = rilvegostomig 750 mg Q3W 2L+ CPI-experienced. Part A4 = rilvegostomig 1500 mg Q3W 2L+ CPI-experienced.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

2L+ = second line and beyond; CTCAE = Common Terminology Criteria for Adverse Events Version 5.0; n = number of participants per category; N = number of participants per treatment group.

Table 37 Overall Summary of AEs in CPI-naïve Participants with NSCLC and the Combined 750 mg Cohort (ARTEMIDE-01; Safety Analysis Set)

Participants with ^a	C 750 mg N = 34 n (%)	D1 750 mg N = 31 n (%)	D2 1500 mg N = 30 n (%)	E 750 mg N = 21 n (%)	Total C + D + E Any dose N = 116 n (%)	Combined 750 mg Cohort ^b 750 mg N = 140
Any AE	33 (97.1)	30 (96.8)	30 (100)	19 (90.5)	112 (96.6)	133 (95.0)
Any AE possibly related to rilvegostomig ^c	24 (70.6)	24 (77.4)	20 (66.7)	11 (52.4)	79 (68.1)	92 (65.7)
Any AE of maximum CTCAE Grade 3 or Grade 4 ^d	13 (38.2)	11 (35.5)	16 (53.3)	6 (28.6)	46 (39.7)	47 (33.6)
Any AE of maximum CTCAE Grade 3 or Grade 4, possibly related to rilvegostomig ^{c,d}	4 (11.8)	4 (12.9)	5 (16.7)	2 (9.5)	15 (12.9)	15 (10.7)
Any AE leading to discontinuation of rilvegostomig	1 (2.9)	2 (6.5)	4 (13.3)	0	7 (6.0)	5 (3.6)
Any AE leading to discontinuation of rilvegostomig, possibly related to rilvegostomig ^c	1 (2.9)	1 (3.2)	2 (6.7)	0	4 (3.4)	4 (2.9)
Any AE leading to dose interruption of rilvegostomig	11 (32.4)	8 (25.8)	7 (23.3)	2 (9.5)	28 (24.1)	32 (22.9)
Any AE leading to dose interruption of rilvegostomig, possibly related to rilvegostomig ^c	7 (20.6)	4 (12.9)	6 (20.0)	2 (9.5)	19 (16.4)	19 (13.6)

Table 37 Overall Summary of AEs in CPI-naïve Participants with NSCLC and the Combined 750 mg Cohort (ARTEMIDE-01; Safety Analysis Set)

Participants with ^a	C 750 mg N = 34 n (%)	D1 750 mg N = 31 n (%)	D2 1500 mg N = 30 n (%)	E 750 mg N = 21 n (%)	Total C + D + E Any dose N = 116 n (%)	Combined 750 mg Cohort ^b 750 mg N = 140
Any SAE ^c	11 (32.4)	5 (16.1)	13 (43.3)	4 (19.0)	33 (28.4)	38 (27.1)
Any SAE possibly related to rilvegostomig ^{c,c}	3 (8.8)	0	5 (16.7)	1 (4.8)	9 (7.8)	8 (5.7)
Any SAE with outcome = death	1 (2.9)	1 (3.2)	3 (10.0)	1 (4.8)	6 (5.2)	3 (2.1)
Any SAE with outcome = death, possibly related to rilvegostomig ^c	0	0	0	0	0	0
Any SAE leading to discontinuation of treatment	1 (2.9)	0	2 (6.7)	0	3 (2.6)	2 (1.4)
Any SAE leading to discontinuation of treatment, possibly related to rilvegostomig ^c	1 (2.9)	0	0	0	1 (0.9)	2 (1.4)
Any AE of special interest to treatment	25 (73.5)	25 (80.6)	22 (73.3)	8 (38.1)	80 (69.0)	91 (65.0)
Any AE of special interest to treatment, possibly related to rilvegostomig ^c	19 (55.9)	18 (58.1)	18 (60.0)	4 (19.0)	59 (50.9)	63 (45.0)
Any imAE	13 (38.2)	14 (45.2)	9 (30.0)	4 (19.0)	40 (34.5)	33 (23.6)
Any imAE, possibly related to rilvegostomig ^c	12 (35.3)	14 (45.2)	9 (30.0)	4 (19.0)	39 (33.6)	32 (22.9)

^a Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

^b The Combined 750 mg Cohort includes participants from Parts A3, B, C, D1, and E.

^c As assessed by the investigator. Missing responses are counted as related.

^d All reported events were Grade 3.

^e Seriousness, as assessed by investigator.

Part A3 + B = rilvegostomig 750 mg Q3W 2L+ CPI-experienced. Part C = rilvegostomig 750 mg Q3W 2L+ CPI-naïve. Part D1 = rilvegostomig 750 mg Q3W 2L CPI-naïve. Part D2 = rilvegostomig 1500 mg Q3W 2L CPI-naïve. Part E = rilvegostomig 750 mg Q3W 2L CPI-naïve.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

2L = second line; 2L+ = second line and beyond; CTCAE = Common Terminology Criteria for Adverse Events Version 5.0; n = number of participants per category; N = number of participants per treatment group.

All Adverse Events

As of the DCO date, 133 participants (95.0%) in the Combined 750 mg Cohort had at least one AE, regardless of causality. The most frequently reported AEs (occurring in $\geq 15\%$ overall) were anemia (25 participants [17.9%]), and constipation and decreased appetite (23 participants [16.4%] each). See [Table 38](#) and [Table 39](#) for all AEs by PT occurring in $\geq 10\%$ of total treatment groups in CPI-experienced participants, and CPI-naïve participants and the Combined 750 mg Cohort, respectively.

Table 38 AEs in CPI-experienced Participants with NSCLC Occurring in $\geq 10\%$ of the Total A + B Group, by Preferred Term (ARTEMIDE-01; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	A1 + A2 70 and 210 mg N = 15 n (%)	A3 + B 750 mg N = 54 n (%)	A4 1500 mg N = 14 n (%)	Total A + B Any dose N = 83 n (%)
Participants with any AE	12 (80.0)	51 (94.4)	12 (85.7)	75 (90.4)
Fatigue	3 (20.0)	10 (18.5)	4 (28.6)	17 (20.5)
Decreased appetite	3 (20.0)	8 (14.8)	5 (35.7)	16 (19.3)
Cough	0	10 (18.5)	4 (28.6)	14 (16.9)
Arthralgia	2 (13.3)	6 (11.1)	5 (35.7)	13 (15.7)
Dyspnoea	1 (6.7)	8 (14.8)	4 (28.6)	13 (15.7)
Nausea	2 (13.3)	5 (9.3)	5 (35.7)	12 (14.5)
COVID-19	4 (26.7)	7 (13.0)	0	11 (13.3)
Constipation	3 (20.0)	6 (11.1)	2 (14.3)	11 (13.3)
Pruritus	2 (13.3)	6 (11.1)	3 (21.4)	11 (13.3)
Rash	0	8 (14.8)	3 (21.4)	11 (13.3)
Alanine aminotransferase increased	2 (13.3)	6 (11.1)	2 (14.3)	10 (12.0)
Aspartate aminotransferase increased	2 (13.3)	6 (11.1)	2 (14.3)	10 (12.0)
Diarrhoea	1 (6.7)	5 (9.3)	4 (28.6)	10 (12.0)
Vomiting	2 (13.3)	5 (9.3)	3 (21.4)	10 (12.0)

Part A1 = rilvegostomig 210 mg Q3W 2L+ CPI-experienced. Part A2 = rilvegostomig 70 mg Q3W 2L+ CPI-experienced. Part A3 + B = rilvegostomig 750 mg Q3W 2L+ CPI-experienced. Part A4 = rilvegostomig 1500 mg Q3W 2L+ CPI-experienced.

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term in the Total A + B Any dose group, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

2L+ = second line and beyond; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Table 39 AEs in CPI-naïve Participants with NSCLC and the Combined 750 mg Cohort, Occurring in $\geq 10\%$ of the Combined 750 mg Cohort, by Preferred Term (ARTEMIDE-01; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	C 750 mg N = 34 n (%)	D1 750 mg N = 31 n (%)	D2 1500 mg N = 30 n (%)	E 750 mg N = 21 n (%)	Total C + D + E Any dose N = 116 n (%)	Combined 750 mg Cohort ^a 750 mg N = 140 n (%)
Participants with any AE	33 (97.1)	30 (96.8)	30 (100)	19 (90.5)	112 (96.6)	133 (95.0)
Anaemia	11 (32.4)	3 (9.7)	8 (26.7)	7 (33.3)	29 (25.0)	25 (17.9)
Constipation	10 (29.4)	6 (19.4)	4 (13.3)	1 (4.8)	21 (18.1)	23 (16.4)
Decreased appetite	5 (14.7)	7 (22.6)	7 (23.3)	3 (14.3)	22 (19.0)	23 (16.4)
Cough	4 (11.8)	4 (12.9)	4 (13.3)	2 (9.5)	14 (12.1)	20 (14.3)
Pruritus	5 (14.7)	6 (19.4)	3 (10.0)	2 (9.5)	16 (13.8)	19 (13.6)
Aspartate aminotransferase increased	6 (17.6)	5 (16.1)	8 (26.7)	1 (4.8)	20 (17.2)	18 (12.9)
Rash	3 (8.8)	5 (16.1)	0	2 (9.5)	10 (8.6)	18 (12.9)
Pyrexia	2 (5.9)	6 (19.4)	6 (20.0)	4 (19.0)	18 (15.5)	17 (12.1)
Fatigue	3 (8.8)	3 (9.7)	5 (16.7)	0	11 (9.5)	16 (11.4)
Alanine aminotransferase increased	3 (8.8)	5 (16.1)	6 (20.0)	1 (4.8)	15 (12.9)	15 (10.7)
Diarrhoea	2 (5.9)	5 (16.1)	6 (20.0)	2 (9.5)	15 (12.9)	14 (10.0)
Dyspnoea	1 (2.9)	3 (9.7)	3 (10.0)	2 (9.5)	9 (7.8)	14 (10.0)
Lipase increased	5 (14.7)	2 (6.5)	3 (10.0)	2 (9.5)	12 (10.3)	14 (10.0)

^a The Combined 750 mg Cohort includes participants from Parts A3, B, C, D1, and E.

Part A3 + B = rilvegostomig 750 mg Q3W 2L+ CPI-experienced. Part C = rilvegostomig 750 mg Q3W 2L+ CPI-naïve. Part D1 = rilvegostomig 750 mg Q3W 2L CPI-naïve. Part D2 = rilvegostomig 1500 mg Q3W 2L CPI-naïve. Part E = rilvegostomig 750 mg Q3W 2L CPI-naïve.

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term in the Combined 750 mg Cohort, then alphabetically. Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

2L = second line; 2L+ = second line and beyond; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Treatment-related Adverse Events

As of the DCO date, in the Combined 750 mg Cohort, AEs (any grade) judged by the investigator as being possibly related to rilvegostomig occurred in 92 participants (65.7%).

The most frequently reported rilvegostomig-related AEs (occurring in $\geq 5\%$ overall) were rash (15 participants [10.7%]), lipase increased and pruritus (11 participants [7.9%] each), and AST increased, constipation, decreased appetite, fatigue, hypercholesterolemia,

hypothyroidism, and myalgia (8 participants [5.7%] each). See [Table 40](#) and [Table 41](#) for rilvegostomig-related AEs by PT occurring in $\geq 3\%$ of total treatment groups in CPI-experienced participants, and CPI-naïve participants and the Combined 750 mg Cohort, respectively.

Table 40 **Rilvegostomig-related AEs in CPI-experienced Participants with NSCLC Occurring in $\geq 3\%$ of the Total A + B Group, by Preferred Term (ARTEMIDE-01; Safety Analysis Set)**

Preferred Term (MedDRA version 28.0)	A1 + A2 70 and 120 mg N = 15 n (%)	A3 + B 750 mg N = 54 n (%)	A4 1500 mg N = 14 n (%)	Total A + B Any dose N = 83 n (%)
Participants with any AE possibly related to rilvegostomig ^a	5 (33.3)	33 (61.1)	8 (57.1)	46 (55.4)
Rash	0	7 (13.0)	1 (7.1)	8 (9.6)
Pruritus	2 (13.3)	2 (3.7)	2 (14.3)	6 (7.2)
Infusion related reaction	0	3 (5.6)	2 (14.3)	5 (6.0)
Lipase increased	0	4 (7.4)	1 (7.1)	5 (6.0)
Alanine aminotransferase increased	1 (6.7)	2 (3.7)	1 (7.1)	4 (4.8)
Aspartate aminotransferase increased	1 (6.7)	2 (3.7)	1 (7.1)	4 (4.8)
Fatigue	0	3 (5.6)	1 (7.1)	4 (4.8)
Pyrexia	1 (6.7)	3 (5.6)	0	4 (4.8)
Amylase increased	0	3 (5.6)	0	3 (3.6)
Constipation	0	3 (5.6)	0	3 (3.6)
Decreased appetite	0	3 (5.6)	0	3 (3.6)
Pneumonitis	1 (6.7)	2 (3.7)	0	3 (3.6)

^a As assessed by the investigator. Missing responses are counted as related.

Part A1 = rilvegostomig 210 mg Q3W 2L+ CPI-experienced. Part A2 = rilvegostomig 70 mg Q3W 2L+ CPI-experienced. Part A3 + B = rilvegostomig 750 mg Q3W 2L+ CPI-experienced. Part A4 = rilvegostomig 1500 mg Q3W 2L+ CPI-experienced.

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term in the Total A + B Any dose group, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

2L+ = second line and beyond; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Table 41 **Rilvegostomig-related AEs in CPI-naïve Participants with NSCLC and the Combined 750 mg Cohort, Occurring in $\geq 3\%$ of the Combined 750 mg Cohort, by Preferred Term (ARTEMIDE-01; Safety Analysis Set)**

Preferred Term (MedDRA version 28.0)	C 750 mg N = 34 n (%)	D1 750 mg N = 31 n (%)	D2 1500 mg N = 30 n (%)	E 750 mg N = 21 n (%)	Total C + D + E Any dose N = 116 n (%)	Combined 750 mg Cohort ^a 750 mg N = 140 n (%)
Participants with any AE possibly related to rilvegostomig ^b	24 (70.6)	24 (77.4)	20 (66.7)	11 (52.4)	79 (68.1)	92 (65.7)
Rash	3 (8.8)	3 (9.7)	0	2 (9.5)	8 (6.9)	15 (10.7)
Lipase increased	4 (11.8)	2 (6.5)	3 (10.0)	1 (4.8)	10 (8.6)	11 (7.9)
Pruritus	3 (8.8)	5 (16.1)	2 (6.7)	1 (4.8)	11 (9.5)	11 (7.9)
Aspartate aminotransferase increased	4 (11.8)	2 (6.5)	5 (16.7)	0	11 (9.5)	8 (5.7)
Constipation	4 (11.8)	1 (3.2)	0	0	5 (4.3)	8 (5.7)
Decreased appetite	0	4 (12.9)	2 (6.7)	1 (4.8)	7 (6.0)	8 (5.7)
Fatigue	2 (5.9)	3 (9.7)	2 (6.7)	0	7 (6.0)	8 (5.7)
Hypercholesterolaemia	6 (17.6)	1 (3.2)	4 (13.3)	1 (4.8)	12 (10.3)	8 (5.7)
Hypothyroidism	5 (14.7)	2 (6.5)	5 (16.7)	0	12 (10.3)	8 (5.7)
Myalgia	3 (8.8)	4 (12.9)	1 (3.3)	1 (4.8)	9 (7.8)	8 (5.7)
Alanine aminotransferase increased	2 (5.9)	2 (6.5)	5 (16.7)	1 (4.8)	10 (8.6)	7 (5.0)
Nausea	2 (5.9)	2 (6.5)	2 (6.7)	1 (4.8)	7 (6.0)	7 (5.0)
Pyrexia	1 (2.9)	2 (6.5)	3 (10.0)	1 (4.8)	7 (6.0)	7 (5.0)
Amylase increased	1 (2.9)	1 (3.2)	1 (3.3)	1 (4.8)	4 (3.4)	6 (4.3)
Diarrhoea	2 (5.9)	3 (9.7)	3 (10.0)	1 (4.8)	9 (7.8)	6 (4.3)
Gamma-glutamyltransferase increased	2 (5.9)	2 (6.5)	3 (10.0)	2 (9.5)	9 (7.8)	6 (4.3)
Hypertriglyceridaemia	5 (14.7)	0	3 (10.0)	1 (4.8)	9 (7.8)	6 (4.3)
Infusion related reaction	2 (5.9)	1 (3.2)	1 (3.3)	0	4 (3.4)	6 (4.3)

^a The Combined 750 mg Cohort includes participants from Parts A3, B, C, D1, and E.

^b As assessed by the investigator. Missing responses are counted as related.

Part A3 + B = rilvegostomig 750 mg Q3W 2L+ CPI-experienced. Part C = rilvegostomig 750 mg Q3W 2L+ CPI-naïve. Part D1 = rilvegostomig 750 mg Q3W 2L CPI-naïve. Part D2 = rilvegostomig 1500 mg Q3W 2L CPI-naïve. Part E = rilvegostomig 750 mg Q3W 2L CPI-naïve.

