22 June 2023
EMA/319185/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TRODELVY

International non-proprietary name: sacituzumab govitecan

Procedure No. EMEA/H/C/005182/II/0020

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
AESI	adverse event(s) of special interest
AST	aspartate aminotransferase
BICR	blinded independent central review
BRCA1/2	breast cancer gene 1 or 2
$CAVG_{SG}$	sacituzumab govitecan average concentration
$CAVG_{tAB}$	total antibody average concentration
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CL2A	hydrolyzable linker that couples SN-38 to hRS7 IgG1κ
CL_{cr}	creatinine clearance
CR	complete response
CSR	clinical study report
DOR	duration of response
EAIR	exposure-adjusted incidence rate (per 100 patient-years of exposure)
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0
ER	estrogen receptor
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
Gilead	Gilead Sciences
HER2−	human epidermal growth factor receptor 2-negative
HR	hazard ratio

HR+	hormone receptor-positive
HRQOL	health-related quality of life
hRS7 IgG1κ	humanized monoclonal antibody that binds to the cell-surface receptor Trop-2
IHC	immunohistochemistry
ISH−	in situ hybridization negative
ISI	Integrated Summary of Immunogenicity
ISS	Integrated Summary of Safety
IV	intravenous/intravenously
ITT	intent to treat
LIR	local investigator review
LSM	least-squares mean
m	module
mBC	metastatic breast cancer
MMRM	mixed model for repeated measures
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NAb	neutralizing antibody
NCCN	National Comprehensive Cancer Network
OR	odds ratio
ORR	objective response rate
OS	overall survival
OS IA2	second planned interim analysis of OS
PARP	poly (ADP-ribose) polymerase
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PI3K	phosphatidylinositol-3-kinase
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PYE	patient-years of exposure
QOL	quality of life
RB1	retinoblastoma-associated protein 1
RECIST	Response Evaluation Criteria in Solid Tumors

SAE	serious adverse event
SAP	statistical analysis plan
SERD	selective estrogen receptor downregulator
SG	sacituzumab govitecan; Trodelvy; GS-0132; IMMU-132
SN-38	camptothecin-derived topoisomerase I inhibitor and active metabolite of irinotecan
$t_{1/2}$	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
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution at steady state

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences Ireland UC submitted to the European Medicines Agency on 27 November 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting, based on final results from study IMMU-132-09 (TROPiCS-02); this is an open-label, randomized, multicenter phase 3 study of sacituzumab govitecan (IMMU-132) versus treatment of physician's choice (TPC) in subjects with hormonal receptor-positive (HR+) human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer (mBC) who have failed at least two prior chemotherapy regimens. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the list of local representatives in the Package Leaflet.

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.

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 13 December 2018 (EMA/CHMP/SAWP/852346/2018). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	27 November 2022
Start of procedure:	31 December 2022
CHMP Rapporteur Assessment Report	24 February 2023
PRAC Rapporteur Assessment Report	3 March 2023
PRAC members comments	8 March 2023
PRAC Outcome	16 March 2023
CHMP members comments	20 March 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 March 2023
Request for supplementary information (RSI)	30 March 2023
CHMP Rapporteur Assessment Report	23 May 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur Assessment Report	15 June 2023
CHMP Opinion	22 June 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The proposed indication for Trodelvy was "as monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH−) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting (see section 5.1)."

Following recommendation by the CHMP the recommended indication is:

"Trodelvy as monotherapy is indicated 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 (see section 5.1)".

Epidemiology

The most commonly diagnosed cancer is breast cancer, accounting for 11.7% of all cancer diagnoses. There were approximately 530,000 new cases of breast cancer and 140,000 deaths reported in the EU in 2020 (*Dyba 2021)*. HR+/HER2− breast cancer (BC) is the most common breast cancer subtype, representing approximately 70% of all new cases (*Howlader 2014)*. The median age at diagnosis of HR+/HER2− breast cancer is 61 years (range: 51-70 years), which is older than all other subtypes (*Kong 2020)*. Incidence of HR+/HER2− mBC increases with age, especially after 65 years, and prognosis is worse in older age groups *(National Cancer Institute 2021)*.

Biologic features

HR+/HER2− breast cancer is characterized by hormone receptor positivity (> 1% IHC expression of the estrogen receptor [ER] and/or progesterone receptor [PR]) and lack of HER2 expression (IHC score of 0, 1+, or 2+ confirmed as negative by fluorescence in situ hybridization [FISH]) (*Allison 2020, Wolff 2018))*.

In early stages, HR+/HER2− breast cancer is less aggressive than other breast cancer subtypes; however, once it has progressed to metastatic disease, it becomes more aggressive and treatment resistant with higher tumor grade and change in biomarker status after treatment progression (*American Cancer Society 2019, Dunnwald 2007, Grinda 2021)*.

High expression of Trop-2 protein in breast cancers, including the HR+/HER2− subtype, has been shown by polyclonal IHC testing *(Ambrogi 2014)*. Monoclonal antibody data showed high (> 90%) expression of Trop 2 protein in TNBC linked with tumor progression and poor prognosis *(Bardia 2021)*, and a recent study showed that TROP2 gene expression is high and appears similar across all breast cancer subtypes *(Vidula 2017)*.

Clinical presentation, diagnosis and stage/prognosis

The majority of patients with advanced HR+ breast cancer will have a history of early-stage breast cancer, with just a minority of patients presenting with advanced disease de novo. The most frequent initial site of metastases in patients with HR+/HER2− breast cancer is bone (77.6%), but this breast cancer subtype is also associated with metastases to visceral sites, including lung (28.5%), liver (20.6%), and brain (5.8%), which are related to even poorer prognosis *(Bertho 2021, Li 2021, Lobbezoo 2013)*. In Stage IV (metastatic disease), HR+/HER2− has the second worst prognosis after metastatic TNBC with a 5-year survival rate of 30% (*National Cancer Institute 2021)*.

Management

Endocrine therapy combined with a CDK 4/6 inhibitor is the current standard of care for patients with newly diagnosed HR+/HER2− mBC.Subsequent treatment options for patients with HR+/HER2− metastatic breast cancer after progression on endocrine therapy and a CDK 4/6 inhibitor include sequential endocrine therapy with an alternative endocrine regimen as a single agent or in combination with targeted agents including mTOR inhibitors and PI3K inhibitors, depending on PI3K mutation status (*Cardoso 2020, National Comprehensive Cancer Network (NCCN) 2022)*.

In a subset of patients (< 10%) with HR+/HER2− mBC and BRCA1/2 mutations, PARP inhibitor monotherapy may be a suitable treatment option after progression on endocrine therapies *(Gennari 2021, National Comprehensive Cancer Network (NCCN) 2022, O'Shaughnessy 2020)*.

Treatment options for endocrine resistant/refractory disease include single-agent chemotherapy such as anthracyclines, taxanes, antimetabolites, and microtubule inhibitors *(Cardoso 2020, National Comprehensive Cancer Network (NCCN) 2022)*. Combination chemotherapy may be used in patients with more advanced disease or a high disease burden; however, a superior OS benefit was not shown and it is generally more toxic *(Dear 2013, Gennari 2021)*.

Efficacy in patients with HR+/HER2− metastatic breast cancer treated with chemotherapy in the metastatic setting is limited. Objective response rates (ORRs) ranged from 14% to 32% in patients treated with single-agent chemotherapy, including eribulin, capecitabine, vinorelbine, paclitaxel, or gemcitabine *(Paclitaxel Summary of product characteristics, Rha 2005, Twelves 2014, Yuan 2019)*. Reported PFS ranges from 4 to 5 months *(Twelves 2016, Twelves 2014, Yuan 2019)*. Similar to PFS, reported median OS is low following treatment with single agent gemcitabine (6.4 months), capecitabine (9.1 months), or eribulin (11 months) *(Kazmi 2020)*. Many of these studies were conducted before the CDK 4/6 inhibitor class of drug was available to patients. As patients progress following each successive treatment, the efficacy of subsequent treatments decreases *(Park 2015, Planchat 2011)*. Moreover, treatments increasingly have a negative impact upon HRQOL *(Davie 2020, Wood 2017, De Laurentiis 2018)*.

The recent Phase 3 DESTINY-Breast04 study compared the anti-drug conjugate (ADC) trastuzumab deruxtecan with chemotherapy of physician's choice in a new population of patients with metastatic/unresectable breast cancer and low HER2 expression (defined as an IHC score of 1+ or 2+/ ISH−) *(Modi 2022b)*. Patients had received 1 to 2 prior lines of chemotherapy in the metastatic setting and 70% had received prior treatment with a CDK 4/6 inhibitor. In the HR+ cohort, treatment with trastuzumab deruxtecan resulted in statistically significant improvements in PFS (10.1 months vs 5.4 months; HR: 0.51; 95% CI: 0.40, 0.64; P < 0.001) and OS (23.9 months vs 17.5 months; HR: 0.64; 95% CI: 0.48, 0.86; P = 0.003) compared with chemotherapy.

Based on results reported with ADC in breast cancer, the future standard of care for a number of breast cancer subtypes may include treatment with ADCs with differing targets such as trastuzumab deruxtecan (targeting HER2) and SG (targeting Trop 2).

In summary, given the poor outcomes (limited effectiveness and poor tolerability) and limited remaining treatment options available, there remains a high unmet need for patients with HR+/HER2− metastatic breast cancer who have received prior endocrine therapy and chemotherapy for locally advanced or metastatic disease. Prolonging OS, improving efficacy, and maintaining or improving quality of life (QOL) with manageable toxicities continues to represent an area of unmet medical need in HR+/HER2− metastatic breast cancer.

2.1.2. About the product

Sacituzumab govitecan is a first-in-class ADC composed of the following 3 components:

1) hRS7 IgG1κ: humanized monoclonal antibody that binds to the cell-surface receptor, Trop 2

2) SN-38: camptothecin derived topoisomerase I inhibitor and active metabolite of irinotecan

3) CL2A: hydrolyzable linker that couples SN 38 to hRS7 IgG1κ

Sacituzumab govitecan binds to Trop-2-expressing cancer 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.

Sacituzumab govitecan was granted a marketing authorization from the European Commission (EU) on 22 November 2021 for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, including at least one of them for advanced disease.

The recommended dose of sacituzumab govitecan is 10 mg/kg body weight administered as an intravenous infusion once weekly on Day 1 and Day 8 of 21-day treatment cycles. Treatment should be continued until disease progression or unacceptable toxicity.

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

EMA scientific advice for HR+/HER2- breast cancer, 2018

The MAH received Scientific advice from the CHMP on 13 December 2018 (EMA/CHMP/SAWP/852346/2018). The Scientific advice pertained to design elements of Study IMMU-132-09, including the proposed eligibility criteria, use of TPC monotherapy as comparator, local determination of HR status, 2:1 randomization scheme, stratification factors, PFS as primary endpoint with OS as key secondary endpoint, QoL assessments, statistical analysis, and planned interim analysis for ORR. The proposed study design was overall considered acceptable; however, following CHMP recommendations, the MAH introduced a blinded independent review of PFS, removed taxanes as a comparator treatment option, removed the interim analysis based on ORR, and revised the requirement that at least 50% of randomized patients should have received 1 prior line of chemotherapy to the need of at least 2 prior systemic chemotherapy regimens for metastatic disease.

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

No updated environmental risk assessment (ERA) was submitted (see discussion on non-clinical aspects).

2.2.1. Discussion on non-clinical aspects

The environmental risk assessment (ERA) was previously submitted for Trodelvy as part of the EU initial MAA. 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 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 calculation made in the existing ERA used the default fraction market penetration value which was refined based on the proposed dosing regimen i.e. maximum dose of 10 mg/kg sacituzumab govitecan

given twice every three weeks. The Predicted Environmental Concentration in Surface Water (PECsw) in the existing ERA was based on an estimation of exposure to the payload SN-38, the active compound, which was below the trigger value of 0.01 µg/L.

An update of the ERA was not submitted as the indication extension is within the environmental exposure predicted by the prior ERA, since the dosing regimen will not change for the extension of indication and the calculation is thus independent of the indication. Furthermore, a more detailed calculation was provided to justify that the PECsw for SN-38 is 2-fold below the action limit of 0.01 µg/L as defined for any indication and the indication extension is within the environmental exposure predicted by the ERA approved for the initial EU MAA.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of sacituzumab govitecan.

Considering the above data, sacituzumab govitecan is not expected to pose a risk to the environment.

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.

Table 1: Tabular overview of clinical studies

Study Number	Description of Study	Data Included in This Submission	Study Population/ Number of Participants
Pivotal study			
IMMU-132-09 (TROPiCS-02)	Phase 3, ongoing, open-label, randomized, multicenter, international study to assess and compare the efficacy of SG to TPC as measured by PFS as determined by BICR using RECIST v1.1.	Efficacy Safety[a] PK Immunogenicity	Participants with metastatic or locally recurrent inoperable **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 or 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[c]: 271 randomized (249 treated)
Supportive studies			
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	Efficacy 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. Participants with **HR+/HER2− metastatic breast** cancer who had progressed on at least 1 prior hormonal therapy in the metastatic setting.

Study Number	Description of Study	Data Included in This Submission	Study Population/ Number of Participants
	acceptable dose[d] 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.		Total: 515 enrolled (402 treated)[e] SG[b]: 54 with confirmed HR+/HER2− (54 treated)[f]
Further clinical studies relevant **for PK**			
IMMU-132-05 (ASCENT)	Phase 3, randomized, open-label, controlled, multicenter study to compare the efficacy of SG to 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[c]: 262 randomized (224 treated)

Study Number	Description of Study	Data Included in This Submission	Study Population/ Number of Participants
IMMU-132-06 (TROPHY-U-01)	Phase 2, ongoing, open-label, multicenter, international study to assess the ORR as centrally reviewed by an IRC (also referred to as independent review assessment).	Safety[a] Immunogenicity	Participants with locally **advanced or metastatic UC** who progressed after prior platinum-based and PD-1/PD-L1–based therapies (Cohort 1). Platinum-ineligible participants with locally advanced or metastatic UC who progressed after prior PD-1/PD-L1–based therapy (Cohort 2). Total: 182 enrolled (135 treated) SG (Cohort 1)[b]: 151 enrolled (113 treated) SG (Cohort 2)[b]: 31 enrolled (22 treated)

BICR = blinded independent central review; BM = brain metastasis; CDK = cyclin-dependent kinase; CSR = clinical study report; GBM = glioblastoma multiforme; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; IRC = independent review committee; ISI = Integrated Summary of Immunogenicity; IV = intravenous; NSCLC = non–small cell lung cancer; ORR = objective response rate; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; SCLC = small cell lung cancer; 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 IMMU-132-06 (30 October 2020) and IMMU-132-09 (01 July 2022), and final safety data from Studies 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 eribulin, capecitabine, gemcitabine, or vinorelbine administered per standard of care.

d Starting doses of 8, 10, 12, and 18 mg/kg were evaluated during the dose escalation phase (Phase 1) of Study IMMU-132-01.

e 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, 81 participants received SG 8 mg/kg, 9 participants received SG 12 mg/kg, and 3 participants received SG 18 mg/kg. The population included the following tumor types: ovarian, endometrial, cervical, TNBC, HR+/HER2− metastatic breast cancer, castration-resistant prostate cancer, colorectal cancer, NSCLC, SCLC, head and neck squamous cell cancer, esophageal, gastric, pancreatic, hepatocellular, renal (clear cell), thyroid (papillary), and metastatic UC. Patients with GBM were also eligible, but were not required to have metastatic disease.

f Overall, 68 participants with non-TNBC were enrolled in Study IMMU-132-01 and received at least 1 dose of SG. Of these 68 participants, 54 were confirmed as HR+/HER2− who had progressed on at least 1 prior hormonal therapy in the metastatic setting, and had received at least 1 dose of SG 10 mg/kg.

2.3.2. Pharmacokinetics

Analytical methods

Four analytes were measured to characterize the pharmacokinetics (PK) of SG:

1) total antibody (hRS7 + hRS7-SN-38)

A validated assay that is capable of distinguishing naked (unconjugated; drug-to-antibody ratio (DAR) 0) hRS7-IgG from SN-38-conjugated SG (DAR 1-8) is not available. Therefore, the amount of SG in serum was calculated using the concentrations of measured total SN-38 and free SN-38. A fixed DAR of 8 was used for calculation purposes only. The amount of circulating SG in serum was then estimated as follows SG = 161 kDa/8 × 392 Da × (Concentration of Bound SN - 38)

2) free SN-38 (the cytotoxic payload, not covalently bound to SG)

3) SN-38G (an inactive metabolite of SN-38, not covalently bound to SG)

4) total SN-38 (free SN-38 + hRS7-SN-38)

Bioanalytical methods for the quantitation of total SN-38, free SN-38, SN-38G, and hRS7-IgG in human serum were developed and fully validated at KCAS, LLC (Shawnee, Kansas, USA).

Quantification of the analytes in serum were conducted using the same validated bioanalytical methods that were used in the initial breast cancer application.

Immunogenicity

To assess the immunogenicity of SG or its components, assay methods to detect the presence of anti-drug antibodies (ADAs) and neutralising antibodies (Nabs) were developed and validated in accordance with agency guidance (European Medicines Agency (EMA) 2017, U.S. Department of Health & Human Services (DHHS) 2019), as stated by the Applicant.

In addition to Studies IMMU 132 01 and IMMU 132 05, the following studies contributed only to the assessment of the immunogenicity of SG.

- Study IMMU 132 06: A Phase II Open-Label, Study of IMMU 132 in Metastatic Urothelial Cancer After Failure of Platinum-Based Regimen or Anti-PD-1/PD-L1 Based Immunotherapy (Cohorts 1 and 2)
- Study IMMU 132 09 (TROPiCS 02): Phase 3 Study of Sacituzumab Govitecan (IMMU 132) Versus Treatment of Physician's Choice (TPC) in Subjects with Hormonal Receptor Positive (HR+) Human Epidermal Grown Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer (MBC) Who Have Failed at least Two Prior Chemotherapy Regimens

Distribution

Based on the PopPK analysis of SG using data from Studies IMMU-132-01, IMMU-132-05, and IMMU-132-09, the Vc and Vp of SG were estimated to be 2.65 and 0.929 L, respectively, corresponding to an estimated Vss of 3.58 L.

Elimination

Based on the PopPK analysis of SG using data from Studies IMMU-132-01, IMMU-132-05, and IMMU-132-09, the CL of SG was estimated to be 0.128 L/h (SG PopPK 2022-02). The median t1/2 of SG and free SN-38 was 23.4 and 17.6 hours, respectively, based on the noncompartmental analyses for Study IMMU-132-05.

Population Pharmacokinetics

Concentration-time data from Studies IMMU-132-01 and IMMU-132-05 were used to develop the PopPK models, and concentration-time data from Study IMMU-132-09 were used for external validation and re-estimation of PK parameters. The PK of SG, free SN-38, and total antibody from Study IMMU-132-09 were described by the previously developed PopPK models based on Studies IMMU-132-01 and IMMU-132-05.

The re-estimated PK parameter values and associated variability using combined data from Studies IMMU-132-01, IMMU-132-05, and IMMU-132-09 were similar to those of the previously developed model (Table 2, Table 3 and Table 4). Serum concentration data from a total of 784, 770, and 786 participants were used for the final PopPK model of SG, free SN-38, and total antibody, respectively. There was no change in the model structure or statistical significance of the previously identified covariates for any of the 3 analytes after inclusion of the Study IMMU-132-09 dataset.

The prediction-corrected visual predictive checks for the final PopPK models of SG, free SN-38, and total antibody (including data from Study IMMU-132-09) are presented in Figure 1.

Table 2: Comparison of Population Pharmacokinetic Model Parameters of Sacituzumab Govitecan With and Without Inclusion of Study IMMU-132-09 Data

Parameter	Previously Developed Model Based on Studies IMMU-132-01 and IMMU-132-05	Updated Model Based on Studies IMMU-132-01, IMMU-132-05, and IMMU-132-09
CL (L/h)	0.133	0.128
V_c (L)	2.77	2.65
Q (L/h)	0.00551	0.00513
V_p (L)	0.908	0.929
Weight exponent on CL and Q	0.508	0.523
Weight exponent on V_c and V_p	0.532	0.540
Baseline serum albumin exponent on CL	−0.355	−0.395
Time after the last dose on residual unexplained variability SD	0.00517	0.00497
Interindividual variability variance on CL	0.0114	0.0136
Residual unexplained variability SD on logarithmic SG	0.204	0.198

PK = pharmacokinetic(s); SD = standard deviation; SG = sacituzumab govitecan
The structure of continuous covariate on any PK parameter (CL, V_c, Q, and V_p) was as follows:
PK parameter = $\text{PK parameter}_{\text{typical}} \times (\text{individual covariate/typical covariate})^{\text{exponent}}$, where $\text{PK parameter}_{\text{typical}}$ was the PK parameter of a typical participant and exponent was the scaling factor for the corresponding covariate. Typical covariate values used were 70 kg for body weight and 38 g/L for albumin. The covariate effect on residual of log-transformed SG concentration was modeled as follows:
Residual unexplained variability SD × (1 + time after the last dose on residual unexplained variability × time after the last dose).
Source: SG PopPK 2022-02

Table 3: Comparison of Population Pharmacokinetic Model Parameters for Free SN-38 With and Without Inclusion of Study IMMU-132-09 Data

Parameter	Previously Developed Model Based on Studies IMMU-132-01 and IMMU-132-05	Updated Model Based on Studies IMMU-132-01, IMMU-132-05, and IMMU-132-09
First-order SG release rate (1/h)	0.096	0.0937
CL/F (L/h)	409	401
Q/F (L/h)	247	243
V_c/F (L)	49	49
V_p/F (L)	2177	2177
Weight exponent on CL/F and Q/F	0.500	0.519
Time after the last dose on residual unexplained variability SD	0.0106	0.00898
Study IMMU-132-01 on residual unexplained variability SD	−0.230	−0.168
Interindividual variability variance on first-order SG release rate	0.332	0.397
Interindividual variability variance on CL/F	0.411	0.630
Logarithmic residual unexplained variability SD on logarithmic SN-38	2.80	0.344
First-order SG release rate ~ CL/F covariance	0.269	0.406

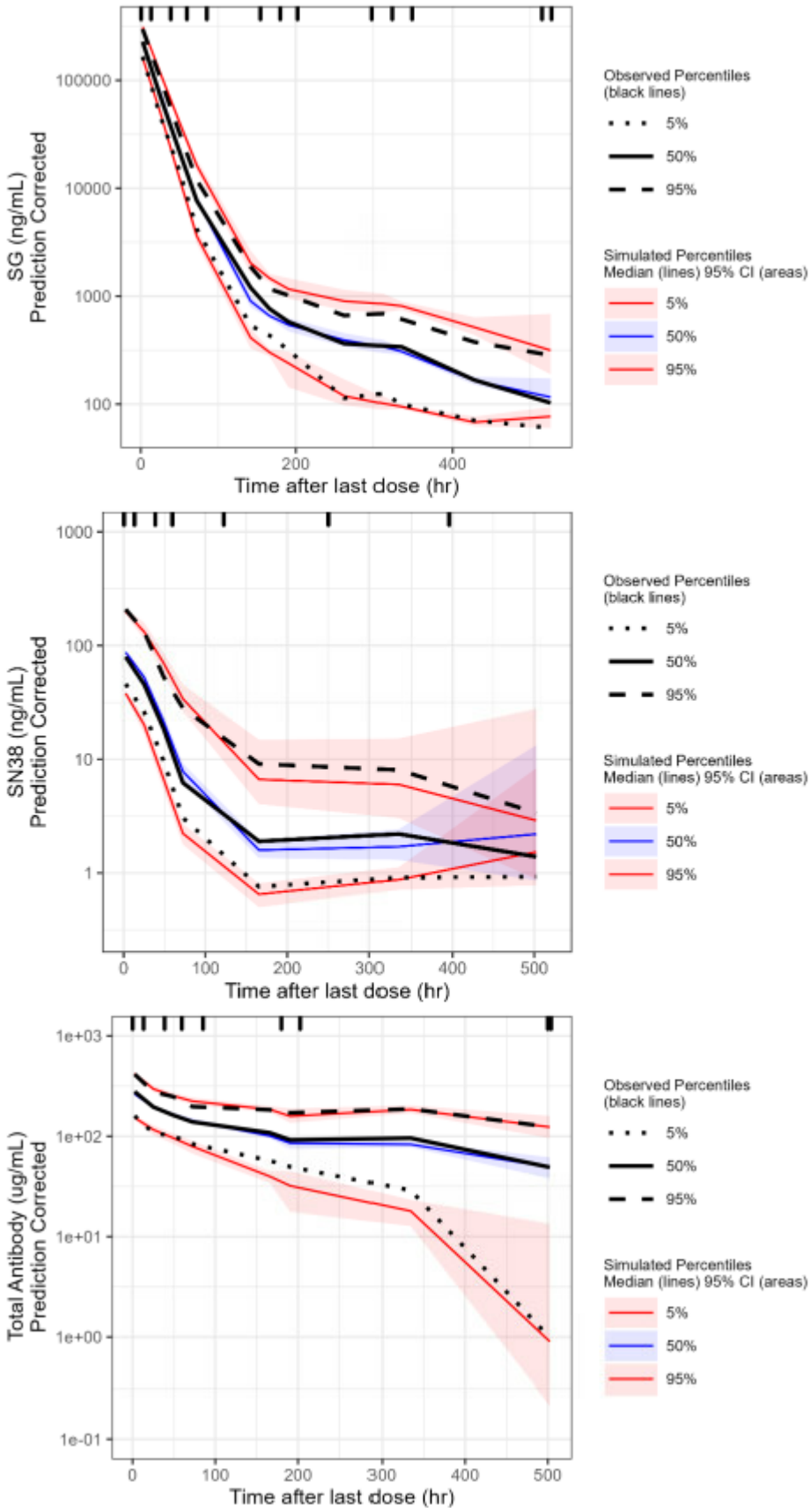
PK = pharmacokinetic(s); SD = standard deviation; SG = sacituzumab govitecan
The structure of continuous covariate on any PK parameter (CL/F and Q/F) was as follows:
PK parameter = $\text{PK parameter}_{\text{typical}} \times (\text{individual covariate/typical covariate})^{\text{exponent}}$, where $\text{PK parameter}_{\text{typical}}$ was the PK parameter of a typical participant and exponent was the scaling factor for the corresponding covariate. The typical covariate value was 70 kg for body weight. The covariate effect on residual of log-transformed free SN-38 concentration was as follows:
Residual unexplained variability SD × (1 + time after the last dose on residual unexplained variability × time after the last dose) × (1 + Study IMMU-132-01 on residual unexplained variability).
Source: SG PopPK 2022-02

Table 4: Comparison of Population Pharmacokinetic Model Parameters for Total Antibody With and Without Inclusion of Study IMMU-132-09 Data

Parameter	Previously Developed Model Based on Studies IMMU-132-01 and IMMU-132-05	Updated Model Based on Studies IMMU-132-01, IMMU-132-05 and IMMU-132-09
CL (L/h)	0.0164	0.0155
V_c (L)	3.06	2.97
Q (L/h)	0.00963	0.0105
V_p (L)	1.20	1.32
Weight exponent on CL and Q	0.372	0.422
Weight exponent on V_c and V_p	0.446	0.458
Baseline serum albumin exponent on CL	−0.735	−0.734
Other tumor type on CL	−0.134	−0.112
Male sex on V_c	0.121	0.153
Study IMMU-132-01 on residual unexplained variability SD	−0.250	−0.140
Maximum relative reduction of CL (%)	16.7	16.8
Rate constant of the time effect on CL (1/h)	0.000608	0.000391
Interindividual variability variance on CL	0.100	0.110
Interindividual variability variance on V_c	0.0457	0.0397
Proportional error CV	0.207	0.191
Additive error SD (µg/mL)	27.3	21.8
CL ~ V_c covariance	0.0452	0.0390

CV = coefficient of variation; PK = pharmacokinetic(s); SD = standard deviation; SG = sacituzumab govitecan
Since the dose used in the model was the SG dose, the true antibody CL and V_d parameters values equal the model estimates multiplied by 0.92 (ratio of the molecular weight of the naked antibody to molecular weight of SG).
The structure of time-dependent CL was as follows:
$CL = CL_{linear} \times (1 - CLT/100 \times [1 - e^{-KEFF \times time}])$, where CL_{linear} was the linear CL at baseline, CLT was the maximum relative change of CL, and KEFF was the rate constant of the time effect.
The structure of continuous covariate on any PK parameter (CL, V_c, Q, and V_p) was as follows:
PK parameter = $PK\ parameter_{typical} \times (individual\ covariate/typical\ covariate)^{exponent}$, where $PK\ parameter_{typical}$ was the PK parameter of a typical participant and exponent was the scaling effect for the corresponding covariate. The typical covariate values were 70 kg for body weight and 38 g/L for albumin.
The structure of categorical covariate on any PK parameter (CL and V_c) was as follows:
PK parameter = $PK\ parameter_{typical} \times (1 +$ specific category on PK parameter).
The covariate effect on residual of total antibody concentration was as follows:
Residual unexplained variability SD × (1 + Study IMMU-132-01 on residual unexplained variability).

Figure 1: Prediction-Corrected Visual Predictive Check for the Final Sacituzumab Govitecan, Free SN-38, and Total Antibody Population Pharmacokinetic Models



Special populations

Effect of Intrinsic Factors

The PopPK analysis of SG evaluated the broader potential impact of demographic and disease-related factors on PK as covariates in participants with various advanced epithelial cancers, participants with metastatic triple-negative breast cancer, and participants with HR+/HER2− metastatic breast cancer from Studies IMMU-132-01, IMMU-132-05, and IMMU-132-09, respectively. A forest plot analysis was performed to further assess the correlations between covariates and SG, free SN-38, and total antibody exposures (AUC and Cmax) over the first treatment cycle relative to exposures in a participant with reference covariate values. The individual-estimated PK parameters from the final PopPK models were used to predict individual AUC and Cmax over the first treatment cycle for the SG 10-mg/kg dose. The exposures for participants were predicted using participants' respective covariate values (including body weight). Covariate correlations for all continuous and categorical covariates were subsequently analyzed based on linear models and predicted at the 5th and 95th percentiles of continuous covariate values or for all categories of categorical covariates. Relative exposures were normalized by the predictions at the median of continuous covariate values and the most common category of categorical covariates. The effect of intrinsic factors on SG, free SN-38, and total antibody exposures is summarized below.

Renal Impairment

Mild or moderate renal impairment had no clinically relevant effect on SG, free SN-38, or total antibody exposure.

Hepatic Impairment

The exposure of sacituzumab govitecan was similar in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN, or bilirubin > 1.0 to ≤ 1.5 ULN and AST of any level; n = 257) to patients with normal hepatic function (bilirubin and AST ≤ ULN; n = 526). Mild hepatic impairment had no clinically relevant effect on SG, free SN-38, or total antibody exposure. Sacituzumab govitecan and free SN-38 exposures are unknown in patients with moderate or severe hepatic impairment.

A Phase 1 study evaluating the PK and safety of SG in participants with moderate hepatic impairment is currently ongoing (Study IMMU-132-15).

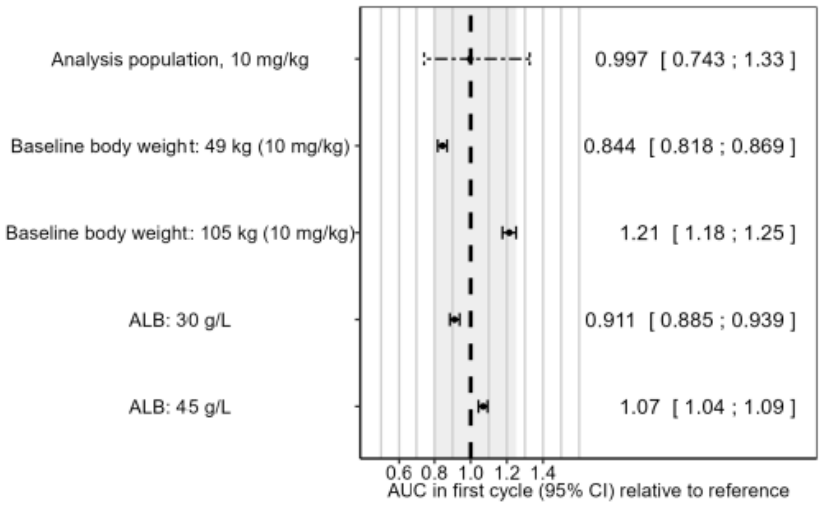
Age

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

Body Weight

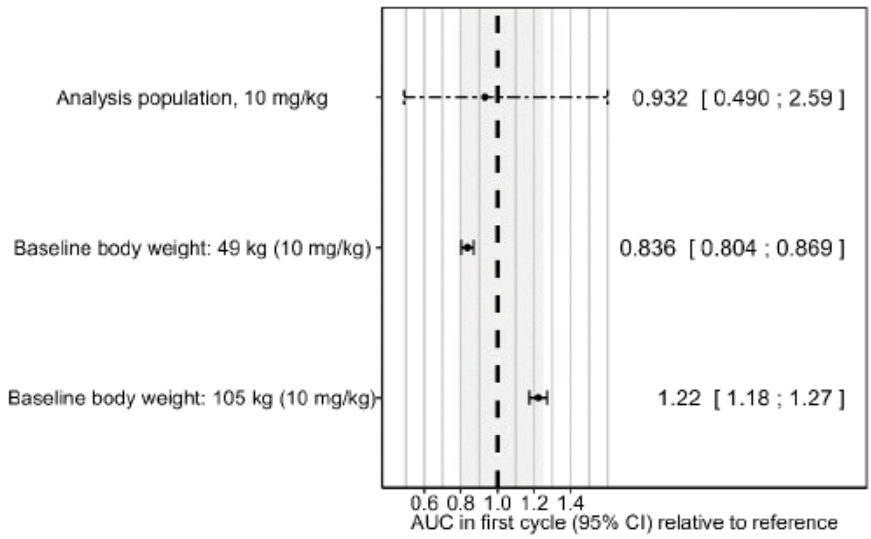
The effect of body weight on model-predicted SG and free SN-38 AUC was within 80% to 125% of the predicted exposures in a typical participant (body weight of 70 kg), with a body weight of 105 kg (95th percentile) estimated to result in 22% higher AUC than a typical participant (Figure 2 and Figure 3). For total antibody, the model-predicted AUC for a body weight of 105 kg (95th percentile) was estimated to be 26% higher than that in a typical participant (Figure 4).

Figure 2: Population Pharmacokinetic Analyses: Impact of Statistically Significant Covariates on Sacituzumab Govitecan AUC Over the First Cycle



ALB = albumin; CI = confidence interval; SG = sacituzumab govitecan
The AUC at the given covariate values was compared with the AUC predicted for a typical participant (defined as a participant with a body weight of 70 kg and baseline ALB of 38 g/L at the beginning of the SG study). Dots and error bars for covariates show the predicted relative AUC with 95% CI reflecting model parameter uncertainty. The dot and dashed error bar show the predicted individual AUC of the analysis population (10 mg/kg) relative to reference, which accounted for interindividual variation.
Source: SG PopPK 2022-02

Figure 3: Population Pharmacokinetic Analyses: Impact of Statistically Significant Covariates on Free SN-38 AUC Over the First Cycle



CI = confidence interval; SG = sacituzumab govitecan
The AUC at the given covariate values was compared with the AUC predicted for a typical participant (defined as a participant with a body weight of 70 kg at the beginning of the SG study). Dots and error bars for covariates show the predicted relative AUC with 95% CI reflecting model parameter uncertainty. The dot and dashed error bar show the predicted individual AUC of the analysis population (10 mg/kg) relative to reference, which accounted for interindividual variation.
Source: SG PopPK 2022-02

Race

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

UGT1A1 Genotype

No significant differences in SG or free SN-38 exposure were observed in participants with the UGT1A1*28/*28 genotype compared with participants with the UGT1A1*1/*1 or UGT1A1*1/*28 genotype.

Baseline Trop-2 Expression Level

A continuous covariate representing Trop-2 expression based on the staining H-score was available for participants from Studies IMMU-132-05 and IMMU-132-09. Baseline Trop-2 expression level was not found to be meaningfully correlated with individual-predicted exposures based on the final PopPK models of SG and total antibody.

Pharmacokinetic interaction studies

Effect of Extrinsic Factors

No drug-drug interaction studies with SG were submitted.

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 patients concomitantly receiving UGT1A1 enzyme inducers.

Among the 789 participants assessed in the PopPK analyses, only a few participants received either UGT1A1 inhibitors (N = 16) or inducers (N = 5) during SG treatment. The model-estimated individual SG and free SN-38 exposures in participants who received UGT1A1 inhibitors or inducers were comparable and within the range of exposures in participants who did not receive UGT1A1 inhibitors or inducers.

2.3.3. Pharmacodynamics

Integrated Antidrug Antibody Responses

An overall summary and cross-study comparison of ADA responses to SG in participants who received at least 1 dose of SG 10 mg/kg are presented in Table 5. Immunogenicity samples for ADA prevalence and incidence assessments were evaluable for 869 and 785 participants, respectively, across Studies IMMU-132-01, IMMU-132-05, IMMU-132-06, and IMMU-132-09.

Only 9 of 785 participants evaluable for ADA incidence (1.1%) had treatment-emergent ADAs to SG. Among participants with treatment-emergent ADAs, the onset of ADAs was typically observed at their last visit (range: 36 to 245 days after first SG dose). The maximum reportable ADA titer observed across the studies was low and varied in range from 10 to 30.

No participant had treatment-boosted ADAs. Six of the 9 participants (0.8% of all patients treated with sacituzumab govitecan) with treatment-emergent ADAs also had positive NAb assessments.

Table 5: IMMU-132-01, IMMU-132-05, IMMU-132-06, and IMMU-132-09: Summary of Antidrug Antibody Response to Sacituzumab Govitecan (IMMU-132 ISI Populations)

	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 = 133)	IMMU-132-09 SG (10 mg/kg) (N = 257)	Total 01, 05, 09 SG (10 mg/kg) (N = 736)	Total 01, 05, 06, 09 SG (10 mg/kg) (N = 869)
Evaluable for ADA prevalence	221	258	133	257	736	869
Any ADA positive (baseline or postbaseline)	2 (0.9%)	4 (1.6%)	4 (3.0%)	0	6 (0.8%)	10 (1.2%)
ADA positive at baseline	1 (0.5%)	0	0	0	1 (0.1%)	1 (0.1%)
ADA positive postbaseline	1 (0.5%)	4 (1.6%)	4 (3.0%)	0	5 (0.7%)	9 (1.0%)
Evaluable for ADA incidence (treatment emergent)	210	242	109	224	676	785
ADA positive postbaseline and not detected at baseline (treatment-induced ADA)	1 (0.5%)	4 (1.7%)	4 (3.7%)	0	5 (0.7%)	9 (1.1%)
Persistent positive[a]	1 (0.5%)	3 (1.2%)	4 (3.7%)	0	4 (0.6%)	8 (1.0%)
Transient positive[b]	0	1 (0.4%)	0	0	1 (0.1%)	1 (0.1%)
ADA positive postbaseline and positive at baseline	0	0	0	0	0	0
Treatment-boosted ADA[c]	0	0	0	0	0	0
ADA incidence (treatment emergent)[d]	1 (0.5%)	4 (1.7%)	4 (3.7%)	0	5 (0.7%)	9 (1.1%)
ADA not detected postbaseline and positive at baseline	1 (0.5%)	0	0	0	1 (0.1%)	1 (0.1%)
NAb incidence (treatment emergent)[e]	1 (0.5%)	3 (1.2%)	2 (1.8%)	0	4 (0.6%)	6 (0.8%)

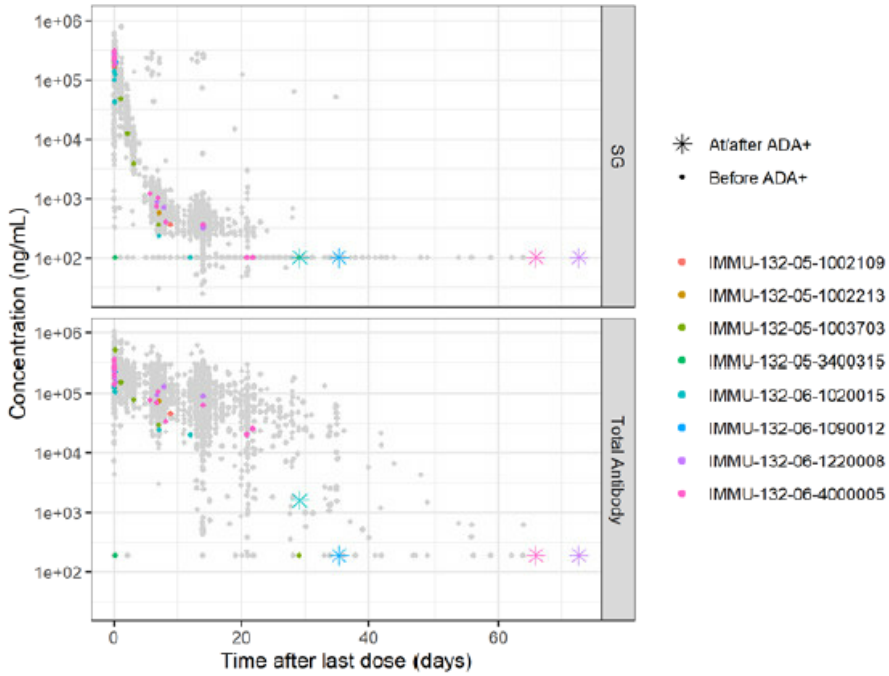
ADA = antidrug antibody; ISI = Integrated Summary of Immunogenicity; NAb = neutralizing antibody; SG = sacituzumab govitecan
a Persistent-positive ADA: positive at > 1 postdose assessments (with ≥ 16 weeks between first and last positive) or positive at last postdose assessment.
b Transient-positive ADA: having ≥ 1 postdose ADA-positive assessment and not fulfilling the conditions of persistent-positive ADA.
c Treatment-boosted ADA: baseline positive ADA titer that was boosted to a 9-fold (2-step dilutions) or higher level following drug administration.
d ADA incidence (treatment-emergent ADA): the sum of both treatment-induced and treatment-boosted ADA.
e NAb incidence (treatment emergent) is defined as NAb-positive assessment on treatment-emergent ADA-positive samples.
Evaluable for ADA prevalence population includes participants who have at least 1 nonmissing reportable ADA result. Evaluable for ADA incidence population includes participants who have at least 1 nonmissing postbaseline ADA result.
Source: ISI, Table 1

Impact of Antidrug Antibodies on Sacituzumab Govitecan and Total Antibody Pharmacokinetics

The impact of immunogenicity on the PK of SG and total antibody was evaluated using available serum concentration and ADA data from Studies IMMU-132-01, IMMU-132-05, IMMU 132 06, and IMMU-132-09. Pharmacokinetic data were available for 8 of 9 participants with treatment-emergent ADA responses. An overlay of time course of SG and total antibody concentrations in ADA-positive (solid-colored symbols) and ADA-negative (solid gray circles) participants is presented in Figure 4. Overall, SG exposures in ADA positive participants were within the range of exposures observed in ADA-negative participants.

Due to the very low incidence of treatment-emergent ADAs (1.1%), a quantitative assessment of the impact of ADAs on SG or total antibody exposure could not be performed in the PopPK analyses.

Figure 4: IMMU-132-01, IMMU-132-05, IMMU-132-06, and IMMU-132-09: Sacituzumab Govitecan and Total Antibody Serum Concentrations Versus Time Since Last Dose by Antidrug Antibody Status Based on Pooled Data



ADA = antidrug antibody; ADA+ = antidrug antibody positivity; PK = pharmacokinetic(s); SG = sacituzumab govitecan
Gray scatter shows PK data from participant-level ADA-negative participants. Asterisks show PK samples in participant-level ADA-positive participants after their first time-matched ADA-positive PK samples.
Source: SG PK/ADA 2022-01

Impact of Antidrug Antibodies on Efficacy

Given the small number of participants with positive ADA responses to SG across Studies IMMU 132-01, IMMU-132-05, IMMU-132-06, and IMMU-132-09, no formal analysis was performed to assess the impact of ADAs on the efficacy of SG. Overall, there was no clear impact of ADA on efficacy.

