23 July 2026
EMADOC-1700519818-3394168
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trodelvy

International non-proprietary name: sacituzumab govitecan

Procedure No. EMA/VR/0000320818

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA antidrug antibody

ADC antibody-drug conjugate

ADR adverse drug reaction

AE adverse event

AEOSI adverse event of special interest for pembrolizumab

AESI adverse event of special interest for sacituzumab govitecan

ALT alanine aminotransferase

ASCO American Society of Clinical Oncology

AUC area under the curve

AUC_{x-xx} partial area under the concentration versus time curve from time "x" to time "xx"

BICR blinded independent central review

BRCA ½ breast cancer gene ½

CBR Clinical Benefit Rate

CHMP Committee for Medicinal Products for Human Use

CI confidence interval

CL clearance

C_{max1} maximum observed concentration of drug after first dose

$C_{max,D1,SG}$ maximum observed concentration after first dose of SG

CPS combined positive score

CR complete response

CSR clinical study report

DAR drug-to-antibody ratio

DNA deoxyribonucleic acid

DOR duration of response

EAIR exposure-adjusted incidence rate

ECL electrochemiluminescence

ECOG Eastern Cooperative Oncology Group

EMA European Medicines Agency

EORTC QLQ-C30 European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0

ESMO European Society for Medical Oncology

EU European Union

G-CSF granulocyte-colony stimulating factor

GI gastrointestinal

HER2− human epidermal growth factor receptor 2 negative

HR hazard ratio

HR+ hormone receptor positive

ICH International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)

ICI immune checkpoint inhibitors

Ig immunoglobulin

IHC immunohistochemistry

IRT Integrated Summary of Safety

ISI Integrated Summary of Immunogenicity

ISS Integrated Summary of Safety

ITT intent-to-treat

IV intravenous

IWRS interactive web response system

mBC metastatic breast cancer

MedDRA Medical Dictionary for Regulatory Activities

MM Michaelis-Menten

nab- nanoparticle albumin-bound

Nab neutralizing antibody

OR odds ratio

ORR objective response rates

OS overall survival

PARP poly adenosine diphosphate-ribose polymerase

PD progressive disease

PD-1 programmed cell death protein 1

PD-L1 positive combined positive score (CPS) ≥ 10 using the PD-L1 IHC 22C3 pharmDx assay

Pembro, pembro pembrolizumab

PFS progression-free survival

PFS2 progression-free survival on next-line therapy

PK pharmacokinetic(s)

PopPK population pharmacokinetic(s)

PR partial response

Q3W	once every 3 weeks
QOL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SG	sacituzumab govitecan
SMQ	standardised MedDRA query
SOC	system organ class
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TNBC	triple-negative breast cancer
TPC	treatment of physician's choice
Trop-2	trophoblast cell-surface antigen 2
TTD	time to deterioration
TTR	time to response
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
US	United States
V_{ss}	volume of distribution at steady state
WES	whole exome sequencing

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences Ireland Unlimited Company submitted to the European Medicines Agency on 22 December 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include Trodelvy, in combination with pembrolizumab, for the treatment of adult patients with unresectable locally advanced or metastatic TNBC who have not received prior systemic therapy for metastatic disease and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10, based on results from study GS-US-592-6173 (ASCENT-04), which is a phase 3 study of sacituzumab govitecan (IMMU-132) and Pembrolizumab versus treatment of physician's choice and Pembrolizumab in patients with previously untreated, locally advanced inoperable or metastatic triple-negative breast cancer, whose tumors express PD-L1. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.2 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0018/2020 on the granting of a product-specific waiver for sacituzumab govitecan for the condition treatment of breast cancer.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 11 November 2021 (EMA/SA/0000069358). The Scientific Advice pertained to clinical aspects of the dossier.

1.1. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus

PRAC Rapporteur: Bianca Mulder

Timetable	Actual dates
Submission date	22 December 2025
Start of procedure:	24 January 2026
CHMP Rapporteur's preliminary assessment report circulated on:	20 March 2026
PRAC Rapporteur's preliminary assessment report circulated on:	26 March 2026
PRAC members' comments:	31 March 2026
PRAC Rapporteur's updated assessment report circulated on:	N/A
PRAC RMP advice and assessment overview adopted by PRAC:	10 April 2026
CHMP members' comments:	13 April 2026
CHMP Rapporteur's updated assessment report circulated on:	16 April 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 April 2026
MAH's responses submitted to the CHMP on:	21 May 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	23 June 2026
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	24 June 2026
PRAC members' comments:	1 July 2026
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on:	3 July 2026
PRAC RMP advice and assessment overview adopted by PRAC:	9 July 2026
CHMP members' comments:	13 July 2026
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	14 July 2026
CHMP opinion:	23 July 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH initially applied for the following indication:

'Trodelvy is indicated in combination with pembrolizumab, for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have not received prior systemic therapy for metastatic disease and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (see SmPC section 5.1).'

This application is based on the results of the ASCENT-04 (GS-US-592-6173) study.

Epidemiology and risk factors

Breast cancer is the most commonly diagnosed cancer and leading cause of cancer death in women globally as of 2022. 2.3 million women globally were diagnosed with breast cancer and 670,000 died from the disease in 2022[1]. Triple negative breast cancer (TNBC) accounts for approximately 15% of invasive breast cancers[2].TNBC is more common in younger women than in older women and in black persons than in persons of other races and ethnic groups. Other risk factors for the disease include the presence of a breast cancer susceptibility gene (BRCA) mutation, premenopausal status, obesity, and maternal-related factors such as parity and age at first pregnancy (Trivers et al. 2009; Plasilova et al. 2016).

Biologic features

TNBC is defined by a lack of oestrogen receptor, progesterone receptor, and HER2 expression in tumour cells (oestrogen receptor/progesterone receptor positivity of < 1% IHC expression, and HER2 IHC 0, IHC 1+ or IHC 2+ and in situ hybridization–negative in accordance with the current ASCO/College of American Pathologists guidelines[3]).

Clinical presentation, diagnosis and stage/prognosis

Compared with hormone receptor-positive and HER2 positive tumours, TNBC is characterized by a more aggressive tumour biology and shorter overall survival with a low 5-year survival rate of approximately 12%[4].

Historically, the majority of patients with TNBC experience disease recurrence, with studies reporting 25% of patients with metastatic TNBC presenting with de novo metastatic disease[5],[6],[7]; however, with recent advances in the curative setting, such as treatment with intensive neoadjuvant and adjuvant chemotherapy, anti PD-1 or anti PD-L1 therapy, and PARP inhibitors, more contemporary data suggest a shift to 33% of patients with metastatic TNBC presenting with de novo metastatic disease[8]. TNBC is most commonly associated with visceral metastases affecting the liver, lung, and brain[9].

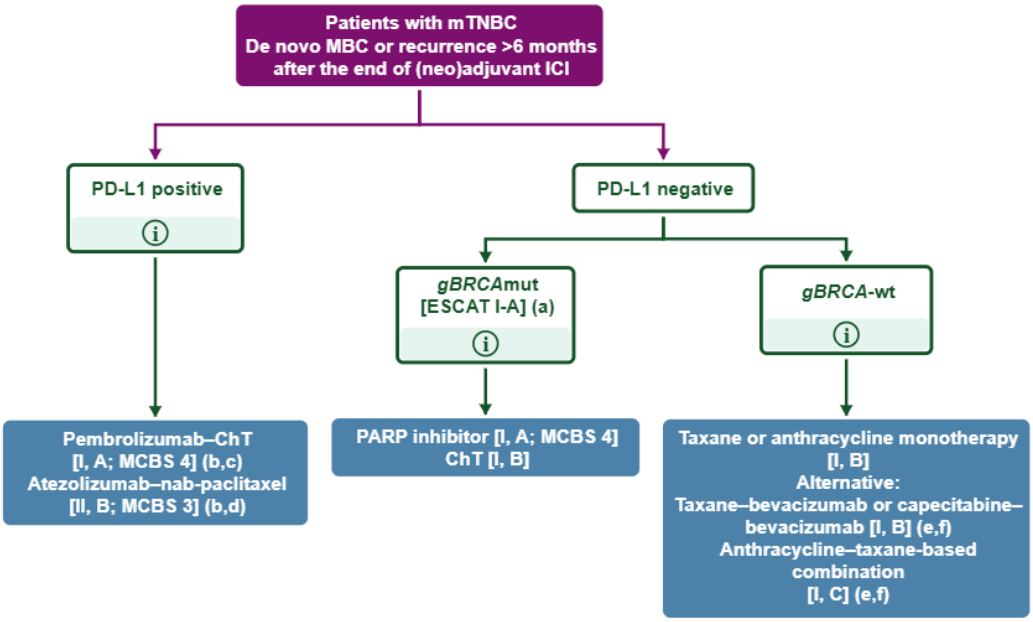
Management

Current standard treatment for recurrent/metastatic TNBC varies by subtypes. For PD-L1 positive patients with de novo metastatic TNBC or recurrence of >6-12 months after the end of (neo)adjuvant immune checkpoint inhibitors (ICI) the most recent ESMO guidance recommends a combination of chemotherapy with an ICI. PD-L1 negative patients with germline BRCA 1/2

[1] WHO. Breast Cancer. Available at: https://www.who.int/news-room/fact-sheets/detail/breast-cancer. Last Updated: 13 March. 2024
[2] Anders et al. The management of early-stage and metastatic triple-negative breast cancer: a review. Hematol Oncol Clin North Am 2013
[3] Allison et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. Arch Pathol Lab Med 2020
[4] American Cancer Society. Triple-negative Breast Cancer. Available at: https://www.cancer.org/cancer/types/breast-cancer/about/types-of-breast-cancer/triple-negative.html. Last Updated: 01 March. 2023
[5] Cardoso F et al. Global analysis of advanced/metastatic breast cancer: Decade report (2005-2015). Breast 2018
[6] Skinner KE et al. Real-world effectiveness outcomes in patients diagnosed with metastatic triple-negative breast cancer. Future Oncol 2021
[7] Tan A et al. San Antonio Breast Cancer Symposium (SABCS) Virtual; 2020
[8] Punie K et al. Evolution of characteristics, real-world treatment landscape, and survival outcomes in patients with previously untreated mTNBC in the United States [Abstract]. ESMO Breast Cancer; 2024
[9] O'Reilly D et al. Overview of recent advances in metastatic triple negative breast cancer. World J Clin Oncol 2021

mutations should be treated with a PARP inhibitor and gBRCA-wt PD-L1 negative patients should receive chemotherapy (ESMO living guideline[10]).

Figure 1 De novo MBC or recurrence > 6-12 months after the end of (neo)adjuvant ICI



(a) ESCAT scores apply to genomic alterations only
(b) Pembrolizumab may be considered as monotherapy in further lines in case of high PD-L1 positivity and no previous exposure to ICI
(c) ChT physician's choice of nab-paclitaxel, paclitaxel or gemcitabine–carboplatin
(d) Disease free interval should be ≥12 months in countries where this indication is approved (EMA approved, not FDA approved)
(e) If not used previously
(f) Preferred if imminent organ failure [V, B]
ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mTNBC, metastatic triple-negative breast cancer; mut, mutation; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; wt, wild-type.

In the EU, Keytruda (pembrolizumab), a PD-1 inhibitor was approved for the first-line treatment of TNBC in October 2021 based on the KEYNOTE-355 study (EMEA/H/C/003820/II/0099): "*in combination with chemotherapy, for the treatment of locally recurrent unresectable or metastatic triple negative breast cancer in adults whose tumours express PD L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease*". The subset of patients with PD L1 positive tumours (defined by CPS ≥ 10 using the PD L1 IHC 22C3 pharmDx assay) accounted for 40% of patients with TNBC based on the KEYNOTE 355 study[11].

2.1.2. About the product

Sacituzumab govitecan is an antibody-drug conjugate (ADC) composed of the following 3 components:

- The humanized monoclonal antibody hRS7 IgG1κ, which binds to trophoblast cell-surface antigen 2 (Trop-2), a transmembrane calcium signal transducer that is overexpressed in many epithelial cancers.

[10] ESMO Living Guideline for Triple-negative metastatic breast cancer; G Curigliano et al., Ann Oncol. 2025.
[11] Cortes et al Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355). Lancet 2020

- The camptothecin-derived agent SN-38, a topoisomerase I inhibitor.
- A hydrolyzable linker, with the company designation as CL2A that links the humanized monoclonal antibody to SN-38.

Binding of Trop 2 by the parental RS7 antibody has been shown to result in internalization and processing of the antibody by the targeted cells. Because of its hydrolyzable linker, sacituzumab govitecan (SG) will release its SN-38 payload both intra- and extracellularly in the tumour microenvironment. SG delivers significantly greater amounts of SN-38 to a Trop 2-expressing tumour than conventional irinotecan chemotherapy. The extracellular release of SN-38 from SG also allows for bystander killing of Trop 2 negative tumour cells. Thus, SG can deliver cytotoxic chemotherapy to tumours, including adjacent cancer cells, in concentrations that are higher than those with standard chemotherapy and may reduce toxic effects in normal tissues that do not express the target.

Sacituzumab govitecan is approved in the EU as monotherapy for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease (EC decision November 2021), as monotherapy for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have not received prior systemic therapy for metastatic disease and who are not candidates for PD-1 or PD-L1 inhibitor therapy (Trodelvy EMA/VR/0000312649, EC decision June 2026) and for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine-based therapy, and at least two additional systemic therapies in the advanced setting (Trodelvy EMEA/H/C/005182/II/0020, EC decision July 2023).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice

The clinical efficacy and safety of SG in combination with pembrolizumab for the treatment of adult participants with locally advanced unresectable or metastatic TNBC who have not received prior systemic therapy for metastatic disease and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 have been evaluated in study GS-US-592-6173 (ASCENT-04). EMA scientific advice regarding the design of the phase 3 study ASCENT-04 was obtained in November 2021 (EMA/SA/0000069358).

Related to eligibility criteria, CHMP was critical of the fact that gBRCA1/2 testing was not mandatory and recommended that patients with BRCA mutation should have received prior PARP inhibitor or alternatively, be excluded. This recommendation was not implemented by the MAH.

The eligibility of patients with recurrence within 6 to 12 months from (neo) adjuvant pembrolizumab treatment was considered arguable because the acquired resistance criteria to previous pembrolizumab and other ICIs should be considered at the time of choosing the treatment regimens at relapse. Overall, only 6 patients with prior PD-L(1) inhibitor treatment were included.

CHMP agreed on the inclusion of patients regardless of TROP-2 expression on tumour cells based on the results from study IMMU-132-05 (ASCENT). It was noted that TROP-2 expression was not used as a stratification factor. It was however supported to investigate its relationship with clinical outcomes.

The choice of primary and secondary endpoints was overall considered acceptable; however, it was noted that CHMP would require sufficiently mature OS data to support approval.

The optional crossover from the control arm at confirmed progression to SG was considered acceptable, since it would mirror the recommended treatment pathway and would likely occur also outside the study, at least for patients who have received chemotherapy also in the (neo)adjuvant setting. The collection of data on sequencing of treatment, information on post-study treatment in both arms, as well as analysis of PFS2 was recommended. Information on post-study treatments and PFS2 data provided.

2.1.4. General comments on compliance with GCP

The assessment of the dossier has not raised concerns regarding GCP compliance of the pivotal study ASCENT-04.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) was previously submitted for Trodelvy as part of the EU initial MAA, considering the overall prevalence of TNBC regardless of the line of treatment. This ERA considered all available data relating to sacituzumab govitecan in accordance with the CHMP guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). The EMA guideline on the Environmental Risk Assessment (ERA) states that *"the evaluation of the environmental impact should be made if there is an increase in the environmental exposure, e.g. a new indication may result in a significant increase in the extent of the use."* The ERA for Trodelvy uses the default Fpen (0.01, i.e. 1% of the population receiving the active substance). In addition, the current treatment regimen (for the already approved and the new applied for extension of indication) is 10 mg/kg body weight considered to be a maximum of 600 mg of Trodelvy i.e. 12 mg of payload SN38 twice within 3 weeks for a worst-case treatment period of 1 year, resulting in a PECsw of 0.0057 µg/L which is. below the action limit of 0.01 µg/L to require a Phase II assessment.

Since the default Fpen (1% of the population) and the treatment regimen remain unchanged with the present extension of indication, an update of the ERA was not considered necessary, which is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1 Overview of key studies included in this submission

Type of Study	Description of Study	Data Included in this Submission	Study Population/ Number of Participants
Pivotal Study			
GS-US-592-6173 (ASCENT-04)	Phase 3, ongoing, open-label, randomized, multicenter, global study to compare efficacy of SG in combination with pembrolizumab versus TPC in combination with pembrolizumab as measured by PFS by BICR	Efficacy Safety[a] PK Immunogenicity	Participants with locally advanced unresectable or metastatic TNBC who have not received previous therapy for advanced disease and whose tumors were PD-L1 positive (CPS ≥ 10 by PD-L1 IHC 22C3 pharmDx assay) at screening. Participants with de novo metastatic TNBC were capped at 35% of the study population. Prior anti–PD-1 or anti-PD-L1 therapy was permitted. Total: 443 randomized (441 treated) SG[b]: 221 randomized (221 treated) TPC[c]: 222 randomized (220 treated)
Supportive Studies			
IMMU-132-09 (TROPiCS-02)	Phase 3, open-label, randomized, multicenter, international study to assess and compare the efficacy of SG with TPC as measured by PFS as determined by BICR using RECIST v1.1	Safety[a] PK Immunogenicity	Participants with locally recurrent inoperable or metastatic HR+/HER2− breast cancer who have been treated with a CDK 4/6 inhibitor, endocrine therapy, taxane, and at least 2 but no more than 4 prior chemotherapy regimens for metastatic disease (1 of which could be in the neoadjuvant/adjuvant setting if development of unresectable, locally advanced, or metastatic disease occurred within 12 months) Total: 543 randomized (517 treated) SG[b]: 272 randomized (268 treated) TPC[d]: 271 randomized (249 treated)
IMMU-132-05 (ASCENT)	Phase 3, randomized, open-label, controlled, multicenter study to compare the efficacy of SG with TPC as measured by independently reviewed PFS in participants who were BM-negative at baseline	Safety[a] PK Immunogenicity	Participants with locally advanced or metastatic TNBC who were either refractory or had relapsed after at least 2 prior standard-of-care chemotherapy regimens. Total: 529 randomized (482 treated) SG[b]: 267 randomized (258 treated) TPC[d]: 262 randomized (224 treated)
IMMU-132-01	Phase 1/2, open-label, single-arm, basket study. Phase 1: To evaluate the safety and tolerability of SG as a single agent and to determine a maximum acceptable dose[e] and select cancer types for a continued expanded study in Phase 2. Phase 2: To evaluate the safety and efficacy of SG administered at a dose selected in Phase 1.	Safety[a] PK Immunogenicity	Participants with metastatic **epithelial cancer** (except for GBM) that was relapsed or refractory to at least 1 standard therapy for their tumor type. Total: 515 enrolled (402 treated)[f]

IMMU-132-06 (TROPHY-U-01)	Phase 2, ongoing, open-label study to assess the efficacy and safety of SG in locally advanced unresectable or metastatic UC.	Safety[a] Immunogenicity	Cohort 1: participants with locally advanced unresectable or metastatic **UC** that progressed after prior platinum-containing and anti–PD-1 or anti–PD-L1 based therapies Total: 141 enrolled (113 treated)[g] Cohort 2: participants with platinum-ineligible locally advanced unresectable or metastatic UC that progressed after prior anti-PD-1 or anti-PD-L1-based therapy Total: 54 enrolled (38 treated)[g]
GS-US-592-6238 (**ASCENT-03**)	Phase 3, ongoing, open-label, randomized, multicenter, global study to compare efficacy of SG versus TPC as measured by PFS as determined by BICR using RECIST v1.1	Efficacy Safety PK Immunogenicity	Participants with previously untreated locally advanced unresectable or metastatic TNBC whose tumors are: PD-L1 negative (tumors with a CPS < 10 using the PD-L1 IHC 22C3 pharmDx assay) OR PD-L1 positive (tumors with a CPS ≥ 10) if the patient previously received an anti-PD-1 or anti-PD-L1 agent in the adjuvant or neoadjuvant setting or if they cannot be treated with an anti-PD-1 or anti-PD-L1 agent due to a comorbidity Total: 558 randomized (551 treated) SG[b]: 279 randomized (275 treated) TPC[c]: 279 randomized (276 treated)

BICR = blinded independent central review; BM = bone marrow; CDK = cyclin-dependent kinase; CPS = combined positive score; GBM = glioblastoma multiforme; HER2− = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; IHC = immunohistochemistry; IV = intravenous; mUC = metastatic urothelial cancer; nab = nanoparticle albumin-bound; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice; UC = urothelial cancer

a The integrated safety dataset includes all available data up to the data cutoff dates from Studies GS-US-592-6173 (03 March 2025) and IMMU-132-06 (28 February 2023), and final safety data from Studies IMMU-132-09 (15 December 2023), IMMU-132-01 (02 April 2021), and IMMU-132-05 (25 February 2021).
b Participants received SG 10 mg/kg IV infusion on Days 1 and 8 of a 21-day treatment cycle.
c TPC was paclitaxel, nab-paclitaxel, or gemcitabine with carboplatin administered per standard of care.
d TPC was eribulin, capecitabine, gemcitabine, or vinorelbine administered per standard of care.
e Starting doses of 8, 10, 12, and 18 mg/kg were evaluated during the dose escalation phase (Phase 1) of Study IMMU-132-01.
f Of the 515 participants enrolled in Study IMMU-132-01, 495 participants were included in the Overall Safety Population. Of these, 402 participants received SG 10 mg/kg. The population included the following tumor types: ovarian, endometrial, cervical, TNBC, HR+/HER2− metastatic breast cancer, castration-resistant prostate cancer, colorectal cancer, non–small-cell lung cancer, small-cell lung cancer, head and neck squamous cell cancer, esophageal, gastric, pancreatic, hepatocellular, renal (clear cell), thyroid (papillary), and mUC. Participants with GBM were also eligible, but were not required to have metastatic disease.
g Study is ongoing and data up to the data cutoff date of 28 February 2023 were included in the integrated safety analysis.

2.3.2. Pharmacokinetics

With this application for extension of indication, the MAH is seeking approval of sacituzumab govitecan (SG) (Trodelvy), a trophoblast cell-surface antigen-2 (Trop-2)-directed ADC, in combination with pembrolizumab compared with treatment of physician's choice (TPC) in

combination with pembrolizumab in participants with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC), who had not received prior systemic therapy for metastatic disease. This includes patients whose tumours express programmed cell death ligand 1 (PD-L1) with a combined positive score (CPS)≥10.

The recommended dose of SG is 10 mg/kg administered intravenously (IV) once weekly on Days 1 and 8 of continuous 21-day treatment cycles until disease progression or unacceptable toxicity and thus is equal to the approved posology.

PK, and immunogenicity of SG were evaluated based on data from study GS-US-592-6173 (ASCENT-04), study GS-US-592-6238 (ASCENT-03) and from 3 additional completed studies: study IMMU-132-01, study IMMU-132-05, and study IMMU-132-09, whereas ongoing study IMMU-132-06 contributed data to the immunogenicity package.

The PK of total antibody, free SN-38, and conjugated SN-38 was characterized in participants with solid tumours using an integrated PopPK model. SG's concentration was derived based on conjugated SN-38 in the PopPK analysis. The integrated population pharmacokinetic (PopPK) model was also used to evaluate the effect of various intrinsic and extrinsic factors on the exposure of total antibody, SG, and free SN-38. Data from studies IMMU-132-01, IMMU 132-05, IMMU-132-09, and GS US 592-6173 were used to develop the model. An updated PopPK analysis was conducted including also study GS-US-592-6238 (ASCENT-03) in the pooled dataset.

Pharmacokinetics of SG have been characterized throughout the initial marketing authorization procedure. In this variation assessment report, only summarized data on SG ADME, dose proportionality, special populations and interaction studies are presented.

In the pivotal study GS-US-592-6173 (ASCENT-04), serum samples for PK analyses for total antibody, total SN-38, and free SN-38 were collected only for participants receiving SG. Collection times for PK samples were predose and after the end of infusion on Day 1 and Day 8 of Cycle 1; Day 8 of Cycles 2, 6, and 10. Thereafter, predose samples were collected on Day 8 of every 8 cycles after Cycle 10 (e.g., Cycle 18 Day 8, Cycle 26 Day 8); and at the end of treatment (EOT) visit.

Table 2 Overview of Clinical Studies Contributing to the Characterization of the Clinical Pharmacology and Immunogenicity of Sacituzumab Govitecan

Study Number (Location)	Study Description	Study Population	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
			Dose and Formulation[a] (Batch/Lot Numbers)	n[b]	
Studies Providing Pharmacokinetic and Immunogenicity Data					
IMMU-132-01 (Section 2.1.1 ; m2.7.4, Section 1.2.2. 1)	Phase 1/2, open-label, single-arm, basket study to evaluate the efficacy, safety, and PK of SG	Participants with metastatic epithelial cancers[c] who had either relapsed after or were refractory to at least 1 standard therapeutic regimen for their tumor type	SG 8, 10, 12, and 18 mg/kg via IV infusion on Days 1 and 8 of a 21-day cycle (1006095, 1301195, 1302208, 1305149, 1310040, 1312001, 1403050, 1406004, 1408197, 1410159, 1412105, 1503277, 1505001,1506060, 1507008, 1509011, 1510264, 1512032, 1601119, 1603027, 1605147, 1606367, 1607432, 1608114,	495	Not applicable

Study Number (Location)	Study Description	Study Population	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
			Dose and Formulation[a] (Batch/Lot Numbers)	n[b]	
			1609399, 1611013, 1611411, 1701095, 1703104, 1612096, 1703159, 1711055, 1801083, PPQ3, and 2018 DP1)		
IMMU-132-05 (Section 2.1.2; m2.7.4, Section 1.2.2.2)	Phase 3, randomized, open-label, active-controlled, multicenter study to evaluate the efficacy and safety of SG vs TPC	Participants with either locally advanced or metastatic triple-negative breast cancer who had either relapsed after or were refractory to at least 2 prior standard-of-care chemotherapy regimens	SG 10 mg/kg via IV infusion on Days 1 and 8 of a 21-day cycle (1703159, 1711055, 1801083, and 2018 DP1)	258	TPC from 1 of the following 4 choices: • Eribulin 1.4 mg/m^2 (North American sites) or 1.23 mg/m^2 (European sites) via IV infusion on Days 1 and 8 of a 21-day cycle • Capecitabine 1000-1250 mg/m^2 PO BID for 2 weeks followed by a 1-week rest period given as a 21-day cycle • Gemcitabine 800-1200 mg/m^2 via IV infusion on Days 1, 8, and 15 of each 28-day cycle • Vinorelbine 25 mg/m^2 via IV infusion on Day 1 weekly[d]
IMMU-132-09 (Section 2.1.3; m2.7.4, Section 1.2.2.4)	Phase 3, randomized, open-label, multicenter, international study to evaluate the efficacy and safety of SG vs TPC	Participants with HR+/HER2− metastatic or locally recurrent unresectable breast cancer who have progressed after a CDK 4/6 inhibitor, endocrine therapy, taxane, and at least 2 (but no more than 4) prior chemotherapy regimens for metastatic disease (1 of which could be in the neoadjuvant or adjuvant setting if development of unresectable, locally advanced, or metastatic disease occurred within 12 months)	SG 10 mg/kg via IV infusion on Days 1 and 8 of a 21-day cycle (S17N001, S18F010, S18F023, S18M010, S18N006, S19I022, S19L023, S19L024, S19M004, S21E019, S21E020, and S21I014)	268	TPC from 1 of the following 4 choices: • Eribulin 1.4 mg/m^2 (North American sites) or 1.23 mg/m^2 (European sites or per institution) via IV infusion on Days 1 and 8 of a 21-day cycle • Capecitabine 1000-1250 mg/m^2 PO BID for 2 weeks followed by a 1-week rest period given as a 21-day cycle • Gemcitabine 800-1200 mg/m^2 via IV infusion on Days 1, 8, and 15 of each 28-day cycle or per institution • Vinorelbine 25 mg/m^2 via IV infusion on Day 1 of a weekly cycle or per institution[d]
GS-US-592-6173	Ongoing Phase 3,	Participants with locally advanced	SG 10 mg/kg IV on Days 1 and 8 of 21-	221	TPC (21- or 28-day cycles) +

Study Number (Location)	Study Description	Study Population	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
			Dose and Formulation[a] (Batch/Lot Numbers)	n[b]	
(Section 2.1.4 ; m2.7.3, Section 2.1)	open-label, randomized, multicenter, global study to evaluate the efficacy and safety of SG + pembrolizumab versus TPC + pembrolizumab	unresectable or metastatic TNBC whose tumors are PD-L1 positive	day cycles + pembrolizumab 200 mg IV on Day 1 of 21-day cycles (S21E019, S21I002, S21I028, S21N014, S22C042, S22E042, S22E043, S22F029, S22N012, S23A002, S23G015, S24D052, and S24F033)		pembrolizumab 200 mg IV on Day 1 of 21-day cycles. TPC from 1 of the following 3 choices: • Gemcitabine 1000 mg/m^2 with carboplatin AUC 2 IV on Days 1 and 8 of 21-day cycles • Paclitaxel 90 mg/m^2 IV on Days 1, 8, and 15 of 28-day cycles • nab-Paclitaxel 100 mg/m^2 IV on Days 1, 8, and 15 of 28-day cycles

Study Number (Location)	Study Description	Study Population	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
			Dose and Formulation[a] (Batch/Lot Numbers)	n[b]	
Additional Study Included for Immunogenicity Data Only					
IMMU-132-06 (Section 2.2.1; m2.7.4, Section 1.2.2.3)	Ongoing Phase 2, open-label, multicenter, international study to evaluate the efficacy and safety of SG	Participants with metastatic urothelial cancer who progressed after failure of a platinum-containing regimen and/or anti–PD-1- and anti–PD-L1-based immunotherapy	SG 10 mg/kg via IV infusion on Days 1 and 8 of a 21-day cycle (1703159, S17C001, S17H003, S17N001, S18F010, S18F023, S18M010, S18N006, S19I022, S19L023, S19L024, S19M004, S20M045, S21E019, S21I010, and S21N015)	151[e]	Not applicable
GS-US 592-6238 (ASCENT-03)	Phase 3, ongoing, open-label, randomized, multicenter, global study to compare efficacy of SG versus TPC as measured by PFS as determined by BICR using RECIST v1.1	Participants with previously untreated locally advanced unresectable or metastatic TNBC whose tumors are: PD L1 negative (tumors with a CPS < 10 using the PD L1 IHC 22C3 pharmDx assay) OR PD L1 positive (tumors with a CPS ≥ 10) if the patient previously received an anti PD 1 or anti PD L1 agent in the adjuvant or neoadjuvant setting or if they cannot be treated with an anti PD 1 or anti PD L1 agent due to a comorbidity	SG 10 mg/kg via IV infusion on Days 1 and 8 of a 21-day cycle	275	

BID = twice daily; CDK = cyclin-dependent kinase; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; IV = intravenous; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetic(s); PO = orally; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice; w/v = weight-to-volume ratio

a Sacituzumab govitecan was formulated as a lyophilized powder for reconstitution composed of SG 10 mg/mL in 22 mM 2-(N-morpholino) ethanesulfonic acid buffer at pH 6.5, 25 mM trehalose, and 0.01% (w/v) polysorbate 80.

b Number of participants who were administered any test treatment.

c Tumor types included ovarian, endometrial, cervical, triple-negative breast cancer, HR+/HER2− metastatic breast cancer, castration-resistant prostate cancer, colorectal cancer, non–small cell lung cancer, small cell lung cancer, head and neck squamous cell cancer, esophageal, gastric, pancreatic, hepatocellular, renal (clear cell), thyroid (papillary), and metastatic urothelial cancer. Participants with glioblastoma multiforme were also eligible but were not required to have metastatic disease.

d Participants with Grade 2 neuropathy were eligible for the study but were not to receive vinorelbine as TPC.

e Cohorts 1 and 2 only.

Analytical methods

Bioanalytical methods

Bioanalytical methods for the quantitation of total SN-38, free SN-38, SN-38G, and total antibody (hRS7-IgG) in human serum were developed and fully validated at KCAS, LLC [Shawnee, Kansas, USA]). The bioanalytical method TP-80150 was partially validated at KCAS Bio (Olathe, Kansas, USA) under KCAS Project Number V1102206E1 and was performed for the determination of free SN-38 in human serum.

According to the MAH, all bioanalytical method validation and sample analysis reports supporting clinical studies were conducted according to the United States (US) Food and Drug Administration Bioanalytical Method Guidelines (2018) (U. S. Department of Health & Human Services (DHHS) 2018), International Council for Harmonisation (ICH)-M10 Bioanalytical Method Validation and Study Sample Analysis Guidance for Industry (2022) International Council for Harmonisation (ICH) 2022, U.S. Department of Health and Human Services (DHHS) 2022, and European Medicines Agency Guidelines on Bioanalytical Method Validation (2011) (European Medicines Agency (EMA) 2011).

Table 3 Summary of Bioanalytical Methods for Individual Studies

Study Number	Matrix	Analyte	Current Validation Report[a]	Calibrated Range	Sample Analysis Report
		Total SN-38	VIMME1701E1 A3	5-2500 ng/mL	BIMME1704E2_revision_1 Project numbers: BIMME1704E2 BIMME1802E2
		Free SN-38 and SN-38G	VIMME1700E2 A3	1-500 ng/mL	BIMME1704E1_revision_1 Project numbers: BIMME1704E1 BIMME1802E1
		Total Antibody	VIMME1706E1 A2	374-3049 ng/mL	BIMME1708E1_revision_1 Project numbers: BIMME1708E1 BIMME1801E1
		Total SN-38	VIMME1701E1 A3	5-2500 ng/mL	BIMME1803E2
		Free SN-38 and SN-38G	VIMME1700E2 A3	1-500 ng/mL	BIMME1803E1
		Total Antibody	VIMME1706E1 A2	374-3049 ng/mL	BIMME1804E1
		Total SN-38	VIMME1701E1 A3	5-2500 ng/mL	B1101809E2
		Free SN-38 and SN-38G	VIMME1700E2 A3	1-500 ng/mL	B1101809E1
		Total Antibody	VIMME1706E1 A2	374-3049 ng/mL	B1101809E3
GS-US-592-6173	Human Serum	Total SN-38	VIMME1701E1 A3	5-2500 ng/mL	B1102201E2
		Free SN-38	V1102206E1	1-500 ng/mL	B1102201E1

Study Number	Matrix	Analyte	Current Validation Report[a]	Calibrated Range	Sample Analysis Report
		Total Antibody	VIMME1706E1 A2	374-3049 ng/mL	B1102201E3

a The most current versions of the validation reports and sample analysis reports are listed and are cumulative for all previous versions. Validation reports and sample analysis reports cited in the corresponding clinical study reports (CSRs) were those in effect at the time of CSR approval.

The bioanalytical methods used in study GS-US-592-6173 for quantification of total SN-38 (the combined amounts of free SN-38 in solution [unbound to the antibody-drug conjugate [ADC] [hRS7-SN-38]] and acid-dissociated (hydrolyzed) SN-38), and total antibody (hRS7-IgG and HRS7-SN-38) in serum were conducted using the same methods that were used in previous applications and will not be further discussed in this report.

The partially-validated bioanalytical method results (method TP-80150; validation report: V1102206E1) are described below.

Validation results

- Method V11022061E1 for free SN-38

The bioanalytical method TP-80150 was partially validated at KCAS Bio (Olathe, Kansas, USA) under KCAS Project Number V1102206E1 and was performed for the determination of free SN-38 in human serum. KCAS method TP-80150 is an LC-MS/MS method identical to KCAS method TP70467 with the exception of SN-38G being removed from the preparations and analysis. Thus, the purpose of this partial validation was to remove SN-38 glucuronide from the existing test procedure showing that free SN-38 analysis is equivalent without SN-38 glucuronide. The assay was analyzed in the range of 1.00 – 500 ng/mL and is for use on human serum samples obtained during clinical trials.

The cross validation consists of evaluation of the following parameters:

1. Accuracy and Precision for SN-38 only

2. Cross validation of TP70467 with TP-80150. Analysis of pooled subject samples from clinical study will be run using both test procedures. Results were compared for cross validation. A total of 84 samples with reportable SN-38 concentrations were chosen to create a pool of 21 samples.

ADA assay

The immunogenicity of SG or its components was assessed in clinical studies by evaluating and characterizing antidrug antibody (ADA) response using a semiquantitative electrochemiluminescence (ECL) immunoassay format to detect anti-SG antibodies and a multitiered approach that includes domain specificity testing. A competitive ligand-based ECL neutralizing antibody (NAb) assay method was developed and validated to evaluate the ability of ADAs to interfere with the activity of SG or its components.

These assay methods to detect the presence of ADAs and Nabs were developed and validated in accordance with agency guidance (the recent FDA guidance "Immunogenicity Testing of Therapeutic Protein Products Developing and Validating Assays for Anti-Drug Antibody Detection" as well as the EMA's "Guidance on Immunogenicity Assessment of Therapeutic Proteins" (European Medicines Agency (EMA) 2017, U.S. Department of Health & Human Services (DHHS) 2019)) and have been used to test for the presence, domain specificity, and titer of SG-specific ADAs in serum samples from participants in all SG clinical studies conducted thus far and for all clinical NAb evaluations, as stated by the MAH.

To assess the immunogenicity of SG or its components, all clinical samples from studies IMMU-132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09, GS-US-592-6238 and GS-US-592-6173, that were available for analysis, were analyzed using the ADA method validated under V1101906E1_A1. All ADA confirmed positive clinical samples using the ADA method validated under V1101906E1_A1 were analyzed for neutralizing activity using the NAb method validated under RSYP2.

Table 4 Summary of method validation reports

Report No.	Report Title	Analytes
VIMME1712E1	Bioanalytical Method Validation Report for the Detection of Anti-hRS7-SN8 Antibodies in Human Serum by Electrochemiluminescence (ECL) Assay	Antibodies to hRS7-SN38
V1101906E1_A1[a]	Validation of an Electrochemiluminescent Assay Method TP70641 for the Screening, Confirmation, Titration, and Assessment of hRS7 Domain Specificity of Anti-hRS7-SN8 (Anti-GS-0132) Antibodies in Human Serum	Antibodies to hRS7-SN38
RSYP2[a]	Validation of an Electrochemiluminescent Ligand Binding Assay Method for the Detection of Anti-GS-0132 Neutralizing Antibodies in Human serum	Neutralizing antibodies to hRS7-SN38

a Denotes methods used to generate the results provided in this Integrated Summary of Immunogenicity document.

These submitted bioanalytical methods /assays for the determination of ADA (V1101906E1_A1) and Nab (RSYP2) were already assessed during previous procedures. No new information is provided with the current dossier, as there is no change in bioanalytical methods / assays. The bioanalytical methods to detect the presence of ADAs (V1101906E1_A1) and NAbs (RSYP2) will therefore not be further discussed in this report.

Population PK

Rationale for developing an integrated PopPK model and context of use

The popPK of SG, free SN-38, and TAb (conjugated and unconjugated anti-Trop-2 antibody), have been previously characterized using the combined concentration-time data from participants with different types of epithelial cancers (study IMMU-132-01), participants with metastatic TNBC (study IMMU-132-05), and from participants with HR+/HER2− metastatic breast cancer (mBC) (study IMMU-132-09).

The current analysis applied an integrated model structure with the measured PK data of three analytes: TAb, free SN-38 and total SN-38. In addition to the data included from three clinical studies in the previously developed popPK model, this analysis included additional data from the phase 3 study GS-US-592-6173 (ASCENT-04) in first-line patients with unresectable locally advanced or metastatic TNBC whose tumours are PD-L1 positive at screening. SG was administered in combination with pembrolizumab in the study. The PK of SG were now derived based on model-estimated kinetics of conjugated SN-38 and potential change in drug-to-antibody ratio (DAR) over time. In contrast, for the purpose of the previous popPK analysis, SG concentrations were calculated based on an assumed DAR of 8 and the molecular weights for free SN-38 and the loaded hRS7 antibody of 392 Da and 161 kDa, respectively.

Compared to the previous three popPK models (2-compartment models) that were developed separately for each analyte, the integrated model was developed to provide a more mechanistic and flexible structure to describe the dynamic change of TAb and free SN-38 at first cycle and at steady state. Covariate assessment for each analyte was performed during the model development of the three-analyte popPK model, including the assessment of pembrolizumab combination effect on the PK of TAb and SN-38. In this regard, this integrated popPK analysis has been updated to integrate relevant PK data collected from study GS-US-592-6238 (ASCENT-03, monotherapy).

The PopPK model was also used to identify the effect of intrinsic and extrinsic factors on the exposure to SG, free SN-38, and Tab and to predict individual exposures of SG, TAb and free SN-38 for subsequent exposure-response analyses.

PK Data Set and Methods

The updated PopPK analysis dataset included a total of 1276, 1284, and 1283 participants, contributing with 9704, 9019, and 9893 observations of total antibody (TAb), total SN-38, and free SN-38, respectively, from 5 clinical studies (IMMU-132-01, IMMU-132-05, IMMU-132-09, GS-US-592-6238 and GS-US-592-6173). For observed Tab, total SN-38 and free SN-38 limit of quantification (BLQ) samples were calculated to 0.7%. 8.3% and 36.5%, respectively. Below the BLQ, observations were flagged in the popPK analysis dataset and a likelihood-based approach (M3) was implemented.

The popPK analysis was conducted via nonlinear mixed-effects modelling (NONMEM) software, Version 7.5 (ICON Development Solutions, Dublin, UK). Data manipulation, postprocessing, summaries, and plotting were performed using R 4.2 or above.

Population and individual model parameters were estimated using the stochastic approximation expectation maximization (SAEM) method followed by importance sampling Monte Carlo (IMP). The 95% CI of parameter estimates were derived from the covariance matrix of the estimates (NONMEM $COV step).

Model structure

The structural model was built on prior knowledge from previous modelling and incorporates several assumptions. Conjugated SN-38 and TAb are assumed to share the same PK parameters of clearances and volume of distributions since kinetics are expected to be driven by the monoclonal antibody. Both linear and nonlinear clearance pathways were tested to investigate the necessity of their inclusion in the model. The compartmental model further accounts for the formation kinetics of free SN-38 whose formation kinetics were driven by the deconjugation process - characterized by the deconjugation rate constant (Kdeg) - from the conjugated SN-38. The model defined a mass balance such that the sum of free SN-38 and conjugated SN-38 amount corresponded to the observed total SN-38. Both 1-compartment and 2-compartment models were assessed for free SN-38 PK, as well as linear and nonlinear elimination pathways. The concentration of SG (CSG) was calculated as the ratio of conjugated SN-38 concentration to the time-varying DAR:

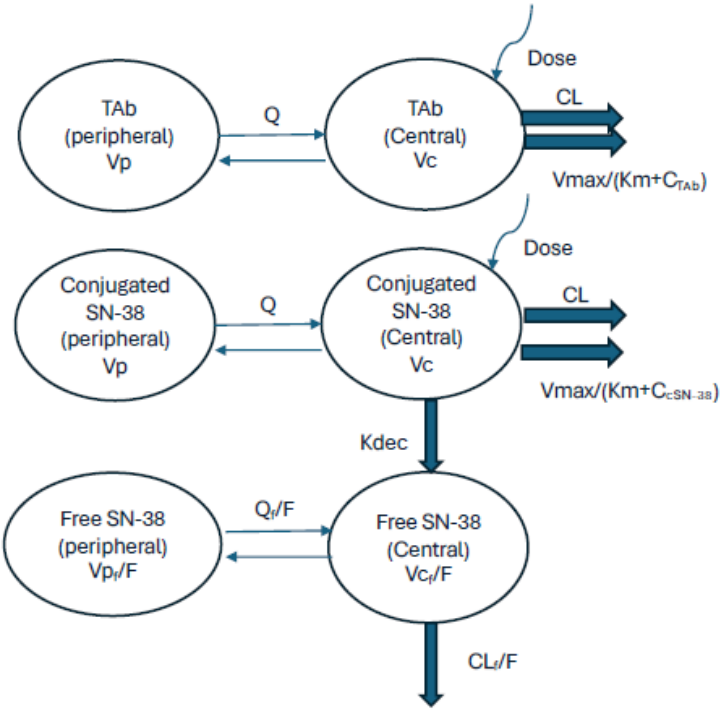
$$C_{SG} = \frac{C_{\text{Conjugated SN-38}}}{DAR}$$

where DAR changes over time according to the following equation:

$$DAR = 1 + 7e^{-Kdec \times TAD}$$

TAD represents time after each SG dose. All concentrations are represented in molar units. The DAR at time zero equals 8 and changes with time. As the concentration of SG was the fraction of conjugated SN-38 over DAR, DAR should not take values below 1. A value less than 1 would suggest lack of conjugated SN-38 and the ratio would not be numerically meaningful. Therefore, a minimum DAR of 1 was assumed to be present for the entire duration of conjugated SN-38 exposure throughout deconjugation.

Figure 2 Integrated model structure



Dose of SG is in molar units. CL: linear clearance of TAb and conjugated SN-38, Km: the exposure eliciting half of the maximum effect, Vmax: maximal Michaelis-Menten clearance, Q: intercompartmental clearance of TAb and conjugated SN-38, Vc: central volume of distribution of TAb and conjugated SN-38, Vp: peripheral volume of distribution of TAb and conjugated SN-38, CL_f/F: apparent clearance of free SN-38, Q_f/F: apparent intercompartmental clearance of free SN-38, Vc_f/F: apparent central volume of distribution of free SN-38, Vp_f/F: apparent peripheral volume of distribution of free SN-38, K_{dec}: first order deconjugation rate constant.

Covariate model and model evaluation

Covariates screened for inclusion into the popPK model were based on mechanistic plausibility, exploratory analysis, and clinical interest. The effects of these covariates on clearance parameters (of both TAb and free SN-38) were included in the full model. The conjugated SN-38 and TAb shared the same PK parameters for clearances and volume of distributions. The covariates, therefore, apply to both analytes. The potential effect of ADA presence during the SG treatment on clearance was explored.

Table 5 Covariates to assess impact of exposures to total antibody, SG and free SN-38

Factors	Covariates Included
Demographic	Sex (male or female), age, race (Asian, White, Black or African American, or other), and body weight
Disease	Tumor type (TNBC, HR+/HER2− mBC, or other), ECOG performance status (0 or ≥ 1), prior cancer treatment (platinum containing, CPI, both platinum containing and CPI, others, or no prior cancer treatment), number of prior cancer treatments (0, 1, 2, 3, 4, or ≥ 5), and baseline tumor size
Participant	SG monotherapy or combination with pembrolizumab, serum albumin, hepatic impairment based on NCI-ODWG classification (normal, mild, moderate, or missing), renal function or impairment (based on eGFR estimated using MDRD equation), and UGT1A1 genotype (*1/*1,*1/*28,*28/*28, *1/*6, *6/*6, or other)

CPI = checkpoint inhibitor; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-

positive; mBC = metastatic breast cancer; MDRD = modification of diet in renal disease; NCI-ODWG = National Cancer Institute Organ Dysfunction Working Group; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

A full covariate modelling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented. The full model was reduced to the final model by removing covariates with 95% CIs of their estimated effects falling within the region of practical equivalence (ROPE), which is commonly defined as 80% to 125% of the null value.

Final model performance was evaluated by visual predictive check (VPC). Post hoc empirical Bayes estimates (EBEs) from the final models were used to calculate exposure metrics (C_{max1}, AUC_{0-168}, and C_{trough}) of total antibody, free SN-38, and SG. Forest plots were generated with simulations informed by model parameter sets and dataset covariates. A total of 1000 sets of parameters were sampled from distributions based on parameter estimates and the associated variance-covariance matrix of the final model. The influence of each covariate was compared against a reference individual PK parameter. Uncertainty was computed as a 95% CI for each exposure metric.

Final popPK model and Results

The PK of the TAb and conjugated SN-38 were described by a two-compartment model with linear and non-linear (Michaelis-Menten [MM]) clearance pathways. Free SN-38 PK were described by a two-compartment model with linear clearance.

Estimates for the effects of age, sex, hepatic function, albumin, Eastern Cooperative Oncology Group (ECOG) performance status, baseline tumour size, and number of prior lines of therapy in the full covariate model fell within the ROPE for AUC_{0-168} and C_{max1} of total antibody, SG, and free SN-38. These effects were considered not clinically meaningful and, therefore, not included in the final model. In the final model, the effects of body weight on CLs and volumes were included using allometric scaling with estimated coefficients. The effects of race, tumour type, renal function, and UGT1A1 genotype were estimated on the CLs of total antibody and free SN-38. An update of the integrated popPK model with PK data from study GS-US-592-6238 resulted in comparable parameter estimates.

Table 6 Population Pharmacokinetic model parameters (integrated and updated popPK model)

Parameter	PopPK Model[a] Estimate (95% CI)	Updated PopPK Model[b] Estimate (95% CI)
Structural Model Parameters		
Total antibody/conjugated SN-38 clearance (CL, L/h)	0.0120 (0.0115, 0.0125)	0.0128 (0.0122, 0.0134)
Total antibody/conjugated SN-38 central volume (Vc, L)	2.83 (2.79, 2.86)	2.81 (2.78, 2.84)
Total antibody/conjugated SN-38 intercompartmental clearance (Q, L/h)	0.00841 (0.00824, 0.00858)	0.00865 (0.00850, 0.00879)
Total antibody/conjugated SN-38 peripheral volume (Vp, L/h)	1.80 (1.71, 1.89)	1.98 (1.89, 2.08)
Apparent free SN-38 clearance (CL_f/F, L/h)	4.45 (3.98, 4.93)	5.27 (4.74, 5.80)
Apparent free SN-38 central volume (Vc_f/F, L)	1.47 (1.08, 1.86)	0.986 (0.540, 1.43)
Apparent free SN-38 inter-compartmental clearance (Q_f/F, L/h)	1.03 (0.839, 1.22)	1.27 (0.969, 1.56)
Apparent free SN-38 peripheral volume (Vp_f/F, L)	20.2 (17.3, 23.0)	15.1 (12.7, 17.5)
Deconjugation rate constant (K_{dec}, 1/h)	0.0419 (0.0416, 0.0423)	0.0419 (0.0413, 0.0424)
Total antibody/conjugated SN-38 maximal MM elimination (V_{max}, µM/h)	0.00227 (0.00197, 0.00256)	0.00269 (0.00240, 0.00299)
Total antibody/conjugated SN-38 half-inhibitory concentration (KM, µM)	0.0328 (0.0263, 0.0394)	0.0404 (0.0318, 0.0490)
Covariate Effects Parameters: Total Antibody		
CL – body weight effect on CL and Q	0.492 (0.433, 0.551)	0.518 (0.468, 0.567)
CL – Black and other race effect on CL	0.0197 (0.00224, 0.0372)	NA
CL – Asian race effect on CL	0.000172 (−0.0375, 0.0378)	NA
CL – mUC, NSCLC, and other tumor effect on CL	−0.287 (−0.294, −0.279)	NA
CL – HR+/HER2− tumor effect on CL	−0.113 (−0.131, −0.0949)	NA
CL – line of therapy (post first line) effect on CL	NA	−0.256 (−0.283, −0.229)
CL – eGFR category (60 to < 90) effect on CL	−0.0486 (−0.0641, −0.0332)	−0.0518 (−0.0846, −0.0191)

Parameter	PopPK Model[a] Estimate (95% CI)	Updated PopPK Model[b] Estimate (95% CI)
CL – eGFR category (< 60) effect on CL	0.0162 (−0.00201, 0.0343)	−0.0142 (−0.104, 0.0753)
CL – UGT1A1 *1/*28 effect on CL	0.00529 (−0.0128, 0.0234)	−0.0171 (−0.0499, 0.0157)
CL – UGT1A1 *28/*28 effect on CL	0.0711 (0.0593, 0.0828)	0.0242 (−0.0311, 0.0795)
CL – UGT1A1 *1/*6, *6/*6, and all others effect on CL	0.121 (0.0943, 0.149)	−0.00151 (−0.0704, 0.0674)
CL – UGT1A1 missing effect on CL	−0.0299 (−0.0500, −0.00989)	−0.0130 (−0.0572, 0.0311)
Vc – body weight effect on Vc and Vp	0.540 (0.487, 0.594)	0.526 (0.480, 0.572)
Covariate Effects Parameters: Free SN-38		
CL_f/F – body weight effect on SN-38 CL and Q	0.469 (0.292, 0.646)	0.475 (0.319, 0.632)
CL_f/F – Black and other race effect on SN-38 CL	−0.0388 (−0.174, 0.0965)	NA
CL_f/F – Asian race effect on SN-38 CL	0.0668 (−0.152, 0.285)	NA
CL_f/F – mUC, NSCLC, and other tumor effect on SN-38 CL	−0.0625 (−0.168, 0.0434)	NA
CL_f/F – HR+/HER2− mBC tumor effect on SN-38 CL	−0.122 (−0.217, −0.0268)	NA
CL_f/F – line of therapy (post first line) effect on SN-38 CL	NA	−0.266 (−0.331, −0.201)
CL_f/F – eGFR category (60 to < 90) effect on SN-38 CL	−0.0647 (−0.151, 0.0220)	−0.0768 (−0.154, 0.000428)
CL_f/F – eGFR category (< 60) effect on SN-38 CL	−0.0781 (−0.224, 0.0678)	−0.0831 (−0.217, 0.0509)
CL_f/F – UGT1A1 *1/*28 effect on SN-38 CL	−0.0119 (−0.111, 0.0875)	−0.0334 (−0.121, 0.0540)
CL_f/F – UGT1A1 *28/*28 effect on SN-38 CL	−0.0905 (−0.231, 0.0504)	−0.0856 (−0.217, 0.0463)
CL_f/F – UGT1A1 *1/*6, *6/*6, and all others effect on SN-38 CL	0.0953 (−0.209, 0.399)	0.118 (−0.129, 0.365)
CL_f/F – UGT1A1 missing effect on SN-38 CL	−0.149 (−0.286, −0.0114)	−0.168 (−0.289, −0.0461)
Vc_f/F body weight effect on SN-38 Vc and Vp	0.494 (0.0915, 0.897)	0.251 (−0.173, 0.675)
Interindividual variance parameters		
IIV-CL	0.102 [%CV=32.8] (0.102, 0.103)	0.0733 [%CV=27.6] (0.0604, 0.0861)

Parameter	PopPK Model[a] Estimate (95% CI)	Updated PopPK Model[b] Estimate (95% CI)
IIV-Vc	0.0292 [%CV=17.2] (0.0272, 0.0311)	0.0262 [%CV=16.3] (0.0235, 0.0290)
IIV-Q	0.0433 [%CV=21.3] (0.0433, 0.0453)	0.0380 [%CV=19.7] (0.0325, 0.0435)
IIV-Vp	0.196 [%CV=46.5] (0.180, 0.212)	0.222 [%CV=49.9] (0.183, 0.261)
IIV-CL_f/F	0.295 [%CV=58.6] (0.219, 0.371)	0.297 [%CV=58.8] (0.246, 0.349)
IIV-Vc_f/F	1.92 [%CV=241] (1.51, 2.33)	2.38 [%CV=314] (1.59, 3.18)
IIV-Q_f/F	1.00 [%CV=131] (FIXED)	1.00 [%CV=131] (FIXED)
IIV-Vp_f/F	1.00 [%CV=131] (FIXED)	1.00 [%CV=131] (FIXED)
IIV-Kdec	N/A	0.0250 [%CV=15.9] (FIXED)
IIV-V_{max}	0.392 [%CV=69.3] (0.311, 0.474)	0.391 [%CV=69.1] (0.317, 0.464)
IIV-KM	0.308 [%CV=60.1] (0.156, 0.460)	0.440 [%CV=74.4] (0.202, 0.678)
Interindividual covariance parameters		
CL-Vc	0.0322 [Corr=0.589] (0.0275, 0.0368)	0.0262 [Corr=0.598] (0.0215, 0.0309)
CL-Q	0.0113 [Corr=0.168] (0.00456, 0.0181)	0.00983 [Corr=0.186] (0.00445, 0.0152)
Vc-Q	0.0321 [Corr=0.893] (0.0307, 0.0335)	0.0277 [Corr=0.877] (0.0241, 0.0313)
CL-Vp	−0.0465 [Corr=−0.328] (−0.0625, −0.0305)	−0.0367 [Corr=−0.288] (−0.0534, −0.0201)
Vc-Vp	0.0317 [Corr=0.420] (0.0257, 0.0378)	0.0295 [Corr=0.386] (0.0205, 0.0385)
Q-Vp	0.0683 [Corr=0.733] (0.0606, 0.0760)	0.0701 [Corr=0.762] (0.0567, 0.0835)
CL_f/F-Vc_f/F	−0.0108 [Corr=−0.0144] (−0.109, 0.0876)	−0.0625 [Corr=−0.0742] (−0.157, 0.0317)
Residual errors		
StD of RUV-free SN-38 (Studies GS-US-592-6238 [only in updated model] and GS-US-592-6173)	0.918 (0.872, 0.965)	0.871 (0.840, 0.902)

Parameter	PopPK Model[a] Estimate (95% CI)	Updated PopPK Model[b] Estimate (95% CI)
StD of RUV-free SN-38 (Study IMMU-132-01)	0.557 (0.535, 0.579)	0.572 (0.548, 0.595)
StD of RUV-free SN-38 (Study IMMU-132-05)	0.611 (0.563, 0.659)	0.613 (0.561, 0.665)
StD of RUV-free SN-38 (Study IMMU-132-09)	0.539 (0.517, 0.561)	0.539 (0.517, 0.560)
RUV-total antibody	0.0638 [StD=0.253] (0.0614, 0.0661)	0.0651 [StD=0.255] (0.0629, 0.0672)
RUV-total SN-38	0.0573 [StD=0.239] (0.0549, 0.0597)	0.0533 [StD=0.231] (0.0514, 0.0552)

%CV = percentage coefficient of variation; CI = confidence interval; Corr = correlation coefficient; eGFR = estimated glomerular filtration rate; HER2− = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; IIV = interindividual variability; mBC = metastatic breast cancer; MM = Michaelis-Menten; mUC = metastatic urothelial cancer; NA = not available; NSCLC = non–small cell lung cancer; PopPK = population pharmacokinetic; RUV = residual unexplained variability; StD = standard deviation; UGT1A1 = uridine diphosphate-glucuronosyltransferase 1A1

a Model-based on Studies IMMU-132-01, IMMU-132-05, updated IMMU-132-09, and GS-US-592-6173.

b Model-based on Studies IMMU-132-01, IMMU-132-05, updated IMMU-132-09, GS-US-592-6173, and GS-US-592-6238.