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term in the Combined 750 mg Cohort, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

2L = second line; 2L+ = second line and beyond; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Adverse Events with Maximum Severity Grade 3 or 4

As of the DCO date, 47 participants (33.6%) in the Combined 750 mg Cohort had at least one AE (regardless of causality) that was maximum Grade 3 or 4 in severity. Overall, maximum Grade 3 or 4 AEs occurred infrequently in each individual dose cohorts. By PT, maximum Grade 3 or 4 AEs reached 5% in this group only for anemia (7 participants [5.0%]).

A total of 15 participants (10.7%) had at least one maximum Grade 3 or 4 AE that was assessed by the investigator as possibly related to rilvegostomig. None of these events were maximum Grade 4. Of note, rilvegostomig-related maximum Grade 3 AEs of AST increased, hepatitis acute, pneumonitis, and rash were reported in 1 participant (0.7%) each. See [Table 42](#) and [Table 43](#) for all maximum Grade 3 or 4 AEs by PT in CPI-experienced participants, and CPI-naïve participants and the Combined 750 mg Cohort, respectively.

Table 42 **Rilvegostomig-related AEs of Maximum Grade 3 or 4 in
CPI-experienced Participants with NSCLC, by Preferred Term
(ARTEMIDE-01; Safety Analysis Set)**

Preferred Term (MedDRA version 28.0)	A1 + A2 70 and 210 mg N = 15 n (%)	A3 + B 750 mg N = 54 n (%)	A4 1500 mg N = 14 n (%)	Total A + B Any dose N = 83 n (%)
Participants with maximum Grade 3 or 4 AE possibly related to rilvegostomig ^{a,b}	0	5 (9.3)	2 (14.3)	7 (8.4)
Alanine aminotransferase increased	0	0	1 (7.1)	1 (1.2)
Aspartate aminotransferase increased	0	0	1 (7.1)	1 (1.2)
Colitis	0	0	1 (7.1)	1 (1.2)
Diarrhoea	0	0	1 (7.1)	1 (1.2)
Fatigue	0	1 (1.9)	0	1 (1.2)
Hepatitis acute	0	1 (1.9)	0	1 (1.2)
Immune system disorder	0	1 (1.9)	0	1 (1.2)
Infusion related reaction	0	1 (1.9)	0	1 (1.2)
Pneumonitis	0	1 (1.9)	0	1 (1.2)
Rash	0	1 (1.9)	0	1 (1.2)

^a As assessed by the investigator. Missing responses are counted as related.

^b All events in Parts A and B were Grade 3, no rilvegostomig-related Grade 4 AEs were reported.

Part A1 = rilvegostomig 210 mg Q3W 2L+ CPI-experienced. Part A2 = rilvegostomig 70 mg Q3W 2L+ CPI-experienced. Part A3 + B = rilvegostomig 750 mg Q3W 2L+ CPI-experienced. Part A4 = rilvegostomig 1500 mg Q3W 2L+ CPI-experienced.

Participants with multiple AEs are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term in the Total A + B Any dose group, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Grade 3: severe, Grade 4: life-threatening. CTCAE Version 5.0.

2L+ = second line and beyond; CTCAE = Common Terminology Criteria for Adverse Events;

MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Table 43 **Rilvegostomig-related AEs of Maximum Grade 3 or 4 in CPI-naïve Participants with NSCLC and the Combined 750 mg Cohort, Occurring in ≥ 1 Participant in the Combined 750 mg Cohort, by Preferred Term (ARTEMIDE-01; Safety Analysis Set)**

Preferred Term (MedDRA version 28.0)	C 750 mg N = 34 n (%)	D1 750 mg N = 31 n (%)	D2 1500 mg N = 30 n (%)	E 750 mg N = 21 n (%)	Total C + D + E Any dose N = 116 n (%)	Combined 750 mg Cohort ^a 750 mg N = 140 n (%)
Participants with maximum Grade 3 or 4 AE possibly related to rilvegostomig ^b	4 (11.8)	4 (12.9)	5 (16.7)	2 (9.5)	15 (12.9)	15 (10.7)
Diarrhoea	1 (2.9)	1 (3.2)	0	0	2 (1.7)	2 (1.4)
Gamma-glutamyltransferase increased	0	2 (6.5)	0	0	2 (1.7)	2 (1.4)
Hypertriglyceridaemia	2 (5.9)	0	1 (3.3)	0	3 (2.6)	2 (1.4)
Aspartate aminotransferase increased	0	1 (3.2)	0	0	1 (0.9)	1 (0.7)
Cerebral infarction	0	0	0	1 (4.8)	1 (0.9)	1 (0.7)
Colitis	1 (2.9)	0	0	0	1 (0.9)	1 (0.7)
Dermatitis	0	0	0	1 (4.8)	1 (0.9)	1 (0.7)
Fatigue	0	0	0	0	0	1 (0.7)
Hepatitis acute	0	0	0	0	0	1 (0.7)
Immune system disorder	0	0	0	0	0	1 (0.7)
Immune-mediated hepatitis	1 (2.9)	0	0	0	1 (0.9)	1 (0.7)
Infusion related reaction	0	0	0	0	0	1 (0.7)
Lipase increased	0	1 (3.2)	1 (3.3)	0	2 (1.7)	1 (0.7)
Pneumonitis	0	0	0	0	0	1 (0.7)

Table 43 **Rilvegostomig-related AEs of Maximum Grade 3 or 4 in CPI-naïve Participants with NSCLC and the Combined 750 mg Cohort, Occurring in ≥ 1 Participant in the Combined 750 mg Cohort, by Preferred Term (ARTEMIDE-01; Safety Analysis Set)**

Preferred Term (MedDRA version 28.0)	C 750 mg N = 34 n (%)	D1 750 mg N = 31 n (%)	D2 1500 mg N = 30 n (%)	E 750 mg N = 21 n (%)	Total C + D + E Any dose N = 116 n (%)	Combined 750 mg Cohort ^a 750 mg N = 140 n (%)
Pruritus	1 (2.9)	0	0	0	1 (0.9)	1 (0.7)
Rash	0	0	0	0	0	1 (0.7)

^a The Combined 750 mg Cohort includes participants from Parts A3, B, C, D1, and E.

^b As assessed by the investigator. Missing responses are counted as related.

Part A3 + B = rilvegostomig 750 mg Q3W 2L+ CPI-experienced. Part C = rilvegostomig 750 mg Q3W 2L+ CPI-naïve. Part D1 = rilvegostomig 750 mg Q3W 2L CPI-naïve. Part D2 = rilvegostomig 1500 mg Q3W 2L CPI-naïve. Part E = rilvegostomig 750 mg Q3W 2L CPI-naïve.

Participants with multiple AEs are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term in the Combined 750 mg Cohort, then alphabetically. Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Grade 3: severe, Grade 4: life-threatening. CTCAE Version 5.0.

2L = second line; 2L+ = second line and beyond; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Serious Adverse Events

As of the DCO date, treatment-emergent SAEs were reported in 38 participants (27.1%) in the Combined 750 mg Cohort. By PT, treatment-emergent SAEs that occurred in more than one participant in the Combined 750 mg Cohort included pneumonia (6 participants [4.3%]), dyspnea (4 participants [2.9%]), and anemia, COVID-19, diarrhea, pleural effusion, pneumothorax, pyrexia, and sepsis (2 participants [1.4%] each). See [Table 44](#) and [Table 45](#) for treatment-emergent SAEs by PT in CPI-experienced participants, and CPI-naïve participants and the Combined 750 mg Cohort, respectively.

Eight participants (5.7%) in the Combined 750 mg Cohort had SAEs that were assessed by the investigator as possibly related to rilvegostomig.

One participant in Cohort A3 had an SAE that was assessed by the investigator as related to rilvegostomig (suspected immune system disorder/other polymyalgia-like immune-related AE). The event occurred 135 days after starting the study drug. The participant initially experienced Grade 1 fever, cough, diffuse muscle soreness, and general malaise. The event became serious, infections were ruled out and following a neurological consultation the

diagnosis of suspected polymyalgia-like immune reaction Grade 3 was made. The participant improved with corticosteroid treatment.

An additional Grade 4 myocarditis event was reported for a participant in Cohort D2 (1500 mg). This event occurred 2 days after the participant began subsequent chemotherapy. The participant received antibiotics and steroids and the event resolved within 17 days. The investigator considered the event possibly related to rilvegostomig.

Table 44 SAEs in CPI-experienced Participants with NSCLC Occurring in $\geq 2\%$ of the Total A + B Group, by Preferred Term (ARTEMIDE-01; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	A1 + A2 70 and 210 mg N = 15 n (%)	A3 + B 750 mg N = 54 n (%)	A4 1500 mg N = 14 n (%)	Total A + B Any dose N = 83 n (%)
Participants with any SAE	4 (26.7)	18 (33.3)	6 (42.9)	28 (33.7)
COVID-19	1 (6.7)	2 (3.7)	0	3 (3.6)
Dyspnoea	1 (6.7)	2 (3.7)	0	3 (3.6)
Pneumonia	1 (6.7)	2 (3.7)	0	3 (3.6)
Diarrhoea	0	0	2 (14.3)	2 (2.4)
Pleural effusion	1 (6.7)	1 (1.9)	0	2 (2.4)
Upper respiratory tract infection	1 (6.7)	1 (1.9)	0	2 (2.4)

Part A1 = rilvegostomig 210 mg Q3W 2L+ CPI-experienced. Part A2 = rilvegostomig 70 mg Q3W 2L+ CPI-experienced. Part A3 + B = rilvegostomig 750 mg Q3W 2L+ CPI-experienced. Part A4 = rilvegostomig 1500 mg Q3W 2L+ CPI-experienced.

Participants with multiple SAEs are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term in the Total A + B Any dose group, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

2L+ = second line and beyond; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Table 45 SAEs in CPI-naïve Participants with NSCLC and the Combined 750 mg Cohort, Occurring in $\geq 1\%$ of the Combined 750 mg Cohort, by Preferred Term (ARTEMIDE-01; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	C 750 mg N = 34 n (%)	D1 750 mg N = 31 n (%)	D2 1500 mg N = 30 n (%)	E 750 mg N = 21 n (%)	Total C + D + E Any dose N = 116 n (%)	Combined 750 mg cohort ^a 750 mg N = 140 n (%)
Participants with any SAE	11 (32.4)	5 (16.1)	13 (43.3)	4 (19.0)	33 (28.4)	38 (27.1)
Pneumonia	4 (11.8)	0	2 (6.7)	0	6 (5.2)	6 (4.3)
Dyspnoea	0	1 (3.2)	2 (6.7)	1 (4.8)	4 (3.4)	4 (2.9)
Anaemia	2 (5.9)	0	1 (3.3)	0	3 (2.6)	2 (1.4)
COVID-19	0	0	0	0	0	2 (1.4)
Diarrhoea	0	1 (3.2)	0	1 (4.8)	2 (1.7)	2 (1.4)
Plural effusion	0	1 (3.2)	0	0	1 (0.9)	2 (1.4)
Pneumothorax	2 (5.9)	0	1 (3.3)	0	3 (2.6)	2 (1.4)
Pyrexia	1 (2.9)	0	0	1 (4.8)	2 (1.7)	2 (1.4)
Sepsis	1 (2.9)	0	0	1 (4.8)	2 (1.7)	2 (1.4)

^a Combined 750 mg Cohort includes participants from Parts A3, B, C, D1, and E.

Part A3 + B = rilvegostomig 750 mg Q3W 2L+ CPI-experienced. Part C = rilvegostomig 750 mg Q3W 2L+ CPI-naïve. Part D1 = rilvegostomig 750 mg Q3W 2L CPI-naïve. Part D2 = rilvegostomig 1500 mg Q3W 2L CPI-naïve. Part E = rilvegostomig 750 mg Q3W 2L CPI-naïve.

Participants with multiple SAEs are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term in the Combined 750 mg Cohort, then alphabetically. Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

2L = second line; 2L+ = second line and beyond; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Adverse Events With Outcome of Death

As of the DCO date, 3 participants (2.1%) had AEs with outcome of death in the Combined 750 mg Cohort in ARTEMIDE-01. The reported AEs with outcome of death were pneumonia, sepsis, and ventricular arrhythmia (1 participant [0.7%] each). No events were judged by the investigator to be possibly related to rilvegostomig treatment.

Adverse Events Leading to Permanent Discontinuation

As of the DCO date, in the Combined 750 mg Cohort, 5 participants (3.6%) had AEs leading to permanent discontinuation of rilvegostomig. By PT, the events were myocarditis and limb injury (both Grade 1), pneumonitis (Grade 2), and hepatitis acute and immune-mediated hepatitis (both Grade 3). The events of myocarditis, pneumonitis, immune-mediated hepatitis,

and hepatitis acute were considered by the investigator to be possibly related to rilvegostomig treatment.

5.3.1.1.3 Efficacy in ARTEMIDE-01 CPI-naïve Cohorts

As of 21 April 2025, 65 participants were enrolled in Cohorts C and D1 (750 mg). Prior treatment with chemotherapy for metastatic disease was allowed. PD-L1 was assessed locally for eligibility and then reviewed centrally, retrospectively.

Based on local assay results, in participants with PD-L1 TPS $\geq 50\%$, ORR was 61.8% (21 of 34 participants), PFS-12 was 55.5%, and mPFS was 12.3 months (95% CI: 8.4, NC). In participants with PD-L1 TPS 1% to 49%, ORR was 29.0% (9 of 31 participants), PFS-12 was 27.2%, and mPFS was 6.1 months (95% CI: 2.7, 8.3). Response was ongoing in 16 responders (53.3%). ORR, DoR and PFS for CPI-naïve and CPI- and chemotherapy-naïve (1L) participants, based on local assay results, are shown in [Table 46](#).

Based on retrospective central assay results (Ventana SP263), in participants with PD-L1 TPS $\geq 50\%$, ORR was 68.2% (15 of 22 participants), and PFS-12 was 63.6%. In participants with PD-L1 TPS 1% to 49%, ORR was 34.8% (8 of 23 participants) and PFS-12 was 30.4%.

Rilvegostomig led to higher T-effector activation and T-cell clonal expansion versus a historical anti-PD-L1 cohort.

Table 46: Best Overall Response, ORR, DoR, and PFS for CPI-naïve and CPI + CT-naïve Participants (ARTEMIDE-01)

PD-L1 TPS (local)	1% to 49%		$\geq 50\%$	
	CPI-naïve (n = 31)	CPI- and CT-naïve (n = 18)	CPI-naïve (n = 34)	CPI- and CT-naïve (n = 31)
Rilvegostomig 750 mg				
Response, n (%)				
ORR	9 (29.0)	8 (44.4)	21 (61.8)	21 (67.7)
Complete response	0	0	1 (2.9)	1 (3.2)
Partial response	9 (29.0)	8 (44.4)	20 (58.8)	20 (64.5)
Stable disease	11 (35.5)	5 (27.8)	9 (26.5)	7 (22.6)
Progression	9 (29.0)	5 (27.8)	4 (11.8)	3 (9.7)
Not evaluable	2 (6.5)	0	0	0
Median (95% CI) DoR, months	9.9 (4.1, 14.6)	8.5 (4.1, NC)	NC (10.3, NC)	NC (10.3, NC)
PFS				
Events, n (%)	27 (87.1)	15 (83.3)	18 (52.9)	15 (48.4)
Median (95% CI) PFS, months	6.1 (2.7, 8.3)	7.8 (1.9, 12.5)	12.3 (8.4, NC)	21.2 (10.2, NC)
PFS-12, % (95% CI)	27.2 (12.9, 43.6)	30.1 (11.1, 52.0)	55.5 (37.3, 70.3)	60.8 (41.4, 75.6)

CT = chemotherapy; n = number of participants per category.

5.3.1.2 MAGELLAN (Cohort A5)

5.3.1.2.1 Exposure in MAGELLAN (Cohort A5)

As of the final DCO date of 23 May 2023, 2 participants had received rilvegostomig monotherapy (750 mg Q3W) in MAGELLAN Cohort A5.

The median duration of exposure was 76.0 days with a range of 21 to 131 days.

5.3.1.2.2 Safety in MAGELLAN (Cohort A5)

Overview of Adverse Events

An overall summary of AEs in Cohort A5 (as of the final DCO date of 23 May 2023) is presented in [Table 47](#). The safety analysis set is defined as all participants who received at least 1 dose of any study intervention.

Both participants (2; 100%) had at least one AE, and both had an AE that was considered by the investigator to be possibly related to rilvegostomig treatment. One participant (50.0%) had maximum Grade 3 or 4 AEs (Grade 3 AST increased and Grade 4 ALT increased) that were assessed by the investigator as possibly related to rilvegostomig. The Grade 3 AE of AST increased led to rilvegostomig dose interruption and the Grade 4 AE of ALT increased led to rilvegostomig dose discontinuation. Both AEs resolved.

Neither participant had an SAE or an AE resulting in death. AESIs and imAEs assessed by the investigator as possibly related to rilvegostomig were reported in both participants (2, 100%).