Impact of Antidrug Antibodies on Safety

All 9 participants (1.1%) with treatment-emergent ADAs received a starting dose of SG 10 mg/kg. None of these participants had treatment-emergent serious adverse events considered related to SG or treatment-emergent AEs that led to premature discontinuation of study drug. Among the participants with treatment-emergent ADAs, only 2 participants had treatment-emergent hypersensitivity+ AEs (1 participant in Study IMMU 132 05 and 1 participant in Study IMMU 132 06), and these did not begin in the time frame of positive ADA results; both participants also had positive NAb assessments. No participant had treatment-emergent immune-mediated AEs.

2.3.4. PK/PD modelling

Exposure-Response Relationships

Exposure-response analyses were previously conducted using data from a total of 277 participants with metastatic triple-negative breast cancer. These analyses characterized the relationships between SG, free SN-38, and total antibody exposures and the efficacy and safety of SG in participants with metastatic triple-negative breast cancer, based on clinical data from Studies IMMU-132-01 and IMMU-

132-05. The exposure-response analyses showed exposure-dependent increases in the probability of response (complete response [CR] and objective response [OR]) and survival (PFS and OS) for the evaluated efficacy endpoints and exposure-dependent increases in the probability of the evaluated AEs (neutropenia, diarrhoea, nausea, vomiting, and hypersensitivity reactions). Relative to lower doses, greater efficacy and a manageable safety profile were estimated with the exposures associated with the SG 10-mg/kg dosing regimen.

Using a similar modeling framework, exposure-response for efficacy analyses were conducted using data from a total of 260 participants with HR+/HER2− metastatic breast cancer from Study IMMU-132-09 and exposure-response for safety and dose reductions/dose delays analyses were conducted using data from a total of 569 participants with metastatic breast cancer who received SG (those with HR+/HER2− metastatic breast cancer or metastatic triple-negative breast cancer in Study IMMU-132-01, those with metastatic triple-negative breast cancer in Study IMMU-132-05, and those with HR+/HER2− metastatic breast cancer in Study IMMU- 132-09). Data from the primary (final) analysis of PFS and first planned interim superiority analysis of OS (OS IA1, data cutoff date of 03 January 2022) for IMMU-132-09 was used for exposure-response analyses of all endpoints except OS. Exploratory analyses using data from the second planned interim analysis of OS (OS IA2, data cutoff date of 01 July 2022) for IMMU- 132-09 indicated that few, if any, new events were reported for CR, ORR, CBR, and PFS and the only meaningful data addition occurred for the OS endpoint. Hence, data from OS IA2 was only used for exposure-response analysis of OS. For all other efficacy and safety endpoints, exposure response analyses were conducted using data from the primary analysis.

Exposure-Efficacy Analyses

Exposure-efficacy relationships were evaluated in participants with HR+/HER2− metastatic breast cancer who received a starting dose of SG 10 mg/kg on Days 1 and 8 of a 21-day cycle in Study IMMU-132-09 (SG E-R 2022-03). The exposure-efficacy analysis dataset included a total of 260 participants with HR+/HER2− metastatic breast cancer from Study IMMU-132-09 who had PopPK parameter estimates to enable estimation of exposure metrics related to SG dosing and had data for the respective efficacy endpoints.

The evaluated efficacy endpoints included CR, ORR, CBR, PFS, and OS.

The exposure-efficacy relationships were analyzed using binomial logistic regression models for CR, ORR, and CBR and Cox proportional-hazards time-to-event models for PFS and OS.

The CAVG was derived based on the individual-estimated concentration of the respective analyte (SG, free SN-38, or total antibody) as follows:

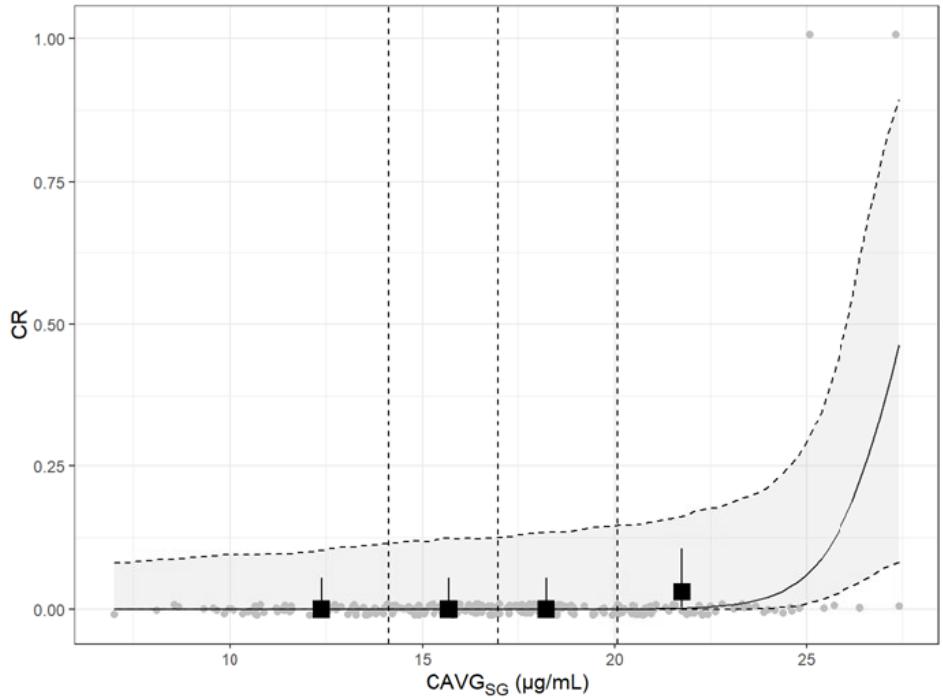
$$CAVG_{analyte} = \int_0^{t_{event}} C_{analyte}\, d\tau \Big/ t_{event}$$

In the equation above, t_{event} is the time to observing the endpoint of interest.

In addition to CAVG, the Cmax and AUC during the first treatment cycle (21 days after the first SG dose) and cumulative exposure (AUC) until the observed response (CR, ORR, and CBR only) for each of the 3 analytes (SG, free SN-38, and total antibody) were also evaluated as exposure metrics related to the efficacy endpoints, and the most statistically significant exposure metric was retained in the model. In addition to exposure, the effect of other covariates was characterized within the modeling framework.

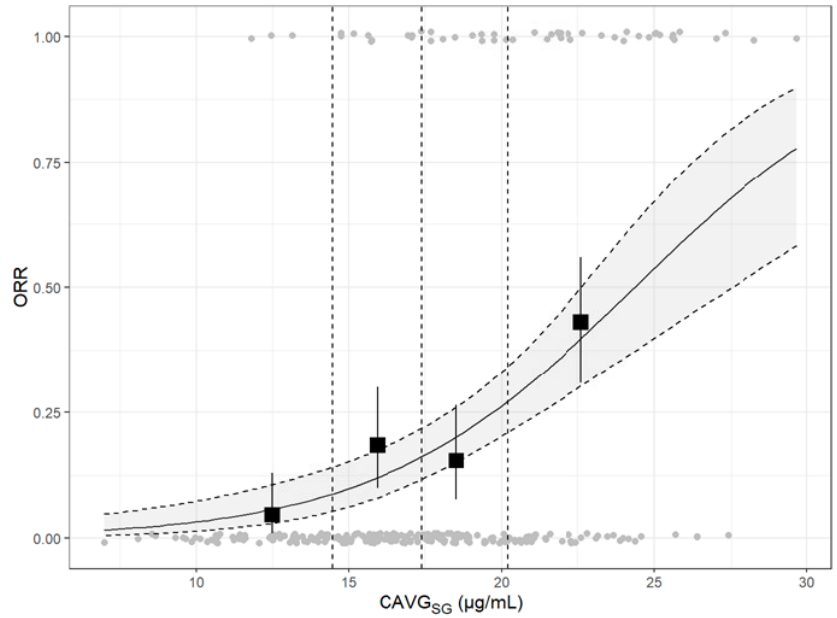
Within the evaluated exposure range, SG average concentration ($CAVG_{SG}$) was identified as the most statistically significant exposure metric correlated with CR, ORR, and CBR, such that higher values of CAVGSG were statistically significantly associated with an increased probability of CR, OR, and CB (see Figures below). A comparison of the observed proportions of participants and model-predicted probabilities of CR, OR, and CB for the SG 10-mg/kg starting dose group is presented in Table 6. Once CAVGSG was included in the models of CR, ORR, and CBR, no additional statistically significant covariates were identified.

Figure 5: IMMU-132-09: Observed Proportion and Model-Predicted Probability of Complete Response Versus Sacituzumab Govitecan Average Concentration



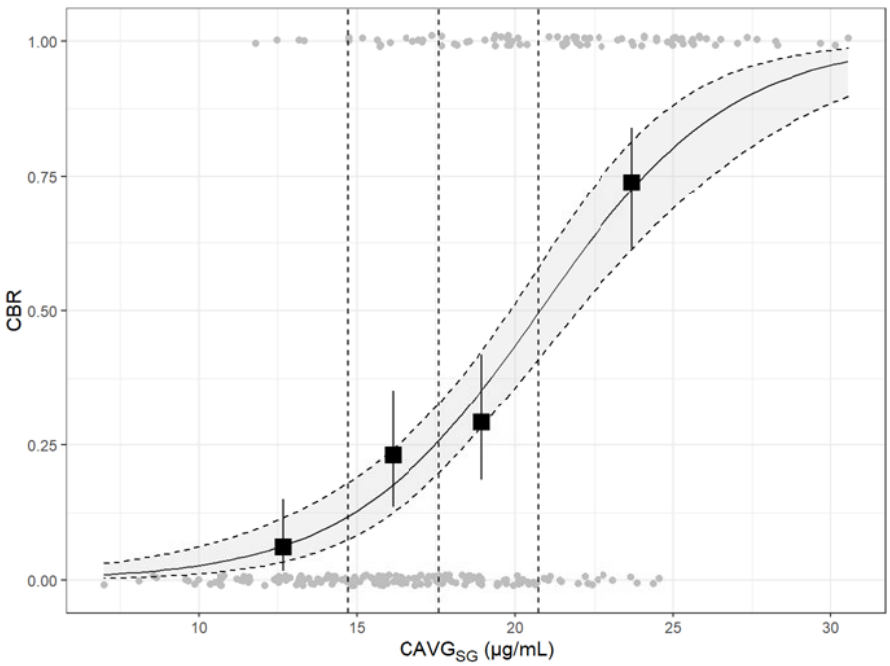
$CAVG_{SG}$ = sacituzumab govitecan average concentration; CI = confidence interval; CR = complete response
Gray circles indicate data from individual participants. Closed squares (error bars) show the observed proportion of participants with CR (95% CI based on the Pearson-Klopper method) by exposure quartile and are plotted at the median exposure of each quartile. Dashed vertical lines show the boundaries of the exposure quartiles. Solid (dashed and gray area) curves show the model-predicted probability of the CR (95% CI).
Source: SG E-R 2022-03

Figure 6: IMMU-132-09: Observed Proportion of Participants with Objective Response and Model-Predicted Objective Response Rate Versus Sacituzumab Govitecan Average Concentration



$CAVG_{SG}$ = sacituzumab govitecan average concentration; CI = confidence interval; ORR = objective response rate
Gray circles indicate data from individual participants. Closed squares (error bars) show the observed proportion of participants with an objective response (95% CI based on the Pearson-Klopper method) by exposure quartile and are plotted at the median exposure of each quartile. Dashed vertical lines show the boundaries of the exposure quartiles. Solid (dashed and gray area) curves show the model-predicted ORR (95% CI).
Source: SG E-R 2022-03

Figure 7: IMMU-132-09: Observed Proportion of Participants With Clinical Benefit and Model-Predicted Clinical Benefit Rate Versus Sacituzumab Govitecan Average Concentration



$CAVG_{SG}$ = sacituzumab govitecan average concentration; CBR = clinical benefit rate; CI = confidence interval
Gray circles indicate data from individual participants. Closed squares (error bars) show the observed proportion of participants with clinical benefit (95% CI based on the Pearson-Klopper method) by exposure quartile and are plotted at the median exposure of each quartile. Dashed vertical lines show the boundaries of the exposure quartiles. Solid (dashed and gray area) curves show the model-predicted CBR (95% CI).
Source: SG E-R 2022-03

Table 6: IMMU-132-09: Observed Proportion of Participants and Model-Predicted Probability of Complete Response, Objective Response, and Clinical Benefit

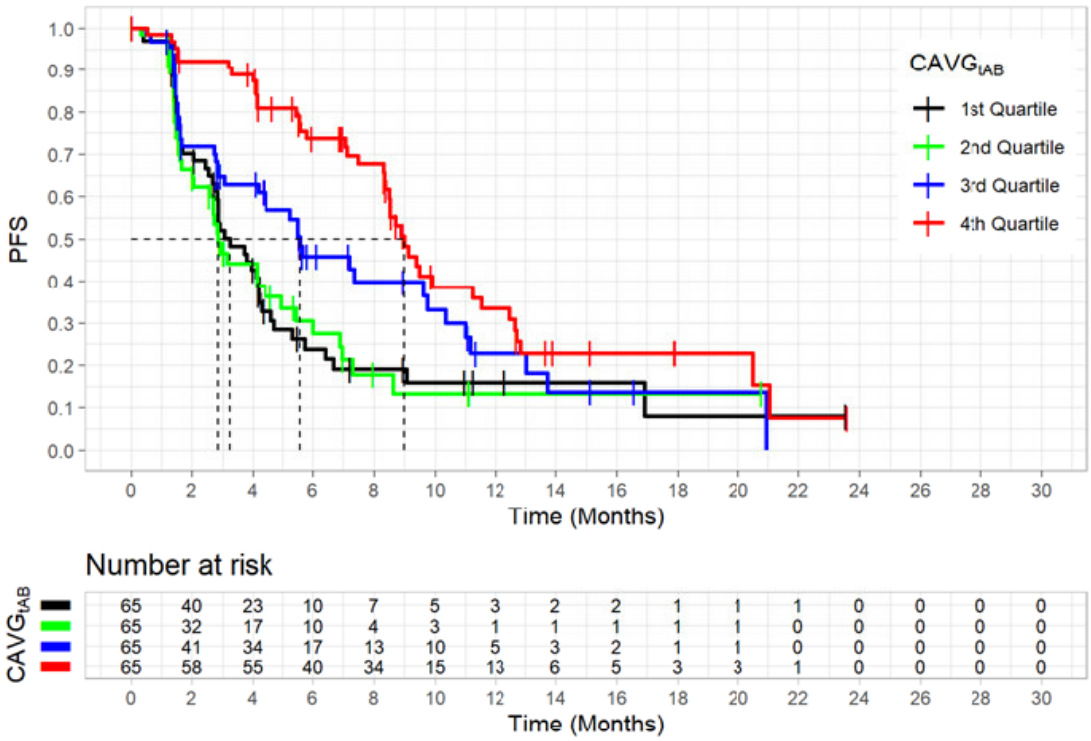
Efficacy Endpoint	Observed Number (%) of Participants Who Achieved Efficacy Response (N = 260)	Mean of Individual Model-Predicted Probability (95% CI)
CR	2 (0.8%)	0.00769 (0, 0.0155)
ORR	53 (20.4%)	0.204 (0.162, 0.250)
CBR	86 (33.1%)	0.331 (0.285, 0.381)

CBR = clinical benefit rate; CI = confidence interval; CR = complete response; ORR = objective response rate
Source: SG E-R 2022-03

For PFS and OS, total antibody average concentration (CAVGtAB) was found to be the most statistically significant exposure metric, such that higher values of CAVGtAB were statistically significantly associated with longer PFS and OS. The median survival times across quartiles of CAVGtAB suggested that higher exposure was associated with longer PFS and OS in participants with HR+/HER2− metastatic breast cancer.

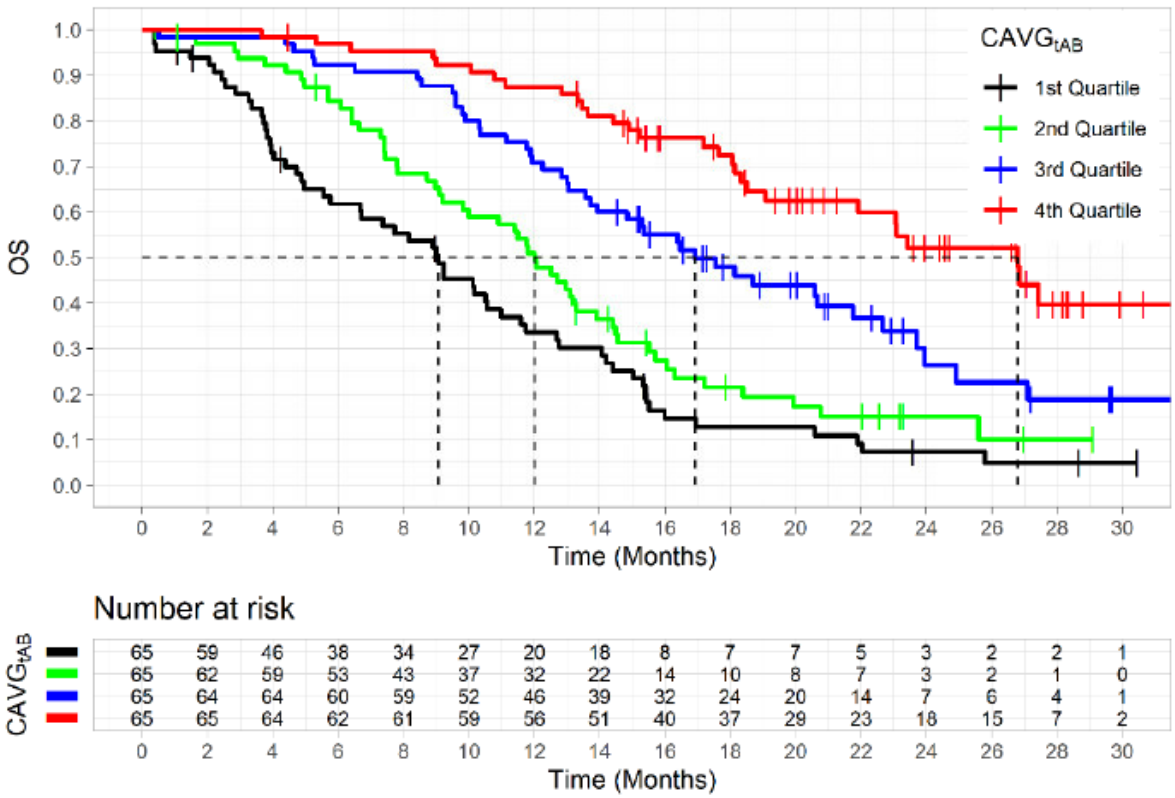
The median survival times for both PFS and OS were longer for participants in the highest quartile of CAVGtAB compared with those in the lower quartiles of CAVGtAB.

Figure 8: IMMU-132-09: Kaplan-Meier Curves of Progression-Free Survival Stratified by Quartiles of Total Antibody Average Concentration



$CAVG_{tAB}$ = total antibody average concentration; PFS = progression-free survival based on blinded independent central review
The vertical dashed lines indicate the median survival time (corresponding to a survival probability of 0.5) associated with each exposure quartile.
Source: SG E-R 2022-03

Figure 9: IMMU-132-09: Kaplan-Meier Curves of Overall Survival Stratified by Quartiles of Total Antibody Average Concentration (OS IA2)



CAVG$_{tAB}$ = total antibody average concentration; OS = overall survival
The vertical dashed lines indicate the median survival time (corresponding to a survival probability of 0.5) associated with each exposure quartile.
Source: SG E-R 2022-03

The demographics and baseline disease characteristics appeared to be comparable among participants in the 4 CAVGtAB quartiles depicted in Figure 9, with the exception of a slightly higher proportion of participants with an ECOG performance status of 1 in the lowest CAVGtAB quartile.

Dose reductions (from a starting dose of SG 10 mg/kg to 7.5 and 5 mg/kg) due to AEs contributed to the spread of exposures among the 4 CAVGtAB quartiles with the lower exposures observed in the first and second CAVGtAB quartiles (Figure 9). The PopPK model-predicted typical CAVGtAB for the 10-mg/kg dose (213 µg/mL, assuming no dose reductions) was more consistent with the exposures observed for the third and fourth CAVGtAB quartiles shown in Figure 9 and Table 6.

For PFS, once CAVGtAB was included in the model, no additional statistically significant covariates were identified. For OS, only higher baseline lactate dehydrogenase levels were found to be statistically significantly associated with shorter OS. Higher levels of lactate dehydrogenase at baseline are known to be associated with worse outcomes across a wide variety of solid tumors, including breast cancer (Forkasiewicz 2020, Pelizzari 2019).

Other evaluated covariates, including age category (< 65 and ≥ 65 years), body weight, race, ECOG performance status, prior cancer treatment, baseline Trop-2 expression level, UGT1A1 genotype, prior

CDK 4/6 inhibitor treatment duration, and number of prior lines of chemotherapy in the metastatic setting, were not found to be significantly associated with any of the evaluated efficacy endpoints.

Exposure-Safety Analyses

Exposure-safety relationships were evaluated in participants with metastatic breast cancer (HR+/HER2− metastatic breast cancer or metastatic triple-negative breast cancer) who received a starting dose of SG 8 mg/kg (16 participants from Studies IMMU-132-01 and IMMU-132-05), 10 mg/kg (550 participants from Studies IMMU-132-01, IMMU-132-05, and IMMU-132-09), or 12 mg/kg (3 participants from Study IMMU-132-01) on Days 1 and 8 of a 21-day cycle (SG E-R 2022-03). The exposure-safety analysis dataset included a total of 569 participants (96.7% in the SG 10-mg/kg starting dose group) from Studies IMMU-132-01, IMMU-132-05, and IMMU-132-09 who had PopPK parameter estimates to enable estimation of exposure metrics related to SG dosing and had data for the respective safety endpoints.

The evaluated safety endpoints included the following selected AEs associated with SG (based on the highest severity grade of the AE reported for each participant): neutropenia (preferred terms: neutropenia and neutrophil count decreased), diarrhoea, nausea, vomiting, and hypersensitivity+ (hypersensitivity Standardized MedDRA Query [SMQ] [broad and narrow] and anaphylactic reaction SMQ [broad and narrow] and only events with onset dates on the day of or 1 day after study drug administration). Other AEs of special interest evaluated as a part of the exposure-safety analyses were neutropenia+ (preferred terms: neutropenia, neutrophil count decreased, and febrile neutropenia) and febrile neutropenia. The exposure-safety relationships were analyzed using nonproportional odds logistic regression models jointly describing the incidence of any grade, Grade 3 or higher, and Grade 4 adverse events (AEs). Nonproportional odds models with grade-specific intercepts and grade-specific slopes were used for diarrhoea, nausea, vomiting, and hypersensitivity+. The observed neutropenia, neutropenia+, and febrile neutropenia events were not adequately described by this model; thus, alternative models based on a common intercept and log-transformed exposure metric were selected for these neutropenia-related AEs.

The average concentration (CAVG) and the Cmax and AUC during the first treatment cycle (21 days after the first SG dose) for each of the 3 analytes (SG, free SN-38, and total antibody) were evaluated as exposure metrics related to the safety endpoints, and the most statistically significant exposure metric was retained in the model; the effect of other covariates was also characterized within the modeling framework.

Overall, CAVGSG was identified as the most statistically significant exposure metric correlated with the evaluated AEs.

Neutropenia

Higher values of CAVGSG were statistically significantly associated with an increased probability of any grade, Grade 3 or higher, and Grade 4 neutropenia. Neutropenia was the only AE where the effect of exposure was significantly associated with the probability of Grade 3 or higher or Grade 4 evaluated AEs. UGT1A1 genotype had a statistically significant effect on the probability of any grade, Grade 3 or higher, and Grade 4 neutropenia, such that participants with the UGT1A1*28/*28 genotype were associated with an increased probability of any grade, Grade 3 or higher, and Grade 4 events compared with participants without the UGT1A1*28/*28 genotype (UGT1A1*1/*1, UGT1A1*1/*28, all others, or missing) ().

Diarrhoea

Higher values of CAVGSG were statistically significantly associated with an increased probability of any grade diarrhoea (Figure 11). Once CAVGSG was included in the model of diarrhoea, no additional statistically significant covariates were identified.

Nausea

Higher values of CAVGSG were statistically significantly associated with an increased probability of any grade nausea. Region had a statistically significant effect on the probability of any grade nausea, such that participants in North America were associated with an increased probability of any grade events compared with participants in Europe. Despite the statistically significant effect of region, plots of the exposure-response relationships indicated that the model-predicted probability of nausea showed considerable overlap between relevant covariate strata. As such, the identified region effect was not considered clinically relevant.

Vomiting

Higher values of CAVGSG were statistically significantly associated with an increased probability of any grade vomiting. Study was found to have a statistically significant effect on the probability of any grade vomiting, such that participants from Study IMMU-132-01 were associated with an increased probability of any grade events compared with participants from Studies IMMU-132-05 and IMMU-132-09. Despite the statistically significant effect of study, plots of the exposure-response relationships indicated that the model-predicted probability of vomiting showed considerable overlap between relevant covariate strata.

Hypersensitivity+

Higher values of CAVGSG were statistically significantly associated with an increased probability of any grade hypersensitivity+. Once CAVGSG was included in the model of hypersensitivity+, no additional statistically significant covariates were identified.

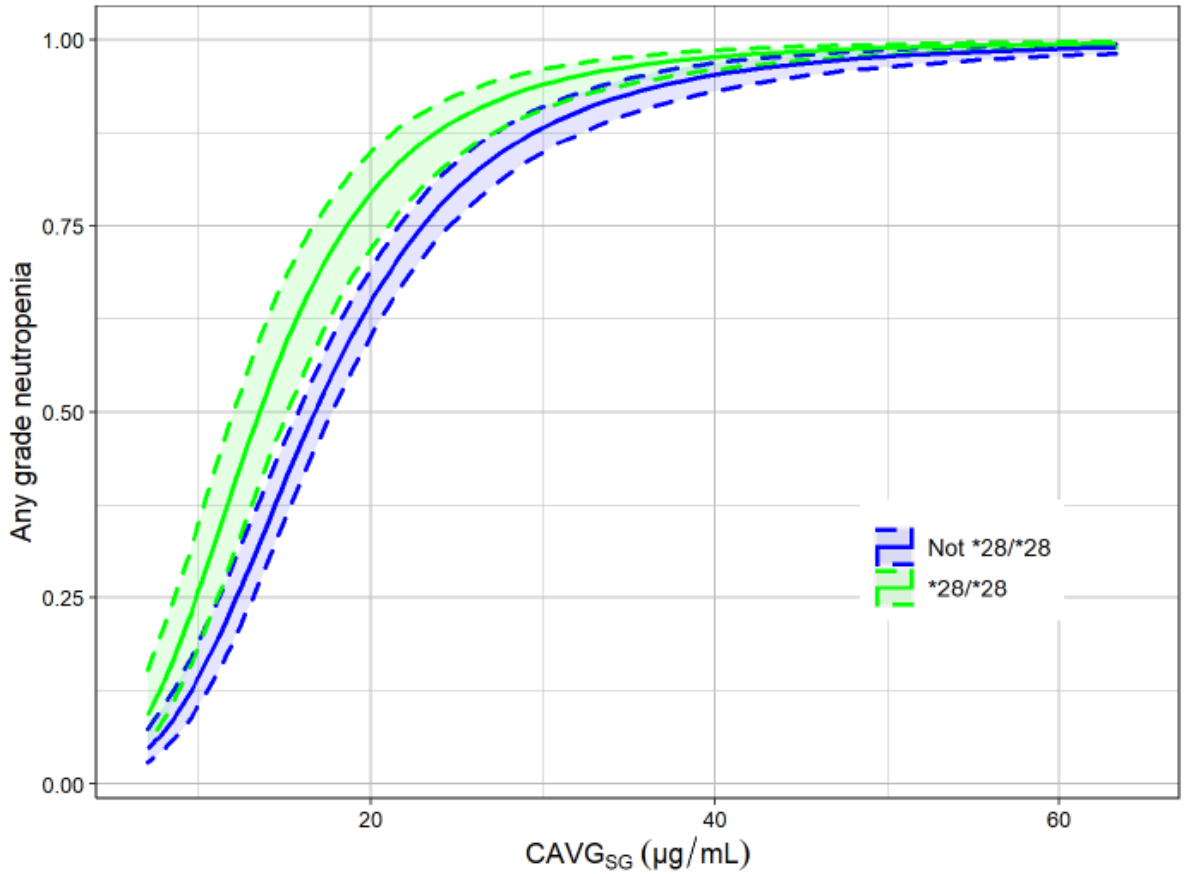
Other Adverse Events of Special Interest

Higher values of CAVGSG were statistically significantly associated with an increased probability of any grade, Grade 3 or higher, and Grade 4 neutropenia+, as well as Grade 3 or higher and Grade 4 febrile neutropenia. UGT1A1 genotype had a statistically significant effect on the probability of any grade, Grade 3 or higher, and Grade 4 neutropenia+, such that participants with the UGT1A1*28/*28 genotype were associated with an increased probability of any grade, Grade 3 or higher, and Grade 4 events compared with participants without the UGT1A1*28/*28 genotype (UGT1A1*1/*1, UGT1A1*1/*28, all others, or missing). Once CAVGSG was included in the model of febrile neutropenia, no additional statistically significant covariates were identified.

The estimated odds ratios associated with increases in CAVGSG for models based on log-transformed or linear exposure and the model-predicted probabilities of any grade and Grade 3 or higher selected AEs associated with SG for the SG 10-mg/kg starting dose group are presented in Table 7 and Table 8.

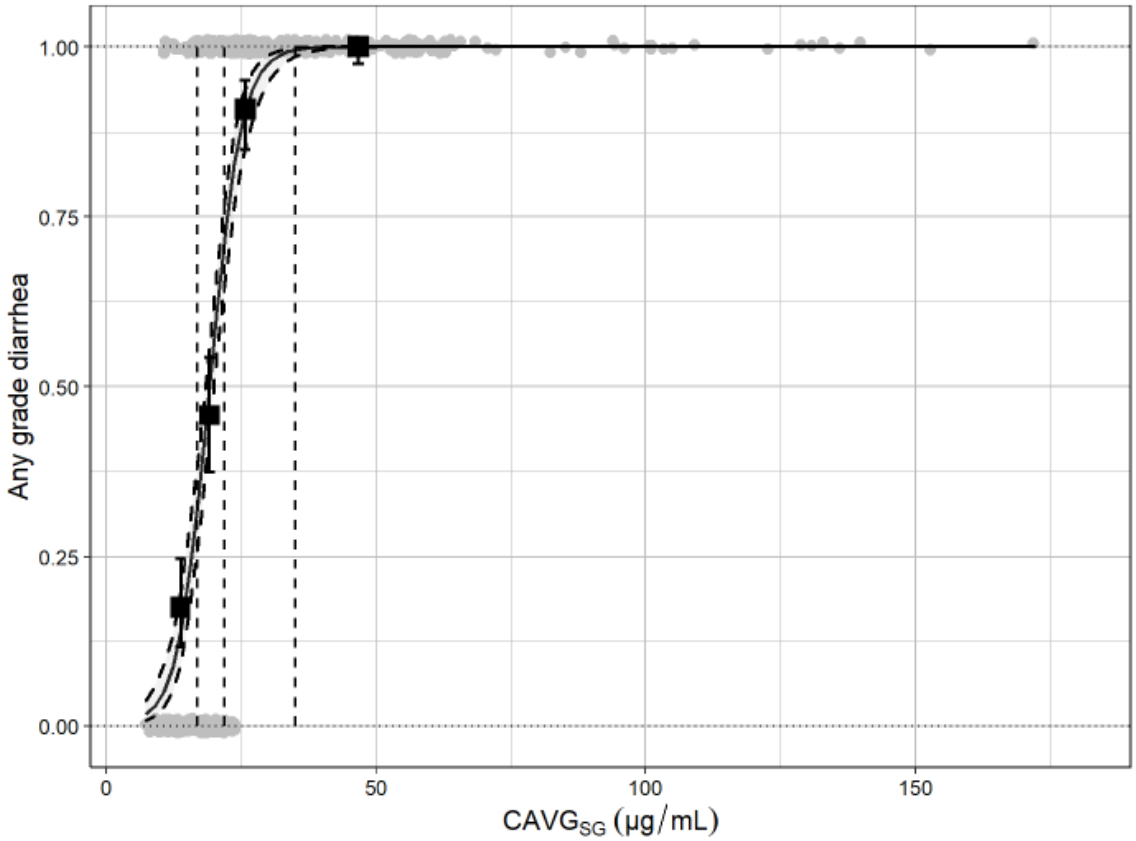
Other evaluated covariates, including race, ECOG performance status, prior cancer treatment, baseline Trop-2 expression level, prior CDK 4/6 inhibitor treatment duration, and number of prior lines of chemotherapy in the metastatic setting, were not found to be significantly associated with any of the evaluated safety endpoints.

Figure 10: IMMU-132-01, IMMU-132-05, and IMMU-132-09: Model-Predicted Probability of Any Grade Neutropenia by UGT1A1 Genotype



AE = adverse event; CAVG$_{SG}$ = sacituzumab govitecan average concentration; CI = confidence interval; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1
Solid (dashed and shaded area) curves show the model-predicted probability of the AE (95% CI).
Source: SG E-R 2022-03

Figure 11: IMMU-132-01, IMMU-132-05, and IMMU-132-09: Observed Proportion and Predicted Probability of Any Grade Diarrhoea



AE = adverse event; $CAVG_{SG}$ = sacituzumab govitecan average concentration; CI = confidence interval
Gray circles indicate data from individual participants. Closed squares (error bars) show the observed proportion of participants with the AE (95% CI based on the Pearson-Klopper method) by exposure quartile and are plotted at the median exposure of each quartile. Dashed vertical lines show the boundaries of the exposure quartiles. Solid (dashed and gray area) curves show the model-predicted probability of the AE (95% CI).
Source: SG E-R 2022-03

Table 7: IMMU-132-01, IMMU-132-05, and IMMU-132-09: Estimated Odds Ratio Associated With an Increase in Sacituzumab Govitecan Average Concentration and Model-Predicted Probability of Neutropenia-Related Adverse Events by Grade for the Sacituzumab Govitecan 10-mg/kg Starting Dose Group

Safety Endpoint	Odds Ratio for an Increase in $CAVG_{SG}$ by 10% (95% CI)	Mean of Individual Model-Predicted Probability of AE (95% CI)
Neutropenia		
Any grade	1.39 (1.33, 1.45)	0.696 (0.660, 0.729)
Grade 3 or higher	1.35 (1.30, 1.41)	0.522 (0.484, 0.560)
Neutropenia+		
Any grade	1.41 (1.35, 1.47)	0.713 (0.678, 0.747)
Grade 3 or higher	1.37 (1.31, 1.43)	0.547 (0.509, 0.585)
Febrile neutropenia[a]		
Grade 3 or higher	2.21 (1.86, 2.64)	0.0618 (0.0455, 0.0782)

AE = adverse event; $CAVG_{SG}$ = sacituzumab govitecan average concentration; CI = confidence interval
a All febrile neutropenia events were reported as Grade 3 or 4.
Source: SG E-R 2022-03

Table 8: IMMU-132-01, IMMU-132-05, and IMMU-132-09: Estimated Odds Ratio Associated With an Increase in Sacituzumab Govitecan Average Concentration and Model-Predicted Probability of Non-Neutropenia-Related Adverse Events by Grade for the Sacituzumab Govitecan 10-mg/kg Starting Dose Group

Safety Endpoint	Odds Ratio for an Increase in $CAVG_{SG}$ by 1 µg/mL (95% CI)	Mean of Individual Model-Predicted Probability of AE (95% CI)
Diarrhea		
Any grade	1.40 (1.32, 1.50)	0.644 (0.616, 0.671)
Grade 3 or higher	1.00 (0.993, 1.02)	0.105 (0.0818, 0.133)
Nausea		
Any grade	1.37 (1.28, 1.46)	0.624 (0.598, 0.651)
Grade 3 or higher	0.996 (0.978, 1.01)	0.0182 (0.00909, 0.0309)
Vomiting		
Any grade	1.29 (1.22, 1.37)	0.304 (0.275, 0.331)
Grade 3 or higher	1.00 (0.977, 1.02)	0.0164 (0.00727, 0.0273)
Hypersensitivity+		
Any grade	1.28 (1.21, 1.35)	0.316 (0.287, 0.347)
Grade 3 or higher	1.00 (0.977, 1.03)	0.0127 (0.00364, 0.0236)

AE = adverse event; $CAVG_{SG}$ = sacituzumab govitecan average concentration; CI = confidence interval
Source: SG E-R 2022-03

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology package of sacituzumab govitecan so far comprised three clinical studies (study IMMU-132-01, study IMMU-132-05 and IMMU-132-09) contributing to the characterization of PK of the 5 analytes SG, free SN-38, total SN-38, SN-38G, and total antibody. In study IMMU-132-01, doses of 4.5 to 18 mg/kg IV were investigated.

The proposed standard dose of SG is 10 mg/kg administered IV once weekly on Days 1 and 8 of 21-day treatment cycles.

The bioanalytical methods used for quantification of SG, free SN-38, total SN-38, SN-38G, and total antibody in serum were conducted using the same methods that were used in the initial BC application and are considered acceptable.

The previous Pop PK model for BC was updated with data from Study IMMU-132-09. Serum concentration data from a total of 784, 770, and 786 participants were used for the final PopPK model of SG, free SN-38, and total antibody, respectively. There was no change in the model structure or statistical significance of the previously identified covariates for any of the 3 analytes after inclusion of the Study IMMU-132-09 dataset. No new covariates were identified. While statistically significant relationships between region and nausea, and study and vomiting were identified and included in addition to CAVGSG in the respective final AE models, the impact of these covariates on the associated AEs was not considered clinically relevant. The final Pop PK model could adequately describe the data from HR+/HER2- BC patients.

The absorption, distribution, metabolism, and excretion of SG, total antibody and free SN-38, total SN-38, SN-38G, is well-characterised and described in the initial TNBC application. The recommended 10 mg/kg weekly dose regimen for HER2-low BC patients applied in Study IMMU-132-09 resulted in comparable exposures to the approved regimen of SG subjects with unresectable or metastatic TNBC.

The recommended dose regimen is weight-based and resulted in increased Cmax and AUC with increasing body weight.

A summary of individual-predicted SG exposures for participants receiving 10 mg/kg estimated based on the final model and stratified by body weight categories was provided (data not shown) and participants with body weight < 49 kg were estimated to have approximately 17% lower SG AUC over the first treatment cycle compared with participants with body weights ranging from 49 to 105 kg, while participants with body weight > 105 kg were estimated to have approximately 24% higher SG AUC than participants with body weights ranging from 49 to 105 kg. However, this difference could be regarded as within the range of the middle weight patients, and it is acknowledged that these differences could be regarded as non-significant.

Exposures of SG, free SN-38, or total antibody were comparable between HR+ HER2-negative subjects with normal hepatic function and mild hepatic impairment and between HR+ HER2-negative subjects with normal renal function, mild or moderate renal impairment. No significant differences in SG or free SN-38 exposure were observed in participants with the UGT1A1*28/*28 genotype compared with participants with the UGT1A1*1/*1 or UGT1A1*1/*28 genotype.

Overall, pharmacokinetic analyses in patients treated with sacituzumab govitecan (n = 789) did not identify an effect of age, race, and mild or moderate renal impairment on the pharmacokinetics of sacituzumab govitecan (see SmPC section 5.2). No adjustment to the starting dose is required when administering sacituzumab govitecan to patients with mild or moderate renal impairment (see SmPC section 4.2). There are no data on the pharmacokinetics of sacituzumab govitecan in patients with severe renal impairment or end-stage renal disease (CrCl < 15 mL/min) (see SmPC sections 4.2 and 5.2).

The exposure of sacituzumab govitecan was similar in patients with mild hepatic impairment to patients with normal hepatic function (see SmPC section 5.2). Sacituzumab govitecan and free SN-38 exposures are unknown in patients with moderate or severe hepatic impairment. A Phase 1 study evaluating the PK and safety of SG in participants with moderate hepatic impairment is currently ongoing (Study IMMU-132-15) (see RMP).

No drug-drug interaction studies with SG were submitted which is acceptable.

The incidence of post-baseline ADAs and NAbs was low, 1.2% in the total SG treated pool.

Exposure-response (E-R) analyses were conducted to evaluate the relationships between SG-related exposure and its efficacy (as described by CR, ORR, CBR, PFS, and OS) (study included IMMU-09) and safety (as described by AEs of vomiting, diarrhoea, 'hypersensitivity+', nausea, neutropenia, febrile neutropenia, and 'neutropenia+'). The previous exposure-response analyses were updated with the data from Study IMMU-132-09.

The E-R relationships were consistent with those detected previously. The exposure-response analyses showed that an OS benefit of SG is dependent on exposure. No additional effect of investigated covariates (e.g., age body weight, race, UGT1A1 genotype, baseline Trop-2 expression level, ECOG performance status, prior cancer treatment, prior CDK 4/6 inhibitor treatment duration, number of prior lines of chemotherapy in the metastatic setting) was identified. Only higher baseline lactate dehydrogenase (LDH) levels were found to be statistically significantly associated with shorter OS, which was expected as LDH is a known predictive marker in this setting (Forkasiewicz 2020, Pelizzari 2019).

Sacituzumab govitecan average concentration (CAVGSG) was correlated with Grade 3 or higher and Grade 4 neutropenia, febrile neutropenia, and 'neutropenia+'. The risk of neutropenia and associated

dose reductions was largest for the UGT1A1 genotype *28/*28 in comparison to other genotype categories evaluated (see clinical safety).

2.3.6. Conclusions on clinical pharmacology

Overall, the clinical pharmacology is considered adequately described for treatment of HR+HER2-negative BC subjects with SG at the recommended dose weekly 10 mg/kg.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Dose selection for SG in participants with HR+/HER2− metastatic breast cancer was based on efficacy and safety data from Study IMMU-132-01. In the Phase 1 part of Study IMMU 132 01, dose escalation was performed according to a standard 3 + 3 design and based on planned initial dose levels of 8, 12, and 18 mg/kg administered on Days 1 and 8 of a 21-day cycle. An SG dose of 12 mg/kg was formally identified as the maximum tolerated dose (MTD), but was associated with dose delays and dose reductions in several participants. In order to determine a maximum acceptable dose, participants in Phase 2 of Study IMMU 132 01 were enrolled in a sequential manner to the 8 mg/kg dose, and subsequently to the 10 mg/kg dose. An interim analysis was performed when 81 and 97 participants with different tumor types had been treated at the 2 dose levels, respectively. Both dose levels were shown to be better tolerated in the first cycle than the formally determined MTD of 12 mg/kg, allowing repeated cycles with a better safety profile. The duration of treatment at the 2 dose levels was similar, and no important differences in safety were observed. However, the 10-mg/kg dose was associated with better efficacy compared with the 8-mg/kg dose in participants with various tumor types (ORR 22% versus 10%, respectively) (*Ocean 2017*).