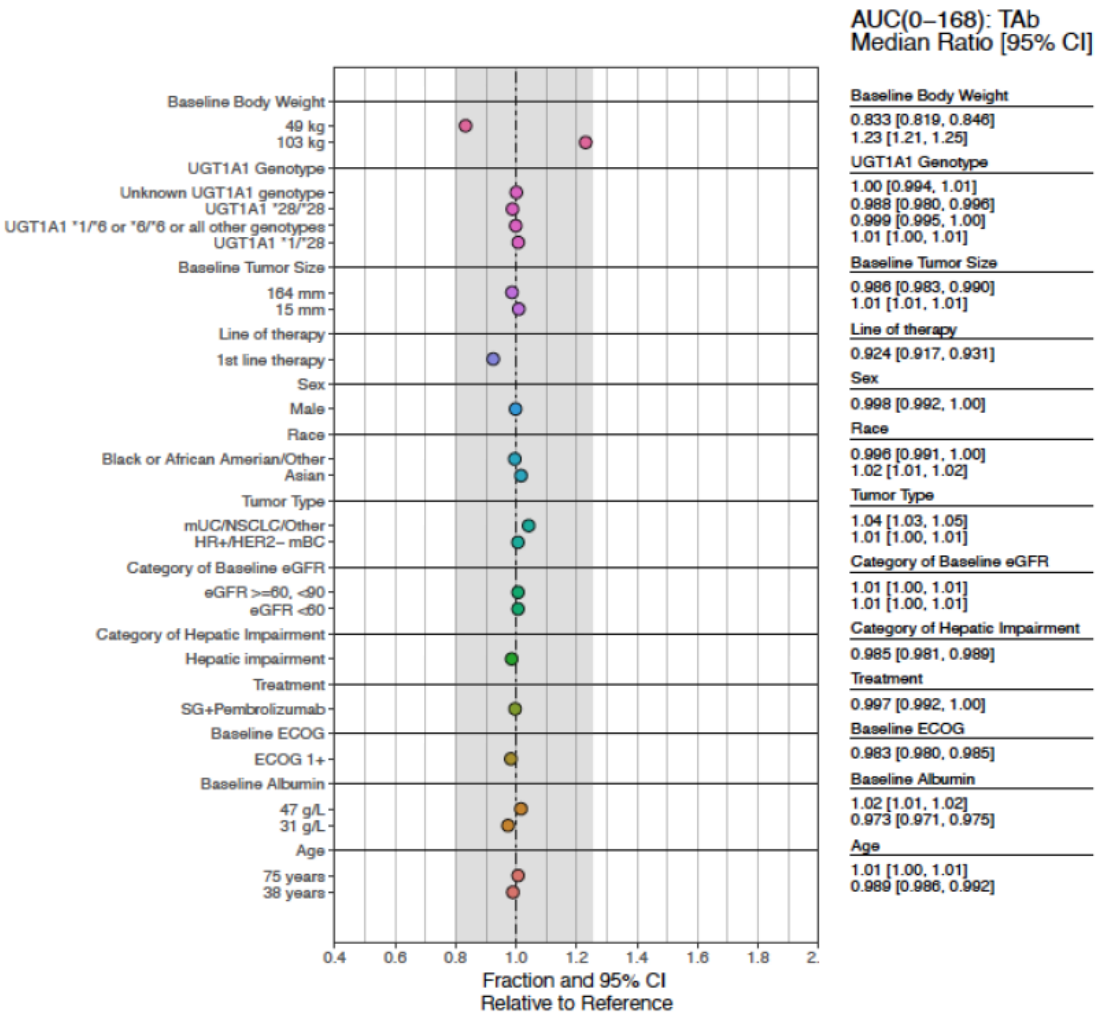
NA indicates the parameter was not included in the PopPK model.

Source: QP-2024-2004 Trodelvy PopPK, Tables 5.8 and 5.9; Source code: final-param-table.R; Source file: pk-param-final-fixed.tex and pk-param-final-random.tex

Impact of Covariates on Exposure

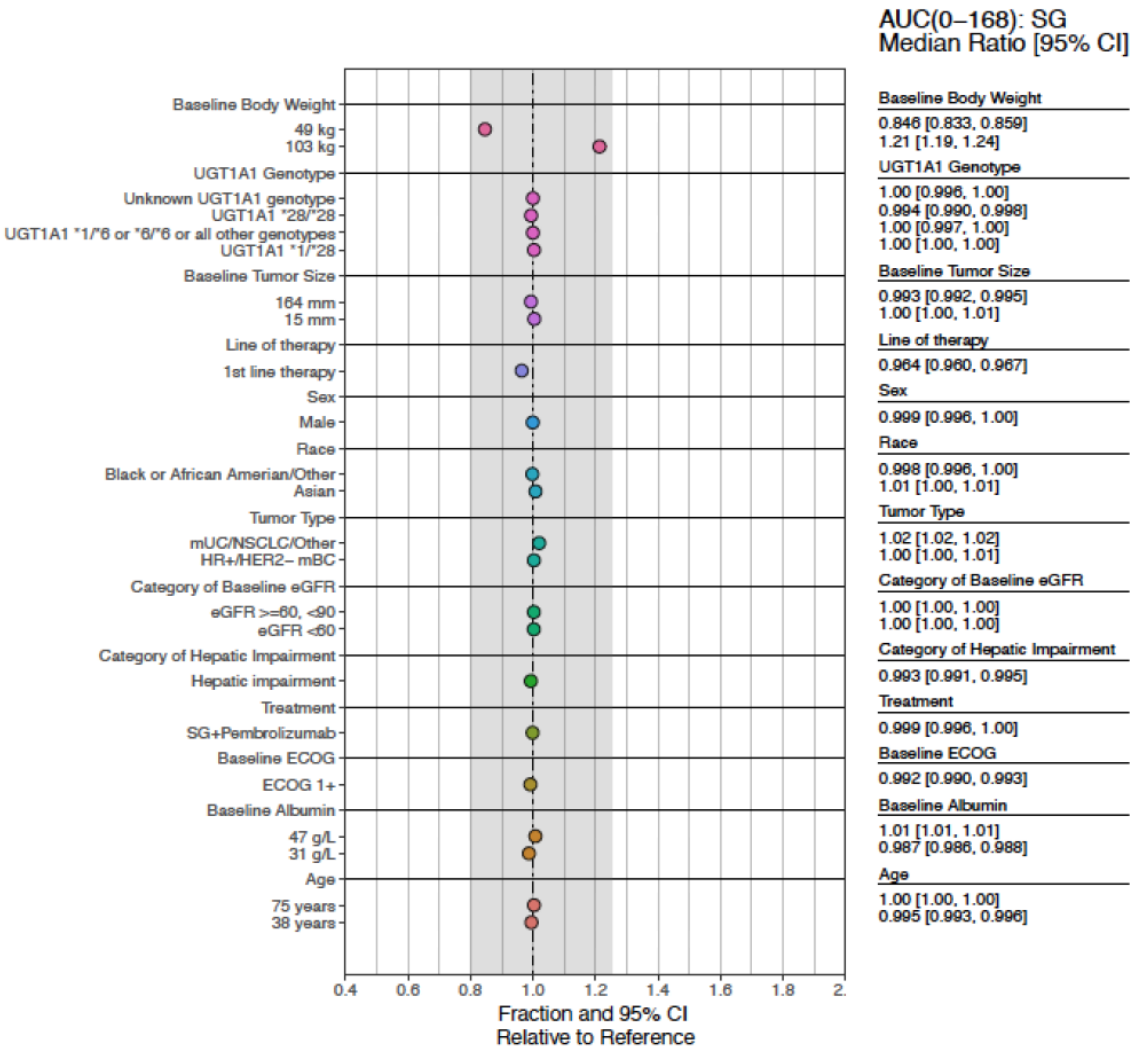
Forest plots depict the impact of the estimated covariate effects on exposure (AUC_{0-168} and C_{max1}) presenting the ratio of exposures of TAb, free SN-38 and model-derived SG, given a covariate effect, relative to the exposure from a reference subject. The reference range was equivalent to a 20% change on the log scale. The reference subject is a 58 years, female with TNBC, ECOG 0, baseline albumin of 40 g/L, baseline tumour size of 38 mm, treated with SG monotherapy as post first-line cancer treatment, eGFR ≥ 90 mL/min/1.73m2, normal hepatic function, UGT1A1 genotype of *1/*1, and treated with SG monotherapy as post first-line cancer treatment,

Figure 3 Forest Plot of Estimated Covariate Effects on AUC0-168 in Final Updated Model: Total Antibody



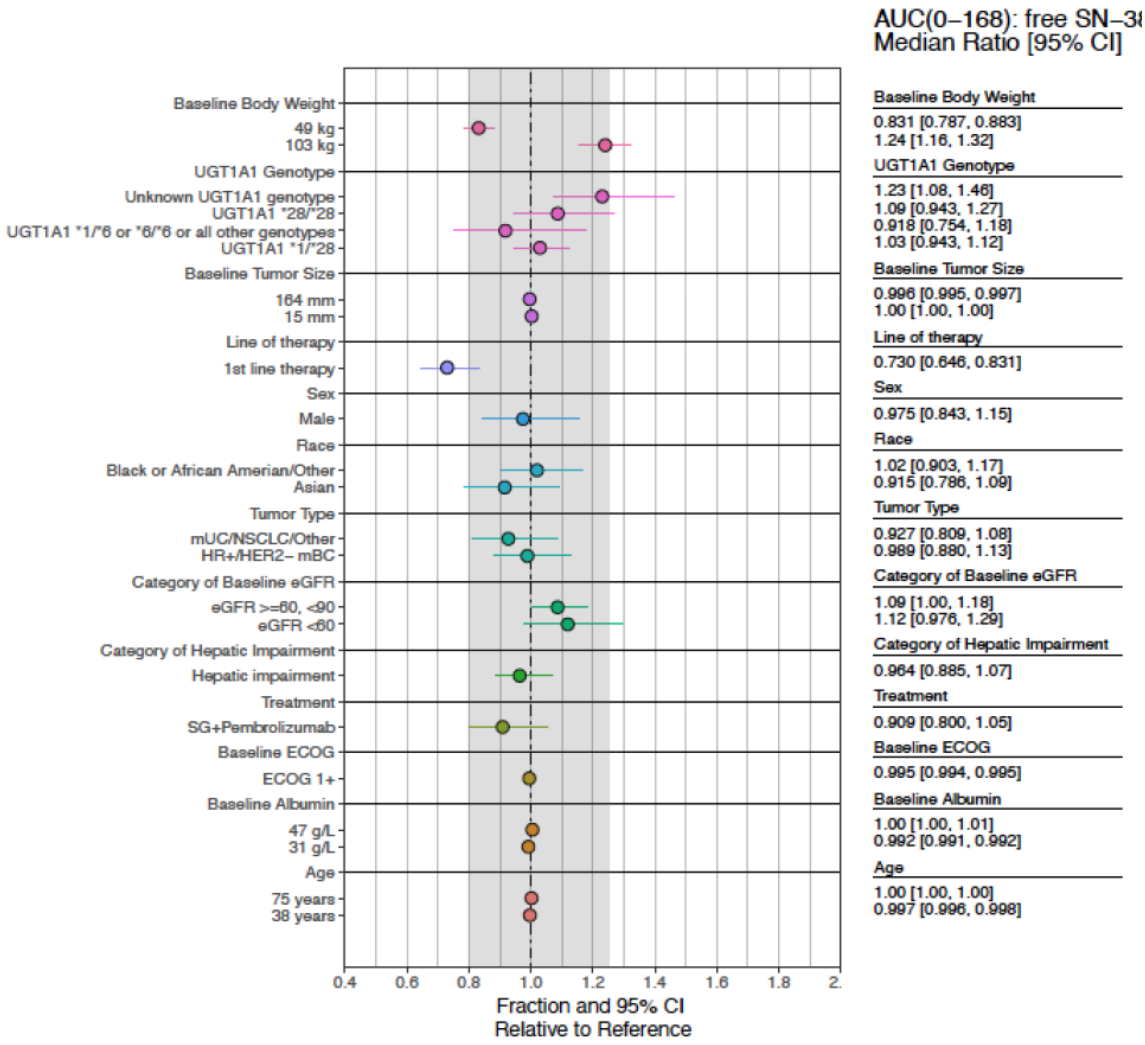
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; HER2− = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; mBC = metastatic breast cancer; mUC = metastatic urothelial cancer; NSCLC = non–small cell lung cancer; PD-1 = programmed cell death protein 1; SG = sacituzumab govitecan; Tab = total antibody; TNBC = tripe-negative breast cancer; UGT1A1 = uridine diphosphate-glucuronosyltransferase 1A1 Reference participant is a, female with TNBC, ECOG 0, baseline albumin of 40 g/L, baseline tumor size of 38 mm, treated with SG monotherapy as post first-line cancer treatment, eGFR ≥ 90 mL/min/1.73m2, normal hepatic function, and UGT1A1 genotype of *1/*1. Points represent the estimated median effect. Horizontal bars represent the 95% CIs of the estimated effects.

Figure 4 Forest Plot of Estimated Covariate Effects on AUC0-168 in Final Updated Model: SG



CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; HER2− = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; mBC = metastatic breast cancer; mUC = metastatic urothelial cancer; NSCLC = non–small cell lung cancer; PD-1 = programmed cell death protein 1; SG = sacituzumab govitecan; Tab = total antibody; TNBC = tripe-negative breast cancer; UGT1A1 = uridine diphosphate-glucuronosyltransferase 1A1 Reference participant is a female with TNBC, ECOG 0, baseline albumin of 40 g/L, baseline tumor size of 38 mm, treated with SG monotherapy as post first-line cancer treatment, eGFR ≥ 90 mL/min/1.73m2, normal hepatic function, and UGT1A1 genotype of *1/*1. Points represent the estimated median effect. Horizontal bars represent the 95% CIs of the estimated effects.

Figure 5 Forest Plot of Estimated Covariate Effects on AUC0-168 in Final Updated Model: Free SN-38

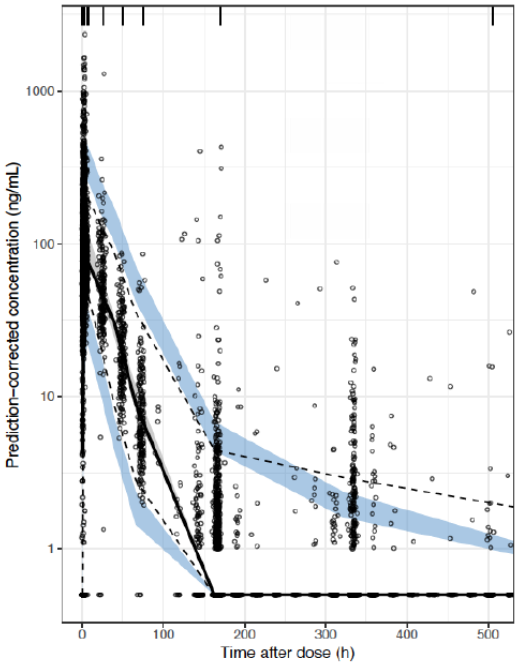


CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; HER2− = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; mBC = metastatic breast cancer; mUC = metastatic urothelial cancer; NSCLC = non–small cell lung cancer; PD-1 = programmed cell death protein 1; SG = sacituzumab govitecan; Tab = total antibody; TNBC = tripe-negative breast cancer; UGT1A1 = uridine diphosphate-glucuronosyltransferase 1A1 Reference participant is a female with TNBC, ECOG 0, baseline albumin of 40 g/L, baseline tumor size of 38 mm, treated with SG monotherapy as post first-line cancer treatment, eGFR ≥ 90 mL/min/1.73m2, normal hepatic function, and UGT1A1 genotype of *1/*1. Points represent the estimated median effect. Horizontal bars represent the 95% CIs of the estimated effects.

Model evaluation

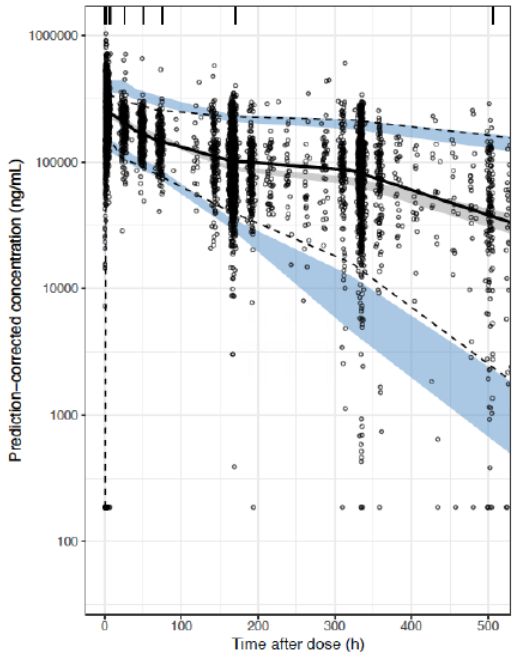
Simulation-based model diagnostics (VPCs) were generated to investigate the predictive performance of the integrated popPK model. Observed data of the three analytes and the model-simulated median, fifth, and 95th percentiles for the final model are opposed.

Figure 6 Final updated model: Prediction-corrected VPC of free SN-38



VPC = visual predictive check
Observed data are represented by black circles and summarized as the median (solid black line) and fifth and 95th percentiles (dashed black lines). Percentiles are overlaid by the simulated 95% confidence intervals from the final model (shaded areas).
Source code: vpc-final-model.R

Figure 7 Final updated model: Prediction-corrected VPC of total antibody vs time after dose



VPC = visual predictive check
Observed data are represented by black circles and summarized as the median (solid black line) and fifth and 95th percentiles (dashed black lines). Percentiles are overlaid by the simulated 95% confidence intervals from the final model (shaded areas).
Source code: vpc-final-model.R

ADME

The PK of total antibody, free SN-38, and conjugated SN-38 was characterized in participants with solid tumours using an integrated PopPK model (including data from studies IMMU-132-01, IMMU-132-05, IMMU-132-09, GS-US-592-6238 and GS-US-592-6173).

Final model EBEs were used to calculate PK parameters and exposure metrics in participants included in the analysis population and receiving IV SG 10 mg/kg on Days 1 and 8 of 21-day treatment cycles.

Absorption

Sacituzumab govitecan is administered via IV infusion. No studies characterizing absorption via other routes of administration have been conducted with SG; thus, drug absorption is not applicable. The T_{max} of SG typically occurred at the end of SG infusion across all clinical studies.

Distribution

Based on the updated PopPK analyses using data from studies IMMU-132-01, IMMU-132-05, IMMU 132 09, GS-US-592-6238 and GS-US-592-6173, the Vc and Vp of SG were estimated to be 2.81 and 1.98 L, respectively, corresponding to an estimated volume of distribution at steady state (Vss) for SG of 4.79 L.

The mean (%CV) of estimated Vc of both total antibody and SG is 2.83 L (18.9 %).

Metabolism

No metabolism studies have been conducted with SG. The metabolism of SG is expected to be mediated by both catabolism of hRS7 IgG1κ into small peptides and amino acids in a manner similar to endogenous IgG.

The metabolism of the payload, SN-38 is mediated by hepatic UGT1A1 to SN-38 glucuronide (SN-38G), an inactive metabolite.

Elimination

The median (range) of terminal half-life ($t_{1/2}$) of SG is 170 hours (90.7, 2.14e+03) and the median (range) of apparent half-life of free SN-38 is 21.4 hours (15.4, 230).

The mean half-life [$t_{1/2}$ (%CV)] of SG is 181 hours (48.2 %) and the mean apparent half-life (%CV) of free SN-38 is 23.0 hours (43.9%).

The mean (%CV) of CL of total antibody and SG is 0.0106 L/h (26.8%) and 0.129 L/h (21.0%), respectively.

No excretion studies have been conducted with SG. SN-38 and SN-38G are reported to be primarily excreted through the hepatobiliary route, with lesser amounts detected in the urine.

Dose proportionality and time dependencies

Final model EBEs were used to calculate PK parameters and exposure metrics in participants included in the analysis population and receiving SG 10 mg/kg on Days 1 and 8 of 21-day treatment cycles.

The model-predicted concentration-time profiles indicated minimal accumulation of SG and free SN-38, while the accumulation of total antibody was moderate.

Results based on the updated population pharmacokinetic (PopPK) analysis from studies IMMU-132-01, IMMU-132-05, IMMU-132-09, GS-US-592-6173 and GS-US-592-6238 are presented in the table below.

Table 7 Summary (Mean [CV%]) of Model-Derived Exposure During Cycles 1 and 6

Exposure Metric	Cycle	Free SN-38	SG	Total Antibody
C_{max1} (ng/mL)	1	96.62266 (40.7)	258377.6 (17.3)	229787.5 (17.1)
$AUC_{0\text{-}168}$ (ng/mL*h)		3119.736 (61.8)	1.228598e+07 (19.0)	2.239870e+07 (19.2)
$C_{trough,168}$ (ng/mL)		1.057718 (444)	5439.687 (50.5)	71493.03 (27.8)
C_{max1} (ng/mL)	6	97.18813 (41.0)	259024.7 (17.3)	324017.1 (22.2)
$AUC_{0\text{-}168}$ (ng/mL*h)		3190.527 (67.5)	1.270762e+07 (19.3)	3.642975e+07 (27.6)
$C_{trough,168}$ (ng/mL)		1.392935 (434)	8263.362 (48.4)	145583.4 (36.2)

%CV = percentage coefficient of variation; SG = sacituzumab govitecan
Participants with metastatic breast cancer: n = 1048
Source code: ebe-sim-ppk.R

Pharmacokinetics in target population

Study GS-US-592-6173 (ASCENT-04)

In the pivotal study GS-US-592-6173 (ASCENT-04), serum samples for PK analyses for total antibody, total SN-38, and free SN-38 were collected. Collection times for PK samples were predose and after the end of infusion on Day 1 and Day 8 of Cycle 1; Day 8 of Cycles 2, 6, and 10. Thereafter, predose samples were collected on Day 8 of every 8 cycles after Cycle 10 (e.g. Cycle 18 Day 8, Cycle 26 Day 8); and at the end of treatment (EOT) visit.

Of the 221 participants who were randomized to receive SG + pembrolizumab in this study, PK samples were available from 150 participants for total antibody, 205 participants for total SN-38, and 207 participants for free SN-38.

The mean C_{max} for total antibody, total SN-38, and free SN-38 from Cycle 1 to Cycle 10 ranged from approximately 235,000 to 318,000 ng/mL, 5060 to 4340 ng/mL, and 114 to 95 ng/mL, respectively.

For total antibody, mean C_{max} slightly increase over time (up to Cycle 10). For total SN-38, mean Cmax slightly decrease over time (up to Cycle 10).

No apparent accumulation over time was observed for total SN-38 or free SN-38.

Table 8 GS-US-592-6173: Mean Serum PK Parameters of Total Antibody, Total SN-38, and Free SN-38 by Visit (PK Analysis Set)

	C1D1	C1D8	C2D8	C6D8	C10D8	C18D8	C26D8
Total Antibody							
N	150	143	140	104	63	—	—
C_{max} (ng/mL)	235,000	279,000	299,000	311,000	318,000	—	—
N	149	146	147	110	65	19	3
C_{trough} (ng/mL)	—	66,100	91,900	119,000	122,000	112,000	127,000
Total SN-38							
N	200	184	183	136	80	—	—
C_{max} (ng/mL)	5060	4870	4740	4430	4340	—	—
N	205	189	191	145	85	26	4
C_{trough} (ng/mL)	—	118	15.8	20.9	17.5	16.5	23.0
Free SN-38							
N	200	184	184	137	80	—	—
C_{max} (ng/mL)	114	96.8	105	102	95.2	—	—
N	207	189	191	144	85	26	4
C_{trough} (ng/mL)	—	—	—	—	—	—	—

BLQ = below the limit of quantitation; CX = Cycle X; DX = Day X; PK = pharmacokinetics; SG = sacituzumab govitecan
Values BLQ were treated as 0 for predose or postdose summary statistics.
C_{max} and C_{trough} are presented as mean.
C_{max} = PK concentration collected at end of infusion at each visit.
C_{trough} was the PK concentration collected predose at each visit.
Lower limit of quantitation was defined as 374 ng/mL for Total Antibody.
Lower limit of quantitation was defined as 5 ng/mL for Total SN-38.
Lower limit of quantitation was defined as 1 ng/mL for Free SN-38.
Pharmacokinetic Analysis Set includes randomized participants who received ≥ 1 SG dose and have ≥ 1 measurable posttreatment SG concentration.

Special populations

Effect of intrinsic factors

The PopPK analysis was used to evaluate the broader potential impact of demographic and disease-related factors on PK as covariates from all 4 studies (IMMU-132-01, IMMU-132-05, IMMU 132 09 and GS-US-592-6173) across various cancer types. Intrinsic factors, including mild or moderate renal impairment, mild hepatic impairment, age, sex, race, tumour type, and UGT1A1 genotype.

Renal Impairment

Mild (n = 454) and moderate (n = 88) renal impairment had no clinically meaningful effect on total antibody, SG, or free SN-38 exposure compared with participants with normal (n = 468) renal function for the population included in the PopPK analysis. The potential effect of severe (n = 2) renal impairment could not be appropriately estimated due to the low number of participants included in the analysis dataset.

As resulted from the updated popPK, relative to patients with eGFR ≥ 90 mL/min/1.73m2, patients with eGFR < 60 mL/min/1.73m2 had an SN-38 AUC_{0-168} ratio of 1.12 (95% CI 0.976, 1.29). The effect was not considered statistically significant.

Hepatic Impairment

Mild (n = 295) hepatic impairment showed no clinically meaningful effect on total antibody, SG, or free SN-38 exposure compared with participants with normal (n = 713) hepatic function for the population included in the PopPK analysis. A slightly potential effect of moderate (n = 4) hepatic impairment cannot be excluded at present. However, the data should be taken with caution as the number of participants included in the dataset is limited and thus limits the ability to draw any conclusion at present.

Age

Age had no effect on total antibody, SG, or free SN-38 exposure for the overall population.

Sex

Sex (male/female) had no effect on total antibody, SG, or free SN-38 exposure for the overall population.

Body Weight

Body weight was found to have a statistically significant impact on exposures of total antibody, SG, and free SN-38. The model predicted $AUC_{0\text{-}168}$ for a participant with metastatic TNBC with body weight of 49 kg (5^{th} percentile) was estimated to be 16.7%, 15.4%, and 16.9% lower, while for a participant with a body weight of 103 kg (95^{th} percentile) was estimated to be 23%, 21%, and 24% higher when compared with a typical participant (69 kg) with metastatic TNBC for total antibody, SG, and free SN-38, respectively.

Race

Race had no effect on total antibody, SG, or free SN-38 exposure for the overall population.

UGT1A1 Genotype

No significant differences in total antibody, SG, or free SN-38 exposure were observed in participants with the UGT1A1*28/*28 (n = 104) or UGT1A1*1/*28 (n = 403) genotype compared with participants with the UGT1A1*1/*1 (n = 390). Based on small sample size, AUC0−168 of free SN-38 appeared to be approximately 30% lower for participants with *1/*6 UGT1A1 genotype (N=9) relative to those with *1/*1 genotype.

As resulted from the updated popPK, the small sample size of participants with the use of UGT1A1 inhibitors or inducers during SG treatment appeared to have similar exposures of TAb and SG relative to participants that did not use UGT1A1 modulators. The exposure of free SN-38 appeared to be lower in participants with the use of UGT1A1 inducers (AUC_{0-168} of 2146.358 ng/mL*h, N=4 vs. 3242.364 ng/mL*h in those without the use of UGT1A1 inducers, N=773).

Relative to patients with UGT1A1 genotype of *1/*1, patients with UGT1A1 *1/*6, *6/*6 or all other genotypes had slightly lower AUC_{0-168} of free SN-38 (ratio 0.918 [95% CI 0.754, 1.18]). Patients with UGT1A1 *28/*28 had slightly higher $AUC_{0\text{-}168}$ of free SN-38 (ratio 1.09 [95% CI 0.943, 1.27]). However, the 95% CI for this effect crossed the null effect value indicating that the effect was not statistically significant. Other assessed genotypes (unknown) resulted in an estimated higher $AUC_{0\text{-}168}$ of free SN-38 (ratio 1.23 [95% CI 1.08, 1.46]).

Tumour Type

No significant differences in total antibody or SG exposure were observed by tumour type.

Pharmacokinetic interaction studies

Effect of extrinsic factors

No drug-drug interaction studies have been conducted with SG. An update of the integrated popPK model with PK data from study GS-US-592-6238 (monotherapy) resulted in comparable parameter estimates, supporting no apparent effect from pembrolizumab on SG's PK.

Concomitant administration of SG with UGT1A1 inhibitors may increase the incidence of adverse reactions due to the potential increase in systemic exposure to SN-38. Exposure to SN-38 may be reduced in participants concomitantly receiving UGT1A1 enzyme inducers.

Among the participants assessed in the updated PopPK analyses, only a few participants received either UGT1A1 inhibitors (n = 17) or inducers (n = 8) during SG treatment in combination with pembrolizumab***.***

2.3.3. Pharmacodynamics

Mechanism of action

Sacituzumab govitecan (SG) is a trophoblast cell-surface antigen-2 (Trop-2)-directed antibody-drug conjugate (ADC) consisting of a humanized anti-Trop-2 monoclonal antibody (hRS7) conjugated with the active metabolite of irinotecan (SN-38) by a hydrolysable linker (CL2A). SG binds to Trop 2-expressing tumour cells and is internalised with the subsequent release of SN-38 from a hydrolysable linker. SN-38 interacts with topoisomerase I and prevents re ligation of topoisomerase I induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death.

Primary and secondary pharmacology

Immunogenicity

GS-US-592-6173 (ASCENT-04)

In study GS-US-592-6173, collection times for immunogenicity (ADA) samples were at predose on Day 1 of Cycle 1; Day 8 of Cycles 2, 6, and 10; and predose on Day 8 every 8 cycles after Cycle 10 (e.g. Cycle 18 Day 8, Cycle 26 Day 8); and at the EOT visit.

Immunogenicity samples for ADA prevalence and incidence assessments were evaluable for 220 and 207 participants, respectively, who received at least 1 dose of SG 10 mg/kg in combination with pembrolizumab. One participant (0.5%) had ADAs to SG at baseline (titer < 10), which were non-neutralizing. No participant (0 out of 207; 0%) had ADAs to SG postbaseline (treatment-emergent ADAs).

Integrated summary of immunogenicity across studies

Studies IMMU-132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09, GS-US-592-6238 (ASCENT-03) and GS-US-592-6173 (ASCENT-04) provide data on the potential immunogenicity of SG.

The Immunogenicity Analysis Set includes all enrolled participants from the studies IMMU-132-01, IMMU-132-05, IMMU-132-06 (Cohorts 1 and 2), IMMU-132-09, Study GS-US-592-6238 and GS-US-592-6173 who received at least 1 dose of SG and had at least 1 non-missing reportable ADA test result. The Immunogenicity Analysis Set was used for the ADA summary and the assessment of ADA's impact on PK, safety, or efficacy when appropriate.

In studies IMMU-132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09 and study GS-US-592-6238 for participants who received SG monotherapy across multiple solid tumours, 13 of 1058 participants evaluable for ADA incidence (1.2%) had treatment-emergent ADAs to SG. The maximum reportable ADA titer observed across the studies was low and ranged from less than 10 to 90. Ten of the 13 participants with treatment-emergent ADAs also had positive NAb assessments (0.9%).

Among participants with treatment-emergent ADAs, the time to onset of ADAs after first dose of SG ranged between 22 to 245 days.

Table 9 Summary of ADA Response to Sacituzumab Govitecan (GS-US-592-6173 ISI Population)

	IMMU-132-01 SG (10 mg/kg) (N = 221)	IMMU-132-05 SG (10 mg/kg) (N = 258)	IMMU-132-06 SG (10 mg/kg) (N = 150)	IMMU-132-09 SG (10 mg/kg) (N = 265)	GS-US-592-6238 SG (10 mg/kg) (N = 264)	GS-US-592-6173 SG (10 mg/kg) (N = 220)	Overall mBC SG (10 mg/kg) (N = 893)	All Treated Mono SG (10 mg/kg) (N = 1158)
Evaluable for ADA prevalence	221	258	150	264	264	220	892	1157
Any ADA positive (baseline or post-baseline)	2 (0.9%)	4 (1.6%)	5 (3.3%)	0	4 (1.5%)	1 (0.5%)	9 (1.0%)	15 (1.3%)
ADA positive at baseline	1 (0.5%)	0	0	0	1 (0.4%)	1 (0.5%)	2 (0.2%)	2 (0.2%)
ADA not detected post-baseline and positive at baseline	1 (0.5%)	0	0	0	1 (0.4%)	1 (0.5%)	2 (0.2%)	2 (0.2%)
ADA positive post-baseline	1 (0.5%)	4 (1.6%)	5 (3.3%)	0	3 (1.1%)	0	7 (0.8%)	13 (1.1%)
Evaluable for ADA incidence	210	242	123	236	247	207	823	1058
ADA incidence (Treatment Emergent)[a]	1 (0.5%)	4 (1.7%)	5 (4.1%)	0	3 (1.2%)	0	7 (0.9%)	13 (1.2%)
ADA positive post-baseline and not positive at baseline (treatment-induced ADA)	1 (0.5%)	4 (1.7%)	5 (4.1%)	0	3 (1.2%)	0	7 (0.9%)	13 (1.2%)
Persistent Positive[b]	1 (0.5%)	3 (1.2%)	5 (4.1%)	0	3 (1.2%)	0	6 (0.7%)	12 (1.1%)
Transient Positive[c]	0	1 (0.4%)	0	0	0	0	1 (0.1%)	1 (< 0.1%)
ADA positive post-baseline and positive at baseline	0	0	0	0	0	0	0	0
Treatment-boosted ADA[d]	0	0	0	0	0	0	0	0
NAb Incidence (Treatment Emergent)[e]	1 (0.5%)	3 (1.2%)	3 (2.4%)	0	3 (1.2%)	0	6 (0.7%)	10 (0.9%)

ADA = antidrug antibody; ISI = Integrated Summary of Immunogenicity; mBC = metastatic breast cancer; mono = monotherapy; NAb = neutralizing antibody; SG = sacituzumab govitecan

a ADA incidence (Treatment-emergent ADA): the sum of both treatment-induced and treatment-boosted ADA.

b Persistent ADA: treatment-induced ADA at ≥ 2 samples during the treatment (with ≥ 16 weeks between first and last positive) or treatment-induced ADA in the last sample or with < 16 weeks before an ADA-negative last sample.

c Transient ADA: treatment-induced ADA that does not meet the definition of persistent ADA.

d Treatment-Boosted ADA: positive baseline and ((max titer of the post-baseline ADA)/(titer of baseline ADA)) ≥ 9.

e NAb incidence: proportion of participants with ≥ 1 positive NAb result based on the total N evaluable for ADA incidence as denominator.

mBC Overall: Studies IMMU-132-01, IMMU-132-05, IMMU-132-09, GS-US-592-6238; All Treated SG mono: Studies IMMU-132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09, GS-US-592-6238.

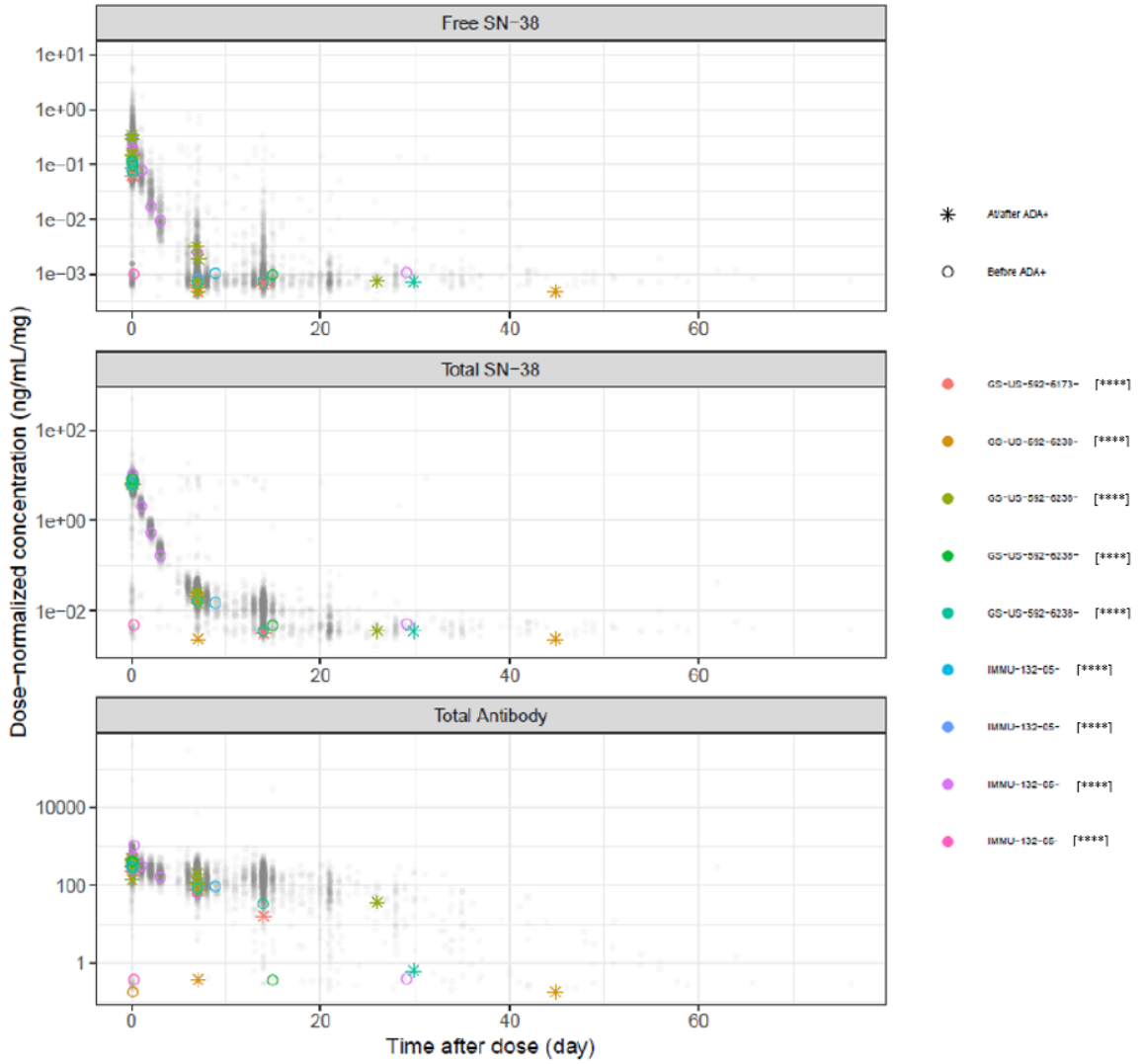
Impact of Antidrug Antibodies on Sacituzumab Govitecan or Total Antibody Pharmacokinetics

The impact of immunogenicity on the PK of free SN-38, total SN-38, and total antibody was evaluated in the PopPK analysis based on available serum concentration and ADA data in the PopPK analysis population from studies IMMU-132-01, IMMU-132-05, IMMU-132-09, GS-US-592-6238 and GS-US-592-6173.

Pharmacokinetic data were available for 2 participants with baseline positive ADA (n=1 from study GS-US-592-6238 and n = 1 from study GS-US-592-6173) and 7 of 13 participants with treatment-emergent ADA responses from other supportive studies in the PopPK analysis dataset (n = 4 from study IMMU-132-05; n = 3 from study GS-US-592-6238). An overlay of time course of SG and total antibody concentrations among ADA-positive (solid-coloured symbols) and ADA-negative participants (solid gray circles) is shown in the figure below.

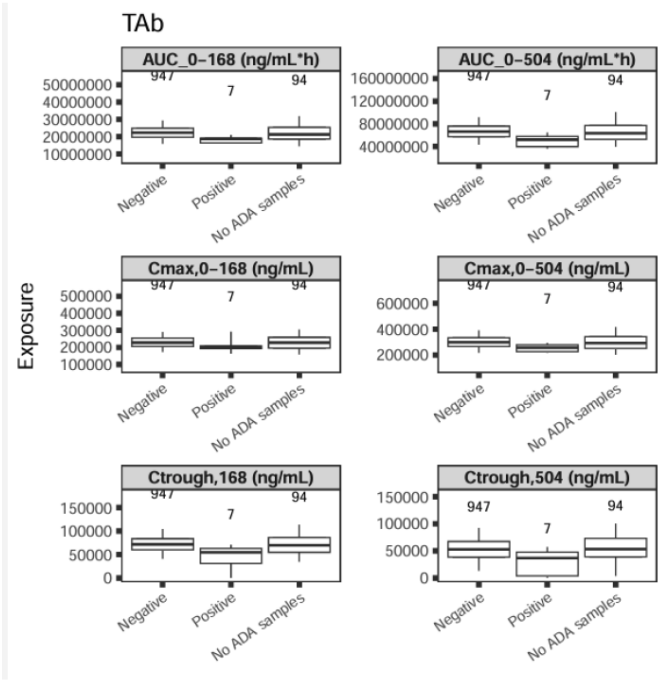
Due to the very low incidence of treatment-emergent ADAs (1.2% based on the all-treated population with 10 mg/kg SG monotherapy and none from study GS-US-592-6173), a quantitative assessment of the impact of ADA on SG or total antibody exposure was not performed in the PopPK analyses.

Figure 8 Observed dose-normalized concentrations versus time after dose stratified by analyte, coloured by study, and shape assigned by ADA status



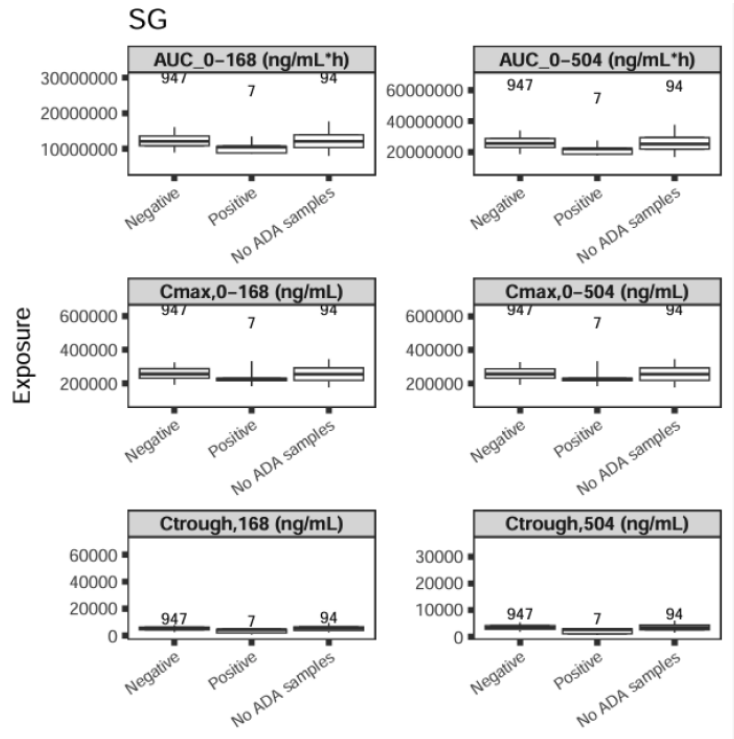
ADA = antidrug antibody
Source code: eda-figures.rmd

Figure 9 Distribution of Model-Estimated Exposure by ADA Status: Total Antibody



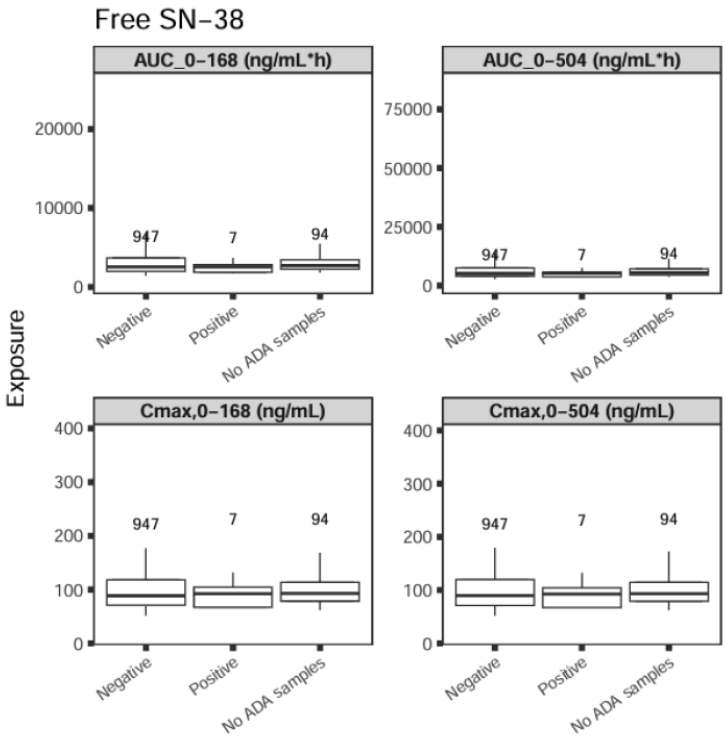
ADA = antidrug antibody; TAb = total antibody
Numbers overlaid on boxplots are the participant numbers in each group; N = 7 represents the 7 participants with treatment-emergent ADAs.
Source code: ebe-sim-ppk.R

Figure 10 Distribution of Model-Estimated Exposure by ADA Status: SG



ADA = antidrug antibody; SG = sacituzumab govitecan
Numbers overlaid on boxplots are the participant numbers in each group; N = 7 represents the 7 participants with treatment-emergent ADAs.
Source code: ebe-sim-ppk.R

Figure 11 Distribution of Model-Estimated Exposure by ADA Status: Free SN-38



ADA = antidrug antibody
Numbers overlaid on boxplots are the participant numbers in each group; N = 7 represents the 7 participants with treatment-emergent ADAs.
Source code: ebe-sim-ppk.R

Impact of Antidrug Antibodies on Efficacy

Antidrug antibody impact on the efficacy of the disease population in study GS-US-592-6173 was not evaluated since no treatment-emergent ADA was observed.

Furthermore, given the small number of participants with positive ADA responses to SG across studies IMMU 132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09, GS-US-592-6238 and GS-US-592-6173, no formal analysis was performed by the MAH to assess the impact of ADAs on the efficacy of SG.

Efficacy results (clinical response parameters) were presented for individual participants with a positive ADA response to SG in study IMMU-132-01, IMMU-132-05 and IMMU-132-06 and as a summary table for PFS, OS and ORR by study (IMMU 132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09, GS-US-592-6238) and by ADA status (ADA positive vs ADA negative). No treatment-emergent ADAs were observed in studies IMMU-132-09 and GS-US-592-6173; therefore, these studies are not included in the summary tables below.

Table 10 Summary of Efficacy for Participants With a Positive Antidrug Antibody Response to Sacituzumab Govitecan in Studies IMMU-132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09, and GS-US-592-6173

Participant ID	Best Overall Response per Independent Review Assessment	Progression-Free Survival (months)	Overall Survival (months)
IMMU-132-01			
[****] (mUC)	NA	5	5
IMMU-132-05			
[****]	PD	1.31	9.4
[****]	SD	2.73	25.07
[****]	SD	1.48	4.44
[****]	NE[a]	1.41	1.41
IMMU-132-06			
[****]	NA[a]	1.4	3.4
[****]	NE[a]	1.1	5.6
[****]	SD	2.8	11.9
[****]	PR	5.0	16.5
[****]	NA[a]	2.7	3.2
IMMU-132-09			
No participants	—	—	—
GS-US-592-6173			
No participants	—	—	—

mUC = metastatic urothelial carcinoma; NA = not assessed/not available; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

a Participants [****], [****], and [****] had a best overall response of PD by investigator assessment. Participant [****] had a best overall response of SD by investigator assessment

Source: ISI Listing 1, IMMU-132-01 Final, Listing 16.2.6.8.3 and Listing 16.2.6.9.3; IMMU-132-05 Final, Listing 16.2.6.5 and Listing 16.2.6.6; IMMU-132-06 Interim (28Feb2023), Listing 16.2.6.4.1 and Listing 16.2.6.4.2.

Table 11 Progression-Free Survival by BICR by ADA Status for Studies With Observed Treatment-Emergent ADAs (GS-US-592-6173 ISI Population)

	IMMU-132-01 SG (All Doses) (N = 223)		IMMU-132-05 SG (10 mg/kg) (N = 258)		IMMU-132-06 SG (10 mg/kg) (N = 150)		GS-US-592-6238 SG (10 mg/kg) (N = 264)	
	ADA+ (N = 1)	ADA− (N = 211)	ADA+ (N = 4)	ADA− (N = 238)	ADA+ (N = 5)	ADA− (N = 118)	ADA+ (N = 3)	ADA− (N = 244)
Number (%) of Participants with Available PFS data	1 (100.0%)	211 (100.0%)	4 (100.0%)	238 (100.0%)	5 (100.0%)	118 (100.0%)	3 (100.0%)	244 (100.0%)
Number (%) of Participants with Events	1 (100.0%)	183 (86.7%)	3 (75.0%)	171 (71.8%)	1 (20.0%)	78 (66.1%)	2 (66.7%)	143 (58.6%)
Disease Progression (PD)	0	162 (76.8%)	2 (50.0%)	163 (68.5%)	1 (20.0%)	72 (61.0%)	1 (33.3%)	137 (56.1%)
Death	1 (100.0%)	21 (10.0%)	1 (25.0%)	8 (3.4%)	0	6 (5.1%)	1 (33.3%)	6 (2.5%)
Number (%) of Participants Censored	0	28 (13.3%)	1 (25.0%)	67 (28.2%)	4 (80.0%)	40 (33.9%)	1 (33.3%)	101 (41.4%)
Kaplan-Meier Estimate of PFS (Months) (95% CI)								
Median	5.00 (NEst, NR)	5.70 (5.30, 6.90)	2.07 (1.31, NR)	5.59 (4.30, 6.34)	4.99 (NEst, NR)	5.68 (5.36, 7.92)	2.33 (1.51, NR)	9.82 (8.34, 12.35)

ADA = antidrug antibody; BICR = blinded independent central review; CI = confidence interval; ISI = Integrated Summary of Immunogenicity; NEst = not estimable; NR = not reached; PD = progressive disease; PFS = progression-free survival; SG = sacituzumab govitecan

PFS (months) = (date of events or censoring - date of randomization + 1)/30.4375.

Participant-level ADA status: "ADA+" if the participant has treatment-emergent ADA; "ADA−" if the participant is evaluable for ADA incidence and does not have treatment-emergent ADA; missing if the participant is not evaluable for ADA incidence.

Denominator of percentages is the number of participants for each ADA status in each study in which treatment-emergent ADAs were observed.

Median PFS is from Kaplan-Meier estimate. The 95% CI is based on log-log transformation.

PFS by investigator assessment was summarized for Study IMMU-132-01 across multiple dose levels (SG 8 mg/kg and 10 mg/kg) and indications, PFS by BICR was summarized for other studies.

Table 12 Overall Survival by ADA Status for Studies With Observed Treatment-Emergent ADAs (GS-US-592-6173 ISI Population)

	IMMU-132-01 SG (All Doses) (N = 223)		IMMU-132-05 SG (10 mg/kg) (N = 258)		IMMU-132-06 SG (10 mg/kg) (N = 150)		GS-US-592-6238 SG (10 mg/kg) (N = 264)	
	ADA+ (N = 1)	ADA− (N = 211)	ADA+ (N = 4)	ADA− (N = 238)	ADA+ (N = 5)	ADA− (N = 118)	ADA+ (N = 3)	ADA− (N = 244)
Number (%) of Participants with Available OS data	1 (100.0%)	211 (100.0%)	4 (100.0%)	238 (100.0%)	5 (100.0%)	118 (100.0%)	3 (100.0%)	244 (100.0%)
Number (%) of Participants with Events (Death)	1 (100.0%)	151 (71.6%)	3 (75.0%)	175 (73.5%)	5 (100.0%)	92 (78.0%)	3 (100.0%)	116 (47.5%)
Number (%) of Participants Censored	0	60 (28.4%)	1 (25.0%)	63 (26.5%)	0	26 (22.0%)	0	128 (52.5%)
Kaplan-Meier Estimate of OS (Months) (95% CI)								
Median	5.00 (NEst, NR)	13.70 (11.90, 16.90)	6.92 (1.41, NR)	13.11 (11.17, 14.32)	5.55 (3.22, NR)	14.29 (11.10, 16.66)	4.86 (3.15, NR)	22.64 (20.14, NR)

ADA = antidrug antibody; CI = confidence interval; ISI = Integrated Summary of Immunogenicity; NEst = not estimable, NR = not reached; OS = overall survival; SG = sacituzumab govitecan
OS (months) = (date of death or censoring - date of randomization + 1)/30.4375.
Participant-level ADA status: "ADA+" if the participant has treatment-emergent ADA; "ADA−" if the participant is evaluable for ADA incidence and does not have treatment-emergent ADA; missing if the participant is not evaluable for ADA incidence.
Denominator of percentages is the number of participants for each ADA status in each study in which treatment-emergent ADAs were observed.
Median OS is from Kaplan-Meier estimate. The 95% CI is based on log-log transformation.
OS for Study IMMU-132-01 was summarized across multiple dose levels (SG 8 mg/kg and 10 mg/kg) and indications.

Table 13 Objective Response Rate by BICR by ADA Status for Studies With Observed Treatment-Emergent ADAs (GS-US-592-6173 ISI Population)

	IMMU-132-01 SG (All Doses) (N = 223)		IMMU-132-05 SG (10 mg/kg) (N = 258)		IMMU-132-06 SG (10 mg/kg) (N = 150)		GS-US-592-6238 SG (10 mg/kg) (N = 264)	
	ADA+ (N = 1)	ADA− (N = 211)	ADA+ (N = 4)	ADA− (N = 238)	ADA+ (N = 5)	ADA− (N = 118)	ADA+ (N = 3)	ADA− (N = 244)
Number (%) of Participants with Available ORR data	0	206 (97.6%)	4 (100.0%)	238 (100.0%)	5 (100.0%)	118 (100.0%)	3 (100.0%)	244 (100.0%)
Objective Response Rate (ORR) (95% CI)	0.0%	35.1% (28.6%, 41.9%)	0.0%	34.9% (28.8%, 41.3%)	20.0% (0.5%, 71.6%)	36.4% (27.8%, 45.8%)	0.0%	52.0% (45.6%, 58.5%)
Responders (CR + PR)	0	74 (35.1%)	0	83 (34.9%)	1 (20.0%)	43 (36.4%)	0	127 (52.0%)
Non-responders (SD + PD + NE)	0	132 (62.6%)	4 (100.0%)	155 (65.1%)	4 (80.0%)	75 (63.6%)	3 (100.0%)	117 (48.0%)

ADA = antidrug antibody; BICR = blinded independent central review; CI = confidence interval; CR = complete response; ISI = Integrated Summary of Immunogenicity; ORR = objective response rate; PD = progressive disease; PR = partial response; NE = not evaluable; SD = stable disease
Participant-level ADA status: "ADA+" if the participant has treatment-emergent ADA; "ADA−" if the participant is evaluable for ADA incidence and does not have treatment-emergent ADA; missing if the participant is not evaluable for ADA incidence.
Denominator of percentages is the number of participants for each ADA status in each study in which treatment-emergent ADAs were observed.
ORR is the proportion of participants who achieved best overall response of CR/PR. The 95% CI is based on Clopper-Pearson method.
ORR by investigator assessment was summarized for Study IMMU-132-01 across multiple dose levels (SG 8 mg/kg and 10 mg/kg) and indications, ORR by BICR was summarized for other studies.

Impact of Antidrug Antibodies on Safety

An evaluation of immunogenicity and safety for participants with treatment-emergent ADAs to SG has been evaluated in studies IMMU-132-01, IMMU-132-05, IMMU-132-06, GS-US-592-6238 and GS-US-592-6173.