Table 47 Overall Summary of AEs (MAGELLAN Monotherapy Cohort A5; Safety Analysis Set)

Participants with ^a	A5 Rilvegostomig 750 mg Q3W N = 2 n (%)
Any AE	2 (100)
Any AE possibly related to rilvegostomig ^b	2 (100)
Any AE of maximum CTCAE Grade 3 or Grade 4	1 (50.0)
Any AE of maximum CTCAE Grade 3 or Grade 4, possibly related to rilvegostomig ^b	1 (50.0)
Any AE leading to discontinuation of rilvegostomig	1 (50.0)
Any AE leading to discontinuation of rilvegostomig, possibly related to rilvegostomig ^b	1 (50.0)
Any AE leading to dose interruption of rilvegostomig	1 (50.0)
Any AE leading to dose interruption of rilvegostomig, possibly related to rilvegostomig ^b	1 (50.0)

Table 47 Overall Summary of AEs (MAGELLAN Monotherapy Cohort A5; Safety Analysis Set)

Participants with ^a	A5 Rilvegostomig 750 mg Q3W N = 2 n (%)
Any SAE ^c	0
Any SAE possibly related to rilvegostomig ^{b,c}	0
Any SAE with outcome = death	0
Any SAE with outcome = death, possibly related to rilvegostomig ^b	0
Any SAE leading to discontinuation of treatment	0
Any SAE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	0
Any AE of special interest to treatment	2 (100)
Any AE of special interest to treatment, possibly related to rilvegostomig ^b	2 (100)
Any imAE	2 (100)
Any imAE, possibly related to rilvegostomig ^b	2 (100)

^a Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

^b As assessed by the investigator. Missing responses are counted as related.

^c Seriousness, as assessed by the investigator.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
CTCAE = Common Terminology Criteria for Adverse Events; n = number of participants per category.

N = number of participants per treatment group.

All Adverse Events

As of the final DCO date, both participants (2, 100%) in Cohort A5 had at least one AE, regardless of causality. The only AE reported in more than one participant was dysuria (2 participants [100%]). See [Table 48](#) for all AEs by PT.

Table 48 AEs by Preferred Term (MAGELLAN Monotherapy Cohort A5; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	A5 Rilvegostomig 750 mg Q3W N = 2 n (%)
Participants with any AE	2 (100)
Dysuria	2 (100)
Abdominal pain	1 (50.0)
Alanine aminotransferase increased	1 (50.0)

Table 48 AEs by Preferred Term (MAGELLAN Monotherapy Cohort A5; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	A5 Rilvegostomig 750 mg Q3W N = 2 n (%)
Arthralgia	1 (50.0)
Aspartate aminotransferase increased	1 (50.0)
Blood thyroid stimulating hormone decreased	1 (50.0)
Constipation	1 (50.0)
Haemoptysis	1 (50.0)
Hypertension	1 (50.0)
Insomnia	1 (50.0)
Urticaria	1 (50.0)

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Treatment-related Adverse Events

As of the final DCO date, AEs (any grade) judged by the investigator as being possibly related to rilvegostomig occurred in both participants (100%) in Cohort A5. None of these AEs were reported in more than 1 participant (see [Table 49](#)).

Table 49 Rilvegostomig-related AEs by Preferred Term (MAGELLAN Monotherapy Cohort A5; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	A5 Rilvegostomig 750 mg Q3W N = 2 n (%)
Participants with any AE possibly related to rilvegostomig ^a	2 (100)
Alanine aminotransferase increased	1 (50.0)
Arthralgia	1 (50.0)
Aspartate aminotransferase increased	1 (50.0)
Blood thyroid stimulating hormone decreased	1 (50.0)
Dysuria	1 (50.0)
Urticaria	1 (50.0)

^a Possibly related to rilvegostomig, as assessed by the investigator. Missing responses are counted as related. Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Adverse Events with Maximum Severity Grade 3 or 4

As of the final DCO date, 1 participant (50.0%) in Cohort A5 had maximum Grade 3 or 4 AEs, comprising Grade 3 AST increased and Grade 4 ALT increased. Both events were assessed by the investigator as possibly related to rilvegostomig (further information is included in the Overview of Adverse Events section).

Serious Adverse Events

As of the final DCO date, neither participant in Cohort A5 had an SAE.

Adverse Events With Outcome of Death

As of the final DCO date, neither participant in Cohort A5 had an AE with outcome of death.

Adverse Events Leading to Permanent Discontinuation

As of the final DCO date, 1 participant (50.0%) in Cohort A5 had an AE leading to permanent discontinuation of rilvegostomig. By PT, the event was ALT increased (Grade 4) and was considered by the investigator to be possibly related to rilvegostomig treatment. The event lasted 16 days and resolved following the administration of steroids.

5.3.2 Rilvegostomig + Chemotherapy

5.3.2.1 MAGELLAN (Cohort B5)

5.3.2.1.1 Exposure in MAGELLAN (Cohort B5)

As of the final DCO date of 23 May 2023, 5 participants had received rilvegostomig (750 mg Q3W) + chemotherapy in MAGELLAN Cohort B5.

The median duration of exposure was 139.0 days with a range of 42 to 176 days.

5.3.2.1.2 Safety in MAGELLAN (Cohort B5)

Overview of Adverse Events

An overall summary of AEs in Cohort B5 (as of the final DCO date of 23 May 2023) is presented in [Table 47](#). The safety analysis set is defined as all participants who received at least 1 dose of any study intervention.

A total of 4 participants (80.0%) had at least one AE, and 1 participant (20.0%) had an AE that was considered by the investigator to be possibly related to rilvegostomig treatment. No participants had maximum Grade 3 or 4 AEs.

SAEs were reported in 1 participant (20.0%), with no SAEs assessed by the investigator as possibly related to rilvegostomig or resulting in death. AESIs and imAEs assessed by the investigator as possibly related to rilvegostomig were reported in 1 (20.0%) participant each.

Table 50 Overall Summary of AEs (MAGELLAN Rilvegostomig + Chemotherapy Cohort B5; Safety Analysis Set)

Participants with ^a	B5 Rilvegostomig 750 mg Q3W + Chemotherapy N = 5 n (%)
Any AE	4 (80.0)
Any AE possibly related to rilvegostomig ^b	1 (20.0)
Any AE of maximum CTCAE Grade 3 or Grade 4	0
Any AE of maximum CTCAE Grade 3 or Grade 4, possibly related to rilvegostomig ^b	0
Any AE leading to discontinuation of any study treatment	0
Any AE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	0
Any AE leading to dose interruption of treatment	0
Any AE leading to dose interruption of treatment, possibly related to rilvegostomig ^b	0
Any SAE ^c	1 (20.0)
Any SAE, possibly related to rilvegostomig ^{b,c}	0
Any SAE with outcome = death	0
Any SAE with outcome = death, possibly related to rilvegostomig ^b	0
Any SAE leading to discontinuation of treatment	0
Any SAE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	0
Any AE of special interest to treatment	1 (20.0)
Any AE of special interest to treatment, possibly related to rilvegostomig ^b	1 (20.0)
Any imAE	1 (20.0)
Any imAE, possibly related to rilvegostomig ^b	1 (20.0)

^a Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

^b As assessed by the investigator. Missing responses are counted as related.

^c Seriousness, as assessed by investigator.

Chemotherapy = carboplatin + cisplatin + pemetrexed.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

CTCAE = Common Terminology Criteria for Adverse Events; n = number of participants per category.
N = number of participants per treatment group.

All Adverse Events

As of the final DCO date, 4 participants (80.0%) in Cohort B5 had at least one AE, regardless of causality. The most frequently reported AEs were constipation and nausea (2 participants [40.0%] each). See [Table 51](#) for all AEs by PT.

Table 51 **AEs by Preferred Term (MAGELLAN Rilvegostomig + Chemotherapy Cohort B5; Safety Analysis Set)**

Preferred Term (MedDRA version 28.0)	B5 Rilvegostomig 750 mg Q3W + Chemotherapy N = 5 n (%)
Participants with any AE	4 (80.0)
Constipation	2 (40.0)
Nausea	2 (40.0)
Decreased appetite	1 (20.0)
Hypothyroidism	1 (20.0)
Insomnia	1 (20.0)
Neutropenia	1 (20.0)
Pneumonia	1 (20.0)
Pruritus	1 (20.0)
Renal failure	1 (20.0)
Upper respiratory tract infection	1 (20.0)
Weight decreased	1 (20.0)

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Chemotherapy = carboplatin + cisplatin + pemetrexed.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Treatment-related Adverse Events

As of the final DCO date, AEs (any grade) judged by the investigator as being possibly related to rilvegostomig occurred in 1 participant (20.0%) in Cohort B5 (PTs of hypothyroidism and pruritus) (see [Table 52](#)).

Table 52 **Rilvegostomig-related AEs by Preferred Term (MAGELLAN
Rilvegostomig + Chemotherapy Cohort B5; Safety Analysis Set)**

Preferred Term (MedDRA version 28.0)	B5 Rilvegostomig 750 mg Q3W + Chemotherapy N = 5 n (%)
Participants with any AE possibly related to rilvegostomig ^a	1 (20.0)
Hypothyroidism	1 (20.0)
Pruritus	1 (20.0)

^a Possibly related to rilvegostomig, as assessed by the investigator. Missing responses are counted as related. Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Chemotherapy = carboplatin + cisplatin + pemetrexed.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Adverse Events with Maximum Severity Grade 3 or 4

As of the final DCO date, no participants in Cohort B5 had maximum Grade 3 or 4 AEs.

Serious Adverse Events

As of the final DCO date, an SAE (pneumonia; Grade 2) was reported in 1 participant (20.0%) in Cohort B5, and was assessed by the investigator as unrelated to rilvegostomig. The event occurred 43 days after starting the study drug. The participant received concomitant/additional treatment and at the final DCO date the event was recovered/resolved.

Adverse Events With Outcome of Death

As of the final DCO date, no participants in Cohort B5 had an AE with outcome of death.

Adverse Events Leading to Permanent Discontinuation

As of the final DCO date, no participants in Cohort B5 had an AE leading to permanent discontinuation of rilvegostomig.

5.3.2.2 GEMINI-Gastric Substudy 2

5.3.2.2.1 Exposure in GEMINI-Gastric Substudy 2

As of the DCO date of 05 July 2025, a total of 40 participants had received rilvegostomig (750 mg Q3W) in GEMINI-Gastric Substudy 2 across 2 cohorts: 27 participants received rilvegostomig + XELOX and 13 participants received rilvegostomig + FOLFOX.

The median duration of exposure to rilvegostomig was 33.93 weeks with a range of 7.3 to 106.6 weeks ([Table 53](#)).

Table 53 **Duration of Rilvegostomig Exposure (GEMINI-Gastric Substudy 2; Safety Analysis Set)**

	Rilvegostomig 750 mg Q3W + FOLFOX or XELOX N = 40
Total treatment duration (weeks) ^a	
Mean (SD)	41.85 (24.815)
Median	33.93
Min, Max	7.3, 106.6

^a Total exposure (weeks) of IP = (min (last dose date where dose > 0 mg + 20), date of death, date of DCO) – first dose date + 1) / 7.

XELOX = capecitabine + oxaliplatin, FOLFOX = 5-FU + oxaliplatin + leucovorin.

max = maximum; min = minimum; N = number of participants per treatment group.

5.3.2.2.2 Safety in GEMINI-Gastric Substudy 2

Overview of Adverse Events

An overall summary of AEs across the rilvegostomig cohorts in GEMINI-Gastric Substudy 2 (as of the DCO date of 05 July 2025) is presented in [Table 54](#).

Across the 2 cohorts, all 40 participants (100%) had at least one AE, and 26 participants (65.0%) had an AE that was assessed by the investigator as possibly related to rilvegostomig treatment. AEs of maximum Grade 3 or 4 were reported in 23 participants (57.5%), with AEs of maximum Grade 3 or 4 assessed by the investigator as possibly related to rilvegostomig in 4 participants (10.0%).

SAEs were reported in 11 participants (27.5%), with SAEs assessed by the investigator as possibly related to rilvegostomig in 1 participant (2.5%); no SAEs resulted in death. Eleven participants (27.5%) had an AE leading to study treatment discontinuation, and in 9 participants (22.5%) treatment dosing was interrupted due to an AE that was assessed by the investigator as possibly related to rilvegostomig. AESIs assessed by the investigator as possibly related to rilvegostomig were reported in 21 participants (52.5%).

Table 54 Overall Summary of AEs (GEMINI-Gastric Substudy 2; Safety Analysis Set)

Participants with ^a	Rilvegostomig + FOLFOX N = 13 n (%)	Rilvegostomig + XELOX N = 27 n (%)	Total N = 40 n (%)
Any AE	13 (100)	27 (100)	40 (100)
Any AE possibly related to rilvegostomig ^b	7 (53.8)	19 (70.4)	26 (65.0)
Any AE of maximum CTCAE Grade 3 or Grade 4	10 (76.9)	13 (48.1)	23 (57.5)
Any AE of maximum CTCAE Grade 3 or Grade 4, possibly related to rilvegostomig ^b	1 (7.7)	3 (11.1)	4 (10.0)
Any AE leading to discontinuation of any study treatment	3 (23.1)	8 (29.6)	11 (27.5)
Any AE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	0	1 (3.7)	1 (2.5)
Any AE leading to dose interruption of treatment	9 (69.2)	21 (77.8)	30 (75.0)
Any AE leading to dose interruption of treatment, possibly related to rilvegostomig ^b	3 (23.1)	6 (22.2)	9 (22.5)
Any SAE ^c	6 (46.2)	5 (18.5)	11 (27.5)
Any SAE, possibly related to rilvegostomig ^b	0	1 (3.7)	1 (2.5)
Any SAE with outcome = death	0	0	0
Any SAE with outcome = death, possibly related to rilvegostomig ^b	0	0	0
Any SAE leading to discontinuation of treatment	1 (7.7)	0	1 (2.5)
Any SAE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	0	0	0
Any AE of special interest to treatment	8 (61.5)	24 (88.9)	32 (80.0)
Any AE of special interest to treatment, possibly related to rilvegostomig ^b	3 (23.1)	18 (66.7)	21 (52.5)
Any imAE	0	0	0
Any imAE, possibly related to rilvegostomig ^b	0	0	0

^a Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

^b As assessed by the investigator. Missing responses are counted as related.

^c Seriousness, as assessed by investigator.

XELOX = capecitabine + oxaliplatin, FOLFOX = 5-FU + oxaliplatin + leucovorin.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). CTCAE = Common Terminology Criteria for Adverse Events Version 5.0; n = number of participants per category; N = number of participants per treatment group.

All Adverse Events

As of the DCO date, all participants (40; 100%) across both cohorts in Substudy 2 had at least one AE, regardless of causality. The most frequently reported AEs ($\geq 35\%$ of participants overall) were nausea (25 participants [62.5%]), neutrophil count decreased (20 participants [50.0%]), decreased appetite (17 participants [42.5%]), asthenia (15 participants [37.5%]), and anemia, lipase increased, and platelet count decreased (14 participants [35.0%] each). See [Table 55](#) for all AEs by PT occurring in $\geq 20\%$ of the total treatment group.

Table 55 AEs Occurring in $\geq 20\%$ of Participants Overall, by Preferred Term (GEMINI-Gastric Substudy 2; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	Rilvegostomig + XELOX N = 27 n (%)	Rilvegostomig + FOLFOX N = 13 n (%)	Total N = 40 n (%)
Participants with any AE	27 (100)	13 (100)	40 (100)
Nausea	16 (59.3)	9 (69.2)	25 (62.5)
Neutrophil count decreased	14 (51.9)	6 (46.2)	20 (50.0)
Decreased appetite	11 (40.7)	6 (46.2)	17 (42.5)
Asthenia	8 (29.6)	7 (53.8)	15 (37.5)
Anaemia	8 (29.6)	6 (46.2)	14 (35.0)
Lipase increased	12 (44.4)	2 (15.4)	14 (35.0)
Platelet count decreased	11 (40.7)	3 (23.1)	14 (35.0)
Diarrhoea	9 (33.3)	4 (30.8)	13 (32.5)
Peripheral sensory neuropathy	8 (29.6)	5 (38.5)	13 (32.5)
Alanine aminotransferase increased	9 (33.3)	3 (23.1)	12 (30.0)
Aspartate aminotransferase increased	10 (37.0)	2 (15.4)	12 (30.0)
Constipation	8 (29.6)	4 (30.8)	12 (30.0)
Hypoalbuminaemia	7 (25.9)	4 (30.8)	11 (27.5)
Neutropenia	5 (18.5)	6 (46.2)	11 (27.5)
White blood cell count decreased	7 (25.9)	4 (30.8)	11 (27.5)
Amylase increased	8 (29.6)	1 (7.7)	9 (22.5)
Blood creatine phosphokinase increased	8 (29.6)	1 (7.7)	9 (22.5)
Pyrexia	5 (18.5)	4 (30.8)	9 (22.5)
Blood bilirubin increased	6 (22.2)	2 (15.4)	8 (20.0)
Pruritus	7 (25.9)	1 (7.7)	8 (20.0)
Stomatitis	4 (14.8)	4 (30.8)	8 (20.0)
Vomiting	6 (22.2)	2 (15.4)	8 (20.0)

Participants with multiple occurrences are counted once for each Preferred Term.
Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

XELOX = capecitabine + oxaliplatin, FOLFOX = 5-FU + oxaliplatin + leucovorin.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Treatment-related Adverse Events

As of the DCO date, AEs (any grade) judged by the investigator as being possibly related to rilvegostomig occurred in 26 participants (65.0%) in Substudy 2. The most frequently reported rilvegostomig-related AEs ($\geq 17.5\%$ of participants overall) 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%]). See [Table 56](#) for rilvegostomig-related AEs by PT.