2.4.2. Main study(ies)

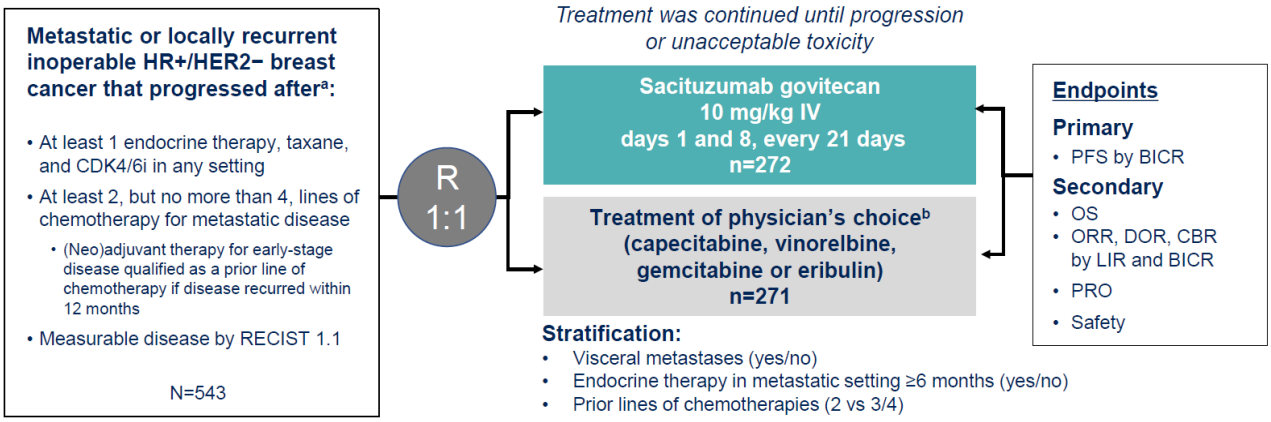
IMMU-132-09 (TROPiCS-02)

Phase 3 Study of Sacituzumab Govitecan (SG, IMMU-132) Versus Treatment of Physician's Choice (TPC) in subjects with Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer (MBC) who have failed at least two prior chemotherapy regimens

Methods

This is an ongoing, open-label, randomized, multicenter, international Phase 3 study with the following study design.

Figure 12: Study design



a Disease histology based on the ASCO/CAP criteria

b Single-agent SOC treatment of physician´s choice was specified prior to randomization by the investigator

BICR: blinded independent central review; LIR: local investigator review

Tumor assessments were performed at screening and every 6 weeks for 54 weeks, then every 12 weeks until the occurrence of PD. Additional scans were performed as clinically indicated. All tumor assessment scans, as well as any unscheduled scans, were sent to a central imaging vendor.

- **Study participants**

Key Inclusion Criteria:

- Female or male participants, adult or aged ≥18 years at the time of signing the ICF.
- Documented evidence of HR+/HER2− metastatic breast cancer confirmed by a local laboratory with the most recently available or newly obtained tumor biopsy (preferably within the last 12 months) from a locally recurrent or metastatic site(s) and defined per American Society of Clinical Oncology/College of American Pathologists criteria as:
    - HR+ (a tumor is considered HR+ if at least 1% of the cells examined have oestrogen and/or progesterone receptors)
    - HER2− defined as immunohistochemistry ≤ 2+ or fluorescence in situ hybridization negative.
- Availability of archival tumor tissue in a formalin-fixed, paraffin-embedded (FFPE) block (preferably within 12 months prior to consent) or newly acquired biopsy (FFPE block) from a metastatic site. *Note*: bone biopsies were not allowed.
- Refractory to or relapsed after at least 2 but no more than 4 prior systemic chemotherapy regimens for metastatic disease. Adjuvant or neoadjuvant therapy for early-stage disease qualified as 1 of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within a 12-month period of time of the therapy.

  Note: treatments for bone metastases (eg, bisphosphonates, denosumab) and hormonal therapy were not considered as prior systemic chemotherapy treatments for advanced disease.
- Should have been previously treated with:
    - At least 1 taxane in any setting

- At least 1 prior anticancer hormonal treatment in any setting
- At least 1 CDK 4/6 inhibitor in any setting.

- Could have received an unlimited number of prior endocrine, biological, or targeted therapies in the absence of coadministered chemotherapy.
- Documented disease progression after the most recent therapy by CT/MRI.
- At least 1 measurable target lesion according to RECIST v1.1 (bony disease only was not allowed) meeting all of the following criteria:
  - Lymph node lesion that measured ≥1.5 cm in the short axis
  - Non-nodal lesion that measured ≥1.0 cm in the longest diameter in the plane of measurement
  - The lesion was suitable for repeat measurement using CT/MRI.
  - Lesions that have had external beam radiotherapy or locoregional therapy must have shown radiographic evidence of disease progression based on RECIST v1.1 to be deemed a target lesion.

  Brain CT/MRI must have been conducted for participants with a history of brain metastasis. The participant must have had stable brain metastasis for at least 4 weeks. Target lesions could not be from brain. Stable brain metastasis was defined as the following:
  - Prior local treatment by radiation, surgery, or stereotactic surgery
  - Imaging–stable or decreasing size after such local treatment
  - Clinically stable signs and symptoms for at least 4 weeks
  - ≥ 2 weeks from discontinuation of antiseizure medication
  - Low and stable doses of corticosteroids ≤ 20 mg prednisone or equivalent daily were permitted *(Note: increased from ≤ 10 mg with Protocol Amendment 4)*.
- ECOG performance status of 0 or 1.
- Adequate renal function: calculated creatinine clearance ≥30 mL/min according to the Cockcroft and Gault formula.
- Adequate bone marrow function, defined as:
  - Absolute neutrophil count of at least 1500 per mm3
  - Hemoglobin ≥9.0 g/dL
  - Platelet count ≥100,000 per mm^3

  Note: blood transfusion or growth factor support was not allowed within 14 days prior to screening labs.
- Adequate liver function, defined as:
  - Total bilirubin ≤1.5 × institutional upper limit of normal (IULN) or ≤3 × IULN for participants with documented Gilbert's syndrome
  - Alanine aminotransferase and aspartate aminotransferase ≤2.5 × IULN (in the case of liver metastases, ≤5 × IULN), and serum albumin ≥3 g/dL

- Alkaline phosphatase (ALP) ≤5.0 × IULN unless there were bone metastases, in which case liver-specific ALP must have been separated from the total and used to assess liver function instead of total ALP.

- Must have voluntarily agreed to provide written informed consent.

Key Exclusion Criteria:

- Previous treatment with a topoisomerase 1 inhibitor as a free form or as other formulations.
- Treatment with chemotherapy, radiation, or small molecule targeted therapy within 2 weeks and biological therapy within 4 weeks prior to the first dose of study treatment.
- Existing anticancer treatment-related AEs of Grade 2 or higher (except for alopecia and Grade 2 neuropathy) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.
- Had known active central nervous system metastases and/or carcinomatous meningitis. Participants could have participated provided they had stable brain metastasis (see inclusion criteria for definition of stability). All participants with carcinomatous meningitis were excluded regardless of clinical stability.
- Locally advanced metastatic breast cancer (Stage IIIc) in participants who were candidates for curative intent therapy at the time of study enrolment.
- History of significant cardiovascular disease (heart failure > NYHA Class II; unstable angina or myocardial infarction within 6 months; serious cardiac arrhythmia
- Had active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) and participants with a history of bowel obstruction.
- Clinically significant ECG abnormality, including prolonged QT/QTc interval > 500 msec or history of risk factors for torsade de pointes
- Had an active serious infection requiring antibiotics.
- Had active hepatitis B or hepatitis C virus infection.
- Had received a live vaccine within 30 days of randomization.

- **Treatments**

SG arm

Sacituzumab govitecan **10 mg/kg** administered as an IV infusion on **Days 1** and **8** of **21-day** cycles.

Treatment continued until disease progression as determined by local investigator review (LIR) using RECIST v1.1, unacceptable toxicity, or another treatment discontinuation criterion was met. Participants were permitted to continue in the treatment period beyond initial RECIST v1.1-defined progression as long as investigator-assessed clinical benefit was observed and the participant was tolerating study drug. Participants were to discontinue study treatment upon evidence of further progression and/or loss of clinical benefit as assessed by the investigator.

The initial infusion should proceed over 3 hours. Subsequent infusions could either be administered over 3 hours or 1-2 hours if vital signs remained stable and no infusion reactions occur.

Participants receiving SG were to be monitored during and for at least 30 minutes after infusion.

Participants in the SG group also received premedications for prevention of infusion-related reactions (ie, antipyretics, H1 blockers, and H2 blockers) and a 2- or 3-drug combination regimen for prevention and treatment of chemotherapy-induced nausea, vomiting, and diarrhoea.

- Dose delays

Scheduled Day 1 and Day 8 dosing could have been delayed for up to 1 week for treatment-related toxicities; however, if the toxicity did not resolve to Grade 2 or lower within 1 week of Day 8, then the scheduled Day 8 dosing could have been cancelled and dosing was to resume with Day 1 of the following cycle. There was to be a minimum of 14 days and a maximum of 21 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

- Dose reductions and discontinuations

Table 9: Recommended Dose Reduction Schedule for Sacituzumab Govitecan

Event NCI CTCAE Version 5.0	Occurrence	Recommended Dose Reduction or Action
Severe Neutropenia		
Grade 4 neutropenia 7 days or more, OR Grade 3-4 febrile neutropenia OR At time of scheduled treatment, Grade 3 or higher neutropenia that delayed dosing by 1 week	First	Administer granulocyte-colony stimulating factor or sooner, if clinically indicated
	Second	25% dose reduction
	Third	50% dose reduction
	Fourth	Discontinue treatment
Grade 3 or higher neutropenia that delayed dosing beyond 3 weeks	First	Discontinue treatment
Severe Non-neutropenic Toxicity		
Grade 4 nonhematologic toxicity of any duration, OR Any Grade 3 or higher nausea, vomiting, or diarrhea due to treatment that was not controlled with antiemetics and antidiarrheal agents, OR Other Grade 3 or higher nonhematologic toxicity that persisted more than 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3 or higher non-neutropenic hematologic or nonhematologic toxicity that delayed dosing by 1 week	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
Grade 3 or higher non-neutropenic hematologic or nonhematologic toxicity that delayed dosing for more than 3 weeks	First	Discontinue treatment

TPC arm

Treatment of physician's choice was a single-agent treatment determined by the investigator before randomization from 1 of the following 4 choices:

☐ Eribulin 1.4 mg/m² for North American sites, 1.23 mg/m2 for European sites, or per institution administered IV on Days 1 and 8 of a 21-day cycle.

☐ Capecitabine (1000 to 1250 mg/m²) orally BID for 2 weeks followed by a 1-week rest period

☐ Gemcitabine (800 to 1200 mg/m²) IV on Days 1, 8, and 15 of each 28-day cycle or per institution.

☐ Vinorelbine (25 mg/m2) weekly IV or per institution
Note: Participants with Grade 2 neuropathy were eligible for the study, but were not to receive vinorelbine as TPC.

- **Objectives**

Primary objective

- To assess and compare the efficacy of sacituzumab govitecan (SG) to treatment of physician's choice (TPC) as measured by progression-free survival (PFS) as determined by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in participants with HR+/HER2− metastatic breast cancer who have progressed after CDK 4/6 inhibitor, endocrine therapy, taxane, and at least 2 but no more than 4 prior chemotherapy regimens for metastatic disease.

Secondary objectives

- To assess and compare SG to TPC in overall survival (OS) in participants with HR+/HER2− metastatic breast cancer who have progressed after CDK 4/6 inhibitor, endocrine therapy, taxane, and at least 2 but no more than 4 prior chemotherapy treatment regimens for metastatic disease.
- To assess and compare ORR, duration of response (DOR), and clinical benefit rate (CBR) between treatment groups as determined by local investigator review (LIR) and BICR using RECIST v1.1.
- To assess and compare the impact of treatment on time to deterioration (TTD) of global health status/QOL, pain, and fatigue domains as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30).
- To assess and compare the overall safety and tolerability.

Exploratory objectives

- To assess and compare efficacy in a subset defined by tumor expression of trophoblast cell-surface antigen 2 (Trop-2) and to ascertain the role of expression of Trop-2 as a predictive biomarker for response
- To investigate the immunogenicity of SG with respect to antidrug antibody (ADA) testing and serum levels of SG for PK
- To identify candidate blood and tumor biomarkers as a predictive biomarker for response
- PROs: To assess and compare the impact of treatment on
    - Health-Related Quality of Life (HRQOL) using the other domains of the EORTC QLQ-C30
    - the European Quality of Life (EuroQOL) EQ-5D-5L instruments
    - treatment-related symptoms using a set of 9 relevant symptom concepts from the PRO-CTCAE item library (decreased appetite, nausea, vomiting, constipation, diarrhea, abdominal pain, shortness of breath, hair loss, and fatigue)

- **Outcomes/endpoints**

Table 10: Efficacy Endpoints

Endpoint	Definition
Primary endpoint	
PFS as determined by BICR using RECIST v1.1	The time from date of randomization to the first observation of documented disease progression based on RECIST v1.1 or death due to any cause, whichever came first. Primary analysis of PFS was based on BICR for the ITT Population.
Secondary endpoints in the hierarchical testing procedure for multiplicity adjustment	
OS	The time from randomization into study to death from any cause.
ORR as determined by BICR using RECIST v1.1	The proportion of participants who had a best overall response of either CR or PR that was confirmed 4 weeks or later according to BICR using RECIST v1.1.
TTD in global health status/QOL, pain, and fatigue domain of EORTC QLQ-C30	Time to deterioration was defined as the time from randomization to the first date a participant achieves ≥ 10-point deterioration from baseline or death due to any cause (whichever occurs first). Participants who have not experienced 10-point deterioration at the time of analysis were censored on the last nonmissing assessment date. Participants without baseline or postbaseline patient-reported outcome assessments were censored at the randomization date.
Other secondary endpoints	
ORR as determined by LIR using RECIST v1.1	The proportion of participants who had a best overall response of either CR or PR that was confirmed 4 weeks or later according to LIR using RECIST v1.1.
DOR as determined by BICR and LIR using RECIST v1.1	For participants experiencing response (a best overall response of CR or PR), DOR was calculated based on the time between the first date showing a documented response of CR or PR and the date of progression or death (whichever occurred first). Participants who did not progress or die after response were censored.
CBR as determined by BICR and LIR using RECIST v1.1	The proportion of participants who had a best overall response of CR, PR, or durable SD (duration of SD 6 months or greater after randomization).
PFS as determined by LIR using RECIST v1.1	The time from date of randomization to the first observation of documented disease progression per LIR based on RECIST v1.1 or death due to any cause, whichever came first.
Selected exploratory endpoints	
Efficacy in relation to Trop-2 expression	Efficacy endpoints (PFS, ORR, OS, DOR, CBR) were analyzed according to Trop-2 expression to identify any potential correlation with clinical outcome-related endpoints.

Selected exploratory endpoints: Efficacy in relation to Trop-2 expression

Trop-2 Immunohistochemistry Assay

The trophoblast cell-surface antigen 2 (Trop-2) immunohistochemistry (IHC) assay was developed and validated to specifically detect expression of Trop-2 protein in formalin-fixed, paraffin-embedded (FFPE) human tissues (101894100 – TROP-2 IHC Assay Validation Report [1168]).

Scoring and Interpretation

The following interpretation criteria were used to assess each breast cancer sample used in study TROPiCS-02:

- Approximate number of viable tumor cells ⩾ 100.

- Scoring included all areas of evaluable viable tumor in the section, even if tumor was discontinuous or in separate tissue fragments in the section.
  Necrotic: areas, poorly preserved, poorly fixed areas, or areas exhibiting artifactual changes were excluded from scoring.
- Intensity of Trop-2 staining and percent of tumor cells demonstrating staining at various levels from 0 to 3+ for membrane staining. Determination of a standard H-score used as a measure of both intensity and percent of positive tumor cells for membrane staining.
- Staining intensity was categorized in standard manner and is described in the validation report. For the validation studies, the H-score was calculated for the tumor membrane staining using the following formula:

$$\text{H-score} = (\_\% \times 0) + (\_\% \times 1+) + (\_\% \times 2+) + (\_\% \times 3+)$$

The H score combines components of staining intensity with the percentage of positive cells.
It has a value between 0 and 300.
For the validation studies, the H-score was calculated **for the tumor membrane staining** using the following formula:

1 * (percentage of cells staining at 1+ intensity)
+ 2 * (percentage of cells staining at 2+ intensity)
+ 3 * (percentage of cells staining at 3+ intensity)
= H score.

- The approximate percent tumor necrosis was noted and overall staining intensity in necrotic areas was noted in the comment section; however, this was not included in the H-score.

- **Sample size**

An overall sample size of approximately 520 participants was planned for randomization in a 1:1 ratio to either SG or TPC.

The sample size was estimated based on the primary endpoint of PFS, but also took into account OS as the main secondary endpoint.

For PFS, assuming an HR of 0.70 (median PFS of 5.3 months for SG and 3.7 months for TPC), a total of 350 PFS events were needed to detect a statistically significant difference at a 2-sided alpha of 0.05 with 92% power. With an estimated average accrual rate of 22 participants per month, a total of 520 participants would provide approximately 350 PFS events approximately 27 months after the first participant was randomized, after accounting for events being censored because of participants missing tumor assessments or starting subsequent anticancer therapies.

For OS, assuming an HR of 0.73 (median OS of 16.5 months for SG and 12 months for TPC), a total of 438 OS events were needed to detect a statistically significant difference at a 2-sided alpha of 0.05 with 86.7% power, based on a recruitment period of 24 months and survival follow-up period of 52 months (from the time of first participant randomized).

It was planned that the Sponsor would closely monitor the number of subjects randomized and discontinued, including subjects who refuse study treatment assigned. As the primary analysis was to be triggered by a targeted number of PFS events, subjects who prematurely discontinue from the study or whose events are censored were not to be counted toward the targeted number. To compensate for such cases, an additional number of subjects was planned to be enrolled to ensure the

targeted number of events is reached within a reasonable timeframe. The additional number of subjects was planned to be determined by the Sponsor on the basis of the number and pattern of accumulated and censored events at the appropriate times as the study progresses.

Initially, a smaller sample size of n=400 patients was planned to be recruited, based on similar assumptions. The number if PFS events was planned to be 350 in the initial study protocol and was not changed.

- **Randomisation**

Participants were planned for randomization in a 1:1 ratio to receive 1 of the 2 following treatments: SG or TPC.

Randomization was planned to be stratified based on prior chemotherapy regimens for treatment of metastatic disease (2 or 3/4 lines), visceral metastasis (yes or no), and endocrine therapy in the metastatic setting for at least 6 months (yes or no).

- **Blinding (masking)**

IMMU-132-09 was an open-label study; however, the independent central reviewer of imaging for primary and secondary endpoints and the sponsor's medical monitors, statisticians, programmers, and personnel directly involved with study analysis remained blinded to study data, including participant treatment assignment, until after data finalization for the combined PFS final analysis and OS IA1. The sponsor's and contract research organization's (CRO) operations and data management personnel and the CRO's medical monitor personnel directly involved with study conduct remained unblinded to study data.

- **Statistical methods**

Analysis sets

The following analysis sets were planned to be used:

- Screened Set was planned to be the group of all subjects who have signed an informed consent and participated in screening procedures at the investigative site to assess eligibility.
- Full Analysis Set (Intent-to-Treat Analysis [ITT] Population) is the group of all randomized subjects. This was planned to be the primary analysis population for all efficacy analyses which were planned to be based on the ITT principle, with subjects analyzed according to the randomized treatment assignment.
- Safety Analysis Set was planned to be the group of subjects who received at least 1 dose of study drug. This was planned to be the analysis population for all safety analyses which will be based on the actual treatment received.
- HRQoL- Evaluable Set was planned to be the all ITT population who had an evaluable assessment of the HRQoL at baseline and at least one evaluable assessment at post-baseline visits. An evaluable assessment at a given visit was to be defined as at least one of the 15 domains/scales were non-missing at that scheduled assessment visit.
- PK Set was planned to be the Safety population subjects who have completed at least one cycle of sacituzumab govitecan treatment and have at least one non-missing PK concentration of total SN-38, free SN-38, total antibody (hRS7 IgG) and/or SN-38G.

Primary outcome variable

Primary analysis of PFS were planned to be based on BICR assessments. PFS, ORR, CBR and DOR analyses were planned to be produced for both BICR and LIR. PFS was defined as the time from the date of randomization to the date of the first documentation of disease progression or death (whichever occurs first) according to BICR using RECIST 1.1.

Censoring

Any subject who progresses or dies after more than one missed scheduled visit was planned to be censored at the last date of radiographic assessment prior to the missed visit. Any subject who receives alternative anticancer treatment before documented PD was planned to be censored at the last date of radiographic assessment prior to receiving alternative anticancer treatment. Otherwise, subjects who do not have progression and are alive were planned to be censored at the last date of radiographic assessment without documented PD. Subjects who did not have any on study tumor assessments and did not die were planned to be censored on their date of randomization.

Analysis model

PFS was planned to be described using Kaplan-Meier (K-M) estimates. The primary analysis of PFS for the comparison between treatment arms was planned to be performed using a stratified log rank test with the stratification factors used in the randomization. Median PFS and its 95% CI as determined by the Brookmeyer and Crowley method with log-log transformation was planned to be presented and the K-M estimates of PFS were planned to be plotted over time. Hazard ratio of PFS and its 95% CI was planned to be estimated using Cox proportional-hazards model stratified by the same stratification factors used in the randomization.

Timing of the primary analysis

The primary analysis of PFS was planned to be carried out after approximately 350 subjects experience disease progression or death events according to the primary definition of PFS as assessed by BICR.

4 analyses for the key secondary endpoint OS were planned (a descriptive analysis at the time of PFS analysis), two interim analyses for efficacy, performed when approximately a total of 272 (62% information fraction) and 350 (80% information fraction) death events have occurred, respectively, and a final OS analysis at 438 events.

Multiplicity and interim analyses

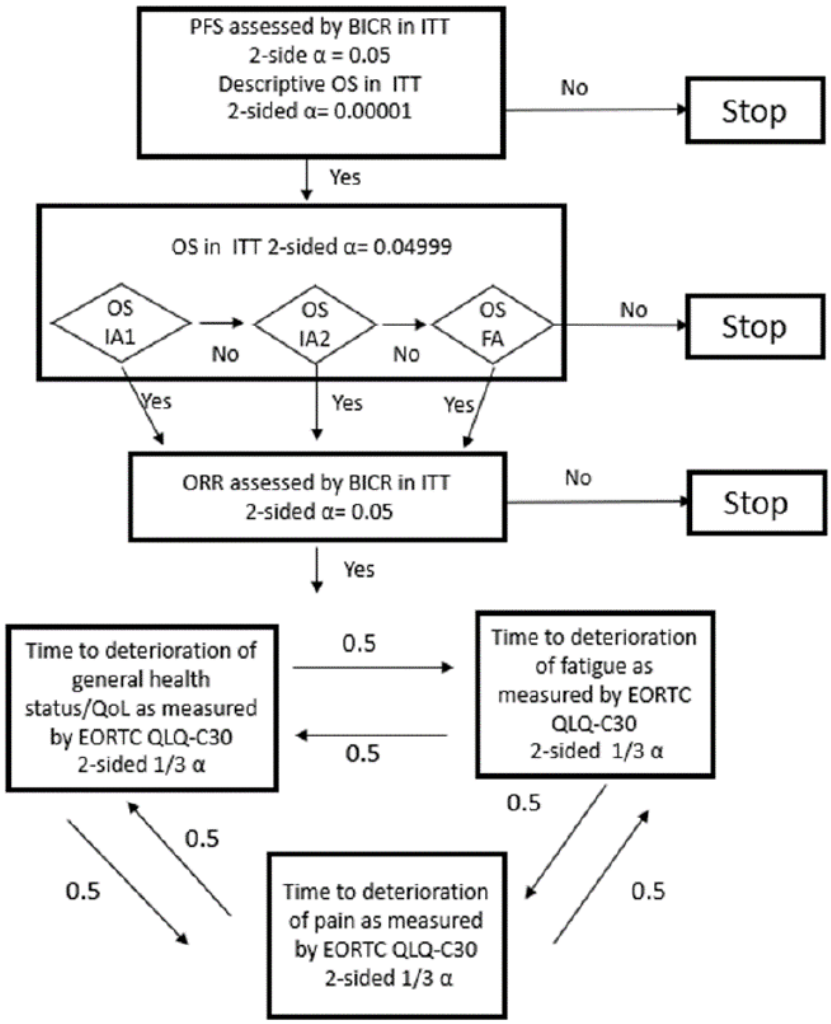
The overall type I error rate for this study was planned to be strictly controlled at a 2-sided alpha of 0.05.

The primary end point analysis of PFS assessed by BICR was planned to serve as the gatekeeper for the secondary end point analyses and be tested at the 2-sided alpha of 0.05. At PFS final analysis, OS was planned to be summarized descriptively only.

The nominal 2-sided alpha of 0.00001 was planned to be spent even without formal hypothesis testing. If the primary PFS analysis is positive, analysis of the main secondary end point of OS was planned to be formally tested sequentially at the 2-sided alpha of 0.04999, ORR (assessed by BICR) and analysis for QOL was planned to be formally tested sequentially at the 2-sided alpha of 0.05, respectively, when the above hypotheses in the hierarchy are also statistically significant. For analysis of QOL, TTD of global health status/QOL, pain, and fatigue domains as measured by EORTC QLQ-C30 was planned to be tested using graphical approach of Maurer and Bretz to control multiplicity (Maurer 2013). A

Bonferroni approach was planned to be used to control the type I error rate at 0.05 (2-sided) alpha for the 3 TTD hypothesis tests.

The Lan-DeMets alpha spending function that approximates a Pocock approach was planned to be used to account for multiplicity introduced by including OS interim analyses for superiority. The first OS efficacy interim analysis was to be tested at the 2-sided significance level of 0.0363 if 62% of the death events (272/438) is available at the time of the analysis. If the first OS interim analysis is not positive, the second OS efficacy interim analysis was planned to be tested at the 2-sided significance level of 0.0206 if 80% of death events (350/438) is available at the time of the analysis. If neither of the interim analyses are positive, final analysis was planned to be tested at the 2-sided significance level of 0.0195. Alpha levels for the OS interim and final analyses were planned to be based on the actual observed events and be adjusted accordingly.



Secondary efficacy analyses were planned to include the following:

- OS was defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cut-off were planned to be censored at the date the subject was last known alive or date of data cut-off, whichever occurs first.

- ORR was defined as the proportion of subjects who have a best overall response of either CR or PR that is confirmed ≥ 4 weeks later according to BICR using RECIST 1.1.
- TTD of global health status/QOL, pain, and fatigue domains of the EORTC QLQ-C30 was defined as the time between randomization and the time a subject experienced a deterioration (i.e., ≥ 10 points worsening from baseline in a given domain).

At the time of primary analysis of PFS is performed, OS was planned to be summarized descriptively. No other formal treatment comparison for OS was planned to be performed at this time.

The analysis of OS was planned to be described using K-M estimates. The primary analysis of OS for comparison between treatment arms was planned to be performed using a stratified log rank test with the same stratification factors used in the randomization. Median OS and the associated 95% CI as determined by the Brookmeyer and Crowley method with log-log transformation was to be presented. Hazard ratio and the associated 95% CI was planned to be estimated using a Cox proportional-hazards model stratified by the same stratification factors used in the randomization.

ORR was planned to be analyzed and compared between the treatment arms using the Cochran Mantel-Haenszel (CMH) test stratified by the stratification factors used in the randomization. The 2-sided 95% CIs was planned to be calculated using the Clopper-Pearson exact method.

Time to deterioration of global health status/QOL, pain, and fatigue domains as measured by EORTC QLQ-C30 was planned to be analyzed similarly as the primary analysis of PFS.

Selected exploratory endpoints: Efficacy in relation to Trop-2 expression

The Trop-2 Evaluable Population, defined as all participants in the Study IMMU-132-09 Intent-to-Treat (ITT) Population with baseline Trop-2 H-score values, was used for all analyses of Trop-2. The ITT Population included all participants who were randomized in the study, regardless of whether they received the study drug or not.

To explore association of Trop-2 expression and clinical benefit, efficacy of SG versus TPC across Trop-2 expression levels was assessed by dividing participants in the Trop-2 Evaluable Population into the following subgroups:

Two subgroups with Trop-2 H-score < 100 and ≥ 100

To further explore clinical benefit in participants with low or no Trop-2 expression, efficacy of SG versus TPC at lower Trop-2–expressing levels was assessed in the following subgroups:

Trop-2 H-score ≤ 38

- Quartile 1 of 4 equal-participant quartile subgroups (Trop-2 H-score ≤ 38, > 38 to ≤ 132, > 132 to ≤ 190, and > 190)
-

Trop-2 H-score ≤ 10

- A very low or no Trop-2–expressing subgroup of the quartile 1 subgroup above

Trop-2 H-score 0

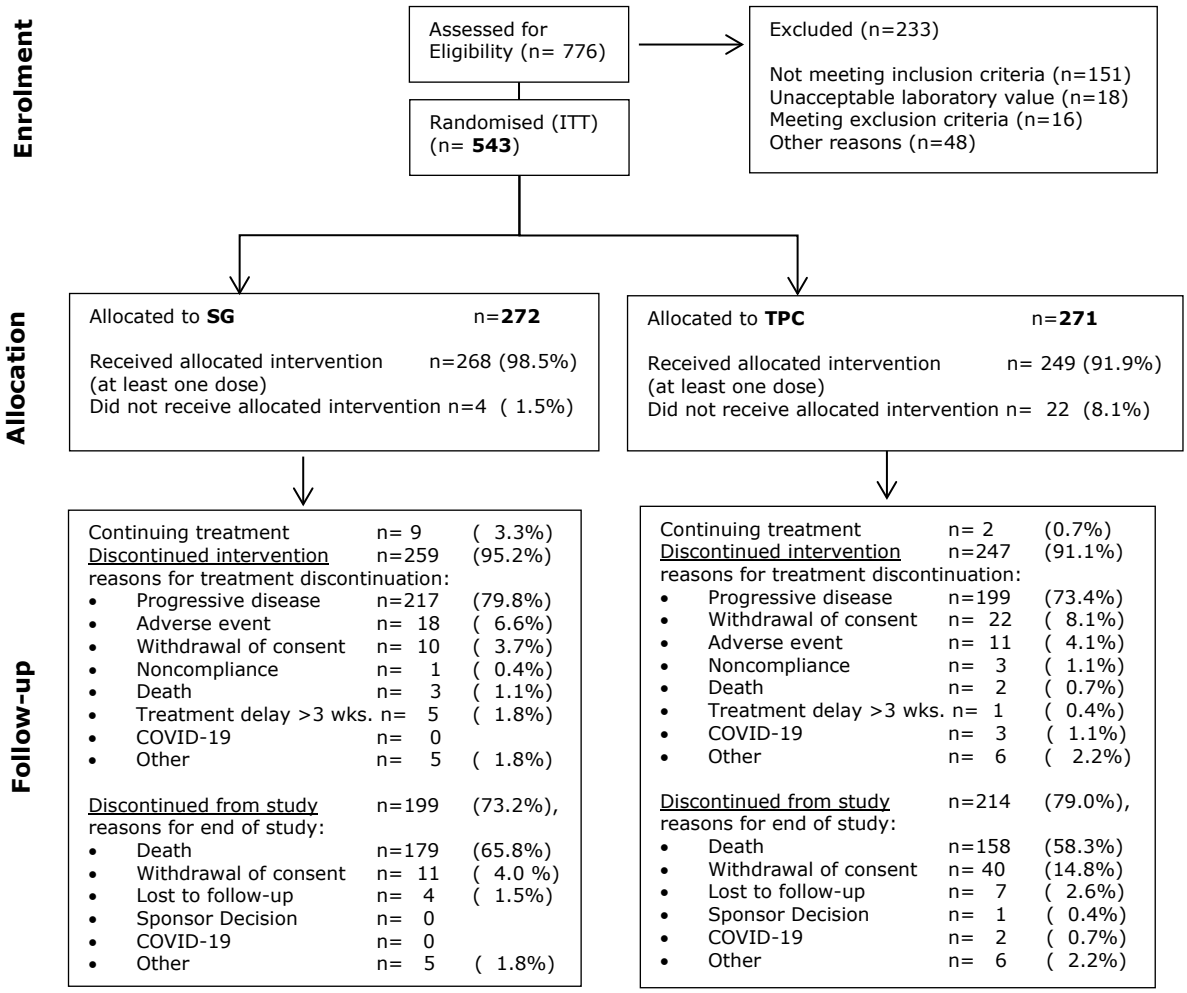
For the subgroups of Trop-2 described above, PFS and OS were plotted using Kaplan-Meier curves, and median PFS and OS were derived by the Kaplan-Meier estimate with the associated 95% CI calculated by the Brookmeyer and Crowley method with log-log transformation. Hazard ratios of SG relative to TPC were estimated using an unstratified Cox proportional hazards model.
Objective response rate and clinical benefit rate with 95% CI were calculated based on the Clopper-

Pearson method. Medians of duration of response were derived based on the Kaplan-Meier method and the associated 95% CIs were based on the Brookmeyer and Crowley method with log-log transformation.
The median Trop-2 H-score was 131.5 (range: 0-290).

Results

- **Participant flow**

Figure 13: Study IMMU-132-09 (TROPiCS-02) participants flow



Note: The denominator for percentages was the number of participants in the ITT Population for each treatment group.

All randomized participants were included in the analysis. Data cutoff date 01 July 2022.

As of the data cutoff date (01 July 2022), the median follow-up duration was 12.48 months (13.80 months [range: 0.03-35.48] in the SG arm and 10.68 months [range: 0.03-33.15] in the TPC arm). 119 participants (21.9%) were continuing in survival follow-up (SG: 64 participants, 23.5%; TPC: 55 participants, 20.3%).

Table 11: Subjects screened but not randomized

	Total n ()
Subjects Screened	776
Subjects Randomized [a]	543 (70.0%)
Subjects Screened but not Randomized [a]	233 (30.0%)
Administrative Reason By Sponsor [b]	2 (0.9%)
AE or SAE [b]	1 (0.4%)
Alternative Therapy [b]	7 (3.0%)
Death [b]	3 (1.3%)
Did Not Meet Inclusion Criteria [b]	151 (64.8%)
Disease Progression [b]	7 (3.0%)
Met Exclusion Criteria [b]	16 (6.9%)
Noncompliance [b]	2 (0.9%)
Other [b]	11 (4.7%)
Unacceptable Laboratory Value [b]	18 (7.7%)
Unacceptable Medical History [b]	2 (0.9%)
Unacceptable Procedure Value [b]	1 (0.4%)
Withdrawn By Investigator [b]	2 (0.9%)
Withdrew Consent [b]	10 (4.3%)

- **Recruitment**

Study IMMU-132-09 enrolled at 91 study centers in 9 countries in Europe (58%) and North America (42%): Belgium (n=25), Canada (n=1), France (n=137), Germany (n=46), Great Britain (n=14), Italy (n=15), Netherlands (n=8), Spain (n=69), and United States (n=228).

Table 12: Study IMMU-132-09 Key Dates

Event	Date
First participant screened	08 May 2019
First participant randomized	30 May 2019
Last participant randomized	05 April 2021
Data cutoff date for the primary PFS analysis	03 January 2022
Data cutoff date for the 2nd IA of OS	01 July 2022

- **Conduct of the study**

Protocol amendments

The original protocol (21 December 2018) was amended 7 times:

Amendment 1 (France-specific; 03 July 2019)

Amendment 2 (Germany-specific; 10 July 2019)

Amendment 3 (global; never implemented; 04 February 2020)

Amendment 4 (global; 13 March 2020) incorporated Amendments 1-3

Key changes were (excerpt):

- Decreased the number of required unstained slides from archived biopsy/surgical specimens at screening from 12 to 6 slides
- Deleted the requirement that the archival tumor tissue had to be derived within 12 months prior to randomisation; new wording: "Availability of archival tumor tissue in a FFPE block (preferably within 12 months prior to consent)".
- Added the infusion duration for SG
- Updated inclusion and exclusion criteria based on health authority recommendations and investigator questions and to ensure consistency with the investigator's brochure and safety guidance (e.g., removal of Gilbert´s disease as exclusion criterion; entry criteria for ALP increased to ≤ 5.0 x IULN; contraception required for 6 months instead of 120 days after study drug discontinuation for females and for 3 months instead of 6 months for males; exclusion of subjects with blood uracil level ≥ 150 ng/ml from receiving capecitabine)
- Decreased the frequency of CT/MRI scans after the start of study drug (every 12 weeks after week 54 instead of every 9 weeks)
- Removed requirement for serum chemistry assessment on each treatment day for participants who received SG and removed PK sample collection on Day 8
- Added text to the determination of sample size to reflect the loss of events due to potential censoring

Amendment 5 (global; 08 October 2020)

- Increased the sample size from approximately 400 to 520 participants to account for withdrawal of consent, COVID-19 discontinuations, and possible dosing interruptions, and updated sample size assumptions in the Statistical Considerations section accordingly
- Increased the duration of enrolment from 17 to 24 months and the overall duration of the study from 48 to 52 months to be consistent with changes in sample size
- Increased the number of required death events for the secondary endpoint of OS (from 335 to 438 OS events) and adjusted power assumptions accordingly (from 83% power to 91% power at a 2-sided alpha of 0.05)

Reason for change as provided in the protocol amendment: *Sample size has been increased to account for withdrawal of consent, COVID 19 discontinuations and possible dosing interruptions. The power used for the secondary endpoint (OS) has been increased to reduce the possible risk of crossover effect when sacituzumab govitecan become commercially available on 22 Apr 2020. This risk of crossover effect was not considered at the time of initial statistical consideration 2 years ago.*

Amendment 6 (global; 27 January 2021)

- Revised the primary objective/endpoint to be assessed by BICR instead of LIR

Reason for change as provided in the protocol amendment: *To align with Health Authority requirements*

- Removed the interim analysis based on ORR

- Moved ORR from a coprimary objective/endpoint to a secondary objective/endpoint

Clarification as provided in the protocol amendment: *Due to the increase in sample size and the actual enrolment rate, the Sponsor deem the time interval between the interim analysis and the targeted final PFS events not sufficiently long to warrant conducting the interim, thus elect not to conduct this interim analysis based on ORR, as originally specified in the protocol above. Thus, the ORR will be analyzed as a secondary endpoint.*

- Revised alpha allocation to evaluate the primary endpoint of PFS and secondary endpoint of OS given that ORR was removed as a coprimary endpoint (*"As the Sponsor elects to not conduct the planned interim analysis, 0.01 alpha allocated to evaluate ORR will be reverted back to primary endpoint PFS, which will be tested at the two-sided alpha of 0.05"*).
- Provided additional detail regarding the OS statistical analysis (*"A descriptive, non-comparative analysis of OS will be performed when the primary analysis of PFS is performed; an administrative alpha of 0.00001 will be spent on this non-comparative analysis of OS. If PFS is positive, the secondary endpoint of OS will be formally tested when approximately 438 subjects have died at the alpha level of 0.04999 (i.e., step-down)".)*
- Added BICR assessment for the secondary objectives/endpoints of ORR, DOR, and CBR
- Added text to define PFS sensitivity analyses *("All three sensitivity analyses will be conducted on both BICR and LIR assessments")*.
- Added text allowing for remote study monitoring due to COVID-19

Amendment 7 (global; 23 August 2021)

- Added 2 interim analyses of OS between the PFS final analysis and the OS final analysis "*to accommodate the long time-interval between PFS final analysis and OS final analysis*". Multiplicity control procedures have been added to control study level type I error rate at a 2-sided alpha of 0.05.
- Removed PFS2 exploratory endpoint and analysis.
- Revised secondary and exploratory patient reported outcomes (PRO) objectives/endpoints such that only TTD in global health status/QOL, pain, and fatigue as measured by EORTC QLQ-C30 remained secondary endpoints, and all other domains of the EORTC QLQ-C30 as well as EQ-5D-5L and PRO-CTCAE were moved from secondary endpoints to exploratory endpoints.
- Moved EQ-5D-5L and PRO-CTCAE from secondary objectives/endpoints to exploratory objectives/endpoints.
- Added 3 new subgroup analyses (early progressors [defined as progressing to metastatic disease within 1 year of neo/adjuvant therapy] [yes or no], baseline documented target or nontarget liver lesions per RECIST 1.1 [yes or no], and chemotherapy in neo/adjuvant setting [yes or no]).
- COVID related changes: Added text regarding the COVID-19 vaccine; clarified that off-site monitoring visits and remote source data verification were allowed if permitted by local regulation; Added an appendix describing the Pandemic Risk Assessment and Mitigation Plan.

Changes from Planned Analyses

Per the study protocol, at the time of the primary (final) PFS analysis, OS was to be summarized descriptively only, and the first interim OS analysis was estimated to occur after the primary (final)

PFS analysis. However, as of 03 January 2022, the target number of events required for the first interim OS analysis was reached. At that time, 329 PFS events for the final PFS analysis were reached. Per the SAP, the sponsor conducted the final (and only) analysis of PFS and the first interim superiority analysis of OS together.

Progression-free survival per LIR was a planned analysis as described in the study protocol, but was not listed as an endpoint in the study protocol. Progression-free survival per LIR was added as a secondary endpoint in the SAP.

Sensitivity analyses of PFS per LIR were included in the study protocol. However, because sensitivity analyses were only required for the primary endpoint of PFS per BICR, sensitivity analyses of PFS per LIR were not planned in the SAP.

The COVID-19 pandemic that began in early 2020 affected the operation of the study, and consequently, data collection. Some protocol-specified data points may not have been collected on schedule or even at all for participants who remain on treatment or for those who discontinued treatment but are still in follow-up. Listings of premature study drug or study discontinuation due to COVID-19, protocol deviations due to COVID-19, and AEs due to COVID-19 were provided to explore the extent to which COVID-19 may have affected inference from study results. Based on these listings, only a few participants were impacted by COVID-19; therefore, the impact of COVID-19 on the study results was considered minimal and no additional analyses were performed.

Additional analyses not specified in the SAP were planned before data finalization of OS IA2 to further characterize the benefit and risk of the study treatment, including additional baseline characteristics, analyses of granulocyte colony-stimulating factor (G-CSF) use, additional subgroup analyses of efficacy endpoints, subgroup analyses of key safety endpoints, summary of potential Hy's Law cases, exposure-adjusted incidence rate (EAIR) of treatment-emergent adverse events (TEAEs), and analyses of physical and role functioning per EORTC QLQ-C30 by mixed-effects model for repeated measures (MMRM). After data finalization of PFS analysis (final) and OS IA1, the subgroup definition for early relapse was updated such that participants without chemotherapy in the neo/adjuvant setting were not considered as having had early relapse, instead of being categorized as unknown early relapse status. Ad hoc subgroup analyses of efficacy endpoints were provided using this updated definition.

Conducted analyses

Initially, ORR and PFS were planned as primary endpoints, with alpha=0.01 allocated to ORR and alpha=0.04 allocated to PFS. This was changed in amendment 6 and ORR was no longer planned as primary endpoint.

Eventually, the analyses were conducted as indicated in the table below.

Table 13. IMMU-132-09: Planned Analyses of Progression-Free Survival and Overall Survival – SCE p.20

Analysis[a]	Number of Events Planned	Number of Events Observed	2-Sided Significance Level per Planned Number of Events	2-Sided Significance Level per Observed Number of Events	Status (Completed or Projected) Data Cutoff Date
Primary PFS Analysis (Final)	Approximately 350 events[b]	329 events	0.05	0.05	Completed 03 January 2022
Interim OS Analysis 1	Approximately 272 deaths	293 deaths	0.0363[c]	0.0383[c]	Completed 03 January 2022
Interim OS Analysis 2	Approximately 350 deaths	390 deaths	0.0207[c]	0.0223[c]	Completed 01 July 2022
Final OS Analysis[d]	Approximately 438 deaths	–	0.0196[c]	0.0179[c]	Projected H1 2023

H1 = first half; OS = overall survival; OS IA2 = second planned interim analysis of OS; PFS = progression-free survival
[a] Analyses are prespecified in the Protocol Amendment 7 and statistical analysis plan Version 5.0.
[b] Actual number of primary PFS events was within ± 10% of the target 350 events. Full alpha is used at the final (and only) analysis for primary endpoint PFS.
[c] The *P* value boundaries at each analysis time point are adjusted by the Lan-DeMets alpha spending function that approximates a Pocock approach.
[d] Because statistical significance of OS was demonstrated, OS IA2 was considered the final test for OS. Any future analysis of OS will be considered descriptive only.