Among participants who received SG 10 mg/kg monotherapy in studies IMMU-132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09 and GS-US-592-6238 across multiple solid tumours, 13 out of 1058 (1.2%) participants were evaluable for ADA incidence developed treatment-emergent ADAs to SG. None of these participants experienced a serious treatment-emergent AE (TEAE) that was considered related to SG. One out of the 13 participants (7.7%) with treatment-emergent ADAs experienced a TEAE that led to premature discontinuation of study drug infusion (study GS-US-592-6238). The TEAE was in the AESI hypersensitivity category (a Grade 2 infusion-related reaction that resolved the same day) and did not recur upon receiving an additional dose of SG. This participant also had a positive NAb assessment.

No participant had treatment-emergent immune-mediated AEs.

The overall incidence of ADAs was low in participants who received SG monotherapy and no treatment emergent ADA was observed in participants who received SG in combination with pembrolizumab (study GS-US-592-6173).

Table 14 Overall Summary of treatment-emergent adverse events by ADA status (GS-US-592-6173 ISI Populations)

	IMMU-132-01 SG (All Doses) (N = 223)		IMMU-132-05 SG (10 mg/kg) (N = 258)		IMMU-132-06 SG (10 mg/kg) (N = 150)		IMMU-132-09 SG (10 mg/kg) (N = 265)		GS-US-592-6238 SG (10 mg/kg) (N = 264)		GS-US-592-6173 SG (10 mg/kg) (N = 220)		Overall mBC SG (10 mg/kg) (N = 893)		All Treated Mono SG (10 mg/kg) (N = 1158)	
Number (%) of Participants with Any	ADA+ (N = 1)	ADA− (N = 211)	ADA+ (N = 4)	ADA− (N = 238)	ADA+ (N = 5)	ADA− (N = 118)	ADA+ (N = 0)	ADA− (N = 236)	ADA+ (N = 3)	ADA− (N = 244)	ADA+ (N = 0)	ADA− (N = 207)	ADA+ (N = 7)	ADA− (N = 816)	ADA+ (N = 13)	ADA− (N = 1045)
TEAE	1 (100.0%)	211 (100.0%)	4 (100.0%)	238 (100.0%)	5 (100.0%)	118 (100.0%)	0	236 (100.0%)	3 (100.0%)	243 (99.6%)	0	206 (99.5%)	7 (100.0%)	815 (99.9%)	13 (100.0%)	1044 (99.9%)
TEAE with Grade 3 or Higher	1 (100.0%)	155 (73.5%)	3 (75.0%)	171 (71.8%)	5 (100.0%)	100 (84.7%)	0	168 (71.2%)	3 (100.0%)	156 (63.9%)	0	149 (72.0%)	6 (85.7%)	567 (69.5%)	12 (92.3%)	748 (71.6%)
TEAE Related to SG	0	210 (99.5%)	4 (100.0%)	233 (97.9%)	5 (100.0%)	116 (98.3%)	0	233 (98.7%)	3 (100.0%)	241 (98.8%)	0	205 (99.0%)	7 (100.0%)	804 (98.5%)	12 (92.3%)	1031 (98.7%)
TEAE Related to SG with Grade 3 or Higher	0	130 (61.6%)	2 (50.0%)	152 (63.9%)	2 (40.0%)	80 (67.8%)	0	151 (64.0%)	2 (66.7%)	144 (59.0%)	0	141 (68.1%)	4 (57.1%)	514 (63.0%)	6 (46.2%)	655 (62.7%)
Serious TEAE	1 (100.0%)	64 (30.3%)	1 (25.0%)	59 (24.8%)	3 (60.0%)	52 (44.1%)	0	60 (25.4%)	2 (66.7%)	54 (22.1%)	0	76 (36.7%)	3 (42.9%)	199 (24.4%)	7 (53.8%)	287 (27.5%)
TEAE Leading to SG Dose Reduction	0	0	1 (25.0%)	54 (22.7%)	1 (20.0%)	57 (48.3%)	0	83 (35.2%)	1 (33.3%)	95 (38.9%)	0	76 (36.7%)	2 (28.6%)	232 (28.4%)	3 (23.1%)	289 (27.7%)
TEAE Leading to SG Interruption	0	108 (51.2%)	1 (25.0%)	151 (63.4%)	4 (80.0%)	77 (65.3%)	0	161 (68.2%)	3 (100.0%)	164 (67.2%)	0	158 (76.3%)	4 (57.1%)	520 (63.7%)	8 (61.5%)	659 (63.1%)
TEAE Leading to SG Discontinuation	0	9 (4.3%)	0	10 (4.2%)	0	17 (14.4%)	0	11 (4.7%)	1 (33.3%)	5 (2.0%)	0	13 (6.3%)	1 (14.3%)	28 (3.4%)	1 (7.7%)	52 (5.0%)
Any Hypersensitivity or Immune-mediated TEAE	0	50 (23.7%)	0	41 (17.2%)	0	18 (15.3%)	0	25 (10.6%)	1 (33.3%)	20 (8.2%)	0	46 (22.2%)	1 (14.3%)	112 (13.7%)	1 (7.7%)	154 (14.7%)
Any Hypersensitivity or Immune-mediated TEAE Related to SG	0	34 (16.1%)	0	25 (10.5%)	0	11 (9.3%)	0	16 (6.8%)	1 (33.3%)	14 (5.7%)	0	36 (17.4%)	1 (14.3%)	77 (9.4%)	1 (7.7%)	100 (9.6%)
TEAE Leading to Death	0	4 (1.9%)	0	0	0	3 (2.5%)	0	3 (1.3%)	0	2 (0.8%)	0	4 (1.9%)	0	5 (0.6%)	0	11 (1.1%)
All Deaths[a]	1 (100.0%)	168 (79.6%)	3 (75.0%)	175 (73.5%)	5 (100.0%)	92 (78.0%)	0	201 (85.2%)	2 (66.7%)	84 (34.4%)	0	44 (21.3%)	5 (71.4%)	541 (66.3%)	11 (84.6%)	719 (68.8%)

ADA = antidrug antibody; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Mono = monotherapy; SG = sacituzumab govitecan; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event
a All Deaths; includes deaths not due to AEs, such as disease progression.
Percentages are based on ADA (N) in column header.
Participant-level ADA status: "ADA+" if the participant has treatment-emergent ADA; "ADA−" if the participant is evaluable for ADA incidence and does not have treatment-emergent ADA; missing if the participant is not evaluable for ADA incidence.
A participant with ≥ 2 AEs in each row is counted only once. A participant may be counted in multiple categories.
Adverse events were coded according to MedDRA Version 27.1. Severity grades were defined by the CTCAE Version 5.0.
Adverse events leading to dose reduction were not collected in Study IMMU-132-01.
mBC Overall: Studies IMMU-132-01, IMMU-132-05, IMMU-132-09, GS-US-592-6238; All Treated SG mono: IMMU-132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09, GS-US-592-6238.
Immune-mediated AE is defined as immune-mediated/autoimmune disorders SMQ (narrow)

2.3.4. PK/PD modelling

Exposure-Response Relationships

Using an integrated population pharmacokinetic (popPK) model that characterized 1) total SN-38, 2) free SN-38, and 3) total SG antibody (tAb) concentrations following SG administration, exposure-response (E-R) analyses were conducted to characterize the relationships between the SG exposure metrics in patients with metastatic triple-negative breast cancer (mTNBC) as first line (1L) treatment for metastatic disease and the efficacy and safety endpoints of clinical interest. Individual empirical Bayes estimates (EBE) of PK parameters from this new integrated popPK model were used to calculate the exposure metrics of tAb, SG and free SN-38, which were tested in the presented E-R analyses. In total 26 metrices were considered for E-R analyses regarding efficacy and 12 additional metrices (for SN38) for E-R analyses regarding safety.

Exposure-response for efficacy analyses were conducted using data from a total of 221 participants with metastatic TNBC from study GS-US-592-6173 (ASCENT-04) and exposure response for safety and dose reductions/dose delays analyses were conducted using data from a total of 1012 participants with solid tumours who received SG in studies IMMU-132-01, IMMU-132-05, IMMU-

132-09, and GS-US-592-6173. The exposure metrics were based on the PopPK models and accounted for individual covariates, including demographics, and clinically relevant covariates.

Exposure-response (E-R) analysis for efficacy

Exposure-efficacy relationships were evaluated in participants with locally advanced unresectable or metastatic TNBC who received a starting dose of SG 10 mg/kg on Days 1 and 8 of a 21-day cycle in study GS-US-592-6173. The exposure-efficacy analysis dataset included a total of 221 participants from study GS-US-592-6173 (ASCENT-04 study) who had PopPK parameter estimates to enable the estimation of exposure metrics related to SG dosing and had data for the respective efficacy endpoints.

The evaluated efficacy endpoints included PFS and ORR.

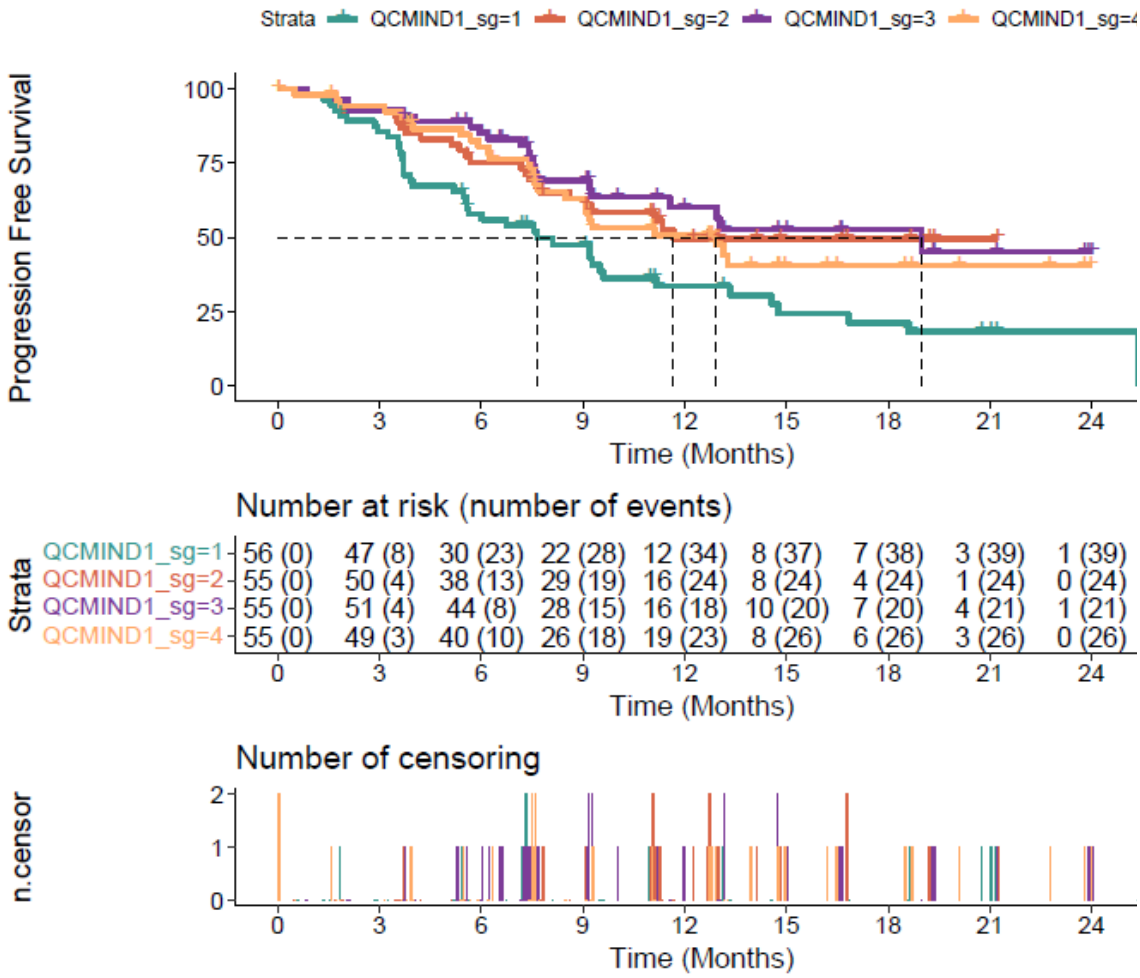
The exposure-efficacy relationships were analysed using binomial logistic regression models for ORR and parametric time-to-event (TTE) models for PFS.

C_{max}, C_{min}, and C_{avg} for SG and total antibody following the first dose, during the first dosing cycle (21 days after the first SG dose), as well as at steady state were explored as the PK metrics to assess the exposure-efficacy relationship. For PFS, time-varying concentration and time varying C_{avg} of SG were also considered as drivers of response.

- *Exposure-PFS*

For PFS, a parametric TTE model was built using a lognormal hazard distribution function. $C_{min,D1,SG}$ was identified as the most significant exposure metric and implemented as an Emax drug effect on the baseline hazard.

Figure 12 GS-US-592-6173: Kaplan-Meier Curves of PFS Stratified by Quartiles of SG Minimum Concentration During First Dose (Cmin,D1,SG)



PFS = progression-free survival; QCMIND1_sg = quartiles of $C_{min,D1,SG}$; SG = sacituzumab govitecan
The vertical dashed lines indicate the median survival time (corresponding to a survival probability of 0.5) associated with each exposure quartile.

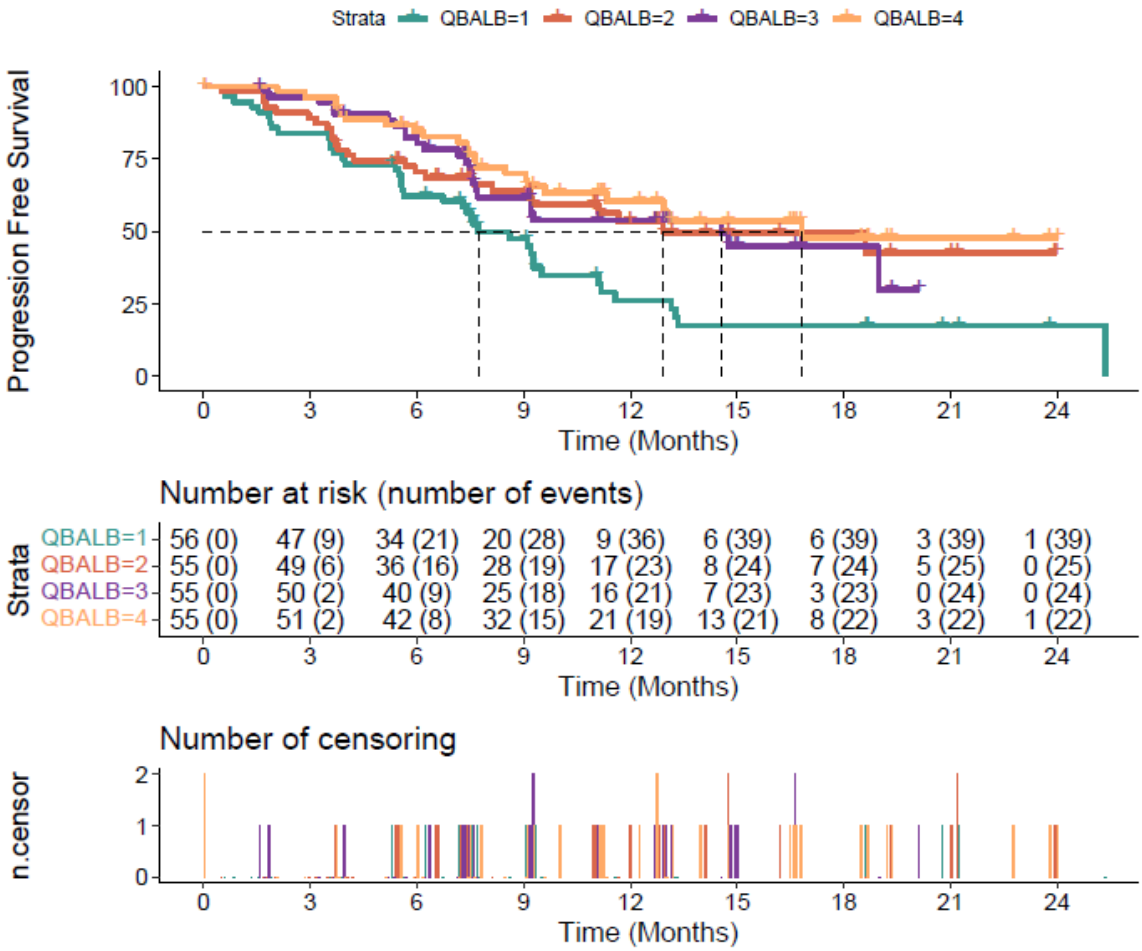
Table 15 GS-US-592-6173: Median Survival Times for PFS in Quartiles of Cmin,D1,SG Exposure

Quartile	Median Exposure (Range)	Median Survival Time (90% CI) (Months)
First	3881 (1570, 4474)	7.66 (5.59, 13.3)
Second	4875 (4498, 5256)	11.7 (9.10, NA)
Third	5484 (5259, 5859)	19.0 (11.6, NA)
Fourth	6434 (5875, 8289)	12.9 (9.07, NA)

CI = confidence interval; NA = not applicable; PFS = progression-free survival (based on blinded independent central review); TPC = treatment of physician's choice
The median PFS for the TPC + pembrolizumab group in Study GS-US-592-6173 was 7.75 months (95% CI: 7.29, 9.26).

Serum albumin was identified as a significant covariate on the hazard function affecting PFS events.

Figure 13 GS-US-592-6173: Kaplan-Meier Curves of PFS Stratified by Quartiles of Baseline Albumin



PFS = progression-free survival; QBALB = quartiles of baseline albumin
The vertical dashed lines indicate the median survival time (corresponding to a survival probability of 0.5) associated with each quartile.

Table 16 Parameter Estimates of Final Parametric Time-to-Event Model for PFS

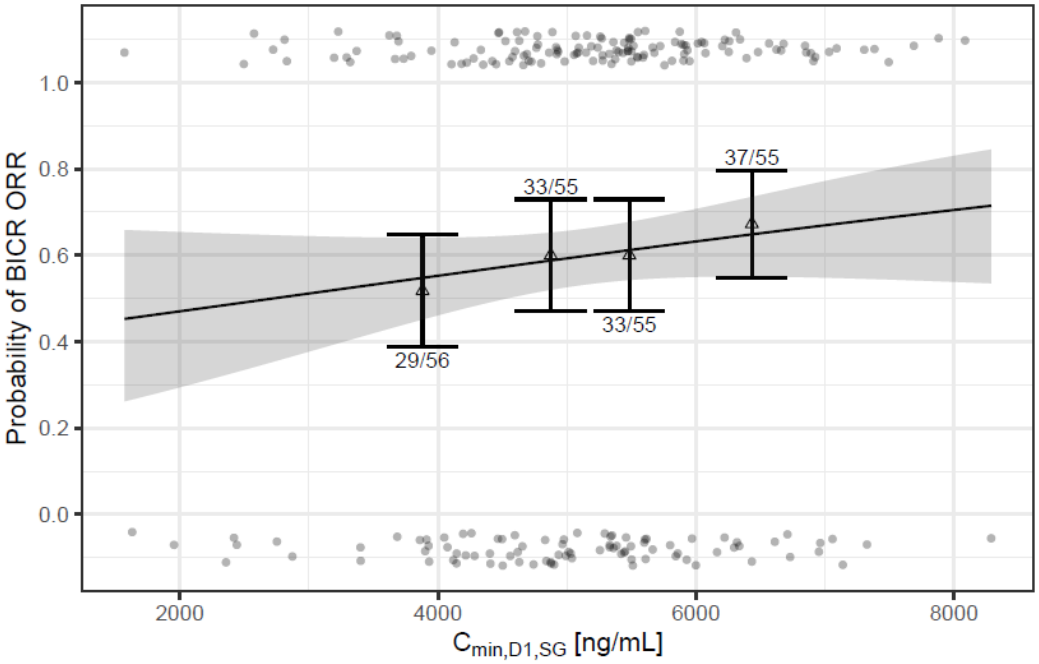
Structural Parameters			**Estimate**	**RSE (%)**
MU	θ_1	Hazard scaling parameter	1.89	17.9
SIG	θ_2	Hazard shape parameter	0.874	14.5
EC_{50} (ng/mL)	θ_3	SG concentration producing half-maximum effect	3460	29.1
E_{max}	θ_4	E_{max} (logit)	0.482	155
GAM	θ_5	Hill coefficient	9.47	103
BALB on MU	θ_6	Baseline albumin covariate effect on scaling parameter	0.0352	30.6

RSE = relative standard error

- *Exposure-ORR*

Clinical efficacy measures of ORR were analyzed using logistic regression models.

Figure 14 GS-US-592-6173: Logistic Regression of Cmin,D1, SG and BICR Objective Response



BICR = blinded independent central review; CI = confidence interval; $C_{min,D1,SG}$ = minimum SG concentration during the first dose; ORR = objective response rate
Solid line is the median prediction and the shaded region is the 95% CI. Triangles and error bars represent the observed rate of objective response per exposure quartile and 95% CI, plotted at the median exposure of the quartile. Points are individual participants, with 0 representing no event and 1 representing event plotted at the individual exposure metric.

Exposure-response (E-R) analysis for safety

Exposure safety relationships were evaluated in participants with various advanced epithelial cancers or advanced or metastatic breast cancers who received a starting dose of SG 8 mg/kg (16 participants from studies IMMU-132-01 and IMMU-132-05), 10 mg/kg (993 participants from studies IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6173), or 12 mg/kg (3 participants from study IMMU-132-01) on Days 1 and 8 of a 21 day cycle.

The exposure safety analysis dataset included a total of 1012 participants (98.1% in the SG 10 mg/kg starting dose group) from studies IMMU-132-01, IMMU-132-05, IMMU 132 09, and GS-US-592-6173 who had PopPK parameter estimates to enable estimation of exposure metrics related to SG dosing and had data for the respective safety endpoints.

Rare events (< 5%) of the selected AEs were not analysed in the exposure-safety analysis. For the following safety endpoints, a parametric logistic regression model was also used to assess the relationship between SG exposure and safety outcome, as well as explore prognostic factors (covariates): neutropenia (any grade/Grade 3 or higher), neutropenia only (preferred term [PT] = neutropenia; any grade/Grade 3 or higher), febrile neutropenia (any grade/Grade 3 or higher), infections (any grade/Grade 3 or higher), vomiting (any grade), diarrhoea (any grade/Grade 3 or higher), hypersensitivity (any grade), and nausea (any grade).

Table 17 Summary of Safety and Tolerability Endpoints

Safety/Tolerability Variable	Preferred Term/Definition	Description
Vomiting	Vomiting	Categorical variables describing the incidence of any grade, Grade 3 or higher, and Grade 4 safety variable for each participant within the treatment period
Diarrhea	Diarrhoea	
Hypersensitivity	Hypersensitivity SMQ (narrow) and anaphylactic reaction SMQ (broad and narrow)	
Nausea	Nausea	
Neutropenia	Neutropenia, neutrophil count decreased, and febrile neutropenia	
Infections	SOC: Infections and infestations (Serious infections occurring after any grade neutropenia AE)	
Dose reductions	NA	Time-to-event variable; defined as the time to first dose reduction event (in participants with reported AEs leading to dose reductions) during the treatment period or right censored
Dose delays	NA	Time-to-event variable; defined as the time to first dose delay event (in participants with reported AEs leading to dose delay) during the treatment period or right censored

AE = adverse event; NA = not applicable; SOC = system organ class; SMQ = Standardised MedDRA Query

In addition, a semi-parametric Cox proportional hazards model was used to assess the relationship for time to AEs leading to dose reductions and time to AEs leading to dose delays versus SG exposure, as well as explore prognostic factors (covariates).

C_{max}, C_{min}, and C_{avg} for total antibody, SG, and free SN-38 during the first dose, during the first dosing cycle (21 days after the first SG dose), as well as at steady state were evaluated as exposure metrics related to the safety endpoints, and the most statistically significant exposure metric was retained in the model.

A statistically significant relationship between $C_{max, D1,SG}$ and any grade/grade 3 or higher neutropenia, neutropenia only, febrile neutropenia and diarrhoea has been observed.

No statistically significant relationship was observed between SG exposure and any grade or Grade 3 or higher infections and infestations. No statistically significant relationship was observed between SG exposure and any grade vomiting, hypersensitivity reactions and nausea.

A statistically significant relationship between $C_{max, D1,SG}$ and the time to AEs leading to dose reduction has been observed. Time to AEs requiring dose reduction was shorter with higher exposure.

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology package for SG comprised study GS-US-592-6173 (ASCENT-04), study GS-US-592-6238 (ASCENT-03) and three completed clinical studies (study IMMU-132-01, study IMMU-132-05, and study IMMU-132-09) contributing to the characterization of PK and

immunogenicity of SG, and one ongoing study (study IMMU-132-06) contributed data to the immunogenicity package.

The PK of SG at the proposed dose of 10 mg/kg on Days 1 and 8 of each 21-day cycle had been previously characterised, including in the initial MAA and the TNBC extension of indication (EMA/VR/0000312649).

Bioanalytical methods

The bioanalytical methods submitted for the determination of total SN-38, free SN-38 and total antibody (hRS7-IgG and HRS7-SN38) in human serum, were found overall acceptable for their intended purpose.

Pharmacokinetics

In the pivotal study GS-US-592-6173 (ASCENT-04), 221 participants were randomized to receive SG + pembrolizumab and sparse PK samples, pre-(C_{trough}) and post-dose (C_{max}) serum concentrations, were collected.

The mean C_{max} for total antibody, total SN-38, and free SN-38 from Cycle 1 to Cycle 10 ranged from approximately 235,000 to 318,000 ng/mL, 5060 to 4340 ng/mL, and 114 to 95 ng/mL, respectively and was similar compared to the concentrations reported in previous studies.

The absorption, distribution, metabolism, and excretion of SG, total antibody and free SN-38, total SN-38, SN-38G, was overall well-characterised and described in the initial MAA in TNBC and have been adjusted based on the results of the updated integrated PopPK model (discussed below). These most recent data of the pharmacokinetic parameters of sacituzumab govitecan and free SN-38 when administered as monotherapy or in combination with pembrolizumab are presented in section 5.2 of the SmPC. There was no impact of pembrolizumab coadministration on pharmacokinetics of sacituzumab govitecan or SN-38.

Integrated popPK model

A population PK analysis was conducted based on data from studies GS-US-592-6173 (ASCENT-04), IMMU-132-01, IMMU-132-05, IMMU-132-09, to characterize the disposition of SG including the assessment of the pembrolizumab combination effect on the PK of TAb and SN-38. In this regard, the integrated popPK analysis has been updated to integrate relevant PK data collected from study GS-US-592-6238 (ASCENT-03, monotherapy). The PK of total antibody, and conjugated and free SN-38, were described by a two-compartment model for each of the species, with linear clearance for free SN-38 and linear and nonlinear clearance for total antibody and conjugated SN-38. Of note, all studies showed a very pronounced percentage of BLQ samples for free SN-38 (overall 36.5%). BLQ observations were flagged in the popPK analysis dataset and a likelihood-based approach (M3) was implemented and is agreed. The current population analysis applied an integrated model structure with the measured PK data of three analytes: TAb, free SN-38 and total SN-38 including additional data from the phase 3 study ASCENT-04 and ASCENT-03. Previous model-based description of these analytes was based on separate popPK models. Along with this change in model structure, two strong assumptions regarding the PK of SG have been considered. Firstly, the PK of SG were now derived based on model-estimated kinetics of conjugated SN-38 and potential change in drug-to-antibody ratio (DAR) over time. In contrast, for the purpose of the previous popPK analysis, SG concentrations were calculated based on an assumed DAR of 8 and the molecular weights for free SN-38 and the loaded hRS7 antibody of 392 Da and 161 kDa, respectively. Secondly, conjugated SN-38 and TAb are assumed to share the same PK parameters of clearances and volume of distributions since kinetics are expected to be driven by the monoclonal antibody. Both assumptions are deemed overall plausible, however, they impact the

concentration of SG, that is solely based on model-based simulations, with no confirmatory data available. The MAH provided a comparison of former and current predictions of SG PK and the cSG-time-course. The provided justifications for changes in $t_{1/2}$ and AUC as well as for the implementation of DAR (which was shown to be the main driver in the mention exposure metrics) are deemed reasonable.

PopPK model parameters and model performance

The updated integrated model is characterized by several covariates on PK parameters for each of the analytes that were observed to be correlated which is expected also due to the integrated new structure.

One pivotal parameter Kdec could be estimated acceptably well, however, covariate selection and inter-individual variability (IIV) parameters (11 parameters in total), that show moderate to high variability (up to 314%CV) with partially fixed variance parameters indicate some model deficiencies. Allometric scaling factors were estimated on CL, Q and Vc, Vp to be 0.475 and 0.251 which are below the expected ones for a monoclonal antibody. This may be attributed to interference with the other covariates that were identified as statistically relevant and on the assumed lumping of Tab and cSN38 PK behavior.

Body weight was found to be the most influential covariate on the PK of the total antibody, Free SN-38, and SG AUC and C_{max1}, almost exceeding the reference range at both the lower (49 kg) and higher (103 kg) body weight range. Covariate analyses indicate that exposures of Tab, SG and free SN-38 increased with increasing body weight under body weight-based dosing, with statistically significant influence. This became relevant for conducted exposure-response-analyses, also showing the trends of increase in safety endpoint with exposure. For exposure-response analyses regarding efficacy, the focus was on study GS-US-592-6173, which is acceptable in general. However, popPK simulated exposure from an integrated model based on pooled data was used in this regard. Given that the weight distribution is considered comparable throughout the integrated pooled data (39-133 kg in study GS-US-592-6173), no major bias is thus expected with regards the most influential covariate (body weight) detected on PK over studies. In addition, UGT1A1 genotype is indicated to have a potentially clinically relevant effect on Free SN-38 exposure (AUC and C_{max1}), which is discussed in the exposure-response analyses section.

Prediction-corrected VPC of free SN-38 indicated a slight underprediction of p95 later than 150 hrs after dose and slight overprediction in the period before. Pronounced BLQ percentage after 150 hrs after dose (data and simulations) were observed. The pcVPCs of Tab is deemed overall acceptable. A trend of partial underprediction of the median Tab and p5 could be identified that to some part confounds the conducted exposure-response analysis considering an early PK measure (cmin after D1).

Immunogenicity

In study GS-US-592-6173 (ASCENT-04), the immunogenicity samples for ADA prevalence and incidence assessments were evaluable for 220 and 207 participants, respectively. One participant (0.5%) had ADAs to SG at baseline (titer < 10), which were non-neutralizing. No participant (0 out of 207; 0%) had ADAs to SG postbaseline (treatment-emergent ADAs). No treatment-emergent ADAs have also been reported for study IMMU-132-09. The incidence of ADA to SG across studies was low in general.

Across studies (IMMU-132-01, IMMU-132-05, IMMU-132-06, IMMU-132-09, GS-US-592-6238 (ASCENT-03) and GS-US-592-6173 (ASCENT-04)), immunogenicity samples for ADA prevalence and incidence assessments were evaluable for 1157 and 1058 participants, respectively.

The currently presented data indicate a low prevalence and incidence of ADA across the studied patient populations. The incidence of treatment-emergent ADA to SG was low (n=13 [1.2%]). Neutralizing antibodies were rare (n=10 [0.9%]). The maximum reportable ADA titer observed across the studies ranged from 10 to 90.

However, a potential trend has been observed, that the ADA status might have an impact on the exposure of free SN-38, SG and total antibody. Due to the low occurrence of ADAs, the **impact of positive ADAs on the PK** is therefore currently uncertain.

The **impact of ADAs on the efficacy** of the disease population in study GS-US-592-6173 (ASCENT-04) was not evaluated since no treatment-emergent ADA was observed. Based on the individual study efficacy results presented for studies IMMU-132-01, IMMU-132-05 and IMMU-132-06, no clear impact of ADA on efficacy was identified, whereas analyses of progression-free survival, overall survival, and objective response rate presented by study and by ADA status (including data from studies IMMU-132-01, IMMU-132-05, IMMU-132-06, and GS-US-592-6238 (ASCENT-03)) showed numerically higher efficacy in the ADA− group when compared with the ADA+ group across studies. However, the prevalence of participants who were ADA+ (≤ 5 participants who were ADA+ in each study) is low and the results should therefore be interpreted with caution. Nevertheless, a trend has been observed and thus a potential impact on the efficacy cannot currently be excluded.

Moreover, no clear **impact of ADAs on safety** have been identified at present. The occurrence of any TEAE was similar between participants with or without ADAs to SG across individual studies and pooled populations. However, in the pooled all treated SG population the incidence (≥10% difference) of the following treatment-emergent AEs: TEAE with Grade 3 or higher, serious TEAE, and all deaths, were higher in participants who were tested positive for ADAs compared to participants tested negative for ADAs. Such differences in the occurrence of treatment-emergent AEs between ADA positive and ADA negative participants was especially observed in study GS-US-592-6238 SG (10 mg/kg). Still, it needs to be considered that the number of participants who were tested positive for ADAs was very low in study GS-US-592-6238 (N=3) and in the pooled all treated SG population (N=13). Therefore, the results should be interpreted with caution.

Overall, the currently limited data of ADA-positive patients available limits the ability to conclusively determine whether positive ADAs have an impact on pharmacokinetics, efficacy, and safety. Therefore, no final conclusion can be drawn at present and the impact of positive ADAs on the PK, efficacy and safety of SG is currently unknown and needs to be further evaluated during the ongoing clinical studies and the clinical development of SG.

Exposure-response (E-R) analyses

Exposure-response analyses were conducted to evaluate the relationships between SG-related exposure and efficacy endpoints (PFS and ORR) and safety endpoints, including neutropenia-related events, gastrointestinal events, hypersensitivity, and AEs leading to dose modifications. Individual exposure metrics for total antibody, SG and free SN-38 were derived from the PopPK model. Body weight was a statistically significant driver of exposure under body weight-based dosing. For efficacy, analyses included 221 participants with metastatic TNBC from ASCENT-04. No statistically significant relationship was demonstrated between SG exposure and PFS or ORR. Although lower SG exposure quartiles appeared to be associated with less favourable PFS in some analyses, no consistent exposure-dependent trend was observed across higher quartiles. Interpretation is limited by the use of a single dose level and by imbalances in patient characteristics across exposure quartiles, including body weight, tumour burden, LDH, ECOG performance status and hepatic function.

For safety, analyses included 1012 participants with solid tumours treated with SG across four studies. Higher SG exposure, particularly $C_{max,D1,SG}$, was associated with increased risks of grade ≥3 neutropenia, febrile neutropenia, diarrhoea and AEs leading to dose reductions. Reduced-function UGT1A1 genotypes (*1/*28 and *28/*28) were also associated with higher risks of grade ≥3 neutropenia-related events and AEs leading to dose reductions compared with 1/1. These findings are consistent with the known safety profile of SG and are addressed in the current SmPC through warnings and precautions for reduced UGT1A1 activity, neutropenia and diarrhoea, as well as information on UGT1A1 inhibitors and inducers.

2.3.6. Conclusions on clinical pharmacology

In general, the pharmacokinetics and pharmacodynamics of sacituzumab govitecan have been sufficiently characterized. Results from the pivotal study GS-US-592-6173 (ASCENT-04), supporting this application for extension of indication, appear overall consistent with the analyses provided in previous applications.

2.4. Clinical efficacy

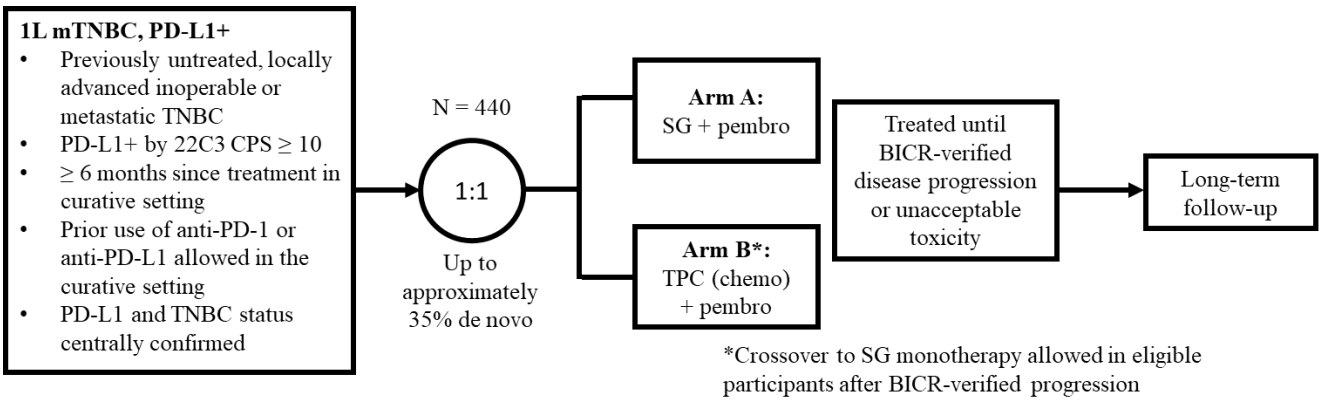
2.4.1. Dose response study(ies)

The dosing regimen of SG in the ASCENT-04 study (10 mg/kg IV D1 and D8, Q3W) is the same as already approved as monotherapy for the treatment of patients with unresectable or metastatic TNBC who have not received prior systemic therapy for metastatic disease and who are not candidates for PD-1 or PD-L1 inhibitor therapy or who have received two or more prior systemic therapies, including at least one of them for advanced disease and HR+, HER2- breast cancer after at least two prior systemic therapies. The SG dose of 10 mg/kg was selected based on results from study IMMU-132-01, a phase 1/2 dose escalation and expansion phase study in metastatic epithelial cancers.

2.4.2. Main study

ASCENT-04 (GS-US-592-6173): A randomized, open-label, phase 3 study of sacituzumab govitecan and pembrolizumab versus treatment of physician's choice and pembrolizumab in patients with previously untreated, locally advanced inoperable or metastatic triple-negative breast cancer, whose tumors express PD-L1

Figure 15 ASCENT-04 Study Schema



Stratification Factors:

- De novo versus recurrent disease within 6-12 months from completion of treatment in the curative setting versus > 12 months from completion of treatment in the curative setting**
- Geographic region (US/Canada/Western Europe versus Rest of World)
- Prior exposure to anti-PD-1 or anti-PD-L1 agent (Yes/No)

**Treatment-free interval is defined as the time between completion of systemic (neo)adjuvant breast cancer therapy or surgery (whichever occurred last) and first local or distant recurrence. Adjuvant radiotherapy is not included in the 6-month interval.

Primary Endpoint: PFS by BICR in ITT population
Key Secondary Endpoints: OS, ORR by BICR, TTD in physical functioning by EORTC QLQ-C30
Other Secondary Endpoints: DOR, TTR, TTD in EORTC QLQ-C30 domains, and safety

1L = first line; BICR = blinded independent central review; CPS = combined positive score; pembro = pembrolizumab; SG = sacituzumab govitecan; TPC = treatment of physician's choice; TTD = time to deterioration; TTR = time to response

Methods

Participants who were randomized to the control group (TPC + pembro) were eligible to receive SG monotherapy through the study, in the **crossover** phase, upon disease progression verified by the BICR and upon meeting eligibility criteria.

Tumour assessments were obtained by computed tomography (CT) or magnetic resonance imaging (MRI) scans every 8 weeks during the first 18 months and then every 12 weeks thereafter. All participants were followed for survival until death, loss to follow-up, or withdrawal of consent, whichever occurred first.

Study participants

Main inclusion criteria:

1) 18 years of age or older, able to understand and give written informed consent.

2) Patients with locally advanced, inoperable, or metastatic TNBC who have not received previous systemic therapy for advanced disease and whose tumors are PD-L1 positive at screening.

a) Patients must have completed treatment for stage I-III breast cancer, if indicated, and ≥ 6 months must have elapsed between completion of treatment with curative intent (e.g. date of primary breast cancer surgery or date of last (neo)adjuvant chemotherapy administration [including anti-PD-(L)1 treatment], whichever occurred last) and first documented local or

distant disease recurrence. Dates of postoperative radiotherapy are not included in this calculation. Prior use of an anti-PD(L)1 agent in the curative TNBC setting is permitted.

i) Patients who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with same class of chemotherapy (taxane or gemcitabine/carboplatin) if ≥ 12 months have elapsed between the completion of treatment with curative intent (e.g. date of primary breast tumor surgery or date of last (neo)adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence. (*Note*: *included with protocol amendment 1)*

ii) Patients enrolled should have received prior anthracycline in the (neo)adjuvant setting or be considered not eligible for anthracyclines as assessed by the treating physician. (*Note*: *included with protocol amendment 1*)

b) Patients presenting with de novo metastatic TNBC are eligible for this study. *Note*: They were capped at approximately 35% of all enrolled participants

c) TNBC status and tumor PD-L1 CPS will be confirmed centrally on a recent or archival tumor specimen.
Patients must have histologically or cytologically documented TNBC, according to current ASCO/CAP criteria, defined as negative for ER, progesterone receptor, and HER2 {Allison et al., 2020, Wolff et al., 2018}. Patients initially diagnosed with hormone receptor-positive or HER2-positive breast cancer must have central confirmation of TNBC in a tumor biopsy obtained from a local recurrence or distant metastasis prior to entry.
Tumor **CPS ≥ 10** using the **PD-L1 IHC 22C3 pharmDx assay** was required for eligibility.

d) Patients must have measurable disease by CT or MRI as per RECIST Version 1.1 criteria as evaluated locally. Tumor lesions situated in a previously irradiated area are considered measurable if unequivocal progression has been documented in such lesions since radiation.

3) Have provided representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in blocks (preferred) or have at least 20 to 25 freshly sectioned unstained slides from fresh biopsy tissue (preferred) or archival tissue block for central testing of ER, progesterone receptor, HER2, PD-L1, Trop-2, and additional biomarker testing.

4) ECOG performance status score of 0 or 1.

5) Life expectancy ≥ 3 months.

6) Recovered from major surgery for ≥ 2 weeks.

7) Adequate hematologic counts without transfusional or growth factor support within 2 weeks of study treatment initiation (hemoglobin ≥ 9 g/dL, ANC ≥ 1500/mm3, and platelets ≥ 100,000/µL).

8) Adequate hepatic function (bilirubin ≤ 1.5 x ULN, AST and ALT ≤ 2.5 x ULN or ≤ 5 x ULN if known liver metastases, and serum albumin > 3 g/dL).

9) Creatinine clearance ≥ 30 mL/min as assessed by the Cockcroft-Gault equation.

10) International Normalized Ratio (INR)/PT and PTT or aPTT ≤ 1.5 ULN unless patient is currently receiving therapeutic anticoagulant therapy.

11) Male patients and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception.

12) Patients with HIV must be on antiretroviral therapy (ART) and have a well-controlled HIV infection/disease

Main exclusion criteria:

- Patients may not have received systemic anticancer treatment (with the exception of endocrine therapy) within the previous 6 months or radiation therapy within 2 weeks prior to enrolment. Patients must have recovered from AEs due to a previously administered agent to ≤ Grade 1 or baseline at the time of study entry.
- Have previously received topoisomerase 1 inhibitors or antibody drug conjugates containing a topoisomerase inhibitor.
- Have received prior therapy with an agent directed to another stimulatory or coinhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137)
- Have known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate (with the exception of those treated with chemotherapy) provided they have stable CNS disease (defined as radiographic stability demonstrated with a minimum of 2 post treatment brain imaging assessments; one performed during screening) for at least 4 weeks prior to enrolment and all neurologic symptoms have returned to baseline, have no evidence of new or enlarging brain metastases, and have also been clinically stable for at least 2 weeks while taking ≤ 10 mg/day of prednisone or its equivalent. All patients with carcinomatous meningitis are excluded regardless of clinical stability.
- Met any of the following criteria for cardiac disease:
  a) Myocardial infarction or unstable angina pectoris within 6 months of enrollment.
  b) History of serious ventricular arrhythmia, high-grade atrioventricular block, or other cardiac arrhythmias requiring antiarrhythmic medications (except for atrial fibrillation that is well controlled with antiarrhythmic medication); history of QT interval prolongation.
  c) New York Heart Association Class III or greater congestive heart failure or known left ventricular ejection fraction of < 40%.
- Have active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) or GI perforation within 6 months of enrollment.
- Have active serious infection requiring systemic antimicrobial therapy.
- Have active HBV or HCV
- Has a diagnosis of immunodeficiency or receiving systemic corticosteroid therapy (higher than physiologic doses) ≥ 10 mg of prednisone per day or equivalent] or any other form of immunosuppressive therapy within 14 days prior to randomization.
- Has received a live vaccine within 30 days prior to randomization.
- Has an active autoimmune disease that has required systemic treatment in the past 2 years (e.g. with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
- Has a history of (non infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

- Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (2 weeks of radiotherapy) to non-CNS disease.

Treatments

Table 18 Summary of study treatments

	Treatment Regimen
SG + pembrolizumab	• SG 10 mg/kg IV on Days 1 and 8 of 21-day cycles[a] • Pembrolizumab 200 mg IV on Day 1 of 21-day cycles[b]
TPC (1 of 3 allowed regimens: paclitaxel, nab-paclitaxel, or gemcitabine + carboplatin) + pembrolizumab	• Paclitaxel 90 mg/m^2 IV on Days 1, 8, and 15 of 28-day cycles OR nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, and 15 of 28-day cycles OR Gemcitabine 1000 mg/m^2 IV with carboplatin AUC 2 IV on Days 1 and 8 of 21-day cycles • Pembrolizumab 200 mg IV on Day 1 of 21-day cycles[b]

IV = intravenous; nab = nanoparticle albumin-bound; SG = sacituzumab govitecan; TPC = treatment of physician's choice
a After completion of 35 cycles of SG treatment, SG treatment may have been continued based on the clinical decision of the treating investigator.
b Pembrolizumab was administered for a maximum of 35 cycles.

The treatment of physician's choice chemotherapy (TPC) was selected prior to randomisation.

Duration of treatment

Participants were treated until blinded independent central review (BICR)-verified disease progression, unacceptable toxicity, withdrawal of consent, or death.

Pembrolizumab was administered for a maximum of 35 cycles (approximately 2 years). Treatment with SG continued for up to 35 cycles, SG treatment may have been continued based on the clinical decision of the treating investigator.

Treatment beyond BICR-verified disease progression per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) was permitted if there was evidence of clinical benefit per the investigator and the patient was tolerating the study drug (note: introduced with protocol amendment 2).

Administration

On infusion days, SG should be administered prior to pembrolizumab.

The first infusion of SG should be administered over 3 hours (± 15 minutes). Subsequent infusions may be administered over 1 to 2 hours if previous infusions were well tolerated. The participant was to be monitored during, and for at least 30 minutes after infusion.

Table 19 Guidance for Premedication and Prophylaxis for Toxicities Associated with Sacituzumab Govitecan

Potential Reaction	Premedication and Prophylaxis Guidance
Infusion-related reaction	• Antipyretics and H1/H2 blockers should be administered before each SG infusion. • Corticosteroids (hydrocortisone 50 mg or equivalent PO or IV) may be administered prior to infusions.
Nausea and vomiting	• Premedication with a 2-drug antiemetic regimen is recommended. • If nausea and vomiting are persistent, a 3-drug regimen may be used, including a 5-HT3 inhibitor (ondansetron or palonosetron, or other agents according to local practices), an NK1-receptor antagonist (fosaprepitant or aprepitant), and dexamethasone (10 mg PO or IV). • Anticipatory nausea can be treated with olanzapine.
Neutropenia	• Complete blood counts must be obtained prior to each SG infusion and treatment should be administered if ANC meets the following criteria: — Day 1: ANC $\geq 1500/mm^3$ — Day 8: ANC $\geq 1000/mm^3$ • The routine prophylactic use of growth factors is not required; however, prophylactic administration should comply with current ASCO/ESMO guidelines for use of growth factors.

Table 20 Recommended Dose Modification Schedule for Sacituzumab Govitecan

Adverse Reaction	Occurrence	Dose Modification or Action
Severe neutropenia		
Grade 4 neutropenia ≥ 7 days, OR Grade 3 or 4 febrile neutropenia, OR At time of scheduled treatment, Grade 3 or 4 neutropenia that delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction and administer G-CSF
	Second	50% dose reduction
	Third	Discontinue Treatment
At time of scheduled treatment, Grade 3 or 4 neutropenia that delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment
Severe nonneutropenic toxicity		
Grade 4 nonhematologic toxicity of any duration, OR Any Grade 3 or 4 nausea, vomiting, or diarrhea due to treatment that is not controlled with antiemetics and antidiarrheal agents OR Other Grade 3 or 4 nonhematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3 or 4 nonneutropenic hematologic or nonhematologic toxicity that delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grade 3 or 4 nonneutropenic hematologic or nonhematologic toxicity that does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment
Infusion-Related Toxicities		
Grade 2 or Grade 3 infusion-related reaction, despite optimal management	Recurrent	Discontinue treatment
Grade 4 infusion-related reaction	First	Discontinue treatment

Objectives

Table 21 Objectives and endpoints

Primary Objective	Primary Endpoint
• To compare PFS as assessed by BICR between SG in combination with pembrolizumab versus TPC in combination with pembrolizumab	• PFS is defined as the time from the date of randomization until the date of objective PD, as assessed by BICR per RECIST v1.1, or death (whichever comes first)
Secondary Objectives	**Secondary Endpoints**

• To compare OS between the 2 groups	• OS is defined as the time from the date of randomization until death due to any cause
• To compare ORR as assessed by BICR between the 2 groups	• ORR is defined as the proportion of participants who achieve CR or PR that is confirmed at least 4 weeks after initial documentation of response as assessed by BICR per RECIST v1.1
• To evaluate DOR as assessed by BICR between the 2 groups	• DOR is defined as the time from the first documentation of CR or PR to the earlier of the first documentation of objective PD or death from any cause (whichever comes first) as assessed by BICR per RECIST v1.1
• To evaluate TTR as assessed by BICR between the 2 groups	• TTR is defined as the time from the date of randomization until the first documentation of CR or PR as assessed by BICR per RECIST v1.1
• To evaluate safety and tolerability between the 2 groups	• Incidence of TEAEs and clinical laboratory abnormalities
• To compare TTD in physical functioning as measured by the EORTC QLQ-C30 Version 3.0 between the 2 groups[a]	• TTD of physical functioning domain of the EORTC QLQ-C30 Version 3.0
• To evaluate TTD in role functioning, global health status/QOL[b], pain, and fatigue[c] as measured by the EORTC QLQ-C30 Version 3.0 between the 2 groups	• TTD of role functioning, global health status/QOL, pain, and fatigue subscale domains of the EORTC QLQ-C30 Version 3.0

Exploratory Objectives	Exploratory End Points
• To assess tumor expression of Trop-2 as a potential biomarker of response to SG plus pembrolizumab	• Correlation of clinical outcome (PFS, OS, ORR, and DOR) with baseline tumor Trop-2 expression
• To explore blood and tumor biomarkers that may be associated with response to SG plus pembrolizumab	• Correlation of clinical outcome (PFS, OS, ORR, and DOR) with tumor, tumor microenvironment, and blood biomarkers at baseline and after SG plus pembrolizumab treatment • Clearance of circulating tumor DNA upon SG plus pembrolizumab treatment
• To explore the relationship of AEs to uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) status	• Correlation of AEs to *UGT1A1* status
• To characterize the pharmacokinetics (PK) and immunogenicity of SG	• Correlation of PK and immunogenicity of SG
• To compare additional QOL outcomes as measured by EuroQoL (EQ-5D-5L), the European Organisation for Research and Treatment of Cancer, Breast Cancer Module (EORTC QLQ-BR23), EORTC QLQ-C30, and Functional Assessment of Cancer Therapy–General item GP5 (FACT-GP5) between the 2 arms	• Additional QOL end points include mean change from baseline, time to deterioration (in addition to the subscales specified as secondary end points), time to improvement, proportion improved, and proportion worsened

a TTD for physical functioning was defined as the time from the date of randomization to the first time a participant experienced a decrease (after applying analysis visit window) from baseline ≥ 13.33 points or death, whichever occurred first.
b TTD for role functioning and global health status/QOL was defined as the time from the date of randomization to the first time a participant experienced a decrease (after applying analysis visit window) from baseline ≥ 10 points or death, whichever occurred first.
c TTD for pain and fatigue was defined as the time from the date of randomization to the first time a participant experienced an increase (after applying analysis visit window) from baseline ≥ 10 points or death, whichever occurred first.

Outcomes/endpoints

Sample size

Approximately 440 eligible participants were planned to be randomly assigned in a 1:1 ratio to receive either SG + pembro or TPC + pembro over a planned nonuniform accrual period of 23 months.

For the primary analysis of PFS as assessed by BICR, approximately 227 events were needed to detect a hazard ratio (HR) of 0.65 with 90% power at a 1-sided significance level of 2.5% using a log-rank test. Assuming a median PFS time for the TPC + pembro group of 12.6 months, 9.7 months for the control arm (corresponding to a HR of 0.771) and that PFS is exponentially distributed, with a sample size of 440 participants, and a 30% annual dropout rate, it was estimated that the primary PFS analysis would occur at approximately 33 months after the first participant was randomized, which was about 10 months after the last participant was randomized.

There were no planned interim analyses for the primary endpoint PFS.

The study was planned to have 1 superiority interim efficacy analysis of the secondary endpoint, OS, which was planned to be performed when a total of approximately 202 (80% information fraction) death events have occurred. The interim analysis was projected to occur approximately 41 months after the first participant is randomized.

For the final analysis of OS, 252 events were needed to detect an average HR of 0.7 with 80% power at a 1-sided significance level of 2.5% using a log-rank test, given 1 efficacy interim analysis at 80% information fraction. Assuming a median OS time for the TPC + pembro group of 23

months, with a total sample size of 440 participants, and a 5% annual dropout rate, it was estimated that the final OS analysis will occur at approximately 53 months after the first participant was randomized.

Randomisation

Randomisation occurred centrally using an IWRS. Participants who met eligibility criteria were randomised in a 1:1 ratio to SG and pembrolizumab or physician's choice of chemotherapy and pembrolizumab starting on Day 1.

Randomisation was stratified by:

- De novo versus recurrent disease within 6-12 months from completion of treatment in the curative setting versus recurrent disease > 12 months from completion of treatment in the curative setting
- Geographic region (US/Canada/Western Europe versus rest of world)
- Prior exposure to anti-PD-1 or anti-PD-L1 agent (yes or no).

Curative treatment interval was defined as the time between completion of systemic (neo)adjuvant breast cancer therapy or surgery (whichever occurred last) and first local or distant recurrence. Adjuvant radiotherapy is not included in the 6-month interval.

In the situation where there was insufficient information in a stratum (i.e. if there were < 10 events in a stratum by combined treatment arms), pooling of the stratum per medical assessment and/or with the smallest adjacent stratum for stratified analyses were considered; the smallest stratum was defined as the stratum having the fewest number of events and the adjacent stratum was defined as a stratum having 2 of the 3 factors at the same level and the other factor at an adjacent level.

Blinding (masking)

This was an open-label study.

Statistical methods

Analysis Population

ITT analysis set: The ITT analysis set included all randomised patients according to the treatment arm to which the patient was randomised to. The ITT Analysis set was the primary analysis set for efficacy analyses, demographic characteristics, baseline assessments, and quality of life assessments.

Safety analysis set: The safety analysis set included all patients who received at least 1 dose of any study treatment, with treatment assignments designated according to the actual treatment received. This analysis set was the primary analysis set for all safety analyses.

PK analysis set: The PK analysis set included all randomised patients who received at least 1 dose of SG per the protocol and had at least 1 measurable posttreatment serum concentration of SG.

Immunogenicity analysis set: The immunogenicity analysis set included all randomised patients who received at least 1 dose of SG and had at least 1 evaluable non missing anti-SG antibody test result.

Efficacy Analysis

Primary endpoint

PFS assessed by BICR

The primary analysis of PFS compared the PFS distributions of the 2 treatment groups for the ITT Analysis Set using the log-rank test stratified by the stratification factors at randomisation. Medians, first quartile (Q1), third quartile (Q3) of the PFS distributions, and the proportion of participants who were event-free at 6, 9, 12, and 18 months from randomisation are provided along with corresponding 95% CIs using the Kaplan-Meier method. Kaplan-Meier curves are provided by treatment group.

Additionally, the treatment effect was estimated by HR between the 2 treatment groups along with its 95% CI using the Cox proportional hazards regression model with Efron's method of tie handling, stratified by the stratification factors at randomisation.

The following sensitivity analyses were planned:

- PFS using different censoring rules
- PFS assessed by investigator
- PFS using the stratification factors as per clinical database.

Censoring rules for the primary and sensitivity analyses are provided in the below table.