Table 56 **Rilvegostomig-related AEs Occurring in $\geq 5\%$ of Participants Overall, by Preferred Term (GEMINI-Gastric Substudy 2; Safety Analysis Set)**

Preferred Term (MedDRA version 28.0)	Rilvegostomig + XELOX N = 27 n (%)	Rilvegostomig + FOLFOX N = 13 n (%)	Total N = 40 n (%)
Participants with any AE possibly related to rilvegostomig ^a	19 (70.4)	7 (53.8)	26 (65.0)
Aspartate aminotransferase increased	7 (25.9)	2 (15.4)	9 (22.5)
Lipase increased	7 (25.9)	2 (15.4)	9 (22.5)
Alanine aminotransferase increased	6 (22.2)	2 (15.4)	8 (20.0)
Blood creatine phosphokinase increased	6 (22.2)	1 (7.7)	7 (17.5)
Platelet count decreased	6 (22.2)	0	6 (15.0)
Diarrhoea	4 (14.8)	1 (7.7)	5 (12.5)
Pruritus	5 (18.5)	0	5 (12.5)
Rash	5 (18.5)	0	5 (12.5)
Amylase increased	3 (11.1)	1 (7.7)	4 (10.0)
Blood bilirubin increased	4 (14.8)	0	4 (10.0)
Nausea	2 (7.4)	2 (15.4)	4 (10.0)
Asthenia	2 (7.4)	1 (7.7)	3 (7.5)
Abdominal pain	2 (7.4)	0	2 (5.0)
C-reactive protein increased	2 (7.4)	0	2 (5.0)
Constipation	1 (3.7)	1 (7.7)	2 (5.0)
Fatigue	1 (3.7)	1 (7.7)	2 (5.0)

Table 56 **Rilvegostomig-related AEs Occurring in $\geq 5\%$ of Participants Overall, by Preferred Term (GEMINI-Gastric Substudy 2; Safety Analysis Set)**

Preferred Term (MedDRA version 28.0)	Rilvegostomig + XELOX N = 27 n (%)	Rilvegostomig + FOLFOX N = 13 n (%)	Total N = 40 n (%)
Hyperglycaemia	2 (7.4)	0	2 (5.0)
Hypoalbuminaemia	2 (7.4)	0	2 (5.0)
Hypocalcaemia	2 (7.4)	0	2 (5.0)
Hypothyroidism	1 (3.7)	1 (7.7)	2 (5.0)
Neutrophil count decreased	2 (7.4)	0	2 (5.0)
Pneumonitis	2 (7.4)	0	2 (5.0)
Pyrexia	1 (3.7)	1 (7.7)	2 (5.0)
Stomatitis	2 (7.4)	0	2 (5.0)
Troponin I increased	1 (3.7)	1 (7.7)	2 (5.0)
White blood cell count decreased	2 (7.4)	0	2 (5.0)

^a Possibly related to study treatment, as assessed by the investigator. Missing responses are counted as related.

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

XELOX = capecitabine + oxaliplatin, FOLFOX = 5-FU + oxaliplatin + leucovorin.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Adverse Events with Maximum Severity Grade 3 or 4

As of the DCO date, 23 participants (57.5%) across both dose cohorts in Substudy 2 had at least one AE that was maximum Grade 3 or 4 in severity (regardless of causality). Overall, maximum Grade 3 or 4 AEs occurred infrequently across both dose cohorts; by PT, neutropenia (6 participants [15.0%]), neutrophil count decreased (5 participants [12.5%]), anemia, asthenia, and lipase increased (3 participants [7.5%] each), and abdominal pain, ascites, blood creatine phosphokinase increased, intestinal obstruction, and upper GI hemorrhage (2 participants [5.0%] each) were reported in more than 1 participant.

A total of 4 participants (10.0%) had at least one maximum Grade 3 or 4 AE that was assessed by the investigator as possibly related to rilvegostomig; the reported events were lipase increased (2 participants [5.0%]), and blood alkaline phosphatase increased, platelet count decreased, and pneumonitis (1 participant [2.5%] each).

Serious Adverse Events

As of the DCO date, SAEs were reported in 11 participants (27.5%) in Substudy 2. By PT, the only reported SAEs occurring in more than 1 participant were intestinal obstruction and upper GI hemorrhage (2 participants [5.0%] each). In 1 participant (2.5%) each, the reported SAEs of platelet count decreased and pneumonitis were assessed by the investigator as possibly related to rilvegostomig.

Adverse Events With Outcome of Death

As of the DCO date, no participants had an AE with outcome of death in both cohorts of Substudy 2.

Adverse Events Leading to Permanent Discontinuation

As of the DCO date, 11 participants (27.5%) in Substudy 2 had AEs leading to permanent discontinuation of study treatment. One participant (2.5%) had an AE (neurotoxicity) leading to permanent discontinuation of study treatment that was assessed by the investigator as possibly related to rilvegostomig.

5.3.2.2.3 Efficacy in GEMINI-Gastric Substudy 2

As of the DCO date (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 (complete response or partial response, or stable disease); none had primary PD. The median (95% CI) PFS was 8.3 (7.0, 9.9) months in response evaluable participants, 7.1 (6.1, 8.8) months in participants with a PD-L1 CPS < 5 , and 11.1 (5.6, NC) months 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.

5.3.2.3 GEMINI-Hepatobiliary (Cohort 2A)

5.3.2.3.1 Exposure in GEMINI-Hepatobiliary (Cohort 2A)

As of the DCO date of 05 July 2025, a total of 30 participants had received rilvegostomig (750 mg Q3W) in combination with gemcitabine and cisplatin in GEMINI-Hepatobiliary (Cohort 2A).

The median duration of exposure to rilvegostomig was 32.00 weeks with a range of 7.0 to 83.7 weeks ([Table 57](#)).

Table 57 **Duration of Rilvegostomig Exposure (GEMINI-Hepatobiliary Cohort 2A; Safety Analysis Set)**

	Rilvegostomig 750 mg Q3W + gemcitabine + cisplatin N = 30
Total treatment duration (weeks)^a	
Mean (SD)	38.80 (22.372)
Median	32.00
Min, Max	7.0, 83.7

^a Total exposure (weeks) of IP = (min (last dose date where dose > 0 mg + 20), date of death, date of DCO) – first dose date + 1) / 7.

max = maximum; min = minimum; N = number of participants per treatment group.

5.3.2.3.2 Safety in GEMINI-Hepatobiliary (Cohort 2A)

Overview of Adverse Events

An overall summary of AEs in participants receiving rilvegostomig in combination with gemcitabine and cisplatin in advanced BTC is presented in [Table 58](#) (as of the DCO date of 05 July 2025). The safety analysis set is defined as all participants who received at least 1 dose of rilvegostomig.

All 30 participants (100%) had at least one AE, and 21 participants (70.0%) had an AE that was considered by the investigator to be possibly related to rilvegostomig treatment. AEs of maximum Grade 3 or 4 were reported in 27 participants (90.0%), with AEs of maximum Grade 3 or 4 assessed by the investigator as possibly related to rilvegostomig in 5 participants (16.7%).

SAEs were reported in 14 participants (46.7%), with SAEs assessed by the investigator as possibly related to rilvegostomig in 3 participants (10.0%). SAEs resulting in death were reported in 2 participants (6.7%), which were both assessed by the investigator as unrelated to rilvegostomig; SAEs led to discontinuation of treatment in 3 participants (10.0%).

Twenty-two participants (73.3%) had AEs leading to dose interruption. AESIs assessed by the investigator as possibly related to rilvegostomig were reported in 15 participants (50.0%).

Table 58 Overall Summary of AEs (GEMINI-Hepatobiliary Cohort 2A; Safety Analysis Set)

Participants with ^a	Rilvegostomig + Gemcitabine + Cisplatin N = 30 n (%)
Any AE	30 (100)
Any AE possibly related to rilvegostomig ^b	21 (70.0)
Any AE of maximum CTCAE Grade 3 or Grade 4	27 (90.0)
Any AE of maximum CTCAE Grade 3 or Grade 4, possibly related to rilvegostomig ^b	5 (16.7)
Any AE leading to discontinuation of any study treatment	6 (20.0)
Any AE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	1 (3.3)
Any AE leading to dose interruption of treatment	22 (73.3)
Any AE leading to dose interruption of treatment, possibly related to rilvegostomig ^b	6 (20.0)
Any SAE ^c	14 (46.7)
Any SAE, possibly related to rilvegostomig ^{b,c}	3 (10.0)
Any SAE with outcome = death	2 (6.7)
Any SAE with outcome = death, possibly related to rilvegostomig ^b	0
Any SAE leading to discontinuation of treatment	3 (10.0)
Any SAE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	1 (3.3)
Any AE of special interest to treatment	18 (60.0)
Any AE of special interest to treatment, possibly related to rilvegostomig ^b	15 (50.0)
Any imAEs	16 (53.3)
Any imAEs, possibly related to rilvegostomig ^b	16 (53.3)

^a Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

^b As assessed by the investigator. Missing responses are counted as related.

^c Seriousness, as assessed by investigator.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). CTCAE = Common Terminology Criteria for Adverse Events Version 5.0; n = number of participants per category; N = number of participants per treatment group.

All Adverse Events

As of the DCO date, all 30 participants (100%) in Cohort 2A had at least one AE, regardless of causality. The most frequently reported AEs ($\geq 30\%$ of participants) were anemia (18 participants [60.0%]), neutrophil count decreased (15 participants [50.0%]), platelet count

decreased (13 participants [43.3%]), pyrexia and white blood cell count decreased (10 participants [33.3%] each), and abdominal pain, nausea, and neutropenia (9 participants [30.0%] each). See [Table 59](#) for all AEs occurring in $\geq 10\%$ participants by PT.

Table 59 AEs Occurring in $\geq 10\%$ of Participants, by Preferred Term
(GEMINI-Hepatobiliary Cohort 2A; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	Rilvegostomig + Gemcitabine + Cisplatin N = 30 n (%)
Participants with any AE	30 (100)
Anaemia	18 (60.0)
Neutrophil count decreased	15 (50.0)
Platelet count decreased	13 (43.3)
Pyrexia	10 (33.3)
White blood cell count decreased	10 (33.3)
Abdominal pain	9 (30.0)
Nausea	9 (30.0)
Neutropenia	9 (30.0)
Alanine aminotransferase increased	7 (23.3)
Vomiting	7 (23.3)
COVID-19	6 (20.0)
Constipation	6 (20.0)
Asthenia	5 (16.7)
Decreased appetite	5 (16.7)
Rash	5 (16.7)
Aspartate aminotransferase increased	4 (13.3)
Cholangitis	4 (13.3)
Diarrhoea	4 (13.3)
Leukopenia	4 (13.3)
Thrombocytopenia	4 (13.3)
Alopecia	3 (10.0)
Arthralgia	3 (10.0)
Dizziness	3 (10.0)
Gamma-glutamyltransferase increased	3 (10.0)
Hypoalbuminaemia	3 (10.0)
Lymphocyte count decreased	3 (10.0)

Table 59 AEs Occurring in $\geq 10\%$ of Participants, by Preferred Term
(GEMINI-Hepatobiliary Cohort 2A; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	Rilvegostomig + Gemcitabine + Cisplatin N = 30 n (%)
Peripheral sensory neuropathy	3 (10.0)
Stomatitis	3 (10.0)

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Treatment-related Adverse Events

As of the DCO date, AEs (any grade) judged by the investigator as being possibly related to rilvegostomig occurred in 21 participants (70.0%) in Cohort 2A. The most frequently reported rilvegostomig-related AEs were ALT increased (6 participants [20.0%]) and rash (4 participants [13.3%]). See [Table 60](#) for rilvegostomig-related AEs by PT occurring in $\geq 5\%$ of participants.

Table 60 Rilvegostomig-related AEs Occurring in $\geq 5\%$ of Participants, by Preferred Term (GEMINI-Hepatobiliary Cohort 2A; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	Rilvegostomig + Gemcitabine + Cisplatin N = 30 n (%)
Participants with any AE possibly related to rilvegostomig ^a	21 (70.0)
Alanine aminotransferase increased	6 (20.0)
Rash	4 (13.3)
Aspartate aminotransferase increased	3 (10.0)
Diarrhoea	3 (10.0)
Platelet count decreased	3 (10.0)
Asthenia	2 (6.7)
Blood alkaline phosphatase increased	2 (6.7)
Constipation	2 (6.7)
Dry mouth	2 (6.7)
Gamma-glutamyltransferase increased	2 (6.7)
Hypothyroidism	2 (6.7)

Table 60 **Rilvegostomig-related AEs Occurring in $\geq 5\%$ of Participants, by Preferred Term (GEMINI-Hepatobiliary Cohort 2A; Safety Analysis Set)**

Preferred Term (MedDRA version 28.0)	Rilvegostomig + Gemcitabine + Cisplatin N = 30 n (%)
Nausea	2 (6.7)
Pneumonitis	2 (6.7)

^a Possibly related to study treatment, as assessed by the investigator. Missing responses are counted as related.

Participants with multiple AEs are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Adverse Events with Maximum Severity Grade 3 or 4

As of the DCO date, 27 participants (90.0%) in Cohort 2A had at least one AE (regardless of causality) that was maximum Grade 3 or 4 in severity. By PT only neutrophil count decreased (13 participants [43.3%]), anemia and neutropenia (9 participants [30.0%] each), platelet count decreased (5 participants [16.7%]), white blood cell count decreased (4 participants [13.3%]), and cholangitis (2 participants [6.7%]) were reported in more than 1 participant.

Five participants (16.7%) had a maximum Grade 3 or 4 AE that was assessed by the investigator as possibly related to rilvegostomig (anemia, blood alkaline phosphatase increased, hepatic function abnormal, lipase increased, and pneumonitis in 1 participant each).

Serious Adverse Events

As of the DCO date, SAEs (regardless of causality) were reported in 14 participants (46.7%) in Cohort 2A. By PT only cholangitis (4 participants [13.3%]), pyrexia (3 participants [10.0%]), and platelet count decreased (2 participants [6.7%]) were reported in more than 1 participant.

Three participants (10.0%) had SAEs that were assessed by the investigator as possibly related to rilvegostomig (hepatic function abnormal, myositis, and pneumonitis in 1 participant each).

Adverse Events With Outcome of Death

As of the DCO date, 2 participants (6.7%) in Cohort 2A had AEs with outcome of death, which were both assessed by the investigator as unrelated to rilvegostomig.

Adverse Events Leading to Permanent Discontinuation

As of the DCO date, 6 participants (20.0%) in Cohort 2A had an AE leading to permanent discontinuation of study treatment. One participant (3.3%) had an AE (hepatic function abnormal) leading to permanent discontinuation of study treatment that was assessed by the investigator as possibly related to rilvegostomig.

5.3.2.3.3 Efficacy in GEMINI-Hepatobiliary (Cohort 2A)

As of the DCO date (04 November 2024), confirmed ORR was 31.0% among 29 evaluable participants and 62.1% participants had stable disease as best overall response. The PFS-6 was 73.0% and the mPFS was 8.3 months (95% CI: 6.7, 9.6) after a median follow-up of 6.9 months (interquartile range: 5.6 to 9.5 months).

5.3.3 Rilvegostomig + Antibody Drug Conjugates

5.3.3.1 TROPION-Lung04 (Cohort 5)

5.3.3.1.1 Exposure in TROPION-Lung04 (Cohort 5)

As of the DCO date of 05 July 2025, 40 participants had received rilvegostomig (750 mg Q3W) in combination with Dato-DXd (6 mg/kg) in TROPION-Lung04 (Cohort 5).

The median duration of exposure to rilvegostomig was 28.43 weeks with a range of 0.3 to 111.0 weeks ([Table 61](#)).

Table 61 Duration of Rilvegostomig Exposure (TROPION-Lung04 Cohort 5; Safety Analysis Set)

	Rilvegostomig 750 mg Q3W + Dato-DXd N = 40
Total treatment duration (weeks)^a	
Mean (SD)	35.28 (26.209)
Median	28.43
Min, Max	0.3, 111.0

^a Total exposure (weeks) of IP = (min (last dose date where dose > 0 mg + 20), date of death, date of DCO) – first dose date + 1) / 7.

max = maximum; min = minimum; N = number of participants per treatment group.

5.3.3.1.2 Safety in TROPION-Lung04 (Cohort 5)

Overview of Adverse Events

An overall summary of AEs in TROPION-Lung04 Cohort 5 (as of the DCO date of 05 July 2025) is presented in [Table 62](#).