Protocol deviations

Table 14: Important Protocol Deviations (ITT Population)

	SG (N = 272)	TPC (N = 271)	Total (N = 543)
Participants with at Least 1 Important Protocol Deviation	138 (50.7%)	121 (44.6%)	285 (52.5%)
01-INCLUSION CRITERIA	26 (9.6%)	26 (9.6%)	52 (9.6%)
02-EXCLUSION CRITERIA	6 (2.2%)	3 (1.1%)	9 (1.7%)
03-STUDY DRUG	27 (9.9%)	3 (1.1%)	30 (5.5%)
04-RANDOMIZATION	0 (0.0%)	1 (0.4%)	1 (0.2%)
05-ASSESSMENT - SAFETY	17 (6.3%)	18 (6.6%)	35 (6.4%)
06-ASSESSMENT - EFFICACY	33 (12.1%)	24 (8.9%)	57 (10.5%)
08-INFORMED CONSENT (ICF)	85 (31.3%)	78 (28.8%)	163 (30.0%)
09-PROHIBITED CO-MEDICATION	5 (1.8%)	4 (1.5%)	9 (1.7%)
10-OTHER	1 (0.4%)	1 (0.4%)	2 (0.4%)

The denominator for percentages was the number of participants in the ITT Population for each treatment group. Participants with multiple IPDs were counted once in each category.

Protocol Deviations Related to COVID-19 Pandemic Study Disruption

Important protocol deviations due to COVID-19 were reported for 7 patients; 6/7 were related to efficacy assessments (3 patients had Week 6 or Week 12 scan not collected, 1 patient performed CT

Scan 14 days out of window, 2 patients had not completed QoL assessments) and 1 subject had not signed the treatment past progression informed consent.

- **Baseline data**

The median age of participants was 56.0 years (range: 27-86), and 25.8% of participants were ≥ 65 years of age. Almost all participants were female (99.1%). The majority of participants were White (66.7%), 3.9% were Black or African American, and 2.9% were Asian. Participants were from the geographical regions of Europe (57.8%) and North America (42.2%).

More participants had a screening ECOG performance status of 1 (55.6%) versus 0 (44.4%). The median time from metastatic disease diagnosis to randomization was approximately 4 years (47.8 months [range: 1.2-248.8]).

At baseline, participants had received a median of 7.0 prior systemic anticancer regimens (range: 3-17), a median of 4.0 prior systemic chemotherapy regimens in any setting (range: 1-9), and a median of 3.0 prior systemic chemotherapy regimens in the metastatic setting (range: 0-8). The majority of participants had received chemotherapy in the neo/adjuvant setting (65.7%). Approximately 42% of patients had 2 prior chemotherapy regimens for metastatic disease compared to 58% of patients who had 3 to 4 prior chemotherapy regimens. All participants had received prior treatment with a CDK 4/6 inhibitor, 66.5% were treated with a CDK 4/6 inhibitor for ≥ 6 months and 38.3% were treated with a CDK 4/6 inhibitor for > 12 months. All participants had received prior endocrine therapy, 86.4% of whom were treated with endocrine therapy for ≥ 6 months in the metastatic setting.

Table 15: Demographics and Other Baseline Characteristics

	SG (N = 272)	TPC (N = 271)	Total (N = 543)
Age at Study Entry (years)			
Median	57.0	55.0	56.0
Minimum	29	27	27
Maximum	86	78	86
Age Group, n (%)			
< 65 years	199 (73.2%)	204 (75.3%)	403 (74.2%)
< 50 years	71 (26.1%)	79 (29.2%)	150 (27.6%)
≥ 50 and < 65 years	128 (47.1%)	125 (46.1%)	253 (46.6%)
≥ 65 years	73 (26.8%)	67 (24.7%)	140 (25.8%)
≥ 75 years	16 (5.9%)	8 (3.0%)	24 (4.4%)
Sex, n (%)			
Male	2 (0.7%)	3 (1.1%)	5 (0.9%)
Female	270 (99.3%)	268 (98.9%)	538 (99.1%)
Race, n (%)			
Asian	11 (4.0%)	5 (1.8%)	16 (2.9%)
Black or African American	8 (2.9%)	13 (4.8%)	21 (3.9%)
White	184 (67.6%)	178 (65.7%)	362 (66.7%)
Other	0 (0.0%)	5 (1.8%)	5 (0.9%)
Not Reported [a]	69 (25.4%)	70 (25.8%)	139 (25.6%)
Region, n (%)			
North America	115 (42.3%)	114 (42.1%)	229 (42.2%)
Europe	157 (57.7%)	157 (57.9%)	314 (57.8%)

	SG (N = 272)	TPC (N = 271)	Total (N = 543)
Baseline Renal Function, n (%)			
Creatinine clearance < 30 mL/min	1 (0.4%)	0 (0.0%)	1 (0.2%)
30 mL/min ≤ Creatinine clearance < 60 mL/min	22 (8.1%)	22 (8.1%)	44 (8.1%)
60 mL/min ≤ Creatinine clearance < 90 mL/min	106 (39.0%)	96 (35.4%)	202 (37.2%)
Creatinine clearance ≥ 90 mL/min	141 (51.8%)	153 (56.5%)	294 (54.1%)
Missing	2 (0.7%)	0 (0.0%)	2 (0.4%)
Baseline Hepatic Function, n (%) [b]			
Normal	120 (44.1%)	114 (42.1%)	234 (43.1%)
Mild	148 (54.4%)	152 (56.1%)	300 (55.2%)
Moderate	2 (0.7%)	5 (1.8%)	7 (1.3%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	2 (0.7%)	0 (0.0%)	2 (0.4%)
UGT1A1 Genotype (SG only), n (%)			
*1|*1	104 (38.2%)		
*1|*28	119 (43.8%)		
*28|*28	25 (9.2%)		
Other	3 (1.1%)		
Missing/Not Done	21 (7.7%)		

[a] Not reported indicates local regulators did not allow collection of race or ethnicity information.

[b] Normal hepatic function: bilirubin ≤ ULN and AST ≤ ULN; mild hepatic impairment: 1) bilirubin ≤ ULN and AST > ULN or 2) ULN < bilirubin ≤ 1.5 × ULN; moderate hepatic impairment: 1.5 × ULN < bilirubin ≤ 3 × ULN; severe hepatic impairment: bilirubin > 3 × ULN.

Table 16: Baseline Disease Characteristics

	SG (N = 272)	TPC (N = 271)	Total (N = 543)
Screening **ECOG Performance Status**, n (%)			
0: Normal Activity	115 (42.3%)	126 (46.5%)	241 (44.4%)
1: Symptoms but Ambulatory	157 (57.7%)	145 (53.5%)	302 (55.6%)
Visceral Metastasis, n (%)			
Yes	259 (95.2%)	258 (95.2%)	517 (95.2%)
Baseline **Liver** Lesion per RECIST v1.1 per LIR, n (%)			
Yes	229 (84.2%)	237 (87.5%)	466 (85.8%)
Brain Metastasis, n (%)			
Yes	11 (4.0%)	14 (5.2%)	25 (4.6%)
Time from Metastatic Disease Diagnosis to Randomization (months) [a]			
Median	48.5	46.6	47.8
Minimum	1.2	3.0	1.2
Maximum	243.8	248.8	248.8

Table 17: Breast Cancer History

	SG (N = 272)	TPC (N = 271)	Total (N = 543)
Breast Cancer Metastasis Stage, n (%)			
M0	1 (0.4%)	1 (0.4%)	2 (0.4%)
M1	262 (96.3%)	264 (97.4%)	526 (96.9%)
Missing	9 (3.3%)	6 (2.2%)	15 (2.8%)
HER2 Status, n (%)			
Positive	0 (0.0%)	2 (0.7%)	2 (0.4%)
Negative	272 (100.0%)	269 (99.3%)	541 (99.6%)
Method of HER2 Status Diagnosis, n (%)			
IHC	195 (71.7%)	206 (76.0%)	401 (73.8%)
0	95 (34.9%)	107 (39.5%)	202 (37.2%)
1+	81 (29.8%)	76 (28.0%)	157 (28.9%)
2+	17 (6.3%)	22 (8.1%)	39 (7.2%)
Missing	2 (0.7%)	1 (0.4%)	3 (0.6%)
FISH	18 (6.6%)	17 (6.3%)	35 (6.4%)
Positive	0 (0.0%)	1 (0.4%)	1 (0.2%)
Negative	18 (6.6%)	16 (5.9%)	34 (6.3%)
FISH and IHC	59 (21.7%)	46 (17.0%)	105 (19.3%)
Negative and 0	6 (2.2%)	9 (3.3%)	15 (2.8%)
Negative and 1+	6 (2.2%)	3 (1.1%)	9 (1.7%)
Negative and 2+	45 (16.5%)	33 (12.2%)	78 (14.4%)
Negative and 3+	2 (0.7%)	1 (0.4%)	3 (0.6%)
Missing Method	0 (0.0%)	2 (0.7%)	2 (0.4%)
Participants with Either Estrogen Receptor or Progesterone Receptor Positive, n (%) [a]			
Yes	272 (100.0%)	266 (98.2%)	538 (99.1%)
No	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	5 (1.8%)	5 (0.9%)
BRCA1/BRCA2 Mutation Status, n (%) [b]			
Negative	109 (40.1%)	114 (42.1%)	223 (41.1%)
Positive	21 (7.7%)	11 (4.1%)	32 (5.9%)
Missing	142 (52.2%)	146 (53.9%)	288 (53.0%)

[a] Positive estrogen receptor or progesterone receptor were defined as ≥ 1%.
[b] Positive denotes participant was either BRCA1 positive or BRCA2 positive. Negative denotes participant was both BRCA1 negative and BRCA2 negative.

Table 18: Prior Systemic Anticancer Therapy

	SG (N = 272)	TPC (N = 271)	Total (N = 543)
Number of Prior Systemic Anticancer Regimens			
Median	7.0	7.0	7.0
Min, Max	3, 17	3, 16	3, 17
Number of Prior Systemic Chemotherapy Regimens			
Median	4.0	4.0	4.0
Min, Max	1, 9	2, 7	1, 9
Number of Prior Systemic Chemotherapy Regimens by Category, n (%)			
1	1 (0.4%)	0	1 (0.2%)
2	39 (14.3%)	35 (12.9%)	74 (13.6%)
3	88 (32.4%)	84 (31.0%)	172 (31.7%)
4	86 (31.6%)	95 (35.1%)	181 (33.3%)
> 4	58 (21.3%)	57 (21.0%)	115 (21.2%)
Number of Prior Lines of Chemotherapy in Metastatic Setting, n (%)			
≤ 2	113 (41.5%)	120 (44.3%)	233 (42.9%)
≥ 3	159 (58.5%)	151 (55.7%)	310 (57.1%)
Number of Prior Lines of Chemotherapy in Metastatic Setting			
Median	3	3	3
Min, Max	0, 8	1, 5	0, 8
Early Relapse, n (%) [a]			
Yes	21 (7.7%)	21 (7.7%)	42 (7.7%)
No	242 (89.0%)	246 (90.8%)	488 (89.9%)
Unknown	9 (3.3%)	4 (1.5%)	13 (2.4%)
Endocrine Therapy in the Metastatic Setting for at Least 6 Months, n (%)			
Yes	235 (86.4%)	234 (86.3%)	469 (86.4%)
Prior CDK 4/6 use, n (%)	272 (100.0%)	271 (100.0%)	543 (100.0%)
≤ 12 months	161 (59.2%)	166 (61.3%)	327 (60.2%)
> 12 months	106 (39.0%)	102 (37.6%)	208 (38.3%)
Missing	5 (1.8%)	3 (1.1%)	8 (1.5%)
Chemotherapy in neo/adjuvant setting, n (%)			
Yes	173 (63.6%)	184 (67.9%)	357 (65.7%)
No	99 (36.4%)	87 (32.1%)	186 (34.3%)
Participants with at least 1 prior anthracycline use in any setting, n (%)	215 (79.0%)	218 (80.4%)	
in the neo/adjuvant setting, n (%)	145 (53.3%)	159 (58.7%)	
in the metastatic setting, n (%)	108 (39.7%)	94 (34.7%)	
Best Response for the Last Therapy Before Entering Study, n (%)			
CR	1 (0.4%)	1 (0.4%)	2 (0.4%)
PR	30 (11.0%)	22 (8.1%)	52 (9.6%)
SD	67 (24.6%)	46 (17.0%)	113 (20.8%)
PD	115 (42.3%)	126 (46.5%)	241 (44.4%)
Not Available [d]	59 (21.7%)	76 (28.0%)	135 (24.9%)
Time from Last Disease Progression to Randomization (months)			

	SG (N = 272)	TPC (N = 271)	Total (N = 543)
N	272	270	542
Median	0.9	0.9	0.9
Min, Max	0.2, 11.3	0.1, 11.7	0.1, 11.7

[a] Early relapse is defined as relapse to metastatic disease within 1 year of the end of neo/adjuvant chemotherapy. Participants without chemotherapy in neo/adjuvant setting are not considered as early relapse.

- **Numbers analysed**

Table 19: Numbers and percentages of participants in each analysis population

	SG n (%)	TPC n (%)	Total n (%)
Screened Population			776
ITT Population	272	271	543
Safety Population	268 (98.5%)	249 (91.9%)	517 (95.2%)
HRQOL-Evaluable Population	236 (86.8%)	210 (77.5%)	446 (82.1%)
EQ-5D-5L-Evaluable Population	238 (87.5%)	207 (76.4%)	445 (82.0%)

Outcomes and estimation

- **Primary endpoint**

PFS per BICR

At the primary PFS analysis (data cutoff date 03 January 2022), a statistically significant improvement in PFS per BICR using RECIST 1.1 was demonstrated with SG versus TPC (HR: 0.661; 95% CI: 0.529, 0.826; P = 0.0003). Median PFS was 5.5 months (95% CI: 4.2, 7.0) in the SG group vs 4.0 months (95% CI: 3.1, 4.4) in the TPC group.

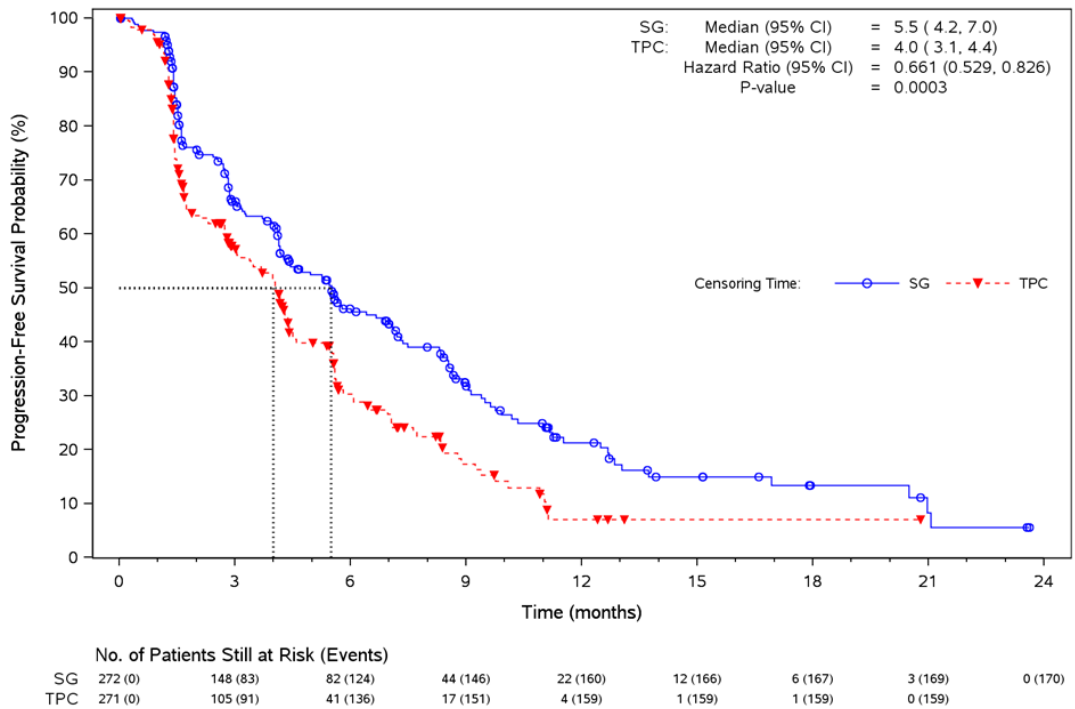
Table 20: PFS per BICR (ITT Population)

	SG (N = 272)	TPC (N = 271)	Treatment Comparison
PFS Events [n (%)]	170 (62.5%)	159 (58.7%)	
Disease Progression	141 (51.8%)	140 (51.7%)	
Death	29 (10.7%)	19 (7.0%)	
Censored [n (%)]	102 (37.5%)	112 (41.3%)	
Death after Starting New Anticancer Therapy	37 (13.6%)	33 (12.2%)	
Death after 2 or More Consecutive Missing Visits	3 (1.1%)	4 (1.5%)	
No PD and No Death	54 (19.9%)	38 (14.0%)	
No Baseline Image or Postbaseline Evaluable Assessment [a]	8 (2.9%)	37 (13.7%)	
Median PFS (95% CI) [b]	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)	

	SG (N = 272)	TPC (N = 271)	Treatment Comparison
Log-rank *P* value (Stratified) [c]			0.0003
Stratified Cox Regression Analysis [c]			
Hazard Ratio (Relative to TPC)			0.661
95% CI for Hazard Ratio			(0.529, 0.826)
Kaplan-Meier Estimate of PFS Rate (%) (95% CI) [d]			
At 3 Months	66.0 (59.6, 71.6)	57.8 (50.8, 64.1)	
At 6 Months	46.1 (39.4, 52.6)	30.3 (23.6, 37.3)	
At 9 Months	32.5 (25.9, 39.2)	17.3 (11.5, 24.2)	
At 12 Months	21.3 (15.2, 28.1)	7.1 (2.8, 13.9)	
At 18 Months	13.3 (7.8, 20.4)	7.1 (2.8, 13.9)	

[a] Censoring due to no baseline or no postbaseline evaluable assessment did not include death event before the second scheduled visit postbaseline.
[b] Median PFS was from KM estimate. The CI for the median was computed using the Brookmeyer-Crowley method.
[c] Stratified log-rank test and stratified Cox regression adjusted for stratification factors (based on IXRS [interactive voice/web response system]): prior chemotherapy regimens for treatment of metastatic disease (2 or 3/4 lines), visceral metastasis (yes or no), and endocrine therapy in the metastatic setting for at least 6 months (yes or no).
[d] The PFS rate was the proportion of participants alive without PD.

Figure 14: KM Plots of PFS per BICR (ITT population)



Updated PFS results per BICR at the final data cutoff (01 December 2022)

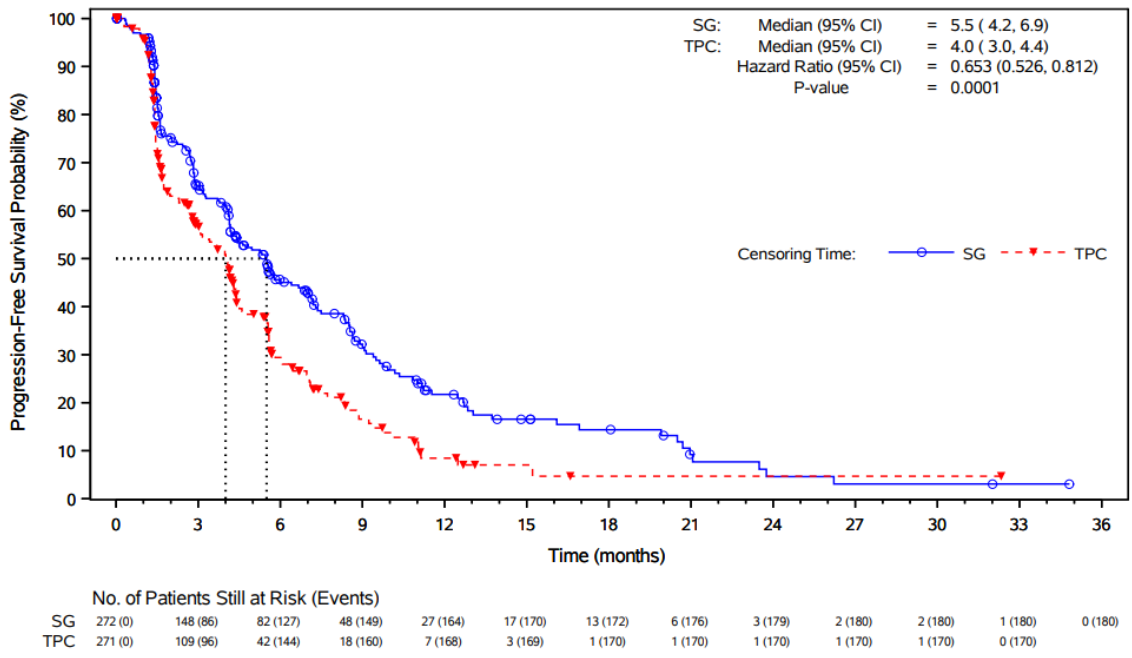
Table 21: PFS Per BICR at Final Analysis (ITT Population)

	SG (N = 272)	TPC (N = 271)	Treatment Comparison
PFS Events [n (%)]	180 (66.2%)	170 (62.7%)	—

	SG (N = 272)	TPC (N = 271)	Treatment Comparison
Disease Progression	148 (54.4%)	142 (52.4%)	—
Death	32 (11.8%)	28 (10.3%)	—
Censored [n (%)]	92 (33.8%)	101 (37.3%)	—
PD after Starting New Anticancer Therapy	0 (0.0%)	1 (0.4%)	—
Death after Starting New Anticancer Therapy	52 (19.1%)	46 (17.0%)	—
Death after 2 or More Consecutive Missing Visits	11 (4.0%)	31 (11.4%)	—
No PD and No Death	28 (10.3%)	19 (7.0%)	—
No Baseline Image or Postbaseline Evaluable Assessment[a]	1 (0.4%)	4 (1.5%)	—
Median PFS (95% CI)[b]	5.5 (4.2, 6.9)	4.0 (3.0, 4.4)	—
Log-rank Nominal *P* value (Stratified)[c]	—	—	0.0001
Stratified Cox Regression Analysis[c]	—	—	
Hazard Ratio (Relative to TPC)	—	—	0.653
95% CI for Hazard Ratio	—	—	(0.526, 0.812)
Kaplan-Meier Estimate of PFS Rate (%) (95% CI)[d]	—	—	—
At 6 Months	45.6 (38.9, 52.0)	29.4 (22.9, 36.2)	—
At 9 Months	32.2 (25.7, 38.8)	16.6 (11.0, 23.1)	—
At 12 Months	21.7 (15.8, 28.3)	8.4 (4.2, 14.5)	—

a Censoring due to no baseline or no postbaseline evaluable assessment did not include death event before the second scheduled visit postbaseline.
b Median PFS was from Kaplan-Meier estimate. The CI for the median was computed using the Brookmeyer-Crowley method.
c Stratified log-rank test and stratified Cox regression adjusted for stratification factors (based on IXRS): prior chemotherapy regimens for treatment of metastatic disease (2 or 3/4 lines), visceral metastasis (yes or no), and endocrine therapy in the metastatic setting for at least 6 months (yes or no).
d The PFS rate was the proportion of participants alive without PD.
Progression-free survival was defined as the number of months (30.4375 days) from the date of randomization to the date of the first radiological disease progression per RECIST v1.1 or death due to any cause, whichever occurred first.

Figure 15: KM Plots of PFS Per BICR at Final Analysis (ITT Population)



- **Secondary endpoints**

OS

Given that the required number of OS events for the **first interim analysis** had occurred as of the time of the primary analysis of PFS, the planned first interim analysis of OS was performed together with the primary (final) PFS analysis (OS events 149 [54.8%] vs 144 [53.1%] in the SG vs the TPC arm, respectively).

Table 22: OS at **IA1** (data cutoff 03 Jan 2022)

Efficacy Endpoint	SG (N = 272)	TPC (N = 271)
Overall Survival (months)[a]		
Median (95% CI)	13.9 (12.7, 15.4)	12.3 (10.8, 14.2)
HR (95% CI); *P*-value	0.842 (0.668, 1.060); *P* = 0.1425[b]	

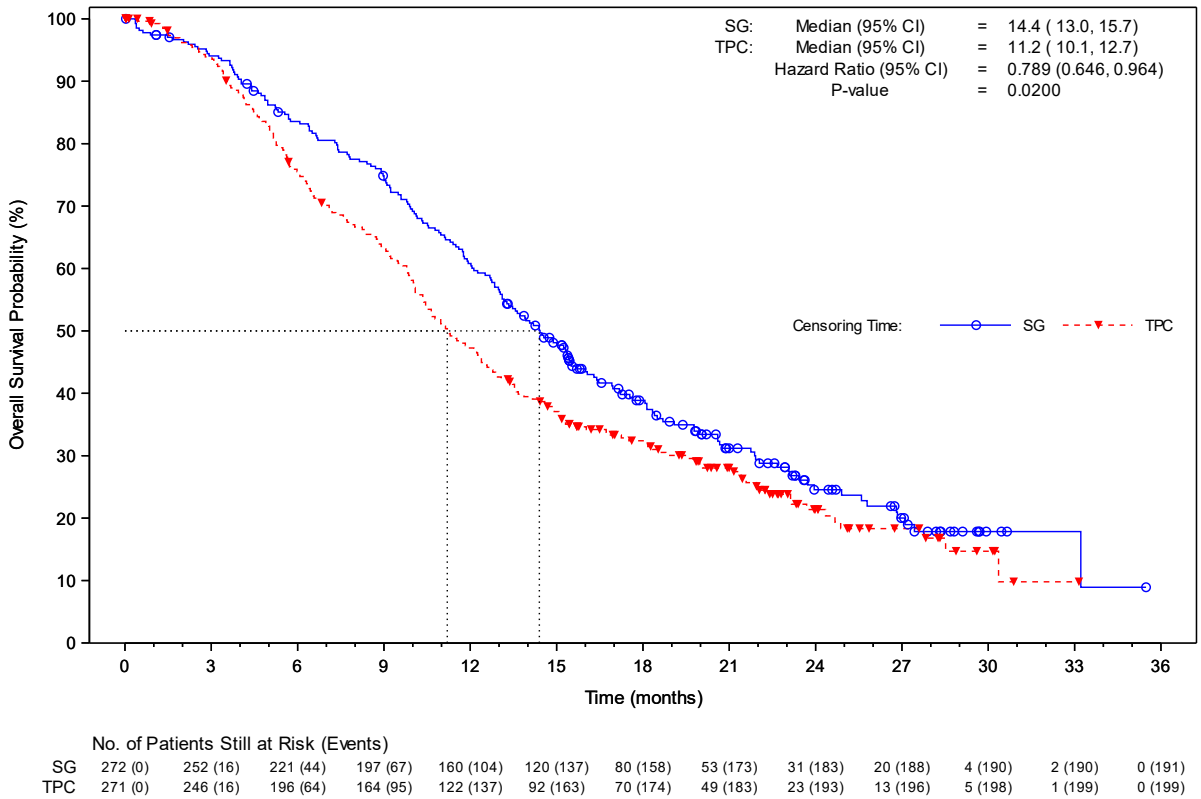
a Median OS were from KM estimates. The CI for the median was computed using the Brookmeyer- Crowley method.
b Stratified log-rank test and stratified Cox regression adjusted for stratification factors (based on IXRS): prior chemotherapy regimens for treatment of metastatic disease (2 or 3/4 lines), visceral metastasis (yes or no), and endocrine therapy in the metastatic setting for at least 6 months (yes or no).

Table 23: Overall Survival at **IA2** (data cutoff 01 July 2022)

	SG (N = 272)	TPC (N = 271)	Treatment Comparison
Participants With Events [n (%)]	191 (70.2%)	199 (73.4%)	
Participants Without Events (Censored) [n (%)]	81 (29.8%)	72 (26.6%)	
Median OS (95% CI) [a]	14.4 (13.0, 15.7)	11.2 (10.1, 12.7)	
Log-rank *P* value (Stratified) [b]			0.0200
Stratified Cox Regression Analysis [b]			
Hazard Ratio (Relative to TPC)			0.789
95% CI for Hazard Ratio			(0.646, 0.964)
Kaplan-Meier Estimate of OS Rate (%) (95% CI) [c]			
At 12 Months	60.8 (54.6, 66.4)	47.3 (41.1, 53.2)	
At 18 Months	38.9 (32.8, 44.9)	32.4 (26.7, 38.2)	
At 24 Months	24.6 (18.8, 30.7)	21.4 (16.0, 27.3)	

[a] Median OS was from KM estimate. The CI for the median was computed using the Brookmeyer-Crowley method.
[b] Stratified log-rank test and stratified Cox regression adjusted for stratification factors (based on IXRS): prior chemotherapy regimens for treatment of metastatic disease (2 or 3/4 lines), visceral metastasis (yes or no), and endocrine therapy in the metastatic setting for at least 6 months (yes or no).
[c] The OS rate was the proportion of participants alive.
Overall survival was defined as the number of months (30.4375 days) from the date of randomization to the date of death due to any cause. Participants without documentation of death were censored on the date they were last known to be alive.
The number of OS events was 390 at the time of the OS IA2, when the 2-sided nominal alpha was 0.0223 based on the Lan-DeMets alpha spending function that approximates a Pocock approach.
Source: IMMU-132-09 Interim 2, Table 18

Figure 16: Kaplan-Meier Plots of Overall Survival (OS IA2)



Updated OS results at the final data cutoff (01 December 2022)

The median survival follow-up durations were 14.39 and 10.97 months for the SG and TPC groups, respectively at the final data cutoff.

Table 24: Overall Survival at Final Analysis (ITT Population)

	SG (N = 272)	**TPC (N = 271)**	**Treatment Comparison**
Participants with Events [n (%)]	214 (78.7%)	224 (82.7%)	—
Participants without Events (Censored) [n (%)]	58 (21.3%)	47 (17.3%)	—
Median OS (95% CI)[a]	14.5 (13.0, 16.0)	11.2 (10.2, 12.6)	—
Log-rank Nominal *P* value (Stratified)[b]	—	—	0.0133
Stratified Cox Regression Analysis[b]	—	—	
Hazard Ratio (Relative to TPC)	—	—	0.788
95% CI for Hazard Ratio	—	—	(0.652, 0.952)
Kaplan-Meier Estimate of OS Rate (%) (95% CI)[c]	—	—	—
At 12 Months	60.9 (54.8, 66.4)	47.1 (41.0, 53.0)	—
At 18 Months	39.2 (33.4, 45.0)	31.7 (26.2, 37.4)	—
At 24 Months	25.7 (204, 31.2)	21.1 (16.3, 26.3)	—

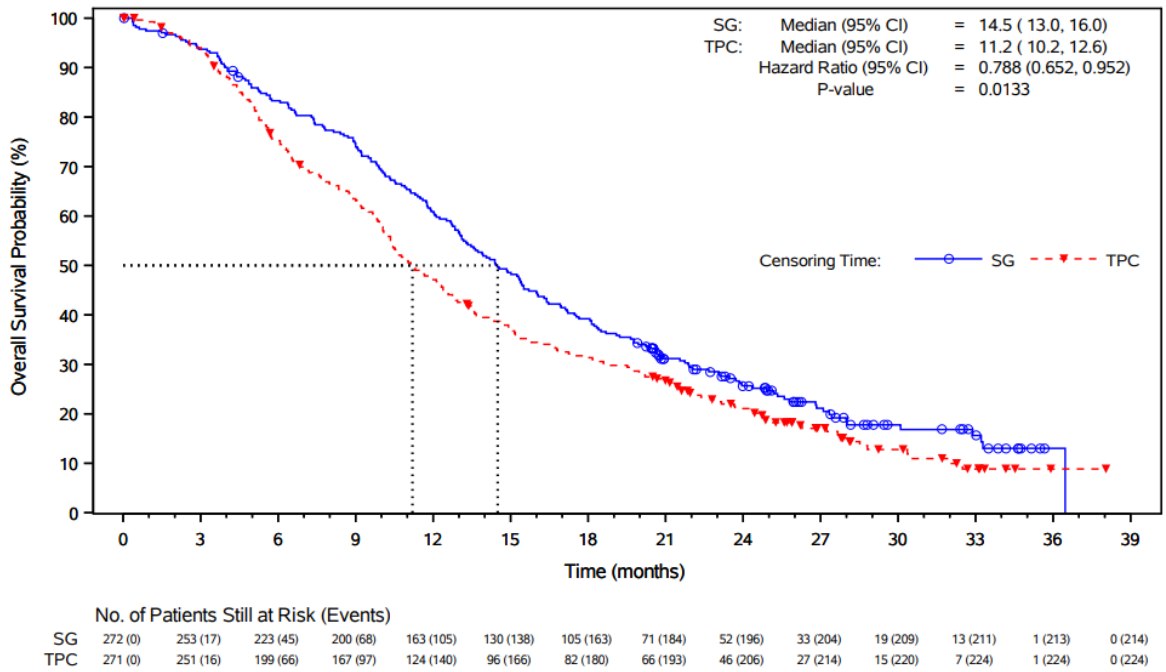
a Median OS was from Kaplan-Meier estimate. The CI for the median was computed using the Brookmeyer-Crowley method.

b Stratified log-rank test and stratified Cox regression adjusted for stratification factors (based on IXRS): prior chemotherapy regimens for treatment of metastatic disease (2 or 3/4 lines), visceral metastasis (yes or no), and endocrine therapy in the metastatic setting for at least 6 months (yes or no)

c The OS rate was the proportion of participants alive.

Overall survival was defined as the number of months (30.4375 days) from the date of randomization to the date of death due to any cause. Participants without documentation of death were censored on the date they were last known to be alive.

Figure 17: Kaplan-Meier Plots of Overall Survival at Final Analysis (ITT Population)



ORR and CBR

- Per BICR

A statistically significantly higher ORR per BICR using RECIST v1.1 was observed in the SG group versus the TPC group. ORR per BICR was tested per the hierarchical testing strategy, because a statistically significant improvement in OS was demonstrated at OS IA2.

Table 25: ORR and CBR **per BICR** (from IMMU-132-09 Interim 2, Table 15.2.3.1)

	SG (N = 272)	**TPC (N = 271)**	**Treatment Comparison**
Participants with Measurable Disease at Baseline	269	267	
Objective Response (CR or PR) n (%)	57 (**21.0%**)	38 (**14.0%**)	
95% CI (Exact)	(16.3, 26.3)	(10.1, 18.7)	
Odds Ratio			1.625
95% CI			(1.034, 2.555)
P value			0.0348
Clinical Benefit Rate (CR, PR, or SD ≥ 6 months) n (%)	92 (33.8%)	60 (22.1%)	
95% CI (Exact)	(28.2, 39.8)	(17.3, 27.6)	
Odds Ratio			1.796
95% CI			(1.227, 2.628)
P value*			0.0025
Best Overall Response, n (%)			
CR	2 (0.7%)	0 (0.0%)	
PR	55 (20.2%)	38 (14.0%)	

	SG (N = 272)	TPC (N = 271)	Treatment Comparison
SD	142 (52.2%)	106 (39.1%)	
SD ≥ 6 months	35 (12.9%)	22 (8.1%)	
PD	58 (21.3%)	76 (28.0%)	
Not Evaluable	15 (5.5%)	51 (18.8%)	

The exact binomial CI for proportion was based on the Beta distribution. The *P* value was based on the Cochran-Mantel-Haenszel test stratified by stratification factors used in randomization. The ORR per BICR was formally tested sequentially per hierarchical testing procedure with 2-sided alpha = 0.05.

* *P* value for CBR nominal

According to the PFS results 8 patients (2.9%) were censored in the SG and 37 patients (13.7%) in the TPC arm due to lack of baseline image or postbaseline evaluable assessment. The number of not evaluable patients for assessment of ORR were 15 (5.5%) in the SG arm and 51 (18.8%) in the TPC arm.

- Per LIR

Table 26: ORR and CBR **per LIR**

	SG (N = 272)	TPC (N = 271)	Treatment Comparison
Participants with Measurable Disease at Baseline	272	270	
Objective Response (CR or PR) n (%)	44 (**16.2%**)	25 (**9.2%**)	
95% CI (Exact)	(12.0, 21.1)	(6.1, 13.3)	
Odds Ratio			1.931
95% CI			(1.138, 3.275)
P value			0.0137
Clinical Benefit Rate (CR, PR, or SD ≥ 6 months) n (%)	88 (32.4%)	57 (21.0%)	
95% CI (Exact)	(26.8, 38.3)	(16.3, 26.4)	
Odds Ratio			1.834
95% CI			(1.237, 2.717)
P value*			0.0024
Best Overall Response, n (%)			
CR	1 (0.4%)	0 (0.0%)	
PR	43 (15.8%)	25 (9.2%)	
SD	134 (49.3%)	113 (41.7%)	
SD ≥ 6 months	44 (16.2%)	32 (11.8%)	
PD	77 (28.3%)	82 (30.3%)	
Not Evaluable	17 (6.3%)	51 (18.8%)	

DOR

Duration of response for participants who experienced a best overall response of CR or PR per BICR/per LIR is summarized below.

Table 27: DOR per BICR and per LIR using RECIST v1.1 (Assessor´s table from CSR IA2 Tables 21 and 22)

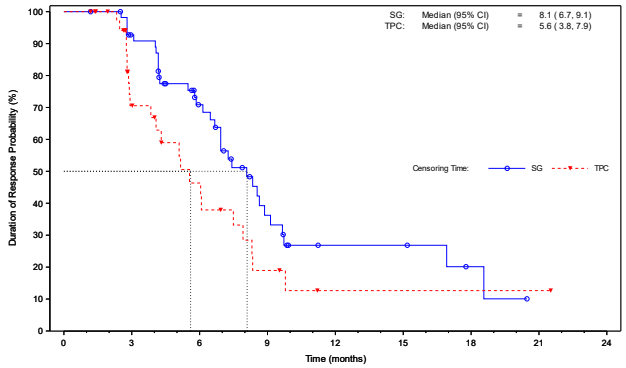
	Assessment **per BICR**			Assessment **per LIR**	
	SG	**TPC**		**SG**	**TPC**
Number of Responders (CR or PR)	N=57	N=38		N=44	N=25

Participants with Events [n (%)]	33 (57.9%)	22 (57.9%)		37 (84.1%)	19 (76.0%)
Participants without Events (Censored) [n (%)]	24 (42.1%)	16 (42.1%)		7 (15.9%)	6 (24.0%)
Median DOR (95% CI) [a]	**8.1** (6.7, 9.1)	**5.6** (3.8, 7.9)		**7.0** (5.6, 9.2)	**4.3** (4.2, 6.1)
Kaplan-Meier Estimates of DOR Rate (%) (95% CI) [b]					
At 3 Months	92.7 (81.8, 97.2)	70.6 (50.9, 83.5)		95.3 (82.5, 98.8)	82.6 (60.1, 93.1)
At 6 Months	70.9 (56.2, 81.4)	46.3 (26.9, 63.7)		58.8 (42.3, 72.0)	37.1 (17.0, 57.4)
At 9 Months	36.2 (21.6, 51.1)	19.0 (6.2, 36.9)		35.8 (21.4, 50.4)	21.2 (6.7, 41.1)
At 12 Months	26.8 (13.7, 41.8)	12.6 (2.6, 30.9)		13.3 (4.5, 27.1)	5.3 (0.4, 21.5)

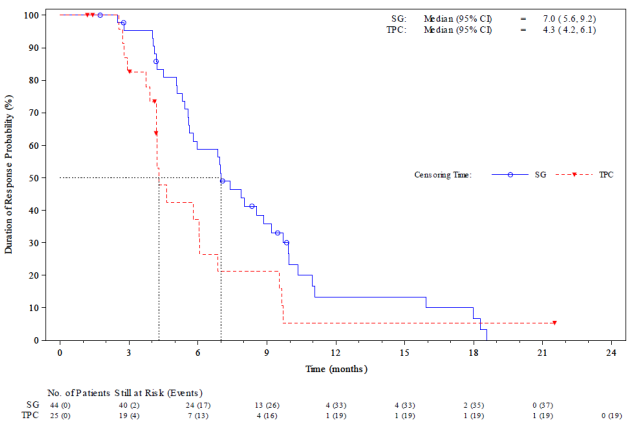
[a] Median DOR was from KM estimate. The CI for the median was computed using the Brookmeyer-Crowley method.
[b] The DOR rate was the proportion of participants alive without PD after the initial response.
Only participants who had a confirmed CR or PR were included in the analysis. Duration of response was defined as the number of months (30.4375 days) from the date of initial response to the date of the event defined as the first documented progression per RECIST v1.1 or death due to any cause, whichever occurred earlier.

Figure 18: KM Estimates of Duration of Response

per BICR



per LIR



PRO – Time to Deterioration in EORTC QLQ-C30 Global Health Status/QOL, Pain, and Fatigue Domains

Because a statistically significant improvement in ORR was demonstrated in the SG group versus the TPC group, the time to deterioration of QOL endpoints was tested per the hierarchical testing strategy (a boundary of 0.05/3 for each of the 3 TTD hypothesis tests was used to control multiplicity). Analyses of TTD in the EORTC QLQ-C30 global health status/QOL, pain, and fatigue scales were conducted for participants in the HRQOL-Evaluable Population who had baseline global health status/QOL score ≥ 10, baseline pain score ≤ 90, and baseline fatigue score ≤ 90, respectively.

A statistically significantly longer time to first deterioration in the EORTC QLQ-C30 global health status/QOL and fatigue domains was demonstrated in the SG group versus the TPC group (event rates 90% vs 89% for SG vs TPC).
No statistically significant difference in TTD in the EORTC QLQ-C30 pain domain was observed between the SG and TPC groups.

Table 28: TTD in EORTC QLQ-C30 **Global Health Status /QOL** Domain (HRQOL-Evaluable Population; Participants with Baseline GHS/QOL Score ≥ 10) (from SCS Table 13)

	SG (N = 234)	**TPC (N = 207)**
Participants with Events [n (%)]	210 (89.7%)	185 (89.4%)
Median (months) (95% CI)	**4.3** (3.1, 5.7)	**3.0** (2.2, 3.9)
HR (95% CI); *P* value (Stratified)	**0.75** (0.61, 0.92); *P* = 0.0059	
KM Estimates of Event-free Rate at 12 months (%) (95% CI)	25.2 (19.6, 31.1)	14.7 (9.9, 20.4)

Note: Sensitivity Analysis of TTD in EORTC QLQ-C30 GHS/QOL (death not considered an event):
HR 0.7 *[0.54, 0.9]; nominal P = 0.0046; median* ***4.3*** *[3.0, 6.1] vs* ***2.6*** *[2.1, 3.3] for SG vs TPC*

Table 29: TTD in EORTC QLQ-C30 **Fatigue** Domain (HRQOL-Evaluable Population; Participants with Baseline Fatigue Score ≤ 90) (excerpt from SCS Table 15)

	SG (N = 234)	**TPC (N = 205)**
Participants with Events [n (%)]	218 (93.2%)	191 (93.2%)
Median (months) (95% CI)	**2.2** (1.6, 2.8)	**1.4** (1.1, 1.9)
HR (95% CI); *P* value (Stratified)	**0.73** (0.60, 0.89); *P* = 0.0021	
KM Estimates of Event-free Rate at 12 months (%) (95% CI)	18.2 (13.4, 23.5)	9.9 (6.1, 14.9)

Note: Sensitivity Analysis of TTD in EORTC QLQ-C30 Fatigue (death not considered an event):
HR: 0.73 *[0.58, 0.92]; nominal P = 0.0064; median* ***2.0*** *[1.5, 2.5] vs* ***1.3*** *[1.1, 1.9] for SG vs TPC*

Table 30: TTD in EORTC QLQ C30 **Pain** Domain (HRQOL-Evaluable Population; Participants With Baseline Pain Score ≤ 90) (excerpt from SCS Table 14)

	SG (N = 229)	**TPC (N = 202)**
Participants with Events [n (%)]	207 (90.4%)	180 (89.1%)
Median (months) (95% CI)	**3.8** (2.8, 5.0)	**3.5** (2.8, 5.0)
HR (95% CI); *P* value (Stratified)	**0.92** (0.75, 1.13); *P* = 0.4151	
KM Estimates of Event-free Rate at 12 months (%) (95% CI)	23.2 (17.7, 29.1)	18.9 (13.5, 25.0)

Note: Sensitivity Analysis of TTD in EORTC QLQ-C30 Pain (death not considered an event):
HR: 0.92 *[0.71, 1.19]; nominal P = 0.5186; median* ***3.7*** *[2.8, 5.0] vs* ***3.2*** *[2.3, 4.3] for SG vs TPC*

- **Exploratory endpoints**

PRO – Change from baseline in physical and role functioning domains

An ad hoc exploratory analysis was conducted to evaluate the change from baseline in the EORTC QLQ-C30 physical functioning and role functioning domains using a mixed-effects model for repeated measures (MMRM). Between-group differences (SG vs TPC) in the overall least-squares mean (LSM) change from baseline were as follows:

- Physical Functioning: LSM difference 3.9; 95% CI: 0.87, 6.86; nominal *P* = 0.012
- Role Functioning: LSM difference 3.1; 95% CI: −1.15, 7.37; nominal *P* = 0.152

Ancillary analyses

Sensitivity analyses of PFS

Results from predefined sensitivity analyses of PFS per BICR and additionally, results of ad hoc sensitivity analyses assessing the impact of imaging interval on PFS results were provided. These were overall consistent with the primary PFS analysis results (PFS HR 0.661 [0.53, 0.83]; median PFS 5.5 vs 4 months for SG vs TPC in the primary PFS analysis).