Table 22 Censoring rules for the primary and sensitivity analyses

Case	Date of Event/Censoring		
	Primary Analysis (PA)	Sensitivity analysis 1 (SA1)	Sensitivity analysis 2 (SA2)
No baseline tumor assessments or no adequate response assessments after randomization			
Did not die	Censored at randomization date	Censored at randomization date	Censored at randomization date
Died prior to second scheduled assessment without initiation of new anti-cancer therapy	Event at death date	Event at death date	Event at death date
Died after 2 consecutive missing assessments without initiation of new anti-cancer therapy	Censored at randomization date	Event at death Date	Censored at Randomization date
Died after initiation of new anti-cancer therapy	Censor at randomization date	Event at death date	Event at date of discontinuation of treatment, if any, or start date of new anti-cancer treatment whichever occurs earlier
Continued scheduled response assessments until objective PD or death			
PD or death before ≥ 2 consecutive missing assessments and before initiation of new anti-cancer treatment, if any	Event at Death date or PD date, whichever occurs first	Event at Death date or PD date, whichever occurs first	Event at Death date or PD date, whichever occurs first
PD or death immediately after ≥ 2 consecutive missing assessments	Censored at date of last adequate tumor assessment before missed assessments	Event at death date or PD date, whichever occurs first	Censored at date of last adequate tumor assessment before missed assessments
Initiated new anti-cancer treatment prior to PD or death	Censored at date of last adequate tumor assessment before starting new anti-cancer treatment	Event at death date or PD date, whichever occurs first	Event at date of discontinuation of treatment, if any, or start date of new anti-cancer treatment whichever occurs earlier
Continued scheduled response assessments without objective PD or death			
Treatment discontinuation or initiated new anti-cancer treatment	Censored at date of last adequate tumor assessment before starting new anti-cancer treatment	Censored at date of last adequate tumor assessment	Event at treatment discontinuation date or start date of new anti-cancer therapy, whichever occurs earlier.
Ongoing in study treatment	Censored at date of last adequate tumor assessment	Censored at date of last adequate tumor assessment	Censored at date of last adequate tumor assessment

Key secondary endpoints

OS

OS was defined as the time from the date of randomisation until death due to any cause. For participants who were not known to have died at the time of the analysis, OS data was censored at the last date that they were known to be alive. The descriptive OS summary included Kaplan-Meier estimates of median, Q1, Q3 of OS and corresponding 95% CI by treatment group and HR between treatment groups using a Cox proportional hazard regression model stratified by the randomization stratification factors.

The formal analyses of OS were planned to be performed using the Kaplan-Meier method for the ITT Analysis Set. The OS distribution of the 2 treatment groups were planned to be compared using the log-rank test, stratified by the stratification factors at randomization. Medians, Q1, Q3, and the proportion of participants who are alive at 12, 18, 24, 30, and 36 months from randomization were planned to be provided along with the corresponding 95% CI. Kaplan-Meier curves were planned by treatment group.

In addition, the HR between the 2 treatment groups and its 95% CI were planned to be estimated using the Cox proportional hazards regression model with Efron's method of tie handling, adjusted for the stratification factors at randomisation.

To account for the effect of crossover on OS, methods such as the rank preserving structural failure time model, two-stage method, or inverse probability censoring weighting method were planned.

ORR as assessed by BICR

A descriptive analysis of ORR was performed at the time of PFS primary analysis using the ITT Analysis Set.

The ORR as assessed by BICR was planned to be compared between the 2 treatment groups using the Cochran-Mantel-Haenszel test adjusted for the stratification factors in the same dataset that is used for OS interim analysis. The ORR and the corresponding 95% CI based on the Clopper-Pearson method were planned to be provided for each treatment group. The odds ratio (OR) comparing the 2 treatment groups adjusted for the randomisation stratification factors were planned to be presented along with 95% CI.

The following sensitivity analyses were planned:

- ORR assessed by investigator

Concordance/discordance of best overall response as assessed by BICR and investigator was planned to be summarised in a frequency table.

Time to deterioration (TTD) in the physical functioning domain of the EORTC QLQ-C30

TTD in physical functioning as measured by EORTC QLQ-C30 was defined as the time between the randomisation date and the date of assessment at which a participant experienced a first deterioration (i.e. greater than or equal to the threshold for worsening from baseline in the physical functioning domain; based on the assessments after applying analysis visit window) or death, whichever occurred first. The threshold of change was documented in a separate PRO SAP.

A descriptive analysis of TTD in physical functioning as measured by EORTC QLQ-C30 was performed at the time of PFS primary analysis using the Kaplan-Meier method for the ITT Analysis Set. Median, Q1, Q3 and corresponding 95% CI were provided for each treatment group. HR between treatment groups and its 95% CI were provided using a Cox proportional hazard regression model stratified by the randomization stratification factors.

The TTD in physical functioning distribution of the 2 treatment groups was planned to be compared using the log-rank test, stratified by the stratification factors at randomization in the same dataset that is used for OS interim analysis. Medians, Q1, and Q3 were planned to be provided along with the corresponding 95% CI. Kaplan-Meier curves were planned to be provided by treatment group. In addition, the HR between the 2 treatment groups and its 95% CI will be estimated using the Cox proportional hazards regression model, adjusted for the stratification factors at randomisation.

Other secondary endpoints

DOR assessed by BICR and time to deterioration in other domains of the EORTC QLQ-C30 were planned to be analysed using Kaplan-Meier methodology including estimates of median and 95% CIs.

TTR assessed by BICR and investigator were planned to be summarised using descriptive statistics by treatment arm for responders. CBR (Clinical Benefit Rate) assessed by BICR and investigator were planned to be analyses similarly to ORR.

Multiplicity

The overall type 1 error rate for this study was controlled at a 1-sided alpha of 2.5%.

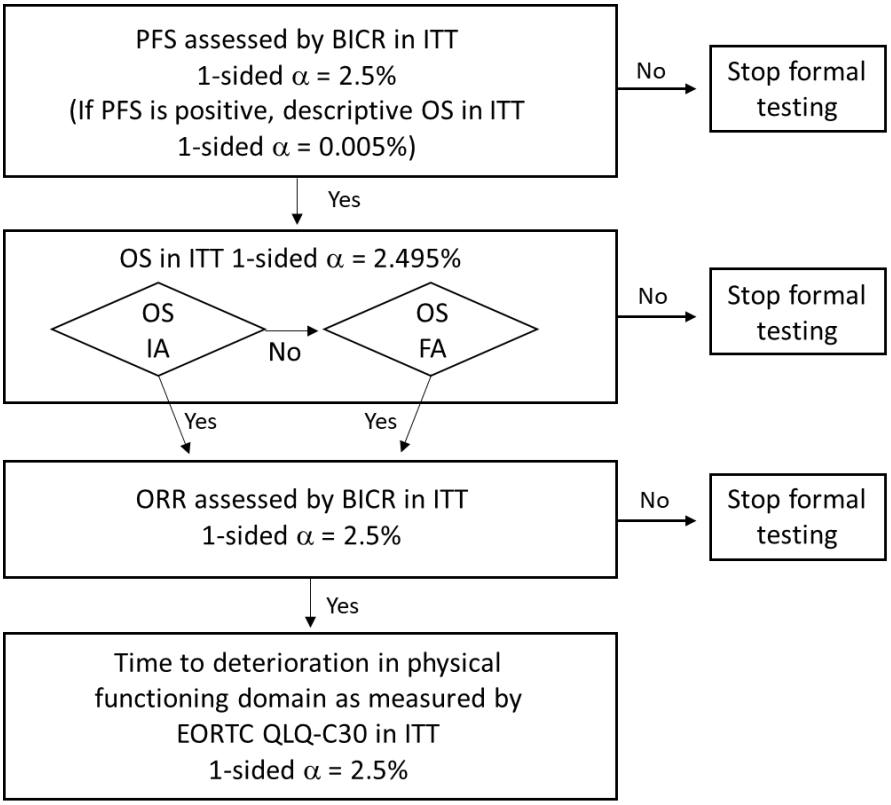
The primary endpoint analysis of PFS assessed by BICR served as the gatekeeper for the secondary endpoint analyses and was tested at the 1-sided alpha of 2.5%. At PFS primary analysis, OS was summarised descriptively only. A nominal 1-sided alpha of 0.005% was spent without formal hypothesis testing, only if the primary PFS analysis was positive. The analysis of the key secondary endpoint of OS was planned to be formally tested sequentially at the 1-sided alpha of 2.495%.

The analysis of ORR (assessed by BICR) and analysis for TTD of physical functioning were planned to be formally tested sequentially at the 1-sided alpha of 2.5% when the above hypotheses in the hierarchy are also statistically significant.

The ORR and TTD of physical functioning were planned to be analysed and tested in the same dataset as used for OS interim analysis.

The hierarchical testing procedure is described in the figure below.

Figure 16 Hierarchical Testing Procedures



Interim Analysis

The study planned for 3 analyses: primary PFS analysis, 1 interim analysis for OS and OS final analysis.

At the primary analysis of PFS, 227 PFS events were planned, which was expected to occur 33 months after the first patient was randomised. At the same time, a descriptive, analysis of OS was planned to be performed using a 1-sidded alpha of 0.005% without formal hypothesis testing. It was expected to observe 156 OS events (62% information fraction of the total 252 OS events).

OS was planned to be formally tested at an interim analysis, when approximately 202 OS events were observed, which was expected to occur 41 after the first patient was randomised. At the same time, secondary endpoints ORR and TTD were planned to be tested.

At the final analysis, OS was planned to be tested when approximately 252 OS events were observed, which was expected to occur 53 months after the first patient was randomised. The analysis of the ORR and TTD of physical functioning at the time of OS final analysis was planned to be descriptive.

To account for the interim analyses of OS, an administrative 1-sided alpha of 0.005% was spent at the primary analysis of PFS and the Lan-DeMets alpha spending function that approximates an O'Brien Fleming approach was used to account for multiplicity introduced by including an OS interim analysis for superiority. The OS efficacy interim analysis was planned to be tested at the 1-sided significance level of 1.2%. If the OS efficacy interim analysis is not positive, the final OS analysis was planned be tested at the 1-sided significance level of 2.1%. The alpha levels for the OS interim and final analyses are based on the actual observed events and be adjusted accordingly.

Details on the expected number of events and 1-sided alpha levels at analysis are provided in the below table.

Table 23 The Expected Number of Events at Interim and Final Analyses and Significance Levels to Reject H0

Description	Expected Events 'n' (Information Fraction)	Expected Timing of Analysis (Months From Randomization)	Stopping Boundary (1-Sided Alpha) (Equivalent 2-Sided Alpha[a])
Primary PFS analysis (final)	~227 PFS events (100%)	33	HR $\leq$ 0.771 ($P \leq 0.025$) ($P \leq 0.05$)
OS analysis concurrent at primary PFS analysis (descriptive summary)	~156 deaths (62%)	33	No formal testing, 1-sided $\alpha = 0.00005$ spent 2-sided $\alpha = 0.0001$ spent
OS interim analysis	~202 deaths (80%)	41	HR $\leq$ 0.729 ($P \leq 0.012$) ($P \leq 0.025$)
OS final analysis	~252 deaths (100%)	53	HR $\leq$ 0.775 ($P \leq 0.021$) ($P \leq 0.043$)

Results

Participant flow

Figure 17 Summary of Participant Flow (DCO: 03 March 2025)

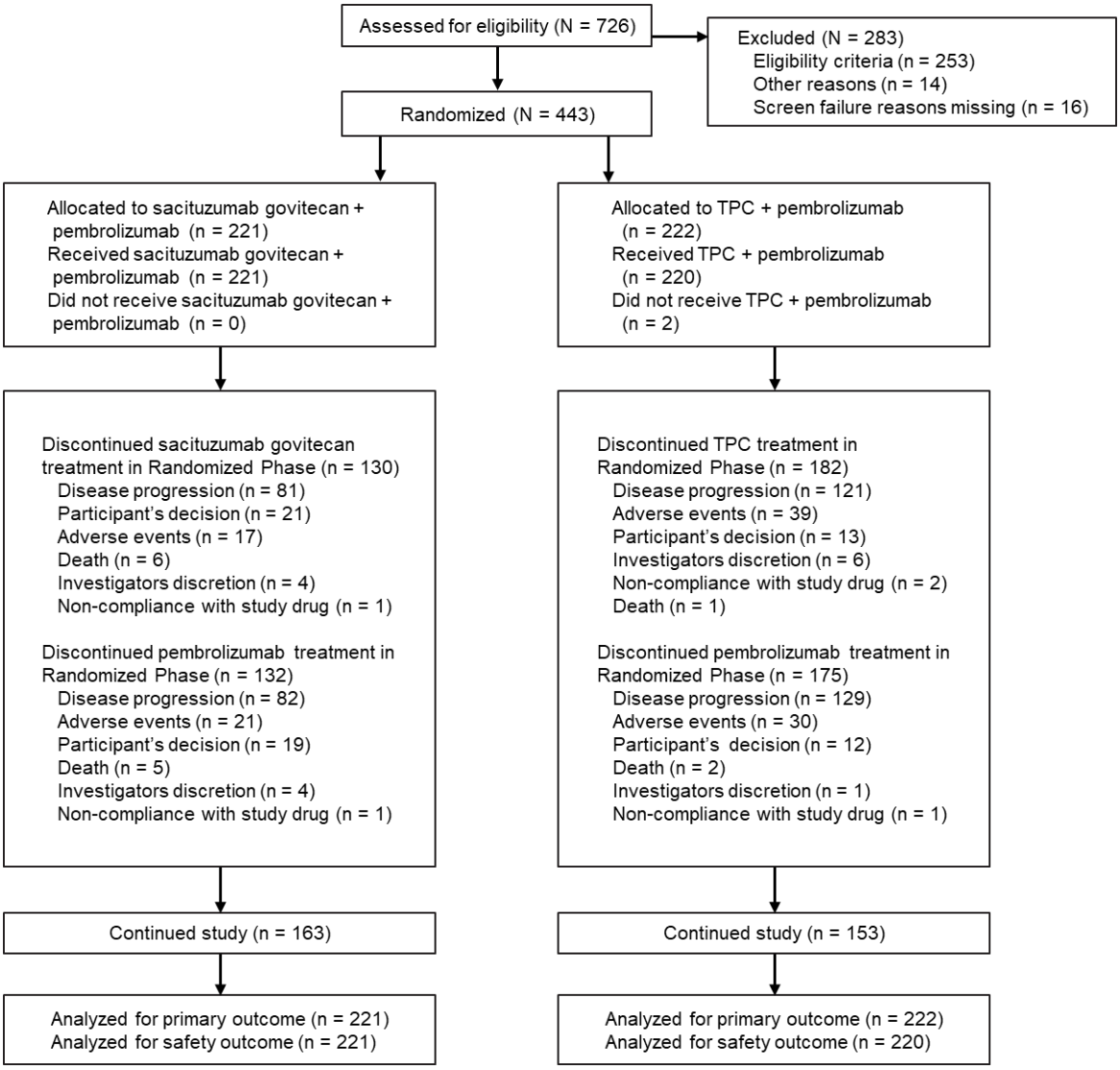


Table 24 Disposition of Participants (All Screened Participants) – DCO 16 Feb 2026

	SG + Pembro	TPC + Pembro	Total
Screened			726
Intent to Treat Analysis Set (ITT)	221	222	443
Randomized but not Treated	0	2	2
Safety Analysis Set	221	220	441
Study Treatment Completion Status (Randomized Phase)			
Continuing any study treatment	40 (18.1%)	14 (6.3%)	54 (12.2%)
Continuing all study treatment	15 (6.8%)	0	15 (3.4%)
Discontinued all study treatment	165 (74.7%)	200 (90.1%)	365 (82.4%)
Adverse Event	11 (5.0%)	16 (7.2%)	27 (6.1%)
Pregnancy	0	0	0
Investigator's Discretion	4 (1.8%)	5 (2.3%)	9 (2.0%)
Non-Compliance with Study Drug	1 (0.5%)	2 (0.9%)	3 (0.7%)
Subject Decision	25 (11.3%)	15 (6.8%)	40 (9.0%)
Study Terminated by Sponsor	0	0	0
Progressive Disease	114 (51.6%)	159 (71.6%)	273 (61.6%)
Lost to Follow-Up	0	0	0
Death	9 (4.1%)	3 (1.4%)	12 (2.7%)
Clinical decision making after 35 cycles (SG only)[a]	1 (0.5%)	0	1 (0.2%)
Completed Pembrolizumab and Discontinued SG/TPC	16 (7.2%)	8 (3.6%)	24 (5.4%)
Adverse Event	4 (1.8%)	3 (1.4%)	7 (1.6%)
Investigator's Discretion	1 (0.5%)	3 (1.4%)	4 (0.9%)
Subject Decision	2 (0.9%)	0	2 (0.5%)
Progressive Disease	4 (1.8%)	2 (0.9%)	6 (1.4%)
Clinical decision making after 35 cycles (SG only)[a]	5 (2.3%)	0	5 (1.1%)
Study Treatment Completion Status for SG/TPC (Randomized Phase)			
Continuing SG/TPC	40 (18.1%)	8 (3.6%)	48 (10.8%)
Discontinued SG/TPC	181 (81.9%)	214 (96.4%)	395 (89.2%)
Adverse Event	19 (8.6%)	43 (19.4%)	62 (14.0%)
Pregnancy	0	0	0
Investigator's Discretion	5 (2.3%)	12 (5.4%)	17 (3.8%)
Non-Compliance with Study Drug	1 (0.5%)	2 (0.9%)	3 (0.7%)
Subject Decision	27 (12.2%)	14 (6.3%)	41 (9.3%)
Study Terminated by Sponsor	0	0	0
Progressive Disease	114 (51.6%)	141 (63.5%)	255 (57.6%)
Lost to Follow-Up	0	0	0
Death	9 (4.1%)	2 (0.9%)	11 (2.5%)
Clinical decision making after 35 cycles (SG only)[a]	6 (2.7%)	0	6 (1.4%)

Study Treatment Completion Status for Pembrolizumab (Randomized Phase)			
Continuing Pembrolizumab	15 (6.8%)	6 (2.7%)	21 (4.7%)
Completed Pembrolizumab	35 (15.8%)	14 (6.3%)	49 (11.1%)
Discontinued Pembrolizumab	171 (77.4%)	202 (91.0%)	373 (84.2%)
Adverse Event	22 (10.0%)	32 (14.4%)	54 (12.2%)
Pregnancy	0	0	0
Investigator's Discretion	4 (1.8%)	3 (1.4%)	7 (1.6%)
Non-Compliance with Study Drug	1 (0.5%)	1 (0.5%)	2 (0.5%)
Subject Decision	24 (10.9%)	14 (6.3%)	38 (8.6%)
Study Terminated by Sponsor	0	0	0
Progressive Disease	112 (50.7%)	149 (67.1%)	261 (58.9%)
Lost to Follow-Up	0	0	0
Death	8 (3.6%)	3 (1.4%)	11 (2.5%)
Received Study Treatment in Crossover Phase[b]		99 (44.6%)	
Study Completion Status			
Continuing Study	118 (53.4%)	104 (46.8%)	222 (50.1%)
Discontinued Study	103 (46.6%)	118 (53.2%)	221 (49.9%)
Death	94 (42.5%)	106 (47.7%)	200 (45.1%)
Withdrew Consent	9 (4.1%)	11 (5.0%)	20 (4.5%)
Lost to Follow-Up	0	1 (0.5%)	1 (0.2%)
Study Terminated by Sponsor	0	0	0

a After completion of 35 cycles of SG treatment, SG treatment may be discontinued based on the clinical decision making from the treating investigator.
b Does not include participants who received subsequent anticancer therapy with SG outside of the study.
Randomized phase excludes crossover phase when participants in TPC + Pembro group started to receive SG.
"Study Treatment Completion Status" is summarized per ITT Analysis Set.
"Discontinued all study treatment" refers to the reason of the last discontinued study treatment.
"Completed Pembrolizumab and Discontinued SG/TPC" includes participants completed 35 cycles of pembrolizumab but
discontinued SG/TPC. Participants in TPC + Pembro group who received SG in crossover phase had progressive disease verified by BICR.

Treatment in the control arm

Among 220 participants in the TPC + Pembro group who received study treatment, 51.4% (113 participants) received a taxane (paclitaxel or nab paclitaxel) and 48.6% (107 participants) received gemcitabine with carboplatin.

Subsequent treatment

Table 25 Subsequent Anti-Cancer Therapy by Category at the primary PFS analysis – DCO 03 Mar 2025

Category Preferred Drug Name	SG+Pembro (N=221)	TPC+Pembro (N=222)	Total (N=443)
Participants with Any Subsequent Anti-Cancer Therapy, n (%)	69 (31.2%)	119 (53.6%)	188 (42.4%)
Taxanes	29 (13.1%)	11 (5.0%)	40 (9.0%)
Platinum	23 (10.4%)	10 (4.5%)	33 (7.4%)

Anthracyclines	9 (4.1%)	10 (4.5%)	19 (4.3%)
PARP inhibitors	3 (1.4%)	2 (0.9%)	5 (1.1%)
Anti-PD-1/PD-L1 agents	6 (2.7%)	9 (4.1%)	15 (3.4%)
Trastuzumab Deruxtecan	10 (4.5%)	6 (2.7%)	16 (3.6%)
Sacituzumab Govitecan	3 (1.4%)	96 (43.2%)	99 (22.3%)
Other	48 (21.7%)	33 (14.9%)	81 (18.3%)
Capecitabine	23 (10.4%)	11 (5.0%)	34 (7.7%)
Cyclophosphamide	6 (2.7%)	10 (4.5%)	16 (3.6%)
Gemcitabine	10 (4.5%)	6 (2.7%)	16 (3.6%)
Bevacizumab	8 (3.6%)	2 (0.9%)	10 (2.3%)
Eribulin	4 (1.8%)	4 (1.8%)	8 (1.8%)
Eribulin Mesilate	3 (1.4%)	2 (0.9%)	5 (1.1%)
Investigational Drug	3 (1.4%)	1 (0.5%)	4 (0.9%)
Vinorelbine	3 (1.4%)	1 (0.5%)	4 (0.9%)

Participants who received Sacituzumab Govitecan during crossover phase on study were counted under the preferred drug name "Sacituzumab Govitecan".
The preferred drug name "Sacituzumab Govitecan" includes both commercial use and crossover to SG on study.

Table 26 Subsequent Anticancer Therapy in Second Line at OS IA – DCO 16 Feb 2026

	SG + Pembro (N =221)	TPC + Pembro (N = 222)	Total (N = 443)
Participants with Subsequent Anticancer Therapy in Second Line, n (%)	122 (55.2%)	159 (71.6%)	281 (63.4%)
ADC	16 (7.2%)	124 (55.9%)	140 (31.6%)
Sacituzumab Govitecan	5 (2.3%)	122 (55.0%)	127 (28.7%)
Received SG in Crossover Phase[a]	—	99 (44.6%)	—

ADC = antibody-drug conjugate; IA = interim analysis; ITT = intent to treat; OS = overall survival; Pembro = pembrolizumab; SG = sacituzumab govitecan; TPC = treatment of physician's choice
a Does not include participants who received subsequent anticancer therapy with SG in second line outside of the study.

Duration of OS follow-up

At the time of the final PFS analysis (DCO: 03 March 2025), the median duration of OS follow-up was 14.0 months (range 0.1 to 28.6) in the overall study population (14.0 months [range: 0.5 to 28.6] in the SG + Pembro group and 14.2 months [range: 0.1 to 27.5] in the TPC + Pembro group).

At the time of the interim analysis of OS (DCO: 16 February 2026), the median duration of OS follow-up was 22.5 months (0.1 to 40.0) in the overall study population (22.6 months [range: 0.5 to 40.0] in the SG + Pembro group and 22.5 months [range: 0.1 to 39.0] in the TPC + Pembro group).

Recruitment

The first participant was randomised on 17 October 2022 (on 13 September 2022 the first patient was screened) and the study completed enrolment on 21 August 2024. The trial is ongoing.

Participants were enrolled in 186 study centres across 28 countries:

- Africa (n=13): South Africa 13
- Asia Pacific (n=112): Australia 14, Hong Kong 5, Japan 26, Malaysia 13, South Korea 41, Taiwan 12, Singapore 1

- Europe (n=143): Austria 3, Belgium 3, Czech Republic 6, Israel 10, France 25, Germany 11, Hungary 3, Italy 19, NL 8, Poland 4, Spain 32, Switzerland 3, Turkey 13, UK 3
- Latin America (n=112): Argentina 17, Brazil 20, Chile 33, Mexico 42
- North America (n=63): Canada 16, United States 47.

Conduct of the study

Protocol amendments

Original protocol dated 20 December 2021

Amendment 1 dated 08 April 2022 (implemented before randomisation of first patient on 17 October 2022)

Overall rationale: The primary reason for this amendment is to address the feedback received from the FDA and CHMP (Note: adoption of CHMP SA in November 2021).

Summary of main changes:

- The sample size was reduced from approximately 570 to 440 patients to address CHMP's comments on low maturity rate and minimum follow-up time for the primary endpoint (PFS).
- The assumption for median overall survival (OS) time in the control arm was changed from 27 months to 23 months, based on the most updated data from KEYNOTE-355 study.
- A descriptive OS analysis was added at the time of PFS primary analysis, and a nominal 1-sided alpha of 0.005% will be spent even without formal hypothesis testing. An efficacy OS interim analysis was added at 80% information fraction with Lan-DeMets alpha spending function approximating an O'Brien Fleming approach, to account for the ~20 months' gap between PFS and OS final analysis.
- The timing of PFS final analysis was adjusted based on the updated sample size (33 instead of 30 months after the first patient is randomized, which is about 10 months after the last patient is randomized). The timing and the required number of events for OS final analysis were adjusted based on the updated median OS in the control arm and the addition of an OS efficacy interim analysis.
- For the endpoints related to patient-reported outcomes, only "time to deterioration in physical functioning as measured by the EORTC QLQ-C30" was included in the hierarchical testing procedure, to address FDA's comments.

Table 27 Summary of changes in planned efficacy analysis (Assessor's table)

	Original protocol	Amendment 1
Date of initiation	20 Dec 2021	08 Apr 2022
Sample size	N=570	N=440
Primary PFS analysis Expected events Expected timing[a] *Stopping boundary[b]*	 227 30 months NR	 227 33 months *HR ≤ 0.771*
Assumed for control arm • **median PFS** • **median OS**	 9.7 months 27 months	 9.7 months 23 months
Descriptive OS analysis[c] Expected events (IF) Expected timing[a] *Stopping boundary[b]*	 130 (53%) 30 months *No formal testing, 1-sided α=0.00005*	 156 (62%) 33 months *No formal testing, 1-sided α=0.00005*
OS IA Expected events n (IF) Expected timing[a] *Stopping boundary[b]*	 Not planned	 202 (80%) 41 months *HR ≤ 0.729*
OS final Expected events n (maturity) Expected timing[a] Stopping boundary[b]	 247 (*/570*=43%) 46 months	 252 (/440=57.3%) 53 months *HR ≤ 0.775*

[a] expected timing of analysis (months from randomization)
[b] Stopping Boundary for primary PFS analysis (1-Sided Alpha)
[c] Descriptive OS analysis concurrent with primary PFS analysis, no formal testing

IF: Information fraction, NR: not reported

Amendment 2 dated 13 October 2023 (219 out of 443 patients have been enrolled*)

Rationale for key changes (excerpt):

- The de novo cap for the mTNBC population was changed from 25% to approximately 35%, and clarification was added for consistency with the Study Design Overview.
  Rationale: Thirty-five percent de novo representation is more reflective of recent real-world data reports.
- PR or CR changes in tumour measurements must be confirmed at least 4 weeks after initial documentation. Changed from 4-6 weeks previously.
- Added language to suggest clinical decision-making should be done after 35 cycles to reassess the appropriateness of continuing SG.
- Added language to allow treatment beyond BICR-verified PD.

Changes from planned analyses

Changes from the analyses specified in Protocol Amendment 2 (13 October 2023) were as follows:

- Time to deterioration for the physical functioning domain, as well as for the role functioning, global health status/QOL, pain, and fatigue subscale domains as measured by EORTC QLQ-C30 Version 3.0 were analysed using the ITT Analysis Set rather than the QOL Analysis Set.
- Two-sided *P* values are reported rather than 1-sided *P* values.

- Concentration and PK parameters reported for SG have been updated.
- Laboratory numerical evaluations are reported in International System of Units (SI) units rather than conventional units.
- The definition of TTD for secondary PRO endpoints was clarified as the time between the date of randomization and the date of assessment at which a participant experienced a first deterioration (i.e. ≥ the threshold for worsening from baseline; based on the assessments after applying analysis visit window) or death.

Statistical Analysis Plan Version 1.0, dated 27 February 2025 (all patients randomised)

The SAP Version 1.0 is based on the Protocol Amendment 2 dated 13 October 2023 and was finalised after all patients have been randomised five days prior to data cut-off for the PFS primary analysis.

Protocol deviations

An important protocol deviation was defined as a protocol deviation that might significantly impact completeness, accuracy, and/or reliability of study data or that may significantly affect a participant's rights, safety, or well-being.

Table 28 Important Protocol Deviations (DCO : 03 Mar 2025)

	SG + Pembro (N = 221)	TPC + Pembro (N = 222)	Total (N = 443)
Participants with at least 1 Important Protocol Deviation	110 (49.8%)	95 (42.8%)	205 (46.3%)
Participants with 1 Important Protocol Deviation	63 (28.5%)	57 (25.7%)	120 (27.1%)
Participants with 2 Important Protocol Deviations	25 (11.3%)	23 (10.4%)	48 (10.8%)
Participants with 3 or more Important Protocol Deviations	22 (10.0%)	15 (6.8%)	37 (8.4%)
Participants with at least 1 Important Protocol Deviation by categories			
Other treatment compliance issue	61 (27.6%)	24 (10.8%)	85 (19.2%)
Other	21 (9.5%)	31 (14.0%)	52 (11.7%)
Eligibility criteria	19 (8.6%)	29 (13.1%)	48 (10.8%)
Missing data	23 (10.4%)	22 (9.9%)	45 (10.2%)
Informed consent	17 (7.7%)	17 (7.7%)	34 (7.7%)
Off schedule procedure	9 (4.1%)	4 (1.8%)	13 (2.9%)
Wrong treatment or incorrect dose	2 (0.9%)	2 (0.9%)	4 (0.9%)

Further clarifications regarding reported categories of important protocol deviations (IPD):

- Other Treatment Compliance Issue

"Treatment Compliance Issues" were reported with higher incidence in the SG + pembro group (27.6%) versus the TPC + pembro group (10.8%). The observed numerical difference was associated with protocol-specified absolute neutrophil count (ANC) requirements that were specifically applicable to SG treatment in the SG + pembrolizumab group (N=30 vs N=0 in the control arm); additional training was conducted by the sponsor. These cases predominantly included SG administration at Grade 2 ANC levels prior to Day 1 dosing across various cycles. The

second largest subcategory contributing to the observed imbalance was associated with study drug administration occurring outside the protocol-specified window. These delays were largely related to administrative circumstances (N=21 in the SG + pembro group vs N=15 in the TPC + pembro group).

- Eligibility criteria

The reasons for ineligibility varied across different eligibility subcriteria without a consistent pattern. The study was analysed using intent to treat principles, and no participants were excluded from analysis even if they were subsequently found to have not met eligibility criteria.

- Missing Data

The IPDs categorized as "Missing Data" were associated with laboratory and tumour assessments that were not performed during the study or were conducted outside the protocol specified assessment window. IPDs did not result in censoring of PFS.

- Informed Consent

Important protocol deviations regarding informed consent primarily involved administrative errors. There were no instances in which informed consent was not obtained from a participant in the clinical study.

- Other

Occurrence of important deviations in the "Other" category were primarily due to stratification errors in the randomization system (IWRS). A sensitivity analysis of the primary endpoint was conducted in the ITT Analysis Set using stratification factor values from the clinical database (note: please see results of PFS sensitivity analysis 4).

- Off Schedule Procedure

Deviations were related to tumour assessments completed outside of the protocol prespecified window. IPDs did not result in PFS censoring.

- Wrong Treatment or Incorrect Dose

Deviations were related to the dosing errors of study treatment. No participants received the wrong study treatment.

Baseline data

Table 29 Demographic and Baseline Characteristics (excerpt from CSR Table 10)

	SG + Pembro (N = 221)	TPC + Pembro (N = 222)	Total (N = 443)
Age (years)			
N	221	222	443
Mean (StD)	54 (13.9)	54 (13.0)	54 (13.4)
Median	54	55	55
Q1, Q3	43, 65	43, 65	43, 65
Min, Max	23, 88	27, 82	23, 88
Age group			
< 65 years	163 (73.8%)	165 (74.3%)	328 (74.0%)
≥ 65 years	58 (26.2%)	57 (25.7%)	115 (26.0%)
Sex at birth			
Male	0	0	0
Female	221 (100.0%)	222 (100.0%)	443 (100.0%)
Race			
American Indian or Alaska Native	14 (6.3%)	13 (5.9%)	27 (6.1%)
Asian	43 (19.5%)	63 (28.4%)	106 (23.9%)
Black	13 (5.9%)	11 (5.0%)	24 (5.4%)
Native Hawaiian or Pacific Islander	0	0	0
White	139 (62.9%)	118 (53.2%)	257 (58.0%)
Other	8 (3.6%)	4 (1.8%)	12 (2.7%)
Not Permitted	4 (1.8%)	13 (5.9%)	17 (3.8%)

Table 30 Baseline disease characteristics (excerpt from CSR Table 11)

	SG + Pembro (N = 221)	TPC + Pembro (N = 222)	Total (N = 443)
Baseline ECOG score			
0	156 (70.6%)	154 (69.4%)	310 (70.0%)
1	65 (29.4%)	67 (30.2%)	132 (29.8%)
2	0	1 (0.5%)	1 (0.2%)
Menopausal status (females only)			
Premenopausal	81 (36.7%)	77 (34.7%)	158 (35.7%)
Postmenopausal	140 (63.3%)	145 (65.3%)	285 (64.3%)
BRCA1/2 mutation status[a]			
Mutant	19 (8.6%)	13 (5.9%)	32 (7.2%)
Wild Type	41 (18.6%)	57 (25.7%)	98 (22.1%)
Unknown	161 (72.9%)	152 (68.5%)	313 (70.7%)
PD-L1 CPS[b]			
< 10	0	0	0
≥ 10	221 (100.0%)	222 (100.0%)	443 (100.0%)
Estrogen receptor status			
Negative (< 1%)	220 (99.5%)	222 (100.0%)	442 (99.8%)
Positive (≥ 1%)	1 (0.5%)[c]	0	1 (0.2%)
Progesterone receptor status			
Negative (< 1%)	221 (100.0%)	222 (100.0%)	443 (100.0%)
Positive (≥ 1%)	0	0	0
HER2 status			
Positive	0	1 (0.5%)	1 (0.2%)
Negative	221 (100.0%)	220 (99.1%)	441 (99.5%)
Missing	0	1 (0.5%)	1 (0.2%)

Prior radiotherapy			
Yes	121 (54.8%)	112 (50.5%)	233 (52.6%)
No	100 (45.2%)	110 (49.5%)	210 (47.4%)
On study radiotherapy			
Yes	12 (5.4%)	22 (9.9%)	34 (7.7%)
No	209 (94.6%)	200 (90.1%)	409 (92.3%)
UGT1A1 genotype			
*1/*1	87 (39.4%)	105 (47.3%)	192 (43.3%)
*1/*28	93 (42.1%)	76 (34.2%)	169 (38.1%)
*1/*36	3 (1.4%)	1 (0.5%)	4 (0.9%)
*1/*37	1 (0.5%)	1 (0.5%)	2 (0.5%)
*1/*6	9 (4.1%)	9 (4.1%)	18 (4.1%)
*27/*27/*28/*28	0	1 (0.5%)	1 (0.2%)
*27/*28/*28	0	1 (0.5%)	1 (0.2%)
*28/*28	13 (5.9%)	23 (10.4%)	36 (8.1%)
*28/*36	1 (0.5%)	0	1 (0.2%)
*28/*37	1 (0.5%)	1 (0.5%)	2 (0.5%)
*6/*28	3 (1.4%)	1 (0.5%)	4 (0.9%)
*6/*37	1 (0.5%)	0	1 (0.2%)
*6/*6	2 (0.9%)	2 (0.9%)	4 (0.9%)
Missing/Not done	7 (3.2%)	1 (0.5%)	8 (1.8%)

Preselected TPC prior to randomization			
Taxane	116 (52.5%)	114 (51.4%)	230 (51.9%)
Gemcitabine/Carboplatin	105 (47.5%)	108 (48.6%)	213 (48.1%)

Breast cancer stage at initial diagnosis			
Stage I	21 (9.5%)	29 (13.1%)	50 (11.3%)
Stage II	64 (29.0%)	64 (28.8%)	128 (28.9%)
Stage III	66 (29.9%)	63 (28.4%)	129 (29.1%)
Stage IV	70 (31.7%)	65 (29.3%)	135 (30.5%)
Missing	0	1 (0.5%)	1 (0.2%)
Subtype of cancer at initial diagnosis			
HR−/HER2− (TNBC)	190 (86.0%)	188 (84.7%)	378 (85.3%)
HR−/HER2+	3 (1.4%)	3 (1.4%)	6 (1.4%)
HR+/HER2+	4 (1.8%)	3 (1.4%)	7 (1.6%)
HR+/HER2−	24 (10.9%)	27 (12.2%)	51 (11.5%)
Missing	0	1 (0.5%)	1 (0.2%)
Disease status at screening			
Metastatic disease	210 (95.0%)	210 (94.6%)	420 (94.8%)
Locally advanced unresectable	11 (5.0%)	12 (5.4%)	23 (5.2%)
Site of metastasis at screening[d]			
Lung	111 (50.2%)	95 (42.8%)	206 (46.5%)
Brain	8 (3.6%)	6 (2.7%)	14 (3.2%)
Liver	55 (24.9%)	57 (25.7%)	112 (25.3%)
Bone	61 (27.6%)	45 (20.3%)	106 (23.9%)
Lymph node	159 (71.9%)	154 (69.4%)	313 (70.7%)
Other	81 (36.7%)	71 (32.0%)	152 (34.3%)
Time from metastatic disease to randomization (months)[e]			
N	210	210	420
Mean (StD)	3.2 (7.96)	2.4 (2.51)	2.8 (5.91)
Median	1.7	1.8	1.8
Q1, Q3	1.2, 2.8	1.4, 2.5	1.3, 2.6
Min, max	0.3, 109.2	0.2, 26.6	0.2, 109.2

a Mutant denotes participant is either BRCA1 or BRCA2 mutant, or both mutant; Wild type denotes participant is both BRCA1 and BRCA2 wild type. Unknown denotes participant is BRCA1 unknown and BRCA2 wild type or unknown, or participant is BRCA1 wild type or unknown and BRCA2 unknown.
b PD-L1 CPS was collected centrally.
d Site of metastasis at screening is summarized for participants in metastatic disease setting at screening.
e Time from metastatic disease to randomization in months is defined as number of days divided by 30.4375 from date of confirmed metastatic disease to date of randomization for participants in metastatic disease at screening.

Table 31 Enrolment by randomization stratum

Randomization Stratum	SG+Pembro (N=221)	TPC+Pembro (N=222)	Total (N=443)
IWRS			
Disease Stratification			
De novo	75 (33.9%)	75 (33.8%)	150 (33.9%)
Recurrent disease within 6 to 12 months	40 (18.1%)	40 (18.0%)	80 (18.1%)
Recurrent disease occurring > 12 months	106 (48.0%)	107 (48.2%)	213 (48.1%)
Geographic Region			
US/Canada/Western Europe	85 (38.5%)	85 (38.3%)	170 (38.4%)
Rest of world	136 (61.5%)	137 (61.7%)	273 (61.6%)
Prior Exposure to Anti-PD-(L)1			
Yes	9 (4.1%)	11 (5.0%)	20 (4.5%)
No	212 (95.9%)	211 (95.0%)	423 (95.5%)
Clincal Database			
Disease Stratification			
De novo	74 (33.5%)	74 (33.3%)	148 (33.4%)
Recurrent disease within 6 to 12 months	39 (17.6%)	48 (21.6%)	87 (19.6%)
Recurrent disease occurring > 12 months	108 (48.9%)	100 (45.0%)	208 (47.0%)
Geographic Region			
US/Canada/Western Europe	85 (38.5%)	85 (38.3%)	170 (38.4%)
Rest of world	136 (61.5%)	137 (61.7%)	273 (61.6%)
Prior Exposure to Anti-PD-(L)1			
Yes	3 (1.4%)	3 (1.4%)	6 (1.4%)
No	218 (98.6%)	219 (98.6%)	437 (98.6%)

Stratified analyses use stratification factors collected in IWRS.

Small strata were pooled for stratified analysis due to insufficient information per SAP.

Table 32 Prior anti-cancer therapy

	SG+Pembro (N=221)	TPC+Pembro (N=222)	Total (N=443)
Participants with Any Prior Anti-Cancer Therapy, n (%)	140 (63.3%)	138 (62.2%)	278 (62.8%)
Prior Neoadjuvant or Adjuvant Anti-cancer Therapy [a]			
Yes	140 (63.3%)	138 (62.2%)	278 (62.8%)
Taxanes	120 (54.3%)	114 (51.4%)	234 (52.8%)
Anthracyclines	118 (53.4%)	108 (48.6%)	226 (51.0%)
Platinum	36 (16.3%)	34 (15.3%)	70 (15.8%)
Anti-PD-1/PD-L1 agents	2 (0.9%)	3 (1.4%)	5 (1.1%)
Capecitabine	42 (19.0%)	45 (20.3%)	87 (19.6%)
PARP inhibitors	1 (0.5%)	0	1 (0.2%)
Cyclophosphamide	116 (52.5%)	111 (50.0%)	227 (51.2%)
Other	38 (17.2%)	40 (18.0%)	78 (17.6%)

According to the clinical database, 1 additional participant in the SG + pembro group received prior combination therapy that included an anti-PD-1 or anti-PD-L1 therapy.

Numbers analysed

Table 33 Numbers in analysis populations

	SG + Pembro	TPC + Pembro	Total
Screened			726
ITT Analysis Set	221 (100.0%)	222 (100.0%)	443 (100.0%)
Safety Analysis Set	221 (100.0%)	220 (99.1%)	441 (99.5%)
Pharmacokinetic Analysis Set	221 (100.0%)	0	221 (49.9%)
Immunogenicity Analysis Set	220 (99.5%)	0	220 (49.7%)

Outcomes and estimation

Primary Efficacy Endpoint

Efficacy data were provided from the primary analysis of PFS for study ASCENT-04 with a data cut-off date of 03 March 2025.

Table 34 PFS by BICR using RECIST v1.1 (ITT) – DCO*:* 03 March 2025

	SG + Pembro (N = 221)	TPC + Pembro (N = 222)
Number (%) of participants with **events**	109 (**49.3%**)	140 (**63.1%**)
Disease progression (PD)	97 (43.9%)	130 (58.6%)
Death	12 (5.4%)	10 (4.5%)
Number (%) of participants censored	112 (50.7%)	82 (36.9%)
PD after starting new anticancer therapy	0	1 (0.5%)
PD right after ≥ 2 consecutive missing and/or not evaluable tumor assessments	0	0
Death after starting new anticancer therapy	4 (1.8%)	8 (3.6%)
Death right after ≥ 2 consecutive missing and/or not evaluable tumor assessments	3 (1.4%)	0
No PD and no death without new anticancer therapy	84 (38.0%)	52 (23.4%)
No PD and no death with new anticancer therapy	19 (8.6%)	17 (7.7%)
No baseline or postbaseline evaluable assessment[a]	2 (0.9%)	4 (1.8%)
Kaplan-Meier estimate of PFS (Months) (95% CI)[b]		
Median	**11.24** (9.26, 16.69)	**7.75** (7.29, 9.26)
Kaplan-Meier estimate of PFS Rate (95% CI)[c]		
At 6 months	0.716 (0.649, 0.773)	0.632 (0.562, 0.694)
At 9 months	0.616 (0.544, 0.680)	0.472 (0.400, 0.540)
At 12 months	0.483 (0.406, 0.556)	0.329 (0.260, 0.400)

At 18 months	0.391 (0.304, 0.478)	0.229 (0.157, 0.309)
Stratified Log-rank *P* value of SG + Pembro vs TPC + Pembro[d]	0.0009	—
Stratified **Hazard Ratio** of SG + Pembro vs TPC + Pembro (95% CI) from Cox Model[d]	**0.654** (0.508, 0.842)	—

BICR = blinded independent central review; CI = confidence interval; ITT = intent-to-treat, IWRS = interactive web response system; NR = not reached, PD = disease progression; pembro = pembrolizumab; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; Q1 = first quartile; Q3 = third quartile; SG = sacituzumab govitecan; TPC = treatment of physician's choice

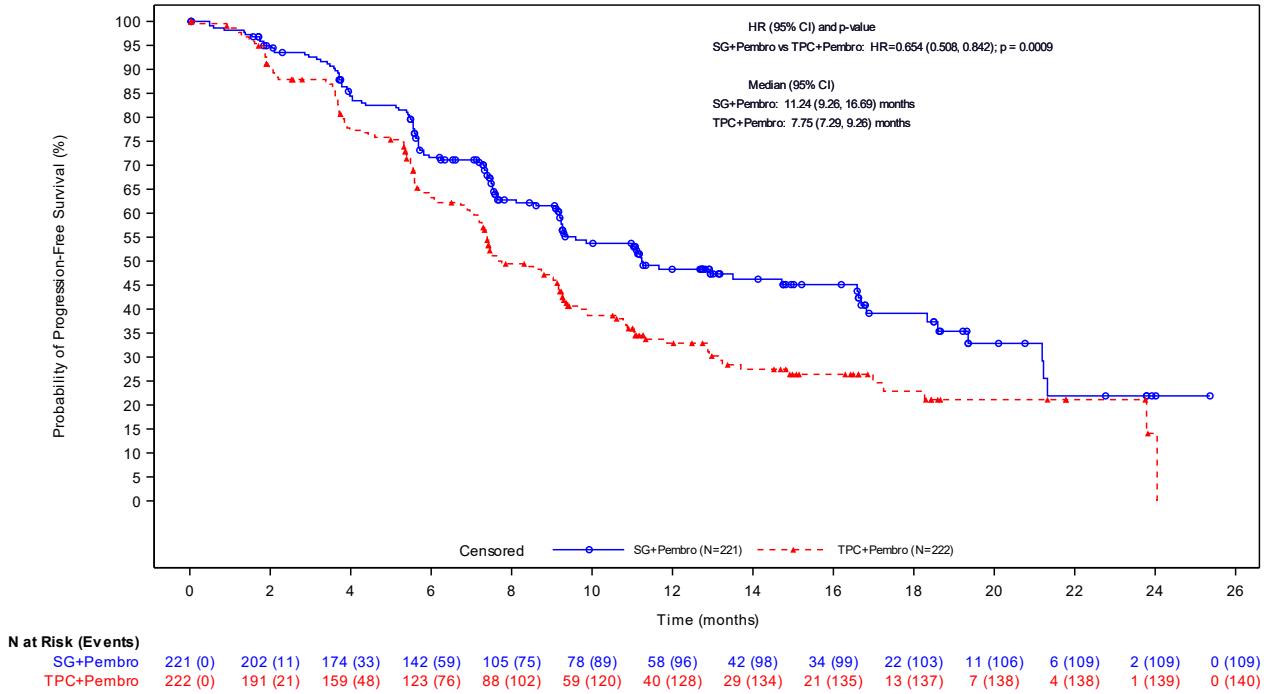
a Censoring due to no baseline or no postbaseline evaluable assessment does not include death event before the second scheduled visit postbaseline.

b PFS (months) = (date of events or censoring − date of randomization + 1)/30.4375. The 95% CI is based on log-log transformation.

c PFS rate is the proportion of participants alive without PD.

d The two-sided *P* value was from stratified log-rank test and the hazard ratio with 95% CI were calculated by Cox proportional hazards model, adjusted for randomization stratification factors (IWRS).

Figure 18 KM Plot of PFS by BICR Using RECIST v1.1 (ITT) – DCO 03 March 2025



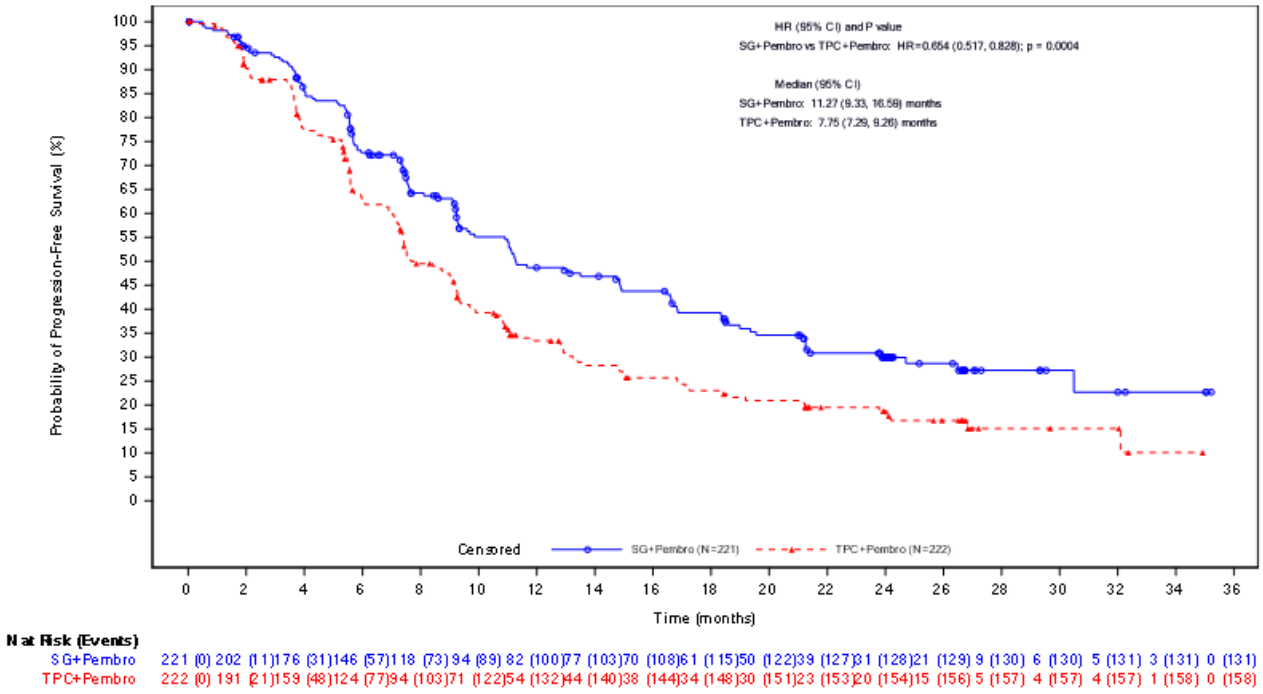
Updated descriptive PFS analysis at OS IA1

Table 35 PFS by BICR using RECIST v1.1 at OS IA1 (ITT) – DCO 16 February 2026

	SG + Pembro (N = 221)	**TPC + Pembro (N = 222)**
Number (%) of Participants with Events	131 (59.3%)	158 (71.2%)
Disease Progression (PD)	119 (53.8%)	145 (65.3%)
Death	12 (5.4%)	13 (5.9%)
Number (%) of Participants Censored	90 (40.7%)	64 (28.8%)
PD after Starting New Anticancer Therapy	0	1 (0.5%)
PD right after ≥ 2 Consecutive Missing and/or Not Evaluable Tumor Assessments	3 (1.4%)	0
Death after Starting New Anticancer Therapy	12 (5.4%)	15 (6.8%)

	SG + Pembro (N = 221)	TPC + Pembro (N = 222)
Death right after ≥ 2 Consecutive Missing and/or Not Evaluable Tumor Assessments	3 (1.4%)	0
No PD and No Death without New Anticancer Therapy	48 (21.7%)	27 (12.2%)
No PD and No Death with New Anticancer Therapy	23 (10.4%)	18 (8.1%)
No Baseline or Postbaseline Evaluable Assessment[a]	1 (0.5%)	3 (1.4%)
Kaplan-Meier Estimate of PFS (Months) (95% CI)[b]		
Median	11.27 (9.33, 16.59)	7.75 (7.29, 9.26)
Stratified Hazard Ratio of SG+Pembro vs TPC+Pembro (95% CI) from Cox Model[d]	0.654 (0.517, 0.828)	--

Figure 19 Plot of PFS by BICR Using RECIST v1.1 at OS IA1 (ITT) – DCO 16 February 2026



Adjustment for randomisation stratification factors

Most participants had no prior exposure to anti-PD-1 or anti-PD-L1 agents (95.5%) according to the IWRS (98.6% according to the clinical database). Due to the insufficient information in each stratum defined by participants having prior exposure to anti-PD-1 or anti-PD-L1 agents (i.e. < 10 events of PFS by BICR in each such stratum), participants who had prior exposure and who had no prior exposure were pooled together and thus stratified analyses were adjusted for the other 2 randomization stratification factors from IWRS.

Results for stratified analyses were presented using data from IWRS rather than the clinical database.

Secondary Efficacy Endpoints

At the time of the PFS primary analysis (DCO: 03 March 2025), descriptive analyses are provided for the secondary endpoints; all P values for secondary efficacy endpoints are considered nominal.

Overall Survival

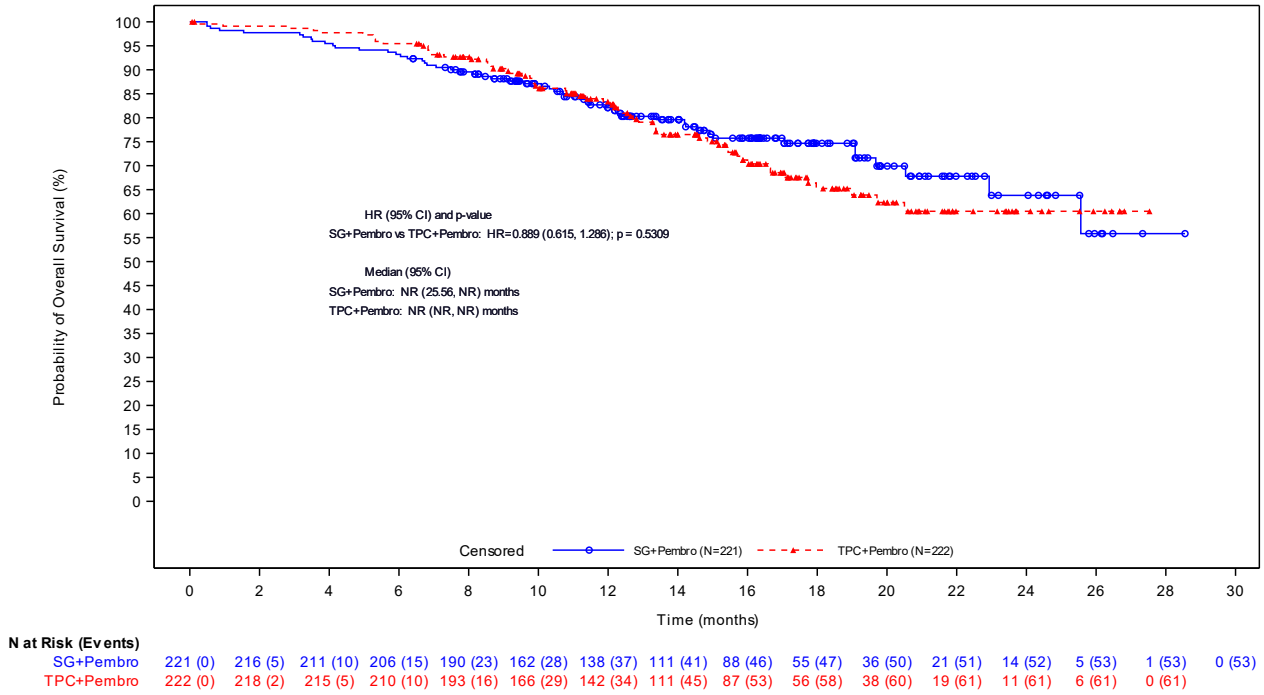
Descriptive analysis of OS at the time of primary analysis for PFS

Table 36 Overall Survival (ITT) – DCO 03 March 2025

	SG + Pembro (N = 221)	**TPC + Pembro (N = 222)**
Number (%) of participants with **events** (death)	53 (**24.0%**)	61 (**27.5%**)
Number (%) of participants censored	168 (76.0%)	161 (72.5%)
Ongoing[a]	163 (73.8%)	153 (68.9%)
Discontinued study	5 (2.3%)	8 (3.6%)
Kaplan-Meier estimate of OS (months) (95% CI)[b]		
Median	NR (25.56, NR)	NR (NR, NR)
Kaplan-Meier estimate of OS Rate (95% CI)		
At 12 months	0.821 (0.761, 0.867)	0.834 (0.775, 0.878)
At 18 months	0.747 (0.674, 0.806)	0.652 (0.569, 0.724)
At 24 months	0.638 (0.514, 0.738)	0.605 (0.510, 0.687)
Stratified **Hazard Ratio** of SG + Pembro vs TPC + Pembro (95% CI) from Cox Model[c]	**0.889** (0.615, 1.286)	
Duration of OS follow-up (months)[d]		
Median (range)	14.0 (0.5, 28.6)	14.2 (0.1, 27.5)

a Ongoing participants are those who have not discontinued participation in the study by the data cutoff date.
b OS (months) = (date of death or censoring − date of randomization + 1)/30.4375. The 95% CI is based on log-log transformation.
c Hazard ratio and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (IWRS).
d Duration of OS follow-up (months) = (date of death or censoring − date of randomization + 1)/30.4375.