All 40 participants (100%) had at least one AE, and 34 participants (85.0%) had an AE that was assessed by the investigator as possibly related to rilvegostomig treatment. AEs of maximum Grade 3 or 4 were reported in 25 participants (62.5%), with AEs of maximum

Grade 3 or 4 assessed by the investigator as possibly related to rilvegostomig in 10 participants (25.0%).

SAEs were reported in 23 participants (57.5%), with SAEs assessed by the investigator as possibly related to rilvegostomig in 6 participants (15.0%). SAEs resulting in death were reported in 7 participants (17.5%), assessed by the investigator as possibly related to rilvegostomig in 1 participant (2.5%). Seventeen participants (42.5%) had an AE leading to discontinuation of any study treatment, with events in 9 participants (22.5%) assessed by the investigator as possibly related to rilvegostomig. Fifteen participants (37.5%) had their treatment interrupted due to an AE that was assessed by the investigator as possibly related to rilvegostomig. AESIs assessed by the investigator as possibly related to rilvegostomig were reported in 30 participants (75.0%).

Table 62 Overall Summary of AEs (TROPION-Lung04 Cohort 5; Safety Analysis Set)

Participants with ^a	Rilvegostomig + Dato-DXd N = 40 n (%)
Any AE	40 (100)
Any AE possibly related to rilvegostomig ^b	34 (85.0)
Any AE of maximum CTCAE Grade 3 or Grade 4	25 (62.5)
Any AE of maximum CTCAE Grade 3 or Grade 4, possibly related to rilvegostomig ^b	10 (25.0)
Any AE leading to discontinuation of any study treatment	17 (42.5)
Any AE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	9 (22.5)
Any AE leading to dose interruption of treatment	25 (62.5)
Any AE leading to dose interruption of treatment, possibly related to rilvegostomig ^b	15 (37.5)
Any SAE ^c	23 (57.5)
Any SAE possibly related to rilvegostomig ^{b,c}	6 (15.0)
Any SAE with outcome = death	7 (17.5)
Any SAE with outcome = death, possibly related to rilvegostomig ^b	1 (2.5)
Any SAE leading to discontinuation of treatment	10 (25.0)
Any SAE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	5 (12.5)
Any AE of special interest to treatment	35 (87.5)
Any AE of special interest to treatment, possibly related to rilvegostomig ^b	30 (75.0)
Any imAE	25 (62.5)
Any imAE, possibly related to rilvegostomig ^b	21 (52.5)

^a Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

^b As assessed by the investigator. Missing responses are counted as related.

^c Seriousness, as assessed by investigator.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
CTCAE = Common Terminology Criteria for Adverse Events Version 5.0; n = number of participants per category; N = number of participants per treatment group.

All Adverse Events

As of the DCO date, all 40 participants (100%) in Cohort 5 had at least one AE, regardless of causality. The most frequently reported AEs ($\geq 32.5\%$ of participants) were stomatitis (22 participants [55.0%]), alopecia and nausea (18 participants [45.0%] each), and rash (13 participants [32.5%]). See [Table 63](#) for all AEs by PT occurring in $\geq 10\%$ of participants.

Table 63 **AEs Occurring in $\geq 10\%$ of Participants, by Preferred Term**
(TROPION-Lung04 Cohort 5; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	Rilvegostomig + Dato-DXd N = 40 n (%)
Participants with any AE	40 (100)
Stomatitis	22 (55.0)
Alopecia	18 (45.0)
Nausea	18 (45.0)
Rash	13 (32.5)
Constipation	12 (30.0)
Decreased appetite	11 (27.5)
Fatigue	11 (27.5)
Pneumonitis	10 (25.0)
Vomiting	10 (25.0)
Amylase increased	9 (22.5)
Dry eye	9 (22.5)
Anaemia	8 (20.0)
Pneumonia	8 (20.0)
Asthenia	7 (17.5)
Pruritus	7 (17.5)
Arthralgia	6 (15.0)
Chills	6 (15.0)
Dysgeusia	6 (15.0)
Hyponatraemia	6 (15.0)
Pyrexia	6 (15.0)
Upper respiratory tract infection	6 (15.0)

Table 63 AEs Occurring in $\geq 10\%$ of Participants, by Preferred Term
(TROPION-Lung04 Cohort 5; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	Rilvegostomig + Dato-DXd N = 40 n (%)
COVID-19	5 (12.5)
Back pain	4 (10.0)
Diarrhoea	4 (10.0)
Dry skin	4 (10.0)
Dysphonia	4 (10.0)
Gamma-glutamyltransferase increased	4 (10.0)
Keratitis	4 (10.0)
Lacrimation increased	4 (10.0)
Oedema peripheral	4 (10.0)
Oropharyngeal pain	4 (10.0)
Weight decreased	4 (10.0)

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Treatment-related Adverse Events

As of the DCO date, AEs (any grade) judged by the investigator as being possibly related to rilvegostomig occurred in 34 participants (85.0%) in Cohort 5. The most frequently reported rilvegostomig-related AEs ($\geq 22.5\%$ of participants) were rash (11 participants [27.5%]), pneumonitis and stomatitis (10 participants [25.0%] each), and alopecia (9 participants [22.5%]). See [Table 64](#) for rilvegostomig-related AEs by PT occurring in $\geq 5\%$ of participants.

Table 64 Rilvegostomig-related AEs Occurring in $\geq 5\%$ of Participants, by Preferred Term (TROPION-Lung04 Cohort 5; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	Rilvegostomig + Dato-DXd N = 40 n (%)
Participants with any AE possibly related to rilvegostomig ^a	34 (85.0)
Rash	11 (27.5)
Pneumonitis	10 (25.0)

Table 64 **Rilvegostomig-related AEs Occurring in $\geq 5\%$ of Participants, by Preferred Term (TROPION-Lung04 Cohort 5; Safety Analysis Set)**

Preferred Term (MedDRA version 28.0)	Rilvegostomig + Dato-DXd N = 40 n (%)
Stomatitis	10 (25.0)
Alopecia	9 (22.5)
Amylase increased	8 (20.0)
Fatigue	8 (20.0)
Nausea	8 (20.0)
Decreased appetite	7 (17.5)
Asthenia	4 (10.0)
Dry eye	4 (10.0)
Dysgeusia	4 (10.0)
Pruritus	4 (10.0)
Anaemia	3 (7.5)
Hypothyroidism	3 (7.5)
Infusion related reaction	3 (7.5)
Pyrexia	3 (7.5)
Vomiting	3 (7.5)
Arthralgia	2 (5.0)
Blood alkaline phosphatase increased	2 (5.0)
Chills	2 (5.0)
Constipation	2 (5.0)
Dry mouth	2 (5.0)
Gamma-glutamyltransferase increased	2 (5.0)
Hyperamylasaemia	2 (5.0)
Interstitial lung disease	2 (5.0)
Lacrimation increased	2 (5.0)
Malaise	2 (5.0)
Skin discolouration	2 (5.0)

^a Possibly related as assessed by investigator. Missing responses are counted as related.

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Adverse Events with Maximum Severity Grade 3 or 4

As of the DCO date, 25 participants (62.5%) in Cohort 5 had at least one AE that was maximum Grade 3 or 4 in severity (regardless of causality). The most frequently reported maximum Grade 3 or 4 AEs ($\geq 10\%$ of participants) were pneumonia and pneumonitis (4 participants [10.0%] each).

Ten participants (25.0%) had at least one maximum Grade 3 or 4 AE that was assessed by the investigator as possibly related to rilvegostomig; the most frequently reported events were pneumonitis (4 participants [10.0%]) and amylase increased and hyperamylasemia (2 participants [5.0%] each).

Serious Adverse Events

As of the DCO date, SAEs were reported in 23 participants (57.5%) in Cohort 5. The most frequently reported SAEs ($\geq 10\%$ of participants) were pneumonia and pneumonitis (5 participants [12.5%] each). Six participants (15.0%) had SAEs that were assessed by the investigator as possibly related to rilvegostomig, with pneumonitis reported in 5 participants (12.5%).

Adverse Events With Outcome of Death

As of the DCO date, 7 participants (17.5%) had AEs with outcome of death in Cohort 5. The AEs with outcome of death were cardiac arrest, death, general physical health deterioration, intestinal perforation, pneumonia, pneumonitis, respiratory failure, and sepsis (1 participant [2.5%] each). One participant [2.5%]) had an AE with outcome of death (pneumonitis) which was judged by the investigator to be possibly related to rilvegostomig treatment.

Adverse Events Leading to Permanent Discontinuation

As of the DCO date, 17 participants (42.5%) in Cohort 5 had an AE leading to permanent discontinuation of any study treatment. The most frequently reported AEs ($\geq 5\%$ of participants) were pneumonitis (8 participants [20.0%]) and ILD (2 participants [5.0%]). In 9 participants (22.5%) the events leading to discontinuation were assessed as being possibly related to rilvegostomig by the investigator (pneumonitis in 8 participants [20.0%] and ILD in 1 participant [2.5%]).

5.3.3.1.3 Efficacy in TROPION-Lung04 (Cohort 5)

Overall, 40 participants (Cohort 5A, n = 20; Cohort 5B, n = 20) had received Dato-DXd + rilvegostomig at DCO (24 October 2024). Median follow-up was 5.60 months (range: 0.1 to 18.3 months).

- Confirmed ORR was 57.7% (95% CI: 40.9, 73.0).

- Disease control rate (defined as patients with CR + PR + stable disease; stable disease includes unconfirmed CR/PR or stable disease ≥ 5 weeks) was 95.0% (95% CI: 83.1, 99.4).

5.3.3.2 TROPION-PanTumor03 (Cohort 6B)

5.3.3.2.1 Exposure in TROPION-PanTumor03 (Cohort 6B)

As of the DCO date of 05 July 2025, 40 participants had received rilvegostomig (750 mg Q3W) in combination with Dato-DXd (6 mg/kg) in TROPION-PanTumor03 (Cohort 6B).

The median duration of exposure to rilvegostomig was 44.43 weeks with a range of 3.0 to 86.0 weeks ([Table 65](#)).

Table 65 Duration of Rilvegostomig Exposure (TROPION-PanTumor03 Cohort 6B; Safety Analysis Set)

	Rilvegostomig 750 mg Q3W + Dato-DXd N = 40
Total treatment duration (weeks)^a	
Mean (SD)	38.85 (21.905)
Median	44.43
Min, Max	3.0, 86.0

^a Total exposure (weeks) of IP = (min (last dose date where dose > 0 mg + 20), date of death, date of DCO) – first dose date + 1) / 7.

max = maximum; min = minimum; N = number of participants per treatment group.

5.3.3.2.2 Safety in TROPION-PanTumor03 (Cohort 6B)

Overview of Adverse Events

An overall summary of AEs in TROPION-PanTumor03 Cohort 6B (as of the DCO date of 05 July 2025) is presented in [Table 66](#).

All 40 participants (100%) had at least one AE, and 33 participants (82.5%) had an AE that was assessed by the investigator as possibly related to rilvegostomig treatment. AEs of maximum Grade 3 or 4 were reported in 14 participants (35.0%), with AEs of maximum Grade 3 or 4 assessed by the investigator as possibly related to rilvegostomig in 8 participants (20.0%).

SAEs were reported in 10 participants (25.0%), with SAEs assessed by the investigator as possibly related to rilvegostomig in 2 participants (5.0%). Two participants (5.0%) experienced AEs that resulted in death with no events being assessed by the investigator as possibly related to rilvegostomig. Three participants (7.5%) had an AE leading to study treatment discontinuation that was assessed by the investigator as possibly related to rilvegostomig, and 13 participants (32.5%) had treatment interruptions due to an AE that was

assessed by the investigator as possibly related to rilvegostomig. AESIs assessed by the investigator as possibly related to rilvegostomig were reported in 24 participants (60.0%).

Table 66 Overall Summary of AEs (TROPION-PanTumor03 Cohort 6B; Safety Analysis Set)

Participants with ^a	Rilvegostomig + Dato-DXd N = 40 n (%)
Any AE	40 (100)
Any AE possibly related to rilvegostomig ^b	33 (82.5)
Any AE of maximum CTCAE Grade 3 or Grade 4	14 (35.0)
Any AE of maximum CTCAE Grade 3 or Grade 4, possibly related to rilvegostomig ^b	8 (20.0)
Any AE leading to discontinuation of any study treatment	7 (17.5)
Any AE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	3 (7.5)
Any AE leading to dose interruption of treatment	20 (50.0)
Any AE leading to dose interruption of treatment, possibly related to rilvegostomig ^b	13 (32.5)
Any SAE ^c	10 (25.0)
Any SAE possibly related to rilvegostomig ^{b,c}	2 (5.0)
Any SAE with outcome = death	2 (5.0)
Any SAE with outcome = death, possibly related to rilvegostomig ^b	0
Any SAE leading to discontinuation of treatment	3 (7.5)
Any SAE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	1 (2.5)
Any AE of special interest to treatment	30 (75.0)
Any AE of special interest to treatment, possibly related to rilvegostomig ^b	24 (60.0)
Any imAE	8 (20.0)
Any imAE, possibly related to rilvegostomig ^b	7 (17.5)

^a Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

^b As assessed by the investigator. Missing responses are counted as related.

^c Seriousness, as assessed by investigator.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). CTCAE = Common Terminology Criteria for Adverse Events Version 5.0; n = number of participants per category; N = number of participants per treatment group.

All Adverse Events

As of the DCO date, all 40 participants (100%) in Cohort 6B had at least one AE, regardless of causality. The most frequently reported AEs were stomatitis (18 participants [45.0%]), nausea (12 participants [30.0%]), and amylase increased, constipation, and decreased appetite

(11 participants [27.5%] each). See [Table 67](#) for all AEs by PT occurring in $\geq 10\%$ of participants.

Table 67 AEs Occurring in $\geq 10\%$ of Participants, by Preferred Term (TROPION-PanTumor03 Cohort 6B; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	Rilvegostomig + Dato-DXd N = 40 n (%)
Participants with any AE	40 (100)
Stomatitis	18 (45.0)
Nausea	12 (30.0)
Amylase increased	11 (27.5)
Constipation	11 (27.5)
Decreased appetite	11 (27.5)
Asthenia	10 (25.0)
Fatigue	10 (25.0)
Alopecia	9 (22.5)
Pruritus	9 (22.5)
Rash	8 (20.0)
Anaemia	7 (17.5)
Dry eye	5 (12.5)
Dry mouth	5 (12.5)
Weight decreased	5 (12.5)
Blood creatinine increased	4 (10.0)

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Treatment-related Adverse Events

As of the DCO date, AEs (any grade) judged by the investigator as being possibly related to rilvegostomig occurred in 33 participants (82.5%) in Cohort 6B. The most frequently reported rilvegostomig-related AEs were asthenia (10 participants [25.0%]), nausea, pruritus, and rash (7 participants [17.5%] each), and fatigue and stomatitis (6 participants [15.0%] each). See [Table 68](#) for rilvegostomig-related AEs by PT occurring in $\geq 5\%$ of participants.

Table 68 Rilvegostomig-related AEs Occurring in $\geq 5\%$ of Participants, by Preferred Term (TROPION-PanTumor03 Cohort 6B; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	Rilvegostomig + Dato-DXd N = 40 n (%)
Participants with any AE possibly related to rilvegostomig ^a	33 (82.5)
Asthenia	10 (25.0)
Nausea	7 (17.5)
Pruritus	7 (17.5)
Rash	7 (17.5)
Fatigue	6 (15.0)
Stomatitis	6 (15.0)
Decreased appetite	5 (12.5)
Amylase increased	4 (10.0)
Anaemia	4 (10.0)
Constipation	4 (10.0)
Alopecia	3 (7.5)
Aspartate aminotransferase increased	3 (7.5)
Urticaria	3 (7.5)
Diarrhoea	2 (5.0)
Hypoalbuminaemia	2 (5.0)
Hypothyroidism	2 (5.0)
Neutrophil count decreased	2 (5.0)
Pneumonitis	2 (5.0)

^a Possibly related as assessed by investigator. Missing responses are counted as related.

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Adverse Events with Maximum Severity Grade 3 or 4

As of the DCO date, 14 participants (35.0%) in Cohort 6B had at least one AE that was maximum Grade 3 or 4 in severity (regardless of causality). The most frequently reported maximum Grade 3 or 4 AE ($\geq 10\%$ of participants) was amylase increased (6 participants [15.0%]).

Eight participants (20.0%) had at least one maximum Grade 3 or 4 AE that was assessed by the investigator as possibly related to rilvegostomig; the reported events were amylase increased (3 participants [7.5%]) and anemia, decreased appetite, neutropenia, neutrophil count decreased, and pneumonitis (1 participant [2.5%] each).

Serious Adverse Events

As of the DCO date, SAEs were reported in 10 participants (25.0%) in Cohort 6B. No SAEs were reported for more than 1 participant. In 2 participants (5.0%), the reported SAEs of decreased appetite and pneumonitis were assessed by the investigator as possibly related to rilvegostomig.

Adverse Events With Outcome of Death

As of the DCO date, 2 participants (5.0%) in Cohort 6B had AEs with outcome of death in Cohort 6B. The AEs with outcome of death were pneumonia and sepsis (1 participant [2.5%] each). No events were judged by the investigator to be possibly related to rilvegostomig treatment.