Table 31: Sensitivity analyses of PFS (assessor´s table from primary CSR, Tables 19 and 15.2.1.2-15.2.1.5)

Sensitivity analyses of PFS (predefined) – **Used the same PFS definition and censoring rules as the primary analysis, except that**	**HR (95% CI) Nominal P**	**SG Median PFS, months (95% CI)**	**TPC Median PFS, Months (95% CI)**
1) any participant who progressed or died after >1 missed tumor assessment was not censored at the last date of radiographic assessment prior to the missed assessment	0.660 (0.53, 0.82) *P* = 0.0002	5.5 (4.2, 7.1)	4.1 (3.1, 4.4)
2) discontinuation of treatment or initiation of alternative anti-cancer treatment, whichever occurred later, was considered a PD event	0.664 (0.55, 0.80) *P* < 0.0001	4.0 (3.1, 4.2)	2.8 (1.9, 3.4)
3) analysis was performed for all treated participants who received at least 1 dose of study drug (ie, the Safety Population)	0.661 (0.53, 0.83) *P* = 0.0003	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)
4) any participant who initiated other anticancer treatment prior to disease progression or death, or who progressed or died after more than 1 missed scheduled tumor assessment, was not censored	0.738 (0.61, 0.90) *P* = 0.0027)	5.7 (4.6, 7.3)	4.3 (3.7, 5.3)

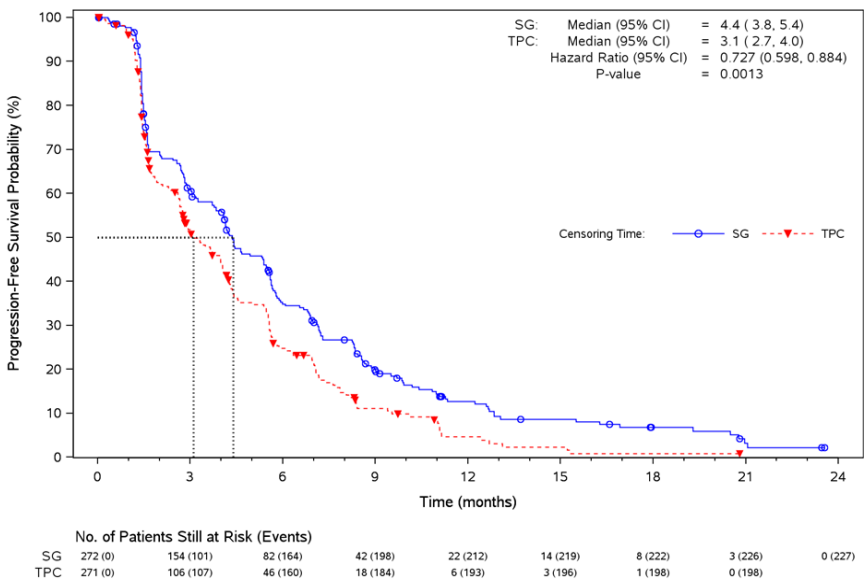
Ad hoc imaging interval sensitivity analyses of PFS – To assess the impact of imaging interval on PFS results	HR (95% CI) Nominal P Stratified	SG Median PFS, months (95% CI)	TPC Median PFS, Months (95% CI)
1) used an **interval censoring method** in which participants with documented PD events were assumed to have had actual PD occur between the last non-PD imaging assessment date and the documented PD date.	0.661 (0.53, 0.83) *P* = 0.0006	5.0 (4.0, 6.7)	3.4 (3.1, 3.7)
2) the **PD** date was **assigned only at scheduled visit dates** to minimize potential bias in tumor assessment schedules. (Participants with PD events in the primary analyses were moved to next scheduled visits.)	0.673 (0.54, 0.84) *P* < 0.0005	5.6 (4.2, 7.0)	4.2 (2.9, 4.3)

PFS per Local Investigator Review (**LIR**) - (other secondary endpoint)

Table 32: PFS per LIR (excerpt from SCE Table 16; data cutoff 03 Jan 2022)

	SG (N = 272)	TPC (N = 271)	Treatment Comparison
PFS Events [n (%)]	227 (83.5%)	198 (73.1%)	
Disease Progression	210 (77.2%)	188 (69.4%)	
Death	17 (6.3%)	10 (3.7%)	
Censored [n (%)]	45 (16.5%)	73 (26.9%)	
Median PFS (95% CI)	**4.4** (3.8, 5.4)	**3.1** (2.7, 4.0)	
Log-rank *P* value (Stratified; nominal)			0.0013
Stratified Cox Regression Analysis			
Hazard Ratio (Relative to TPC)			**0.727**
95% CI for Hazard Ratio			(0.598, 0.884)

Figure 19: KM Plots of PFS per LIR (data cutoff 03 Jan 2022)

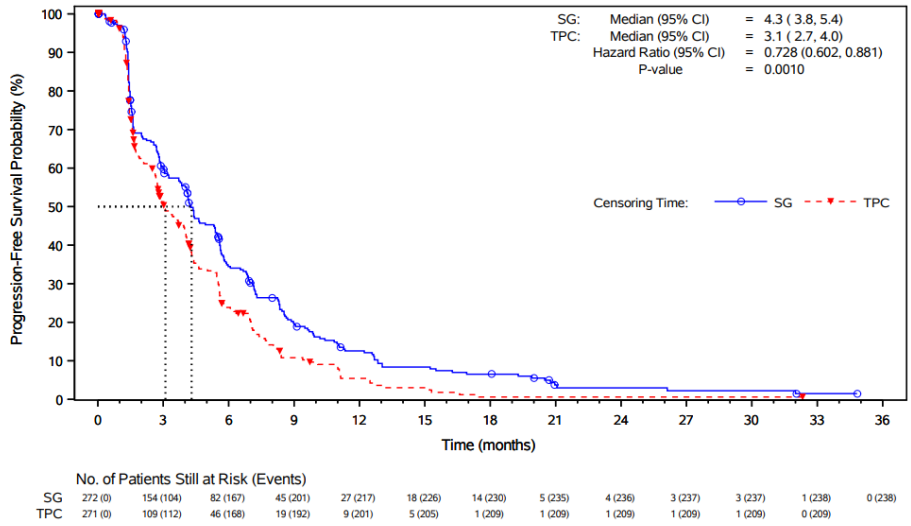


Updated PFS per LIR at the Final Data Cutoff (01 Dec 2022)

Table 33: PFS Per Local Investigator Review (final data cutoff 01 Dec 2022) (excerpt)

	SG (N = 272)	TPC (N = 271)	Treatment Comparison
PFS Events [n (%)]	238 (87.5%)	209 (77.1%)	—
Disease Progression	218 (80.1%)	191 (70.5%)	—
Death	20 (7.4%)	18 (6.6%)	—
Censored [n (%)]	34 (12.5%)	62 (22.9%)	—
Median PFS (95% CI)[b]	**4.3** (3.8, 5.4)	**3.1** (2.7, 4.0)	—
Log-rank Nominal *P* value (Stratified)[c]	—	—	0.0010
Stratified Cox Regression Analysis[c]	—		—
Hazard Ratio (Relative to TPC)	—	—	**0.728**
95% CI for Hazard Ratio	—	—	(0.602, 0.881)

Figure 20: KM Plots of PFS per LIR (final data cutoff 01 Dec 2022)



Sensitivity Analyses of Overall Survival

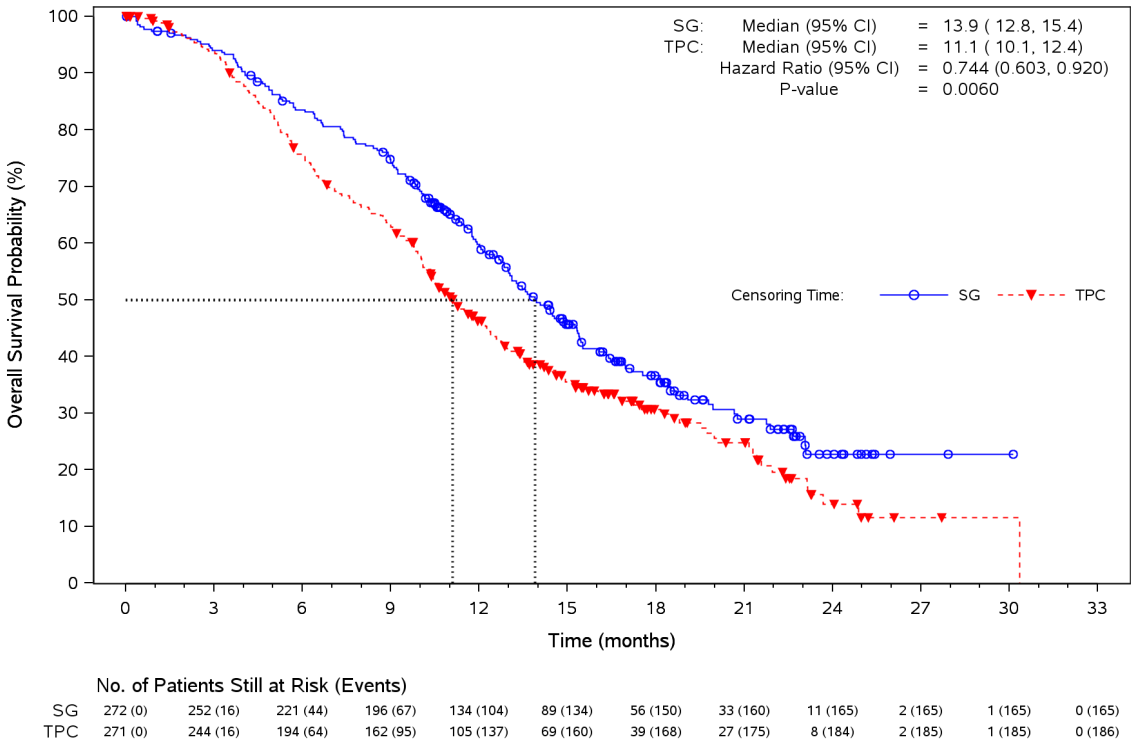
Two ad hoc sensitivity analyses were conducted to assess the impact of the timing of the OS analyses on the OS results.

Ad Hoc Sensitivity Analysis Based on the **First 351 OS Events**

At OS IA1, 12.2% (n=66) of participants was noted to be censored due to unknown/missing survival status. Additional public data searches (consistent with local regulations) were conducted to determine participant survival status; therefore, a number of additional OS events that occurred prior to the data cutoff date for OS IA1 (03 January 2022) were collected and included in OS IA2.

The targeted number of events required for the OS IA2, approximately 350, was reached as of 01 July 2022. Any events that occurred before the data cutoff date (01 July 2022) and were entered before database lock (09 August 2022) were included in the OS interim analyses. Therefore, OS IA2 was conducted based on a total of 390 OS events observed as of 01 July 2022. Given the observed number of OS events was greater than 110% of the targeted number of events, a sensitivity analysis was conducted based on the first 351 events (the 350th and 351st deaths occurred on the same date). Results of this ad hoc sensitivity analysis showed an improvement in OS in the SG group versus the TPC group (nominal *P* = 0.0060).

Figure 21: Sensitivity Analysis for OS Based on the First 351 OS Events[a] (data cutoff 27 Jan 2022)

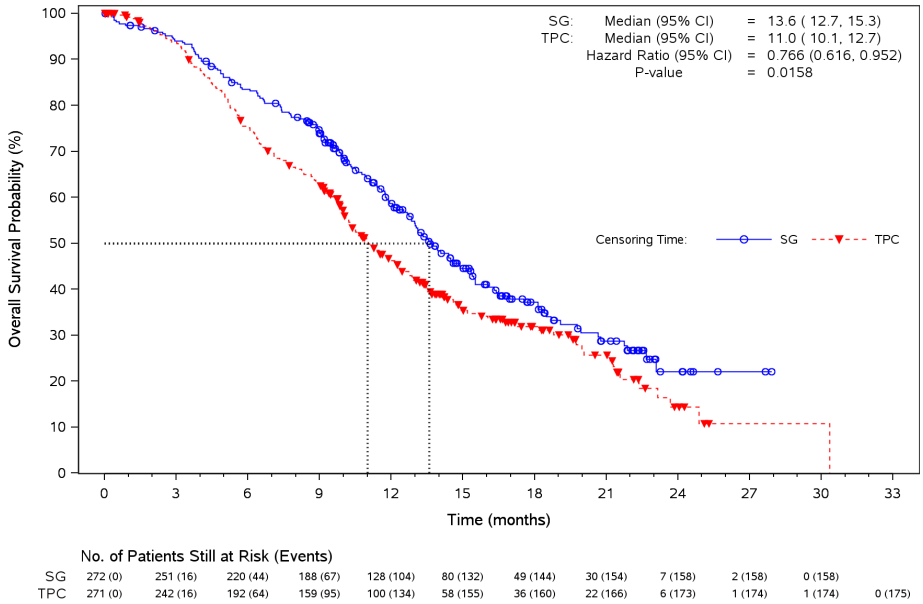


a Based on the data cut at the 351st event date (27 January 2022) (350th and 351st deaths occurred on the same date).

Ad Hoc Sensitivity Analysis Based on **OS Events** That Occurred **Before the Data Cutoff for OS IA1**

Between OS IA1 and OS IA2, 97 OS events were entered into the clinical database. Of those 97 OS events, 40 had occurred before the data cutoff date for OS IA1 (03 January 2022). Therefore, a sensitivity analysis was conducted based on 333 (293 [number of observed events at OS IA1]+40) OS events that occurred before the data cutoff date for OS IA1 (03 January 2022). Results of this ad hoc sensitivity analysis showed an improvement in OS in the SG group versus the TPC group (nominal *P* = 0.0158).

Figure 22: Sensitivity Analysis for OS Based on OS Events That Occurred Before the Data Cutoff for OS IA1 [a]



a Based on data cut at clinical cutoff date (03 January 2022) for OS IA1 and including new deaths entered after OS IA1 with death date prior to the clinical cutoff date for OS IA1.

Ad Hoc OS Sensitivity Analysis in the Safety Population

In line with PFS sensitivity analysis 3, an ad hoc sensitivity analysis was provided for OS in the safety population (all participants in the ITT Population who received at least 1 dose of study drug) to address the higher number of participants in the TPC group that were randomized but did not receive study drug.

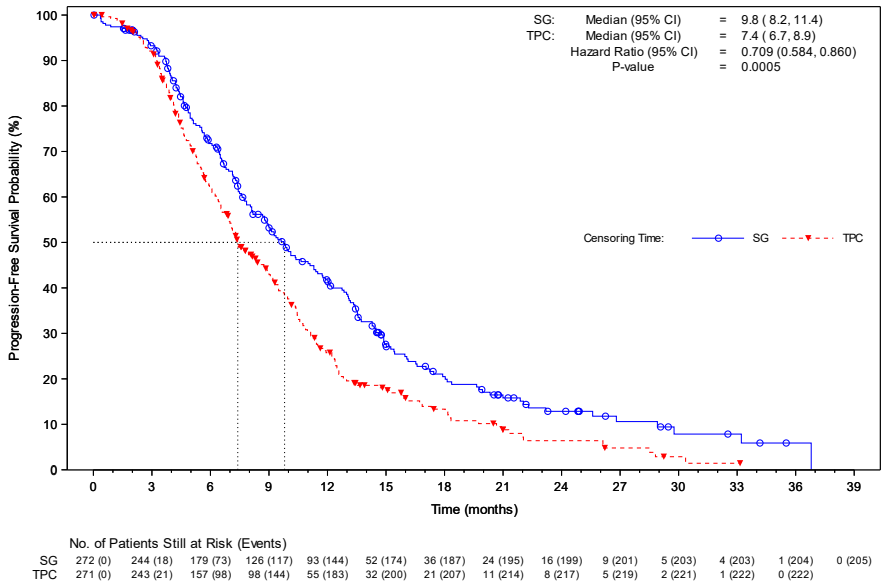
Table 34: Ad Hoc Sensitivity Analysis: OS Safety Population (excerpt from Interim 2 CSR Ad hoc 11215 Table 1.3)

	SG (N = 268)	TPC (N = 249)	Treatment Comparison
Subjects with Events [n (%)]	188 (70.1%)	183 (73.5%)	
Subjects without Events (Censored) [n (%)]	80 (29.9%)	66 (26.5%)	
Median OS (95% CI) [a]	14.5 (13.0, 16.0)	11.7 (10.4, 13.1)	
Log-rank P-value (Stratified) [b]			0.0527
Stratified Cox Regression Analysis [b]			
Hazard Ratio (Relative to TPC)			0.817
95% CI for Hazard Ratio			(0.665, 1.003)

PFS on next-line therapy (**PFS2**) at final analysis

A longer median PFS2 was observed in the SG group versus the TPC group (hazard ratio: 0.709; 95% CI: 0.584, 0.860), median PFS was 9.8 months (95% CI: 8.2, 11.4) vs 7.4 months (95% CI: 6.7, 8.9) for SG arm vs TPC, respectively (data cutoff date 01 Dec 2022).

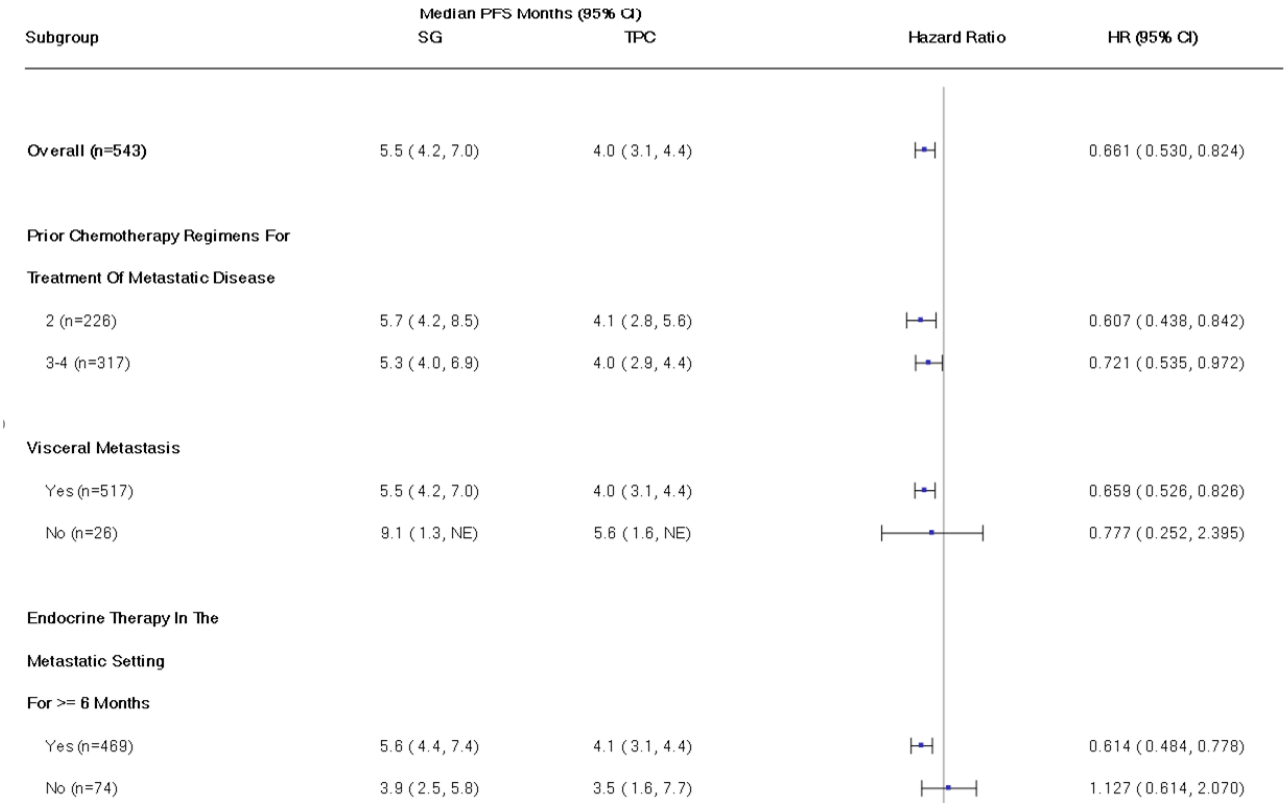
Figure 23: KM Estimates of PFS on Next-Line Therapy at Final Analysis (ITT Population)

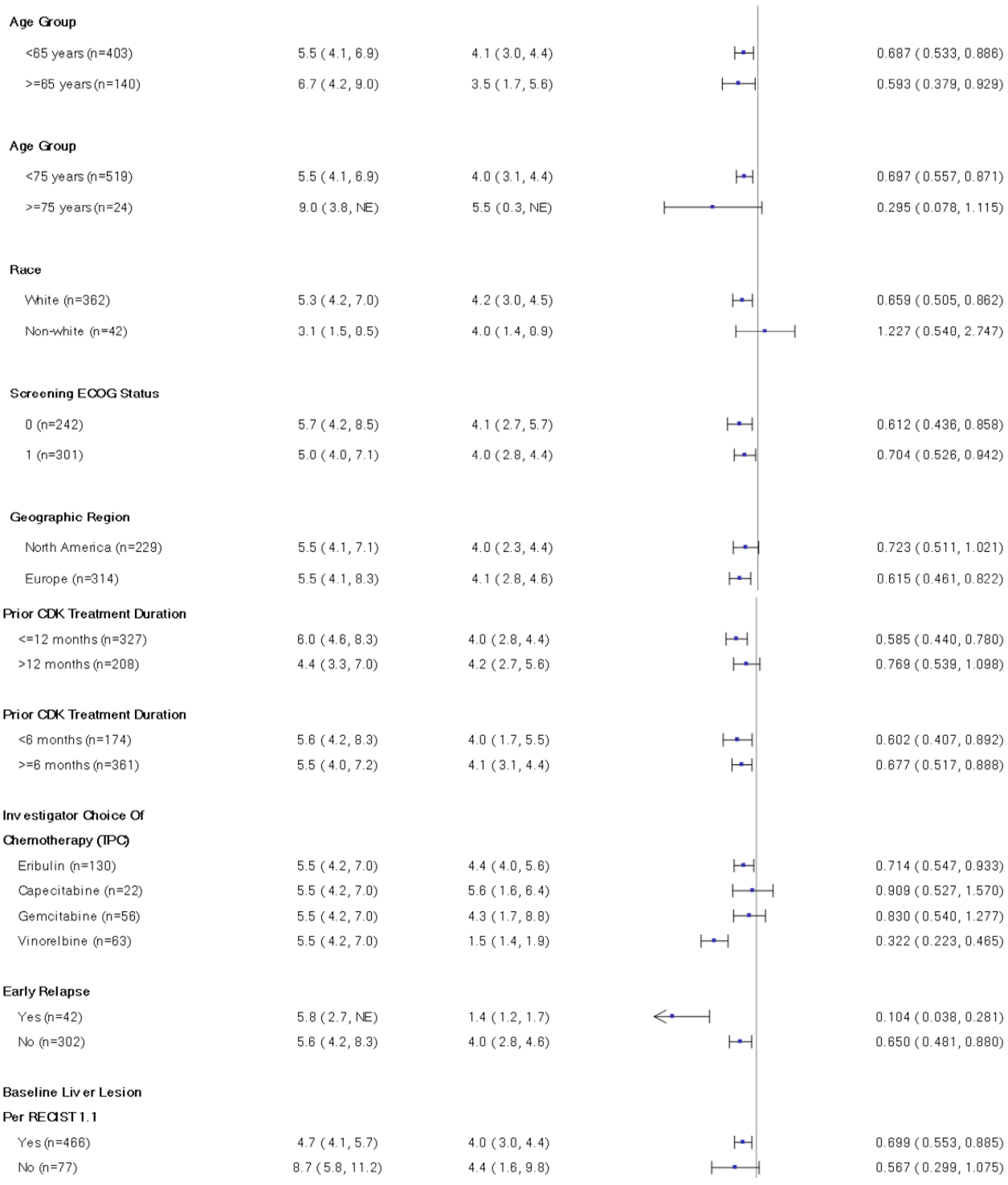


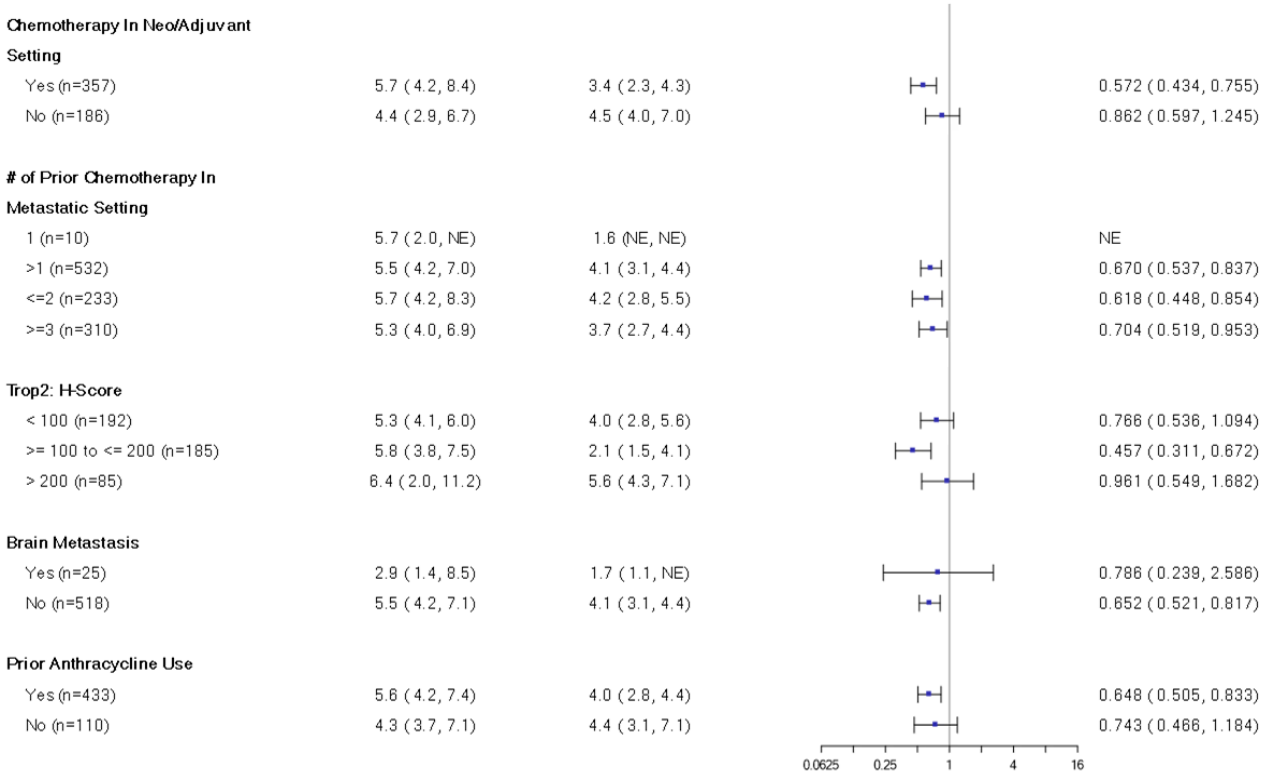
Subgroup analyses

Subgroup Analyses of PFS per BICR, OS and ORR per BICR

Figure 24: Forest Plot for **PFS** per BICR for Selected Subgroups

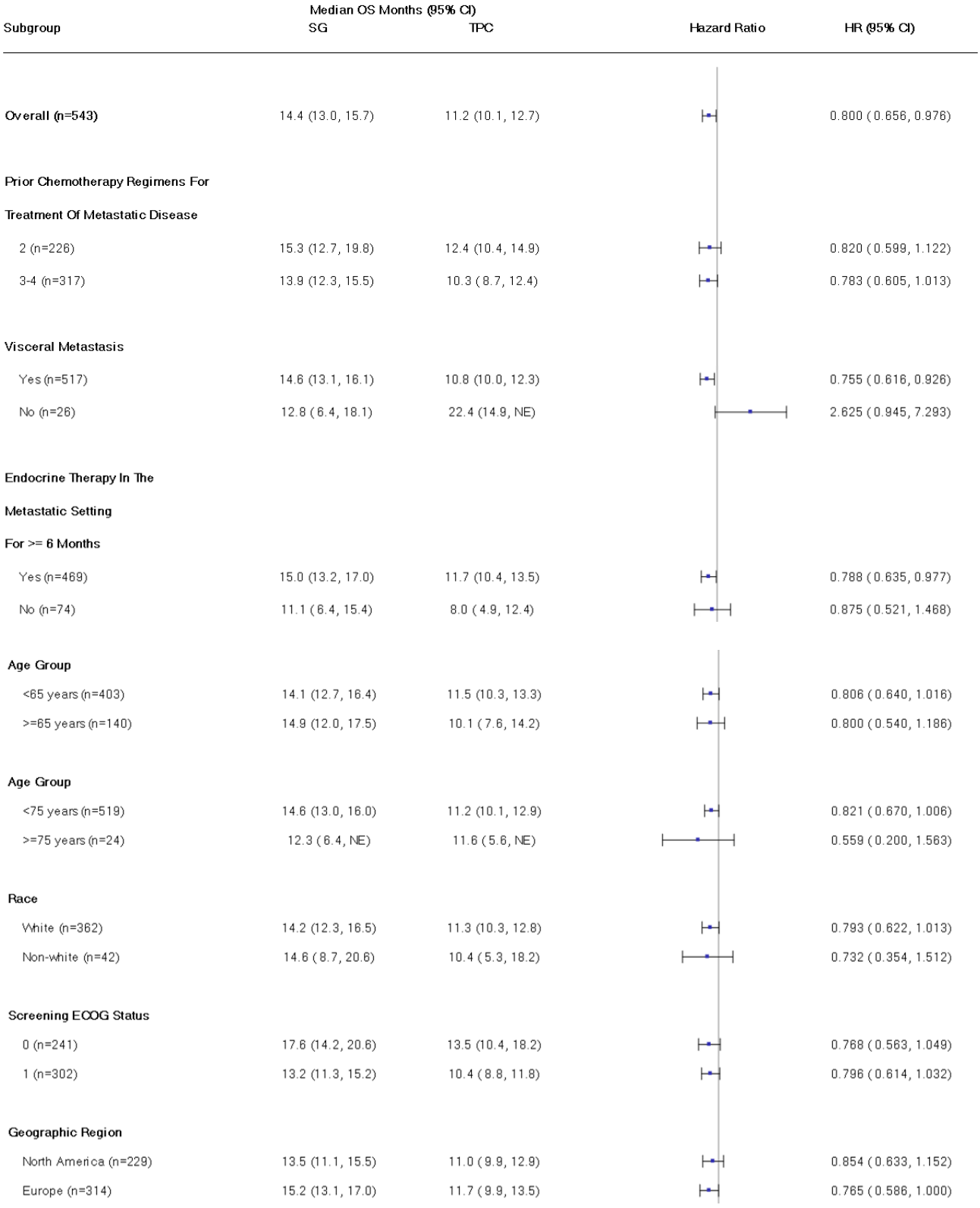



Age Group
<65 years (n=403) 5.5 (4.1, 6.9) 4.1 (3.0, 4.4) 0.687 (0.533, 0.886)
>=65 years (n=140) 6.7 (4.2, 9.0) 3.5 (1.7, 5.6) 0.593 (0.379, 0.929)
Age Group
<75 years (n=519) 5.5 (4.1, 6.9) 4.0 (3.1, 4.4) 0.697 (0.557, 0.871)
>=75 years (n=24) 9.0 (3.8, NE) 5.5 (0.3, NE) 0.295 (0.078, 1.115)
Race
White (n=362) 5.3 (4.2, 7.0) 4.2 (3.0, 4.5) 0.659 (0.505, 0.862)
Non-white (n=42) 3.1 (1.5, 8.5) 4.0 (1.4, 8.9) 1.227 (0.540, 2.747)
Screening ECOG Status
0 (n=242) 5.7 (4.2, 8.5) 4.1 (2.7, 5.7) 0.612 (0.436, 0.858)
1 (n=301) 5.0 (4.0, 7.1) 4.0 (2.8, 4.4) 0.704 (0.526, 0.942)
Geographic Region
North America (n=229) 5.5 (4.1, 7.1) 4.0 (2.3, 4.4) 0.723 (0.511, 1.021)
Europe (n=314) 5.5 (4.1, 8.3) 4.1 (2.8, 4.6) 0.615 (0.461, 0.822)
Prior CDK Treatment Duration
<=12 months (n=327) 6.0 (4.6, 8.3) 4.0 (2.8, 4.4) 0.585 (0.440, 0.780)
>12 months (n=208) 4.4 (3.3, 7.0) 4.2 (2.7, 5.6) 0.769 (0.539, 1.098)
Prior CDK Treatment Duration
<6 months (n=174) 5.6 (4.2, 8.3) 4.0 (1.7, 5.5) 0.602 (0.407, 0.892)
>=6 months (n=361) 5.5 (4.0, 7.2) 4.1 (3.1, 4.4) 0.677 (0.517, 0.888)
Investigator Choice Of Chemotherapy (TPC)
Eribulin (n=130) 5.5 (4.2, 7.0) 4.4 (4.0, 5.6) 0.714 (0.547, 0.933)
Capecitabine (n=22) 5.5 (4.2, 7.0) 5.6 (1.6, 6.4) 0.909 (0.527, 1.570)
Gemcitabine (n=56) 5.5 (4.2, 7.0) 4.3 (1.7, 8.8) 0.830 (0.540, 1.277)
Vinorelbine (n=63) 5.5 (4.2, 7.0) 1.5 (1.4, 1.9) 0.322 (0.223, 0.465)
Early Relapse
Yes (n=42) 5.8 (2.7, NE) 1.4 (1.2, 1.7) 0.104 (0.038, 0.281)
No (n=302) 5.6 (4.2, 8.3) 4.0 (2.8, 4.6) 0.650 (0.481, 0.880)
Baseline Liver Lesion Per RECIST 1.1
Yes (n=466) 4.7 (4.1, 5.7) 4.0 (3.0, 4.4) 0.699 (0.553, 0.885)
No (n=77) 8.7 (5.8, 11.2) 4.4 (1.6, 9.8) 0.567 (0.299, 1.075)



The HR was from an unstratified Cox regression analysis (including overall and subgroups). For each subgroup, the bar is the 95% CI for the HR. An arrow indicates that the 95% CI was beyond the HR range in the forest plot. Prior chemotherapy regimens for treatment of metastatic disease, visceral metastasis, and endocrine therapy in the metastatic setting for ≥ 6 months were from IXRS. Early relapse was defined as relapse to metastatic disease within 1 year of the end of neo/adjuvant chemotherapy. Participants without chemotherapy in the neo/adjuvant setting were not considered as having had early relapse. For the investigator's choice of chemotherapy (TPC) subgroup, the HR was obtained from comparison between SG and each TPC drug.

Figure 25: Forest Plot of **Overall Survival** for Selected Subgroups



Prior CDK Treatment Duration				
<=12 months (n=327)	15.2 (13.1, 16.9)	10.5 (9.5, 12.4)		0.680 (0.528, 0.876)
>12 months (n=208)	13.9 (11.8, 17.6)	12.6 (10.1, 16.8)		0.984 (0.707, 1.370)
Prior CDK Treatment Duration				
<6 months (n=174)	15.4 (13.0, 18.4)	10.2 (8.0, 12.5)		0.610 (0.430, 0.867)
>=6 months (n=361)	14.2 (12.5, 16.1)	11.5 (10.4, 13.5)		0.884 (0.692, 1.130)
Investigator Choice Of Chemotherapy (TPC)				
Eribulin (n=130)	14.4 (13.0, 15.7)	11.8 (10.1, 14.4)		0.875 (0.681, 1.124)
Capecitabine (n=22)	14.4 (13.0, 15.7)	20.1 (10.1, NE)		1.504 (0.857, 2.639)
Gemcitabine (n=56)	14.4 (13.0, 15.7)	11.1 (8.0, 13.5)		0.725 (0.522, 1.006)
Vinorelbine (n=63)	14.4 (13.0, 15.7)	8.3 (6.3, 11.3)		0.547 (0.401, 0.746)
Early Relapse				
Yes (n=42)	12.8 (6.7, 26.8)	9.0 (3.4, 12.7)		0.594 (0.291, 1.211)
No (n=488)	14.5 (13.0, 16.0)	11.3 (10.2, 13.1)		0.826 (0.670, 1.019)
Baseline Liver Lesion Per RECIST 1.1				
Yes (n=466)	13.7 (12.5, 15.4)	11.0 (10.0, 12.4)		0.847 (0.685, 1.048)
No (n=77)	19.8 (13.5, NE)	14.0 (9.8, 15.3)		0.621 (0.348, 1.108)
Chemotherapy In Neo/Adjuvant Setting				
Yes (n=357)	14.5 (13.0, 16.0)	11.0 (10.0, 12.4)		0.763 (0.596, 0.977)
No (n=186)	13.9 (11.1, 17.2)	12.8 (9.1, 15.2)		0.865 (0.617, 1.214)
# of Prior Chemotherapy In Metastatic Setting				
1 (n=10)	9.9 (5.7, NE)	18.0 (NE, NE)		1.737 (0.201, 14.980)
>1 (n=532)	14.5 (13.1, 16.0)	11.1 (10.1, 12.6)		0.791 (0.647, 0.967)
<=2 (n=233)	15.5 (13.1, 18.7)	12.5 (10.4, 15.3)		0.850 (0.624, 1.157)
>=3 (n=310)	13.6 (11.9, 15.4)	10.3 (8.6, 12.3)		0.754 (0.581, 0.979)
Trop2: H-Score				
< 100 (n=192)	14.6 (12.7, 18.1)	11.3 (10.0, 13.3)		0.747 (0.537, 1.039)
>= 100 to <= 200 (n=185)	13.9 (12.1, 16.0)	10.3 (7.3, 11.8)		0.746 (0.530, 1.051)
> 200 (n=85)	15.3 (11.4, 21.9)	14.9 (10.7, 24.3)		1.068 (0.616, 1.854)
Brain Metastasis				
Yes (n=25)	22.7 (5.2, NE)	9.8 (2.6, 24.7)		0.676 (0.254, 1.801)
No (n=518)	14.4 (13.0, 15.7)	11.2 (10.2, 12.7)		0.805 (0.656, 0.986)
Prior Anthracycline Use				
Yes (n=433)	14.4 (13.0, 16.1)	11.0 (10.1, 12.5)		0.797 (0.639, 0.996)
No (n=110)	14.4 (10.3, 20.7)	12.8 (9.2, 14.4)		0.802 (0.511, 1.257)