Figure 20 KM plots of OS (ITT) – DCO 03 March 2025



OS IA1 (First interim analysis of OS) - DCO 16 February 2026

Table 37 Overall Survival at OS IA1 – DCO 12 February 2026

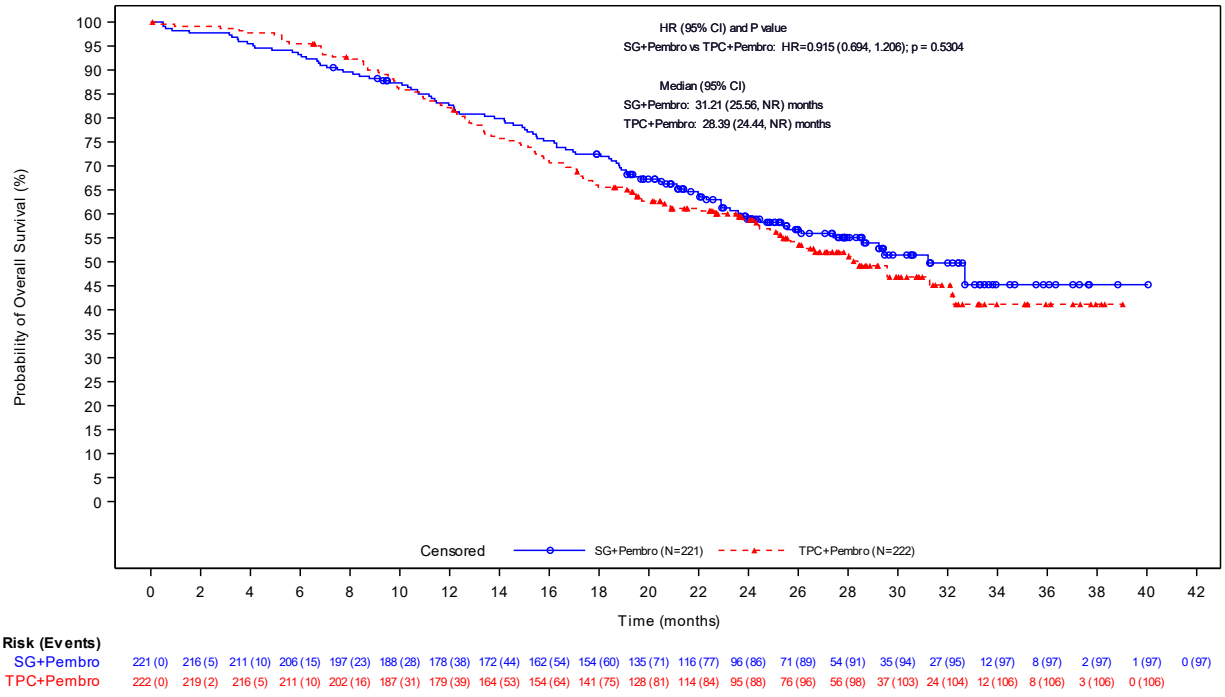
	SG + Pembro (N = 221)	TPC + Pembro (N = 222)
Number (%) of Participants with Events (Death)	97 (43.9%)	106 (47.7%)
Number (%) of Participants Censored	124 (56.1%)	116 (52.3%)
Ongoing[a]	118 (53.4%)	104 (46.8%)
Discontinued Study	6 (2.7%)	12 (5.4%)
Kaplan-Meier Estimate of OS (Months) (95% CI)[b]		
Median	**31.21** (25.56, NR)	**28.39** (24.44, NR)
Kaplan-Meier Estimate of OS Rate (95% CI)		
At 12 Months	0.827 (0.770, 0.871)	0.822 (0.764, 0.866)
At 18 Months	0.724 (0.660, 0.779)	0.655 (0.588, 0.714)
At 24 Months	0.589 (0.518, 0.653)	0.588 (0.518, 0.651)
At 30 Months	0.514 (0.434, 0.588)	0.468 (0.390, 0.543)
At 36 Months	0.452 (0.355, 0.544)	0.411 (0.320, 0.501)
Stratified Log-rank ***P* value** of SG+Pembro vs TPC+Pembro[c]	0.5304	—

	SG + Pembro (N = 221)	TPC + Pembro (N = 222)
Stratified **Hazard Ratio** of SG+Pembro vs TPC+Pembro (95% CI) from Cox Model[d]	**0.915** (0.694, 1.206)	—
Duration of **OS Follow-up** (Months)[e]		
Median	22.6	22.5
Min, Max	0.5, 40.0	0.1, 39.0

a Ongoing participants are those who have not discontinued participation in the study by the data cutoff date.
a OS (months) = (date of death or censoring − date of randomization + 1)/30.4375. The 95% CI is based on log-log transformation.
b The 2-sided P value is from stratified log-rank test adjusted for randomization stratification factors (IWRS).
c Hazard ratio and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (IWRS).
d Duration of OS follow-up (months) = (date of death or censoring − date of randomization + 1)/30.4375.
Number of OS events is 203 at the time of OS IA analysis. Overall survival at OS IA was tested at two-sided nominal alpha of 0.025 based on Lan-DeMets alpha spending function that approximates an O'Brien Fleming approach.
ITT Analysis Set includes all participants who were randomized in the study.

At the time of the OS IA1, the minimum time on study was approximately 18 months.

Figure 21 KM Plot of OS at OS IA – DCO 16February 2026



Objective Response Rate

Table 38 ORR and CBR by BICR Using RECIST v1.1 (ITT) - DCO 03 March 2025

	SG + Pembro (N = 221)	TPC + Pembro (N = 222)
Best Overall Response (**BOR**)		
Complete response (CR)	28 (12.7%)	18 (8.1%)
Partial response (PR)	104 (47.1%)	100 (45.0%)

Stable disease (SD)	70 (31.7%)	70 (31.5%)
SD ≥ 6 months	23 (10.4%)	29 (13.1%)
Progressive disease (PD)	9 (4.1%)	26 (11.7%)
Not evaluable (NE)	10 (4.5%)	8 (3.6%)
Objective Response Rate (**ORR**) (95% CI)[a]	**59.7%** (52.9%, 66.3%)	**53.2%** (46.4%, 59.9%)
Responders (CR + PR)	132 (59.7%)	118 (53.2%)
Non-responders (SD + PD + NE)	89 (40.3%)	104 (46.8%)
Stratified **Odds Ratio** for ORR of SG + Pembro vs TPC + Pembro (95% CI)	1.306 (0.898, 1.899)	
Clinical Benefit Rate (**CBR**) (95% CI)[b]	70.1% (63.6%, 76.1%)	66.2% (59.6%, 72.4%)
Responders (CR + PR + SD ≥ 6 months)	155 (70.1%)	147 (66.2%)
Non-responders (SD < 6 months + PD + NE)	66 (29.9%)	75 (33.8%)
Stratified **Odds Ratio** for CBR of SG + Pembro vs TPC + Pembro (95% CI)	1.205 (0.807, 1.801)	

BOR (= best overall response) is derived from overall response per BICR at each tumor assessment per RECIST v1.1. Response of CR/PR is **confirmed** at least 4 weeks after initial documentation of response. SD requires at least 49 days on study since randomization to be classified as SD. Participants without any evaluable postbaseline tumor assessment are included in Not Evaluable.

a **ORR** is the proportion of participants who achieved BOR of CR/PR. The 95% CI is based on Clopper-Pearson method.

b **CBR** is defined as the proportion of participants who achieved BOR of CR/PR or durable SD with duration ≥ 6 months. The 95% CI is based on Clopper-Pearson method.

Table 39 ORR by BICR using RECIST v1.1 at OS IA1 – DCO 16 February 2026

	SG + Pembro (N = 221)	**TPC + Pembro (N = 222)**
Objective Response Rate (**ORR**) (95% CI)	**61.5%** (54.8, 68.0)	**54.1%** (47.3, 60.7)
Stratified **Odds Ratio** for ORR of SG + Pembro vs TPC + Pembro (95% CI)	1.361 (0.934, 1.984)	

Duration of response (DOR)

Table 40 DOR and Time to Response by BICR Using RECIST v1.1 in Participants with Confirmed CR or PR - DCO 03 March 2025

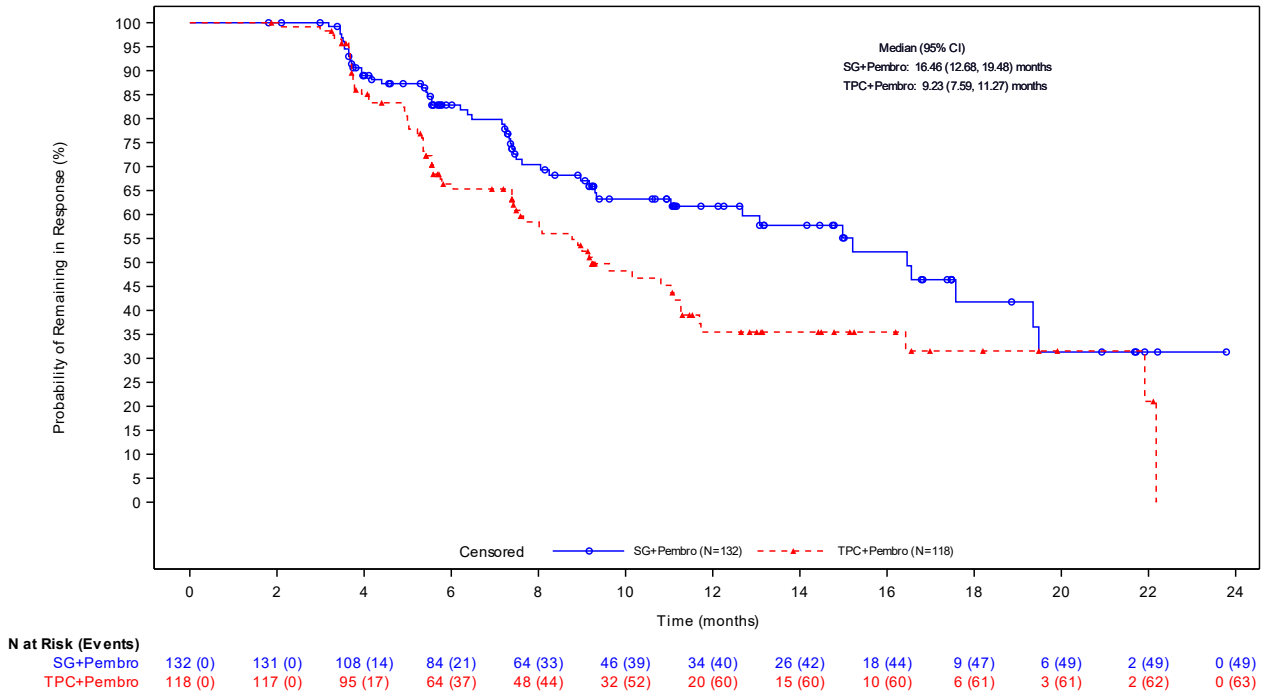
	SG + Pembro (N = 132)	**TPC + Pembro (N = 118)**
Number (%) of Participants with Events	49 (37.1%)	63 (53.4%)
Disease Progression (PD)	45 (34.1%)	56 (47.5%)
Death	4 (3.0%)	7 (5.9%)
Number (%) of Participants Censored	83 (62.9%)	55 (46.6%)
Kaplan-Meier Estimate of **DOR** (Months) (95% CI)[a]		
Median	**16.46** (12.68, 19.48)	**9.23** (7.59, 11.27)
Time to Response (Months)[b]		
Median	1.9	1.9
Min, Max	1.0, 9.3	1.1, 11.4

The denominator of percentages was the number of participants with confirmed CR or PR by BICR in each treatment group in the ITT Analysis Set.

a DOR (months) = (date of event or censoring − date of first documented CR or PR + 1)/30.4375.

b Time to response (months) = (date of first documented CR or PR − date of randomization + 1)/30.4375.

Figure 22 KM Plot of DOR by BICR Using RECIST v1.1 in Participants With confirmed CR or PR (ITT) – DCO 03 March 2025



PRO (Patient-Reported Outcomes)

Table 41 Summary of PRO data (DCO 03 Mar 2025)

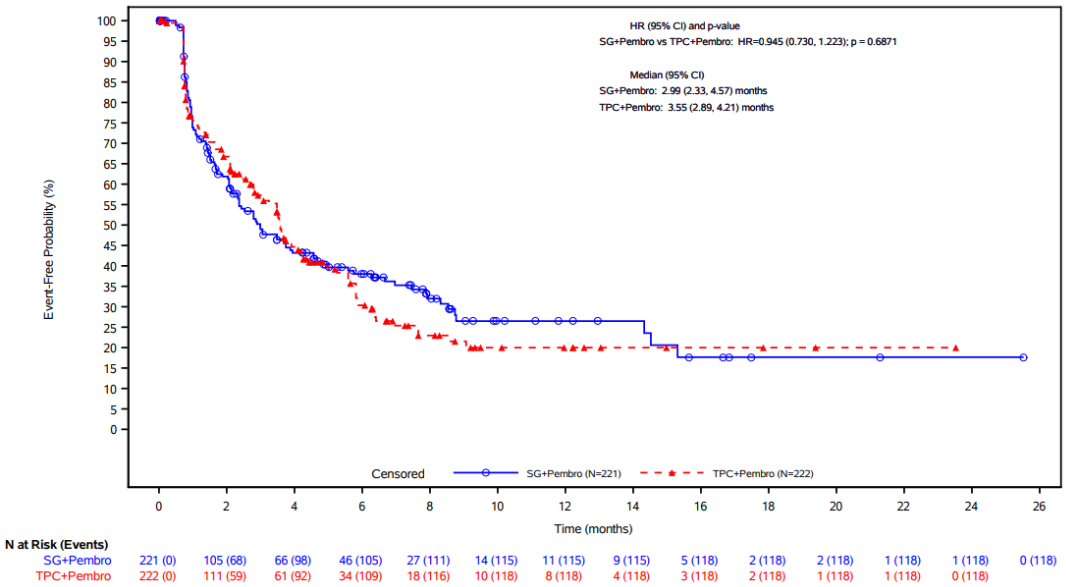
Secondary Efficacy Endpoints	SG + pembro (N = 221)	TPC + pembro (N = 222)
Time to Deterioration in Physical Functioning Domain of the EORTC QLQ-C30 Version 3.0 (months)[b]		
Median (95% CI)	2.99 (2.33, 4.57)	3.55 (2.89, 4.21)
HR (95% CI)	0.945 (0.730, 1.223)	
Time to Deterioration in Role Functioning Domain of the EORTC QLQ-C30 Version 3.0 (months)[c]		
Median (95% CI)	1.68 (1.08, 2.17)	1.51 (1.41, 2.30)
HR (95% CI)	1.011 (0.791, 1.291)	
Time to Deterioration in Global Health Status/QOL Domain of the EORTC QLQ-C30 Version 3.0 (months)[c]		
Median (95% CI)	2.20 (2.07, 3.25)	3.52 (2.27, 4.21)
HR (95% CI)	0.977 (0.753, 1.268)	
Time to Deterioration in Pain Domain of the EORTC QLQ-C30 Version 3.0 (months)[d]		
Median (95% CI)	4.30 (2.37, 5.75)	3.19 (2.17, 4.21)
HR (95% CI)	0.749 (0.572, 0.980)	
Time to Deterioration in Fatigue Domain of the EORTC QLQ-C30 Version 3.0 (months)[d]		
Median (95% CI)	1.08 (0.99, 1.45)	0.95 (0.85, 1.45)
HR (95% CI)	0.910 (0.721, 1.147)	

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; QOL = quality of life;

a n/a (above table excerpt from Table 4 clinical overview)

b Time to deterioration for physical functioning was defined as the time from the date of randomization to the first time a participant experienced a decrease from baseline greater than or equal to 13.33 points or death, whichever occurred first.
c Time to deterioration for role functioning and global health status/QOL was defined as the time from the date of randomization to the first time a participant experienced a decrease from baseline greater than or equal to 10 points or death, whichever occurred first.
d Time to deterioration for pain and fatigue was defined as the time from the date of randomization to the first time a participant experienced an increase from baseline greater than or equal to 10 points or death, whichever occurred first.

Figure 23 KM Plot of Time to Deterioration of the Physical Functioning Domain of the EORTC QLQ-C30 – DCO 03 March 2025



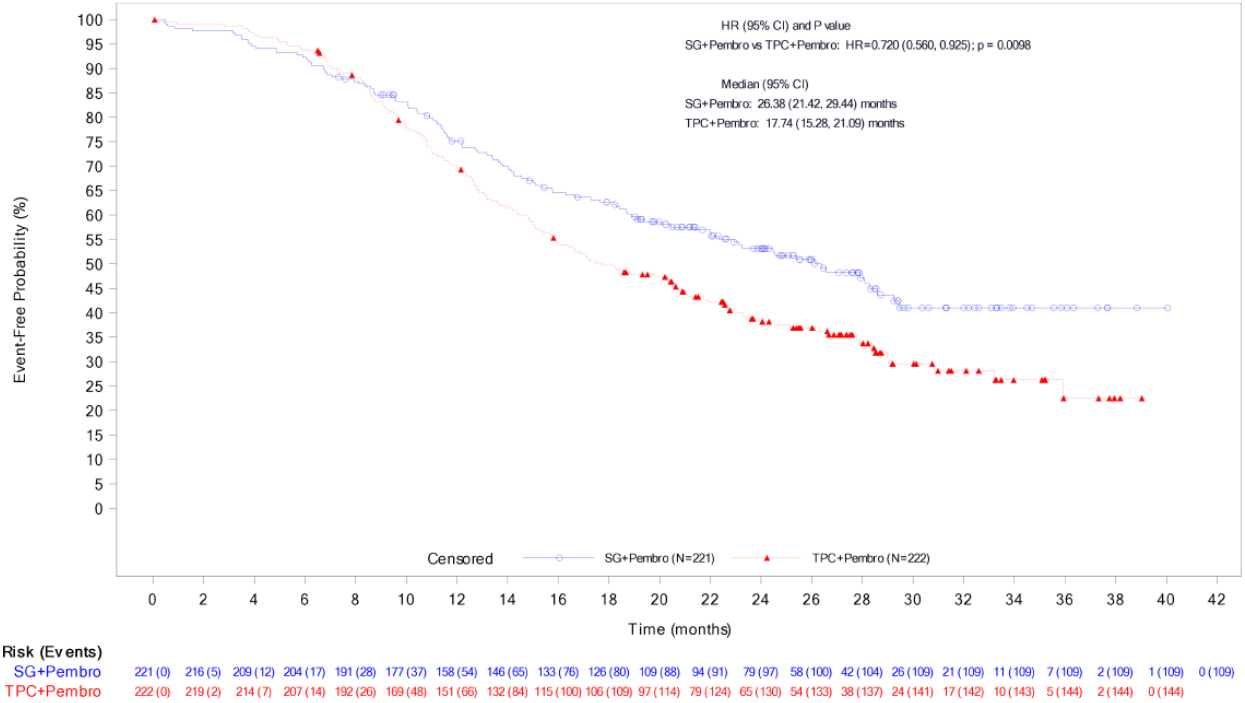
Progression-Free Survival on Next-line Therapy **(PFS2)** - **Exploratory** endpoint

Table 42 Progression-free Survival on Next-line Therapy (PFS2) at OS IA1 - DCO: 16 February 2026

	SG + Pembro (N = 221)	TPC + Pembro (N = 222)
Number (%) of Participants with Events	109 (49.3%)	144 (64.9%)
Disease Progression (PD)	59 (26.7%)	105 (47.3%)
Death	50 (22.6%)	39 (17.6%)
Number (%) of Participants Censored	112 (50.7%)	78 (35.1%)
Kaplan-Meier Estimate of PFS2 (Months) (95% CI)		
Median	26.38 (21.42, 29.44)	17.74 (15.28, 21.09)
Stratified **Hazard Ratio** of SG+Pembro vs TPC+Pembro (95% CI) from Cox Model[c]	**0.720** (0.560, 0.925)	—

PFS2 is defined as the time from date of randomization to the first documented progression on next-line therapy based on investigator assessment of PD or death due to any cause, whichever occurs first. Next line therapy is defined as the first new systemic anti-cancer therapy (including cross-over treatment) initiated after discontinuation of study treatment regardless of end of treatment reason.

Figure 24 KM of Progression-free Survival on Next-line Therapy (PFS2) at OS IA1– DCO 16 February 2026



The 2-sided P value was from stratified log-rank test and the HR with 95% CIs were calculated using Cox proportional hazards model, adjusted for randomization stratification factors (IWRS).

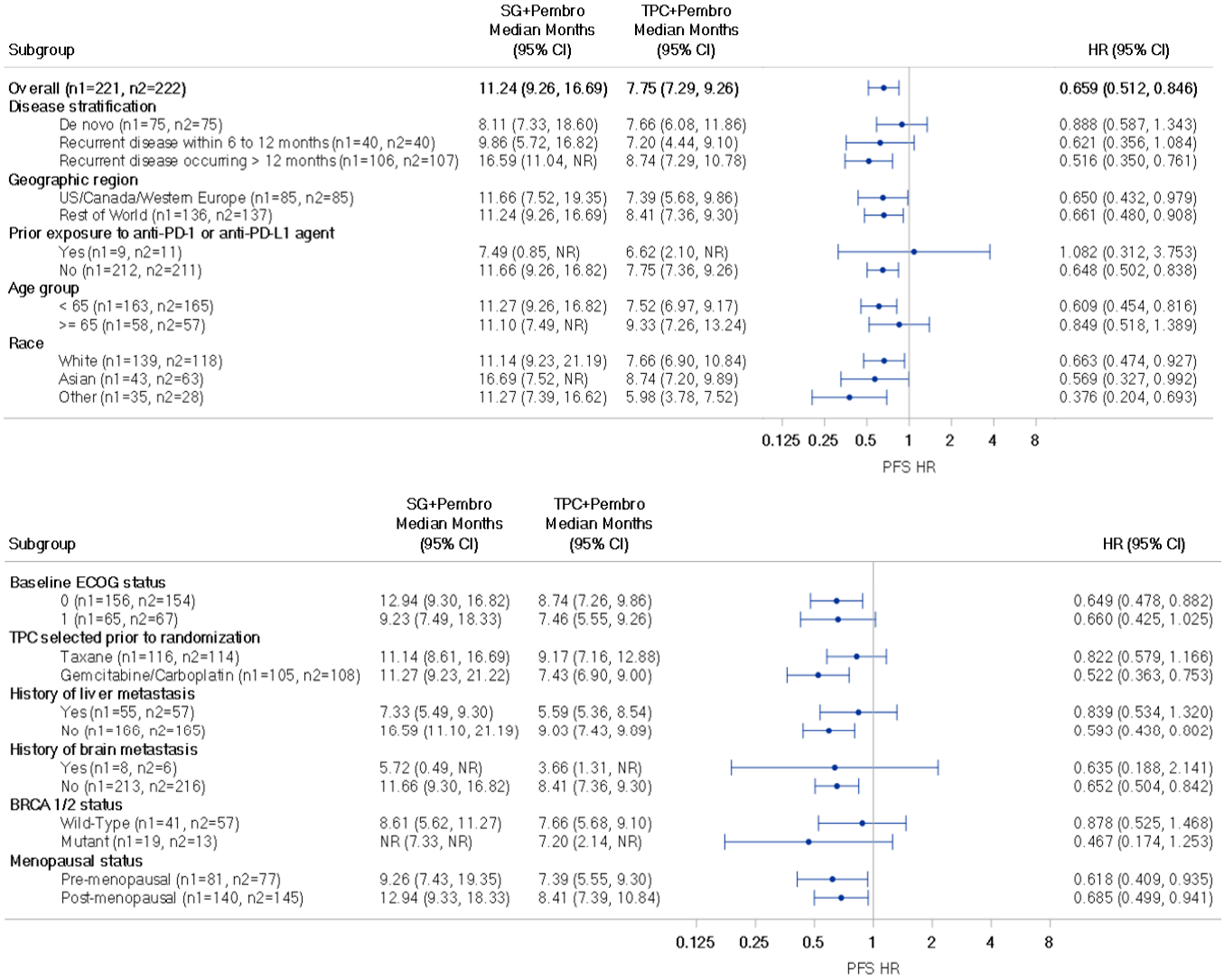
Ancillary analyses

- **Subgroup Analyses**

Subgroup analysis was performed for subgroups prespecified in the SAP. The subgroups defined by stratification factors were based on IWRS stratification.

Subgroup Analysis of PFS

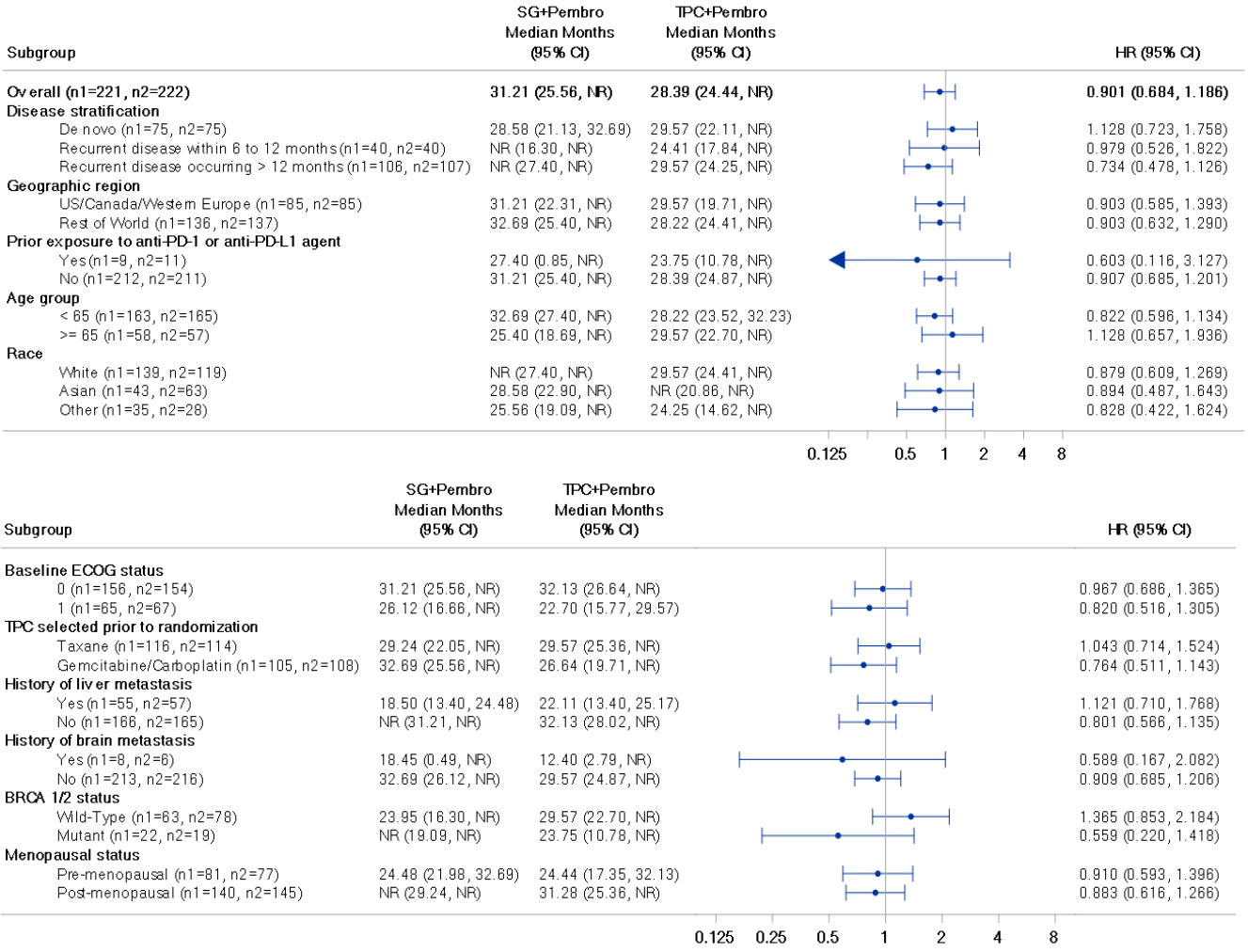
Figure 25 Forest Plot of Progression-Free Survival by BICR for Subgroups (ITT) – DCO: 03 March 2025



HR and 95% CIs are calculated using the unstratified Cox proportional hazards model without any adjustment.
Disease stratification, geographic region, and prior exposure to anti-PD-1 or anti-PD-L1 were collected from IWRS.

Subgroup analysis of OS

Figure 26 Forest Plot of OS for Subgroups at OS IA1 – DCO 16 February 2026

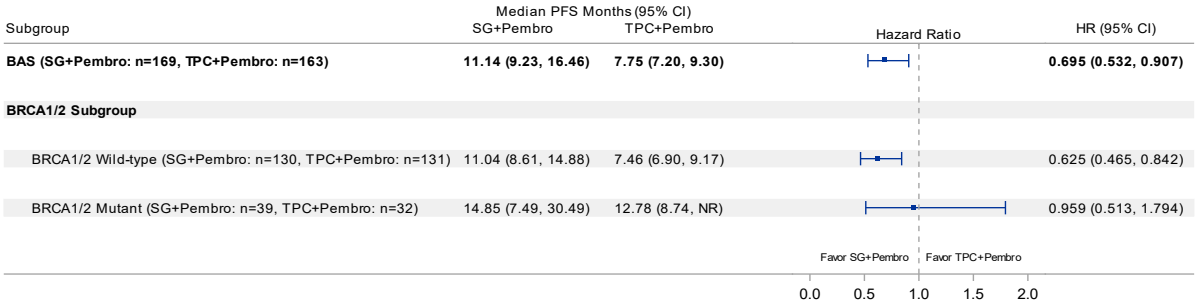


ITT Analysis Set includes all participants who were randomized in the study.
Median OS is from Kaplan-Meier estimate. The 95% CI is based on log-log transformation.
HR and 95% CIs are calculated using the unstratified Cox proportional hazards model without any adjustment. Efron method was used to handle ties.
Disease stratification, geographic region, and prior exposure to anti-PD-1 or anti-PD-L1 were collected from IWRS.
Race subgroup "Other" included American Indian/Alaska Native, Black, Native Hawaiian/Pacific Islander and other as collected in clinical database.
The participant with baseline ECOG status 2 was excluded in the subgroup. Participants with unknown BRCA1/2 status were excluded in the subgroup.

Efficacy **by BRCA** central testing at OS IA1

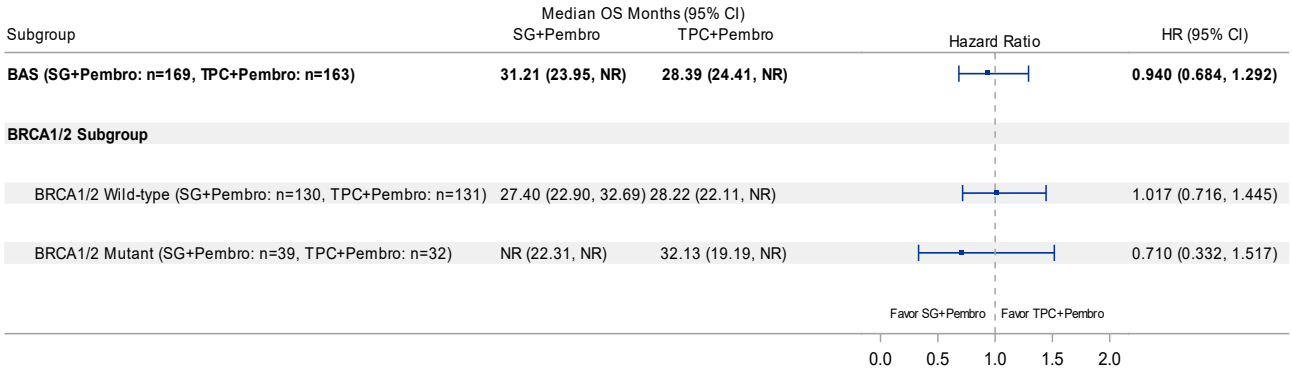
An exploratory objective of the study as per the protocol was to conduct whole exome sequencing (WES) analyses in a central laboratory. In participants with sufficient formalin-fixed paraffin-embedded (FFPE) tumour material, BRCA1/BRCA2 mutation status was determined and was correlated with efficacy endpoints. The BRCA 1 and 2 Biomarker Analysis Set (BAS) comprised 332 participants, of which 21.4% had a BRCA1/2 mutation.

Figure 27 Forest Plot of PFS by BICR Across BRCA 1 and 2 Subgroups (BAS) – DCO 16 February 2026



BAS = Biomarker Analysis Set; BRCA = breast cancer gene; WES = whole exome sequencing
BRCA1/2 status was derived from WES using tumor samples.
Survival time was estimated with the Kaplan-Meier method. The CI for the median was computed using the Brookmeyer-Crowley method. Hazard Ratio and CI are derived from an unstratified Cox regression analysis, with treatment as the only predictor.

Figure 28 Forest Plot of OS by BICR Across BRCA 1 and 2 Subgroups (BAS) – DCO 16 February 2026



BAS = Biomarker Analysis Set; BRCA = breast cancer gene; WES = whole exome sequencing
BRCA1/2 status was derived from WES using tumor samples.
Survival time was estimated with the Kaplan-Meier method. The CI for the median was computed using the Brookmeyer-Crowley method. Hazard Ratio and CI are derived from an unstratified Cox regression analysis, with treatment as the only predictor.

Table 43 Summary of ORR by BICR by treatment within BRCA 1 and 2 subgroups (BAS) – DCO 16 February 2026

	BRCA1/2 Wild-type		BRCA1/2 Mutant		BRAC1/2 BAS	
Outcome	**SG + Pembro (N = 130)**	**TPC + Pembro (N = 131)**	**SG + Pembro (N = 39)**	**TPC + Pembro (N = 32)**	**SG + Pembro (N = 169)**	**TPC + Pembro (N = 163)**
Objective Response Rate						
n (%)	75 (57.7%)	69 (52.7%)	29 (74.4%)	22 (68.8%)	104 (61.5%)	91 (55.8%)
95% CI	(48.7%, 66.3%)	(43.8%, 61.5%)	(57.9%, 87.0%)	(50.0%, 83.9%)	(53.8%, 68.9%)	(47.9%, 63.6%)
Odds Ratio (95% CI)	1.225 (0.752, 1.997)		1.318 (0.467, 3.718)		1.266 (0.817, 1.961)	

BRCA1/2 status was derived from whole-exome-sequencing using tumor samples.
Objective response rate is the proportion of participants who achieved best overall response of CR/PR. The 95% CI is based on Clopper-Pearson method.
Odds ratio and 95% CI are derived from an unstratified model.

Efficacy by **age** groups

Excerpts of forest plots of PFS, OS and ORR for the age cut-offs of 65 and 75 years at OS IA1 (DCO: 16 February 2026):

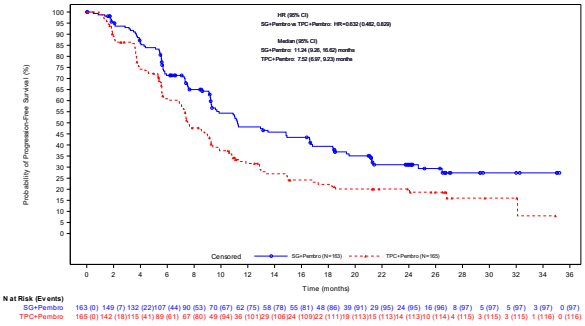
Age group < 65 versus ≥ 65 years

Figure 29 Forest Plot of PFS by BICR at OS IA1

Subgroup	SG+Pembro Median Months (95% CI)	TPC+Pembro Median Months (95% CI)	HR (95% CI)
Overall (n1=221, n2=222)	11.27 (9.33, 16.59)	7.75 (7.29, 9.26)	0.658 (0.521, 0.830)
Age group			
< 65 (n1=163, n2=165)	11.24 (9.26, 16.62)	7.52 (6.97, 9.23)	0.632 (0.482, 0.829)
>= 65 (n1=58, n2=57)	14.72 (7.59, 18.99)	9.17 (7.16, 12.78)	0.749 (0.476, 1.178)

Figure 30 KM plots of PFS by age group at OS IA1

KM of PFS for age < 65 years



KM of PFS for age ≥ 65 years

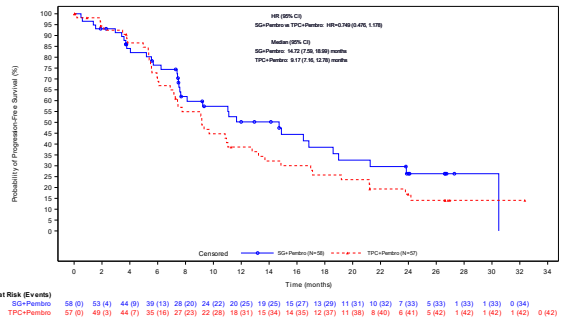


Figure 31 Forest Plot of OS at OS IA1

Subgroup	SG+Pembro Median Months (95% CI)	TPC+Pembro Median Months (95% CI)	HR (95% CI)
Overall (n1=221, n2=222)	31.21 (25.56, NR)	28.39 (24.44, NR)	0.901 (0.684, 1.186)
Age group			
< 65 (n1=163, n2=165)	32.69 (27.40, NR)	28.22 (23.52, 32.23)	0.822 (0.596, 1.134)
>= 65 (n1=58, n2=57)	25.40 (18.69, NR)	29.57 (22.70, NR)	1.128 (0.657, 1.936)

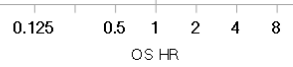
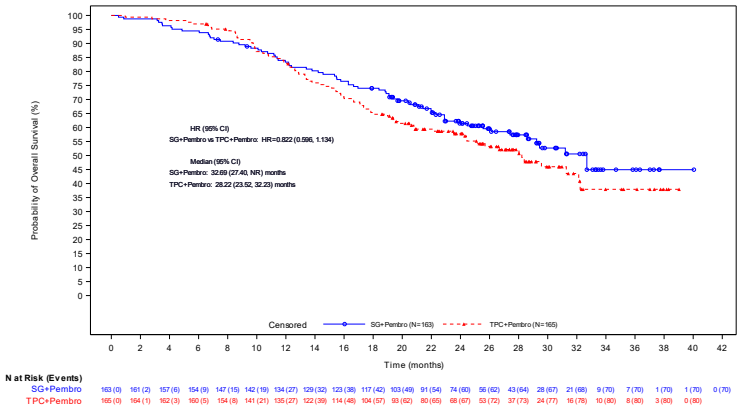


Figure 32 KM plots of OS by age group at OS IA1

KM of OS for age < 65 years



KM of OS for age ≥ 65 years

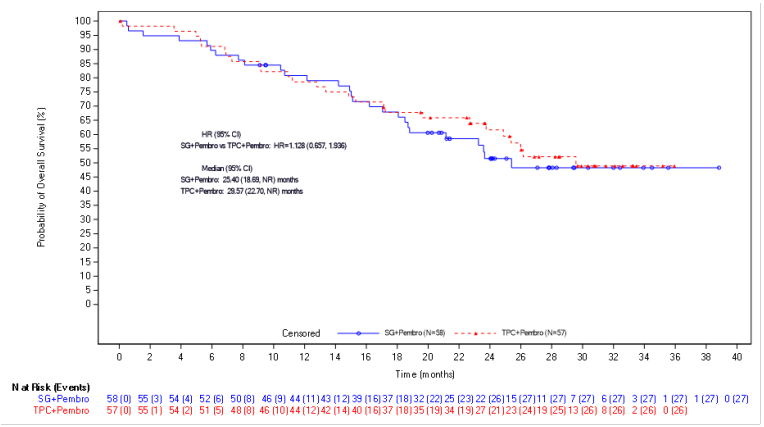
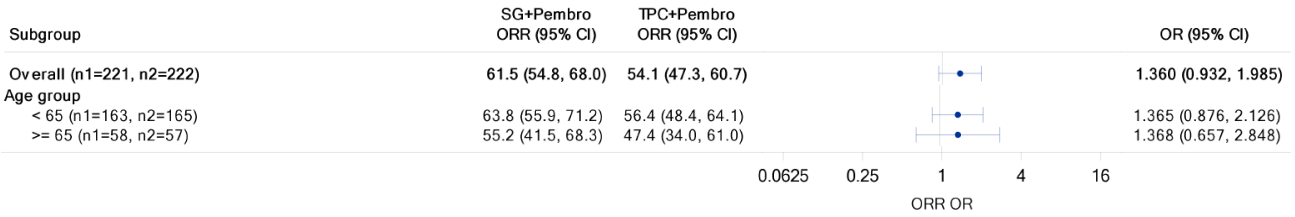


Figure 33 Forest Plot of ORR by BICR at OS IA1



Age group < 75 versus ≥ 75 years

Figure 34 Forest Plot of PFS by BICR at OS IA1

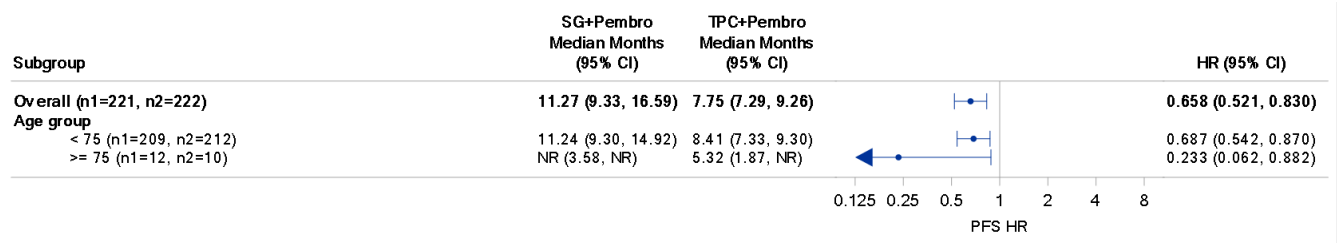


Figure 35 Forest Plot of OS at OS IA1

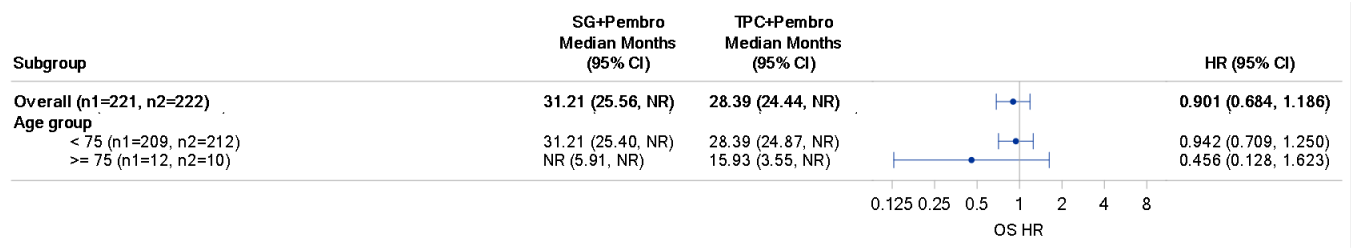


Table 44 ORR by BICR at OS IA

Overall study population	**SG + Pembro (N = 221)**	**TPC + Pembro (N = 222)**
ORR (95% CI)	**61.5%** (54.8%, 68.0%)	**54.1%** (47.3%, 60.7%)
Stratified **Odds Ratio** for ORR of SG + Pembro vs TPC + Pembro (95% CI)	**1.361** (0.934, 1.984)	
Age group < 75	**SG + Pembro (N = 209)**	**TPC + Pembro (N = 212)**

Overall study population	SG + Pembro (N = 221)	TPC + Pembro (N = 222)
ORR (95% CI)	**62.2%** (55.3%, 68.8%)	**55.7%** (48.7%, 62.5%)
Stratified **Odds Ratio** for ORR of SG + Pembro vs TPC + Pembro (95% CI)	**1.311** (0.888, 1.935)	
Age group ≥ 75	**SG + Pembro (N = 12)**	**TPC + Pembro (N = 10)**
ORR (95% CI)	**50.0%** (21.1%, 78.9%)	**20.0%** (2.5%, 55.6%)
Stratified **Odds Ratio** for ORR of SG + Pembro vs TPC + Pembro (95% CI)	**4.000** (0.587, 27.248)	

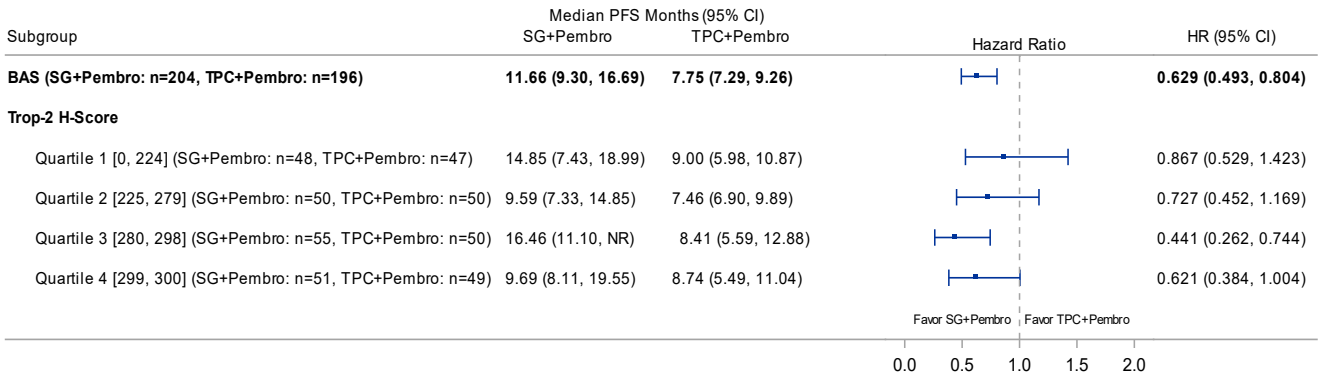
Trop-2 correlation with efficacy (exploratory analysis)

Evaluation of baseline trophoblast cell-surface antigen 2 (Trop-2) expression in fresh or archival tumour tissue as a biomarker for efficacy was an exploratory endpoint. Trop-2 expression in tumour tissue was assessed by immunohistochemistry (IHC) using a fit-for-purpose, validated EPR20043 formulation locked assay (FLA) at Roche Tissue Diagnostics (RTD). Trop-2 testing was conducted in an exploratory and retrospective manner, neither to select patients nor stratify endpoints, as such H-score was selected as the scoring approach for Trop-2 expression analysis. Given the exploratory and retrospective nature of the Trop-2 analyses in this study, validation of empirically derived cut-offs was not conducted. H-scores were therefore assessed independently as raw continuous values. Only NSCLC samples were used to demonstrate assay precision across instruments and days. NSCLC tissues were selected as the primary matrix for precision evaluation, as they exhibit a broad dynamic range of Trop-2 membranous expression and were considered a sensitive tissue type for assessing assay performance and reproducibility across the full spectrum of staining intensity. At the time of validation, a dedicated precision dataset utilizing breast cancer specimens was not available at Ventana.

Trop-2 data were available from 400 participants (90.3%) in the Intent to Treat (ITT) Analysis Set = Biomarker Analysis Set (BAS).

PFS Analysis for Trop-2 H-score Quartiles

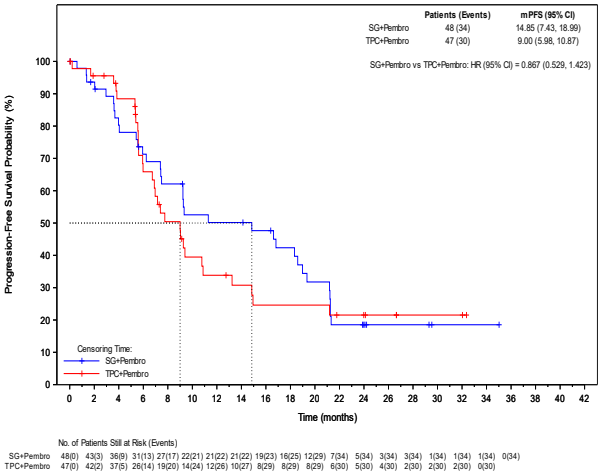
Figure 36 Forest Plot of PFS by BICR Across Trop-2 H-score Subgroups at OS IA (BAS) (DCO: 16 February 2026)



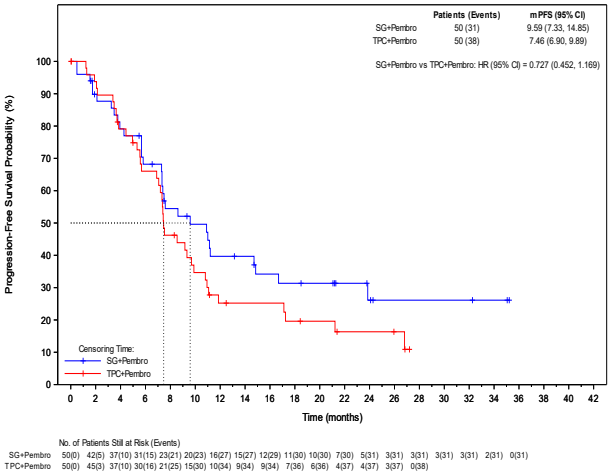
Survival time was estimated with the KM method. The CI for the median was computed using the Brookmeyer-Crowley method.
Hazard ratio and CI were derived from an unstratified Cox regression analysis, with treatment as the only predictor.

Figure 37 KM Estimates of PFS by BICR by Treatment and Trop 2 Membrane H-Score Quartiles at OS IA (DCO: 16 February 2026)

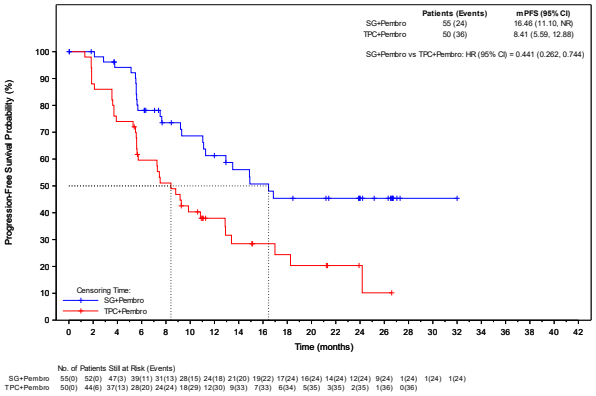
H-score Quartile 1 [0, 224]



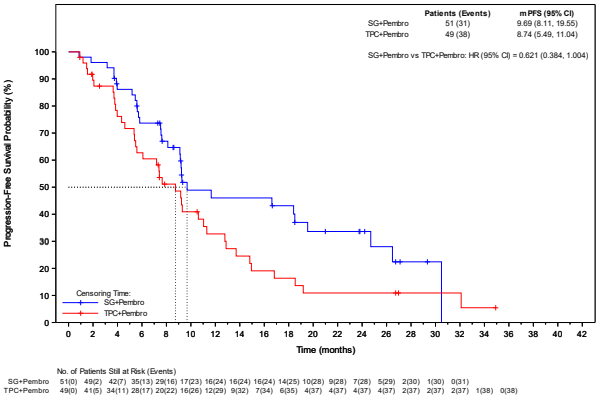
H-score Quartile 2 [225, 279]



H-score Quartile 3 [280, 298]



H-score Quartile 4 [299, 300]

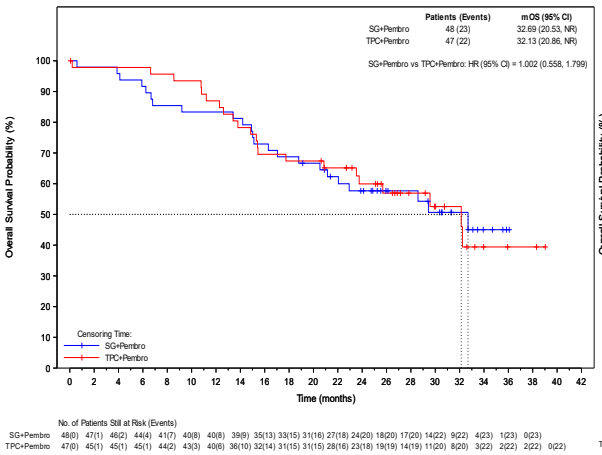


OS Analysis for Trop-2 H-score Quartiles

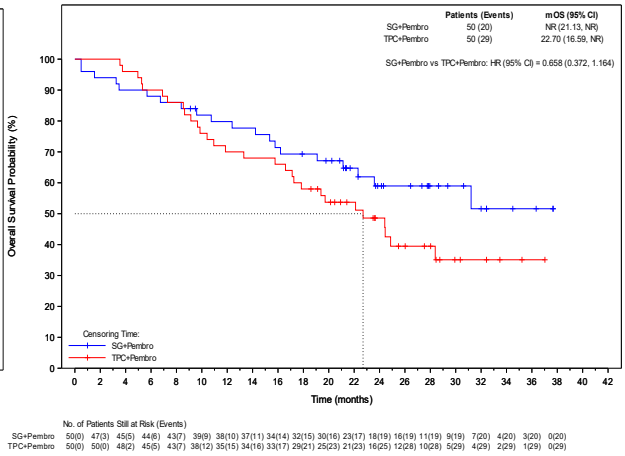
Figure 38 Forest Plot of OS Across Trop-2 H-score Subgroups at OS IA (BAS) (DCO: 16 February 2026)

Figure 39 KM Estimates of OS by Treatment and Trop 2 Membrane H Score Quartiles at OS IA (BAS)

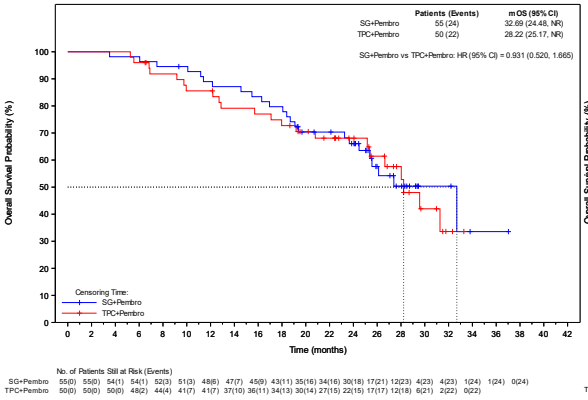
H-score Quartile 1 [0, 224]



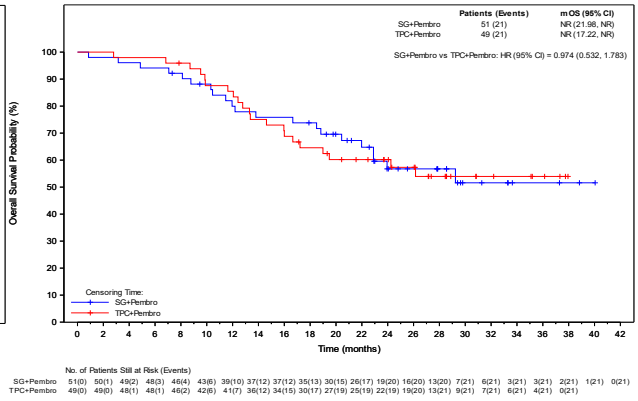
H-score Quartile 2 [225, 279]



H-score Quartile 3 [280, 298]



H-score Quartile 4 [299, 300]



- **Supplementary analyses**

Sensitivity Analyses of PFS

Table 45 Sensitivity analyses of PFS (Assessor's Table)

Analysis	**Summary statistics**
Primary analysis	Strat. **HR: 0.65** (95% CI: 0.51, 0.84) Median PFS 11.24 (9.3, 16.7) vs 7.75 (7.3, 9.3) months for the SG + pembro group vs the TPC + pembro group
Sensitivity analyses	
1. Same as primary analysis except that objective documented PD or death were counted as events regardless of missed study visits or initiation of new anti-cancer therapy	Strat. **HR: 0.65** (95% CI: 0.51, 0.83) Median PFS 11.20 (9.2, 16.6) vs 7.75 (7.3, 9.3) months
2. Same as primary analysis except that discontinuation of treatment or initiation of alternative anticancer treatment, whichever occurred earlier, was considered to be a PD event for participants censored in the primary analysis	Strat. **HR: 0.69** (95% CI: 0.55, 0.86) Median PFS 9.13 (7.5, 9.9) vs 7.33 (6.1, 7.7) months
3. PFS by **Investigator Assessment**	Strat. **HR: 0.67** (95% CI: 0.52, 0.87) Median PFS 11.33 (9.2, 14.6) vs 8.31 (7.3, 9.3) months

Analysis	Summary statistics
4. PFS using stratification factor data from the clinical database (instead of using stratification factors from the IWRS as in the primary PFS analysis)	Strat. **HR: 0.66** (95% CI: 0.51, 0.85)
5. Unstratified PFS analysis	Unstratified **HR: 0.66** (95% CI: 0.51, 0.85)

Sensitivity Analyses of OS

Sensitivity analysis to account for the crossing of the OS KM curves

As the Kaplan-Meier curves of OS for SG + pembro and TPC + pembro groups crossed at approximately 10 months after randomization, additional sensitivity analyses including restricted mean survival time (RMST) and piecewise exponential models were conducted to evaluate the robustness of OS results.

Overall Survival Based on RMST

Table 46 Overall Survival Based on Restricted Mean Survival Time by Cutoff Time Point (at OS IA1)

	0-Tau1 (39.0) Months	0-Tau2 (32.2) Months
RMST		
SG + Pembro (95% CI)	27.2 (25.4, 29.0)	24.1 (22.8, 25.5)
TPC + Pembro (95% CI)	26.4 (24.6, 28.1)	23.6 (22.3, 24.9)
Difference of SG + Pembro vs TPC + Pembro (95% CI)	0.8 (−1.7, 3.3)	0.5 (−1.3, 2.4)
P Value	0.5151	0.5787

CI = confidence interval; ITT = intent to treat; Pembro = pembrolizumab; RMST = restricted mean survival time; SG = sacituzumab govitecan; TPC = treatment of physician's choice
ITT Analysis Set includes all participants who were randomized in the study.
Cutoff point of RMST: Tau1 (months) is the minimum of each treatment group's last observed time regardless of event or censoring; Tau2 (months) is the minimum of each treatment group's last event time.