Adverse Events Leading to Permanent Discontinuation

As of the DCO date, 7 participants (17.5%) in Cohort 6B had an AE leading to permanent discontinuation of treatment. The reported AEs were interstitial lung disease (2 participants [5.0%]) and asthenia, myositis, pneumonia, pneumonitis, and sepsis (1 participant [2.5%] each). AEs reported in 3 participants (7.5%) were considered to be possibly related to rilvegostomig by the investigator (asthenia, myositis, and pneumonitis in 1 participant [2.5%] each).

5.3.3.2.3 Efficacy in TROPION-PanTumor03 (Cohort 6B)

As of 17 February 2025 a total of 40 participants (cisplatin ineligible n = 22; platinum treated n = 18) had received Dato-DXd + rilvegostomig. Median follow-up in cisplatin ineligible participants was 6.7 months (range: 2.6 to 15.3 months) and in platinum treated participants was 6.9 months (range: 4.1 to 13.6 months).

- Confirmed ORR in cisplatin ineligible participants was 68.2% (95% CI: 45.1, 86.1) and in platinum treated participants was 33.3% (95% CI: 13.3, 59.0).
- Median DoR was not calculable as the data were immature at the DCO.
- Disease control rate (defined as patients with CR + PR + stable disease; stable disease includes unconfirmed CR/PR or stable disease $\geq$ 5 weeks) was 95.5% (95% CI: 83.4, 99.5) for cisplatin ineligible participants and 83.3% (95% CI: 66.6, 93.7) for platinum treated participants.

5.3.3.3 DESTINY-Gastric03 (Arms 4A and 4B)

5.3.3.3.1 Exposure in DESTINY-Gastric03 (Arms 4A and 4B)

As of the DCO date of 05 July 2025, a total of 60 participants had received rilvegostomig (750 mg Q3W) in combination with T-DXd (5.4 mg/kg) and fluoropyrimidine in DESTINY-Gastric03 across 2 arms: Arm 4A, participants with HER2-positive GC (28 participants) and Arm 4B, participants with HER2-low GC (32 participants).

The median duration of exposure to rilvegostomig was 16.57 weeks with a range of 3.0 to 45.1 weeks ([Table 69](#)).

Table 69 Duration of Rilvegostomig Exposure (DESTINY-Gastric03 Arms 4A and 4B; Safety Analysis Set)

	Rilvegostomig 750 mg Q3W + T-DXd + fluoropyrimidine N = 60
Total treatment duration (weeks) ^a	
Mean (SD)	17.44 (9.136)
Median	16.57
Min, Max	3.0, 45.1

^a Total exposure (weeks) of IP = (min (last dose date where dose > 0 mg + 20), date of death, date of DCO) – first dose date + 1) / 7.

max = maximum; min = minimum; N = number of participants per treatment group.

5.3.3.3.2 Safety in DESTINY-Gastric03 (Arms 4A and 4B)

Overview of Adverse Events

An overall summary of AEs in DESTINY-Gastric03 across Arms 4A and 4B (as of the DCO date of 05 July 2025) is presented in [Table 70](#).

Across the 2 arms, 54 participants (90.0%) had at least one AE, and 33 participants (55.0%) had an AE that was assessed by the investigator as possibly related to rilvegostomig treatment. AEs of maximum Grade 3 or 4 were reported in 20 participants (33.3%), with AEs of maximum Grade 3 or 4 assessed by the investigator as possibly related to rilvegostomig in 9 participants (15.0%).

SAEs were reported in 15 participants (25.0%), with SAEs assessed by the investigator as possibly related to rilvegostomig in 5 participants (8.3%), and resulting in death in 1 participant (1.7%; this death was not related to rilvegostomig). Three participants (5.0%) had an AE leading to study treatment discontinuation that was assessed by the investigator as possibly related to rilvegostomig, and in 7 participants (11.7%) treatment dosing was interrupted due to an AE that was assessed by the investigator as possibly related to rilvegostomig. AESIs assessed by the investigator as possibly related to rilvegostomig were reported in 21 participants (35.0%).

Table 70 Overall Summary of AEs (DESTINY-Gastric03 Arms 4A and 4B; Safety Analysis Set)

Participants with ^a	Rilvegostomig + T-DXd + fluoropyrimidine N = 60 n (%)
Any AE	54 (90.0)
Any AE possibly related to rilvegostomig ^b	33 (55.0)
Any AE of maximum CTCAE Grade 3 or Grade 4	20 (33.3)
Any AE of maximum CTCAE Grade 3 or Grade 4, possibly related to rilvegostomig ^b	9 (15.0)
Any AE leading to discontinuation of any study treatment	5 (8.3)
Any AE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	3 (5.0)
Any AE leading to dose interruption of treatment	22 (36.7)
Any AE leading to dose interruption of treatment, possibly related to rilvegostomig ^b	7 (11.7)
Any SAE ^c	15 (25.0)
Any SAE possibly related to rilvegostomig ^{b,c}	5 (8.3)
Any SAE with outcome = death	1 (1.7)
Any SAE with outcome = death, possibly related to rilvegostomig ^b	0
Any SAE leading to discontinuation of treatment	1 (1.7)
Any SAE leading to discontinuation of treatment, possibly related to rilvegostomig ^b	0
Any AE of special interest to treatment	26 (43.3)
Any AE of special interest to treatment, possibly related to rilvegostomig ^b	21 (35.0)
Any imAE	7 (11.7)
Any imAE, possibly related to rilvegostomig ^b	7 (11.7)

^a Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

^b As assessed by the investigator. Missing responses are counted as related.

^c Seriousness, as assessed by investigator.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). CTCAE = Common Terminology Criteria for Adverse Events Version 5.0; n = number of participants per category; N = number of participants per treatment group.

All Adverse Events

As of the DCO date, 54 participants (90.0%) across both arms had at least one AE, regardless of causality. The most frequently reported AEs were nausea (30 participants [50.0%]), anemia (21 participants [35.0%]), and diarrhea (19 participants [31.7%]). See [Table 71](#) for all AEs by PT occurring in $\geq 10\%$ of participants.

Table 71 **AEs Occurring in $\geq 10\%$ of Participants, by Preferred Term**
(DESTINY-Gastric03 Arms 4A and 4B; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	Rilvegostomig + T-DXd + fluoropyrimidine N = 60 n (%)
Participants with any AE	54 (90.0)
Nausea	30 (50.0)
Anaemia	21 (35.0)
Diarrhoea	19 (31.7)
Decreased appetite	16 (26.7)
Fatigue	13 (21.7)
Neutrophil count decreased	12 (20.0)
Vomiting	12 (20.0)
Palmar-plantar erythrodysaesthesia syndrome	10 (16.7)
Stomatitis	10 (16.7)
Aspartate aminotransferase increased	9 (15.0)
Constipation	9 (15.0)
Weight decreased	7 (11.7)
Alanine aminotransferase increased	6 (10.0)
Asthenia	6 (10.0)
Dysgeusia	6 (10.0)
Hypokalaemia	6 (10.0)

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Treatment-related Adverse Events

As of the DCO date, AEs (any grade) judged by the investigator as being possibly related to rilvegostomig occurred in 33 participants (55.0%) across both arms. The most frequently reported rilvegostomig-related AEs were nausea (13 participants [21.7%]), diarrhea (8 participants [13.3%]), and AST increased and decreased appetite (7 participants [11.7%] each) ([Table 72](#)).

Table 72 Rilvegostomig-related AEs Occurring in $\geq 5\%$ of Participants, by Preferred Term (DESTINY-Gastric03 Arms 4A and 4B; Safety Analysis Set)

Preferred Term (MedDRA version 28.0)	Rilvegostomig + T-DXd + fluoropyrimidine N = 60 n (%)
Participants with any AE possibly related to rilvegostomig ^a	33 (55.0)
Nausea	13 (21.7)
Diarrhoea	8 (13.3)
Aspartate aminotransferase increased	7 (11.7)
Decreased appetite	7 (11.7)
Anaemia	6 (10.0)
Fatigue	6 (10.0)
Alanine aminotransferase increased	5 (8.3)
Vomiting	5 (8.3)
Asthenia	4 (6.7)
Dyspepsia	4 (6.7)
Stomatitis	4 (6.7)
Weight decreased	4 (6.7)
Blood alkaline phosphatase increased	3 (5.0)
Constipation	3 (5.0)
Dry skin	3 (5.0)
Hiccups	3 (5.0)
Hypocalcaemia	3 (5.0)
Hypokalaemia	3 (5.0)
Hypothyroidism	3 (5.0)

^a Possibly related as assessed by investigator. Missing responses are counted as related.

Participants with multiple occurrences are counted once for each Preferred Term.

Table is sorted by decreasing frequency of Preferred Term, then alphabetically.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants per category; N = number of participants per treatment group.

Adverse Events with Maximum Severity Grade 3 or 4

As of the DCO date, 20 participants (33.3%) across both arms had at least one AE that was maximum Grade 3 or 4 in severity (regardless of causality). The most frequently reported maximum Grade 3 or 4 AEs ($\geq 5\%$ of participants) were neutrophil count decreased (5 participants [8.3%]) and decreased appetite (3 participants [5.0%]).

Nine participants (15.0%) had at least one maximum Grade 3 or 4 AE that was assessed by the investigator as possibly related to rilvegostomig; the only event reported in more than 1 participant was febrile neutropenia (2 participants [3.3%]).

Serious Adverse Events

As of the DCO date, SAEs were reported in 15 participants (25.0%) across both arms. The most frequently reported SAEs were decreased appetite, febrile neutropenia, and upper GI hemorrhage (2 participants [3.3%] each). In 5 participants (8.3%), the reported SAEs of febrile neutropenia (2 participants [3.3%]) and blood alkaline phosphatase increased, hypokalemia, septic shock, and troponin I increased (1 participant [1.7%] each) were assessed by the investigator as possibly related to rilvegostomig.

Adverse Events With Outcome of Death

As of the DCO date, 1 participant (1.7%) had an AE of respiratory failure with outcome of death across Arms 4A and 4B. The event was not judged by the investigator to be possibly related to rilvegostomig treatment.

Adverse Events Leading to Permanent Discontinuation

As of the DCO date, 5 participants (8.3%) across both arms had an AE leading to permanent discontinuation of treatment. The reported AEs were ALT increased, AST increased, ILD, malaise, pneumonia, and respiratory failure (1 participant [1.7%] each). Four events (ALT increased, AST increased, ILD, and pneumonia in 1 participant [1.7%] each) were considered to be possibly related to rilvegostomig by the investigator.

5.4 Marketing Experiences

Rilvegostomig has not been marketed or approved for clinical use by any country.

5.5 Emerging Safety Profile

This section includes ADRs from the rilvegostomig clinical development program. ADRs are events determined by the Sponsor to have a reasonable possibility of a causal relationship with rilvegostomig. Note, the data presented in this section includes all participants who received at least 1 dose of 750 mg rilvegostomig as monotherapy (studies include ARTEMIDE-01 and MAGELLAN). [Table 73](#) details the incidence of ADRs in the pooled monotherapy safety dataset. The frequencies of ADRs were calculated based on all observed events (irrespective of causality).

Table 73 Frequency of ADRs by Severity Grade and CIOMS Frequency Indicator Classification for the Rilvegostomig Monotherapy Pool (Safety Analysis Set)

MedDRA SOC	ADR PT	CIOMS frequency indicator ^a / Overall frequency All CTC Grades	Number of participants exposed (N = 142)	
			All CTCAE grades n (%)	CTCAE Grade 3 + 4 n (%)
Gastrointestinal disorders	Colitis	Uncommon	1 (0.7)	1 (0.7)
	Diarrhoea	Common	14 (9.9)	3 (2.1)
Hepatobiliary disorders	Hepatitis acute	Uncommon	1 (0.7)	1 (0.7)
	Immune-mediated hepatitis	Uncommon	1 (0.7)	1 (0.7)
Injury, poisoning and procedural complications	Infusion related reaction	Common	7 (4.9)	1 (0.7)
Investigations	Alanine aminotransferase increased	Very common	16 (11.3)	3 (2.1)
	Aspartate aminotransferase increased	Very common	19 (13.4)	4 (2.8)
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease	Uncommon	1 (0.7)	0
	Pneumonitis	Common	4 (2.8)	1 (0.7)
Skin and subcutaneous tissue disorders	Rash	Very common	18 (12.7)	1 (0.7)
	Rash maculo-papular	Common	4 (2.8)	0

^a CIOMS III convention and is defined as: (1) very common ($> 1/10$); (2) common ($\geq 1/100$ to $< 1/10$); (3) uncommon ($> 1/1,000$ to $< 1/100$); (4) rare ($> 1/10,000$ to $< 1/1,000$); (5) very rare ($< 1/10,000$); and (6) NR (cannot be estimated from available data).

This table includes events for rilvegostomig 750 mg from the ARTEMIDE-01 and MAGELLAN studies. Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). MedDRA version 28.0.

CIOMS = Council for International Organizations of Medical Sciences; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants who have experienced the ADR; N = total number of participants; NR = not reported; PT = Preferred Term; SOC = System Organ Class.

5.6 Summary of Risks

This section includes identified risks for rilvegostomig and potential risks related to the mechanism of action of rilvegostomig and related to mAb therapeutics in general.

The frequencies presented in this section for identified risks are based on the rilvegostomig monotherapy pool.

The following risks can be mitigated through close monitoring, early detection, and/or prompt treatment with corticosteroids, immunosuppressants, and/or endocrine therapy. Toxicity Management Guidelines have been prepared by the Sponsor to assist the investigator in the exercise of their clinical judgment in treating imAEs and AEs considered causally related to the study drug/study regimen by the reporting investigator.

5.6.1 Identified Risks for Rilvegostomig Monotherapy

5.6.1.1 Infusion-related Reactions

Administration of checkpoint inhibitors has been associated with infusion reactions that may present with signs and symptoms of chest tightness, cough, wheezing, rigors, flushing, headache, myalgia, back pain, tongue swelling, dizziness, rash, pruritus, fever, dyspnea, angioedema, tachycardia, hypotension or hypertension, and, rarely, anaphylaxis. The onset of reactions typically occurs within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. ([Brahmer et al 2021](#), [Lenz 2007](#)).

In the rilvegostomig monotherapy population (N = 142), IRRs have been reported in 4.9% of participants. One participant (0.7%) experienced a Grade 3 event. The majority of events occurred with the second or higher dose of rilvegostomig. There were no fatal events of IRR with rilvegostomig and no events that resulted in permanent discontinuation of therapy. Slower infusion rates and premedication with antihistamines and acetaminophen, with or without steroids, can reduce the incidence of infusion reactions.

Patients should be monitored closely for early signs and symptoms of IRRs such as changes in blood pressure, fever, chills, rash, flushing, itching, shortness of breath, chest tightness, hypotension, or back pain. Patients should be educated on the signs and symptoms of IRRs and instructed to immediately report any new symptoms during and within 24 hours of each infusion.

5.6.1.2 Rash

Dermatological toxicities are one of the most common immune-mediated toxicities associated with the use of immune CPIs. Immune-mediated rash is generally mild and presents as mild local or diffuse maculo-papular, erythematous rash on the trunk or extremities, which may be accompanied by pruritus, alopecia, and vitiligo, suggestive of inflammatory response to melanocytes ([Lacouture et al 2014](#)). In rare cases, severe dermatitis has been reported to manifest as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or hemorrhagic manifestations ([Kaehler et al 2010](#), [Tarhini 2013](#)), although this has not been observed so far with the administration of rilvegostomig.

In the rilvegostomig monotherapy population (N = 142), AESIs of rash and rash maculo-papular have been reported in 12.7% and 2.8% of participants, respectively. Two participants (1.4%) experienced Grade 3 rashes. There were no Grade 4 or fatal events reported in the rilvegostomig-treated population and none of the events resulted in discontinuation of rilvegostomig.

Patients should have their skin inspected at every clinic visit for the development of new skin eruptions and be monitored for new onset itching, burning, soreness, pain, peeling, blisters, or changes in skin sensation.

5.6.1.3 Pneumonitis/ILD

Presentations of pneumonitis can range from asymptomatic lung infiltrates to those that mimic severe bacterial pneumonia ([Tepley and Lipson 2014](#)). Radiologic features of ILD may include ground-glass opacities, consolidations, or bronchiectasis with a pattern of organizing pneumonia ([Delaunay et al 2017](#)). Pneumonitis or ILD should be considered early when patients present with new onset or worsening of respiratory symptoms such as dyspnea or cough.

In the rilvegostomig monotherapy population (N = 142), AESIs of ILD and pneumonitis have been reported in 0.7% and 2.8% of participants, respectively. One participant (0.7%) experience a Grade 3 pneumonitis event. There were no Grade 4 or fatal events. One participant (0.7%) experienced a pneumonitis event that resulted in discontinuation of rilvegostomig.

Patients should be monitored for signs (eg, tachypnea) and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough), and evaluated with imaging and pulmonary function tests, including other diagnostic procedures. Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (eg, infection, progressive disease).