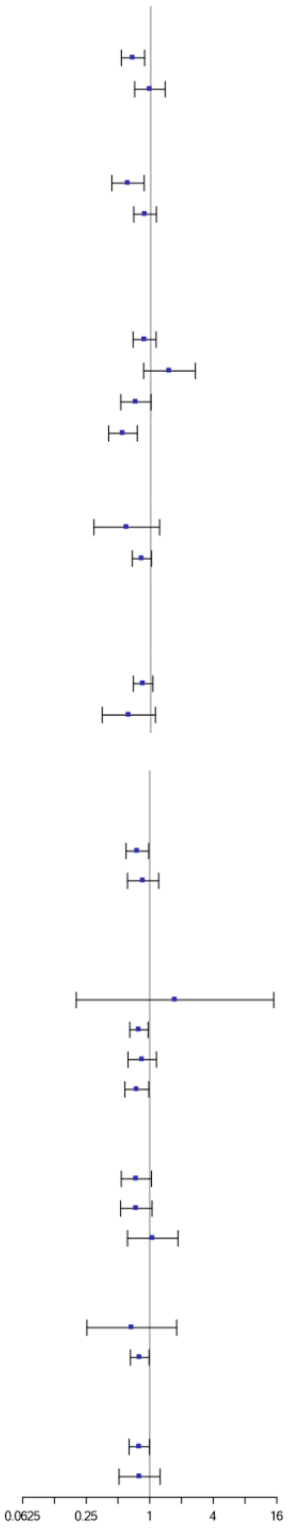
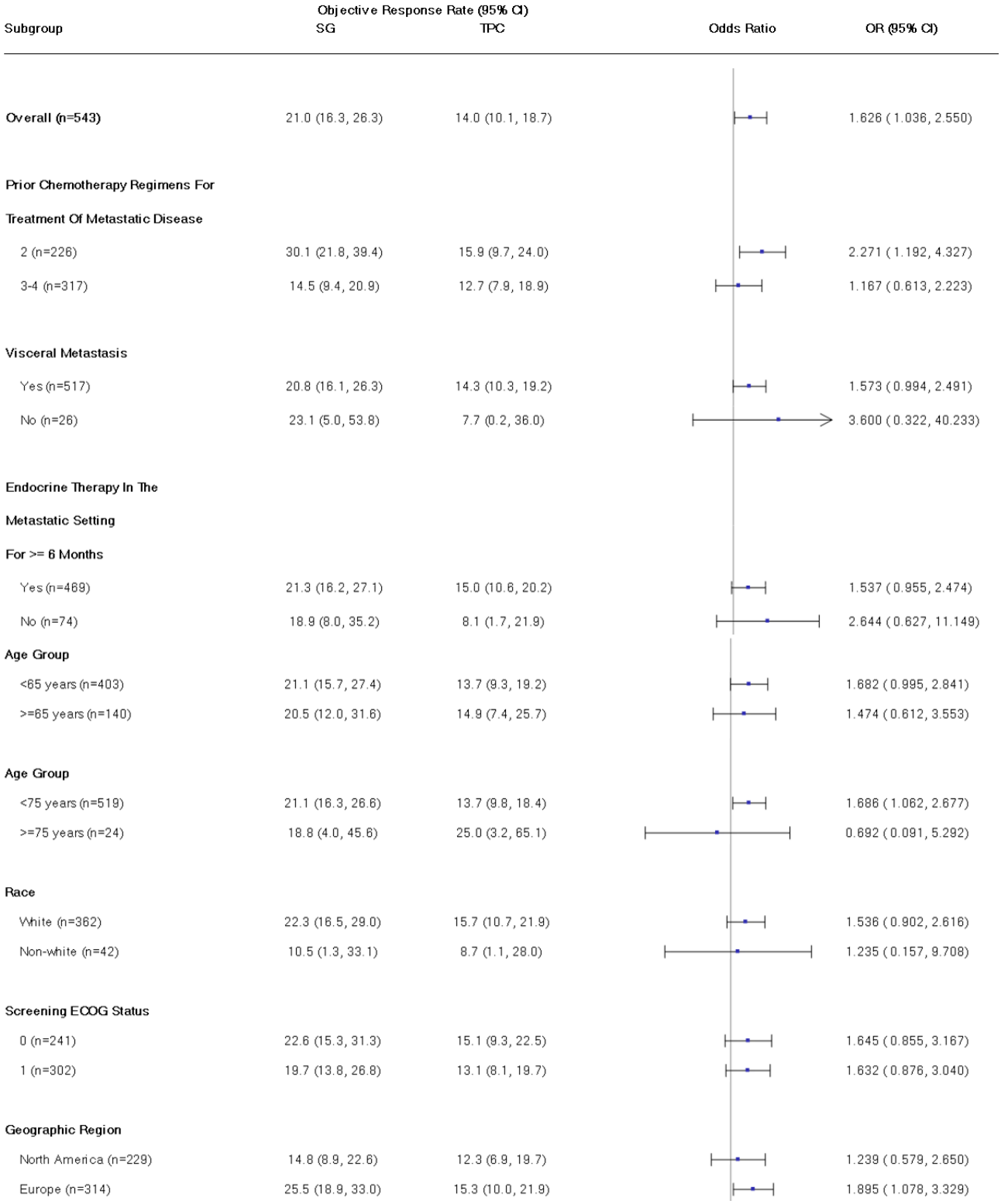
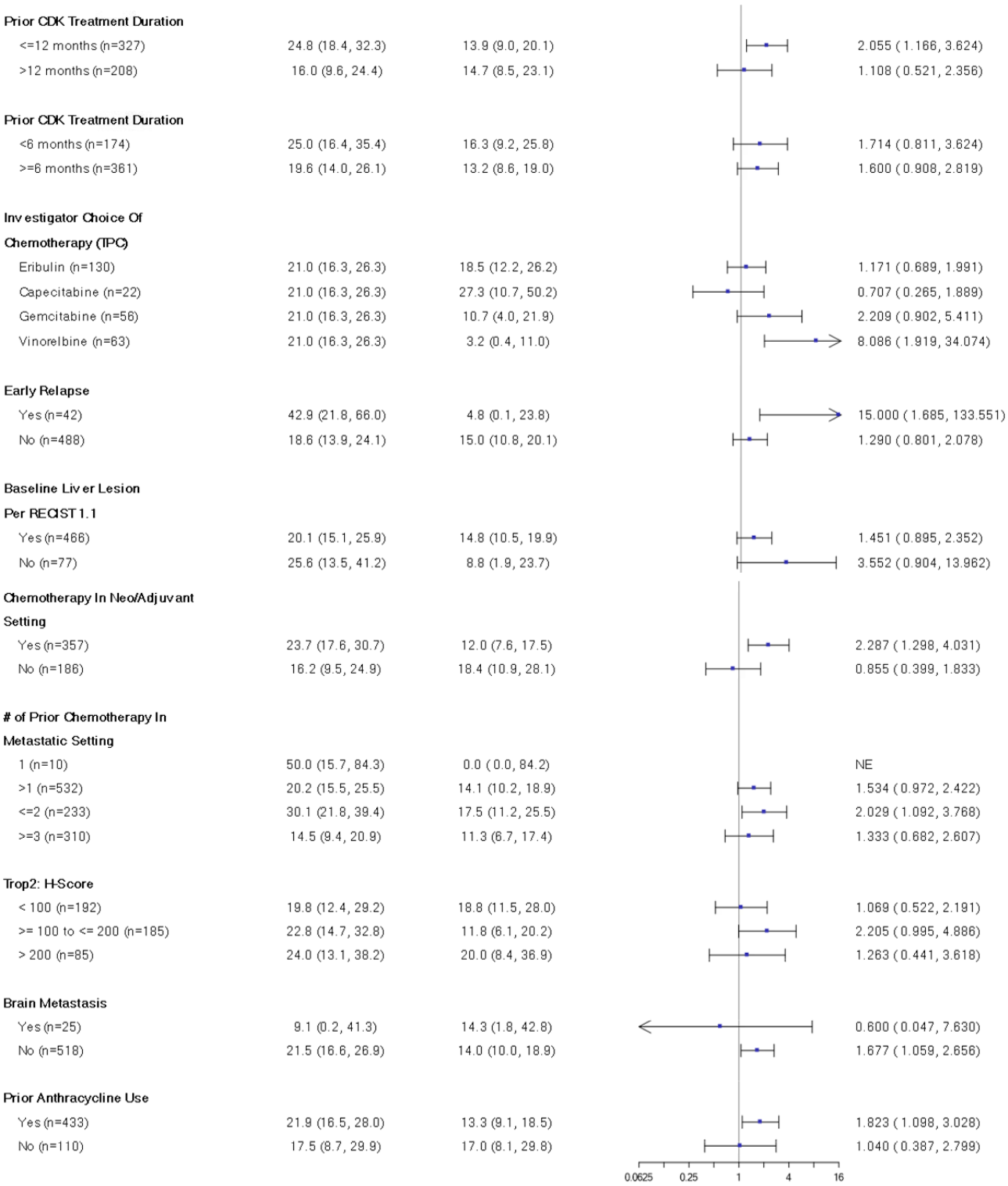


Figure 26: Forest Plot of **ORR** per BICR for Selected Subgroups





Efficacy data by UGT1A1 Genotype

Table 35: Overview of Efficacy by UGT1A1 Genotype (Participants Randomized to SG)

	UGT1A1*1/*1 (N = 104)	UGT1A1*1/*28 (N = 119)	UGT1A1*28/*28 (N = 25)
Progression-Free Survival (months) per BICR using RECIST v1.1 at IA1			
Median[a] (95% CI)	5.5 (4.1, 8.4)	5.8 (4.4. 8.5)	4.1 (1.6, 5.5)
Kaplan-Meier Estimate of Progression-Free Survival Rate (%)[b] by BICR (95% CI) at IA1			
At 6 months	48.3 (37.3, 58.4)	49.2 (39.1, 58.5)	28.6 (10.7, 49.6)
At 9 months	28.9 (18.4, 40.2)	37.8 (28.0, 47.6)	28.6 (10.7, 49.6)
At 12 Months	17.3 (8.5, 28.7)	24.6 (15.7, 34.6)	28.6 (10.7, 49.6)
Overall Survival at IA2			
Median[a] (95% CI)	14.5 (13.0, 19.8)	15.2 (12.7, 17.6)	14.9 (8.7, 16.4)
Kaplan-Meier Estimate of OS Rate (%)[c] (95% CI) at IA2			
At 12 Months	63.2 (52.9, 71.8)	63.3 (53.9, 71.3)	54.3 (32.8, 71.5)
At 18 Months	45.2 (35.1, 54.8)	40.5 (31.3, 49.4)	21.5 (7.2, 40.6)
At 24 Months	24.5 (15.6, 34.5)	28.0 (19.1, 37.6)	21.5 (7.2, 40.6)
Objective Response Rate (CR or PR) at IA2			
n (%)	21 (20.2%)	32 (26.9%)	2 (8.0%)
95% CI (Exact)	(13.0, 29.2)	(19.2, 35.8)	(1.0, 26.0)
Clinical Benefit Rate (CR, PR, or SD ⩾ 6 months) at IA2			
n (%)	34 (32.7%)	48 (40.3%)	5 (20.0%)
95% CI (Exact)	(23.8, 42.6)	(31.4, 49.7)	(6.8, 40.7)

UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

a Median PFS and OS are from the Kaplan-Meier estimate. CIs for median were computed using the Brookmeyer-Crowley method.

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

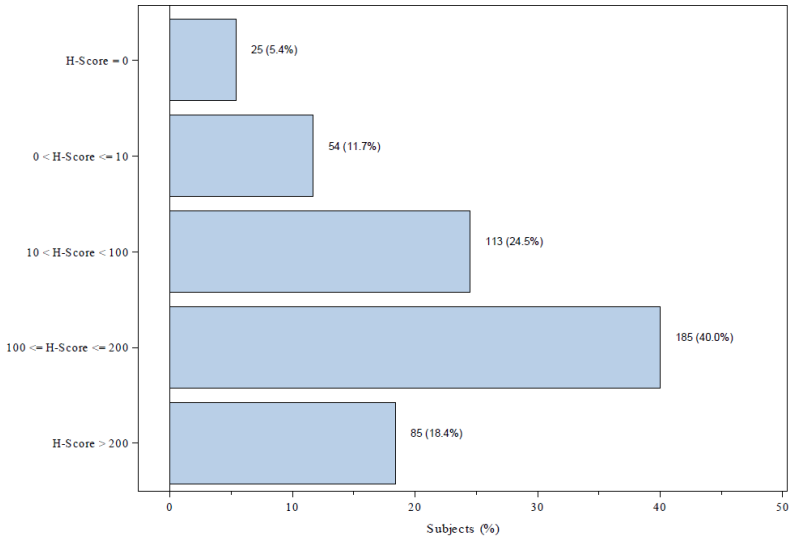
c OS rate is the proportion of participants alive.

Trop-2 expression

Exploratory analyses of the association of clinical benefit with Trop-2 expression

The planned exploratory analyses of the association of clinical benefit with Trop-2 expression in participants treated with SG in Study IMMU-132-09 were based on tertile subgroups by Trop-2 H-scores of < 100, ≥ 100 to ≤ 200, and > 200; however, there was an uneven distribution of participants between these subgroups: low Trop-2 expression (H-score < 100) was observed in 41.6% of participants, medium Trop-2 expression (H-score ≥ 100 to ≤ 200) in 40.0 % of participants, and high Trop-2 expression (H-score > 200) in 18.4% of participants in the Trop-2 Evaluable Population. Baseline Trop-2 expression was missing in 14.9% of participants.

Figure 27: Distribution of Trop-2 H-Scores in Tumor Tissue Samples from Participants in Study IMMU-132-09 (Trop-2–Evaluable Population)



Since Trop-2 expression status was not a stratification factor, the proportions of tertile H-Scores were not fully balanced between treatment arms (eg, H-Score > 200: n=50 (21%) in the SG group and n=35 (15.6%) in the TCP group) *(Ad Hoc 11223 Table 1.1, not copied)*.

Efficacy results by tertile subgroups of Trop-2 H-scores are presented as part of the forest plots of the subgroup analyses (see figures below):

Figure 28: Forest plot of **PFS** per BICR

Subgroup	Median PFS Months (95% CI) SG	TPC	Hazard Ratio	HR (95% CI)
Overall (n=543)	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)		0.661 (0.530, 0.824)
Trop2: H-Score				
< 100 (n=192)	5.3 (4.1, 6.0)	4.0 (2.8, 5.6)		0.766 (0.536, 1.094)
>= 100 to <= 200 (n=185)	5.8 (3.8, 7.5)	2.1 (1.5, 4.1)		0.457 (0.311, 0.672)
> 200 (n=85)	6.4 (2.0, 11.2)	5.6 (4.3, 7.1)		0.961 (0.549, 1.682)

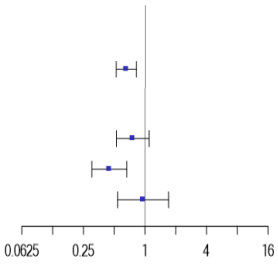


Figure 29: Forest plot of **OS**

Subgroup	Median OS Months (95% CI) SG	TPC	Hazard Ratio	HR (95% CI)
Overall (n=543)	14.4 (13.0, 15.7)	11.2 (10.1, 12.7)		0.800 (0.656, 0.976)
Trop2: H-Score				
< 100 (n=192)	14.6 (12.7, 18.1)	11.3 (10.0, 13.3)		0.747 (0.537, 1.039)
>= 100 to <= 200 (n=185)	13.9 (12.1, 16.0)	10.3 (7.3, 11.8)		0.746 (0.530, 1.051)
> 200 (n=85)	15.3 (11.4, 21.9)	14.9 (10.7, 24.3)		1.068 (0.616, 1.854)

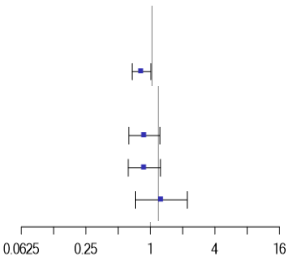
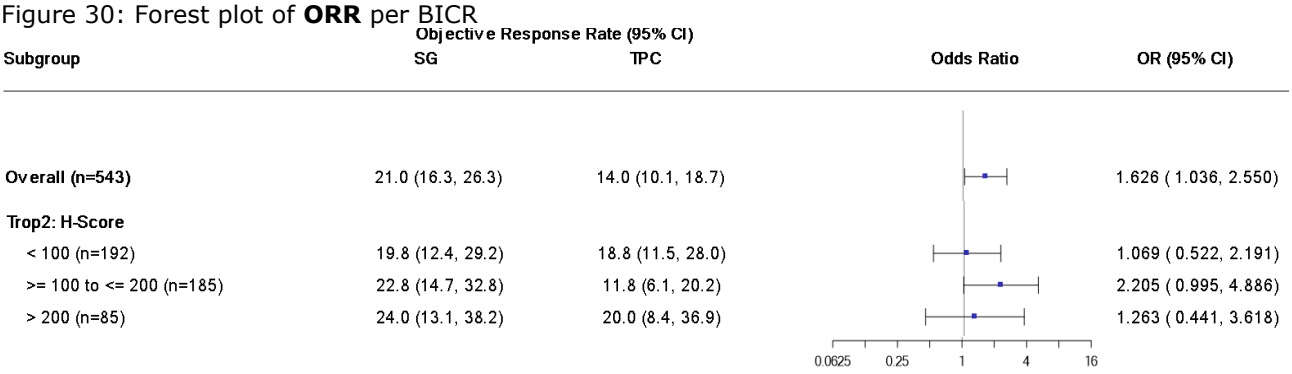


Figure 30: Forest plot of **ORR** per BICR



SG Versus TPC in **Trop-2 H-Score < 100 and ≥ 100 Subgroups**

Efficacy of SG versus TPC was assessed by dividing participants into two subgroups with Trop-2 H-score instead of 3. The ≥ 100 to ≤ 200 and > 200 H-score subgroups from the tertile analysis were combined to define a single H-score ≥ 100 subgroup for comparison with the H-score < 100 subgroup.

Table 36: Clinical Outcomes with SG Versus TPC in Trop-2 H-Score < 100 and ≥ 100 Subgroups (Trop-2–Evaluable Population), Assessor´s table from Figures 2-5 clinical overview addendum

Outcome	Trop-2 Subgroup (<100 and ≥ 100)	SG (N = 238)		TPC (N = 224)		HR (95% CI)
		N (Events)	Median, months (95% CI)	N (Events)	Median, months (95% CI)	
PFS	H-Score < 100	96 (62)	**5.3** (4.1, 6.0)	96 (60)	**4.0** (2.8, 5.6)	**0.766** (0.536, 1.094)
	H-Score ≥ 100	142 (88)	**6.4** (4.0, 8.3)	128 (81)	**4.1** (2.1, 4.5)	**0.595** (0.436, 0.813)
OS	H-Score < 100	96 (67)	**14.6** (12.7,18.1)	96 (76)	**11.3** (10.0, 13.3)	**0.747** (0.537, 1.039)
	H-Score ≥ 100	142 (99)	**14.4** (12.7, 16.4)	128 (88)	**11.2** (9.9, 12.9)	**0.829** (0.622, 1.106)

Figure 31: **PFS** per BICR in Trop-2 H-Score **<100**

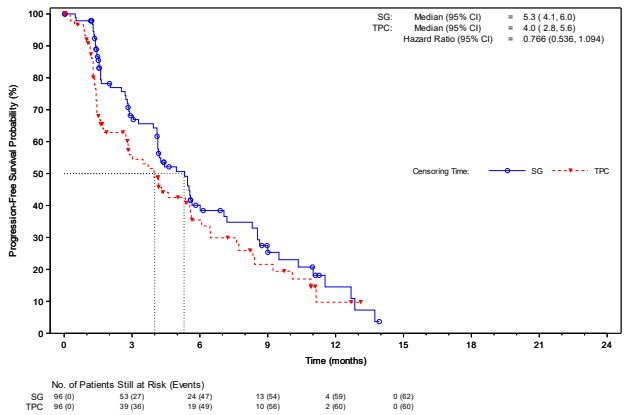


Figure 32: **OS** in Trop-2 H-Score **<100**

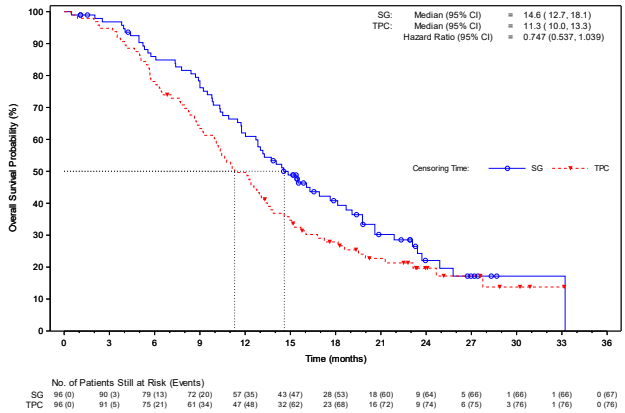
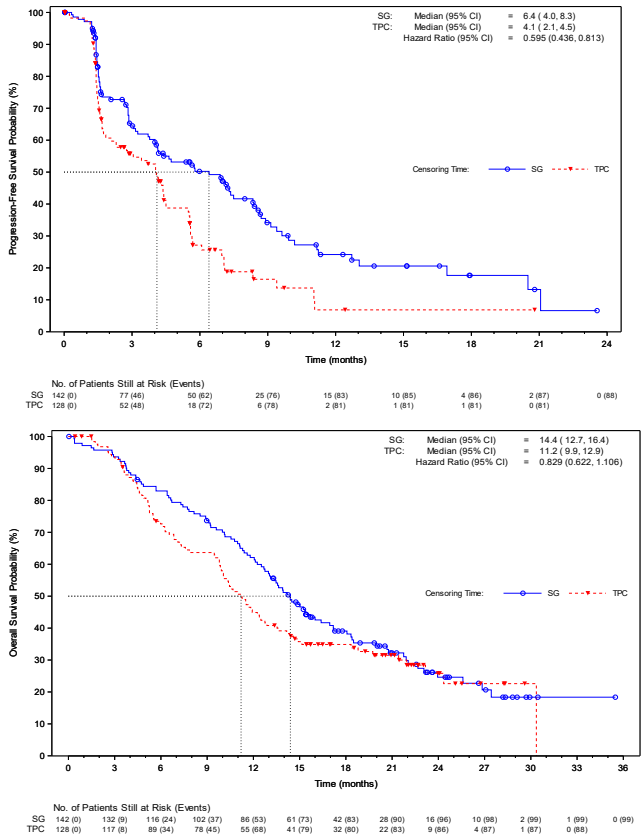


Figure 33: **PFS** per BICR in Trop-2 H-Score **≥100**

Figure 34:**OS** in Trop-2 H-Score **≥100**



SG Versus TPC in **Trop-2 H-Score Quartile subgroups (including ≤ 38 Subgroup)**

An analysis was conducted in equal-participant Trop-2 H-score quartile subgroups with H-score divisions of ≤ 38, > 38 to ≤ 132, > 132 to ≤ 190, and > 190 (Q1 to Q4, respectively).

Table 37: 1 Summary of Clinical Outcomes in Trop-2 H-Score Quartile Subgroup Analysis

Outcome	Trop-2 Subgroup (Quartile)	SG (N = 238)		TPC (N = 224)		HR (95% CI)
		N (Events)	Median (Months)	N (Events)	Median (Months)	
PFS	**Q1** (H-Score ≤ 38)	56 (35)	**4.4**	60 (38)	**4.2**	**0.739** (0.466, 1.171)
	Q2 (38 < H-Score ≤ 132)	66 (42)	5.6	50 (33)	3.0	0.586 (0.368, 0.931)

	Q3 (132 < H-Score ≤ 190)	56 (35)	5.6	62 (38)	2.1	0.492 (0.300, 0.805)
	Q4 (H-Score > 190)	60 (38)	5.8	52 (32)	5.5	0.843 (0.521, 1.363)
OS	**Q1** (H-Score ≤ 38)	56 (35)	**17.6**	60 (47)	**11.0**	**0.642** (0.414, 0.996)
	Q2 (38 < H-Score ≤ 132)	66 (48)	14.1	50 (39)	10.5	0.741 (0.484, 1.134)
	Q3 (132 < H-Score ≤ 190)	56 (43)	13.6	62 (45)	10.3	0.780 (0.513, 1.188)
	Q4 (H-Score > 190)	60 (40)	14.4	52 (33)	14.5	1.030 (0.648, 1.635)

ORR results in the SG group were **23.2%**, 22.7%, 19.6% and 21.7% in **Q1**, Q2, Q3 and Q4 subgroups, respectively. Median **DOR** (duration of response) was 7.4, 9.1, 8.5 and 8.5 months, respectively *(clinical overview addendum Ad Hoc 11223 Table 2.1.)*

KM curves of PFS per BICR and OS for SG versus TPC were provided by Trop-2 H-Score quartiles:

Figure 35: **PFS** per BICR in **Q1** (Trop-2 H-Score **≤ 38)**

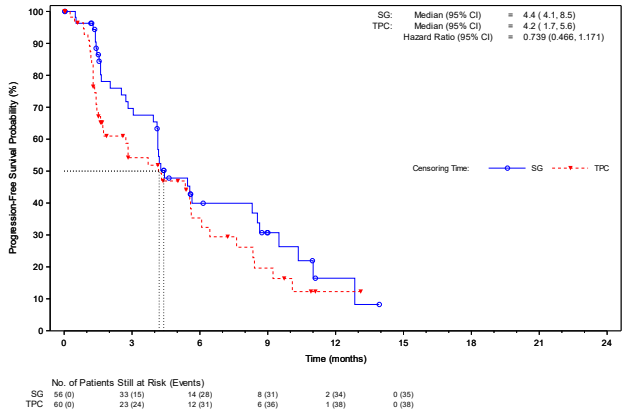


Figure 36: **OS** in **Q1 (**Trop-2 H-Score **≤ 38**)

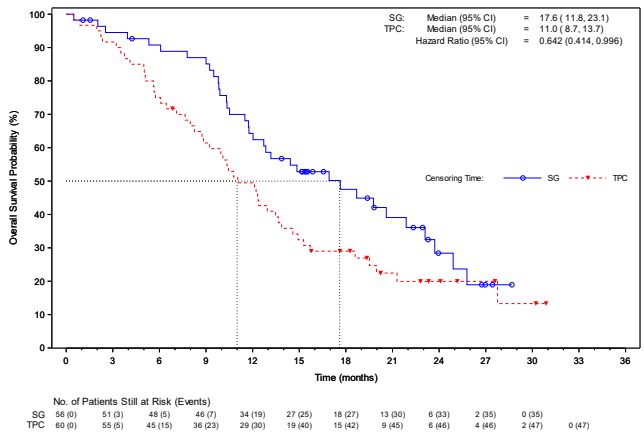
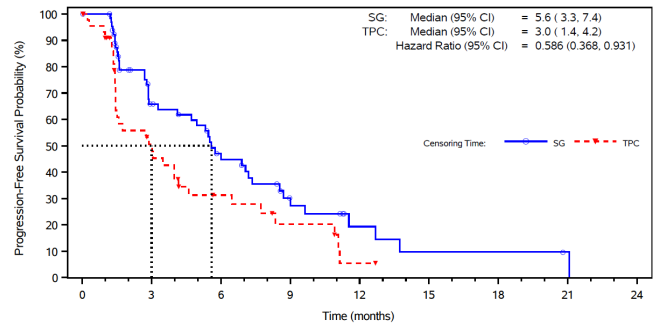


Figure 37: **PFS** per BICR in **Q2** (38<Trop-2 H-Score ≤ 132)

Figure 38: **OS** in **Q2** (38<Trop-2 H-Score

≤ 132)



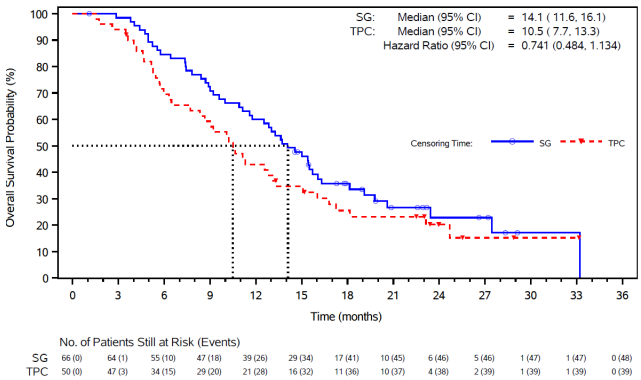
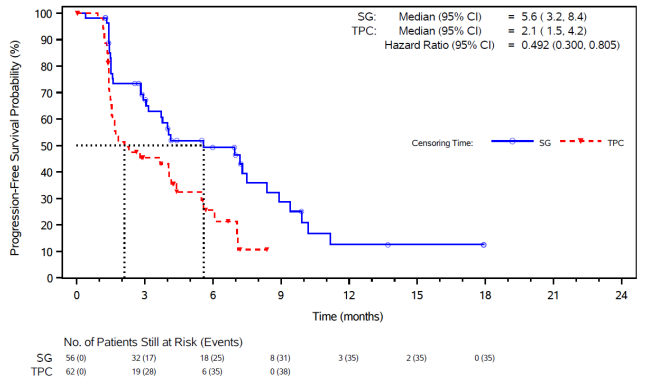


Figure 39: **PFS** per BICR in **Q3** (132<Trop-2 H-Score ≤ 190)

Figure 40: **OS** in **Q3** (132<Trop-2 H-Score ≤ 190)



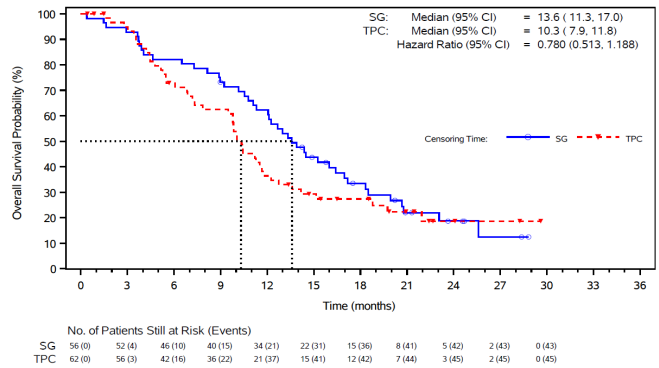
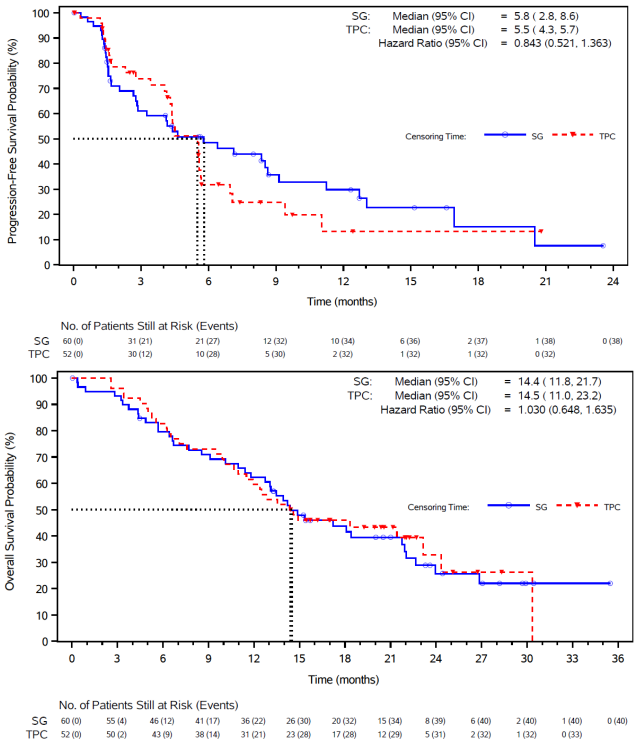


Figure 41: **PFS** per BICR in **Q4** (Trop-2 H-Score > 190)

Figure 42: **OS** in **Q4** (Trop-2 H-Score > 190)



SG Versus TPC in **Trop-2 H-Score ≤ 10 Subgroup**

Table 38: Clinical Outcomes with SG Versus TPC in Trop-2 H-Score ≤ 10 Subgroup (Trop-2–Evaluable Population), Assessor´s table from Figures 8-9 clinical overview addendum

Outcome	SG (N = 238)		TPC (N = 224)		HR (95% CI)
	N (Events)	Median, months (95% CI)	N (Events)	Median, months (95% CI)	
PFS	34 (22)	**5.5** (2.8, 9.5)	45 (27)	**4.3** (1.7, 6.4)	**0.892** (0.507, 1.568)
OS	34 (18)	**17.6** (11.5, NE)	45 (34)	**12.3** (8.0, 15.3)	**0.609** (0.342, 1.082)

ORR was **23.5%** (95% CI: 10.7%, 41.2%) in Trop-2 H-Score ≤ 10 Subgroup of the SG arm (see Table 5.4.28).

KM curves of PFS per BICR and OS in the Trop-2 H-Score ≤ 10 subgroups were as follows *(figures 8 and 9, clinical overview addendum)*:

Figure 43: **PFS** per BICR in Trop-2 H-Score **≤ 10**

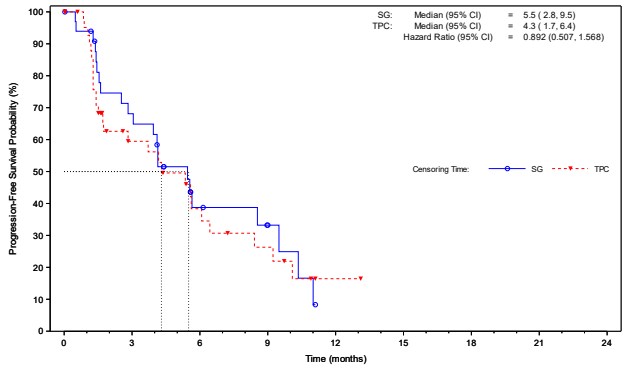
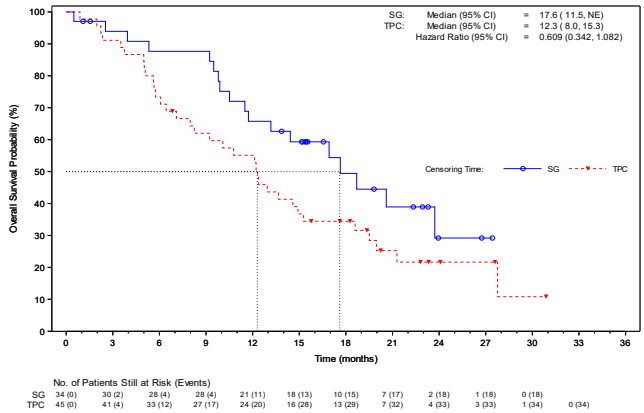


Figure 44: **OS** in Trop-2 H-Score **≤ 10**



SG Versus TPC in **Trop-2 H-Score 0 Subgroup**

Overall, 25 participants (5.4%) were Trop-2 negative (n=10 in the SG arm and n=15 in the TPC arm). The **ORR** in participants in the SG group whose tumor tissues had no detectable Trop-2 expression by IHC (H-score 0) was **10%.**

Table 39: Summary of ORR and DoR by Trop-2 Membrane H-Score Negative, Very Low, Low, Medium, and High in the SG group

(excerpt from clinical overview addendum Ad Hoc 11223 Table 2.2)

Outcome	H-Score =0 (N=10)	0<H-Score ≤10 (N=24)	H-Score ≤10 (N=34)	10<H-Score<100 (N=62)	100≤H-Score≤200 (N=92)	H-Score>200 (N=50)
ORR (95% CI)	10.0% (0.3, 44.5)	29.2% (12.6, 51.1)	23.5% (10.7, 41.2)	17.7% (9.2, 29.5)	22.8% (14.7, 32.8)	24.0% (13.1, 38.2)
DoR (months)	9.7	6.9	7.5	7.4	8.5	8.6

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Versus Treatment of Physician's Choice (TPC) in subjects with Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor

2 (HER2) Negative Metastatic Breast Cancer (MBC) who have failed at least two prior chemotherapy regimens		
Study identifier	IMMU-132-09 NCT No.: 03901339 EudraCT No.: 2018-004201-33	
Design	This study is an ongoing, open-label, randomized, multicenter, international Phase 3 study designed to compare the efficacy and safety of SG versus TPC in participants with metastatic or locally recurrent inoperable HR+/HER2− breast cancer who had progressed after a CDK 4/6 inhibitor, endocrine therapy, taxane, and at least 2 but no more than 4 prior chemotherapy treatment regimens for metastatic disease (1 of which could have been in the neoadjuvant or adjuvant setting if the development of unresectable, locally advanced, or metastatic disease occurred within 12 months)	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	08 May 2019 – 03 January 2022 (last participant last visit for the primary analysis) 08 May 2019 – 01 July 2022 (last participant last visit for the interim 2) not applicable not applicable
Hypothesis	Superiority	
Treatment group	Sacituzumab govitecan (SG)	SG 10 mg/kg was administered as an intravenous (IV) infusion on Days 1 and Day 8 of a 21-day treatment cycle. Treatment was continued until disease progression as determined by local investigator review (LIR) using RECIST 1.1, unacceptable toxicity, or other treatment discontinuation criterion was met.
	Treatment of Physicians choice (TPC) i.e, 1 of the following single-agent treatments	Eribulin (1.4 mg/m^2 for North American sites, 1.23 mg/m^2 for European sites, or per institution) administered IV on Days 1 and 8 of a 21-day cycle Capecitabine (1000 to 1250 mg/m^2) administered orally twice daily for 2 weeks followed by a 1-week rest period given as a 21-day cycle Gemcitabine (800 to 1200 mg/m^2) administered IV on Days 1, 8, and 15 of each 28-day cycle or per institution Vinorelbine (25 mg/m^2) administered IV on Day 1 of a weekly cycle or per institution (Note: participants with Grade 2 neuropathy were eligible for the study, but were not to receive vinorelbine as TPC.) Treatment was continued until disease progression as determined by LIR using RECIST 1.1, unacceptable toxicity, or other treatment discontinuation criterion was met.

Endpoints and definitions	Primary endpoint	Progression free survival (PFS) by blinded independent central review (BICR)	Defined as the time from date of randomization to the first observation of documented disease progression based on BICR using RECIST 1.1 or death due to any cause, whichever came first.
	Secondary endpoint	Overall survival (OS)	Defined as the time from randomization into the study to death from any cause.
	Secondary endpoint	Objective response rate (ORR)	Defined as the proportion of participants who had a best overall response of either complete response (CR) or partial response (PR) confirmed at least 4 weeks after initial response according to BICR and LIR using RECIST 1.1.
	Secondary endpoint	Duration of response (DOR)	Time between the first date showing a documented response of CR or PR and the date of progression or death, whichever occurred first as determined by BICR and LIR using RECIST v1.1.
	Secondary endpoint	Clinical benefit rate (CBR)	Defined as the proportion of participants who had a best overall response of CR, PR, or durable stable disease (SD) (defined as SD with a duration of at least 6 months after randomization) determined by BICR and LIR using RECIST v1.1.
	Secondary endpoint	PFS by LIR	Defined as the time from date of randomization to the first observation of documented disease progression based on LIR using RECIST 1.1 or death due to any cause, whichever came first.
	Secondary endpoint	Treatment on Time to deterioration (TTD)	Defined as the time from randomization to the first date a participant had a ≥ 10-point deterioration from baseline or died due to any cause, whichever occurred first.
Data cut off dates	03 January 2022 (primary analysis) 01 July 2022 (interim 2)		
<u>Results and Analysis</u>			
Analysis Description	**Primary Analysis**		

Analysis population and time point description	Primary analysis of PFS was based on BICR using RECIST 1.1 for the Intended to treat (ITT) Population. The time from date of randomization to the first observation of documented disease progression based on RECIST v1.1 or death due to any cause, whichever came first.		
Descriptive statistics and estimate variability	Treatment group	SG (N=272)	TPC (271)
	Patients with events	170 (62.5%)	159 (58.7%)
	PFS (median months)	5.5	4.0
	Confidence interval (CI)	4.2, 7.0	3.1, 4.4
Effect estimate per comparison	PFS	Comparison groups	SG vs TPC
		Hazard ratio (Relative to TPC)	0.661
		CI	0.529, 0.826
		P-value	0.0003
Analysis population and time point description	PFS by LIR using RECIST v1.1 for ITT population. The time from date of randomization to the first observation of documented disease progression per LIR based on RECIST v1.1 or death due to any cause, whichever comes first.		
Descriptive statistics and estimate variability	Treatment group	SG (N=272)	TPC (271)
	Patients with events	227 (83.5%)	198 (73.1%)
	PFS (median months)	4.4	3.1
	CI	3.8, 5.4	2.7, 4.0
Effect estimate per comparison	PFS	Comparison groups	SG vs TPC
		Hazard ratio (Relative to TPC)	0.727
		CI	0.598, 0.884
		Nominal P-value	0.0013
Analysis Description	**Interim 2**		
Analysis population and time point description	OS for the ITT Population. The time from randomization into study to death from any cause.		
Descriptive statistics and estimate variability	Treatment group	SG (N=272)	TPC (271)
	Patients with events	191 (70.2%)	199 (73.4%)
	OS (median months)	14.4	11.2

	CI	13.0, 15.7	10.1, 12.7
Effect estimate per comparison	OS	Comparison groups	SG vs TPC
		Hazard ratio (Relative to TPC)	0.789
		CI	0.646, 0.964
		P-value	0.0200
Analysis population and time point description	ORR by BICR for the ITT population, defined as the proportion of participants who had a best overall response of either CR or PR that was confirmed 4 weeks or later after initial response.		
Descriptive statistics and estimate variability	Treatment group	SG (N=272)	TPC (271)
	ORR n (%)	57 (21.0%)	38 (14.0%)
	CI	16.3, 26.3	10.1, 18.7
Effect estimate per comparison	ORR	Comparison groups	SG vs TPC
		Odds ratio	1.625
		CI	1.034, 2.555
		P-value	0.0348
Analysis population and time point description	ORR by LIR using RECIST v1.1 for ITT population, defined as the proportion of participants who had a best overall response of either CR or PR that was confirmed 4 weeks or later after initial response.		
Descriptive statistics and estimate variability	Treatment group	SG (N=272)	TPC (271)
	ORR n (%)	44 (16.2%)	25 (9.2%)
	CI	12.0, 21.1	6.1, 13.3
Effect estimate per comparison	ORR	Comparison groups	SG vs TPC
		Odds ratio	1.931
		CI	1.138, 3.275
		Nominal P-value	0.0137
Analysis population and time point description	DOR by BICR using RECIST v1.1 for the ITT Population Time between the first date showing a documented response of CR or PR and the date of progression or death, whichever occurred first.		
Descriptive statistics and estimate variability	Treatment group	SG (N=272)	TPC (271)
	Number of Responder	57	38
	Patients with events n(%)	33 (57.9%)	22 (57.9%)
	DOR (median months)	8.1	5.6

	CI	6.7, 9.1	3.8, 7.9
Effect estimate per comparison	Not applicable		
Analysis population and time point description	DOR by LIR using RECIST v1.1 for the ITT Population Time between the first date showing a documented response of CR or PR and the date of progression or death, whichever occurred first.		
Descriptive statistics and estimate variability	Treatment group	SG (N=272)	TPC (271)
	Number of Responder	44	25
	Patients with events n(%)	37 (84.1%)	19 (76.0%)
	DOR (median months)	7.0	4.3
	CI	5.6, 9.2	4.2, 6.1
Effect estimate per comparison	Not Applicable		
Analysis population and time point description	CBR by BICR using RECIST v1.1 for the ITT population, defined as the proportion of participants who had a best overall response of CR, PR, or durable SD (duration of SD 6 months or greater after randomization).		
Descriptive statistics and estimate variability	Treatment group	SG (N=272)	TPC (271)
	CBR n (%)	92 (33.8%)	60 (22.1%)
	CI	28.2, 39.8	17.3, 27.6
Effect estimate per comparison	CBR	Comparison groups	SG vs TPC
		Odds ratio	1.796
		CI	1.227, 2.628
		Nominal P-value	0.0025
Analysis population and time point description	CBR by LIR using RECIST v1.1 for the ITT population, defined as the proportion of participants who had a best overall response of CR, PR, or durable SD (duration of SD 6 months or greater after randomization).		
Descriptive statistics and estimate variability	Treatment group	SG (N=272)	TPC (271)
	CBR n (%)	88 (32.4%)	57 (21.0%)
	Confidence interval	26.8, 38.3	16.3, 26.4
Effect estimate per comparison	CBR	Comparison groups	SG vs TPC
		Odds ratio	1.834
		CI	1.237, 2.717
		Nominal P-value	0.0024

Analysis population and time point description	TTD defined as the time from randomization to the first date a participant had a ≥ 10-point deterioration from baseline or died due to any cause, whichever occurred first in the EORTC QLQ-C30 global health status/QOL domain for the HRQOL-Evaluable Population.		
Descriptive statistics and estimate variability	Treatment group	SG (N=234)	TPC (207)
	Patients with events	210 (89.7%)	185 (89.4%)
	TTD (median months)	4.3	3.0
	CI	3.1, 5.7	2.2, 3.9
Effect estimate per comparison	TTD	Comparison groups	SG vs TPC
		Hazard ratio (Relative to TPC)	0.751
		CI	0.612, 0.922
		P-value	0.0059
Analysis population and time point description	TTD defined as the time from randomization to the first date a participant had a ≥ 10-point deterioration from baseline or died due to any cause, whichever occurred first in the EORTC QLQ-C30 pain domain for the HRQOL-Evaluable Population.		
Descriptive statistics and estimate variability	Treatment group	SG (N=229)	TPC (202)
	Patients with events	207 (90.4%)	180 (89.1%)
	TTD (median months)	3.8	3.5
	CI	2.8, 5.0	2.8, 5.0
Analysis population and time point description	TTD	Comparison groups	SG vs TPC
		Hazard ratio (Relative to TPC)	0.918
		CI	0.748, 1.126
		P-value	0.4151
Analysis population and time point description	TTD defined as the time from randomization to the first date a participant had a ≥ 10-point deterioration from baseline or died due to any cause, whichever occurred first in the EORTC QLQ-C30 fatigue domain for the HRQOL-Evaluable Population.		
Descriptive statistics and estimate variability	Treatment group	SG (N=234)	TPC (205)
	Patients with events	218 (93.2%)	191 (93.2%)
	TTD (median months)	2.2	1.4
	CI	1.6, 2.8	1.1, 1.9
Analysis population and time point description	TTD	Comparison groups	SG vs TPC

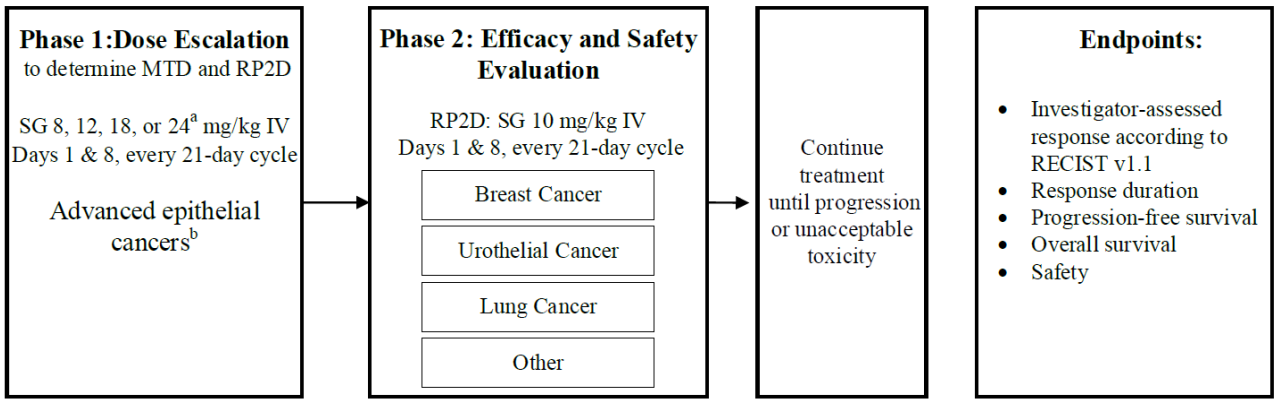
		Hazard ratio (Relative to TPC)	0.732
		CI	0.598, 0.894
		P-value	0.0021

Supportive studies

Study IMMU-132-01 was an uncontrolled, Phase 1/2 basket study in which SG monotherapy was evaluated in metastatic epithelial cancers who had either relapsed or were refractory after at least 1 standard therapeutic regimen for their tumor type.