Table 47 Overall Survival Based on Restricted Mean Survival Time by Cutoff Time Point (at OS IA1)

	RMST Estimate (95% CI), Months			
	SG+Pembro (N = 221)	TPC+Pembro (N = 222)	RMST Difference of SG+Pembro vs TPC+Pembro (95% CI), Months	P Value
0-3 Months	3.0 (2.9, 3.0)	3.0 (2.9, 3.0)	-0.03 (-0.08, 0.03)	0.3234
0-6 Months	5.8 (5.7, 5.9)	5.9 (5.8, 6.0)	-0.10 (-0.24, 0.04)	0.1718
0-9 Months	8.5 (8.3, 8.7)	8.7 (8.5, 8.8)	-0.18 (-0.44, 0.08)	0.1793
0-12 Months	11.1 (10.8, 11.4)	11.3 (11.0, 11.5)	-0.18 (-0.59, 0.24)	0.4100
0-15 Months	13.5 (13.0, 13.9)	13.6 (13.2, 14.0)	-0.10 (-0.70, 0.51)	0.7561
0-18 Months	15.7 (15.1, 16.3)	15.7 (15.2, 16.2)	0.03 (-0.78, 0.83)	0.9477
0-21 Months	17.8 (17.0, 18.5)	17.6 (16.9, 18.3)	0.17 (-0.85, 1.18)	0.7461
0-24 Months	19.7 (18.8, 20.6)	19.4 (18.6, 20.3)	0.24 (-1.00, 1.48)	0.7052
0-27 Months	21.4 (20.3, 22.4)	21.1 (20.0, 22.1)	0.31 (-1.16, 1.77)	0.6814

	RMST Estimate (95% CI), Months			
	SG+Pembro (N = 221)	TPC+Pembro (N = 222)	RMST Difference of SG+Pembro vs TPC+Pembro (95% CI), Months	P Value
0-30 Months	23.0 (21.8, 24.2)	22.6 (21.4, 23.8)	0.43 (-1.27, 2.13)	0.6202
0-33 Months	24.5 (23.1, 25.9)	23.9 (22.6, 25.3)	0.59 (-1.36, 2.53)	0.5549
0-36 Months	25.9 (24.3, 27.4)	25.1 (23.6, 26.7)	0.71 (-1.50, 2.91)	0.5291
0-39 Months	27.2 (25.4, 29.0)	26.4 (24.6, 28.1)	0.83 (-1.67, 3.33)	0.5152

Overall Survival Based on Piecewise Exponential Models

Table 48 Overall Survival – Piecewise Hazard Ratio (at OS IA1)

	SG + Pembro (N = 221)	TPC + Pembro (N = 222)
Number (%) of Participants with Events (Death)		
≤ 3 Months	5 (2.3%)	3 (1.4%)
>3 - ≤ 6 Months	10 (4.5%)	7 (3.2%)
>6 - ≤ 9 Months	11 (5.0%)	12 (5.4%)
>9 - ≤ 12 Months	12 (5.4%)	17 (7.7%)
>12 - ≤ 15 Months	10 (4.5%)	17 (7.7%)
>15 - ≤ 18 Months	12 (5.4%)	19 (8.6%)
≤ 6 Months	15 (6.8%)	10 (4.5%)
>6 - ≤ 12 Months	23 (10.4%)	29 (13.1%)
>12 - ≤ 18 Months	22 (10.0%)	36 (16.2%)
Piecewise Stratified Hazard Ratio of SG + Pembro vs TPC + Pembro (95% CI)		
≤ 3 Months	1.670 (0.399, 6.987)	—
>3 - ≤ 6 Months	1.468 (0.559, 3.856)	
>6 - ≤ 9 Months	0.934 (0.412, 2.118)	
>9 - ≤ 12 Months	0.724 (0.345, 1.518)	
>12 - ≤ 15 Months	0.576 (0.263, 1.262)	
>15 - ≤ 18 Months	0.602 (0.291, 1.244)	
≤ 6 Months	1.529 (0.687, 3.403)	
>6 - ≤ 12 Months	0.811 (0.469, 1.403)	
>12 - ≤ 18 Months	0.590 (0.347, 1.005)	

OS (months) = (date of death or censoring − date of randomization + 1)/30.4375.
Hazard ratio and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (IWRS).
> 18 months not reported due to heavy censoring.

Analysis of early deaths

Table 49 Death by Time Interval (at OS IA1)

	SG+Pembro (N = 221)	TPC+Pembro (N = 222)	Total (N = 443)
Deaths occurred ≤ 6 months after randomization	15 (6.8%)	10 (4.5%)	25 (5.6%)
Adverse Event	5 (2.3%)	4 (1.8%)	9 (2.0%)
Death during randomized phase due to Adverse Event	5 (2.3%)	4 (1.8%)	9 (2.0%)
Death during crossover phase due to Adverse Event		0	
Progressive Disease	10 (4.5%)	6 (2.7%)	16 (3.6%)
Death reported during Long-term or Survival Follow-up, that is not due to Progressive Disease, and not related to study drug	0	0	0
Deaths occurred > 6 - ≤ 12 months after randomization	23 (10.4%)	29 (13.1%)	52 (11.7%)
Adverse Event	2 (0.9%)	6 (2.7%)	8 (1.8%)
Death during randomized phase due to Adverse Event	2 (0.9%)	2 (0.9%)	4 (0.9%)
Death during crossover phase due to Adverse Event		4 (1.8%)	
Progressive Disease	18 (8.1%)	20 (9.0%)	38 (8.6%)
Death reported during Long-term or Survival Follow-up, that is not due to Progressive Disease, and not related to study drug	3 (1.4%)	3 (1.4%)	6 (1.4%)
Deaths occurred > 12 months after randomization	59 (26.7%)	67 (30.2%)	126 (28.4%)
Adverse Event	1 (0.5%)	2 (0.9%)	3 (0.7%)
Death during randomized phase due to Adverse Event	1 (0.5%)	1 (0.5%)	2 (0.5%)
Death during crossover phase due to Adverse Event		1 (0.5%)	
Progressive Disease	46 (20.8%)	58 (26.1%)	104 (23.5%)
Death reported during Long-term or Survival Follow-up, that is not due to Progressive Disease, and not related to study drug	12 (5.4%)	7 (3.2%)	19 (4.3%)

Deaths due to AE which occurred on or after the first crossover treatment date with second line use of SG are presented in the crossover phase row.
All other deaths due to AE throughout the duration of the study are presented in the randomized phase row. Deaths due to AE with second line use of other therapies (e.g, chemotherapy agents) are not presented separately in the table.
Study drug is any study treatment in randomized phase.

Prior to the crossing of the OS KM curves at approximately 10 months, the maximum numerical difference in OS events between treatment groups occurred at approximately 8 months.

Table 50 Characterization of early deaths at OS IA1 (*Assessor's table*)

	SG + Pembro (N = 221)	TPC + Pembro (N = 222)	Total (N = 443)
Number of deaths during the first 8 months	23	16	39
Death due to AE	6	6	12
Deaths due to PD	15	10	25
Death reported during survival FU (not due to PD and not related to study drug)	2	0	2

Table 51 Demographic and Baseline Characteristics for Deaths by Time Interval (⩽6 Months, >6-12 Months, and >12 Months) for Participants who Died on or Before the DCO: 16 February 2026 (excerpt)

	Participants Died ≤ 6 Months			Participants Died >6 - ≤ 12 Months			Participants Died >12 Months		
	SG+Pembro (N = 15)	TPC+Pembro (N = 10)	Total (N = 25)	SG+Pembro (N = 23)	TPC+Pembro (N = 29)	Total (N = 52)	SG+Pembro (N = 59)	TPC+Pembro (N = 67)	Total (N = 126)
Age (years)									
N	15	10	25	23	29	52	59	67	126
Median	63	65	63	46	48	48	50	54	54
Baseline ECOG Score									
0	6 (40.0%)	3 (30.0%)	9 (36.0%)	15 (65.2%)	16 (55.2%)	31 (59.6%)	43 (72.9%)	47 (70.1%)	90 (71.4%)
1	9 (60.0%)	7 (70.0%)	16 (64.0%)	8 (34.8%)	12 (41.4%)	20 (38.5%)	16 (27.1%)	20 (29.9%)	36 (28.6%)
Brain Metastasis at Screening									
Yes	2 (13.3%)	2 (20.0%)	4 (16.0%)	1 (4.3%)	1 (3.4%)	2 (3.8%)	2 (3.4%)	2 (3.0%)	4 (3.2%)
Liver Metastasis at Screening									
Yes	8 (53.3%)	5 (50.0%)	13 (52.0%)	8 (34.8%)	12 (41.4%)	20 (38.5%)	23 (39.0%)	19 (28.4%)	42 (33.3%)

- **Sensitivity analysis to adjust for crossover or treatment switch**

At the time of OS IA1, a total of 122 participants (55%) in the TPC + pembro group received SG in the second-line setting; 99 (44.6%) received SG during the crossover phase of the study and the remainder received commercial SG.

To adjust for the effect of crossover on OS, prespecified sensitivity analyses using simplified 2-stage model [TSE], inverse probability of censoring weighting [IPCW], and rank preserving structural failure time model [RPSFT] were performed, in which the crossover to SG by participants in the TPC + pembro group per protocol was considered (n = 99).

Using the TSE method, 97 (43.9%) and 78 (35.1%) participants in the SG + pembro and TPC + pembro groups had OS events after re-censoring survival times for participants in the TPC + pembro group and the adjusted OS HR (95% CI) of SG + pembro versus TPC + pembro was 0.679 (0.491, 0.938).

Using the IPCW method, 97 (43.9%) and 57 (25.7%) participants in the SG + pembro and TPC + pembro groups had OS events after censoring crossover participants in the TPC + pembro group. The adjusted OS HR (95% CI) of SG + pembro versus TPC + pembro was 0.752 (0.487, 1.210).

Using the RPSFT method, 97 (43.9%) and 101 (45.5%) participants in the SG + pembro and TPC + pembro groups had OS events after re-censoring survival times for participants in the TPC +

pembro group. The adjusted OS HR (95% CI) of SG + pembro versus TPC + pembro was 0.839 (0.632, 1.105).

In addition, exploratory analyses were performed to adjust for the treatment switch to second line SG in the TPC + pembro group (including participants in the TPC + pembro group who received SG provided by the study in the crossover phase and also those who received SG through commercial means in the second line [n = 122]) which resulted in similar HR point estimates (range: 0.679-0.837).

A total of 124 participants (55.9%) in the TPC + pembro group received subsequent antibody-drug conjugate (ADC), including SG in the crossover phase, commercial SG or any other ADC in the second-line setting (compared to 7.2% in the SG + pembro group). Additional post-hoc exploratory analyses to adjust for the effect of imbalance in subsequent ADC use yielded HR point estimates in the range of 0.595 to 0.865.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 52 Summary of Efficacy for trial GS-US-592-6173 (ASCENT-04)

Title: A Randomized, Open-label, Phase 3 Study of Sacituzumab Govitecan and Pembrolizumab Versus Treatment of Physician's Choice and Pembrolizumab in Patients With Previously Untreated, Locally Advanced Inoperable or Metastatic Triple-Negative Breast Cancer, Whose Tumors Express PD-L1	
Study identifier	GS-US-592-6173 Eu CT No.: 2023-504194-21-00 ClinicalTrials.gov Identifier: NCT05382286

Design	Study GS-US-592-6173 is an ongoing international, multicenter, open-label, randomized, Phase 3 study designed to compare the efficacy and safety of treatment regimens comprised of SG and pembrolizumab or TPC and pembrolizumab (hereafter referred to as SG + pembro and TPC + pembro, respectively) in participants with locally advanced unresectable or metastatic triple-negative breast cancer (TNBC) who have not received previous therapy for advanced disease and whose tumors were programmed death-ligand 1 (PD-L1) positive (defined by combined positive score [CPS] ≥ 10 using the PD-L1 immunohistochemistry [IHC] 22C3 pharmDx assay) at screening. Participants presenting with de novo metastatic TNBC were eligible for this study and were capped at approximately 35% of all enrolled participants. Approximately 440 eligible participants were planned to be randomized in a 1:1 ratio to receive 1 of the following 2 treatments: • SG + pembro: SG 10 mg/kg intravenously (IV) on Days 1 and 8 of 21-day cycles and pembrolizumab 200 mg IV on Day 1 of 21-day cycles • TPC + pembro: TPC (21- or 28-day cycles) and pembrolizumab 200 mg IV on Day 1 of 21-day cycles The TPC was selected prior to randomization from 1 of the 3 allowed regimens: 1)paclitaxel 90 mg/m2 IV on Days 1, 8, and 15 of 28-day cycles; 2)nanoparticle albumin-bound (nab)-paclitaxel 100 mg/m2 IV on Days 1, 8, and 15 of 28-day cycles; or 3) gemcitabine 1000 mg/m2 IV with carboplatin area under the curve (AUC) 2 IV on Days 1 and 8 of 21-day cycles. Randomization was stratified by the following factors: • De novo versus recurrent disease within 6 to 12 months from completion of treatment in the curative setting versus recurrent disease occurring > 12 months from completion of treatment in the curative setting. Treatment-free interval was defined as the time between completion of systemic neoadjuvant/adjuvant breast cancer therapy or surgery (whichever occurred last) and first local or distant recurrence. Adjuvant radiotherapy was not included in the 6-month interval. • Geographic region (United States [US]/Canada/Western Europe versus rest of world). • Prior exposure to an anti PD-1 or PD-L1 agent (yes versus no).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	13 September 2022 – present (study is ongoing) Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	Sacituzumab govitecan (SG) + pembro	SG 10 mg/kg intravenously (IV) on Days 1 and 8 of 21-day cycles and pembrolizumab 200 mg IV on Day 1 of 21-day cycles Participants were treated until BICR-verified disease progression, unacceptable toxicity, withdrawal of consent, or death. Pembrolizumab was administered for a maximum of 35 cycles (approximately 2 years). Treatment with SG continued until BICR-verified disease progression, unacceptable toxicity, withdrawal of consent, or death for up to 35 cycles (approximately 2 years). After completion of 35 cycles of SG treatment, SG treatment may have been continued based on the clinical decision of the treating investigator. Long-term follow-up began at the time of completion of the end of treatment (EOT) visit, which occurred within 30 days (+ 7 days) after the last dose of study drug. Number randomized: 221

	Treatment of Physician's choice (TPC) + pembro i.e., 1 of the following single-agent treatments		Paclitaxel 90 mg/m2 intravenously on Days 1, 8, and 15 of 28-day cycles; or nab-Paclitaxel 100 mg/m2 intravenously on Days 1, 8, and 15 of 28-day cycles; or Gemcitabine 1000 mg/m2 intravenously plus carboplatin AUC 2 intravenously on Days 1 and 8 of 21-day cycles. Pembrolizumab 200 mg IV on Day 1 of 21-day cycles Participants were treated until BICR-verified disease progression, unacceptable toxicity, withdrawal of consent, or death. Long-term follow-up began at the time of completion of the end of treatment (EOT) visit, which occurred within 30 days (+ 7 days) after the last dose of study drug. Participants who were randomized to the control group (TPC + pembro) were eligible to receive SG monotherapy through the study, in the crossover phase, upon disease progression verified by BICR and upon meeting eligibility criteria. All participants were followed for survival until death, lost to follow-up, or withdrawal of consent, whichever occurred first. Number randomized: 222
Endpoints and definitions	Primary endpoint	Progression free survival (PFS) by blinded independent central review (BICR)	Defined as the time from the date of randomization until the date of objective progressive disease (PD), as assessed by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, or death (whichever comes first).
	Secondary endpoint	Overall survival (OS)	Defined as the time from the date of randomization until death due to any cause.
	Secondary endpoint	Objective response rate (ORR)	Defined as the proportion of participants who achieve a complete response (CR) or partial response (PR) that is confirmed at least 4 weeks after initial documentation of response as assessed by BICR per RECIST v1.1.
	Secondary endpoint	Duration of response (DOR)	Defined as the time from the first documentation of CR or PR to the earlier of the first documentation of definitive PD or death from any cause (whichever comes first) as assessed by BICR per RECIST v1.1.
	Secondary endpoint	Time to response (TTR)	Defined as the time from the date of randomization until the first documentation of CR or PR as assessed by BICR per RECIST v1.1.
	Secondary endpoint	Safety and tolerability	Incidence of treatment-emergent adverse events and clinical laboratory abnormalities.
	Secondary endpoint	Time to deterioration (TTD) in physical functioning	TTD of physical functioning domain as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Version 3.0)
	Secondary endpoint	TTD in role functioning, global health status/quality of life (QOL), pain, and fatigue	TTD of role functioning, global health status/QOL, pain, and fatigue subscale as measured by the EORTC QLQ-C30 (Version 3.0)

Database lock	11 April 2025 (clinical cut-off date for primary analysis:3 March 2025)				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Primary analysis of PFS was based on BICR using RECIST 1.1 for the Intent- to- Treat (ITT) Population. ITT Analysis Set includes all participants who were randomized in the study. Participants were treated until BICR-verified disease progression, unacceptable toxicity, withdrawal of consent, initiation of other anticancer therapy (including any investigational agent), or death.				
Descriptive statistics and estimate variability	Treatment group	SG + pembro (N=221)	TPC + pembro (N=222)		
	Number (%) of participants with events	109 (49.3%)	140 (63.1%)		
	PFS (median months)	11.24	7.75		
	95% Confidence interval (CI)	9.26, 16.69	7.29, 9.26		
Effect estimate per comparison			PFS	Comparison groups	SG + pembro vs TPC + pembro
		Hazard ratio (relative to TPC + pembro)	0.654		
		Confidence Interval	0.508, 0.842		
		P-value	0.0009		
Analysis population and time point description	A descriptive analysis of OS was performed at the time of PFS primary analysis using the ITT Analysis Set				
Descriptive statistics and estimate variability		Treatment group	SG + pembro (N=221)	TPC + pembro (N=222)	
	Number (%) of participants with events	53 (24.0%)	61 (27.5%)		
	OS (median months)	Not reached (NR)	NR		
	95% CI	25.56, NR	NR, NR		
Effect estimate per comparison			OS	Comparison groups	SG + pembro vs TPC + pembro
		Hazard ratio (relative to TPC + pembro)	0.889		

		Confidence Interval	0.615, 1.286	
		P-value	Not tested	
Analysis population and time point description	A descriptive analysis of ORR by BICR was performed at the time of PFS primary analysis using the ITT Analysis Set.			
Descriptive statistics and estimate variability		Treatment group	SG + pembro (N=221)	TPC + pembro (N=222)
	ORR (%)	59.7	53.2	
	95% CI	52.9, 66.3	46.4, 59.9	
Effect estimate per comparison		ORR	Comparison groups	SG + pembro vs TPC + pembro
		Odds ratio (relative to TPC + pembro)	1.306	
		Confidence Interval	0.898, 1.899	
		P-value	Not tested	
Analysis population and time point description	Duration of Response per BICR			
Descriptive statistics and estimate variability		Treatment group	SG + pembro (N=221)	TPC + pembro (N=222)
	DOR (%)	16.46	9.23	
	95% CI	12.68, 19.48	7.59, 11.27	
Effect estimate per comparison	Not applicable			
Analysis population and time point description	Time to Deterioration in Physical Functioning Domain of the EORTC QLQ-C30 Version 3.0 (months)			
Descriptive statistics and estimate variability	Treatment group	SG + pembro (N=221)	TPC + pembro (N=222)	
	Median TTD	2.99	3.55	
	95% CI	2.33, 4.57	2.89, 4.21	
Effect estimate per comparison	TTD	Comparison groups	SG + pembro vs TPC + pembro	
		Hazard ratio (relative to TPC + pembro)	0.945	
		Confidence Interval	0.730, 1.223	
		P-value	Not tested	

Clinical studies in special populations

Table 53 Clinical Studies in Special Populations

	Number of participants	
	Controlled Studies[a] N = 443	**Non-controlled Studies N = 0**
Baseline renal function		
Severe (Creatinine clearance < 30 mL/min)	1	0
Moderate (30 mL/min ≤ creatinine clearance < 60 mL/min)	39	0
Mild (60 mL/min ≤ creatinine clearance < 90 mL/min)	149	0
Normal (Creatinine clearance ≥ 90 mL/min)	254	0
Baseline hepatic function		
Normal (BILI ≤ ULN and AST ≤ ULN)	379	0
Mild ([BILI ≤ ULN and AST > ULN] or [ULN < BILI ≤ 1.5 X ULN])	63	0
Moderate (1.5 X ULN < BILI ≤ 3 X ULN)	1	0
Severe (BILI > 3 X ULN)	0	0
Age group		
Pediatric patients < 18 years	0	0
18-64	328	0
65-74	93	0
75-84	21	0
≥ 85	1	0

AST = aspartate transaminase; BILI = bilirubin; ULN = upper limit of normal
[a] Includes only Study GS-US-592-6173
Primary PFS analysis data were used.
The ITT Analysis Set includes all participants who were randomized in the study.
For baseline hepatic function and baseline renal function, baseline value was derived based on the last assessment on or before the date/time of first study drug administration if dosed, or randomization if not dosed.Age (in years) was collected on the date of first study drug administration (Day 1) if dosed, or randomization.

In vitro biomarkers test for patient selection for efficacy

In study ASCENT-04, patients were required to have tumours that are PD-L1 positive at screening. PD-L1 positivity was defined as CPS ≥ 10 using the PD-L1 IHC 22C3 pharmDx assay. Tumour PD-L1 expression status was confirmed centrally on a recent or archival tumour specimen.

The PD-L1 IHC 22C3 pharmDx assay and the cut-off of CPS ≥10 is analytically and clinically validated and approved as a companion diagnostic, a CE-marked IVD with the corresponding intended purpose.

In study ASCENT-04, pembrolizumab and chemotherapy was the backbone therapy, in the experimental arm sacituzumab govitecan was applied in combination with pembrolizumab and chemotherapy. In the EU, Keytruda (pembrolizumab) was approved for the 1L treatment of TNBC in October 2021 based on the KEYNOTE-355 study: "in combination with chemotherapy, for the treatment of locally recurrent unresectable or metastatic triple negative breast cancer in adults whose tumours express PD L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease" ()). In study KEYNOTE-355, the PD L1 IHC 22C3 pharmDx assay was used to determine tumour PD-L1 expression status. The biomarker restricted approval status of pembrolizumab in the same setting (with a tumour expression cut-off of CPS ≥10 using the PD-L1

IHC 22C3 pharmDx assay) serves as the rationale for the biomarker restricted study population of the ASCENT-04 study. The biomarker PD-L1 is not assumed to be predictive for the sacituzumab govitecan treatment effect.

2.4.3. Discussion on clinical efficacy

The MAH submitted ASCENT-04 study results to support an extension of indication for Trodelvy, in combination with pembrolizumab, for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have not received prior systemic therapy for metastatic disease and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

Design and conduct of clinical studies

The global, open-label study ASCENT-04 enrolled 443 patients with locally advanced, inoperable, or metastatic PD-L1 positive TNBC who have not received previous systemic therapy for advanced disease.

Patients were randomized to receive either sacituzumab govitecan (SG) and pembrolizumab or treatment of physician's choice chemotherapy (TPC) and pembrolizumab. SG and pembrolizumab were applied in line with approved dosing regimens. TPC was selected prior to randomisation to be either paclitaxel, nab-paclitaxel or gemcitabine/carboplatin. Retreatment with taxane, gemcitabine, or platinum agents were allowed in case of a treatment-free interval of ≥ 12 months. Patients should have received prior anthracycline in the (neo)adjuvant setting or be considered not eligible for anthracyclines as assessed by the treating physician. Participants in the control group were eligible to receive SG in the crossover phase upon disease progression verified by BICR.

The randomised study design, the eligibility criteria and the control arm are regarded as overall adequate and in line with pivotal studies supporting approval of other products in similar indications (Keytruda EMEA/H/C/003820/II/0099). The MAH designed a similar study: study ASCENT-03 with SG as monotherapy for the 1L treatment of patients with TNBC who are not candidates for PD-(L)1 inhibitor therapy (Trodelvy EMA/VR/0000312649).

Patients were stratified by prior exposure to anti-PD-L1 or anti-PD-L1 agents (yes versus no), geographic region (US/Canada/Western Europe versus Rest of World), and de novo disease versus recurrent disease with a treatment-free interval of 6-12 months versus recurrent disease > 12 months from completion of treatment in the curative setting. The stratification factors are considered acceptable. Participants presenting with de novo metastatic TNBC were planned to be capped at approximately 35% of all enrolled participants; the study finally recruited 33% of participants with de novo disease which is in line with expected rates in more recent publications[12]. 47% of participants had a disease-free interval of > 12 months and 20% had a disease recurrence within 6 to 12 months (clinical database). More participants were enrolled in the Rest of World (62%) as compared to the US/Canada/Western Europe (38%).

Baseline demographic and disease characteristics were overall balanced between treatment arms and representative of a 1L TNBC study population. 100% of patients recruited in the ASCENT-04 study were female. Since breast cancer is rare in men, the results from the pivotal trial are considered extrapolatable to men with TNBC in line with previous EMA decisions.

[12] Punie K et al. Evolution of characteristics, real-world treatment landscape, and survival outcomes in patients with previously untreated mTNBC in the United States [Abstract]. ESMO Breast Cancer; 2024.

As nearly all study participants had metastatic TNBC, only 23 patients (5.2%) were enrolled with locally advanced and inoperable disease. No efficacy subgroup analyses by disease status were reported given the very small number of patients with unresectable locally advanced disease. Disease status is unlikely to act as a major effect modifier and treatment recommendations do not differ between patients with unresectable locally advanced and metastatic disease; therefore, the extrapolation of study results to the small subgroup of patients with unresectable disease is agreed upon. The proposed indication wording is in line with precedents within the same treatment setting.

According to the clinical database, only 6 (1.4%) patients received a **prior PD-(L)1 inhibitor**, although these were allowed as part of (neo)adjuvant systemic treatment. Prior exposure to anti-PD-(L)1 agents was one of the stratification factors and the actual enrolment of patients with prior anti–PD-L1 treatment was obviously lower than expected. The MAH clarified that this could be in part due to the time it took between the approval/implementation and reimbursement of the (neo)adjuvant KN522 regimen in different countries. Additionally, there needed to be at least 6 months between completion of treatment in the curative setting and a patient's metastatic recurrence prior to enrolling in the ASCENT-04 study. This is acknowledged; nonetheless, it is considered unfortunate that no data are available to inform on the treatment effect of the combination of SG with pembrolizumab for patients with prior PD-(L)1 inhibitors. This lack of data creates an uncertainty considering that PD-(L)1 inhibitors are now a standard component of (neo)adjuvant treatment regimens in TNBC.

The study population characteristics are clearly reflected in section 5.1 of the SmPC. A cross-reference to section 5.1 of the SmPC has been already proposed by the MAH in the indication wording in section 4.1 of the SmPC which is agreed on.

The MAH did not implement the EMA SA recommendations to require gBRCA1/2 testing for all participants and prior PARPi treatment for patients with BRCA1/2 mutant tumours, but referred to global disparities in resources for testing and drug availability. BRCA1/2 mutation status at baseline (local testing) was known for only 29.3% of study participants; 7.2% of participants (n=32) had positive mutations status; only 1 participant received prior treatment with a PARPi and 1.1% (5 patients) received PARPi post progression. The most recent ESMO guidance[13][14] recommends a combination of PD-(L)1 inhibitors with chemotherapy for patients with PD-L1 positive TNBC independent of BRCA mutation status.

The original protocol (20 December 2021) was amended 2 times (08 April 2022 and 13 October 2023). Only protocol amendment 1 introduced relevant changes in the efficacy analysis, but this was implemented before randomisation of the first patient on 17 October 2022.

A high number of important protocol deviations was reported (46.3% across both treatment arms at the time of the primary PFS analysis); but after further review it can be agreed that these are not expected to have had a significant impact on the interpretation of the study results overall.

Efficacy data and additional analyses

Efficacy data were provided from the primary (final) analysis of PFS with a data cut-off date of 03 March 2025 and a median duration of follow-up of approximately 14 months. Analyses of secondary endpoints of OS, ORR, DOR and TTR by BICR as well as PRO data are descriptive only; key secondary endpoints were not formally tested at the time of the PFS primary analysis based on the testing hierarchy.

[13] ESMO Living Guideline for Triple-negative metastatic breast cancer; G Curigliano et al., Ann Oncol. 2025
[14] Azamuja et al., Metastatic breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up, published online 29 May 2026 – Annals of Oncology

Study ASCENT-04 demonstrated a statistically significant **PFS** improvement with SG + Pembrolizumab versus TPC + Pembrolizumab (HR: 0.654, 95% CI: 0.508, 0.842; 2-sided P < 0.0009). Median PFS was 11.24 months (95% CI: 9.26, 16.69) in the SG + Pembro group and 7.75 months (95% CI: 7.29, 9.26) in the TPC + Pembro group at the time of the primary PFS analysis. Sensitivity analyses of PFS and updated PFS results at OS IA1 were consistent with the primary analysis.

Descriptive **OS results** at the time of the primary PFS analysis were immature (114 events; 45% IF; 26% maturity rate) and showed an HR of 0.889 (95% CI: 0.615, 1.286). Updated OS results at the time of OS Interim Analysis were based on 203 events (46% maturity rate, 80.6% information fraction and a median duration of OS follow-up of 22.5 months at the DCO of 16 February 2026). Results remained overall consistent with longer follow-up; the OS HR was 0.915 (95% CI: 0.69, 1.21, P = 0.53) with a median OS of 31.2 months (95% CI: 25.6, NR) in the SG + Pembro group and 28.4 months (95% CI: 24.4, NR) in the TPC + Pembro group. The OS KM curves first crossed after about 10 months, overlapped until approximately 12 months, at this point they began to slightly diverge in favour of SG + Pembro, but converged again at month 24. There was substantial censoring that occurred after 18 months in the Kaplan-Meier plots, thereby limiting the interpretation of the curves beyond the minimum follow-up period. For this reason, the median OS estimates should be interpreted with caution.

Evaluation of early deaths

Sensitivity analyses to account for the crossing of the OS KM curves were conducted based on using restricted mean survival time (RMST) and piecewise exponential models. RMST differences between the SG + Pembro group and the TPC + Pembro group based on empirical choices of 39 and 32 months were 0.8 months (95% CI: −1.7, 3.3) and 0.5 months (95% CI: −1.3, 2.4), respectively, supporting no OS detriment in the SG + Pembro group over the entire course of the OS follow-up time. Additional RMST analyses using time points with 3-month increments showed more favourable OS outcomes for the control group in the first 15 months after randomization and a trend toward more favourable outcomes for the SG + Pembro arm with longer follow-up. Results from piecewise exponential models showed that the crossing of the OS curve was mainly driven by early events in the first 6 months after randomization, with a HR point estimates of 1.529 (95% CI 0.687, 3.403) for ≤ 6 months in favour of the TPC + Pembro group; with follow up times exceeding 6 months, HR point estimates remained below 1 (0.811 for >6- ≤12 months and 0.59 for >12 - ≤ 18 months).

In both treatment arms, deaths within ≤ 6 months, compared with deaths occurring at later time intervals, generally occurred in older participants, in patients with poorer ECOG performance status, and in a higher proportion of patients with brain and liver metastases. No apparent differences in the characteristics of deaths were observed between treatment arms. A relatively higher proportion of participants died due to AEs during the first 6 months after randomization, which might be expected considering that early deaths occurred in a clinically more vulnerable subgroup. The initial OS detriment observed in the SG + Pembro group compared with the TPC + Pembro group is based on a limited number of events; during the first 6 months, 15 patients in the SG + Pembro group died compared to 10 patients in the TPC + Pembro group. The maximum numerical difference in OS events between treatment groups occurred at approximately 8 months, at which time 23 OS events occurred in the SG + Pembro group and 16 in the TPC + Pembro group. The most common reasons were deaths due to progressive disease (15 in the SG + Pembro group and 10 in the TPC + Pembro group), whereas Grade 5 AEs occurred with similar rates across both groups (6 in each).

Impact of second-line treatment on OS results

In total, 122 (55%) participants in the TPC + Pembro group received SG monotherapy in the second-line setting, of whom 99 (44.6%) received SG through the study during the crossover phase. It is acknowledged that the ability to demonstrate an OS improvement is impacted by the high rate of SG use post-progression. Nonetheless, the high proportion of patients receiving SG at PD reflects the currently recommended standard of clinical practice. Given the established OS benefit of SG compared with chemotherapy in previously treated metastatic TNBC (study ASCENT), sensitivity analyses to adjust for participants in the TPC + Pembro group who received second-line SG monotherapy provided by the study in the crossover phase were prespecified. Results showed HR point estimates (range: 0.679-0.839) in favour of the SG + Pembro group. Additional exploratory analyses including also participants who received SG through commercial means and participants who received any other ADC in the second-line use yielded similar results (HR point estimates in the range of 0.595 to 0.865). The point estimates vary depending on each method and are accompanied by wide confidence intervals which limits the robustness and interpretation of the results. Furthermore, no adjustment was performed in the SG + Pembro group for 2L treatment, which may have affected the OS and thus adjusted HR. Given the limitations of the analyses, the results can only be considered supportive of no detrimental OS of SG but they cannot support a demonstration of a survival benefit of SG.

In conclusion, the OS results of the study ASCENT-04 did not show a clinically relevant OS advantage of SG + Pembro over standard first-line chemotherapy + Pembro. Additional sensitivity analyses using RMST to account for the crossing of the OS KM curves indicated no detriment of SG + Pembro over the entire OS follow-up period, but suggest more favourable OS outcomes for the control group in the first 15 months after randomization and a trend toward more favourable outcomes for the SG + Pembro arm with longer follow-up. However, as early deaths tended to occur in older participants with less favourable baseline performance status and considering the comparable rates of deaths due to AEs during the initial follow-up period, a safety detriment associated with the use of SG in combination with pembrolizumab compared to TPC in combination with pembrolizumab is considered unlikely. In light of the persistently high rate of censoring beyond 18 months, the MAH will provide the results from the final OS analysis post-approval **(REC).**

Results for the secondary efficacy endpoints of **ORR** (60% vs 53%; Odds Ratio 1.3), time to response (1.9 months for both arms), median **TTD in physical function** (3.0 vs 3.6 months; HR 0.95) or other PRO endpoints were similar between the SG + Pembro group and the TPC + Pembro group (thus, neither supporting a benefit nor indicating a detriment). Median DOR was numerically longer with SG + Pembro compared with TPC + Pembro (16.5 versus 9.2 months) in line with PFS results.

An exploratory analysis of **PFS2** showed an improvement in the SG + Pembro group versus the TPC + Pembro group (HR: 0.72; 95% CI: 0.56, 0.92); the median PFS2 was 26.4 months in the SG + Pembro group vs 17.7 months in the TPC + Pembro group at OS IA1. There was substantial censoring that occurred after 18 months in the Kaplan-Meier plots.

Subgroups

Subgroup results of PFS generally showed a consistent benefit of SG + Pembro compared to TPC + Pembro; however, interpretation of some subgroups is limited by the small sample sizes.

Only 14 patients with stable **brain metastasis** were enrolled (N=8 in the SG + Pembro group and 6 in the TPC + Pembro group). PFS, OS and ORR subgroup results were numerically in favour of the SG + Pembro treatment arm. Systematic response assessment of brain metastasis was not conducted. MRI brain scan was mandatory at screening in all patients and follow-up was required if brain metastasis was known or suspected. But numeric measurements of the brain lesions were not

collected, since brain lesions, per protocol, were captured as nontarget lesions at baseline or as new lesions at the time of progression. The best nontarget lesion response in the brain by BICR at the primary PFS analysis was noncomplete response/nonprogressive disease (NCR-NPD) for 5 participants, and not evaluable (NE) for 3 participants. In the TPC + Pembro group, NCR-NPD was reported for 3 participants, progressive disease for 1 participant, and NE for 2 participants. No firm conclusions can be drawn from these results.

Subgroup results for patients with known **BRCA1/2 mutations** at baseline based on local testing (N=32) indicated a benefit of SG + Pembro compared to TPC + Pembro. The MAH provided additional analyses based on retrospective central BRCA assessment using whole exome sequencing (WES) analyses. BRCA1/2 mutations status could be determined in 332 participants (Biomarker Analysis Set), of whom 71 participants (21.4%) were BRCA1/2 mutation positive. Subgroup results in these BRCA1/2 mutation positive participants based on central testing did not show a clinically meaningful PFS benefit (PFS HR: 0.96 [95% CI 0.51, 1.79], median PFS 14.9 months for SG + Pembro vs 12.8 months for TPC + Pembro, but OS results were more favourable for participants with positive mutation status (OS HR: 0.71 [95% CI 0.33, 1.52]) compared to wild-type participants and ORR results were similar for both subgroups. The value of the analysis of central BRCA test results based on whole exome sequencing is limited by its exploratory and retrospective nature and the non-randomised comparisons in a Biomarker Analysis Set. Interpretation of these results is also limited by the small sample size and wide confidence intervals even in the BRCA1/2 mutations positive subgroup based on central testing; nonetheless available data do not indicate a detrimental effect for the treatment with SG + pembrolizumab.

Subgroup results by **age** were provided for the cut-offs of 65 and 75 years at OS IA1 (DCO: 16 February 2026). For patients beyond 65 years (N=115), the PFS and ORR benefit was similar compared to the younger subgroup, despite wider confidence intervals due to the smaller sample size in the elderly. The point estimate of the OS HR in the age group of patients ≥ 65 years was above 1 with a wide confidence interval (OS HR: 1.13; 95% CI: 0.66, 1.94); however, the OS KM curves did not support a possible OS detriment in this age group, because the curves largely overlapped and only separated beyond 18 months when the interpretation of the KM curves was less reliable due to heavy censoring. For the age group of ≥ 75 years, the interpretation of data is limited by the small sample size of participants (N=22) and wide confidence intervals; nonetheless, available data indicated a PFS, OS and ORR benefit in these elderly patients. Section 4.2 of the SmPC currently includes a statement that "data from sacituzumab govitecan in patients ≥ 75 years are limited."

Evaluation of baseline **Trop-2 expression** in fresh or archival tumour tissue as a biomarker for efficacy was an exploratory endpoint. Trop-2 expression in tumour tissue was assessed by IHC using a fit-for-purpose, validated EPR20043 formulation locked assay (FLA) at Roche Tissue Diagnostics (RTD). Trop-2 data were available from 400 participants (90.3%) in the Intent to Treat (ITT) Analysis Set.

PFS results indicated a small trend towards a less pronounced PFS benefit in the two lower Trop-2 H-score quartiles (PFS HR: 0.87 and 0.73 vs 0.44 and 0.62 for Q1, Q2, Q3 and Q4, respectively); PFS KM curves separated only beyond 7 months in Q1 and Q2 in favour of the SG + Pembro arm. However, updated OS data at OS IA1 did not show a detriment and no clear association with Trop-2 expression status. ORR results indicated a detriment only in the lowest Trop-2 H-score quartile (odds ratio 0.66; ORR 58% for SG + Pembro vs 68% vs TPS and Pembro).

Trop-2 expression results need to be interpreted with caution since Trop-2 expression status was not a stratification factor and though expression data were analysed in a large proportion, they were not available for all study participants. In addition, no specific analytical validation for the

Trop-2 expression scoring system in breast cancer tissue was performed. Subgroup results by quartiles showed large and overlapping confidence intervals and there is no clear consistent correlation with respect to levels of Trop-2 expression and increased efficacy data in TNBC participants of study ASCENT-04 with generally high levels of Trop-2 expression. Nonetheless, available data from study ASCENT-03 for SG monotherapy in 1L TNBC patients who are not candidates for PD-1 or PD-L1 inhibitor therapy (Trodelvy EMA/VR/0000312649) and particularly final OS results from study ASCENT for SG monotherapy in TNBC after prior therapy indicated that the OS benefit might be less pronounced for patients with lower tumour Trop-2 expression. Considering SG's mechanism of action as a targeted therapy, an association between Trop-2 expression status and OS outcome would be biologically plausible, however, no reliable data on subgroups were presented, so the predictive value of Trop-2 expression in breast cancer remains uncertain.

2.4.4. Conclusions on the clinical efficacy

Study ASCENT-04 demonstrated a statistically significant PFS improvement for the combination therapy of SG with pembrolizumab compared to first-line chemotherapy with pembrolizumab in patients with PD-L1 positive TNBC. This improvement can also be considered clinically relevant.

The OS results can be considered sufficiently mature to exclude an OS detriment over the entire course of the OS follow-up time (based on an OS maturity rate of 46%).

The ability to demonstrate an OS improvement is impacted by the high rate of SG use post-progression; 55% of participants in the control arm received SG after disease progression. Nonetheless, administering SG after the failure of 1L treatment reflects standard clinical practice.

In view of the still high rate of censoring beyond 18 months, the MAH will provide the results from the final OS analysis post-approval (REC).

2.5. Clinical safety

Introduction

The safety data supporting this application for extension of indication are based on data derived from study GS-US-592-6173 (ASCENT-04) and pooled data for the Overall mBC and the All Treated (Expanded) SG populations.

The dataset of pivotal **study GS-US-592-6173** includes information for 441 participants with unresectable locally advanced or metastatic TNBC who have not received previous systemic therapy for metastatic disease and whose tumours are PD-L1 positive (i.e. CPS ≥ 10 using the PD-L1 IHC 22C3 pharmDx assay) at screening. Participants in this study received either SG 10 mg/kg + pembrolizumab 200 mg[15] (study GS-US-592-6173 SG + pembolizumab group, for short SG + Pembro group, N = 221) or TPC (paclitaxel 90 mg/m^2, nab-paclitaxel 100 mg/m^2, or gemcitabine 1000 mg/m^2 with carboplatin AUC 2) + pembrolizumab 200 mg[16] (study GS-US-592-6173 TPC + pembrolizumab group, for short TPC + Pembro group, N = 220).

Pooled data are provided for context and are presented side by side with the safety data from study GS-US-592-6173. Specifically, the pooled data from four clinical studies (IMMU-132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238) in 963 participants with metastatic TNBC or HR+/ HER2− mBC (**Overall mBC pool)** act as a comparison between the safety profile of SG 10

[15] (SG 10 mg/kg IV on Days 1 and 8 of 21-day cycles + pembro 200 mg IV on Day 1 of 21-day cycles)
[16] (TPC (21 or 28-day cycles) + pembro 200 mg IV on Day 1 of 21-day cycles)

mg/kg as monotherapy and the safety profile of the SG and pembrolizumab combination regimen. Furthermore, the pooled data from seven clinical studies (studies IMMU-132-01, IMMU-132-05, IMMU-132-06 Cohorts 1 and 2, IMMU-132-09, GS-US-592-6238, GS-US-577-6153, and IMMU-132-13) in 1999 participants a**cross different tumor types** act as an additional comparison between the safety profile of SG 10 mg/kg as **monotherapy** and the **SG and pembrolizumab combination regimen** (**All Treated (Expanded) SG pool).** The table below provides an overview of these four populations.

Of note, the safety data from the All Treated (Expanded) SG pool are only discussed in specific cases due to the very heterogenous patient populations.

Safety data from the SG + pembro group were used for the selection of adverse drug reactions for the Summary of Product Information (SmPC).

Table 54 Studies and Population Groups Included in the Summary of Clinical Safety Addendum and Integrated Summary of Safety (Expanded)

Study Number	Data Cutoff Date[a]	Patient Population	Population Groups for ISS Analysis			
			GS-US-592-6173 SG + Pembro (N = 221)[b]	GS-US-592-6173 TPC + Pembro (N = 220)[c]	Overall mBC SG (N = 963)[d]	All Treated (Expanded) SG (N = 1999)[e]
GS-US-592-6173	03 March 2025	Participants with previously untreated, locally advanced unresectable or metastatic TNBC whose tumors express PD-L1	221	220	—	—
IMMU-132-01	02 April 2021; final data	Participants with epithelial cancer who received SG 10 mg/kg, including participants with mTNBC and HR+/HER2− mBC	—	—	mTNBC: 108 HR+/HER2− mBC: 54	402 (any tumor type)
IMMU-132-05	25 February 2021; final data	Participants with mTNBC who received ≥ 2 prior treatments	—	—	258	258
IMMU-132-06[f]	28 February 2023	Cohort 1: participants with mUC who progressed after prior platinum-containing and anti-PD-1 or anti-PD-L1-based therapies	—	—	—	113
		Cohort 2: participants with platinum-ineligible mUC who progressed after prior anti-PD-1 or anti-PD-L1-based therapy	—	—	—	38
IMMU-132-09	15 December 2023; final data	Participants with HR+/HER2− mBC who failed at least 2 prior chemotherapy regimens	—	—	268	268
GS-US-592-6238	02 April 2025	Participants with locally advanced unresectable or metastatic TNBC who have not received previous therapy for advanced disease and who are not candidates for PD-1 or PD-L1 inhibitors	—	—	275	275
IMMU-132-13	08 March 2024	Participants with metastatic or locally advanced unresectable UC who have progressed after prior therapy with platinum-containing regimen and a PD-1 or PD-L1 inhibitor	—	—	—	349
GS-US-577-6153	29 November 2023	Participants with advanced or metastatic NSCLC who progressed on or after platinum-based chemotherapy and anti-PD-1 or anti-PD-L1 immunotherapy received either in combination or sequentially	—	—	—	296

AUC = area under the curve; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormonal receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; mTNBC = metastatic triple-negative breast cancer; mUC = metastatic urothelial cancer; nab = nanoparticle albumin-bound; NSCLC = non-small-cell lung cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; Pembro = pembrolizumab; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice; UC = urothelial cancer

a Studies GS-US-592-6173, IMMU-132-06, GS-US-592-6238, IMMU-132-13, and GS-US-577-6153 are ongoing, and data up to the specified data cutoff dates were included in the expanded integrated safety analysis. Studies IMMU-132-01, IMMU-132-05, and IMMU-132-09 were completed, and data up to final database lock were included in the integrated safety analysis.

b Includes participants treated with SG 10 mg/kg + pembrolizumab 200 mg in Study GS-US-592-6173.

c Includes participants treated with TPC (paclitaxel 90 mg/m^2, nab-paclitaxel 100 mg/m^2, or gemcitabine 1000 mg/m^2 with carboplatin AUC 2) + pembrolizumab 200 mg in Study GS-US-592-6173.

d Includes all participants with mTNBC or HR+/HER2− mBC treated with SG 10 mg/kg in Studies IMMU 132-01, IMMU-132-05, IMMU-132-09, and GS-US-592-6238.

e Includes all participants treated with SG 10 mg/kg regardless of indication from Studies IMMU-132-01, IMMU-132-05, IMMU-132-06 (Cohorts 1 and 2), IMMU-132-09, GS-US-592-6238, IMMU-132-13, and GS-US-577-6153.

f Safety data from Cohorts 1 and 2 were included in this expanded integrated safety analysis.

Patient exposure

The extent of exposure of participants to SG and pembrolizumab as well as to TPC and pembrolizumab in the SG + Pembro and TPC + pembro groups (study GS-US-592-6173), in the Overall mBC pool, and in the All Treated (Expanded) SG pool is summarised in Table 55.

Participant disposition and reason for discontinuation from treatment are presented in Table 56.

Table 55 Exposure to Study Drug (Study GS-US-592-6173 ISS Populations [Expanded])

	GS-US-592-6173 SG + Pembro (N = 221)		GS-US-592-6173 TPC + Pembro (N = 220)			
	SG (N = 221)	Pembro (N = 221)	TPC (N = 220)	Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Treatment Duration (months) [a]						
N	221	221	220	220	963	1999
Mean (StD)	9.85 (6.128)	9.53 (6.098)	7.53 (5.131)	7.94 (5.713)	7.10 (6.890)	6.03 (6.429)
Median	8.90	8.54	6.24	6.42	5.29	4.17
Min, Max	0.03, 27.07	0.03, 26.84	0.03, 26.32	0.03, 25.63	0.03, 62.55	0.03, 62.55
≥ 3 months, n, (%)	195 (88.2%)	193 (87.3%)	192 (87.3%)	181 (82.3%)	650 (67.5%)	1196 (59.8%)
≥ 6 months, n, (%)	154 (69.7%)	152 (68.8%)	115 (52.3%)	117 (53.2%)	423 (43.9%)	740 (37.0%)
≥ 12 months, n, (%)	71 (32.1%)	66 (29.9%)	33 (15.0%)	46 (20.9%)	169 (17.5%)	251 (12.6%)
≥ 24 months, n, (%)	4 (1.8%)	4 (1.8%)	1 (0.5%)	2 (0.9%)	31 (3.2%)	44 (2.2%)
≥ 36 months, n, (%)	0	0	0	0	6 (0.6%)	12 (0.6%)
Number of Participants with Number of Cycles Received, n (%) [b]						
1	7 (3.2%)	8 (3.6%)	—	7 (3.2%)	55 (5.7%)	190 (9.5%)
2	8 (3.6%)	8 (3.6%)	—	6 (2.7%)	125 (13.0%)	298 (14.9%)
3	7 (3.2%)	9 (4.1%)	—	16 (7.3%)	63 (6.5%)	166 (8.3%)
≥ 4	199 (90.0%)	196 (88.7%)	—	191 (86.8%)	720 (74.8%)	1345 (67.3%)
Number of Doses Received						
N	221	221	—	220	963	1999
Mean (StD)	27 (16.2)	14 (8.2)	—	12 (7.5)	20 (18.7)	17 (17.3)
Median	24	12	—	10	15	12
Min, Max	1, 73	1, 35	—	1, 35	1, 178	1, 178
Cumulative Dosage [c]						
N	221	221	—	220	960	1995
Mean (StD)	236.6 (147.52)	2717.9 (1649.86)	—	2300.5 (1503.83)	183.5 (167.22)	154.0 (153.37)
Median	205.2	2400.0	—	2000.0	138.9	111.7
Min, Max	10.0, 722.3	200.0, 7000.0	—	200.0, 7000.0	9.2, 1340.8	8.0, 1757.9
Relative Dose Intensity (%) [d]						
N	221	221	—	220	960	1995
Mean (StD)	81.7 (16.59)	92.1 (8.46)	—	93.3 (7.67)	85.9 (14.63)	85.3 (15.78)

	GS-US-592-6173 SG + Pembro (N = 221)		GS-US-592-6173 TPC + Pembro (N = 220)			
	SG (N = 221)	Pembro (N = 221)	TPC (N = 220)	Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Median	83.1	94.4	—	95.6	89.5	89.1
Min, Max	43.9, 127.3	60.0, 106.9	—	60.0, 109.5	39.0, 138.6	30.4, 138.6
Relative Dose Intensity						
< 70%	54 (24.4%)	5 (2.3%)	—	3 (1.4%)	151 (15.7%)	365 (18.3%)
70% to < 90%	77 (34.8%)	64 (29.0%)	—	61 (27.7%)	338 (35.1%)	665 (33.3%)
90% to < 110%	88 (39.8%)	152 (68.8%)	—	156 (70.9%)	460 (47.8%)	938 (46.9%)
≥ 110%	2 (0.9%)	0	—	0	11 (1.1%)	27 (1.4%)
Number of Participants with Dose Reductions						
Any	99 (44.8%)	—	117 (53.2%)	—	314 (32.6%)	678 (33.9%)
1	62 (28.1%)	—	63 (28.6%)	—	244 (25.3%)	529 (26.5%)
2	36 (16.3%)	—	40 (18.2%)	—	64 (6.6%)	141 (7.1%)
3	1 (0.5%)	—	10 (4.5%)	—	2 (0.2%)	4 (0.2%)
> 3	0	—	4 (1.8%)	—	4 (0.4%)	4 (0.2%)
Time to First Dose Reduction (days)						
N	99	—	117	—	314	678
Mean (StD)	98 (114.4)	—	104 (78.7)	—	92 (119.0)	77 (116.4)
Median	50	—	91	—	46	41
Min, Max	8, 610	—	1, 306	—	1, 925	1, 1647
Number of Participants with Treatment Delays > 3 Weeks [e]	22 (10.0%)	—	—	—	51 (5.3%)	113 (5.7%)
Number of Participants with Infusion Interruptions	16 (7.2%)	6 (2.7%)	—	3 (1.4%)	34 (3.5%)	85 (4.3%)

ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; Pembro = pembrolizumab; SG = sacituzumab govitecan; StD = standard deviation; TPC = treatment of physician's choice

Percentages are based on the total number of participants in the corresponding column.

[a] Treatment duration (in months) is (date of the last treatment administration − date of the first treatment administration + 1) / 30.4375.

[b] Number of cycles includes cycles during which participants received at least 1 dose of study drug.

[c] The dosage unit is mg/kg for SG, mg for Pembro.

[d] Relative Dose Intensity = (Total Amount of Study Drug Administered / Total Amount of Actual Study Drug Planned by Protocol) × 100

[e] Treatment delay > 3 weeks: > 28 days between Day 1 of any cycle and the next dose, or > 35 days between Day 8 of any cycle and the next dose.

Table 56 Participant Disposition and Reason for Discontinuation From Treatment (Study GS-US-592-6173 ISS Populations [Expanded])

	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro [a] (N = 220)	Overall mBC [b] (N = 963)	All Treated (Expanded) SG (10 mg/kg) [c] (N = 1999)
Participants Treated	221 (100.0%)	220 (100.0%)	963 (100.0%)	1999 (100.0%)
On Treatment of SG/TPC	91 (41.2%)	40 (18.2%)	75 (7.8%)	124 (6.2%)
Permanently Discontinued Treatment of SG/TPC	130 (58.8%)	180 (81.8%)	888 (92.2%)	1875 (93.8%)
Reason of End of Treatment of SG/TPC				
Progressive Disease	81 (36.7%)	121 (55.0%)	735 (76.3%)	1441 (72.1%)
Protocol Deviation	0	0	1 (0.1%)	1 (< 0.1%)
Death	6 (2.7%)	1 (0.5%)	10 (1.0%)	31 (1.6%)
Treatment Delay > 3 Weeks	0	0	6 (0.6%)	9 (0.5%)
Treatment Delay for Any Reason > 5 Weeks	0	0	0	15 (0.8%)
Participant Decision	21 (9.5%)	11 (5.0%)	37 (3.8%)	94 (4.7%)
Adverse Event	17 (7.7%)	39 (17.7%)	47 (4.9%)	180 (9.0%)
Lost to Follow-Up	0	0	0	3 (0.2%)
Investigator's Discretion	4 (1.8%)	6 (2.7%)	30 (3.1%)	45 (2.3%)
Non-compliance with Study Drug	1 (0.5%)	2 (0.9%)	0	1 (< 0.1%)
Study Drug Not Administered (After Randomization)	0	0	1 (0.1%)	1 (< 0.1%)
Sponsor's Decision	0	0	1 (0.1%)	2 (0.1%)
COVID-19	0	0	0	1 (< 0.1%)
Failure to Resolve a Toxicity Within 3 Weeks of The Last Dose of Study Drug	0	0	0	2 (0.1%)
Other	0	0	20 (2.1%)	48 (2.4%)
Missing	0	0	0	1 (< 0.1%)

COVID-19 = coronavirus disease 2019; HER2− = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; nab = nanoparticle albumin-bound; Pembro = pembrolizumab; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice

[a] GS-US-592-6173 TPC + Pembro group includes participants who received paclitaxel, nab-paclitaxel, or gemcitabine/carboplatin with pembro.

[b] Overall mBC group includes participants from Study IMMU-132-01 with metastatic TNBC and HR+/HER2− mBC treated with SG 10 mg/kg, and all participants from Studies IMMU-132-05, IMMU-132-09 and GS-US-592-6238 treated with SG 10 mg/kg.

[c] All Treated (Expanded) SG (10 mg/kg) group includes all participants who were treated with SG 10 mg/kg regardless of tumor type in IMMU-132-01 and all participants treated with SG from Studies IMMU-132-05, IMMU-132-06 Cohorts 1 and 2, IMMU-132-09, GS-US-592-6238, IMMU-132-13, and GS-US-577-6153.

On-treatment participants are those still on treatment with SG/TPC regardless of pembro by the date of clinical database cutoff.

One participant from Study IMMU-132-01 who received study drug was mistakenly marked as 'study drug not administered after randomization.'

Adverse events

Adverse event summary

All AEs discussed in the following sections are treatment-emergent, unless otherwise specified.

As the median treatment duration was longer in the SG + Pembro group than the TPC + Pembro group in Study GS-US-592-6173, both "naïve" incidence rates (Table 57) and exposure-adjusted incidence rates (EAIRs) (Table 58) are provided for the adverse event summary.

Table 57 Overall Summary of Adverse Events (Study GS-US-592-6173 ISS Populations [Expanded])

	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
AEs	220 (99.5%)	219 (99.5%)	960 (99.7%)	1991 (99.6%)
Grade 3 or higher	158 (71.5%)	154 (70.0%)	687 (71.3%)	1465 (73.3%)
Treatment-related AEs	218 (98.6%)	215 (97.7%)	942 (97.8%)	1937 (96.9%)
SAEs	84 (38.0%)	68 (30.9%)	266 (27.6%)	763 (38.2%)
Treatment-related SAEs	61 (27.6%)	42 (19.1%)	148 (15.4%)	420 (21.0%)
AEs leading to death	7 (3.2%)	6 (2.7%)	15 (1.6%)	63 (3.2%)
Treatment-related AEs leading to death	3 (1.4%)	1 (0.5%)	7 (0.7%)	28 (1.4%)
AEs leading to any study drug withdrawal/discontinuation	26 (11.8%)	68 (30.9%)	45 (4.7%)	177 (8.9%)
AEs leading to SG/TPC dose reduction	78 (35.3%)	96 (43.6%)	249/801 (31.1%)	532/1597 (33.3%)
AEs leading to any study drug interruption	171 (77.4%)	162 (73.6%)	598 (62.1%)	1214 (60.7%)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; SAE = serious adverse event; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Treatment-emergent adverse events (TEAEs) are any AEs that started on or after the first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Adverse events were coded according to MedDRA Version 27.1.