5.6.1.4 Hepatic Events

Immune-mediated hepatitis/hepatic toxicity is the inflammation of the liver. Hepatic AEs induced by PD-1/PD-L1 inhibitors commonly present as asymptomatic increase of AST and ALT, rarely total bilirubin. A proportion of patients may present with fatigue, fever, and radiologic appearances including hepatomegaly, periportal lymphadenopathy, and periportal edema ([Zhang et al 2016](#)).

Hepatitis, ALT increased, and AST increased are ADRs for rilvegostomig monotherapy. In the rilvegostomig monotherapy pooled dataset (N = 142), hepatitis (immune-mediated hepatitis and hepatitis acute) was reported at a frequency of 1.4% and ALT increased and AST increased were reported at a frequency of 11.3% and 13.4%, respectively. Hepatitis (immune-mediated hepatitis and hepatitis acute) events of maximum Grade 3 or 4 occurred in

2 participants (1.4%); no participants had a fatal event. Maximum Grade 3 or 4 ALT increased and AST increased were reported in 3 participants (2.1%) and 4 participants (2.8%), respectively; no participants had a fatal event. Rilvegostomig was discontinued in both participants with hepatitis.

Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and alternative etiologies should be ruled out (eg, viral hepatitis, disease progression, cholestatic drug-induced liver injury, concomitant medications, alcohol use, autoimmune hepatitis related to autoantibodies, portal vein thrombosis, Wilson's disease, etc).

5.6.1.5 Diarrhea/Colitis

Immune-mediated diarrhea and colitis are AEs that can develop in patients treated with immune checkpoint inhibitors, reflecting inflammation of the GI tract triggered by immune system activation. These conditions typically present with increased stool frequency, abdominal pain, and, in severe cases, rectal bleeding. Other symptoms may include mucus in stools, fever, vomiting, and nausea. Symptoms most often begin within the first few weeks to months of therapy ([Zoghbi et al 2024](#)).

In the rilvegostomig monotherapy pooled dataset (N = 142), diarrhea was reported at a frequency of 9.9% (14 participants). Approximately 50% of these events were Grade 1 in severity. Maximum Grade 3 or 4 events of diarrhea were reported in 3 participants (2.1%); no participants had a fatal event of diarrhea. Colitis was reported at a frequency of 0.7% (1 participant) and was Grade 3. No participants had a Grade 4 or fatal event of colitis. None of the diarrhea or colitis events resulted in discontinuation of rilvegostomig.

Patients should be monitored for GI signs and symptoms that may be indicative of diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or bowel perforation (such as sepsis, peritoneal signs, and ileus). Investigations should be performed upon presentation of diarrhea or colitis to exclude infectious or other alternate etiologies. Consider further evaluation with imaging study with contrast or lower GI endoscopy/sigmoidoscopy, if clinically appropriate and consult GI specialist for consideration of further work-up.

5.6.2 Potential Risks Based on Mechanism of Action

Checkpoint blockade of TIGIT and PD-1 predominantly inhibits their negative regulatory mechanism and subsequently invigorates T lymphocytes to unleash antitumor T-cell responses (ie, cytotoxicity, proliferation, and cytokine secretion). Based on this mechanism and the identified risks of the marketed PD-1 blocking antibodies nivolumab (OPDIVO™), pembrolizumab (KEYTRUDA™), cemiplimab (LIBTAYO™), and dostarlimab-gxly (JEMPERLI™), imAEs are potential risks of rilvegostomig.

5.6.3 Potential Risks Based on Clinical Data with Other Immune Checkpoint Inhibitors

The potential risks described are based on the clinical experience with marketed antibodies directed against PD-1 used as monotherapy or in combination therapy. These risks are associated with imAEs which can affect any organ system but are most frequently observed in the skin, GI tract, lung, endocrine, musculoskeletal, and other organ systems. ImAEs, excluding IRRs, hypersensitivity, or anaphylactic reactions, are caused by immune system reactivity or dysregulation that resembles autoimmune disease. ImAEs require treatment with corticosteroids, other immunosuppressants, or endocrine therapy. ImAEs are potential risks of rilvegostomig and are considered AESIs which are defined as events that are of particular scientific or medical importance to the Sponsor's product or program, and for which ongoing monitoring and rapid communication by the investigator to the Sponsor is appropriate.

Known imAEs with PD-1 inhibitors include but are not limited to:

- GI disorders: including intestinal perforation and ileus
- Endocrinopathies: hypo-/hyperthyroidism; hypophysitis; adrenal insufficiency; Type 1 diabetes mellitus
- Renal disorders: nephritis; elevation of blood creatinine
- Cardiac disorders: myocarditis
- 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/arthritis, Guillain Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, aplastic anemia, sarcoidosis.

Abnormal investigations: changes in laboratory parameters are frequently observed in patients treated with antibodies directed against PD-1, and include elevation of amylase, lipase; increased triglycerides and cholesterol; hyperkalemia; hyponatremia. Abnormal investigations are considered a potential risk for rilvegostomig.

5.6.4 Potential Risks Based on Nonclinical Data

All therapeutic proteins can be potentially immunogenic. The formation of ADA can pose a risk to the patient and impact on the antibody's efficacy. Therapeutic antibodies bound to cell surface protein targets may attract circulating ADA leading to formation of ICs on cell membranes in tissues. The ICs activate complement and subsequently lead to a Type III allergic reaction (ICD). ADA bound to drug in circulation gives rise to circulating ICs. ICs can lead to activation of the complement system and FcγRs which then trigger an inflammatory reaction. Adverse reactions in patients can range from mild to severe

hypersensitivity reactions which can occur within minutes to hours after infusion, depending on the type of allergic reaction (Type I, II and III have all been described for ADA-IC reactions) ([Davda et al 2019](#)).

Based on the toxicology data presented above, immunogenicity (ADA formation) has been identified as a potential risk for rilvegostomig. However, immunogenicity in animal models is not predictive of immunogenicity in humans, but data from such models may reveal potential antibody related toxicities that could be monitored in clinical studies. In cynomolgus monkeys all but one rilvegostomig dosed animals (n = 43 of 44 [98%]) showed ADA formation with some (n = 9) affecting the PK of rilvegostomig.

5.6.5 Potential Risks Related to TIGIT and PD-1 Inhibition Based on Literature Review

Cytokine release syndrome

Cytokine release syndrome is a rare systemic inflammatory response that can be triggered by antibody-based therapies including CPIs ([Ceschi et al 2020](#), [Rotz et al 2017](#)). CRS can present with a variety of symptoms ranging from mild, flu-like symptoms to severe life-threatening manifestations of the over-activated inflammatory response. Mild symptoms of CRS can usually be treated with nonsteroidal anti-inflammatory drugs. More severe cases are characterized by hypotension as well as high fever and can progress to an uncontrolled systemic inflammatory response and circulatory shock requiring vasopressors. Laboratory abnormalities that are common in patients with CRS include cytopenias, elevated creatinine and liver enzymes, abnormal coagulation parameters, and high C-reactive protein. As of the DCO date, CRS has not been observed in the rilvegostomig monotherapy population but is considered a potential risk.

Embryo-fetal toxicity

Several literature reports indicate a role for both TIGIT and PD-1 in maintaining immune tolerance to the fetus during pregnancy ([Fu et al 2020](#), [Zhang et al 2015](#)). Humanized IgG1 can cross the placenta. Embryo-fetal toxicity is therefore considered a potential risk of rilvegostomig. Female study participants of reproductive potential need to be advised of the potential risk to the fetus, and use of effective contraception during treatment with rilvegostomig. The same applies for male study participants with a partner of reproductive potential.

Complications of allogeneic HSCT: Graft-versus-host-disease

The administration of immune-activating antibodies like immune CPIs carries the risk of leading or aggravating graft-versus-host disease in patients who underwent an allogeneic stem cell transplant (or who undergo it after immune CPI therapy) ([Ijaz et al 2019](#)). Complications

of allogeneic HSCT is considered a potential risk at this time, and individuals who underwent allogeneic HSCT are excluded from study participation.

Rejection of transplanted organs

Due to the immune-activating mechanism of action, graft rejection is a known risk in solid organ transplant recipients treated with CPIs (Fisher et al 2020). Rejection of transplanted organs is considered a potential risk at this time, and individuals with an organ transplant are excluded from study participation.

5.6.6 Risks Common to Any Biologic

5.6.6.1 Potential Risks

Hypersensitivity reactions including severe allergy and anaphylaxis

As with the administration of any foreign protein, severe allergic reactions to rilvegostomig are possible. Patients affected by such severe reactions may experience symptoms including paresthesia, hypotension, laryngeal edema, mental status changes, facial or pharyngeal angioedema, airway obstruction, bronchospasm, urticaria and pruritus, and kidney failure. Medication and medical equipment to treat anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis and anaphylactic shock. The study site must have immediate access to emergency resuscitation teams and equipment. In addition, the site must have the ability to admit participants to an intensive care unit if necessary. Hypersensitivity reactions are considered to be potential risks of rilvegostomig.

5.6.7 Potential Risks Associated with Immune Reactivity

The administration of any recombinant protein has the potential to induce local and systemic immunologic responses to the product. It is possible that rilvegostomig is immunogenic in humans, and that ADA develop in study participants. The occurrence of such ADA could result in ICD with manifestations such as arthralgias, serum sickness, abdominal pain, and vasculitis, or altered rilvegostomig exposure levels. Participants will be monitored via laboratory analyses for the development of ADA and monitored clinically during treatment with rilvegostomig.

5.6.8 Summary of Risks for Rilvegostomig

IRRs, rash, pneumonitis/ILD, hepatic events, and diarrhea/colitis are identified risks for rilvegostomig.

ImAEs are considered potential risks.

Other potential risks are abnormal investigations, CRS, embryo-fetal toxicity, complications of allogeneic HSCT, rejection of transplanted organs, hypersensitivity reactions, and ICD.

5.7 Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions

This section acts as the RSI and presents those serious adverse reactions including laboratory abnormalities that are to be regarded as expected for safety reporting purposes. The information within the RSI does not present a comprehensive overview of the safety profile of rilvegostomig. Please refer to Section 5.5 “Emerging Safety Profile,” Section 5.6 “Summary of Risks,” and Section 6 “Summary of Data and Guidance for the Investigators” for the safety profile of rilvegostomig.

All fatal and life-threatening SARs are considered unexpected for SUSAR reporting purposes. The overall frequency of SARs was calculated based on reported events that were serious, assessed by the investigator as causally related to rilvegostomig and reported in at least 2 patients.

5.7.1 Rilvegostomig Monotherapy

For rilvegostomig monotherapy, the following SARs are considered expected by the sponsor for the purpose of expedited reporting and identification of SUSARs in the “cumulative summary tabulation of serious adverse reactions” in the Annual Safety Report for rilvegostomig (Table 74).

Table 74 SARs for the Rilvegostomig 750 mg Pool Considered Expected for Safety Reporting Purposes and Considered Causally Related (Safety Analysis Set)

MedDRA SOC	ADR PT	Number of participants exposed (N = 142)		
		Suspected SARs n (%)	Occurrence of life-threatening suspected SARs n (%)	Occurrence of fatal suspected SARs n (%)
Gastrointestinal disorders	Diarrhoea	2 (1.4)	0	0
Hepatobiliary disorders	Hepatitis ^a	2 (1.4)	0	0

^a Includes hepatitis acute and immune-mediated hepatitis.

Only participants exposed to rilvegostomig 750 mg are included.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 (+ 7 days) days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). MedDRA version 28.0.

MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants who have experienced the serious adverse reaction; N = total number of participants; PT = Preferred Term; SOC = System Organ Class.

5.7.2 Rilvegostomig Combination Therapy

There are currently no expected SARs that are unique to any combination therapy with rilvegostomig, and therefore, regulatory safety reporting is based on the RSI for each of the monotherapy components.

6 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATORS

Table 75 Summary of Rilvegostomig Data and Guidance for Investigator

Indications and usage	Anticancer therapy in solid tumors.
Dosage and administration	Intravenous administration over 60 minutes (up to a total of 90 minutes). Information for proper handling and preparation of rilvegostomig is provided in the clinical protocols.
Dosage forms and strengths	Intravenous rilvegostomig is supplied as a sterile concentrate for solution for infusion. Subcutaneous rilvegostomig is supplied as a sterile solution for injection. For both forms, each vial contains 750 mg (label claim) of active IP.
Description	Rilvegostomig is a monovalent, bispecific, humanized, IgG1 mAb with an engineered Fc domain (TM [L234F/L235E/P331S]) to reduce Fc-mediated effector function. Rilvegostomig specifically binds to and inhibits human TIGIT and PD-1. TIGIT and PD-1 are part of a complex system of cell surface receptors that, upon binding to their cognate ligands (ie, CD155 and PD-L1, respectively), negatively regulate T-cell activity. Dual blockade of TIGIT and PD-1 by rilvegostomig is expected to restore antitumor activity of dysfunctional T cells and NK cells.
Precautions and/or special monitoring	Precautions/special monitoring for participants receiving rilvegostomig: • Monitor for the emergence of known and unknown imAEs. Rilvegostomig should not be administered to: • Participants with a known history of allergy or reaction to any component of rilvegostomig formulation. Relevant inclusion/exclusion criteria, as well as management strategies are listed in the clinical study protocol.
Potential risks	• ImAEs • Abnormal investigations • Cytokine release syndrome • Embryo-fetal toxicity • Complications of allogeneic HSCT • Rejection of transplanted organs • Hypersensitivity reactions • ICD

Table 75 Summary of Rilvegostomig Data and Guidance for Investigator

Identified risks ^a	• IRRs • Rash • Pneumonitis/ILD • Hepatic events • Diarrhea/colitis
Observed adverse events	As of the DCO date of 05 July 2025, a total of 343 of 357 participants (96.1%) who received rilvegostomig 750 mg Q3W across the rilvegostomig program had at least one AE, regardless of causality, including: Rilvegostomig Monotherapy • 133 participants (95.0%) treated with 750 mg rilvegostomig Q3W in the CPI-experienced and CPI-naïve cohorts (Parts A3, B, C, D1, and E) in ARTEMIDE-01. The most frequently reported AEs in these participants, regardless of causality, were anemia (25 participants [17.9%]), and constipation and decreased appetite (23 participants [16.4%] each). • 2 participants (100%) treated with 750 mg rilvegostomig Q3W in MAGELLAN Cohort A5. The only AE reported in more than 1 participant, regardless of causality, was dysuria (2 participants [100%]). Rilvegostomig + Chemotherapy • 4 participants (80.0%) treated with 750 mg rilvegostomig Q3W + chemotherapy in MAGELLAN Cohort B5. The most frequently reported AEs in these participants, regardless of causality, were constipation and nausea (2 participants [40.0%] each); all other AEs reported in only 1 participant. • 40 participants (100%) treated with 750 mg rilvegostomig Q3W + XELOX or FOLFOX in GEMINI-Gastric Substudy 2. The most frequently reported AEs in these participants, regardless of causality, were nausea (25 participants [62.5%]), neutrophil count decreased (20 participants [50.0%]), decreased appetite (17 participants [42.5%]), asthenia (15 participants [37.5%]), and anemia, lipase increased, and platelet count decreased (14 participants [35.0%] each). • 30 participants (100%) treated with 750 mg rilvegostomig Q3W + gemcitabine and cisplatin in GEMINI-Hepatobiliary Cohort 2A. The most frequently reported AEs in these participants, regardless of causality, were anemia (18 participants [60.0%]), neutrophil count decreased (15 participants [50.0%]), platelet count decreased (13 participants [43.3%]), pyrexia and white blood cell count decreased (10 participants [33.3%] each), and abdominal pain, nausea, and neutropenia (9 participants [30.0%] each). Rilvegostomig + ADCs • 40 participants (100%) treated with 750 mg rilvegostomig Q3W + Dato-DXd in TROPION-Lung04 Cohort 5. The most frequently reported AEs in these participants, regardless of causality, were stomatitis (22 participants [55.0%]), alopecia and nausea (18 participants [45.0%] each), and rash (13 participants [32.5%]). • 40 participants (100%) treated with 750 mg rilvegostomig Q3W + Dato-DXd in TROPION-PanTumor03 Cohort 6B. The most frequently reported AEs in these