The study included 54 participants with HR+/HER2− metastatic breast cancer, whose disease progressed on endocrine-based therapy and at least 1 prior chemotherapy for metastatic breast cancer in the metastatic setting and who were treated with the 10 mg/kg dose regimen.

Figure 45: IMMU-132-01: Study Schema



IV = intravenous; MTD = maximum tolerated dose; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; v = version

a Starting doses of 8, 12, 18, and 24 mg/kg were planned during the dose escalation phase (Phase 1) of this study. Dose escalation halted after the 18-mg/kg dose, and the 10-mg/kg dose was determined as the recommended Phase 2 dose for the remainder of the study.

b Advanced epithelial cancers, including ovarian, endometrial, cervical, breast (TNBC and non-TNBC), prostate (hormone refractory), colorectal, lung (non–small cell and small cell), head and neck (squamous cell), esophageal, gastric, pancreatic, hepatocellular, renal (clear cell), papillary thyroid, and urothelial cancers. Participants with glioblastoma multiforme were also eligible but were not required to have metastatic disease.

The primary efficacy endpoint of Phase 2 in Study IMMU 132 01 was ORR per RECIST v1.1 as assessed by local investigator review (LIR). Key secondary efficacy endpoints included OS, PFS, and DOR.

Baseline characteristics in Study IMMU-132-01 were similar to those of participants in the pivotal Study IMMU-132-09 with the majority of patients being White (78%) and ≤65 years of age (80%). About 60% had received prior CDK 4/6 inhibitor treatment in Study IMMU-132-01 (as opposed to 100% in IMMU-132-09). Patients had to have received at least 1 prior chemotherapy for metastatic breast cancer (as opposed to 2 prior lines in Study IMMU-132-09).

Table 40: IMMU-132-01: Summary of Efficacy

Parameter	**Participants with HR+/HER2− mBC (N = 54)**
ORR by LIR	31.5%

Median DOR by LIR	8.7 months
Median TTR by LIR	2.1 months
CBR by LIR	44.4%
Median PFS by LIR	5.5 months
Median OS	12.0 months

Table 41: Efficacy results for Study IMMU-132-09 per BICR and for Study IMMU-132-01 per local assessment (excerpt from SCE Table 18)

Efficacy Endpoint	IMMU-132-09 SG (N = 272)	IMMU-132-01 HR+/HER2- (N = 54)
Duration of Treatment (Months)		
Median	4.11	4.6
Duration of Follow-up		
Median	13.80	11.50
Min, Max	0.03, 35.48	0.70, 38.41
Progression-free Survival (Months)		
Median (95% CI)	5.5 (4.2, 7.0)	5.5 (3.6, 7.6)
Kaplan-Meier Estimate of PFS Rate		
At 6 months, % (95% CI)	46.1 (39.4, 52.6)	46.3 (32.4, 59.1)
At 9 months, % (95% CI)	32.5 (25.9, 39.2)	NA
At 12 months, % (95% CI)	21.3 (15.2, 28.1)	21.1 (10.7, 33.8)
Overall Survival (Months)		
Median (95% CI)	14.4 (13.0, 15.7)	12.0 (9.0, 18.2)
Objective Response Rate [d, e]		
n (%), (95% CI)	57 (21.0), (16.3, 26.3)	17 (31.5), (19.5, 45.6)
Duration of Response (Months)		
Median (95% CI)	8.1 (6.7, 9.1)	8.7 (3.7, 12.7)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The open-label, randomized Phase 3 study IMMU-132-09 evaluated the efficacy of SG versus TPC as control in 543 participants with metastatic HR+/HER2− breast cancer. Patients had been treated with a CDK 4/6 inhibitor, endocrine therapy, taxane, and at least 2 but no more than 4 prior chemotherapy treatment 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).

The dose regimen of SG for Study IMMU-132-09 (10 mg/kg D1 and D8, Q3W) is the same as already approved for the treatment of patients with TNBC. It was selected based on results from the dose escalation and expansion phases of Study IMMU-132-01 in metastatic epithelial cancers, which is acceptable.

The randomized study design of IMMU-132-09 and the stratification factors are overall endorsed. Given the choice of different treatment options in the control arm, the open-label design is acceptable. Overall, the eligibility criteria were considered adequate to select an advanced HR+/HER2- mBC population and the choice of comparator treatments were acceptable for this pre-treated patient population. However, it is noted that patients were required to be pre-treated with a taxane, but not with an anthracycline, which is also recommended as preferable and efficacious treatment options for HR+/HER2- BC. Anthracycline was not included as a possible treatment option in the control arm, since "these agents are typically given earlier for breast cancer" as claimed by the MAH. The majority of study participants had received prior anthracycline, but 20% had not. Considering the toxicity profile of anthracyclines, this proportion of patients might represent clinical practice. Given the consistent efficacy outcomes across both subgroups, the risk of undertreatment in the comparator arm could be considered limited.

HER2 and hormonal receptor status was determined locally on a recently or newly obtained tumor biopsy, as agreed in the scientific advice. It is however noted that HER2 negativity was defined as IHC ≤ 2+ or fluorescence in situ hybridization negative. The IMMU-132-09 protocol did not require HER2 IHC2+ patients to be tested negative by fluorescence in situ hybridization (ISH) to confirm HER2-negativity which is not fully in line with the definition of HER2-negativity according to the ASCO/CAP criteria. Thirty-nine participants (17 participants in the SG group and 22 participants in the TPC group) were verified to have IHC2+ only without ISH-negative confirmation captured in the database. Sensitivity analyses of PFS and OS at the final OS data cutoff (01 December 2022) excluding the 39 participants with IHC2+ only without ISH negative confirmation were overall consistent with the results of the ITT population. This suggests that the inclusion of these patients did not have a major impact on the study results. It is however relevant that the SmPC reflects the correct definition of HER2-negativity according to current standard.

An archival tumor tissue or a newly acquired biopsy from a metastatic site had to be submitted to the Sponsor´s central laboratory by C2D1, but analysis results were not required from the central laboratory prior to enrolment. Thus, adequacy of the tumor biopsy for e.g. determination of Trop-2 expression status could not be guaranteed for all patients.

The MAH initially proposed following indication: "*Trodelvy as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH−) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting (see section 5.1)".* The indication wording aims at a population with an advanced endocrine-resistant HR+/HER2− breast cancer population after prior standard treatments. It is considered acceptable not to explicitly state that patients need to have exhausted all possible hormonal treatments, since several lines of endocrine-based therapies (± targeted therapies) are recommended as standard treatments before chemotherapy (for patients without risk of organ failure, *ESMO guidelines*).

Since the eligibility criteria for Study IMMU-132-09 required at least 2 prior systemic chemotherapy regimens for metastatic disease, the more general wording of "at least two additional systemic therapies" required further justification. Given the recent approval of trastuzumab deruxtecan (T-DXd) for the treatment of HER2-low (IHC 1+ or 2+/FISH−) breast cancer, T-DXd is a valid treatment option for patients with HER2-low BC prior to the use of SG and CHMP questioned whether an extrapolation could be acceptable to allow prior treatment with trastuzumab deruxtecan as one prior systemic therapy instead of conventional chemotherapy. It has to be considered that both ADCs (SG and T-DXd) have different targets but similar payloads with similar mechanism of action (both topoisomerase inhibitors) which make resistance very likely. The MAH argued that, with a different antigen target and

evidence suggesting that resistance is not entirely determined by the payload (Abelman et al, Cancers, 2023), SG may be effective after T-DXd. Currently, there are no clinical data to determine the benefit of SG after T-DXd. While the concerns regarding expected resistance to the similar payload are still considered valid, it is acknowledged that other mechanisms of resistance to T-DXd might leave SG as an effective treatment option even after failure of T-DXd.

Further, in the context of required pre-treatments the MAH revised "metastatic" to "advanced" since the current indication wording could include patients with unresectable BC that could not have received prior treatment for metastatic disease. Finally, the Applicant accepted deletion of spelling out "human epidermal growth factor receptor 2" and the definition of HER2-negativity from the indication to improve readability.

The claim to treat patients with unresectable BC in the advanced setting has not been supported by data, because the pivotal study explicitly required inclusion of patients with metastatic disease; 2 participants were enrolled with M0 disease as protocol deviations. Nonetheless, an extrapolation can be considered acceptable, since locally advanced disease are not treated differently in clinical practice and the assumption of a heterogeneous treatment effect between disease settings would not be likely.

The planned efficacy analyses are overall considered adequate. However, relevant planned and unplanned changes were introduced rather late in this open-label study. The sample size and number of required OS events was increased, eventually the primary PFS analysis was conducted before reaching the prespecified number of PFS events (329/350). Initially, ORR and PFS had been planned as primary endpoints, with α=0.01 allocated to ORR and α=0.04 to PFS. ORR was downgraded to a secondary endpoint in a late amendment, following Scientific Advice. The applicant provided reassurance that PFS results were robust and the choice of timing of the analysis did not relevantly affect the interpretation. Results of an updated analysis using PFS data from the "final" data cut-off were consistent with the primary results. Further, the Applicant conducted a tipping point analysis as requested to investigate the sensitivity of the primary PFS analysis to the decision to analyse or wait. These analyses suggest that results could not have been substantially different, even if the sponsor had waited until 350 PFS events. This provides reassurance that the timing of data-cut-off/analysis did not matter.

The study randomized 543 patients across 82 centers in Europe and the US during May 2019 and April 2021. A higher proportion of patients in the control arm were randomized but not treated or discontinued treatment early due to consent withdrawal (16% in the TPC group vs 5% in the SG group). In view of the open-label study, this is likely due to patients´ preference for experimental treatment. Tipping-point analyses (data not shown) provided by the applicant provided good reassurance that results are robust despite this imbalance.

Demographics and baseline disease characteristics were generally balanced between both treatment arms and reflect a heavily pre-treated patient population with a median of 7 prior systemic anticancer regimens overall and 3 prior chemotherapy regimens in the metastatic setting. Although the study population can be considered overall representative of the target population, some characteristics still suggest selection of a study population with overall more favourable prognosis compared to a general metastatic HR+/HER2− BC population (e.g. long median time of approximately 4 years from metastatic disease diagnosis to randomization, 30% screen failures, low proportions of patients with ≥75 years of age (4.4%) and brain metastasis (4.6%)). Moreover, the low proportion of Black study participants (3.9%) is considered a drawback, given the high rate of patients homozygous for the UGT1A1*28 allele (please refer to safety in special populations). While the proportion of men in the study program is very low, it is still considered possible to extrapolate results to men, based on the common biological and pharmacological rationale.

Efficacy data and additional analyses

Efficacy data were provided for two data cutoff dates. The primary (final) analysis for **PFS** was conducted with a cutoff date of 03 Jan 2022. The PFS analysis per BICR met statistical significance with a HR of 0.661 (95% CI 0.54, 0.83) in favour of SG vs TPS; an only modest improvement of 1.5 months was observed for median PFS (5.5 vs 4.0 months in the SG and TPC groups). PFS sensitivity analyses provided consistent results.

The first interim analysis of **OS** was performed together with primary PFS analysis and showed a trend of improved OS in the SG group versus the TPC group (HR 0.84; 95% CI 0.67, 1.06). At the data cutoff of 01 July 2022, the second interim analysis of OS met statistical significance for SG vs TPC (OS HR 0.789; 95% CI: 0.646, 0.964; *P* = 0.0200; [P-value boundary 0.0223]). An improvement of 3.2 months in median OS was observed for SG over TPC (14.4 vs 11.2 months) which can be considered clinically relevant also in view of the heavily pre-treated study population. Two ad hoc sensitivity analyses were conducted to assess the impact of deviations from the planned timing of the OS analyses; these indicated that the changes appeared not to have a relevant impact on the OS results.

Updated PFS and OS data at the final data cutoff of 01 December 2022 were provided and confirmed the previous results. **PFS2** data also supported the benefit of SG over TPC: A longer median PFS2 was shown in the SG group versus the TPC group (9.8 [95% CI: 8.2, 11.4] vs 7.4 months [95% CI: 6.7, 8.9] for SG arm vs TPC; HR 0.709 [95% CI: 0.584, 0.860], data cutoff date 01 Dec 2022).

Analyses of other secondary endpoints have been presented with the later data cutoff of 01 July 2022 and can be considered overall supportive. Statistically significant more patients had an **ORR** per BICR in the SG group than in the TPC group (n=57 [21%] vs n=38 [14%]). However, the considerably higher number of not evaluable patients in the TPC group (n=51 for TPC vs n=15 for SG) raised some uncertainty on the extent of effect of SG on ORR. The MAH provided sensitivity analyses to address uncertainty due to imbalances in patients with not evaluable response. A conservative sensitivity analysis with a "jump to reference" like imputation for NE response resulted in a considerably smaller but still favourable effect estimate (Odds Ratio under conservative assumptions: 1.38).

Response assessment by local investigator review and results for **DOR** showed numerically higher response rates and longer response duration in the SG group versus the TPC group.

Time to deterioration of **QOL** endpoints was tested per the hierarchical testing strategy. A statistically significantly longer time to first deterioration in the EORTC QLQ-C30 global health status/QOL and fatigue domains was demonstrated in the SG group versus the TPC group (median 4.3 vs 3 and 2.2 vs 1.1 months for GHS/QOL and fatigue, respectively). No statistically significant difference was observed for the pain domain between both treatment groups (3.8 vs 3.5 months for SG vs TPC, respectively). Exploratory analysis of change from baseline in the physical functioning and role functioning domains showed similar results for both treatment arms with a small trend in favour of the SG group versus the TPC group. It is considered reassuring that for the average of study population, the toxicity of SG did not appear to have negatively impacted quality of life as compared to the control arm. However, the validity of the PRO results has to be viewed in the context of the open-label trial design. The PRO data were not included in the SmPC due to the concern that PRO results might be impacted by a possible bias introduced by the open-label study design.

Overall, **subgroup** analyses showed longer median PFS and OS and higher ORR values in the SG groups versus the TPC groups with some exceptions. In participants without visceral metastases OS HR was 2.63 (95% CI 0.95, 7.29; n = 26) and no PFS benefit was observed for participants who received prior endocrine therapy for less than 6 months (n = 74). However, results were not fully consistent across endpoints and the small sample sizes hampers a conclusive interpretation of these findings.

TPC was determined by the investigator before randomization, but TPC was not included as stratification factor. Eribulin was used most commonly (48.0%), followed by vinorelbine (23%), gemcitabine (21%), and capecitabine (8%). Highly variable efficacy results were observed. The worst outcome was detected for patients treated with vinorelbine (ORR 3.2%, and 1.5 and 8.3 months for median PFS and OS) and the most favourable outcome was detected for patients treated with capecitabine (ORR 27.3%, and 5.6 and 20.1 months for median PFS and OS). SG did not appear to derive any benefit compared to treatment with capecitabine. These results are difficult to interpret due to the small sample size and differences in prognostic factors in the capecitabine subgroup (n=22). HRs were obtained from comparison between SG (overall) and each TPC drug, which did not take potential differences in baseline characteristics into account. Results from efficacy analyses of PFS, OS and ORR stratified by physician's choice of chemotherapy agent in the ITT population (evaluating the treatment effect of SG vs TPC by providing odds ratio for ORR and HRs for PFS and OS for the subgroups of patients as determined to be treated by each chemotherapy agent prior to randomization) were provided. These analyses did not provide substantially different results. The heterogeneous subgroup results by TPC remain difficult to interpret also with the updated analysis. Overall, it has to be acknowledged that the subgroup results do not appear plausible, and the sample sizes are too small to draw reliable conclusions on a differential effect in subgroups by TPC.

Efficacy analyses by **Trop-2 expression** were performed in the Trop-2 Evaluable Population (baseline Trop-2 expression was missing in 14.9%). Questions were raised to the MAH regarding the analytical validation of the used Trop-2 Immunohistochemistry Assay to evaluate whether patient's Trop-2 testing results are sufficiently robust and reliable, considering also the retrospectively defined clinical cut-offs.

It was clarified that the analytical validation approach for the Trop-2 expression IHC assay for the concerned IMMU-132-09 trial was intended for a retrospective / explorative testing setting. Regarding this "retrospective / exploratory" intended purpose the assay could be considered as suitable. However, since some essential analytical validation studies were not fully performed (e.g. full validation of "precision" [Intra- and Inter-Assay Reproducibility] for ER+ BC, full analytical validation at the different clinical cut-offs, or epitope stability evaluation), the (retrospectively/exploratory) obtained results in the IMMU-132-09 trial cannot be considered as being similarly robust and reliable as achievable for an assay analytically fully validated at pre-specified cut-offs in the (HR+ BC) target cells. In addition, age of used tumor tissue FFPE blocks was between 2 and 5 years for 28% and 8% of tumor tissue was more than 5 years old. Apart from the technical question of uncertain epitope stability, it might be questioned whether the biomarker status of a >5-year-old sample is still representative of the tumor at the time of enrolment. A dynamic change of the tumor biology and its environment may be assumed that is also likely impacted by prior treatments. In consequence, these limitations regarding an adequate robustness of the data should be considered when interpreting the testing result data (see below).

Planned exploratory subgroup analyses were based on tertile subgroups by Trop-2 H-scores of < 100, ≥ 100 to ≤ 200, and > 200, leading to an uneven distribution with 41.6% of participants in the low Trop-2 expression group and 18.4% in the high Trop-2 expression group. Efficacy data indicated a possible association of benefit with Trop-2 expression levels, as there was a numerical increase in median PFS with higher Trop-2 expression (median PFS was 5.3, 5.8, and 6.4 months for the < 100, ≥ 100 to ≤ 200, and > 200 subgroups, respectively). PFS and OS HRs favoured treatment with SG over the control arm in the low and medium Trop-2 subgroups; however, for patients with high Trop-2-expressing tumors, no PFS and OS benefit of SG relative to TPC was observed that did not appear plausible considering the mechanism of action of SG. Moreover, in view of the large size of the low Trop-2 expression group, a more in-depth analysis was considered necessary to analyse clinical benefit of SG in participants with low or no Trop-2 expression.

The MAH provided results from additional exploratory analyses to further explore association of Trop-2 expression and clinical benefit. Efficacy of SG versus TPC was assessed by dividing participants into two subgroups with Trop-2 H-score < 100 and ≥ 100. To examine whether a minimum level of Trop-2 expression is required for clinical benefit with SG, efficacy of SG versus TPC at lower Trop-2–expressing levels was assessed in participants with H-score ≤ 38 (Quartile 1 of 4 equal-participant quartile subgroups), in participants with Trop-2 H-score ≤ 10, as well as in participants without Trop-2 expression (see Trop-2 expression data in section "ancillary analyses" for detailed results).

The additionally provided efficacy data indicate that patients with low and no Trop-2 expression might benefit less from SG compared to patients with higher Trop-2 tumor expression levels. This is suggested by higher PFS HRs for SG vs TPC in the lower Trop-2 expression groups (PFS HR 0.74 vs 0.59 and 0.49 for Q1, Q2 and Q3, respectively). In the subgroup of patients with even lower Trop-2 expression of ≤ 10, the PFS HR was 0.89 (95% CI 0.51, 1.57). For patients with no detectable Trop-2 expression (H-Score 0, n=10), SG resulted in an ORR of 10% (as compared to 21% in the ITT). However, it is acknowledged that results from small subgroups have to be interpreted with caution and are more likely to be impacted by heterogeneity.

Overall, Trop-2 expression data suggest an association of Trop2 expression with efficacy of SG, but the evidence of the provided data is not considered valid enough to determine a cutoff of Trop-2 expression below that patients would certainly not derive any benefit from SG. Thus, a restriction of the indication to a subgroup of patients with higher Trop-2 tumor expression is not considered justified. It has however to be emphasized that any conclusions on efficacy by Trop-2 expression is hampered by the retrospective/explorative testing and the described deficiencies regarding analytical and clinical validation.

Efficacy results in the small cohort of 54 HR+/HER2− mBC patients of Study IMMU-132-01 can be overall considered supportive for the proposed indication. Response rates of SG, as evaluated by local assessment, were higher compared to results in the pivotal Study IMMU-132-09 (ORR by LIR 31.5% in IMMU-132-01 vs 16.2% ORR by LIR and 21% ORR per BICR in IMMU-132-09). However, these differences might be attributed to the small sample size in the non-randomized cohort of Study IMMU-132-01 and due to differences in patient populations with more intensive pre-treatment in the pivotal study.

2.4.4. Conclusions on the clinical efficacy

Efficacy data were provided from a randomized Phase 3 study in heavily pre-treated patients with HR+/HER2− metastatic breast cancer. Sacituzumab govitecan demonstrated statistically significant improvements in PFS and OS over an acceptable comparator of TPC with single-agent chemotherapies. The overall data package can be considered relevant to demonstrate the efficacy of SG in this advanced disease setting.

2.5. Clinical safety

All safety analyses were conducted based on the Safety Population, which was defined as all participants in the ITT Population who received at least 1 dose of study drug and included data up to the cutoff date of 01 July 2022.

Introduction

Table 42: Overview of the Integrated Safety Analysis for the HR+/HER2− Metastatic Breast Cancer Program

Group Name	Description	Number of Participants	Studies
Study IMMU-132-01 Targeted HR+/HER2− mBC	Participants with HR+/HER2− mBC who received SG 10 mg/kg in Study IMMU-132-01	54[a]	IMMU-132-01[b]
Study IMMU-132-09 SG	Participants who received SG 10 mg/kg in Study IMMU-132-09	268	IMMU-132-09
Study IMMU-132-09 TPC	Participants who received eribulin, capecitabine, gemcitabine, or vinorelbine as a single agent in Study IMMU-132-09	249	IMMU-132-09
Overall Targeted HR+/HER2− mBC	Participants with HR+/HER2− mBC from Study IMMU-132-01 who received SG 10 mg/kg and all participants from Study IMMU-132-09 who received SG 10 mg/kg	322	IMMU-132-01[b] IMMU-132-09[c]
Overall Targeted mBC	Participants with HR+/HER2− mBC and participants with TNBC from Study IMMU-132-01 who received SG 10 mg/kg and all participants from Studies IMMU-132-09 and IMMU-132-05 who received SG 10 mg/kg	688	IMMU-132-01[b] IMMU-132-05[c] IMMU-132-09[c]
All Treated SG 10 mg/kg	All participants who received SG 10 mg/kg regardless of tumor type	1063	IMMU-132-01[b] IMMU-132-05[c] IMMU-132-06[b] IMMU-132-09[c]

HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; mBC = metastatic breast cancer; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice

a Overall, 68 participants with non-TNBC were enrolled in Study IMMU-132-01 and received at least 1 dose of SG. Of these 68 participants, 54 were confirmed as HR+/HER− who had progressed on at least 1 prior hormonal therapy in the metastatic setting, and had received at least 1 dose of SG 10 mg/kg.

b Only participants who received a starting dose of SG 10 mg/kg monotherapy were included (only safety data from Cohorts 1 and 2 of Study IMMU-132-06 were included).

c All SG-treated participants from study were included in pooled analysis.

Source: m2.7.4, Table 2

Patient exposure

Table 43: Exposure to Study Drug (IMMU-132-09 ISS Populations)

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Treatment Duration (Months)[2]				
N	268	249	688	1063
Mean (SD)	5.81 (5.748)	3.55 (3.659)	6.33 (6.823)	5.95 (6.794)
Median	4.11	2.33	4.63	4.11
Min, Max	0.03, 30.62	0.03, 22.31	0.03, 62.55	0.03, 62.55

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
≥ 3 months	159 (59.3%)	109 (43.8%)	428 (62.2%)	634 (59.6%)
≥ 6 months	95 (35.4%)	47 (18.9%)	255 (37.1%)	366 (34.4%)
≥ 12 months	35 (13.1%)	8 (3.2%)	93 (13.5%)	121 (11.4%)
≥ 24 months	5 (1.9%)	0	22 (3.2%)	31 (2.9%)
≥ 36 months	0	0	4 (0.6%)	8 (0.8%)
Number of Cycles Received[3]				
N	268	249	688	1063
Mean (SD)	8.56 (7.962)	5.34 (4.913)	9.24 (9.356)	8.69 (9.219)
Median	6.00	4.00	7.00	6.00
Min, Max	1, 44	1, 33	1, 90	1, 90
Number of Doses Received				
N	268		688	1063
Mean (SD)	16.52 (15.611)		17.97 (18.492)	16.88 (18.250)
Median	12.00		13.00	12.00
Min, Max	1, 87		1, 178	1, 178
Cumulative Dosage (mg/kg)				
N	265		685	1060
Mean (SD)	150.58 (137.947)		164.71 (163.358)	153.48 (161.535)
Median	110.14		120.12	110.12
Min, Max	9.88, 868.51		9.16, 1340.92	8.02, 1757.68
Number of Participants with Treatment Delays > 3 Weeks[4]	7 (2.6%)		25 (3.6%)	40 (3.8%)
Number of Participants with Infusion Interruptions	5 (1.9%)		28 (4.1%)	53 (5.0%)
Number of Participants with Dose Reductions				
Any	93 (34.7%)	100 (40.2%)	213 (31.0%)	355 (33.4%)
1	70 (26.1%)	73 (29.3%)	159 (23.1%)	274 (25.8%)
2	21 (7.8%)	19 (7.6%)	49 (7.1%)	75 (7.1%)
3	1 (0.4%)	3 (1.2%)	1 (0.1%)	2 (0.2%)
> 3	1 (0.4%)	5 (2.0%)	4 (0.6%)	4 (0.4%)

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Time to First Dose Reduction (Days)				
N	93	100	213	355
Mean (SD)	75 (84.1)	50 (58.1)	86 (122.9)	78 (135.1)
Median	43	29	43	40
Min, Max	1, 588	1, 260	1, 925	1, 1647
Relative Dose Intensity (%)[5]				
N	265		685	1060
Mean (SD)	91.94 (11.967)		92.93 (11.500)	92.29 (11.683)
Median	98.89		99.32	99.07
Min, Max	50.00, 106.06		47.42, 107.34	45.32, 107.34
Relative Dose Intensity				
< 70%	21 (7.8%)		43 (6.3%)	66 (6.2%)
70% to < 90%	61 (22.8%)		148 (21.5%)	258 (24.3%)
90% to < 110%	183 (68.3%)		494 (71.8%)	736 (69.2%)
≥ 110%	0		0	0

HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor–positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAP = statistical analysis plan; SG = sacituzumab govitecan; TPC = treatment of physician's choice
[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.
[2] Treatment duration (in months) is (date of the last treatment administration − date of the first treatment administration + 1)/30.4375.
[3] Cycles are counted if participant received at least 1 dose in that cycle.
[4] Treatment delay > 3weeks is defined as > 28 days between the first 2 doses of the same cycle or > 35 days between Dose 2 and Dose 1 of the next cycle.
[5] Relative Dose Intensity = cumulative dosage received (mg/kg) / total assigned dosage (mg/kg). Details are provided in the ISS SAP.

Source: ISS IA2, Table 14.3.1.1

Adverse event

Adverse event summary

Table 44: Participant Disposition and Reason for Discontinuation from Treatment

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants Treated	268 (100.0%)	249 (100.0%)	688 (100.0%)	1063 (100.0%)
Permanently Discontinued Treatment	259 (96.6%)	247 (99.2%)	679 (98.7%)	1046 (98.4%)
Reason of End of Treatment				
Progressive Disease	217 (81.0%)	199 (79.9%)	568 (82.6%)	816 (76.8%)
Protocol Deviation	1 (0.4%)	3 (1.2%)	1 (0.1%)	1 (< 0.1%)
Death	3 (1.1%)	2 (0.8%)	4 (0.6%)	16 (1.5%)
Treatment Delay > 3 Weeks	5 (1.9%)	1 (0.4%)	6 (0.9%)	9 (0.8%)
Treatment Delay for Any Reason > 5 Weeks	0	0	0	3 (0.3%)
Withdrawal of Consent	10 (3.7%)	22 (8.8%)	20 (2.9%)	46 (4.3%)

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Adverse Event	18 (6.7%)	11 (4.4%)	37 (5.4%)	76 (7.1%)
Pregnancy	0	0	0	0
Lost to Follow-Up	0	0	0	1 (< 0.1%)
Physician Decision	0	0	23 (3.3%)	33 (3.1%)
COVID-19	0	3 (1.2%)	0	0
Study Drug Not Administered (After Randomization)	0	0	1 (0.1%)	1 (< 0.1%)
Other	5 (1.9%)	6 (2.4%)	19 (2.8%)	43 (4.0%)
Missing	0	0	0	1 (< 0.1%)
On Treatment	9 (3.4%)	2 (0.8%)	9 (1.3%)	17 (1.6%)

Table 45: Overall Summary of Adverse Events (IMMU-132-09 ISS Populations)

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs	268 (100.0%)	239 (96.0%)	687 (99.9%)	1060 (99.7%)
Grade 3 or higher	198 (73.9%)	150 (60.2%)	506 (73.5%)	808 (76.0%)
Participants with Treatment-related TEAEs	260 (97.0%)	217 (87.1%)	671 (97.5%)	1034 (97.3%)
Grade 3 or higher	173 (64.6%)	128 (51.4%)	448 (65.1%)	678 (63.8%)
Participants with Treatment-emergent SAEs	74 (27.6%)	48 (19.3%)	195 (28.3%)	366 (34.4%)
Grade 3 or higher	67 (25.0%)	44 (17.7%)	176 (25.6%)	333 (31.3%)
Participants with Treatment-related Treatment-emergent SAEs	36 (13.4%)	25 (10.0%)	102 (14.8%)	177 (16.7%)
Grade 3 or higher	32 (11.9%)	23 (9.2%)	93 (13.5%)	161 (15.1%)
Participants with TEAEs Leading to Death	6 (2.2%)	0	8 (1.2%)	21 (2.0%)
Participants with Treatment-related TEAEs Leading to Death	1 (0.4%)	0	1 (0.1%)	3 (0.3%)
Participants with TEAEs Leading to Study Drug Interruption	178 (66.4%)	109 (43.8%)	417 (60.6%)	615 (57.9%)
Participants with TEAEs Leading to Study Drug Dose Reduction	90 (33.6%)	82 (32.9%)	147/526 (27.9%)	205/661 (31.0%)
Participants with TEAEs Leading to Study Drug Withdrawal/Discontinuation	17 (6.3%)	11 (4.4%)	36 (5.2%)	78 (7.3%)
Participants with Treatment-related TEAEs Leading to Study Drug Interruption	161 (60.1%)	91 (36.5%)	372 (54.1%)	531 (50.0%)
Participants with Treatment-related TEAEs Leading to Study Drug Dose Reduction	88 (32.8%)	79 (31.7%)	145/526 (27.6%)	199/661 (30.1%)
Participants with Treatment-related TEAEs Leading to Study Drug Withdrawal/Discontinuation	7 (2.6%)	9 (3.6%)	16 (2.3%)	37 (3.5%)

CTCAE = Common Terminology Criteria for Adverse Events; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

Denominator for percentages was big N.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Treatment-related is defined as events reported as "Possibly Related," "Related," or missing; "Unlikely Related" or "Not Related" is not included.

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

Table 46: Overall Summary of Adverse Events: Exposure-Adjusted Incidence Rates

	IMMU-132-09 SG Treated (N = 268)	**IMMU-132-09 TPC (N = 249)**	**Overall Targeted mBC (N = 688)**	**All Treated SG (10 mg/kg) (N = 1063)**
Participants with Any TEAEs				
PYE	3.7	5.1	9.1	14.0
EAIR (95% CI)	72.67 (64.23, 81.91)	46.71 (40.97, 53.02)	75.53 (69.99, 81.40)	75.71 (71.22, 80.41)
EAIR Diff vs TPC (95% CI)	25.96 (15.42, 36.84)			
Participants with Grade 3 or Higher TEAEs				
PYE	50.9	39.1	140.3	202.0
EAIR (95% CI)	3.89 (3.37, 4.47)	3.83 (3.24, 4.50)	3.61 (3.30, 3.94)	4.00 (3.73, 4.29)
EAIR Diff vs TPC (95% CI)	0.06 (-0.79, 0.88)			
Participants with Treatment-Related TEAEs				
PYE	5.4	9.8	16.0	23.7
EAIR (95% CI)	47.99 (42.33, 54.19)	22.22 (19.36, 25.38)	41.84 (38.73, 45.13)	43.69 (41.06, 46.43)
EAIR Diff vs TPC (95% CI)	25.77 (19.29, 32.59)			
Participants with Grade 3 or Higher Treatment-Related TEAEs				
PYE	57.8	42.4	155.5	234.2
EAIR (95% CI)	2.99 (2.56, 3.47)	3.02 (2.52, 3.59)	2.88 (2.62, 3.16)	2.90 (2.68, 3.12)
EAIR Diff vs TPC (95% CI)	-0.02 (-0.74, 0.67)			
Participants with Treatment-Emergent SAEs				
PYE	106.7	64.7	298.9	421.6
EAIR (95% CI)	0.69 (0.54, 0.87)	0.74 (0.55, 0.98)	0.65 (0.56, 0.75)	0.87 (0.78, 0.96)
EAIR Diff vs TPC (95% CI)	-0.05 (-0.33, 0.21)			

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Grade 3 or Higher Treatment-Emergent SAEs				
PYE	111.3	65.0	307.4	433.2
EAIR (95% CI)	0.60 (0.47, 0.76)	0.68 (0.49, 0.91)	0.57 (0.49, 0.66)	0.77 (0.69, 0.86)
EAIR Diff vs TPC (95% CI)	-0.07 (-0.34, 0.17)			
Participants with Treatment-Related Treatment-Emergent SAEs				
PYE	119.7	66.6	322.6	465.5
EAIR (95% CI)	0.30 (0.21, 0.42)	0.38 (0.24, 0.55)	0.32 (0.26, 0.38)	0.38 (0.33, 0.44)
EAIR Diff vs TPC (95% CI)	-0.07 (-0.27, 0.10)			
Participants with Grade 3 or Higher Treatment-Related Treatment-Emergent SAEs				
PYE	121.5	66.9	329.8	474.7
EAIR (95% CI)	0.26 (0.18, 0.37)	0.34 (0.22, 0.52)	0.28 (0.23, 0.35)	0.34 (0.29, 0.40)
EAIR Diff vs TPC (95% CI)	-0.08 (-0.27, 0.09)			
Participants with TEAEs Leading to Study Drug Interruption				
PYE	58.7	44.9	188.2	277.6
EAIR (95% CI)	3.03 (2.60, 3.51)	2.43 (1.99, 2.93)	2.22 (2.01, 2.44)	2.22 (2.04, 2.40)
EAIR Diff vs TPC (95% CI)	0.61 (-0.05, 1.25)			
Participants with TEAEs Leading to Study Drug Dose Reduction				
PYE	88.0	50.5	190.9	220.5
EAIR (95% CI)	1.02 (0.82, 1.26)	1.62 (1.29, 2.01)	0.77 (0.65, 0.91)	0.93 (0.81, 1.07)
EAIR Diff vs TPC (95% CI)	-0.60 (-1.04, -0.19)			
Participants with TEAEs Leading to Study Drug Withdrawal/Discontinuation				
PYE	129.8	73.6	361.9	526.9
EAIR (95% CI)	0.13 (0.08, 0.21)	0.15 (0.07, 0.27)	0.10 (0.07, 0.14)	0.15 (0.12, 0.18)
EAIR Diff vs TPC (95% CI)	-0.02 (-0.15, 0.09)			
Participants with Treatment-Related TEAEs Leading to Study Drug Interruption				
PYE	63.8	48.0	204.8	304.6
EAIR (95% CI)	2.52 (2.15, 2.94)	1.90 (1.53, 2.33)	1.82 (1.64, 2.01)	1.74 (1.60, 1.90)
EAIR Diff vs TPC (95% CI)	0.63 (0.06, 1.19)			

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Treatment-Related TEAEs Leading to Study Drug Dose Reduction				
PYE	88.9	51.3	191.8	223.0
EAIR (95% CI)	0.99 (0.79, 1.22)	1.54 (1.22, 1.92)	0.76 (0.64, 0.89)	0.89 (0.77, 1.03)
EAIR Diff vs TPC (95% CI)	-0.55 (-0.98, -0.16)			
Participants with Treatment-Related TEAEs Leading to Study Drug Withdrawal/Discontinuation				
PYE	129.9	73.5	363.5	528.2
EAIR (95% CI)	0.05 (0.02, 0.11)	0.12 (0.06, 0.23)	0.04 (0.03, 0.07)	0.07 (0.05, 0.10)
EAIR Diff vs TPC (95% CI)	-0.07 (-0.18, 0.02)			
Participants with TEAEs Leading to Death				
PYE	130.0	73.6	363.4	528.3
EAIR (95% CI)	0.05 (0.02, 0.10)	0.00 (0.00, 0.05)	0.02 (0.01, 0.04)	0.04 (0.02, 0.06)
EAIR Diff vs TPC (95% CI)	0.05 (-0.01, 0.10)			
Participants with Treatment-Related TEAEs Leading to Death				
PYE	129.9	73.6	363.2	527.7
EAIR (95% CI)	0.01 (0.00, 0.04)	0.00 (0.00, 0.05)	0.00 (0.00, 0.02)	0.01 (0.00, 0.02)
EAIR Diff vs TPC (95% CI)	0.01 (-0.04, 0.04)			

CI = confidence interval; Diff. = difference; EAIR = exposure-adjusted incidence rate; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; PYE = patient-years of exposure; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

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). For participants without specific events, exposure time was calculated from first dose date up to data cutoff date if the participants were on study drug, or up to last dose if the participant discontinued study drug. For each specific event, total exposure time is the sum of exposure time over 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.

Table 47: Adverse Events in ⩾ 10% of Participants in Selected ISS populations[1] by System Organ Class[2] and Preferred Term

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs	268 (100.0%)	239 (96.0%)	687 (99.9%)	1060 (99.7%)
Blood and lymphatic system disorders	221 (82.5%)	160 (64.3%)	553 (80.4%)	823 (77.4%)
Neutropenia	189 (70.5%)	136 (54.6%)	465 (67.6%)	653 (61.4%)
Anaemia	98 (36.6%)	69 (27.7%)	280 (40.7%)	430 (40.5%)
Leukopenia	38 (14.2%)	25 (10.0%)	118 (17.2%)	195 (18.3%)
Lymphopenia	32 (11.9%)	29 (11.6%)	77 (11.2%)	113 (10.6%)
Thrombocytopenia	17 (6.3%)	41 (16.5%)	59 (8.6%)	87 (8.2%)
Gastrointestinal disorders	251 (93.7%)	174 (69.9%)	643 (93.5%)	984 (92.6%)
Nausea	157 (58.6%)	87 (34.9%)	431 (62.6%)	684 (64.3%)
Diarrhoea	166 (61.9%)	57 (22.9%)	430 (62.5%)	681 (64.1%)
Constipation	93 (34.7%)	61 (24.5%)	249 (36.2%)	391 (36.8%)
Vomiting	64 (23.9%)	39 (15.7%)	231 (33.6%)	374 (35.2%)
Abdominal pain	53 (19.8%)	34 (13.7%)	139 (20.2%)	234 (22.0%)
General disorders and administration site conditions	196 (73.1%)	174 (69.9%)	520 (75.6%)	811 (76.3%)
Fatigue	105 (39.2%)	82 (32.9%)	327 (47.5%)	538 (50.6%)
Asthenia	62 (23.1%)	50 (20.1%)	112 (16.3%)	152 (14.3%)
Pyrexia	39 (14.6%)	45 (18.1%)	103 (15.0%)	171 (16.1%)
Oedema peripheral	17 (6.3%)	15 (6.0%)	65 (9.4%)	128 (12.0%)
Infections and infestations	101 (37.7%)	67 (26.9%)	322 (46.8%)	495 (46.6%)
Urinary tract infection	26 (9.7%)	24 (9.6%)	89 (12.9%)	148 (13.9%)
Upper respiratory tract infection	7 (2.6%)	4 (1.6%)	69 (10.0%)	100 (9.4%)
Investigations	87 (32.5%)	95 (38.2%)	250 (36.3%)	415 (39.0%)
Aspartate aminotransferase increased	33 (12.3%)	44 (17.7%)	89 (12.9%)	121 (11.4%)
Alanine aminotransferase increased	30 (11.2%)	37 (14.9%)	80 (11.6%)	113 (10.6%)
Blood alkaline phosphatase increased	25 (9.3%)	27 (10.8%)	67 (9.7%)	101 (9.5%)
Weight decreased	15 (5.6%)	14 (5.6%)	55 (8.0%)	124 (11.7%)
Metabolism and nutrition disorders	111 (41.4%)	85 (34.1%)	356 (51.7%)	610 (57.4%)
Decreased appetite	57 (21.3%)	52 (20.9%)	177 (25.7%)	323 (30.4%)
Hypokalaemia	29 (10.8%)	9 (3.6%)	104 (15.1%)	162 (15.2%)
Hypomagnesaemia	16 (6.0%)	9 (3.6%)	82 (11.9%)	146 (13.7%)
Hypophosphataemia	11 (4.1%)	5 (2.0%)	57 (8.3%)	112 (10.5%)
Dehydration	10 (3.7%)	9 (3.6%)	43 (6.3%)	108 (10.2%)

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Musculoskeletal and connective tissue disorders	117 (43.7%)	108 (43.4%)	320 (46.5%)	498 (46.8%)
Arthralgia	40 (14.9%)	30 (12.0%)	108 (15.7%)	164 (15.4%)
Back pain	35 (13.1%)	32 (12.9%)	110 (16.0%)	172 (16.2%)
Nervous system disorders	101 (37.7%)	100 (40.2%)	312 (45.3%)	454 (42.7%)
Headache	44 (16.4%)	36 (14.5%)	129 (18.8%)	165 (15.5%)
Dizziness	22 (8.2%)	11 (4.4%)	85 (12.4%)	127 (11.9%)
Psychiatric disorders	47 (17.5%)	38 (15.3%)	142 (20.6%)	226 (21.3%)
Insomnia	21 (7.8%)	19 (7.6%)	75 (10.9%)	105 (9.9%)
Respiratory, thoracic and mediastinal disorders	112 (41.8%)	77 (30.9%)	337 (49.0%)	533 (50.1%)
Dyspnoea	49 (18.3%)	39 (15.7%)	131 (19.0%)	206 (19.4%)
Cough	33 (12.3%)	18 (7.2%)	132 (19.2%)	201 (18.9%)
Skin and subcutaneous tissue disorders	165 (61.6%)	95 (38.2%)	436 (63.4%)	668 (62.8%)
Alopecia	128 (47.8%)	46 (18.5%)	314 (45.6%)	483 (45.4%)
Rash	24 (9.0%)	14 (5.6%)	91 (13.2%)	136 (12.8%)
Pruritus	32 (11.9%)	6 (2.4%)	83 (12.1%)	130 (12.2%)

AE = adverse event; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

[2] This table presents only those PTs that occurred in ≥ 10% of participants in the ISS groups shown. In the source table, the frequencies of the SOCs are based on all PTs under the SOC, not only the PTs of TEAEs reported in ≥ 10% of participants in the groups/pools in the table.