Treatment related includes 'Related,' 'Likely Related,' 'Possibly Related,' and missing relation.

Severity grades were defined by CTCAE: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Life-threatening; 5 = Death.

Dose reduction due to an AE was not collected in IMMU-132-01 so participants of this study were excluded from the summary of AEs leading to dose reduction.

Table 58 Overall Summary of Adverse Events: Exposure-Adjusted Incidence Rate (EAIR) (Study GS-US-592-6173 ISS Populations [Expanded])

	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Participants with any AEs	220 (99.5%)	219 (99.5%)	960 (99.7%)	1991 (99.6%)
PYE	3.2	6.0	15.9	34.2
EAIR (95% CI)	69.09 (60.26, 78.85)	36.68 (31.98, 41.87)	60.43 (56.67, 64.38)	58.26 (55.73, 60.87)
EAIR Diff (95% CI): SG + Pembro vs		32.42 (22.17, 43.25)	8.66 (−1.01, 19.12)	
Participants with Grade 3 or higher AEs	158 (71.5%)	154 (70.0%)	687 (71.3%)	1465 (73.3%)
PYE	72.1	72.4	238.5	427.3
EAIR (95% CI)	2.19 (1.86, 2.56)	2.13 (1.81, 2.49)	2.88 (2.67, 3.10)	3.43 (3.26, 3.61)
EAIR Diff (95% CI): SG + Pembro vs		0.06 (−0.43, 0.55)	−0.69 (−1.09, −0.26)	
Participants with treatment-related AEs	218 (98.6%)	215 (97.7%)	942 (97.8%)	1937 (96.9%)
PYE	5.1	9.5	27.6	56.4
EAIR (95% CI)	43.04 (37.52, 49.15)	22.67 (19.74, 25.91)	34.08 (31.93, 36.32)	34.33 (32.81, 35.89)
EAIR Diff (95% CI): SG + Pembro vs		20.37 (13.97, 27.14)	8.96 (3.00, 15.44)	
Participants with SAEs	84 (38.0%)	68 (30.9%)	266 (27.6%)	763 (38.2%)
PYE	143.0	130.1	477.5	791.8
EAIR (95% CI)	0.59 (0.47, 0.73)	0.52 (0.41, 0.66)	0.56 (0.49, 0.63)	0.96 (0.90, 1.03)
EAIR Diff (95% CI): SG + Pembro vs		0.06 (−0.12, 0.25)	0.03 (−0.11, 0.18)	
Participants with treatment-related SAEs	61 (27.6%)	42 (19.1%)	148 (15.4%)	420 (21.0%)
PYE	150.4	142.4	511.9	873.6
EAIR (95% CI)	0.41 (0.31, 0.52)	0.29 (0.21, 0.40)	0.29 (0.24, 0.34)	0.48 (0.44, 0.53)
EAIR Diff (95% CI): SG + Pembro vs		0.11 (−0.03, 0.25)	0.12 (0.01, 0.24)	
Participants with AEs leading to any study drug interruption	171 (77.4%)	162 (73.6%)	598 (62.1%)	1214 (60.7%)
PYE	62.2	62.5	276.6	500.2
EAIR (95% CI)	2.75 (2.35, 3.19)	2.59 (2.21, 3.02)	2.16 (1.99, 2.34)	2.43 (2.29, 2.57)
EAIR Diff (95% CI): SG + Pembro vs		0.16 (−0.43, 0.75)	0.59 (0.15, 1.06)	
Participants with AEs leading to SG/TPC dose reduction	78 (35.3%)	96 (43.6%)	249/801 (31.1%)	532/1597 (33.3%)
PYE	125.6	102.6	341.0	544.0
EAIR (95% CI)	0.62 (0.49, 0.78)	0.94 (0.76, 1.14)	0.73 (0.64, 0.83)	0.98 (0.90, 1.06)
EAIR Diff (95% CI): SG + Pembro vs		−0.31 (−0.56, −0.08)	−0.11 (−0.27, 0.07)	
Participants with AEs leading to any study drug withdrawal/discontinuation	26 (11.8%)	68 (30.9%)	45 (4.7%)	177 (8.9%)
PYE	178.4	128.9	569.8	1007.0
EAIR (95% CI)	0.15 (0.10, 0.21)	0.53 (0.41, 0.67)	0.08 (0.06, 0.11)	0.18 (0.15, 0.20)
EAIR Diff (95% CI): SG + Pembro vs		−0.38 (−0.53, −0.25)	0.07 (0.01, 0.14)	
Participants with AEs leading to death	7 (3.2%)	6 (2.7%)	15 (1.6%)	63 (3.2%)
PYE	187.3	159.2	571.4	1008.3
EAIR (95% CI)	0.04 (0.02, 0.08)	0.04 (0.01, 0.08)	0.03 (0.01, 0.04)	0.06 (0.05, 0.08)
EAIR Diff (95% CI): SG + Pembro vs		0.00 (−0.05, 0.05)	0.01 (−0.02, 0.05)	
Participants with treatment-related AEs leading to death	3 (1.4%)	1 (0.5%)	7 (0.7%)	28 (1.4%)
PYE	187.1	158.7	571.2	1007.0
EAIR (95% CI)	0.02 (0.00, 0.05)	0.01 (0.00, 0.04)	0.01 (0.00, 0.03)	0.03 (0.02, 0.04)
EAIR Diff (95% CI): SG + Pembro vs		0.01 (−0.02, 0.04)	0.00 (−0.01, 0.04)	

AE = adverse event; CI = confidence interval; Diff = difference; EAIR = exposure-adjusted incidence rate; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; Pembro = pembrolizumab; PYE = patient-years of exposure; SAE = serious adverse event; SG = sacituzumab govitecan; TPC = treatment of physician's choice
EAIR is defined as the number of participants with a specific event divided by the total exposure time (in years) in each group (ie, PYE: patient-years of exposure).
For participants with events, exposure time was calculated from first dose date up to onset date of the first event.
For participants without events, exposure time was calculated from first dose date up to data cutoff date (if on study drug)/last dose date (if discontinued study drug), or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.
For each event, total exposure time is the sum of exposure time for all participants in each group.
Poisson distribution with exact method was applied to compute the 95% CI of EAIR.
The method of variance estimates recovery was used to compute the 95% CI of the difference between 2 EAIRs.
Dose reduction due to AE was not collected in IMMU-132-01 so participants of this study were excluded from summary of AEs leading to dose reduction.
Source: ISS (Expanded), Adhoc 202349 Table 2

Common adverse events

The most common AEs by Preferred Term (incidence rate ≥ 10%) are presented in the below table.

Table 59 Adverse Events in ≥ 10% of Participants by Preferred Term (Study GS-US-592-6173 ISS Populations [Expanded])

Preferred Term	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Number (%) of participants with any AEs	220 (99.5%)	219 (99.5%)	960 (99.7%)	1991 (99.6%)

Preferred Term	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Diarrhoea	155 (70.1%)	63 (28.6%)	577 (59.9%)	1192 (59.6%)
Nausea	150 (67.9%)	83 (37.7%)	598 (62.1%)	1139 (57.0%)
Neutropenia	139 (62.9%)	130 (59.1%)	648 (67.3%)	1122 (56.1%)
Fatigue	129 (58.4%)	123 (55.9%)	553 (57.4%)	1165 (58.3%)
Alopecia	114 (51.6%)	71 (32.3%)	465 (48.3%)	907 (45.4%)
Constipation	90 (40.7%)	76 (34.5%)	353 (36.7%)	692 (34.6%)
Anaemia	81 (36.7%)	112 (50.9%)	386 (40.1%)	850 (42.5%)
Vomiting	65 (29.4%)	31 (14.1%)	301 (31.3%)	593 (29.7%)
Headache	55 (24.9%)	38 (17.3%)	176 (18.3%)	261 (13.1%)
Rash	47 (21.3%)	44 (20.0%)	123 (12.8%)	229 (11.5%)
Alanine aminotransferase increased	44 (19.9%)	66 (30.0%)	136 (14.1%)	222 (11.1%)
Leukopenia	42 (19.0%)	46 (20.9%)	188 (19.5%)	376 (18.8%)
Decreased appetite	39 (17.6%)	31 (14.1%)	224 (23.3%)	550 (27.5%)
Cough	38 (17.2%)	41 (18.6%)	179 (18.6%)	320 (16.0%)
Aspartate aminotransferase increased	35 (15.8%)	56 (25.5%)	137 (14.2%)	202 (10.1%)
Upper respiratory tract infection	32 (14.5%)	23 (10.5%)	103 (10.7%)	160 (8.0%)
Abdominal pain	31 (14.0%)	15 (6.8%)	179 (18.6%)	356 (17.8%)
Pruritus	31 (14.0%)	27 (12.3%)	110 (11.4%)	223 (11.2%)
Urinary tract infection	31 (14.0%)	32 (14.5%)	116 (12.0%)	238 (11.9%)
Stomatitis	30 (13.6%)	24 (10.9%)	102 (10.6%)	194 (9.7%)
Pyrexia	26 (11.8%)	26 (11.8%)	132 (13.7%)	304 (15.2%)
Arthralgia	25 (11.3%)	40 (18.2%)	134 (13.9%)	243 (12.2%)
Dizziness	24 (10.9%)	17 (7.7%)	108 (11.2%)	197 (9.9%)
Myalgia	23 (10.4%)	20 (9.1%)	56 (5.8%)	99 (5.0%)
Abdominal pain upper	22 (10.0%)	15 (6.8%)	75 (7.8%)	116 (5.8%)
COVID-19	22 (10.0%)	15 (6.8%)	33 (3.4%)	108 (5.4%)
Weight decreased	22 (10.0%)	11 (5.0%)	80 (8.3%)	198 (9.9%)
Hypokalaemia	21 (9.5%)	17 (7.7%)	128 (13.3%)	252 (12.6%)
Back pain	20 (9.0%)	29 (13.2%)	138 (14.3%)	269 (13.5%)
Blood alkaline phosphatase increased	20 (9.0%)	16 (7.3%)	103 (10.7%)	169 (8.5%)
Lymphopenia	20 (9.0%)	20 (9.1%)	108 (11.2%)	185 (9.3%)
Oedema peripheral	20 (9.0%)	27 (12.3%)	89 (9.2%)	197 (9.9%)
Dyspnoea	19 (8.6%)	21 (9.5%)	175 (18.2%)	354 (17.7%)
Hypothyroidism	15 (6.8%)	35 (15.9%)	5 (0.5%)	10 (0.5%)
Neuropathy peripheral	15 (6.8%)	46 (20.9%)	47 (4.9%)	87 (4.4%)
Hypomagnesaemia	13 (5.9%)	18 (8.2%)	97 (10.1%)	208 (10.4%)
Thrombocytopenia	10 (4.5%)	63 (28.6%)	71 (7.4%)	149 (7.5%)
Peripheral sensory neuropathy	7 (3.2%)	24 (10.9%)	28 (2.9%)	49 (2.5%)

AE = adverse event; COVID-19 = coronavirus disease 2019; ISS = Integrated Summary of Safety; LLT = lower level term; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; PT = preferred term; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Treatment-emergent adverse events (TEAEs) are any AEs that started on or after the first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

MedDRA Version 27.1 used for coding.

Multiple AEs are counted only once per participant for each PT.
PTs were presented by descending order of frequency in the GS-US-592-6173 SG + Pembro treatment group.
The following terms are mapped: Neutrophil count decreased → Neutropenia; White blood cell count decreased → Leukopenia; Lymphocyte count decreased → Lymphopenia; Haemoglobin decreased → Anaemia; Red blood cell count decreased → Anaemia; Platelet count decreased → Thrombocytopenia; Asthenia → Fatigue; Typhlitis (LLT) → Neutropenia colitis; Dyspnoea exertional → Dyspnoea.

Treatment-related adverse events

Table 60 Treatment-Related Adverse Events Reported in ≥ 10% of Participants by Preferred Term (Study GS-US-592-6173 ISS Populations [Expanded])

	GS-US-592-6173 SG + Pembro (N = 221)			GS-US-592-6173 TPC + Pembro (N = 220)				
Preferred Term	**SG Related**	**Pembro Related**	**SG and Pembro Related**	**TPC Related**	**Pembro Related**	**TPC and Pembro Related**	**Overall mBC (N = 963)**	**All Treated (Expanded) SG (10 mg/kg) (N = 1999)**
Number (%) of participants with treatment-related AEs	218 (98.6)	172 (77.8)	162 (73.3)	214 (97.3)	186 (84.5)	163 (74.1)	942 (97.8)	1937 (96.9)
Nausea	145 (65.6)	51 (23.1)	51 (23.1)	68 (30.9)	28 (12.7)	25 (11.4)	557 (57.8)	1051 (52.6)
Diarrhoea	143 (64.7)	61 (27.6)	59 (26.7)	40 (18.2)	23 (10.5)	18 (8.2)	527 (54.7)	1093 (54.7)
Neutropenia	136 (61.5)	49 (22.2)	48 (21.7)	128 (58.2)	48 (21.8)	48 (21.8)	644 (66.9)	1113 (55.7)
Fatigue	123 (55.7)	74 (33.5)	74 (33.5)	110 (50.0)	68 (30.9)	64 (29.1)	498 (51.7)	1032 (51.6)
Alopecia	112 (50.7)	28 (12.7)	28 (12.7)	70 (31.8)	10 (4.5)	10 (4.5)	453 (47.0)	877 (43.9)
Anaemia	75 (33.9)	28 (12.7)	27 (12.2)	95 (43.2)	30 (13.6)	29 (13.2)	348 (36.1)	734 (36.7)
Vomiting	58 (26.2)	16 (7.2)	16 (7.2)	23 (10.5)	9 (4.1)	8 (3.6)	257 (26.7)	507 (25.4)
Constipation	55 (24.9)	29 (13.1)	28 (12.7)	48 (21.8)	28 (12.7)	25 (11.4)	194 (20.1)	347 (17.4)
Leukopenia	39 (17.6)	16 (7.2)	16 (7.2)	44 (20.0)	23 (10.5)	23 (10.5)	184 (19.1)	371 (18.6)
Alanine aminotransferase increased	33 (14.9)	24 (10.9)	20 (9.0)	47 (21.4)	48 (21.8)	35 (15.9)	79 (8.2)	130 (6.5)
Decreased appetite	32 (14.5)	16 (7.2)	16 (7.2)	21 (9.5)	13 (5.9)	10 (4.5)	178 (18.5)	446 (22.3)
Headache	30 (13.6)	13 (5.9)	13 (5.9)	13 (5.9)	6 (2.7)	5 (2.3)	82 (8.5)	110 (5.5)
Stomatitis	28 (12.7)	14 (6.3)	13 (5.9)	22 (10.0)	8 (3.6)	6 (2.7)	94 (9.8)	175 (8.8)
Rash	27 (12.2)	26 (11.8)	13 (5.9)	25 (11.4)	29 (13.2)	17 (7.7)	88 (9.1)	172 (8.6)

	GS-US-592-6173 SG + Pembro (N = 221)			GS-US-592-6173 TPC + Pembro (N = 220)				
Preferred Term	**SG Related**	**Pembro Related**	**SG and Pembro Related**	**TPC Related**	**Pembro Related**	**TPC and Pembro Related**	**Overall mBC (N = 963)**	**All Treated (Expanded) SG (10 mg/kg) (N = 1999)**
Aspartate aminotransferase increased	25 (11.3)	17 (7.7)	14 (6.3)	38 (17.3)	39 (17.7)	27 (12.3)	71 (7.4)	106 (5.3)
Abdominal pain	23 (10.4)	6 (2.7)	6 (2.7)	4 (1.8)	1 (0.5)	0	109 (11.3)	195 (9.8)
Lymphopenia	19 (8.6)	14 (6.3)	14 (6.3)	17 (7.7)	11 (5.0)	10 (4.5)	101 (10.5)	166 (8.3)
Neuropathy peripheral	13 (5.9)	2 (0.9)	2 (0.9)	42 (19.1)	4 (1.8)	3 (1.4)	30 (3.1)	56 (2.8)
Thrombocytopenia	9 (4.1)	4 (1.8)	4 (1.8)	63 (28.6)	24 (10.9)	24 (10.9)	64 (6.6)	136 (6.8)
Peripheral sensory neuropathy	5 (2.3)	2 (0.9)	2 (0.9)	23 (10.5)	3 (1.4)	3 (1.4)	19 (2.0)	33 (1.7)
Hypothyroidism	2 (0.9)	13 (5.9)	1 (0.5)	3 (1.4)	32 (14.5)	1 (0.5)	0	2 (0.1)

AE = adverse event; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; PT = preferred term; SG = sacituzumab govitecan; TPC = treatment of physician's choice
Treatment-emergent adverse events (TEAEs) are any AEs that started on or after the first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.
MedDRA Version 27.1 was used for coding.
PTs sorted by descending order of frequency in the SG Related column.
SG and Pembro related means related to both SG and Pembro; TPC and Pembro related means related to both TPC and Pembro.
The following terms are mapped: Neutrophil count decreased → Neutropenia; White blood cell count decreased → Leukopenia; Lymphocyte count decreased → Lymphopenia; Haemoglobin decreased → Anaemia; Red blood cell count decreased → Anaemia; Platelet count decreased → Thrombocytopenia; Asthenia → Fatigue.

Severe adverse events

The most common severe (CTCAE Grade 3 or higher) AEs by Preferred Term (incidence rate ≥ 5%) are presented in the below table.

Table 61 Grade 3 or Higher Adverse Events Reported in ≥ 5% of Participants by Preferred Term (Study GS-US-592-6173 ISS Populations [Expanded])

Preferred Term	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Number (%) of participants with any Grade 3 or higher AEs	158 (71.5%)	154 (70.0%)	687 (71.3%)	1465 (73.3%)
Neutropenia	95 (43.0%)	98 (44.5%)	468 (48.6%)	808 (40.4%)
Diarrhoea	22 (10.0%)	5 (2.3%)	96 (10.0%)	224 (11.2%)
Fatigue	18 (8.1%)	7 (3.2%)	56 (5.8%)	181 (9.1%)
Febrile neutropenia	17 (7.7%)	4 (1.8%)	54 (5.6%)	142 (7.1%)
Anaemia	16 (7.2%)	35 (15.9%)	74 (7.7%)	210 (10.5%)
Alanine aminotransferase increased	8 (3.6%)	13 (5.9%)	17 (1.8%)	29 (1.5%)
Leukopenia	7 (3.2%)	19 (8.6%)	92 (9.6%)	192 (9.6%)
Thrombocytopenia	1 (0.5%)	30 (13.6%)	12 (1.2%)	26 (1.3%)

AE = adverse event; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; PT = preferred term; SG = sacituzumab govitecan; TPC = treatment of physician's choice
Treatment-emergent adverse events (TEAEs) are any AEs that started on or after the first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.
MedDRA Version 27.1 was used for coding.
Multiple AEs are counted only once per participant for each PT.
PTs were presented by descending order of frequency in the GS-US-592-6173 SG + Pembro treatment group.
The following terms are mapped: Neutrophil count decreased → Neutropenia; White blood cell count decreased → Leukopenia; Haemoglobin decreased → Anaemia; Red blood cell count decreased → Anaemia; Platelet count decreased → Thrombocytopenia; Asthenia → Fatigue.

Adverse Drug Reactions (ADR) in the SmPC

Section 4.8 of the SmPC is updated to include the GS-US-592-6173 (ASCENT-04) study population of patients with unresectable locally advanced or metastatic triple-negative breast cancer who have not received prior systemic therapy for metastatic disease and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10, receiving SG in combination with pembrolizumab.

Table 62 List of adverse reactions

System organ class (SOC) and Frequency	Monotherapy	In combination with pembrolizumab
Infections and infestations		
Very common	Urinary tract infection Upper respiratory tract infection	Urinary tract infection Upper respiratory tract infection
Common	Sepsis Pneumonia	Sepsis Pneumonia

	Influenza Bronchitis Nasopharyngitis Sinusitis Oral herpes	Influenza Bronchitis Nasopharyngitis Sinusitis Oral herpes
Blood and lymphatic system disorders		
Very common	Neutropenia[1] Anaemia[2] Leukopenia[3] Lymphopenia[4]	Neutropenia[1] Anaemia[2] Leukopenia[3]
Common	Febrile neutropenia Thrombocytopenia[5]	Febrile neutropenia Lymphopenia[4] Thrombocytopenia[5]
Immune system disorders		
Very common	Hypersensitivity[6]	Hypersensitivity[6]
Metabolism and nutrition disorders		
Very common	Decreased appetite Hypokalaemia Hypomagnesaemia	Decreased appetite
Common	Dehydration Hyperglycaemia Hypophosphataemia Hypocalcaemia Hyponatraemia	Dehydration Hyperglycaemia Hypokalaemia Hypomagnesaemia Hypophosphataemia Hypocalcaemia Hyponatraemia
Psychiatric disorders		
Very common	Insomnia	
Common	Anxiety	Insomnia Anxiety
Nervous system disorders		
Very common	Headache Dizziness	Headache Dizziness
Common	Dysgeusia	Dysgeusia
Vascular disorders		
Common	Hypotension	Hypotension
Respiratory, thoracic and mediastinal disorders		
Very common	Dyspnoea[7] Cough	Cough

Common	Epistaxis Productive cough Rhinorrhoea Nasal congestion Upper airway cough syndrome	Dyspnoea[7] Epistaxis Productive cough Rhinorrhoea Nasal congestion
Uncommon		Upper airway cough syndrome
Gastrointestinal disorders		
Very common	Diarrhoea Vomiting Nausea Constipation Abdominal Pain	Diarrhoea Vomiting Constipation Stomatitis Nausea Abdominal Pain
Common	Neutropenic colitis[8] Colitis Stomatitis Abdominal pain upper Dyspepsia Gastrooesophageal reflux disease Abdominal distension	Colitis Abdominal pain upper Dyspepsia Gastrooesophageal reflux disease Abdominal distension
Uncommon	Enteritis	Neutropenic colitis[8] Enteritis
Skin and subcutaneous tissue disorders		
Very common	Alopecia Rash Pruritus	Alopecia Rash Pruritus
Common	Rash maculopapular Skin hyperpigmentation Dermatitis acneiform Dry skin	Rash maculopapular Skin hyperpigmentation Dermatitis acneiform Dry skin
Musculoskeletal and connective tissue disorders		
Very common	Back pain Arthralgia	Back pain Arthralgia
Common	Musculoskeletal chest pain Muscle spasms	Musculoskeletal chest pain Muscle spasms
Renal and urinary disorders		
Common	Haematuria Proteinuria Dysuria	Haematuria Proteinuria Dysuria

General disorders and administration site conditions		
Very common	Fatigue[9]	Fatigue[9]
Common	Pain Chills	Pain Chills
Investigations		
Very common		Weight decreased Blood alkaline phosphatase increased
Common	Weight decreased Blood alkaline phosphatase increased Activated partial thromboplastin time prolonged Blood lactate dehydrogenase increased	Blood lactate dehydrogenase increased
Injury, poisoning and procedural complications		
Common		Infusion related reaction
Uncommon	Infusion related reaction	

1: Includes the following preferred terms: neutropenia; neutrophil count decreased.
2: Includes the following preferred terms: anaemia; haemoglobin decreased; red blood cell count decreased.
3: Includes the following preferred terms: leukopenia; white blood cell count decreased.
4: Includes the following preferred terms: lymphopenia; lymphocyte count decreased.
5: Includes the following preferred terms: thrombocytopenia; platelet count decreased.
6: Hypersensitivity events reported up to the end of the day after treatment was administered. Includes events coded to the following preferred terms: rash, infusion related reaction, hypersensitivity, periorbital oedema, catheter site dermatitis, contrast media reaction, dermatitis allergic, dermatitis contact, eczema, rash erythematous, urticaria, anaphylactic reaction, bronchospasm, conjunctivitis allergic, dermatitis, dermatitis acneiform, dermatitis exfoliative generalised, drug hypersensitivity, infusion related hypersensitivity reaction, rash macular, rash maculo-papular, rash papular, rash pustular, rhinitis allergic, swelling face, swelling of eyelid, swollen tongue, Type IV hypersensitivity reaction, cough with pruritus, cough with rash, dyspnoea with pruritus, dyspnoea with rash, dyspnoea with wheezing and rash, hypotension with dyspnoea
7: Includes the following preferred terms: dyspnoea; dyspnoea exertional
8: Includes the preferred term of neutropenic colitis and events reported as typhlitis
9: Includes the following preferred terms: fatigue, asthenia

Serious adverse event/deaths/other significant events

Serious adverse events

The most common serious AEs by Preferred Term (incidence rate ≥ 1%) are shown in the below table.

Table 63 Serious Adverse Events in ≥ 1% of the Participants by Preferred Term (Study GS-US-592-6173 ISS Populations [Expanded])

Preferred Term	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Number (%) of Participants with Any Treatment-Emergent Serious Adverse Events	84 (38.0%)	68 (30.9%)	266 (27.6%)	763 (38.2%)
Febrile neutropenia	15 (6.8%)	4 (1.8%)	43 (4.5%)	119 (6.0%)
Neutropenia	13 (5.9%)	11 (5.0%)	28 (2.9%)	73 (3.7%)
Diarrhoea	6 (2.7%)	3 (1.4%)	36 (3.7%)	99 (5.0%)
Colitis	5 (2.3%)	0	6 (0.6%)	14 (0.7%)

Preferred Term	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Fatigue	5 (2.3%)	0	5 (0.5%)	19 (1.0%)
Pneumonia	4 (1.8%)	2 (0.9%)	20 (2.1%)	50 (2.5%)
Pneumonitis	3 (1.4%)	2 (0.9%)	1 (0.1%)	3 (0.2%)
Pyrexia	3 (1.4%)	2 (0.9%)	9 (0.9%)	29 (1.5%)
Sepsis	3 (1.4%)	4 (1.8%)	10 (1.0%)	35 (1.8%)
Urinary tract infection	2 (0.9%)	2 (0.9%)	8 (0.8%)	33 (1.7%)
Acute kidney injury	1 (0.5%)	1 (0.5%)	5 (0.5%)	25 (1.3%)
Anaemia	1 (0.5%)	4 (1.8%)	8 (0.8%)	22 (1.1%)
Neutropenic colitis	1 (0.5%)	0	11 (1.1%)	26 (1.3%)
Pleural effusion	1 (0.5%)	1 (0.5%)	10 (1.0%)	17 (0.9%)
Thrombocytopenia	1 (0.5%)	7 (3.2%)	4 (0.4%)	8 (0.4%)
Vomiting	1 (0.5%)	3 (1.4%)	15 (1.6%)	31 (1.6%)
Abdominal pain	0	0	11 (1.1%)	23 (1.2%)
Dyspnoea	0	1 (0.5%)	11 (1.1%)	22 (1.1%)
Skin infection	0	3 (1.4%)	0	0

AE = adverse event; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; PT = preferred term; SAE = serious adverse event; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Treatment-emergent adverse events (TEAEs) are any AEs that started on or after the first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

MedDRA Version 27.1 was used for coding.

Multiple AEs were counted only once per participant for each PT.

PTs were presented by descending order of frequency in the GS-US-592-6173 SG + Pembro treatment group.

The following terms are mapped: Neutrophil count decreased → Neutropenia, Haemoglobin decreased → Anaemia; Red blood cell count decreased → Anaemia; Platelet count decreased → Thrombocytopenia; Asthenia → Fatigue; Typhlitis (LLT) → Neutropenia colitis; Dyspnoea exertional → Dyspnoea.

Deaths

A summary of deaths is presented in Table 64. Further details regarding participant deaths, as extracted from their narratives, are provided in Table 66.

Adverse events leading to death by System Organ Class and Preferred Term are shown in Table 71.

Table 64 Summary of Deaths (Study GS-US-592-6173 ISS Populations [Expanded])

	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
All Deaths	53 (24.0%)	61 (27.7%)	665 (69.1%)	1426 (71.3%)
Adverse Event	7 (3.2%)	8 (3.6%)	21 (2.2%)	73 (3.7%)
Progressive Disease	37 (16.7%)	49 (22.3%)	606 (62.9%)	1255 (62.8%)
Death reported during Long-term or Survival Follow-up, that is not due to Progressive Disease, and not related to study drug[a]	9 (4.1%)	4 (1.8%)	10 (1.0%)	24 (1.2%)

	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Other	0	0	27 (2.8%)	70 (3.5%)
Missing	0	0	1 (0.1%)	4 (0.2%)
Deaths within 30 Days of the last dose of study drug[a]	10 (4.5%)	7 (3.2%)	53 (5.5%)	165 (8.3%)
Adverse Event	6 (2.7%)	3 (1.4%)	15 (1.6%)	64 (3.2%)
Progressive Disease	4 (1.8%)	4 (1.8%)	37 (3.8%)	95 (4.8%)
Death reported during Long-term or Survival Follow-up, that is not due to Progressive Disease, and not related to study drug[a]	0	0	0	0
Other	0	0	1 (0.1%)	5 (0.3%)
Missing	0	0	0	1 (< 0.1%)
Deaths after 30 Days of the last dose of study drug[a]	43 (19.5%)	54 (24.5%)	612 (63.6%)	1261 (63.1%)
Adverse Event	1 (0.5%)	5 (2.3%)	6 (0.6%)	9 (0.5%)
Progressive Disease	33 (14.9%)	45 (20.5%)	569 (59.1%)	1160 (58.0%)
Death reported during Long-term or Survival Follow-up, that is not due to Progressive Disease, and not related to study drug[a]	9 (4.1%)	4 (1.8%)	10 (1.0%)	24 (1.2%)
Other	0	0	26 (2.7%)	65 (3.3%)
Missing	0	0	1 (0.1%)	3 (0.2%)
Deaths within 60 Days of the last dose of study drug[a]	14 (6.3%)	17 (7.7%)	119 (12.4%)	356 (17.8%)
Adverse Event	6 (2.7%)	6 (2.7%)	20 (2.1%)	70 (3.5%)
Progressive Disease	8 (3.6%)	11 (5.0%)	98 (10.2%)	271 (13.6%)
Death reported during Long-term or Survival Follow-up, that is not due to Progressive Disease, and not related to study drug[a]	0	0	0	1 (< 0.1%)
Other	0	0	1 (0.1%)	12 (0.6%)
Missing	0	0	0	2 (0.1%)
Deaths after 60 Days of the last dose of study drug[a]	39 (17.6%)	44 (20.0%)	546 (56.7%)	1070 (53.5%)
Adverse Event	1 (0.5%)	2 (0.9%)	1 (0.1%)	3 (0.2%)
Progressive Disease	29 (13.1%)	38 (17.3%)	508 (52.8%)	984 (49.2%)
Death reported during Long-term or Survival Follow-up, that is not due to Progressive Disease, and not related to study drug[a]	9 (4.1%)	4 (1.8%)	10 (1.0%)	23 (1.2%)
Other	0	0	26 (2.7%)	58 (2.9%)
Missing	0	0	1 (0.1%)	2 (0.1%)
Deaths within 90 Days of the last dose of study drug[a]	22 (10.0%)	19 (8.6%)	174 (18.1%)	515 (25.8%)
Adverse Event	7 (3.2%)	7 (3.2%)	21 (2.2%)	71 (3.6%)
Progressive Disease	15 (6.8%)	12 (5.5%)	150 (15.6%)	424 (21.2%)

	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Death reported during Long-term or Survival Follow-up, that is not due to Progressive Disease, and not related to study drug[a]	0	0	2 (0.2%)	5 (0.3%)
Other	0	0	1 (0.1%)	13 (0.7%)
Missing	0	0	0	2 (0.1%)
Deaths after 90 Days of the last dose of study drug[a]	31 (14.0%)	42 (19.1%)	491 (51.0%)	911 (45.6%)
Adverse Event	0	1 (0.5%)	0	2 (0.1%)
Progressive Disease	22 (10.0%)	37 (16.8%)	456 (47.4%)	831 (41.6%)
Death reported during Long-term or Survival Follow-up, that is not due to Progressive Disease, and not related to study drug[a]	9 (4.1%)	4 (1.8%)	8 (0.8%)	19 (1.0%)
Other	0	0	26 (2.7%)	57 (2.9%)
Missing	0	0	1 (0.1%)	2 (0.1%)

ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; Pembro = pembrolizumab; SG = sacituzumab govitecan; TPC = treatment of physician's choice

[a] For the GS-US-592-6173 TPC + pembro group, study drug refers to the drug taken in the randomized phase.

Percentages are based on the total number of participants in the corresponding column.

Adverse events leading to death included treatment-emergent and non–treatment-emergent events.

For the GS-US-592-6173 TPC + pembro group, deaths that occurred in the crossover phase are included.

Table 65 Adverse Events Leading to Death by System Organ Class and Preferred Term (Study GS-US-592-6173 ISS Populations [Expanded])

System Organ Class Preferred Term	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Number (%) of Participants with Any Treatment-Emergent Adverse Events Leading to Death	7 (3.2%)	6 (2.7%)	15 (1.6%)	63 (3.2%)
Blood and lymphatic system disorders	0	0	0	2 (0.1%)
Febrile neutropenia	0	0	0	1 (< 0.1%)
Leukopenia	0	0	0	1 (< 0.1%)
Cardiac disorders	0	1 (0.5%)	1 (0.1%)	4 (0.2%)
Arrhythmia	0	0	1 (0.1%)	1 (< 0.1%)
Cardiac arrest	0	1 (0.5%)	0	1 (< 0.1%)
Cardiac failure	0	0	0	1 (< 0.1%)
Myocardial ischaemia	0	0	0	1 (< 0.1%)
Gastrointestinal disorders	0	1 (0.5%)	1 (0.1%)	3 (0.2%)
Haematemesis	0	0	0	1 (< 0.1%)
Large intestine perforation	0	1 (0.5%)	0	0
Neutropenic colitis	0	0	1 (0.1%)	2 (0.1%)

System Organ Class Preferred Term	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
General disorders and administration site conditions	2 (0.9%)	1 (0.5%)	0	2 (0.1%)
Death	2 (0.9%)	1 (0.5%)	0	2 (0.1%)
Hepatobiliary disorders	0	0	0	1 (< 0.1%)
Hepatobiliary disease	0	0	0	1 (< 0.1%)
Infections and infestations	3 (1.4%)	2 (0.9%)	8 (0.8%)	28 (1.4%)
Neutropenic sepsis	1 (0.5%)	0	0	4 (0.2%)
Pneumonia	1 (0.5%)	1 (0.5%)	2 (0.2%)	3 (0.2%)
Sepsis	1 (0.5%)	1 (0.5%)	3 (0.3%)	9 (0.5%)
COVID-19	0	0	0	1 (< 0.1%)
COVID-19 pneumonia	0	0	1 (0.1%)	1 (< 0.1%)
Enterocolitis infectious	0	0	0	1 (< 0.1%)
Pneumonia aspiration	0	0	0	1 (< 0.1%)
Pseudomonal sepsis	0	0	0	1 (< 0.1%)
Pulmonary sepsis	0	0	0	1 (< 0.1%)
Septic shock	0	0	2 (0.2%)	6 (0.3%)
Injury, poisoning and procedural complications	0	1 (0.5%)	0	0
Post procedural complication	0	1 (0.5%)	0	0
Metabolism and nutrition disorders	0	0	0	1 (< 0.1%)
Hypoglycaemia	0	0	0	1 (< 0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.1%)	2 (0.1%)
Metastases to central nervous system	0	0	0	1 (< 0.1%)
Metastases to spine	0	0	1 (0.1%)	1 (< 0.1%)
Nervous system disorders	0	0	1 (0.1%)	4 (0.2%)
Cerebral infarction	0	0	0	1 (< 0.1%)
Cerebrovascular accident	0	0	0	1 (< 0.1%)
Ischaemic stroke	0	0	0	1 (< 0.1%)
Nervous system disorder	0	0	1 (0.1%)	1 (< 0.1%)
Psychiatric disorders	1 (0.5%)	0	0	1 (< 0.1%)
Completed suicide	1 (0.5%)	0	0	1 (< 0.1%)
Renal and urinary disorders	0	0	0	1 (< 0.1%)
Acute kidney injury	0	0	0	1 (< 0.1%)
Respiratory, thoracic and mediastinal disorders	1 (0.5%)	0	3 (0.3%)	14 (0.7%)
Pulmonary embolism	1 (0.5%)	0	1 (0.1%)	2 (0.1%)
Acute respiratory distress syndrome	0	0	0	1 (< 0.1%)
Acute respiratory failure	0	0	1 (0.1%)	1 (< 0.1%)
Apnoea	0	0	0	1 (< 0.1%)
Epistaxis	0	0	0	1 (< 0.1%)
Hypoxia	0	0	0	1 (< 0.1%)

System Organ Class Preferred Term	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Respiratory distress	0	0	0	1 (< 0.1%)
Respiratory failure	0	0	1 (0.1%)	6 (0.3%)

AE = adverse event; COVID-19 = coronavirus disease 2019; ISS = Integrated Summary of Safety; LLT = lower level term; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TPC = treatment of physician's choice

Treatment-emergent adverse events (TEAEs) are any AEs that started on or after the first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

MedDRA Version 27.1 was used for coding.

Multiple AEs are counted only once per participant for each SOC and PT.

SOCs presented alphabetically and PTs within each SOC were presented by descending order of frequency in the GS-US-592-6173 SG + Pembro treatment group.

The following term is mapped: Typhlitis (LLT) to Neutropenia colitis.

Table 66 Details regarding patient deaths, as extracted from their narratives (Assessor`s Table based on information from document 5351-narratives.pdf, sorted by treatment group and participant ID)

Participant ID	Preferred Term (Verbatim)	Age	UGT1A1 genotype	TTO (Study Day)	Treatment Group	Treatment Group (Crossover Phase)	Investigator Relationship to SG / TPC	Investigator Relationship to Pembrolizumab	Investigator Relationship to SG (Crossover Phase)	Event Associated with Underlying Disease
[****]	Death (Death unknown cause)	75	*1/*1	246	SG+ Pembro	NA	Not related	Not related	NA	**Yes**
[****]	Completed suicide (Suicide)	63	*1/*28	96	SG+ Pembro	NA	Not related	Not related	NA	No
[****]	Death (The death of unknown cause)	73	Not available	190	SG+ Pembro	NA	Not related	Not related	NA	No
[****]	Neutropenic sepsis (Neutropenic sepsis)	62	Not available	14	SG+ Pembro	NA	**Related**	Not related	NA	No
[****]	Pneumonia (Pneumonia)	64	*1/*1	106	SG+ Pembro	NA	**Related**	Not related	NA	No
[****]	Pulmonary embolism (Possible pulmonary embolism)	74	*1/*28	168	SG+ Pembro	NA	**Related**	**Related**	NA	No
[****]	Sepsis (Sepsis)	72	*1/*28	15	SG+ Pembro	NA	Not related	Not related	NA	No
[****]	Death (Unknown cause of death)	71	*1/*1	447	TPC+ Pembro	NA	Not related	Not related	NA	No
[****]	Post procedural complication (Superior vena cava lesion after catheter placement)	68	*1/*28	5	TPC+ Pembro	NA	Not related	Not related	NA	No
[****]	Cardiac arrest (Cardiac arrest)	82	*1/*1	107	TPC+ Pembro	NA	Not related	Not related	NA	No
[****]	Pneumonia (Pneumonia)	46	*28/*28	258	TPC+ Pembro	**SG**	Not related	Not related	**Related**	No
[****]	Sepsis (Sepsis)	76	*1/*1	147	TPC+ Pembro	NA	Not related	Not stated	NA	No
[****]	Sepsis (Sepsis)	47	Not available	207	TPC+ Pembro	**SG**	Not related (TPC)	Not related	**Related**	No
[****]	Pneumonia (Pneumonia)	67	*1/*28	209	TPC+ Pembro	NA	**Related**	Not related	NA	No
[****]	Large intestine perforation (Colonic perforation)	79	*1/*28	158	TPC+ Pembro	NA	Not related	Not related	NA	No

NA: Not Applicable, SG: Sacituzumab Govitecan TPC, Treatment of Physician's Choice; TTO: Time to Outcome

Other significant events - Adverse Events of Special Interest

Adverse Events of Special Interest for SG

AESIs for SG (Table 67) include serious infections secondary to neutropenia (Table 68), severe diarrhoea (Table 69), hypersensitivity (Table 70), and neutropenia (Table 71).

Table 67 Adverse Events of Special Interest For SG: Overall Summary (Study GS-US-592-6173 ISS Populations [Expanded])

AESI	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Serious infections secondary to neutropenia	6 (2.7%)	3 (1.4%)	28 (2.9%)	73 (3.7%)
Severe diarrhea	22 (10.0%)	5 (2.3%)	96 (10.0%)	224 (11.2%)
Hypersensitivity	43 (19.5%)	51 (23.2%)	123 (12.8%)	237 (11.9%)
Neutropenia	143 (64.7%)	132 (60.0%)	663 (68.8%)	1185 (59.3%)

AE = adverse event; AESI = adverse event of special interest for sacituzumab govitecan; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; PT = preferred term; SAE = serious adverse event; SG = sacituzumab govitecan; SMQ = standardised MedDRA query; SOC = system organ class; TPC = treatment of physician's choice

Treatment-emergent adverse events (TEAEs) are any AEs that started on or after the first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Adverse events were coded according to MedDRA Version 27.1.

AESI of SG has neutropenia (PT of neutropenia, neutrophil count decreased, febrile neutropenia); Serious infections secondary to neutropenia (SAEs from SOC of Infections and Infestations that occurred within 11 days of the AESI of neutropenia); Severe diarrhea (PT of diarrhoea with Grade ≥ 3); and Hypersensitivity, which is a grouped AE term that occurred within 1 day after study drug administration, including Hypersensitivity SMQ (narrow only) and Anaphylactic Reaction SMQ (broad and narrow) Category A or (B and C) or (D and [B or C]) in the same window.

Serious infections secondary to neutropenia

Table 68 Adverse Event of Special Interest for SG: Serious Infections Secondary to Neutropenia (Study GS-US-592-6173 ISS Populations [Expanded])

Number (%) of Participants With Any	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
AESI: Serious Infections Secondary to Neutropenia				
AEs	6 (2.7%)	3 (1.4%)	28 (2.9%)	73 (3.7%)
Grade 3 or higher	5 (2.3%)	3 (1.4%)	27 (2.8%)	71 (3.6%)
Treatment-related AEs	1 (0.5%)	2 (0.9%)	15 (1.6%)	46 (2.3%)
AEs leading to SG/TPC dose reduction	0	1 (0.5%)	3/801 (0.4%)	7/1597 (0.4%)
AEs leading to any study drug interruption	2 (0.9%)	1 (0.5%)	11 (1.1%)	32 (1.6%)
AEs leading to any study drug withdrawal/discontinuation	1 (0.5%)	0	2 (0.2%)	8 (0.4%)
AEs leading to death	2 (0.9%)	1 (0.5%)	1 (0.1%)	11 (0.6%)
Treatment-related AEs leading to death	1 (0.5%)	0	1 (0.1%)	10 (0.5%)

AE = adverse event; AESI = adverse event of special interest for sacituzumab govitecan; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TPC = treatment of physician's choice
Treatment-emergent adverse events (TEAEs) are any AEs that started on or after the first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.
Adverse events were coded according to MedDRA Version 27.1.
AESI of neutropenia (PT of neutropenia, neutrophil count decreased, febrile neutropenia); Serious infections secondary to neutropenia (SAEs from SOC of Infections and Infestations that occurred within 11 days of the AESI of neutropenia).

Severe diarrhoea

Table 69 Adverse Event of Special Interest for SG: Severe Diarrhea (Study GS-US-592-6173 ISS Populations [Expanded])

Number (%) of Participants With Any	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
AESI: Severe Diarrhea				
AEs	22 (10.0%)	5 (2.3%)	96 (10.0%)	224 (11.2%)
Treatment-related AEs	19 (8.6%)	3 (1.4%)	87 (9.0%)	206 (10.3%)
SAEs	6 (2.7%)	3 (1.4%)	30 (3.1%)	86 (4.3%)
AEs leading to SG/TPC dose reduction	9 (4.1%)	0	28/801 (3.5%)	72/1597 (4.5%)
AEs leading to any study drug interruption	8 (3.6%)	3 (1.4%)	23 (2.4%)	51 (2.6%)
AEs leading to any study drug withdrawal/discontinuation	0	1 (0.5%)	3 (0.3%)	9 (0.5%)
AEs leading to death	0	0	0	0

AE = adverse event; AESI = adverse event of special interest for sacituzumab govitecan; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; PT = preferred term; SAE = serious adverse event; SG = sacituzumab govitecan; TPC = treatment of physician's choice
Treatment-emergent adverse events (TEAEs) are any AEs that started on or after the first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.
Adverse events were coded according to MedDRA Version 27.1.
AESI of severe diarrhea (PT of diarrhoea with Grade ≥ 3).

Hypersensitivity

Table 70 Adverse Event of Special Interest for SG: Hypersensitivity (Study GS-US-592-6173 ISS Populations [Expanded])

Number (%) of Participants With Any	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
AESI: Hypersensitivity				
AEs	43 (19.5%)	51 (23.2%)	123 (12.8%)	237 (11.9%)
Grade 3 or higher	4 (1.8%)	5 (2.3%)	5 (0.5%)	9 (0.5%)
Treatment-related AEs	33 (14.9%)	44 (20.0%)	86 (8.9%)	170 (8.5%)
SAEs	2 (0.9%)	2 (0.9%)	1 (0.1%)	5 (0.3%)
AEs leading to SG/TPC dose reduction	1 (0.5%)	1 (0.5%)	0/801	1/1597 (< 0.1%)

AEs leading to any study drug interruption	10 (4.5%)	5 (2.3%)	5 (0.5%)	19 (1.0%)
AEs leading to any study drug withdrawal/discontinuation	3 (1.4%)	12 (5.5%)	2 (0.2%)	7 (0.4%)
AEs leading to death	0	0	0	0

AE = adverse event; AESI = adverse event of special interest for sacituzumab govitecan; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; SAE = serious adverse event; SG = sacituzumab govitecan; SMQ = Standardised MedDRA Query; TPC = treatment of physician's choice

Treatment-emergent adverse events (TEAEs) are any AEs that started on or after the first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Adverse events were coded according to MedDRA Version 27.1.

AESI of hypersensitivity, which is a grouped AE term that occurred within 1 day after study drug administration, including Hypersensitivity SMQ (narrow only) and Anaphylactic Reaction SMQ (broad and narrow) Category A or (B and C) or (D and [B or C]) in the same window.

Neutropenia

Table 71 Adverse Event of Special Interest for SG: Neutropenia (Study GS-US-592-6173 ISS Populations [Expanded])

Number (%) of Participants With Any	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
AESI: Neutropenia				
AEs	143 (64.7%)	132 (60.0%)	663 (68.8%)	1185 (59.3%)
Grade 3 or higher	104 (47.1%)	100 (45.5%)	491 (51.0%)	893 (44.7%)
Treatment-related AEs	141 (63.8%)	130 (59.1%)	658 (68.3%)	1174 (58.7%)
Grade 3 or higher	104 (47.1%)	97 (44.1%)	487 (50.6%)	881 (44.1%)
SAEs	**28 (12.7%)**	**15 (6.8%)**	**70 (7.3%)**	187 (9.4%)
AEs leading to SG/TPC dose reduction	41 (18.6%)	39 (17.7%)	131/801 (16.4%)	241/1597 (15.1%)
AEs leading to any study drug interruption	106 (48.0%)	91 (41.4%)	429 (44.5%)	699 (35.0%)
AEs leading to any study drug withdrawal/discontinuation	2 (0.9%)	5 (2.3%)	4 (0.4%)	22 (1.1%)
AEs leading to death	0	0	0	1 (< 0.1%)
Treatment-related AEs leading to death	0	0	0	1 (< 0.1%)

AE = adverse event; AESI = adverse event of special interest for sacituzumab govitecan; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; PT = preferred term; SAE = serious adverse event; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Treatment-emergent adverse events (TEAEs) are any AEs that started on or after the first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Adverse events were coded according to MedDRA Version 27.1.

AESI of neutropenia (PT of neutropenia, neutrophil count decreased, febrile neutropenia).

Adverse Events of Special Interest for pembrolizumab

AEOSIs for pembrolizumab include immune-mediated AEs and infusion reactions (see below table).

Table 72 Overall Summary of Adverse Events of Special Interest for Pembrolizumab (Study GS-US-592-6173 ISS Populations [Expanded])

	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
AEOSI Pembrolizumab	67 (30.3%)	87 (39.5%)	76 (7.9%)	169 (8.5%)
Pneumonitis				
AEs	6 (2.7%)	17 (7.7%)	7 (0.7%)	17 (0.9%)
Grade 3 or higher	4 (1.8%)	3 (1.4%)	2 (0.2%)	3 (0.2%)
SAEs	5 (2.3%)	4 (1.8%)	1 (0.1%)	4 (0.2%)
AEs leading to any study drug withdrawal/discontinuation	4 (1.8%)	9 (4.1%)	4 (0.4%)	7 (0.4%)
AEs leading to SG/TPC dose reduction	0	0	1/801 (0.1%)	1/1597 (< 0.1%)
AEs leading to any study drug interruption	4 (1.8%)	9 (4.1%)	1 (0.1%)	6 (0.3%)
AEs leading to death	0	0	0	0
Colitis				
AEs	13 (5.9%)	3 (1.4%)	14 (1.5%)	35 (1.8%)
Grade 3 or higher	4 (1.8%)	1 (0.5%)	6 (0.6%)	19 (1.0%)
SAEs	5 (2.3%)	1 (0.5%)	6 (0.6%)	15 (0.8%)
AEs leading to any study drug withdrawal/discontinuation	1 (0.5%)	0	2 (0.2%)	4 (0.2%)
AEs leading to SG/TPC dose reduction	4 (1.8%)	1 (0.5%)	1/801 (0.1%)	2/1597 (0.1%)
AEs leading to any study drug interruption	6 (2.7%)	1 (0.5%)	2 (0.2%)	8 (0.4%)
AEs leading to death	0	0	0	0
Hepatitis				
AEs	1 (0.5%)	4 (1.8%)	0	2 (0.1%)
Grade 3 or higher	0	3 (1.4%)	0	0
SAEs	0	1 (0.5%)	0	0
AEs leading to any study drug withdrawal/discontinuation	0	2 (0.9%)	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	0	3 (1.4%)	0	0
AEs leading to death	0	0	0	0
Nephritis				
AEs	0	1 (0.5%)	0	1 (< 0.1%)
Grade 3 or higher	0	0	0	1 (< 0.1%)
SAEs	0	0	0	1 (< 0.1%)
AEs leading to any study drug withdrawal/discontinuation	0	0	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	0	1 (0.5%)	0	0

	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
AEs leading to death	0	0	0	0
Adrenal Insufficiency				
AEs	3 (1.4%)	4 (1.8%)	1 (0.1%)	5 (0.3%)
Grade 3 or higher	0	2 (0.9%)	1 (0.1%)	2 (0.1%)
SAEs	0	2 (0.9%)	1 (0.1%)	2 (0.1%)
AEs leading to any study drug withdrawal/discontinuation	0	1 (0.5%)	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	0	2 (0.9%)	0	0
AEs leading to death	0	0	0	0
Hypophysitis				
AEs	2 (0.9%)	2 (0.9%)	0	0
Grade 3 or higher	0	0	0	0
SAEs	0	0	0	0
AEs leading to any study drug withdrawal/discontinuation	1 (0.5%)	0	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	0	2 (0.9%)	0	0
AEs leading to death	0	0	0	0
Hyperthyroidism				
AEs	8 (3.6%)	14 (6.4%)	0	0
Grade 3 or higher	0	0	0	0
SAEs	0	0	0	0
AEs leading to any study drug withdrawal/discontinuation	0	0	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	0	3 (1.4%)	0	0
AEs leading to death	0	0	0	0
Hypothyroidism				
AEs	16 (7.2%)	35 (15.9%)	5 (0.5%)	10 (0.5%)
Grade 3 or higher	1 (0.5%)	0	0	0
SAEs	0	0	0	0
AEs leading to any study drug withdrawal/discontinuation	0	0	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	1 (0.5%)	1 (0.5%)	0	0
AEs leading to death	0	0	0	0
Thyroiditis				

	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
AEs	0	2 (0.9%)	0	0
Grade 3 or higher	0	0	0	0
SAEs	0	0	0	0
AEs leading to any study drug withdrawal/discontinuation	0	0	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	0	0	0	0
AEs leading to death	0	0	0	0
Type 1 Diabetes Mellitus				
AEs	1 (0.5%)	1 (0.5%)	0	1 (< 0.1%)
Grade 3 or higher	1 (0.5%)	1 (0.5%)	0	0
SAEs	1 (0.5%)	1 (0.5%)	0	0
AEs leading to any study drug withdrawal/discontinuation	0	0	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	0	0	0	0
AEs leading to death	0	0	0	0
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)				
AEs	6 (2.7%)	8 (3.6%)	12 (1.2%)	21 (1.1%)
Grade 3 or higher	3 (1.4%)	5 (2.3%)	10 (1.0%)	18 (0.9%)
SAEs	1 (0.5%)	1 (0.5%)	0	0
AEs leading to any study drug withdrawal/discontinuation	2 (0.9%)	2 (0.9%)	0	3 (0.2%)
AEs leading to SG/TPC dose reduction	0	0	2/801 (0.2%)	4/1597 (0.3%)
AEs leading to any study drug interruption	1 (0.5%)	1 (0.5%)	1 (0.1%)	3 (0.2%)
AEs leading to death	0	0	0	0
Pancreatitis				
AEs	0	4 (1.8%)	1 (0.1%)	2 (0.1%)
Grade 3 or higher	0	2 (0.9%)	1 (0.1%)	2 (0.1%)
SAEs	0	1 (0.5%)	1 (0.1%)	2 (0.1%)
AEs leading to any study drug withdrawal/discontinuation	0	2 (0.9%)	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	0	1 (0.5%)	0	0
AEs leading to death	0	0	0	0
Encephalitis				

	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
AEs	1 (0.5%)	0	0	0
Grade 3 or higher	1 (0.5%)	0	0	0
SAEs	0	0	0	0
AEs leading to any study drug withdrawal/discontinuation	0	0	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	0	0	0	0
AEs leading to death	0	0	0	0
Infusion Reactions				
AEs	11 (5.0%)	19 (8.6%)	28 (2.9%)	59 (3.0%)
Grade 3 or higher	3 (1.4%)	5 (2.3%)	1 (0.1%)	4 (0.2%)
SAEs	1 (0.5%)	2 (0.9%)	1 (0.1%)	5 (0.3%)
AEs leading to any study drug withdrawal/discontinuation	2 (0.9%)	9 (4.1%)	2 (0.2%)	5 (0.3%)
AEs leading to SG/TPC dose reduction	0	1 (0.5%)	0/801	1/1597 (< 0.1%)
AEs leading to any study drug interruption	6 (2.7%)	5 (2.3%)	6 (0.6%)	16 (0.8%)
AEs leading to death	0	0	0	0
Myelitis				
AEs	0	1 (0.5%)	0	0
Grade 3 or higher	0	1 (0.5%)	0	0
SAEs	0	1 (0.5%)	0	0
AEs leading to any study drug withdrawal/discontinuation	0	0	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	0	0	0	0
AEs leading to death	0	0	0	0
Gastritis				
AEs	10 (4.5%)	7 (3.2%)	10 (1.0%)	18 (0.9%)
Grade 3 or higher	0	0	2 (0.2%)	2 (0.1%)
SAEs	0	0	0	0
AEs leading to any study drug withdrawal/discontinuation	0	0	0	0
AEs leading to SG/TPC dose reduction	0	0	1/801 (0.1%)	1/1597 (< 0.1%)
AEs leading to any study drug interruption	0	1 (0.5%)	0	0
AEs leading to death	0	0	0	0
Exocrine Pancreatic Insufficiency				
AEs	0	1 (0.5%)	0	0
Grade 3 or higher AEs	0	0	0	0

	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
SAEs	0	0	0	0
AEs leading to any study drug withdrawal/discontinuation	0	0	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	0	0	0	0
AEs leading to death	0	0	0	0
Pericarditis				
AEs	1 (0.5%)	0	0	0
Grade 3 or higher	1 (0.5%)	0	0	0
SAEs	1 (0.5%)	0	0	0
AEs leading to any study drug withdrawal/discontinuation	1 (0.5%)	0	0	0
AEs leading to SG/TPC dose reduction	0	0	0/801	0/1597
AEs leading to any study drug interruption	1 (0.5%)	0	0	0
AEs leading to death	0	0	0	0

AE = adverse event; AEOSI = adverse event of special interest for pembrolizumab; CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; SAE = serious adverse event; SAP = statistical analysis plan; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice;

TEAEs are defined as any AEs that started on or after the first dose date up to and including 30 days (90 days for SAEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

Treatment-related includes 'Related', 'Likely Related', 'Possibly Related', and missing relation. AEs were coded according to MedDRA Version 27.1.

Severity grades were defined by CTCAE: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Life-Threatening; 5 = Death.

Categories of AEOSI for pembrolizumab were sorted as specified in SAP.

Dose reduction due to AE was not collected in IMMU-132-01 so participants of this study were excluded from summary of TEAE leading to dose reduction.

For the Study GS-US-592-6173 SG + Pembro and TPC + Pembro groups, the AEOSI categories of pembrolizumab are based on the definition in the GS-US-592-6173 SAP with the modification of excluding the Immune-mediated = "Yes" or "No" condition.