Table 75 Summary of Rilvegostomig Data and Guidance for Investigator

	participants, regardless of causality, were stomatitis (18 participants [45.0%]), nausea (12 participants [30.0%]), and amylase increased, constipation, and decreased appetite (11 participants [27.5%] each). 54 participants (90.0%) treated with 750 mg rilvegostomig Q3W + T-DXd and fluoropyrimidine in DESTINY-Gastric03 Arms 4A and 4B. The most frequently reported AEs in these participants, regardless of causality, were nausea (30 participants [50.0%]), anemia (21 participants [35.0%]), and diarrhea (19 participants [31.7%]). Detailed information about all AEs can be found in Section 5.3.
Drug interactions	No formal drug-drug interaction studies have been conducted with rilvegostomig.
Overdose	There are no clinical data on rilvegostomig overdose as of the date of this document.
Nonclinical toxicology	There are no pharmacology mediated toxicity findings that have been identified as a risk for clinical dosing. Evidence of minor, reversible immune-mediated changes in the spleen and brain of cynomolgus monkeys are indicative of a response by the monkey to the humanized bispecific and are not predictive for a human response following exposure to rilvegostomig. The findings in both the 1-month and 3-month studies were not considered due to pharmacologically-mediated effects but rather, based on weight of evidence considerations, due to ADA formation and secondary immunological reaction to biotherapeutics. Therefore, the findings are not predictive for a human response following exposure to rilvegostomig. The microscopic finding of minimal mixed cell infiltrates at the injection site in the 3-month study was considered non-adverse due to the low level of severity.
Clinical PK	Preliminary PK data, based on a bioanalytical DCO date of 21 March 2024, were evaluated using noncompartmental analysis in 182 participants who received rilvegostomig monotherapy at 70, 210, 750 and 1500 mg Q3W, in the dose escalation and expansion parts of ARTEMIDE-01. Rilvegostomig systemic exposure over 70 to 1500 mg increased in a near dose proportional manner. There was no target-mediated drug disposition observed at 70, 210, 750 and 1500 mg Q3W dose levels. Following a single dose iv administration, rilvegostomig levels declined in a bi-phasic manner with a mean terminal elimination half-life of about 8-10 days. Detailed information about clinical PK data can be found in Section 5.1.
Target engagement (peripheral receptor occupancy)	Evaluation of target engagement in peripheral blood of NSCLC participants showed that 750 mg and 1500 mg rilvegostomig Q3W achieved sustained > 90% PD-1 and TIGIT RO in CPI-experienced and CPI-naïve participants.
Clinical pharmacodynamics	Preliminary pharmacodynamic analysis showed a robust and higher level of clonal expansion at Cycle 2 Day 1 relative to baseline in CPI-naïve NSCLC participants versus historical data observed with durvalumab (McCoon et al 2021). A higher number of expanded T-cell clones was observed with rilvegostomig at 750 mg versus 1500 mg. Rilvegostomig showed a higher level of activated CD8 T cells at Cycle 1 Day 8 associated with response (partial response/unconfirmed partial

Table 75 Summary of Rilvegostomig Data and Guidance for Investigator

	response), versus historical data with durvalumab in CPI-naïve 1L NSCLC (Antonia et al 2019).
Clinical immunogenicity	Based on a sample DCO date of 21 March 2024, a total of 177 participants in dose escalation and expansion cohorts in ARTEMIDE-01 had at least one available ADA result. ADA incidence was 38.1% (45 of 118 participants) at the 750 mg dose level and 34.1% (15 of 44 participants) at the 1500 mg dose level. Upon preliminary evaluation, the impact of treatment-emergent ADA on PK was significant for participants with high ADA titers (≥ 2560 ; 11.9% [21 of 177 participants]; 41.8% decrease in steady-state AUC compared to ADA negative), however there was no clinically meaningful impact of treatment-emergent ADA on efficacy or safety (see Section 5.1.2).
Clinical efficacy	ARTEMIDE-01 CPI-naïve Cohorts Data from Cohorts C and D1, based on the DCO date of 21 April 2025, were evaluated for efficacy. Based on local assay results, in participants with PD-L1 TPS $\geq 50\%$, ORR was 61.8% (21 of 34 participants), PFS-12 was 55.5%, and mPFS was 12.3 months (95% CI: 8.4, NC). In participants with PD-L1 TPS 1% to 49%, ORR was 29.0% (9 of 31 participants), PFS-12 was 27.2%, and mPFS was 6.1 months (95% CI: 2.7, 8.3). Response was ongoing in 16 responders (53.3%). Based on retrospective central assay results (Ventana SP263), in participants with PD-L1 TPS $\geq 50\%$, ORR was 68.2% (15 of 22 participants), and PFS-12 was 63.6%. In participants with PD-L1 TPS 1% to 49%, ORR was 34.8% (8 of 23 participants) and PFS-12 was 30.4%. GEMINI-Gastric Substudy 2 As of the DCO date (04 July 2024), confirmed ORR was 62.5% among 40 evaluable participants in GEMINI-Gastric Substudy 2, 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 (complete response, partial response, or stable disease). The median PFS in response evaluable participants was 8.3 months, and was 7.1 months in participants with a PD-L1 CPS < 5 and 11.1 months in participants with a PD-L1 CPS ≥ 5 after a median follow-up for PFS of 7.4 months. GEMINI-Hepatobiliary (Cohort 2A) As of the DCO date (04 November 2024), confirmed ORR was 31.0% among 29 evaluable participants and 62.1% participants had stable disease as best overall response. The PFS-6 was 73.0% and the mPFS was 8.3 months (95% CI: 6.7, 9.6) months after a median follow-up of 6.9 months (interquartile range: 5.6 to 9.5). TROPION-Lung04 (Cohort 5) Overall, 40 participants had received Dato-DXd + rilvegostomig at DCO (24 October 2024). Median follow-up was 5.60 months (range: 0.1 to 18.3 months). Confirmed ORR was 57.7% (95% CI: 40.9, 73.0) and the disease control rate was 95.0% (95% CI: 83.1, 99.4). TROPION-PanTumor03 (Cohort 6B) As of 17 February 2025, a total of 40 participants (cisplatin ineligible n = 22; platinum treated n = 18) had received Dato-DXd + rilvegostomig. Median follow-up in cisplatin ineligible participants was 6.6 months (range: 1.0 to

Table 75 Summary of Rilvegostomig Data and Guidance for Investigator

	15.3 months) and in platinum treated participants was 6.1 months (range: 1.2 to 13.6 months). Confirmed ORR in cisplatin ineligible participants was 68.2% (95% CI: 45.1, 86.1) and in platinum treated participants was 33.3% (95% CI: 13.3, 59.0). Median DoR was not calculable as the data were immature at the DCO. Disease control rate was 95.5% (95% CI: 83.44, 99.52) for cisplatin ineligible participants and 83.3% (95% CI: 66.56, 93.71) for platinum treated participants.
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^a An identified risk is defined as an untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the European Union).

PT = Preferred Term.

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Appendix A Nonclinical Summary Tables

A 1 Summary of Nonclinical Pharmacology

Table 76 Summary of Nonclinical Pharmacology

Study number (GLP status)	Study title	Type of study	Methods	Noteworthy findings
ONC2936-001 (non-GLP)	Sequence Homology Comparison of Human PD-1 and TIGIT with Orthologs in Cynomolgus Monkey, Rhesus Monkey, Rat and Mouse	In vitro	Computer-based sequence alignment	The amino acid sequence of TIGIT and PD-1 in humans are conserved among non-human primates, while sequence homology is reduced upon comparison to rodent species.
ONC2936-002 (non-GLP)	Derivation and In Vitro Characterization of Rilvegostomig	In vitro	Surface plasmon resonance	Rilvegostomig demonstrated binding to human PD-1 and TIGIT and is cross-reactive with cynomolgus monkey PD-1 and TIGIT within a biologically acceptable range. Intrinsic binding affinities were determined: human PD-1 = 0.32 nM; human TIGIT = 15 pM; cynomolgus monkey PD-1 = 0.34 nM; and cynomolgus monkey TIGIT = 41.1 nM. Rilvegostomig showed binding cross-reactivity to murine TIGIT (2.9 nM) and exhibited only residual binding to the murine ortholog of PD-1 (950 nM).
ONC2936-003 (non-GLP)	In Vitro Cellular Binding Characteristics of Rilvegostomig to Human and Cynomolgus Monkey PD-1 and TIGIT Receptors	In vitro	Flow cytometry assay	Rilvegostomig bound to both human PD-1 and TIGIT receptors irrespective of the presence of both receptors on engineered cell lines, with an approximately 2-fold increased binding affinity to human TIGIT single expressing cells, compared to PD-1 single or PD-1⁺TIGIT⁺ double positive cell lines. Rilvegostomig bound to cynomolgus monkey PD-1 and TIGIT receptors on engineered cell lines.
ONC2936-004 (non-GLP)	Assessment of Rilvegostomig Internalization in Human T cells	In vitro	Fluorescence microscopy imaging assay	Rilvegostomig internalized into activated primary human T cells at an intermediate rate between that measured for the parental anti-PD-1 mAb and the parental anti-TIGIT mAb.

Table 76 Summary of Nonclinical Pharmacology

Study number (GLP status)	Study title	Type of study	Methods	Noteworthy findings
ONC2936-005 (non-GLP)	Effects of Rilvegostomig on a Jurkat T cell Reporter Cell Line	In vitro	Reporter cell assay	Rilvegostomig induced NFAT activity in the Jurkat reporter cell assay by inhibiting TIGIT and PD-1 binding to their primary ligands (CD155 and PD-L1, respectively). Rilvegostomig promoted increased NFAT activity greater than bivalent anti-TIGIT or anti-PD-1 and led to similar levels of activity (IC₅₀: 5.818 nM) as the combination of bivalent parental anti-TIGIT and anti-PD-1 antibodies (IC₅₀ 6.269 nM).
ONC2936-006 (non-GLP)	Effects of Rilvegostomig on the In Vitro Cytolytic Activity of Antigen-Specific T cells Co-cultured with Tumor Cells	In vitro	CD8 T-cell-mediated killing assay	Rilvegostomig induced a statistically greater amount of tumor cell cytolysis by antigen-specific T cells as compared to the cytolysis induced individually by the isotype control or anti-PD-1 antibody ($p < 0.0001$). The activity of rilvegostomig in this assay is similar to that of the combination of bivalent anti-TIGIT and anti-PD-1 antibodies.
ONC2936-007 (non-GLP)	Activity of Rilvegostomig in Xenograft Mouse Models of Human Cancers	In vivo	Humanized tumor model	Administration of rilvegostomig to animals significantly ($p < 0.05$) inhibited the growth of tumors as compared to the activity of its parental bivalent anti-PD-1 antibody and an isotype control.
ONC2936-008 (non-GLP)	Assessment of Rilvegostomig ADCC and CDC activities	In vitro	Cell killing assay	Rilvegostomig had a low probability of inducing ADCC or CDC against Jurkat cells expressing PD-1 and TIGIT.

ADCC = antibody-dependent cell-mediated cytotoxicity; CD = cluster of differentiation; CDC = complement-dependent cytotoxicity; GLP = good laboratory practice; IC₅₀ = half maximal inhibitory concentration; Ig = immunoglobulin; NFAT = nuclear factor of activated T cells; PD-1 = programmed cell death protein-1; PD-L1 = programmed cell death-ligand 1; TIGIT = T-cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif domains.

A 2 Summary of Nonclinical PK

Table 77 Summary of Nonclinical PK

Study number (GLP status)	Study title	Test system	Noteworthy findings
8399632 (non-GLP)	Rilvegostomig (TIGIT/PD-1) and LO115 (PD-1 mAb): A Single-Dose Pharmacokinetic and Pharmacodynamic Study in the Cynomolgus Monkey	22 naïve female cynomolgus monkeys	- Exposure to rilvegostomig increased with the increase in dose level from 5 to 100 mg/kg. - At 5 mg/kg, rilvegostomig exposure was similar for up to 15 days postdose when rilvegostomig was dosed at 5 mg/kg alone or with abatacept. Higher clearance was observed after 15 days postdose when rilvegostomig was dosed at 5 mg/kg alone compared to abatacept. - Exposure to LO115 increased with the increase in dose level from 5 to 100 mg/kg.
8529365 (GLP)	AZD2936 (Rilvegostomig): A Single Subcutaneous or Intravenous Dose Pharmacokinetic, Pharmacodynamic and Tolerability Study in the Non-Human Primate	15 male cynomolgus monkeys	- Exposure to rilvegostomig increased in proportion to dose for the tested range of 50 mg/kg to 200 mg/kg sc. - Bioavailability, assessed by the comparison of the AUC ratio between the 200 mg/kg sc and iv administrations was 67.1%.
20260563 (GLP)	Rilvegostomig: 1 Month Intravenous Toxicity Study with 6-Week Assessment of Recovery in the Cynomolgus Monkey Toxicokinetic Evaluation	18 female and 18 male cynomolgus monkeys	- Exposure to rilvegostomig, as assessed by mean C_{max} and AUC values, increased in a dose proportional manner from 50 to 200 mg/kg/week iv. - There were no sex differences in exposure. - Accumulation of rilvegostomig was observed after multiple weekly doses of 50, 100, or 200, mg/kg/week iv to male and female cynomolgus monkeys.

Table 77 Summary of Nonclinical PK

Study number (GLP status)	Study title	Test system	Noteworthy findings
8522498 (GLP)	Rilvegostomig: A 3-Month Once Weekly Intravenous (Slow Bolus) Injection Toxicity and Toxicokinetic Study in Cynomolgus Monkeys	12 female and 12 male cynomolgus monkeys	- Exposure, as assessed by rilvegostomig mean $C_{\max}$ and AUC_{0-168h} values, increased in a generally dose proportional manner from 50 to 200 mg/kg/week iv. - There were no sex differences in exposure. - Accumulation was observed after multiple weekly doses of 50, 100, and 200 mg/kg/week iv.

AUC = area under the curve; $C_{\max}$ = maximum concentration; GLP = good laboratory practice; Ig = immunoglobulin; iv = intravenous; mAb = monoclonal antibody; PD-1 = programmed cell death protein-1; PK = pharmacokinetic; sc = subcutaneous; TIGIT = T-cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif domains.

A 3 Summary of Nonclinical Toxicology

Table 78 Summary of Nonclinical Toxicology

Study number (GLP Status)	Study title	Type of study	Doses	Noteworthy findings
8529365 (GLP)	AZD2936 (Rilvegostomig): A Single Subcutaneous or Intravenous Dose Pharmacokinetic, Pharmacodynamic and Tolerability Study in the Non-Human Primate	In vivo Single dose PK, PD and tolerability	sc: 50 mg/kg (n = 3 males) 100 mg/kg (n = 3 males) 200 mg/kg (n = 3 males) iv: 200 mg/kg (n = 3 males)	<u>Dose site observation</u> - Edema and erythema at the sc or iv dose site with 200 mg/kg sc or iv. - Edema and erythema were mild in severity for animals dosed with 200 mg/kg sc and resolved within 1 day. - Edema and erythema generally persisted for a longer duration for animals dosed with 200 mg/kg iv, but resolved by Day 6 for all animals. <u>Cytokines</u> - Increases in IL-6 level above the lower limit of quantitation and control values noted at 6 hours postdose on Day 1 (1 to 2 animals at each dose level).
20260563 (GLP)	1-Month Repeat Dose Toxicity Study with a 6-week Assessment of Recovery in the Cynomolgus Monkey	In vivo Repeat-dose toxicity	50 mg/kg/wk (n = 4 males, 4 females) 100 mg/kg/wk (n = 4 males, 4 females) 200 mg/kg/wk (n = 5 males, 5 females; includes 2/sex for recovery assessment)	- All findings were reversible or showing evidence of reversibility at the end of the 6-week recovery treatment-free period. <u>Hematology</u> - Decreased red cell mass (red blood cell count, hemoglobin, and hematocrit) with minimally increased reticulocytes. - Increases in monocytes and large unstained cells on Day 15. <u>Clinical chemistry</u> - Decreased albumin, increased C-reactive protein, minimally increased globulin and mildly decreased cholesterol all evidence of an acute phase response. <u>Organ weights</u> - Spleen: Increased absolute weight, and relative to body weight and brain weight. <u>Histopathology</u> - Spleen: increased cellularity. - Brain: Minimal to mild mononuclear cell infiltrates within the choroid plexus and/or within the meninges/parenchyma of the brain.

Table 78 Summary of Nonclinical Toxicology

Study number (GLP Status)	Study title	Type of study	Doses	Noteworthy findings
8522498 (GLP)	Rilvegostomig: A 3-Month Once Weekly Intravenous (Slow Bolus) Injection Toxicity and Toxicokinetic Study in Cynomolgus Monkeys	In vivo Repeat dose toxicity	50 mg/kg/wk (n = 3 males, 3 females) 100 mg/kg/wk (n = 3 males, 3 females) 200 mg/kg/wk (n = 3 males, 3 females)	<u>Hematology</u> - Decreased red cell mass (red blood cell count, hemoglobin, and hematocrit). - Markedly decreased platelet count on Day 51. <u>Clinical chemistry</u> - Evidence of a transient muscle perturbation (markedly increased creatine kinase activity and minimally increased AST and ALT activities) on Day 57. - Increase in IL-6 at 6 hours postdose on Days 15 and 57. <u>Organ weights</u> - Spleen: Increased absolute weight, and relative to body weight and brain weight. <u>Histopathology</u> - Spleen: increased lymphoid cellularity. - Lymph nodes (axillary and mesenteric): increased lymphoid cellularity. - Aorta and blood vessels of the brain (choroid plexus and meninges), colon, epididymis, heart, kidney, stomach, connective tissue (eye, testes, and sciatic nerve), spinal cord (meninges), tongue, rectum and/or injection site: perivascular mononuclear cell infiltrates, perivascular mixed cell infiltrates, and/or intimal mixed cell infiltrates.

GLP = good laboratory practice; IL = interleukin; iv = intravenous; n = number of monkeys; PD = pharmacodynamics; PK = pharmacokinetics; sc = subcutaneous; wk = week.