Laboratory findings

Grade 3 or 4 Laboratory Abnormalities (incidence rate ≥ 5%) are presented in the below table.

Table 73 Grade 3 or 4 Laboratory Abnormalities That Occurred in ≥ 5% of Participants in the SG + Pembro or TPC + Pembro Groups (Study GS-US-592-6173 ISS Populations [Expanded])

Maximum Postbaseline Toxicity Grade	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Participants with postbaseline value	219	220	954	1970
Grade 3 or 4	148 (67.6%)	146 (66.4%)	606 (63.5%)	1184 (60.1%)
Grade 3	86 (39.3%)	91 (41.4%)	368 (38.6%)	727 (36.9%)
Grade 4	62 (28.3%)	55 (25.0%)	238 (24.9%)	457 (23.2%)

Maximum Postbaseline Toxicity Grade	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Hematology				
Hemoglobin (anemia)	219	220	954	1966
Grade 3 or 4	21 (9.6%)	40 (18.2%)	73 (7.7%)	197 (10.0%)
Grade 3	21 (9.6%)	40 (18.2%)	73 (7.7%)	197 (10.0%)
Leukocytes (white blood cell decreased)	219	219	954	1966
Grade 3 or 4	70 (32.0%)	68 (31.1%)	327 (34.3%)	575 (29.2%)
Grade 3	52 (23.7%)	62 (28.3%)	248 (26.0%)	408 (20.8%)
Grade 4	18 (8.2%)	6 (2.7%)	79 (8.3%)	167 (8.5%)
Lymphocytes (lymphocyte count decreased)	219	219	950	1942
Grade 3 or 4	46 (21.0%)	41 (18.7%)	194 (20.4%)	456 (23.5%)
Grade 3	43 (19.6%)	36 (16.4%)	173 (18.2%)	397 (20.4%)
Grade 4	3 (1.4%)	5 (2.3%)	21 (2.2%)	59 (3.0%)
Neutrophils (neutrophil count decreased)	219	219	953	1962
Grade 3 or 4	109 (49.8%)	104 (47.5%)	444 (46.6%)	759 (38.7%)
Grade 3	58 (26.5%)	71 (32.4%)	274 (28.8%)	452 (23.0%)
Grade 4	51 (23.3%)	33 (15.1%)	170 (17.8%)	307 (15.6%)
Platelets (platelet count decreased)	219	220	954	1965
Grade 3 or 4	11 (5.0%)	38 (17.3%)	33 (3.5%)	68 (3.5%)
Grade 3	7 (3.2%)	16 (7.3%)	14 (1.5%)	27 (1.4%)
Grade 4	4 (1.8%)	22 (10.0%)	19 (2.0%)	41 (2.1%)
Chemistry				
Alanine aminotransferase (alanine aminotransferase increased)	218	220	953	1965
Grade 3 or 4	9 (4.1%)	18 (8.2%)	18 (1.9%)	25 (1.3%)
Grade 3	8 (3.7%)	17 (7.7%)	18 (1.9%)	25 (1.3%)
Grade 4	1 (0.5%)	1 (0.5%)	0	0
Magnesium (hypermagnesemia)	218	219	949	1962
Grade 3 or 4	12 (5.5%)	8 (3.7%)	18 (1.9%)	31 (1.6%)
Grade 3	12 (5.5%)	8 (3.7%)	16 (1.7%)	25 (1.3%)
Grade 4	0	0	2 (0.2%)	6 (0.3%)

CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; Pembro = pembrolizumab; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Severity grades were defined by the CTCAE Version 5.0.

For maximum postbaseline toxicity grade, the most severe graded abnormality from all tests was counted for each participant.

For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant.

A treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from baseline at any time postbaseline up to and including the date of last study drug dose plus 30 days or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1

observed within the time frame specified above will be considered treatment emergent. Percentages were based on participant with nonmissing postbaseline values within the treatment-emergent window.

Safety in special populations

Race

An overall summary of AEs by race is presented in the below table.

Table 74 Treatment-Emergent Adverse Events: Overall Summary by Race (Assessor's table)

Race	GS-US-592-6173 SG+ Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded SG (10 mg/kg) (N =1999)
Race: White	**139**	**117**	**692**	**1427**
Any AEs	138 (99.3%)	116 (99.1%)	689 (99.6%)	1420 (99.5%)
Grade 3 or higher	102 (73.4%)	74 (63.2%)	499 (72.1%)	1039 (72.8%)
SAEs	55 (39.6%)	40 (34.2%)	198 (28.6%)	551 (38.6%)
AEs Leading to Death	5 (3.6%)	4 (3.4%)	11 (1.6%)	47 (3.3%)
AEs Leading to Any Study Drug Withdrawal / Discontinuation	22 (15.8%)	38 (32.5%)	33 (4.8%)	123 (8.6%)
Race: Black or African American	**13**	**11**	**50**	**70**
Any AEs	13 (100.0%)	11 (100.0%)	50 (100.0%)	70 (100.0%)
Grade 3 or higher	11 (84.6%)	10 (90.9%)	37 (74.0%)	52 (74.3%)
SAEs	5 (38.5%)	6 (54.5%)	12 (24.0%)	22 (31.4%)
AEs Leading to Death	1 (7.7%)	0	0	1 (1.4%)
AEs Leading to Any Study Drug Withdrawal / Discontinuation	0	3 (27.3%)	1 (2.0%)	3 (4.3%)
Race: Asian	**43**	**62**	**92**	**212**
Any AEs	43 (100.0%)	62 (100.0%)	92 (100.0%)	211 (99.5%)
Grade 3 or higher	27 (62.8%)	45 (72.6%)	61 (66.3%)	164 (77.4%)
SAEs	14 (32.6%)	11 (17.7%)	17 (18.5%)	73 (34.4%)

Race	GS-US-592-6173 SG+ Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded SG (10 mg/kg) (N =1999)
AEs Leading to Death	0	0	1 (1.1%)	8 (3.8%)
AEs Leading to Any Study Drug Withdrawal / Discontinuation	4 (9.3%)	12 (19.4%)	5 (5.4%)	20 (9.4%)
Race: Other	**26**	**30**	**129**	**290**
Any AEs	26 (100.0%)	30 (100.0%)	129 (100.0%)	290 (100.0%)
Grade 3 or higher	18 (69.2%)	25 (83.3%)	90 (69.8%)	210 (72.4%)
SAEs	10 (38.5%)	11 (36.7%)	39 (30.2%)	117 (40.3%)
AEs Leading to Death	1 (3.8%)	2 (6.7%)	3 (2.3%)	7 (2.4%)
AEs Leading to Any Study Drug Withdrawal / Discontinuation	0	15 (50.0%)	6 (4.7%)	31 (10.7%)

Treatment-emergent adverse events (TEAEs) are any AEs that started on or after first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first. Adverse events were coded according to MedDRA Version 27.1.
Treatment-related includes 'Related', 'Likely Related', 'Possibly Related', and missing relation.
Severity grades were defined by CTCAE: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Life-Threatening; 5 = Death.
The subgroup 'Other' also includes participants whose race was not reported, not permitted or missing.
Dose reduction due to AE was not collected in IMMU-132-01 so participants of this study were excluded from summary of TEAE leading to dose reduction.

Age

An overall summary of AEs by age is presented in the below table.

Table 75 Treatment-Emergent Adverse Events: Overall Summary by Age Group (Assessor's table)

Age group	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
Age Group: < 50 years	**85**	**82**	**301**	**372**
Any AEs	84 (98.8%)	81 (98.8%)	299 (99.3%)	370 (99.5%)
Grade 3 or higher	61 (71.8%)	57 (69.5%)	209 (69.4%)	247 (66.4%)
SAEs	34 (40.0%)	25 (30.5%)	74 (24.6%)	93 (25.0%)
AEs Leading to Death	0	0	2 (0.7%)	2 (0.5%)
AEs Leading to Any Study Drug Withdrawal / Discontinuation	7 (8.2%)	24 (29.3%)	12 (4.0%)	15 (4.0%)
Age Group: 50-64 years	**78**	**82**	**447**	**837**
Any AEs	78 (100.0%)	82 (100.0%)	446 (99.8%)	835 (99.8%)
Grade 3 or higher	50 (64.1%)	54 (65.9%)	315 (70.5%)	593 (70.8%)
SAEs	22 (28.2%)	19 (23.2%)	116 (26.0%)	305 (36.4%)
AEs Leading to Death	3 (3.8%)	0	3 (0.7%)	20 (2.4%)
AEs Leading to Any Study Drug Withdrawal / Discontinuation	12 (15.4%)	26 (31.7%)	15 (3.4%)	55 (6.6%)
Age Group: < 65 years	**163**	**164**	**748**	**1209**
Any AEs	162 (99.4%)	163 (99.4%)	745 (99.6%)	1205 (99.7%)
Grade 3 or higher	111 (68.1%)	111 (67.7%)	524 (70.1%)	840 (69.5%)
SAEs	56 (34.4%)	44 (26.8%)	190 (25.4%)	398 (32.9%)

Age group	GS-US-592-6173 SG + Pembro (N = 221)	GS-US-592-6173 TPC + Pembro (N = 220)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
AEs Leading to Death	3 (1.8%)	0	5 (0.7%)	22 (1.8%)
AEs Leading to Any Study Drug Withdrawal / Discontinuation	19 (11.7%)	50 (30.5%)	27 (3.6%)	70 (5.8%)
Age Group: >= 65 years	**58**	**56**	**215**	**790**
Any AEs	58 (100.0%)	56 (100.0%)	215 (100.0%)	786 (99.5%)
Grade 3 or higher	47 (81.0%)	43 (76.8%)	163 (75.8%)	625 (79.1%)
SAEs	28 (48.3%)	24 (42.9%)	76 (35.3%)	365 (46.2%)
AEs Leading to Death	4 (6.9%)	6 (10.7%)	10 (4.7%)	41 (5.2%)
AEs Leading to Any Study Drug Withdrawal / Discontinuation	7 (12.1%)	18 (32.1%)	18 (8.4%)	107 (13.5%)
Age Group: 65-74 years	**46**	**46**	**167**	**558**
Any AEs	46 (100.0%)	46 (100.0%)	167 (100.0%)	555 (99.5%)
Grade 3 or higher	36 (78.3%)	34 (73.9%)	124 (74.3%)	429 (76.9%)
SAEs	19 (41.3%)	18 (39.1%)	51 (30.5%)	237 (42.5%)
AEs Leading to Death	3 (6.5%)	3 (6.5%)	8 (4.8%)	33 (5.9%)
AEs Leading to Any Study Drug Withdrawal / Discontinuation	7 (15.2%)	16 (34.8%)	10 (6.0%)	71 (12.7%)
Age Group: >= 75 years	**12**	**10**	**48**	**232**
Any AEs	12 (100.0%)	10 (100.0%)	48 (100.0%)	231 (99.6%)
Grade 3 or higher	11 (91.7%)	9 (90.0%)	39 (81.3%)	196 (84.5%)
SAEs	9 (75.0%)	6 (60.0%)	25 (52.1%)	128 (55.2%)
AEs Leading to Death	1 (8.3%)	3 (30.0%)	2 (4.2%)	8 (3.4%)
AEs Leading to Any Study Drug Withdrawal / Discontinuation	0	2 (20.0%)	8 (16.7%)	36 (15.5%)

Percentages are based on the total number of participants in the corresponding subgroup.
Treatment-emergent adverse events (TEAEs) are any AEs that started on or after first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first. Adverse events were coded according to MedDRA Version 27.1.
Treatment-related includes 'Related', 'Likely Related', 'Possibly Related', and missing relation.
Severity grades were defined by CTCAE: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Life-Threatening; 5 = Death.
Dose reduction due to AE was not collected in IMMU-132-01 so participants of this study were excluded from summary of TEAE leading to dose reduction.

UGT1A1 genotype

An overall summary of AEs by UGT1A1 genotype is presented in the below table.

Table 76 Overall Summary of Adverse Events by UGT1A1 Genotype in Participants Treated With SG (Study GS-US-592-6173 ISS Populations [Expanded])

Number (%) of Participants with Any	GS-US-592-6173 SG + Pembro (N = 221)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
UGT1A1 Genotype: *1/*1	**87**	**396**	**723**
AEs	86 (98.9%)	396 (100.0%)	722 (99.9%)
Grade 3 or higher	55 (63.2%)	266 (67.2%)	497 (68.7%)
Treatment-related AEs	85 (97.7%)	391 (98.7%)	706 (97.6%)

Number (%) of Participants with Any	GS-US-592-6173 SG + Pembro (N = 221)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
SAEs	26 (29.9%)	93 (23.5%)	243 (33.6%)
Treatment-related SAEs	18 (20.7%)	49 (12.4%)	130 (18.0%)
AEs leading to SG dose reduction	25 (28.7%)	86/327 (26.3%)	161/575 (28.0%)
AEs leading to any study drug interruption	61 (70.1%)	245 (61.9%)	425 (58.8%)
AEs leading to any study drug withdrawal/discontinuation	12 (13.8%)	16 (4.0%)	51 (7.1%)
Treatment-related AEs leading to any study drug withdrawal/discontinuation	11 (12.6%)	7 (1.8%)	32 (4.4%)
AEs leading to death	2 (2.3%)	4 (1.0%)	20 (2.8%)
Treatment-related AEs leading to death	1 (1.1%)	3 (0.8%)	8 (1.1%)
UGT1A1 Genotype: *1/*28	**93**	**375**	**701**
AEs	93 (100.0%)	372 (99.2%)	697 (99.4%)
Grade 3 or higher	75 (80.6%)	272 (72.5%)	517 (73.8%)
Treatment-related AEs	93 (100.0%)	362 (96.5%)	675 (96.3%)
SAEs	40 (43.0%)	106 (28.3%)	250 (35.7%)
Treatment-related SAEs	30 (32.3%)	62 (16.5%)	126 (18.0%)
AEs leading to SG dose reduction	39 (41.9%)	111/318 (34.9%)	190/551 (34.5%)
AEs leading to any study drug interruption	76 (81.7%)	232 (61.9%)	422 (60.2%)
AEs leading to any study drug withdrawal/discontinuation	12 (12.9%)	17 (4.5%)	48 (6.8%)
Treatment-related AEs leading to any study drug withdrawal/discontinuation	11 (11.8%)	7 (1.9%)	22 (3.1%)
AEs leading to death	3 (3.2%)	9 (2.4%)	21 (3.0%)
Treatment-related AEs leading to death	1 (1.1%)	4 (1.1%)	7 (1.0%)
UGT1A1 Genotype: *28/*28	**13**	**94**	**184**
AEs	13 (100.0%)	94 (100.0%)	183 (99.5%)
Grade 3 or higher	12 (92.3%)	78 (83.0%)	150 (81.5%)
Treatment-related AEs	13 (100.0%)	93 (98.9%)	176 (95.7%)
SAEs	9 (69.2%)	37 (39.4%)	92 (50.0%)
Treatment-related SAEs	9 (69.2%)	26 (27.7%)	59 (32.1%)
AEs leading to SG dose reduction	8 (61.5%)	26/82 (31.7%)	48/148 (32.4%)
AEs leading to any study drug interruption	11 (84.6%)	61 (64.9%)	123 (66.8%)
AEs leading to any study drug withdrawal/discontinuation	2 (15.4%)	7 (7.4%)	18 (9.8%)
Treatment-related AEs leading to any study drug withdrawal/discontinuation	2 (15.4%)	6 (6.4%)	15 (8.2%)
AEs leading to death	0	1 (1.1%)	6 (3.3%)
Treatment-related AEs leading to death	0	0	3 (1.6%)
UGT1A1 Genotype: *1/*6	**9**	**13**	**19**

Number (%) of Participants with Any	GS-US-592-6173 SG + Pembro (N = 221)	Overall mBC (N = 963)	All Treated (Expanded) SG (10 mg/kg) (N = 1999)
AEs	9 (100.0%)	13 (100.0%)	19 (100.0%)
Grade 3 or higher	4 (44.4%)	9 (69.2%)	14 (73.7%)
Treatment-related AEs	9 (100.0%)	12 (92.3%)	18 (94.7%)
SAEs	3 (33.3%)	5 (38.5%)	10 (52.6%)
Treatment-related SAEs	1 (11.1%)	2 (15.4%)	7 (36.8%)
AEs leading to SG dose reduction	3 (33.3%)	5/13 (38.5%)	9/19 (47.4%)
AEs leading to any study drug interruption	8 (88.9%)	9 (69.2%)	14 (73.7%)
AEs leading to any study drug withdrawal/discontinuation	0	1 (7.7%)	4 (21.1%)
AEs leading to death	0	1 (7.7%)	2 (10.5%)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; Pembro = pembrolizumab; SAE = serious adverse event; SG = sacituzumab govitecan; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

Treatment-emergent adverse events (TEAEs) are any AEs that started on or after first dose date up to and including 30 days (90 days for serious AEs in cohorts with pembro) after the last dose date or the day prior to initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first.

AEs were coded according to MedDRA Version 27.1.

Treatment related includes 'Related', 'Likely Related', 'Possibly Related', and missing relation.

Severity grades were defined by CTCAE: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Life-threatening; 5 = Death.

Dose reduction due to AE was not collected in IMMU-132-01, so participants of this study were excluded from summary of AEs leading to dose reduction.

Low number of genotypes not belonging to *1/*1, *1/*6, *1/*28, or *28/*28, are combined into "Other" in the summary tables by UGT1A1 genotype.

Safety related to drug-drug interactions and other interactions

General considerations made about DDI for SG are valid also for this extension of indication. No dedicated DDI studies have been performed.

Discontinuation due to adverse events

Participant disposition and reason for discontinuation from treatment are presented in Table 56.

Table 77 Treatment-Emergent Adverse Events Leading to Discontinuation of Any Study Drug by System Organ Class and Preferred Term GS-US-592-6173 ISS Populations (Expanded) (Assessor's Table)

System Organ Class Preferred Term	GS-US-592-6173 SG+Pembro (N=221)	GS-US-592-6173 TPC+Pembro (N=220)	Overall mBC (N=963)	All Treated (Expanded) SG (10 mg/kg) (N=1999)
Number (%) of Participants with Any Treatment-Emergent Adverse Events Leading to Discontinuation of Any Study Drug	26 (11.8%)	68 (30.9%)	45 (4.7%)	177 (8.9%)
Blood and lymphatic system disorders	3 (1.4%)	16 (7.3%)	6 (0.6%)	31 (1.6%)
Anaemia	1 (0.5%)	2 (0.9%)	1 (0.1%)	4 (0.2%)
Febrile neutropenia	1 (0.5%)	1 (0.5%)	1 (0.1%)	11 (0.6%)
Neutropenia	1 (0.5%)	4 (1.8%)	3 (0.3%)	11 (0.6%)
Leukopenia	0	2 (0.9%)	1 (0.1%)	3 (0.2%)
Myelosuppression	0	0	0	1 (<0.1%)
Thrombocytopenia	0	7 (3.2%)	1 (0.1%)	2 (0.1%)
Gastrointestinal disorders	2 (0.9%)	4 (1.8%)	9 (0.9%)	30 (1.5%)
Colitis	1 (0.5%)	0	2 (0.2%)	4 (0.2%)
Nausea	1 (0.5%)	0	0	3 (0.2%)
Abdominal pain	0	0	1 (0.1%)	2 (0.1%)
General disorders and administration site conditions	0	5 (2.3%)	9 (0.9%)	24 (1.2%)
Chills	0	0	0	1 (<0.1%)
Death	0	0	0	1 (<0.1%)
Fatigue	0	4 (1.8%)	4 (0.4%)	12 (0.6%)
Infections and infestations	5 (2.3%)	1 (0.5%)	7 (0.7%)	31 (1.6%)
Anal abscess	1 (0.5%)	0	0	0
Bronchiolitis	1 (0.5%)	0	0	0
Laryngitis	1 (0.5%)	0	0	0
Injury, poisoning and procedural complications	2 (0.9%)	7 (3.2%)	1 (0.1%)	4 (0.2%)
Infusion related reaction	2 (0.9%)	6 (2.7%)	1 (0.1%)	3 (0.2%)
Post procedural complication	0	1 (0.5%)	0	0
Pouchitis	0	0	0	1 (<0.1%)
Investigations	3 (1.4%)	5 (2.3%)	1 (0.1%)	4 (0.2%)
Aspartate aminotransferase increased	2 (0.9%)	2 (0.9%)	1 (0.1%)	3 (0.2%)
Alanine aminotransferase increased	1 (0.5%)	3 (1.4%)	1 (0.1%)	2 (0.1%)
Blood alkaline phosphatase increased	0	0	0	1 (<0.1%)
Nervous system disorders	1 (0.5%)	15 (6.8%)	1 (0.1%)	4 (0.2%)
Peripheral sensory neuropathy	1 (0.5%)	1 (0.5%)	0	0
Amnesia	0	0	0	1 (<0.1%)
Cerebral infarction	0	0	0	1 (<0.1%)
Hypoaesthesia	0	1 (0.5%)	0	0
Nervous system disorder	0	0	1 (0.1%)	1 (<0.1%)
Neuropathy peripheral	0	11 (5.0%)	0	1 (<0.1%)
Polyneuropathy	0	2 (0.9%)	0	0
Respiratory, thoracic and mediastinal disorders	5 (2.3%)	10 (4.5%)	7 (0.7%)	24 (1.2%)
Pneumonitis	3 (1.4%)	7 (3.2%)	1 (0.1%)	4 (0.2%)
Interstitial lung disease	1 (0.5%)	1 (0.5%)	3 (0.3%)	3 (0.2%)
Pulmonary embolism	1 (0.5%)	0	0	0
Skin and subcutaneous tissue disorders	3 (1.4%)	6 (2.7%)	1 (0.1%)	7 (0.4%)
Rash	2 (0.9%)	2 (0.9%)	0	1 (<0.1%)
Pruritus	1 (0.5%)	1 (0.5%)	0	3 (0.2%)
Rash maculo-papular	1 (0.5%)	0	0	2 (0.1%)

Table 78 Treatment-Emergent Adverse Events Leading to Interruption of Any Study Drug by System Organ Class and Preferred Term GS-US-592-6173 ISS Populations (Expanded) (Assessor's Table)

System Organ Class Preferred Term	GS-US-592-6173 SG+Pembro (N=221)	GS-US-592-6173 TPC+Pembro (N=220)	Overall mBC (N=963)	All Treated (Expanded) SG (10 mg/kg) (N=1999)
Blood and lymphatic system disorders	111 (50.2%)	102 (46.4%)	452 (46.9%)	780 (39.0%)
Neutropenia	102 (46.2%)	89 (40.5%)	424 (44.0%)	684 (34.2%)
Anaemia	14 (6.3%)	23 (10.5%)	34 (3.5%)	100 (5.0%)
Leukopenia	7 (3.2%)	15 (6.8%)	46 (4.8%)	87 (4.4%)
Febrile neutropenia	6 (2.7%)	4 (1.8%)	12 (1.2%)	28 (1.4%)
Thrombocytopenia	2 (0.9%)	38 (17.3%)	10 (1.0%)	22 (1.1%)
Endocrine disorders	2 (0.9%)	8 (3.6%)	0	0
Central hypothyroidism	1 (0.5%)	0	0	0
Hypothyroidism	1 (0.5%)	1 (0.5%)	0	0
Adrenal insufficiency	0	1 (0.5%)	0	0
Gastrointestinal disorders	38 (17.2%)	26 (11.8%)	76 (7.9%)	208 (10.4%)
Diarrhoea	16 (7.2%)	9 (4.1%)	41 (4.3%)	100 (5.0%)
Nausea	8 (3.6%)	6 (2.7%)	17 (1.8%)	44 (2.2%)
Vomiting	6 (2.7%)	3 (1.4%)	13 (1.3%)	43 (2.2%)
General disorders and administration site conditions	25 (11.3%)	26 (11.8%)	57 (5.9%)	204 (10.2%)
Fatigue	12 (5.4%)	14 (6.4%)	21 (2.2%)	116 (5.8%)
Pyrexia	8 (3.6%)	4 (1.8%)	16 (1.7%)	54 (2.7%)
Influenza like illness	2 (0.9%)	0	4 (0.4%)	9 (0.5%)
Hepatobiliary disorders	4 (1.8%)	6 (2.7%)	5 (0.5%)	14 (0.7%)
Bile duct stone	1 (0.5%)	0	0	0
Cholecystitis acute	1 (0.5%)	0	0	0
Hepatic failure	1 (0.5%)	0	0	0
Infections and infestations	70 (31.7%)	50 (22.7%)	122 (12.7%)	298 (14.9%)
Upper respiratory tract infection	19 (8.6%)	10 (4.5%)	20 (2.1%)	34 (1.7%)
COVID-19	14 (6.3%)	12 (5.5%)	23 (2.4%)	62 (3.1%)
Influenza	7 (3.2%)	1 (0.5%)	8 (0.8%)	12 (0.6%)
Urinary tract infection	6 (2.7%)	7 (3.2%)	8 (0.8%)	36 (1.8%)
Injury, poisoning and procedural complications	7 (3.2%)	5 (2.3%)	14 (1.5%)	29 (1.5%)
Infusion related reaction	6 (2.7%)	3 (1.4%)	4 (0.4%)	11 (0.6%)
Seroma	1 (0.5%)	0	0	0
Clavicle fracture	0	1 (0.5%)	0	1 (<0.1%)
Investigations	25 (11.3%)	27 (12.3%)	18 (1.9%)	57 (2.9%)
Alanine aminotransferase increased	10 (4.5%)	18 (8.2%)	6 (0.6%)	13 (0.7%)
Aspartate aminotransferase increased	5 (2.3%)	13 (5.9%)	3 (0.3%)	12 (0.6%)
Blood alkaline phosphatase increased	3 (1.4%)	3 (1.4%)	3 (0.3%)	7 (0.4%)
Metabolism and nutrition disorders	10 (4.5%)	3 (1.4%)	17 (1.8%)	68 (3.4%)
Dehydration	4 (1.8%)	1 (0.5%)	5 (0.5%)	18 (0.9%)
Hypokalaemia	3 (1.4%)	1 (0.5%)	3 (0.3%)	9 (0.5%)
Hypomagnesaemia	2 (0.9%)	1 (0.5%)	0	2 (0.1%)
Musculoskeletal and connective tissue disorders	6 (2.7%)	7 (3.2%)	13 (1.3%)	34 (1.7%)
Back pain	2 (0.9%)	1 (0.5%)	2 (0.2%)	9 (0.5%)
Arthralgia	1 (0.5%)	3 (1.4%)	0	2 (0.1%)
Fasciitis	1 (0.5%)	0	0	0
Nervous system disorders	11 (5.0%)	10 (4.5%)	11 (1.1%)	38 (1.9%)
Dizziness	3 (1.4%)	2 (0.9%)	1 (0.1%)	5 (0.3%)
Neuropathy peripheral	3 (1.4%)	2 (0.9%)	0	2 (0.1%)
Headache	2 (0.9%)	0	5 (0.5%)	6 (0.3%)
Respiratory, thoracic and mediastinal disorders	18 (8.1%)	22 (10.0%)	40 (4.2%)	84 (4.2%)
Cough	5 (2.3%)	6 (2.7%)	4 (0.4%)	5 (0.3%)
Dyspnoea	5 (2.3%)	6 (2.7%)	17 (1.8%)	30 (1.5%)
Interstitial lung disease	2 (0.9%)	2 (0.9%)	0	1 (<0.1%)
Skin and subcutaneous tissue disorders	12 (5.4%)	8 (3.6%)	11 (1.1%)	29 (1.5%)
Rash	7 (3.2%)	1 (0.5%)	4 (0.4%)	10 (0.5%)
Skin exfoliation	2 (0.9%)	0	0	0
Cellulite	1 (0.5%)	0	1 (0.1%)	1 (<0.1%)

Table 79 Treatment-Emergent Adverse Events Leading to Dose Reduction of Any Study Drug by System Organ Class and Preferred Term GS-US-592-6173 ISS Populations (Expanded) (Assessor's Table)

System Organ Class Preferred Term	GS-US-592-6173 SG+Pembro (N=221)	GS-US-592-6173 TPC+Pembro (N=220)	Overall mBC (N=963)	All Treated (Expanded) SG (10 mg/kg) (N=1999)
Blood and lymphatic system disorders	44 (19.9%)	54 (24.5%)	139/801 (17.4%)	270/1597 (16.9%)
Neutropenia	33 (14.9%)	39 (17.7%)	114/801 (14.2%)	190/1597 (11.9%)
Febrile neutropenia	8 (3.6%)	0	22/801 (2.7%)	58/1597 (3.6%)
Anaemia	2 (0.9%)	12 (5.5%)	11/801 (1.4%)	32/1597 (2.0%)
Lymphopenia	1 (0.5%)	2 (0.9%)	0/801	2/1597 (0.1%)
Febrile bone marrow aplasia	0	0	0/801	2/1597 (0.1%)
Leukopenia	0	3 (1.4%)	6/801 (0.7%)	14/1597 (0.9%)
Pancytopenia	0	1 (0.5%)	0/801	1/1597 (<0.1%)
Thrombocytopenia	0	10 (4.5%)	1/801 (0.1%)	4/1597 (0.3%)
Gastrointestinal disorders	26 (11.8%)	8 (3.6%)	68/801 (8.5%)	163/1597 (10.2%)
Diarrhoea	12 (5.4%)	3 (1.4%)	49/801 (6.1%)	119/1597 (7.5%)
Vomiting	5 (2.3%)	0	7/801 (0.9%)	19/1597 (1.2%)
Colitis	4 (1.8%)	1 (0.5%)	1/801 (0.1%)	2/1597 (0.1%)
General disorders and administration site conditions	14 (6.3%)	12 (5.5%)	38/801 (4.7%)	105/1597 (6.6%)
Fatigue	13 (5.9%)	11 (5.0%)	34/801 (4.2%)	98/1597 (6.1%)
Oedema	1 (0.5%)	0	0/801	0/1597
Malaise	0	0	1/801 (0.1%)	1/1597 (<0.1%)
Investigations	5 (2.3%)	12 (5.5%)	10/801 (1.2%)	19/1597 (1.2%)
Alanine aminotransferase increased	2 (0.9%)	7 (3.2%)	1/801 (0.1%)	3/1597 (0.2%)
Weight decreased	2 (0.9%)	2 (0.9%)	7/801 (0.9%)	11/1597 (0.7%)
Aspartate aminotransferase increased	1 (0.5%)	3 (1.4%)	1/801 (0.1%)	2/1597 (0.1%)
Nervous system disorders	1 (0.5%)	26 (11.8%)	7/801 (0.9%)	10/1597 (0.6%)
Neuropathy peripheral	1 (0.5%)	16 (7.3%)	2/801 (0.2%)	2/1597 (0.1%)
Balance disorder	0	0	0/801	1/1597 (<0.1%)
Dizziness	0	1 (0.5%)	1/801 (0.1%)	2/1597 (0.1%)

Post marketing experience

Sacituzumab govitecan in combination with pembrolizumab was approved by the FDA on 24 June 2026. No post-marketing safety data are included in the submission.

Cumulative patient exposure to Trodelvy from the first marketing approval in the US on 22 April 2020 up to 21 April 2025 is estimated to be 66,804 patients, including 21,518 patients in the EU.

2.5.1. Discussion on clinical safety

The safety population of interest are patients from the pivotal study GS US-592-6173 (n=221 who received SG + Pembrolizumab). Study GS-US-592-6173 (ASCENT-04) is still ongoing, and 41.2% of participants in the SG + Pembro group (vs 18.2% of participants in the TPC + pembro group) remained on treatment as of the data cut-off date of 3 March 2025 (Table 56). Median treatment duration was longer in the SG + Pembro group (8.90 months for SG, 8.54 months for pembrolizumab) than the TPC + pembro group (6.24 months for TPC, 6.42 months for pembrolizumab) and than the Overall mBC pool (8.90 months for SG in study GS-US-592-6173 vs 5.29 months in the Overall mBC pool) (Table 55).

The SG + Pembro and TPC + pembro regimens in study GS-US-592-6173 were associated with a similarly high overall toxicity burden, but the qualitative safety profiles of both regimens differ in a clinically relevant way. Overall AE incidence rates and the proportion of patients experiencing Grade 3 or higher AEs were virtually identical between the SG + Pembro and TPC + Pembro arms (SG + Pembro arm and TPC + Pembro arm: 99.5% vs 99.5% for any AE; 71.5% vs 70.0% for Grade ≥3 AEs), and AEs leading to death were roughly comparable (3.2% vs 2.7%) (Table 57), indicating that the total high grade toxicity was similar between regimens. Infections, especially sepsis and pneumonia, accounted for the majority of deaths in both treatment groups (Table 65)

Participants in the SG + Pembro group experienced sepsis shortly (14 and 15 days, respectively) after initiation of treatment (Table 66). However, current data do not indicate a new safety signal. The SG + Pembro group, however, showed a higher crude incidence rate of SAEs than in the TPC + Pembro group (38.0% vs 30.9%), although when adjusted for exposure using event adjusted incidence rates, the incidence rates of Grade ≥3 AEs and SAEs were similar between groups (Table 58), suggesting that the higher incidence rate of SAE in the SG + Pembro group largely reflects the longer time-at-risk. Compared with SG monotherapy (in the Overall mBC pool), SG + Pembro had similar incidence rates of any AE and Grade ≥3 AEs (99.5% vs 99.7%; 71.5% vs 71.3%), but higher incidence rates of SAEs (38.0% vs 27.6%) and AEs leading to death (3.2% vs 1.6%) (Table 57), which is indicative of additive toxicity when pembrolizumab is combined with SG.

The most striking difference between the SG + Pembro group and TPC + Pembro group is the qualitative shift from predominantly haematologic and hepatic toxicity under the TPC + Pembro group towards gastrointestinal and neutropenia-related events under the SG + Pembro group. In study GS-US-592-6173, the three most common AEs under the SG + Pembro group were diarrhoea (70.1%), nausea (67.9%), and neutropenia (62.9%), whereas under the TPC + Pembro group they were neutropenia (59.1%), fatigue (55.9%), and anaemia (50.9%) (Table 59). AEs occurring with at least a 5% higher absolute incidence rate in the SG + Pembro group than in the TPC + Pembro group included diarrhoea, nausea, alopecia, constipation, vomiting, headache, abdominal pain, weight decreased, oropharyngeal pain, and febrile neutropenia, underscoring the more gastrointestinal and neutropenia-related safety profile of SG + Pembro. Conversely, anaemia, thrombocytopenia, peripheral neuropathy (including peripheral sensory neuropathy), transaminase elevations (ALT and AST increased), hypothyroidism, and arthralgia were at least 5% more frequent in the TPC + pembro group, consistent with the myelosuppressive and hepatotoxic safety profile of the TPC backbone plus pembrolizumab and the neurotoxicity of many chemotherapy agents (e.g. taxane-containing regimens).

These qualitative differences are also reflected in the Grade ≥3 AE spectrum of both regimens. Overall Grade ≥3 AE incidence rates were similar, but the SG + Pembro group had notably higher incidence rates of Grade ≥3 diarrhoea (10.0% vs 2.3%), fatigue (8.1% vs 3.2%), and febrile neutropenia (7.7% vs 1.8%) compared with the TPC + Pembro group, highlighting the more gastrointestinal and neutropenia-related safety profile of SG + Pembro. In contrast, TPC + Pembro showed higher incidence rates of Grade ≥3 anaemia (TPC + Pembro vs SG + Pembro: 15.9% vs 7.2%), thrombocytopenia (13.6% vs 0.5%), leukopenia (8.6% vs 3.2%), and ALT increased (5.9% vs 3.6%) (Table 61), again highlighting a more pronounced haematologic and hepatic toxicity pattern in the TPC + Pembro group. Laboratory data support these trends: while Grade 3–4 laboratory abnormalities were overall similar between groups (Grade 3–4: 67.6% vs 66.4%; Grade 4: 28.3% vs 25.0%) (Table 73), TPC + Pembro showed additional Grade 3–4 anaemia and thrombocytopenia signals beyond the neutropenia-dominated picture common to both regimens.

Based on the presented data, section 4.8 of the SmPC concludes that adverse reactions occurring in patients treated with sacituzumab govitecan in combination with pembrolizumab were generally similar to those observed with sacituzumab govitecan or pembrolizumab in breast cancer treatment.

The combination of sacituzumab govitecan with pembrolizumab did not increase the frequency or severity of pembrolizumab-associated immune-mediated adverse reactions.

Adverse reactions known to occur with sacituzumab govitecan or combination therapy components given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with combination therapy.

With regard to SG AEs of special interest (AESIs) (Table 67), the combination of SG + Pembro was associated with a higher risk of severe diarrhoea than TPC + Pembro (any severe diarrhoea AESIs 10.0% vs 2.3%), with similarly higher incidence rates for treatment-related events, SAEs, and events leading to dose reduction or interruption (Table 69), confirming that SG + Pembro confers a clinically relevant increase in diarrhoea risk compared with the standard of care. Severe diarrhoea AESI incidence rates in the SG + Pembro group were, however, consistent with those observed for SG monotherapy (overall mBC pool, 10.0% vs 10.0%), suggesting that the addition of pembrolizumab does not substantially aggravate the intrinsic SG-related diarrhoea risk. For neutropenia AESIs, SG + Pembro tended to have slightly higher incidence rates in several categories than TPC + Pembro, with differences of at least 5% observed for neutropenia SAEs (12.7% vs 6.8%) and neutropenia leading to treatment interruption (48.0% vs 41.4% (Table 71), indicating a slightly increased risk of neutropenia complications with the SG + Pembro combination. When compared to the Overall mBC pool, the SG + Pembro group displayed no clear pattern for neutropenia AESIs: the combination SG + Pembro had lower incidence rates for "any AE", Grade ≥3 AEs, and treatment-related AEs, but higher incidence rates of SAEs and AEs leading to dose modifications, with a ≥5% excess in neutropenia SAEs (12.7% vs 7.3%), pointing again to an additive burden, particularly at the SAE level.

Regarding pembrolizumab AESIs (Table 72), the overall AESI incidence rate was actually lower in the SG + Pembro group than in the TPC + Pembro group (30.3% vs 39.5%). This difference was mainly driven by lower incidence rates of pneumonitis (2.7% vs 7.7%) and hypothyroidism (7.2% vs 15.9%) in the SG + Pembro group, while colitis occurred slightly more often under SG + Pembro (5.9% vs 1.4%). Overall, the addition of SG to pembrolizumab did not appear to exacerbate immune-mediated toxicities typically associated with pembrolizumab; only pneumonitis and hypothyroidism showed clinically meaningful (≥5%) differences between groups, both being less frequent in the SG + Pembro group. However, when the SG + Pembro combination is compared with SG monotherapy, hypersensitivity AESIs (largely non-severe rash and infusion-related reactions) were clearly increased: any hypersensitivity AESI occurred in 19.5% vs 12.8%, and treatment-related hypersensitivity in 14.9% vs 8.9%, with slightly higher incidence rates of serious or Grade ≥3 events and AEs leading to dose reductions and discontinuations due to hypersensitivity in the SG + Pembro group (Table 70). This pattern indicates additive hypersensitivity when pembrolizumab is combined with SG, although it does not represent an unexpected signal.

Furthermore, the pattern of dose modifications and discontinuations is informative for assessing treatment-limiting toxicity. Crude incidence rates show that AEs leading to discontinuation of any study drug were substantially less frequent in the SG + Pembro group than in the TPC + Pembro group (11.8% vs 30.9%) (Table 57), despite similar overall AE severity. Exposure adjusted analyses (Table 58) confirm that the incidence rate of AEs leading to any study drug discontinuation per patient year was lower in the SG + Pembro group than in the TPC + Pembro group (0.15 vs 0.53 per PYE), and AEs leading to SG or TPC dose reduction were also less frequent on an exposure-adjusted basis (0.62 vs 0.94 per PYE). These data suggest that, although the SG + Pembro combination was associated with a higher frequency of AEs overall (EAIR of any AE 69.09 vs 36.68; treatment-related AEs 43.04 vs 22.67), these events were less likely to necessitate permanent treatment cessation than the more haematologic and neuropathic toxicity linked to the TPC + Pembro combination. Importantly, when the SG + Pembro combination is compared against SG monotherapy, AEs leading to any study drug discontinuation were clearly higher (11.8% vs 4.7%), (Table 57), and the SG + Pembro combination was also associated with more AEs leading to interruption or dose reduction in most subgroups of race and age (Table 74, Table 75), corroborating the presence of additive toxicity from pembrolizumab on a background of SG.

The comparison of the SG + Pembro combination with the Overall mBC pool further underscores the additive toxicity of the combination. While the overall AE and Grade ≥3 AE incidence rates were similar, the SG + Pembro combination showed higher incidence rates of SAEs, AEs leading to death, and treatment-modifying events (Table 57). At the level of specific AEs, the SG + Pembro combination had markedly higher incidence rates than the Overall mBC pool for diarrhoea (10.2% absolute difference), rash (8.5%), hypothyroidism (6.3%), alanine aminotransferase increased (5.8%), and COVID 19 (6.6%) (Table 59), with all but COVID 19 being typical pembrolizumab-associated events. Hypersensitivity AESIs were also more frequent in the SG + Pembro group (Table 67). In UGT1A1 reduced-function genotypes (*1/*28 and *28/*28) (Table 76), the SG + Pembro combination was associated with particularly increased incidence rates of SAEs and AEs leading to dose modifications when compared with SG monotherapy, highlighting a subgroup with heightened susceptibility to the toxic effects of the SG + Pembro regimen. The fact that variants in other alleles potentially associated with reduced UGT1A1 enzyme activities might be prevalent in certain populations has been reflected in section 4.4 of the SmPC.

Generally, the incidence rates in all AE categories increased with age. In study GS-US-592-6173, the SG + Pembro group and the TPC + Pembro group had similar incidence rates of high-grade AEs, with the SG + Pembro group often showing numerically more SAEs, but the TPC + Pembro group consistently exhibited higher incidence rates of AEs leading to any study drug discontinuation in nearly all age subgroups. Across some age subgroups, the SG + Pembro group had higher incidence rates of any AE and high-grade AEs compared with SG monotherapy (Overall mBC pool) and was generally associated with higher incidence rates of SAEs and AEs leading to death in several age groups, as well as higher incidence rates of AEs leading to any study drug discontinuation in most subgroups, pointing to the additive toxicity of the combination (Table 75). In study GS-US-592-6238 (ASCENT-03), the toxicity of SG also increased with age and was higher than that observed with TPC.

The available data suggest that the SG + Pembro regimen has a safety profile that is overall comparable in severity but qualitatively distinct from the standard of care TPC + Pembro regimen: the combination SG + Pembro shifts the toxicity towards gastrointestinal events and neutropenia-related complications, while reducing the burden of anaemia, thrombocytopenia, neuropathy, and liver enzyme elevations. Additive toxicity of SG + Pembro compared with SG monotherapy manifests as increased SAEs, AEs leading to death, hypersensitivity, immune-mediated AEs and AEs leading to dose modifications. However, there are no new safety signals beyond the known profiles of SG and pembrolizumab. Importantly, the lower exposure-adjusted incidence rates of AEs leading to treatment discontinuation and dose reduction with SG + Pembro compared to TPC + Pembro suggest that, despite its more frequent AEs, the SG + Pembro combination toxicity profile may be manageable in clinical practice, provided that diarrhoea, neutropenia, hypersensitivity, and other combination-related toxicities are proactively monitored and appropriately managed (including G-CSF use and standard immunotherapy toxicity algorithms). Appropriate warnings and dose modifications for adverse reactions are already included in section 4.4 and 4.2 of the SmPC respectively.

2.5.2. Conclusions on clinical safety

Overall, the SG + Pembro combination shows a similarly high but qualitatively distinct toxicity burden compared with the TPC + Pembro combination, shifting the profile towards more gastrointestinal events and neutropenia-related complications, while reducing anaemia, thrombocytopenia, neuropathy, and liver enzyme elevations, and with fewer discontinuations. At the same time, the combination of SG + Pembro clearly exhibits additive toxicity versus SG monotherapy (more SAEs, AEs leading to death, hypersensitivity, and immune-mediated AEs, and

more AEs leading to treatment modifications). This was particularly apparent in patients with UGT1A1 reduced-function genotypes (*1/*28 and *28/*28). The overall types and frequencies of AEs for the combination of SG and pembrolizumab in study GS-US-592-6173 are generally consistent with the known safety profiles of the individual agents in metastatic breast cancer. No new safety signals were detected, and the safety profile may be manageable with dose modifications and guideline-concordant care.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6.0 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Table 80 Summary of Safety Concerns

Important Identified Risks	Serious infections secondary to neutropenia
Important Potential Risks	None
Missing Information	Use in patients with moderate or severe hepatic impairment
	Immunogenicity

Pharmacovigilance plan

Table 81 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Study IMMU-132-15	To identify the safe starting dose of SG in	Use in patients with moderate or	Protocol finalised	30-Oct-2020

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects with Advanced or Metastatic Solid Tumour and Moderate Liver Impairment Ongoing	subjects with solid tumour and moderate hepatic impairment. To evaluate the PK of SG, free SN-38, total SN-38, and SN-38G in subjects with solid tumour and moderate hepatic impairment. To assess the occurrences of human antibodies against SG in subjects with solid tumour and moderate hepatic impairment.	severe hepatic impairment	First subject enrolled	Apr-2021
			Last subject completed	Dec-2026
			CSR filing	Jun-2027

Risk minimisation measures

Table 82 Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important identified risk		
Serious infections secondary to neutropenia	Routine risk minimisation measures: • Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) should be considered starting in the first cycle inpatients at increased risk of febrile neutropenia in SmPC sections 4.2 and 4.4 • Dose modifications based on severity and occurrence in SmPC section 4.2 • Warnings of severe or life-threatening neutropenia, including fatal infections in the setting of neutropenia observed in clinical studies with SG primarily in the first two cycles of treatment, in SmPC section 4.4 • Warning for UGT1A1*28 allele homozygous patients in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • Guidance for treating severe neutropenia relating to overdose in SmPC section 4.9 • Warning in PL section 2 • Side effect in PL section 4 • Restricted medical prescription Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None
Important potential risk(s)		
None		
Missing information		
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: • Guidance that no dose adjustment is necessary for mild hepatic impairment in SmPC Section 4.2 • Guidance that TRODELVY should be avoided in patients with moderate or severe hepatic impairment in SmPC Section 4.2 • Information on SG exposure in patients with hepatic impairment in SmPC Section 5.2 • Guidance for the patient to talk to their doctor or nurse if they have liver problems in PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Restricted medical prescription Additional risk minimisation measures: • None	• Study IMMU-132-15
Immunogenicity	Routine risk minimisation measures: • Available clinical data on SG immunogenicity SG SmPC section 4.8 • Restricted medical prescription Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the package leaflet has been amended to reflect the new indication for the treatment of first-line metastatic TNBC in adult patients in combination with pembrolizumab but the updates are considered limited. The key safety messages as well as the design and layout of the package leaflet are not significantly affected.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The finally agreed indication is:'Trodelvy is indicated in combination with pembrolizumab, for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have not received prior systemic therapy for metastatic disease and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (see sections 4.2 and 5.1).'

3.1.1. Disease or condition

TNBC is defined by a lack of ER, PR, and HER2 expression in tumour cells, and accounts for approximately 15% of invasive breast cancers. It is characterized by a more aggressive tumour biology and shorter overall survival with a low 5-year survival rate of approximately 15% (American Cancer Society 2023[17]). Approximately 33% of patients with metastatic TNBC present with de novo metastatic disease (Punie et al. 2024[18]), and TNBC is most commonly associated with visceral metastases affecting the liver, lung, and brain (O'Reilly et al. 2021[19]).

[17] American Cancer Society. Triple-negative Breast Cancer. Available at: https://www.cancer.org/cancer/types/breast-cancer/about/types-of-breast-cancer/triple-negative.html. Last Updated: 01 March. 2023
[18] Punie K et al. Evolution of characteristics, real-world treatment landscape, and survival outcomes in patients with previously untreated mTNBC in the United States [Abstract]. ESMO Breast Cancer; 2024
[19] O'Reilly D et al. Overview of recent advances in metastatic triple negative breast cancer. World J Clin Oncol 2021

3.1.2. Available therapies and unmet medical need

Current standard treatment for recurrent/metastatic TNBC varies by subtypes. For PD-L1 positive patients with de novo metastatic TNBC or recurrence of >6-12 months after the end of (neo)adjuvant immune checkpoint inhibitors (ICI), the most recent ESMO guidance recommends a combination of chemotherapy with an ICI. PD-L1 negative patients with germline BRCA 1/2 mutations should be treated with a PARP inhibitor and gBRCA-wt PD-L1 negative patients should receive chemotherapy (ESMO living guideline[20]).

In the EU, Keytruda (pembrolizumab, a PD-1 inhibitor) was approved for first-line treatment of TNBC in combination with chemotherapy in October 2021 based on the KEYNOTE-355 study (EMEA/H/C/003820/II/0099). Tecentriq (atezolizumab) was also approved in the EU in March 2019 for the first-line treatment of TNBC based on the Impassion130 study (EMEA/H/C/004143/X/0017) in combination with paclitaxel.

3.1.3. Main clinical studies

Study ASCENT-04 is a global, open-label phase 3 study to evaluate the efficacy and safety of SG in combination with pembrolizumab compared with TPC chemotherapy plus pembrolizumab in participants with locally advanced unresectable or metastatic TNBC who have not received previous systemic therapy for advanced disease. The study enrolled participants with tumours that were PD-L1 positive (CPS ≥ 10).

443 participants were randomized 1:1 to receive SG + Pembro or TPC (paclitaxel, nab-paclitaxel or gemcitabine plus carboplatin) + Pembro. The primary endpoint was PFS as assessed by BICR. Participants in the control group were eligible to receive SG through the study in the crossover phase upon disease progression verified by BICR.

3.2. Favourable effects

Efficacy data were provided from the primary (final) analysis of PFS with a median duration of follow-up of 14 months (data cut-off date: 03 March 2025) and from the first OS interim analysis (OS IA1) with a median duration of OS follow-up of 22.5 months (DCO: 16 February 2026).

Study ASCENT-04 demonstrated a statistically significant PFS improvement with SG + Pembro versus TPC + Pembro at the primary PFS analysis (HR: 0.654, 95% CI: 0.508, 0.842; 2-sided P < 0.0009). The median PFS was 11.24 months (95% CI: 9.26, 16.69) in the SG + Pembro arm and 7.75 months (95% CI: 7.29, 9.26) in the TPC + Pembro arm. Sensitivity analysis of PFS at the time of the primary PFS analysis and updated PFS results at OS IA1 were consistent with the primary analysis.

OS data from OS IA based on a maturity rate of 46% (information 80.6%) showed a HR of 0.915 (95% CI: 0.69, 1.21, P = 0.53) with a median OS of 31.2 months (95% CI: 25.6, NR) in the SG + Pembro arm and 28.4 months (95% CI: 24.4, NR) in the TPC + Pembro arm.

3.3. Uncertainties and limitations about favourable effects

- The interpretation of OS data is limited by substantial censoring beyond 18 months and by the high cross-over rate, with 55% of participants in the TPC + pembrolizumab arm receiving SG in the second-line setting. Therefore, the OS estimates, including the median

[20] ESMO Living Guideline for Triple-negative metastatic breast cancer; G Curigliano et al., Ann Oncol. 2025.

OS values should be interpreted with caution at this stage. The MAH will provide the final OS results post-approval (**REC**)

- Data in elderly are limited, especially in patients older than 75 years.

3.4. Unfavourable effects

In study GS-US-592-6173, the SG + Pembro regimen was associated with similar incidence rates of any AEs and Grade 3 or higher AEs and a higher incidence rate of SAEs compared to the TPC + Pembro regimen. The most common adverse events in the SG + Pembro group were diarrhoea, nausea, and neutropenia, with higher incidence rates of Grade ≥3 diarrhoea, fatigue, and febrile neutropenia compared to the TPC + Pembro group. Additionally, SG + Pembro showed a higher risk of severe diarrhoea and infection-related AESIs, but the overall incidence rate of pembrolizumab-related AEOSIs was lower in the SG + Pembro group than in the TPC + Pembro group. Generally, there was a shift towards more symptomatic, mainly gastrointestinal toxicity and neutropenia-related complications with the SG + Pembro combination and towards more myelosuppression and hepatotoxicity with the TPC + Pembro combination.

For SG + Pembro in study GS-US-592-6173 vs SG monotherapy in the Overall mBC pool, there was an increase in the seriousness of AEs and a treatment modifying impact on toxicity, reflecting the additive toxicity of combining pembrolizumab with SG. Overall and Grade ≥3 AE incidence rates were similar, but the SG + Pembro combination had higher incidence rates of SAEs, of AEs leading to death and of AEs leading to discontinuation, interruption, and dose reductions, along with clear increases in hypersensitivity AEOSIs and typical immune-mediated adverse events (e.g. diarrhoea, rash, hypothyroidism, ALT increased, decreased appetite).

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Effects Table

Table 83 Effects Table for Trodelvy + Pembrolizumab for the 1L treatment of patients with TNBC whose tumours express PD-L1 (CPS ⩾ 10) (DCO: 03 March 2025 for PFS analysis and safety; DCO 16 February 2026 for OS IA)

Effect	Short description	**Unit**	**Treatment SG + Pembro**	**TPC + Pembro Control**	**Uncertainties / Strength of evidence**
Favourable Effects					
PFS	Median, by BICR per RECIST 1.1	Months	11.2	7.8	Statistical significance met for primary PFS endpoint (p=0.0009);
		HR, 95% CI	0.65 (0.51, 0.84)		
OS	Median	Months	31.2 (25.6, NR)	28.4 (24.4, NR)	Interpretation of OS data confounded by high rate of participants (55%) who received SG in 2L in control arm
		HR, 95% CI	0.915 (0.69, 1.21)		

Effect	Unit	Treatment SG + Pembro		Control TPC+ Pembro	Overall mBC pool
Unfavourable Effects					
Drug-related AEs		%	98.6	97.7	97.8
Grade ≥ 3 AEs		%	71.5	70.0	71.3
SAEs	%	38.0		30.9	27.6
AEs leading to death	%	3.2		2.7	1.6
AEs leading to any study drug withdrawal / discontinuation	%	11.8		30.9	4.7
Nausea	%	67.9		37.7	62.1
Febrile neutropenia (Grade ≥ 3)	%	7.7		1.8	5.6
Severe diarrhoea	%	10.0		2.3	10.0
Serious infections secondary to neutropenia (small patient numbers)	%	2.7		1.4	2.9

Reference: CSR ASCENT-04

Abbreviations: AE = Adverse Event; AESI = Adverse Event of Special Interest; mBC = metastatic breast cancer; Pembro = pembrolizumab; SAE = Serious Adverse Event; SG: Sacituzumab govitecan; TPC = Treatment of Physician's Choice.

Notes: BOLD = higher incidence rate in the comparison SG + Pembro vs TPC + Pembro; UNDERLINED = higher incidence rate in the comparison SG + Pembro vs SG monotherapy

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Study ASCENT-04 demonstrated a statistically significant PFS improvement for the combination therapy of SG with pembrolizumab compared to first-line chemotherapy in combination with pembrolizumab in patients with PD-L1 positive TNBC. This improvement is considered clinically relevant. The OS results can be considered sufficiently mature to exclude an OS detriment over the entire course of the OS follow-up time (based on an OS maturity rate of 46%).

The interpretation of OS data is confounded by the large proportion of patients (55%) in the control arm who received SG after disease progression. Nonetheless, administering SG after the failure of 1L treatment reflects standard clinical practice and the available OS data do not allow a robust conclusion on the magnitude of any OS advantage with first-line SG in combination with pembrolizumab compared with later-line use of SG.

The combination of SG and pembrolizumab is associated with a high toxicity burden, broadly comparable in magnitude to that observed with TPC and pembrolizumab, although with a qualitatively distinct safety profile. The SG-containing regimen is characterised by a higher frequency of gastrointestinal events and neutropenia-related complications, while haematological

and hepatic toxicity, neuropathy, and treatment discontinuations were less frequent. Compared to SG monotherapy, the addition of pembrolizumab was associated with a higher incidence rate in several categories of adverse events (SAEs, AEs leading to death, immune-mediated AEs, hypersensitivity reactions, and AEs leading to treatment modifications). This was particularly apparent in patients with UGT1A1 reduced-function genotypes (*1/*28 and *28/*28). Overall, the types and frequencies of AEs observed with SG in combination with pembrolizumab in study ASCENT-04 are consistent with the known safety profiles of the individual agents in metastatic breast cancer. No new safety signals were identified, no new risks have been added to the RMP, and the safety profile is considered manageable with appropriate dose modifications and guideline-concordant supportive care.

3.7.2. Balance of benefits and risks

In view of the demonstrated benefit in PFS for the treatment of SG in combination with pembrolizumab and its manageable safety profile, the combination therapy can be considered a viable treatment option for first-line therapy in patients with TNBC.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Trodelvy in the new claimed indication is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable

and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication for Trodelvy in combination with pembrolizumab for the treatment of adult patients with unresectable locally advanced or metastatic triple negative breast cancer (TNBC) who have not received prior systemic therapy for metastatic disease and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10, based on the results from study GS-US-592-6173 (ASCENT-04), which is a phase 3 study of sacituzumab govitecan (IMMU-132) and pembrolizumab versus treatment of physician's choice (TPC) and pembrolizumab in patients with previously untreated, locally advanced inoperable or metastatic triple-negative breast cancer, whose tumours express PD-L1. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.0 of the RMP has also been agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.