Denominator for percentages was big N.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Multiple adverse events are counted only once per participant for each SOC and PT. MedDRA Version 25.0 was used for coding. System organ classes were presented alphabetically and PTs within SOC were presented by descending order of the total frequencies.The following terms are mapped: Neutrophil count decreased à Neutropenia, White blood cell count decreased à Leukopenia, Lymphocyte count decreased à Lymphopenia, Haemoglobin decreased à Anaemia, Red blood cell count decreased à Anaemia, Platelet count decreased à Thrombocytopenia

Grade ≥ 3 Adverse Events

Table 48: Grade 3 or Higher Adverse Events Reported in ≥ 5% of Participants in Selected ISS Populations[1] by System Organ Class[2] and Preferred Term

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any Grade 3 or Higher TEAEs	198 (73.9%)	150 (60.2%)	506 (73.5%)	808 (76.0%)
Blood and lymphatic system disorders	155 (57.8%)	111 (44.6%)	390 (56.7%)	579 (54.5%)

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Neutropenia	138 (51.5%)	97 (39.0%)	349 (50.7%)	487 (45.8%)
Leukopenia	23 (8.6%)	15 (6.0%)	72 (10.5%)	119 (11.2%)
Anaemia	20 (7.5%)	9 (3.6%)	64 (9.3%)	123 (11.6%)
Febrile neutropenia	16 (6.0%)	11 (4.4%)	42 (6.1%)	67 (6.3%)
Gastrointestinal disorders	43 (16.0%)	17 (6.8%)	114 (16.6%)	205 (19.3%)
Diarrhoea	27 (10.1%)	3 (1.2%)	71 (10.3%)	112 (10.5%)
General disorders and administration site conditions	26 (9.7%)	16 (6.4%)	64 (9.3%)	116 (10.9%)
Fatigue	16 (6.0%)	9 (3.6%)	36 (5.2%)	74 (7.0%)

AE = adverse event; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

[2] This table presents only those PTs that occurred in ⩾ 5% of participants in the ISS groups shown. In the source table, the frequencies of the SOCs are based on all PTs under the SOC, not only the PTs of Grade 3 or higher AEs reported in ⩾ 5% of participants.

Denominator for percentages was big N.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Multiple adverse events are counted only once per participant for each SOC and PT. MedDRA Version 25.0 was used for coding.

System organ classes were presented alphabetically and PTs within SOC were presented by descending order of the total frequencies.

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.

Source: ISS IA2, Table 14.3.2.6.1

Treatment-related Adverse Events

Table 49: Treatment-Related Adverse Events Reported in ≥ 10% of Participants in Selected ISS Populations[1] by System Organ Class[2] and Preferred Term

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any Treatment-Related TEAEs	260 (97.0%)	217 (87.1%)	671 (97.5%)	1034 (97.3%)
Blood and lymphatic system disorders	218 (81.3%)	157 (63.1%)	539 (78.3%)	790 (74.3%)
Neutropenia	188 (70.1%)	134 (53.8%)	462 (67.2%)	647 (60.9%)
Anaemia	91 (34.0%)	62 (24.9%)	252 (36.6%)	374 (35.2%)
Leukopenia	37 (13.8%)	23 (9.2%)	115 (16.7%)	191 (18.0%)
Lymphopenia	31 (11.6%)	25 (10.0%)	70 (10.2%)	98 (9.2%)
Thrombocytopenia	17 (6.3%)	41 (16.5%)	52 (7.6%)	77 (7.2%)
Gastrointestinal disorders	229 (85.4%)	135 (54.2%)	588 (85.5%)	899 (84.6%)
Nausea	148 (55.2%)	77 (30.9%)	397 (57.7%)	629 (59.2%)

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Diarrhoea	152 (56.7%)	42 (16.9%)	391 (56.8%)	621 (58.4%)
Vomiting	51 (19.0%)	30 (12.0%)	200 (29.1%)	321 (30.2%)
Constipation	50 (18.7%)	36 (14.5%)	131 (19.0%)	191 (18.0%)
Abdominal pain	34 (12.7%)	17 (6.8%)	82 (11.9%)	127 (11.9%)
General disorders and administration site conditions	168 (62.7%)	130 (52.2%)	427 (62.1%)	651 (61.2%)
Fatigue	101 (37.7%)	73 (29.3%)	297 (43.2%)	476 (44.8%)
Asthenia	53 (19.8%)	37 (14.9%)	90 (13.1%)	120 (11.3%)
Investigations	44 (16.4%)	54 (21.7%)	144 (20.9%)	236 (22.2%)
Aspartate aminotransferase increased	11 (4.1%)	28 (11.2%)	36 (5.2%)	51 (4.8%)
Metabolism and nutrition disorders	69 (25.7%)	48 (19.3%)	237 (34.4%)	433 (40.7%)
Decreased appetite	42 (15.7%)	34 (13.7%)	140 (20.3%)	256 (24.1%)
Skin and subcutaneous tissue disorders	148 (55.2%)	73 (29.3%)	383 (55.7%)	589 (55.4%)
Alopecia	123 (45.9%)	41 (16.5%)	304 (44.2%)	462 (43.5%)

AE = adverse event; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

[2] This table presents only those PTs that occurred in ≥ 10% of participants in the ISS groups shown. In the source table, the frequencies of the SOCs are based on all PTs under the SOC, not only the PTs of treatment-related AEs reported in ≥ 10% of participants.

Denominator for percentages was big N.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Treatment-related is defined as events reported as "Possibly Related," "Related," or missing; "Unlikely Related" or "Not Related" is not included.

Multiple adverse events are counted only once per participant for each SOC and PT. MedDRA Version 25.0 was used for coding.

System organ classes were presented alphabetically and PTs within SOC were presented by descending order of the total frequencies.

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.

Treatment-related Grade ≥3 Adverse Events

Table 50:Grade 3 or Higher Treatment-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (excerpt from ISS)

System Organ Class Preferred Term	IMMU-132-01 HR+/HER2- mBC (N=54)	IMMU-132-09 SG Treated (N=268)	IMMU-132-09 TPC (N=249)	Overall Targeted HR+/HER2- mBC (N=322)	Overall Targeted mBC (N=688)	All Treated SG(10 mg/kg) (N=1063)
Subjects with Any Grade 3 or Higher Treatment-Related Treatment-Emergent Serious Adverse Events	7 (13.0%)	32 (11.9%)	23 (9.2%)	39 (12.1%)	93 (13.5%)	161 (15.1%)
Blood and lymphatic system disorders	3 (5.6%)	20 (7.5%)	14 (5.6%)	23 (7.1%)	55 (8.0%)	82 (7.7%)
Febrile neutropenia	2 (3.7%)	11 (4.1%)	10 (4.0%)	13 (4.0%)	33 (4.8%)	52 (4.9%)
Neutropenia	1 (1.9%)	7 (2.6%)	2 (0.8%)	8 (2.5%)	17 (2.5%)	24 (2.3%)
Anaemia	0	2 (0.7%)	0	2 (0.6%)	6 (0.9%)	8 (0.8%)
Thrombocytopenia	0	1 (0.4%)	1 (0.4%)	1 (0.3%)	3 (0.4%)	5 (0.5%)
Leukopenia	0	1 (0.4%)	0	1 (0.3%)	2 (0.3%)	3 (0.3%)
Lymphopenia	0	0	0	0	1 (0.1%)	1 (<0.1%)
Thrombocytosis	0	0	1 (0.4%)	0	0	0
Cardiac disorders	0	0	0	0	0	1 (<0.1%)
Cardiac arrest	0	0	0	0	0	1 (<0.1%)
Gastrointestinal disorders	2 (3.7%)	18 (6.7%)	5 (2.0%)	20 (6.2%)	36 (5.2%)	65 (6.1%)
Diarrhoea	1 (1.9%)	9 (3.4%)	1 (0.4%)	10 (3.1%)	19 (2.8%)	33 (3.1%)
Nausea	1 (1.9%)	2 (0.7%)	4 (1.6%)	3 (0.9%)	6 (0.9%)	9 (0.8%)
Neutropenic colitis	0	5 (1.9%)	0	5 (1.6%)	6 (0.9%)	9 (0.8%)
Colitis	0	3 (1.1%)	0	3 (0.9%)	4 (0.6%)	9 (0.8%)
Vomiting	1 (1.9%)	1 (0.4%)	2 (0.8%)	2 (0.6%)	5 (0.7%)	8 (0.8%)
Stomatitis	0	1 (0.4%)	0	1 (0.3%)	1 (0.1%)	2 (0.2%)

Denominator for percentages was big N.
Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.
Treatment-related is defined as events reported as 'Possibly Related', 'Related' or missing; 'Unlikely Related' or 'Not Related' is not included.
Multiple adverse events are counted only once per subject for each SOC and PT. MedDRA Version 25.0 was used for coding.
SOCs were presented alphabetically and PTs within SOC were presented by descending order of the total frequencies.
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.

Serious adverse event/death/other significant events

Serious Adverse Events (SAEs)

Table 51: Serious Adverse Events in ≥ 1% of the Participants in Selected ISS Populations[1] by System Organ Class[2] and Preferred Term

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any Treatment-Emergent SAEs	74 (27.6%)	48 (19.3%)	195 (28.3%)	366 (34.4%)
Blood and lymphatic system disorders	21 (7.8%)	15 (6.0%)	57 (8.3%)	89 (8.4%)
Febrile neutropenia	11 (4.1%)	10 (4.0%)	33 (4.8%)	53 (5.0%)
Neutropenia	8 (3.0%)	2 (0.8%)	18 (2.6%)	26 (2.4%)
Anaemia	2 (0.7%)	1 (0.4%)	7 (1.0%)	12 (1.1%)
Gastrointestinal disorders	30 (11.2%)	9 (3.6%)	60 (8.7%)	117 (11.0%)
Diarrhoea	13 (4.9%)	1 (0.4%)	27 (3.9%)	44 (4.1%)
Vomiting	5 (1.9%)	2 (0.8%)	13 (1.9%)	18 (1.7%)
Abdominal pain	6 (2.2%)	0	10 (1.5%)	15 (1.4%)
Nausea	2 (0.7%)	5 (2.0%)	8 (1.2%)	14 (1.3%)

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Colitis	4 (1.5%)	1 (0.4%)	6 (0.9%)	11 (1.0%)
Neutropenic colitis	5 (1.9%)	0	6 (0.9%)	9 (0.8%)
General disorders and administration site conditions	7 (2.6%)	5 (2.0%)	23 (3.3%)	39 (3.7%)
Pyrexia	3 (1.1%)	2 (0.8%)	7 (1.0%)	12 (1.1%)
Infections and infestations	25 (9.3%)	11 (4.4%)	57 (8.3%)	105 (9.9%)
Pneumonia	4 (1.5%)	5 (2.0%)	14 (2.0%)	26 (2.4%)
Urinary tract infection	3 (1.1%)	2 (0.8%)	6 (0.9%)	16 (1.5%)
Sepsis	3 (1.1%)	1 (0.4%)	6 (0.9%)	12 (1.1%)
Musculoskeletal and connective tissue disorders	2 (0.7%)	4 (1.6%)	6 (0.9%)	13 (1.2%)
Back pain	0	3 (1.2%)	1 (0.1%)	5 (0.5%)
Nervous system disorders	3 (1.1%)	3 (1.2%)	6 (0.9%)	16 (1.5%)
Hypoaesthesia	0	0	1 (0.1%)	1 (< 0.1%)
Psychiatric disorders	1 (0.4%)	2 (0.8%)	4 (0.6%)	11 (1.0%)
Mental status changes	0	0	2 (0.3%)	4 (0.4%)
Renal and urinary disorders	4 (1.5%)	2 (0.8%)	6 (0.9%)	20 (1.9%)
Acute kidney injury	3 (1.1%)	1 (0.4%)	4 (0.6%)	10 (0.9%)
Respiratory, thoracic, and mediastinal disorders	7 (2.6%)	7 (2.8%)	32 (4.7%)	56 (5.3%)
Dyspnoea	2 (0.7%)	4 (1.6%)	9 (1.3%)	16 (1.5%)
Pleural effusion	2 (0.7%)	2 (0.8%)	7 (1.0%)	10 (0.9%)

Deaths

Table 52: Summary of Deaths

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Overall Number of Deaths	188 (70.1%)	183 (73.5%)	521 (75.7%)	812 (76.4%)
Primary Cause of Death				
Progressive Disease	170 (63.4%)	165 (66.3%)	482 (70.1%)	738 (69.4%)
Adverse Event	8 (3.0%)	0	12 (1.7%)	28 (2.6%)
Other[2]	10 (3.7%)[3]	18 (7.2%)[4]	26 (3.8%)	42 (4.0%)
Missing	0	0	1 (0.1%)	4 (0.4%)
Number of Deaths within 30 Days of Last Dose of Study Drug	18 (6.7%)	8 (3.2%)	43 (6.3%)	80 (7.5%)
Primary Cause of Death				
Progressive Disease	12 (4.5%)	8 (3.2%)	34 (4.9%)	54 (5.1%)
Adverse Event	6 (2.2%)	0	8 (1.2%)	22 (2.1%)
Other[2]	0	0	1 (0.1%)	3 (0.3%)
Missing	0	0	0	1 (< 0.1%)

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Number of Deaths > 30 Days of Last Dose of Study Drug	170 (63.4%)	175 (70.3%)	478 (69.5%)	732 (68.9%)
Primary Cause of Death				
Progressive Disease	158 (59.0%)	157 (63.1%)	448 (65.1%)	684 (64.3%)
Adverse Event	2 (0.7%)	0	4 (0.6%)	6 (0.6%)
Other[2]	10 (3.7%)	18 (7.2%)	25 (3.6%)	39 (3.7%)
Missing	0	0	1 (0.1%)	3 (0.3%)
Treatment-related TEAE Leading to Death	1 (0.4%)	0	1 (0.1%)	3 (0.3%)

HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; PT = preferred term; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

[2] "Other" was selected when the cause of death was neither PD nor reported as an AE per study protocol.

[3] "Other" cause of death was reported as follows: Unknown for 6 participants (183, 308, 411, 445, 488, and 570 days after last dose of SG); "medical records" for 1 participant (181 days after last dose of SG); "cause of death not specified in source" for 1 participant (366 days after last dose of SG); "cerebrovascular accident" for 1 participant (516 days after last dose of SG); and "acute respiratory failure" for 1 participant (318 days after last dose of SG)

[4] "Other" cause of death was reported as follows: Unknown for 11 participants (117, 125, 126, 147, 195, 318, 324, 349, 417, 723, and 917 days after last dose of TPC); Unknown (determined through public record search) for 2 participants (45 and 668 days after last dose of TPC); "cause of death is unknown due to participant withdrawing consent" for 1 participant (146 days after last dose of TPC); viral pneumonia/respiratory failure complicated by metastatic carcinoma for 1 participant (72 days after last dose of TPC); "failure to thrive" for 1 participant (57 days after last dose of TPC); "subdural hematoma" for 1 participant (175 days after last dose of TPC); and "respiratory distress (probable lung infection)" for 1 participant (54 days after the last dose of TPC).

Table 53: Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs Leading to Death	6 (2.2%)	0	8 (1.2%)	21 (2.0%)
Cardiac disorders	1 (0.4%)	0	1 (0.1%)	1 (< 0.1%)
Arrhythmia	1 (0.4%)	0	1 (0.1%)	1 (< 0.1%)
Infections and infestations	3 (1.1%)	0	3 (0.4%)	7 (0.7%)
Pneumonia	1 (0.4%)[2]	0	1 (0.1%)	2 (0.2%)
COVID-19 pneumonia	1 (0.4%)[2]	0	1 (0.1%)	1 (< 0.1%)
Septic shock	1 (0.4%)[3]	0	1 (0.1%)	1 (< 0.1%)
Enterocolitis infectious	0	0	0	1 (< 0.1%)
Pneumonia aspiration	0	0	0	1 (< 0.1%)

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Sepsis	0	0	0	1 (< 0.1%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0	0	1 (0.1%)	2 (0.2%)
Metastases to spine	0	0	1 (0.1%)	1 (< 0.1%)
Metastases to central nervous system	0	0	0	1 (< 0.1%)
Nervous system disorders	1 (0.4%)	0	1 (0.1%)	1 (< 0.1%)
Nervous system disorder	1 (0.4%)	0	1 (0.1%)	1 (< 0.1%)
Psychiatric disorders	0	0	0	1 (< 0.1%)
Completed suicide	0	0	0	1 (< 0.1%)
Respiratory, thoracic, and mediastinal disorders	1 (0.4%)	0	2 (0.3%)	9 (0.8%)
Pulmonary embolism	1 (0.4%)	0	1 (0.1%)	2 (0.2%)
Respiratory failure	0	0	1 (0.1%)	4 (0.4%)
Epistaxis	0	0	0	1 (< 0.1%)
Hypoxia	0	0	0	1 (< 0.1%)
Respiratory distress	0	0	0	1 (< 0.1%)

AE = adverse event; 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; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not included in the table.

[2] Participants with these AEs leading to death in the infections and infestations SOC were not neutropenic at event onset.

[3] One participant experienced a treatment-related AE leading to death of septic shock due to neutropenic colitis with large intestine perforation.

Denominator for percentages was big N.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Multiple adverse events are counted only once per participant for each SOC and PT. MedDRA Version 25.0 was used for coding.

System organ classes were presented alphabetically and PTs within SOC were presented by descending order of the total frequencies.

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.

Table 54: IMMU-132-09: Participants in the SG Group With Adverse Events Leading to Death (Safety Population)

Age / Sex UGT1A1 Genotype	Last Dose Day[1]	Relationship to Study Drug	AE Preferred Term[2]	AE Start Day[1]	Disease Progression Contributory Per Investigator (Yes/No)
72 / F UGT1A1*1/*28	8	Possibly related	Septic shock[3]	14	No
65 / F UGT1A1*1/*28	1	Not related	Arrhythmia	7	Yes

Age / Sex UGT1A1 Genotype	Last Dose Day[1]	Relationship to Study Drug	AE Preferred Term[2]	AE Start Day[1]	Disease Progression Contributory Per Investigator (Yes/No)
51 / F UGT1A1*1/*28	337	Unlikely related	Pulmonary embolism	342	No
71 / F UGT1A1*1/*1	365	Not related	COVID-19 pneumonia [4]	395	No
65 / F UGT1A1*1/*28	121	Not related	Pneumonia[4]	131	No
67 / F UGT1A1*28/*28	1	Unlikely related	Nervous system disorder	11	No
84 / F Unknown	167	Not related	Sepsis[4]	201	No
57 / F UGT1A1*1/*28	245	Not related	Respiratory failure	276	Yes[5]

AE = adverse event; COVID-19 = coronavirus disease 2019; F = female; ID = identifier; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; SG = sacituzumab govitecan; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

[1] Relative to the day of the first dose of study treatment.

[2] MedDRA Version 25.0 was used for coding AEs.

[3] The participant experienced a treatment-related AE leading to death of septic shock due to neutropenic colitis with large intestine perforation.

[4] Participants with these AEs leading to death in the infections and infestations SOC were not neutropenic at event onset.

[5] Additional case event details provided by the investigator stated that disease progression was considered as contributory to the death of this participant.

Source: IMMU-132-09 Primary, Listings 16.2.4.6, 16.2.8.1, 16.2.8.9, and 16.2.8.10

Other significant events - Adverse Events of Special Interest (AESI)

Table 55: Definition of Adverse Events of Special Interest

Adverse Event of Special Interest	Definition
Diarrhea	Preferred term: diarrhoea
Neutropenia+	Preferred terms: neutropenia, neutrophil count decreased, and febrile neutropenia
Febrile neutropenia	Preferred term: febrile neutropenia
Infections+	SOC: infections and infestations
Neuropathy+	Preferred terms: gait disturbance, hypoaesthesia, muscular weakness, neuropathy peripheral, paraesthesia, and peripheral sensory neuropathy
Hypersensitivity+[1]	Hypersensitivity SMQ (broad and narrow) and Anaphylactic reaction SMQ (broad and narrow)
Pulmonary events+	Interstitial lung disease SMQ (narrow)

MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Query; SOC = system organ class

\+ Grouped adverse event terms.

[1] For the category of Hypersensitivity+, only events where onset dates are on the day of or 1 day after study drug administration are included.

All definitions based on MedDRA Version 25.0.

Source: ISS SAP, Table 3-1

Table 56: Incidence of Adverse Events of Special Interest

AESI	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Diarrhea	166 (61.9%)	57 (22.9%)	430 (62.5%)	681 (64.1%)
Neutropenia+	195 (72.8%)	138 (55.4%)	476 (69.2%)	675 (63.5%)
Febrile neutropenia	16 (6.0%)	11 (4.4%)	42 (6.1%)	68 (6.4%)
Infections+	101 (37.7%)	67 (26.9%)	322 (46.8%)	495 (46.6%)
Neuropathy+	44 (16.4%)	62 (24.9%)	123 (17.9%)	184 (17.3%)
Hypersensitivity+[2]	71 (26.5%)	48 (19.3%)	227 (33.0%)	369 (34.7%)
Pulmonary events+	0	2 (0.8%)	3 (0.4%)	6 (0.6%)

AE = adverse event; AESI = adverse event of special interest; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TPC = treatment of physician's choice

\+ Grouped adverse event terms.

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

[2] For the category of Hypersensitivity+, only events where onset dates are on the day of or 1 day after an infusion are included.

Denominator for percentages was big N.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Multiple adverse events are counted only once per participant for each SOC and PT. MedDRA Version 25.0 was used for coding.

System organ classes were presented alphabetically and PTs within SOC were presented by descending order of the total frequencies.

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.

Source: ISS IA2, Table 14.3.2.10.2.1

Diarrhoea

Adverse Events of Diarrhoea

Adverse events and treatment-related AEs of diarrhoea occurred in a higher percentage of participants in the SG group (61.9% and 56.7% of participants, respectively) than in the TPC group (22.9% and 16.9% of participants, respectively) in Study IMMU-132-09. One participant (0.4%) discontinued SG treatment in Study IMMU-132-09 because of diarrhoea (Table 57).

The percentage of participants with diarrhoea was generally similar in participants across the Overall Targeted HR+/HER2– mBC, Overall Targeted mBC, and All Treated SG pools.

Table 57: Adverse Events of Special Interest: Diarrhoea

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs	166 (61.9%)	57 (22.9%)	430 (62.5%)	681 (64.1%)
Grade 3 or higher	27 (10.1%)	3 (1.2%)	71 (10.3%)	112 (10.5%)
Participants with Treatment-related TEAEs	152 (56.7%)	42 (16.9%)	391 (56.8%)	621 (58.4%)
Participants with Treatment-emergent SAEs	13 (4.9%)	1 (0.4%)	27 (3.9%)	44 (4.1%)
Participants with Treatment-related Treatment-emergent SAEs	12 (4.5%)	1 (0.4%)	25 (3.6%)	40 (3.8%)

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
TEAEs Leading to Study Drug Interruption	8 (3.0%)	3 (1.2%)	25 (3.6%)	37 (3.5%)
TEAEs Leading to Study Drug Dose Reduction	21 (7.8%)	0	34/526 (6.5%)	49/661 (7.4%)
TEAEs Leading to Study Drug Withdrawal/Discontinuation	1 (0.4%)	0	3 (0.4%)	6 (0.6%)
Participants with TEAEs Leading to Death	0	0	0	0
Participants with Treatment-related TEAEs Leading to Death	0	0	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

Denominator for percentages was big N.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Treatment-related is defined as events reported as "Possibly Related," "Related," or missing; "Unlikely Related" or "Not Related" is not included.

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

Adverse events leading to study drug dose reduction were not collected in IMMU-132-01, therefore IMMU-132-01 participants were excluded from denominator for percentages of TEAEs leading to study drug dose reduction.

See definitions of AEs of special interest in the statistical analysis plan, clinical study report, and/or Summary of Clinical Safety.

Source: ISS IA2, Table 14.3.2.10.1.1

Time to Onset and Duration of Diarrhoea

Median time to onset of the first event of diarrhoea was shorter in the SG group versus the TPC group (15 vs 38 days, respectively), and the median time to onset of the first event of Grade 3 or higher diarrhoea was shorter in the SG group compared with the TPC group (16 versus 28 days, respectively) in Study IMMU-132-09.

The median time to first onset, median duration of diarrhoea, and Grade 3 or higher diarrhoea were similar in the individual Study IMMU-132-01 HR+/HER2− mBC group, the Overall Targeted HR+/HER2− mBC pool, and the broader Overall Targeted mBC and All Treated SG pools.

Management of Diarrhoea

In Study IMMU-132-09, a higher percentage of participants in the SG group (88.6%, 109 participants) compared with the TPC group (81.8%, 18 participants) received antidiarrheal medication. In the SG group, 1 participant (0.8%), who was on antidiarrheal medication, permanently discontinued study drug due to diarrhoea. For participants in the SG group receiving antidiarrheal medication, 6 participants (4.9%) experienced diarrhoea events leading to study drug interruption and 21 participants (17.1%) experienced diarrhoea events leading to study drug dose reduction. Demographic characteristics and prior systemic anticancer therapy were similar in participants who used antidiarrheal medications and participants who did not use antidiarrheal medications.

Neutropenia

Adverse Events of Neutropenia

Table 58: Adverse Events of Special Interest: Neutropenia

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)

Participants with Any TEAEs	195 (72.8%)	138 (55.4%)	476 (69.2%)	675 (63.5%)
Grade 3 or higher	147 (54.9%)	99 (39.8%)	366 (53.2%)	518 (48.7%)
Participants with Treatment-related TEAEs	193 (72.0%)	136 (54.6%)	472 (68.6%)	667 (62.7%)
Participants with Treatment-emergent SAEs	19 (7.1%)	12 (4.8%)	50 (7.3%)	77 (7.2%)
Participants with Treatment-related Treatment-emergent SAEs	19 (7.1%)	12 (4.8%)	50 (7.3%)	75 (7.1%)
TEAEs Leading to Study Drug Interruption	135 (50.4%)	63 (25.3%)	309 (44.9%)	416 (39.1%)
TEAEs Leading to Study Drug Dose Reduction	48 (17.9%)	47 (18.9%)	76/526 (14.4%)	95/661 (14.4%)
TEAEs Leading to Study Drug Withdrawal/Discontinuation	2 (0.7%)	0	3 (0.4%)	9 (0.8%)
Participants with TEAEs Leading to Death	0	0	0	0
Participants with Treatment-related TEAEs Leading to Death	0	0	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

\+ Grouped adverse event term.

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

Denominator for percentages was big N.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Treatment-related is defined as events reported as "Possibly Related," "Related," or missing; "Unlikely Related" or "Not Related" is not included.

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

Adverse events leading to study drug dose reduction were not collected in IMMU-132-01, therefore IMMU-132-01 participants were excluded from denominator for percentages of TEAEs leading to study drug dose reduction.

See definitions of AEs special interest in the statistical analysis plan, clinical study report, and/or Summary of Clinical Safety.

Source: ISS IA2, Table 14.3.2.10.1.1

Time to Onset and Duration of Neutropenia+

Median time to onset of the first event of neutropenia+ in the SG and TPC groups in Study IMMU-132-09 was 19 and 15 days, respectively, and the median time to onset of the first event of Grade 3 or higher neutropenia+ was 16 and 15 days, respectively.

The median time to first onset and duration of TEAEs and treatment-related TEAEs of neutropenia+ and Grade 3 or higher neutropenia+ were similar across individual Study IMMU-132-01 HR+/HER2− mBC group, Overall Targeted HR+/HER− mBC pool, and the broader Overall Targeted mBC and All Treated SG pools.

Management of Neutropenia+

G-CSF use at any time during the study includes participants with at least 1 G-CSF medication taken before the first dose date and ongoing while on treatment, or G-CSF medications taken on or after the first dose date and up to 30 days after the last dose. G-CSF initiation is defined as the start date of G-CSF administration between the first study drug dose date up to 30 days after the last study drug dose date.

The number of participants with G-CSF use and G-CSF initiation at any time during the study was higher in the SG group compared with the TPC group in Study IMMU-132-09 (G-CSF use: 54.1% vs 34.1%, respectively; G-CSF initiation: 53.7% vs 33.7%, respectively). In the SG group, 32.8% and 31.7% of participants used and initiated G-CSF in Cycle 1, respectively, compared with 18.9% and 18.5% in the TPC group, respectively, in Study IMMU-132-09.

The percentage of participants who received G-CSF as prophylaxis at any time during the study was higher in the SG group compared with the TPC group (35.4% vs 21.7%, respectively) (ISS IA2, Table 14.1.5.4). The majority of participants in the SG and TPC groups with Grade 3 or higher neutropenia+ initiated G-CSF in Cycle 1.

Febrile Neutropenia

Adverse Events of Febrile Neutropenia

Table 59: Adverse Events of Special Interest: Febrile Neutropenia

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs	16 (6.0%)	11 (4.4%)	42 (6.1%)	68 (6.4%)
Grade 3 or higher	16 (6.0%)	11 (4.4%)	42 (6.1%)	67 (6.3%)
Participants with Treatment-related TEAEs	14 (5.2%)	11 (4.4%)	40 (5.8%)	65 (6.1%)
Participants with Treatment-emergent SAEs	11 (4.1%)	10 (4.0%)	33 (4.8%)	53 (5.0%)
Participants with Treatment-related Treatment-emergent SAEs	11 (4.1%)	10 (4.0%)	33 (4.8%)	52 (4.9%)
TEAEs Leading to Study Drug Interruption	1 (0.4%)	5 (2.0%)	10 (1.5%)	17 (1.6%)
TEAEs Leading to Study Drug Dose Reduction	8 (3.0%)	3 (1.2%)	15/526 (2.9%)	19/661 (2.9%)
TEAEs Leading to Study Drug Withdrawal/Discontinuation	0	0	0	3 (0.3%)
Participants with TEAEs Leading to Death	0	0	0	0
Participants with Treatment-related TEAEs Leading to Death	0	0	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

Denominator for percentages was big N.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Treatment-related is defined as events reported as 'Possibly Related', 'Related' or missing; 'Unlikely Related' or 'Not Related' is not included.

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

Adverse events leading to study drug dose reduction were not collected in IMMU-132-01, therefore IMMU-132-01 participants were excluded from denominator for percentages of TEAEs leading to study drug dose reduction.

See definitions of AEs special interest in the statistical analysis plan, CSR, and/or Summary of Clinical Safety.

Source: ISS IA2, Table 14.3.2.10.1.1

Time to Onset and Duration of Febrile Neutropenia

Median time to onset of the first event of febrile neutropenia in the SG and TPC groups in Study IMMU-132-09 was 30 and 17 days, respectively, and the median time to onset of the first event of Grade 3 or higher febrile neutropenia was also 30 and 17 days, respectively.

Management of Febrile Neutropenia

The percentage of participants with febrile neutropenia who had G-CSF initiation at any time during Study IMMU-132-09 was higher in the SG group compared with the TPC group (81.3% vs 63.6%, respectively).

Infections

Adverse Events of Infections

Table 60: Adverse Events of Special Interest: Infections

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs	101 (37.7%)	67 (26.9%)	322 (46.8%)	495 (46.6%)
Grade 3 or higher	26 (9.7%)	12 (4.8%)	67 (9.7%)	129 (12.1%)
Participants with Treatment-related TEAEs	32 (11.9%)	21 (8.4%)	95 (13.8%)	151 (14.2%)
Participants with Treatment-emergent SAEs	25 (9.3%)	11 (4.4%)	57 (8.3%)	105 (9.9%)
Participants with Treatment-related Treatment-emergent SAEs	8 (3.0%)	2 (0.8%)	22 (3.2%)	40 (3.8%)
TEAEs Leading to Study Drug Interruption	26 (9.7%)	11 (4.4%)	66 (9.6%)	103 (9.7%)
TEAEs Leading to Study Drug Dose Reduction	2 (0.7%)	1 (0.4%)	4/526 (0.8%)	9/661 (1.4%)
TEAEs Leading to Study Drug Withdrawal/Discontinuation	3 (1.1%)	1 (0.4%)	6 (0.9%)	11 (1.0%)
Participants with TEAEs Leading to Death	3 (1.1%)	0	3 (0.4%)	7 (0.7%)
Participants with Treatment-related TEAEs Leading to Death	1 (0.4%)	0	1 (0.1%)	3 (0.3%)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

\+ Grouped adverse event term.

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

Denominator for percentages was big N.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Treatment-related is defined as events reported as "Possibly Related," "Related," or missing; "Unlikely Related" or "Not Related" is not included.

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

Adverse events leading to study drug dose reduction were not collected in IMMU-132-01, therefore IMMU-132-01 participants were excluded from denominator for percentages of TEAEs leading to study drug dose reduction.

See definitions of AEs of special interest in the statistical analysis plan, clinical study report, and/or Summary of Clinical Safety.

Source: ISS IA2, Table 14.3.2.10.1.1

Neuropathy

Adverse Events of Neuropathy

Table 61: Adverse Events of Special Interest: Neuropathy

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs	44 (16.4%)	62 (24.9%)	123 (17.9%)	184 (17.3%)
Grade 3 or higher	7 (2.6%)	9 (3.6%)	8 (1.2%)	10 (0.9%)
Participants with Treatment-related TEAEs	24 (9.0%)	39 (15.7%)	59 (8.6%)	85 (8.0%)
Participants with Treatment-emergent SAEs	1 (0.4%)	1 (0.4%)	2 (0.3%)	4 (0.4%)

Participants with Treatment-related Treatment-emergent SAEs	1 (0.4%)	0	1 (0.1%)	1 (< 0.1%)
TEAEs Leading to Study Drug Interruption	1 (0.4%)	4 (1.6%)	5 (0.7%)	9 (0.8%)
TEAEs Leading to Study Drug Dose Reduction	1 (0.4%)	11 (4.4%)	1/526 (0.2%)	1/661 (0.2%)
TEAEs Leading to Study Drug Withdrawal/Discontinuation	1 (0.4%)	1 (0.4%)	1 (0.1%)	1 (< 0.1%)
Participants with TEAEs Leading to Death	0	0	0	0
Participants with Treatment-related TEAEs Leading to Death	0	0	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

\+ Grouped adverse event term.

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

Denominator for percentages was big N.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Treatment-related is defined as events reported as "Possibly Related," "Related," or missing; "Unlikely Related" or "Not Related" is not included.

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

Adverse events leading to study drug dose reduction were not collected in IMMU-132-01, therefore IMMU-132-01 participants were excluded from denominator for percentages of TEAEs leading to study drug dose reduction.

See definitions of AEs of special interest in the statistical analysis plan, clinical study report, and/or Summary of Clinical Safety.

Time to Onset and Duration of Neuropathy

Median time to onset of the first event of neuropathy+ was longer in the SG group than in the TPC group in Study IMMU-132-09 (85 and 50 days, respectively), and the median time to onset of the first event of Grade 3 or higher neuropathy was similar in the SG group versus the TPC group (86 vs 85 days, respectively).

Hypersensitivity

Adverse Events of Hypersensitivity

Table 62: Adverse Events of Special Interest: Hypersensitivity+ (IMMU-132-09 ISS Populations[1])

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs	71 (26.5%)	48 (19.3%)	227 (33.0%)	369 (34.7%)
Grade 3 or higher	4 (1.5%)	2 (0.8%)	12 (1.7%)	17 (1.6%)
Participants with Treatment-related TEAEs	44 (16.4%)	26 (10.4%)	134 (19.5%)	201 (18.9%)
Participants with Treatment-emergent SAEs	1 (0.4%)	1 (0.4%)	3 (0.4%)	5 (0.5%)
Participants with Treatment-related Treatment-emergent SAEs	0	0	1 (0.1%)	2 (0.2%)
TEAEs Leading to Study Drug Interruption	2 (0.7%)	1 (0.4%)	7 (1.0%)	13 (1.2%)
TEAEs Leading to Study Drug Dose Reduction	0	3 (1.2%)	0/526 (0.0%)	0/661 (0.0%)

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
TEAEs Leading to Study Drug Withdrawal/Discontinuation	0	0	1 (0.1%)	2 (0.2%)
Participants with TEAEs Leading to Death	0	0	0	0
Participants with Treatment-related TEAEs Leading to Death	0	0	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

\+ Grouped adverse event term.

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

Denominator for percentages was big N.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Treatment-related is defined as events reported as "Possibly Related," "Related," or missing; "Unlikely Related" or "Not Related" is not included.

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

Adverse events leading to study drug dose reduction were not collected in IMMU-132-01, therefore IMMU-132-01 participants were excluded from denominator for percentages of TEAEs leading to study drug dose reduction.

See definitions of AEs of special interest in the statistical analysis plan, clinical study report, and/or Summary of Clinical Safety.

Source: ISS IA2, Table 14.3.2.10.1.1

Time to Onset and Duration of Hypersensitivity

Median time to onset of the first event of hypersensitivity was longer in the SG and TPC groups in Study IMMU-132-09 (29 and 19 days, respectively), and the median time to onset of the first event of Grade 3 or higher hypersensitivity was also longer in the SG group versus the TPC group (51 vs 26 days).

Pulmonary Events

Adverse Events of Pulmonary Events

Table 63: Adverse Events of Special Interest: Pulmonary Events

	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs	0	2 (0.8%)	3 (0.4%)	6 (0.6%)
Grade 3 or higher	0	1 (0.4%)	1 (0.1%)	2 (0.2%)
Participants with Treatment-related TEAEs	0	2 (0.8%)	2 (0.3%)	4 (0.4%)
Participants with Treatment-emergent SAEs	0	0	1 (0.1%)	3 (0.3%)
Participants with Treatment-related Treatment-emergent SAEs	0	0	1 (0.1%)	3 (0.3%)
TEAEs Leading to Study Drug Interruption	0	0	0	1 (< 0.1%)
TEAEs Leading to Study Drug Dose Reduction	0	0	0/526 (0.0%)	0/661 (0.0%)
TEAEs Leading to Study Drug Withdrawal/Discontinuation	0	1 (0.4%)	1 (0.1%)	2 (0.2%)
Participants with TEAEs Leading to Death	0	0	0	0
Participants with Treatment-related TEAEs Leading to Death	0	0	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

\+ Grouped adverse event term.

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

Denominator for percentages was big N.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Treatment-related is defined as events reported as "Possibly Related," "Related," or missing; "Unlikely Related" or "Not Related" is not included.

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

Adverse events leading to study drug dose reduction were not collected in IMMU-132-01, therefore IMMU-132-01 participants were excluded from denominator for percentages of TEAEs leading to study drug dose reduction.

See definitions of AEs of special interest in the statistical analysis plan, clinical study report, and/or Summary of Clinical Safety.

Source: ISS IA2, Table 14.3.2.10.1.1

Laboratory findings

Table 64: Grade 3 or 4 Treatment-Emergent Haematology Laboratory Abnormalities

Maximum Postbaseline Toxicity Grade	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Hematology				
Hemoglobin (Anemia)	265	241	680	1048
Grade 3 or 4	20 (7.5%)	12 (5.0%)	56 (8.2%)	101 (9.6%)
Grade 3	20 (7.5%)	12 (5.0%)	56 (8.2%)	101 (9.6%)
Hemoglobin (Increased)	265	241	680	1048
Grade 3 or 4	3 (1.1%)	0	3 (0.4%)	3 (0.3%)
Grade 3	3 (1.1%)	0	3 (0.4%)	3 (0.3%)
Leukocytes (Decreased)	265	241	680	1048
Grade 3 or 4	101 (38.1%)	62 (25.7%)	247 (36.3%)	335 (32.0%)
Grade 3	69 (26.0%)	51 (21.2%)	193 (28.4%)	258 (24.6%)
Grade 4	32 (12.1%)	11 (4.6%)	54 (7.9%)	77 (7.3%)
Leukocytes (Leukocytosis)	265	241	680	1048
Grade 3 or 4	1 (0.4%)	1 (0.4%)	2 (0.3%)	3 (0.3%)
Grade 3	1 (0.4%)	1 (0.4%)	2 (0.3%)	3 (0.3%)
Lymphocytes (Decreased)	265	241	676	1028
Grade 3 or 4	56 (21.1%)	33 (13.7%)	148 (21.9%)	245 (23.8%)
Grade 3	52 (19.6%)	30 (12.4%)	133 (19.7%)	218 (21.2%)
Grade 4	4 (1.5%)	3 (1.2%)	15 (2.2%)	27 (2.6%)
Lymphocytes (Increased)	265	241	676	1028
Grade 3 or 4	5 (1.9%)	5 (2.1%)	7 (1.0%)	14 (1.4%)
Grade 3	5 (1.9%)	5 (2.1%)	7 (1.0%)	14 (1.4%)
Neutrophils (Decreased)	265	241	679	1046
Grade 3 or 4	139 (52.5%)	97 (40.2%)	315 (46.4%)	427 (40.8%)
Grade 3	84 (31.7%)	65 (27.0%)	201 (29.6%)	268 (25.6%)
Grade 4	55 (20.8%)	32 (13.3%)	114 (16.8%)	159 (15.2%)
Platelets (Decreased)	265	241	680	1048
Grade 3 or 4	5 (1.9%)	9 (3.7%)	17 (2.5%)	38 (3.6%)
Grade 3	2 (0.8%)	4 (1.7%)	5 (0.7%)	12 (1.1%)
Grade 4	3 (1.1%)	5 (2.1%)	12 (1.8%)	26 (2.5%)

CTCAE = Common Terminology Criteria for Adverse Events; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SG = sacituzumab govitecan; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

Severity grades were defined by 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. 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.

Grade 3 or 4 laboratory abnormalities with a frequency of 0 are not shown in this table

Source: ISS IA2, Table 14.3.3.6.2.1

Table 65: Grade 3 or 4 Treatment-Emergent Chemistry and Urinalysis Laboratory Abnormalities (IMMU-132-09 ISS Populations[1])

Maximum Postbaseline Toxicity Grade	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Chemistry				
Alanine Aminotransferase (Increased)	264	237	679	1047
Grade 3 or 4	3 (1.1%)	5 (2.1%)	7 (1.0%)	12 (1.1%)
Grade 3	3 (1.1%)	5 (2.1%)	7 (1.0%)	12 (1.1%)
Albumin (Hypoalbuminemia)	262	236	677	1044
Grade 3 or 4	0	1 (0.4%)	3 (0.4%)	12 (1.1%)
Grade 3	0	1 (0.4%)	3 (0.4%)	12 (1.1%)
Alkaline Phosphatase (Increased)	263	237	678	1046
Grade 3 or 4	0	2 (0.8%)	0	5 (0.5%)
Grade 3	0	2 (0.8%)	0	5 (0.5%)
Aspartate Aminotransferase (Increased)	264	237	679	1047
Grade 3 or 4	4 (1.5%)	3 (1.3%)	9 (1.3%)	15 (1.4%)
Grade 3	4 (1.5%)	3 (1.3%)	9 (1.3%)	15 (1.4%)
Bilirubin (Increased)	264	237	679	1047
Grade 3 or 4	6 (2.3%)	2 (0.8%)	14 (2.1%)	21 (2.0%)
Grade 3	5 (1.9%)	2 (0.8%)	12 (1.8%)	18 (1.7%)
Grade 4	1 (0.4%)	0	2 (0.3%)	3 (0.3%)
Creatinine (Increased)	263	237	678	1046
Grade 3 or 4	1 (0.4%)	4 (1.7%)	3 (0.4%)	17 (1.6%)
Grade 3	1 (0.4%)	3 (1.3%)	2 (0.3%)	9 (0.9%)
Grade 4	0	1 (0.4%)	1 (0.1%)	8 (0.8%)
Creatinine Clearance (Decreased)	263	237	678	1046
Grade 3 or 4	6 (2.3%)	3 (1.3%)	9 (1.3%)	34 (3.3%)
Grade 3	6 (2.3%)	2 (0.8%)	8 (1.2%)	23 (2.2%)
Grade 4	0	1 (0.4%)	1 (0.1%)	11 (1.1%)
Glucose (Hypoglycemia)	262	237	677	1045

Maximum Postbaseline Toxicity Grade	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Grade 3 or 4	3 (1.1%)	2 (0.8%)	8 (1.2%)	17 (1.6%)
Grade 4	3 (1.1%)	2 (0.8%)	8 (1.2%)	17 (1.6%)
Magnesium (Hypermagnesemia)	260	233	675	1043
Grade 3 or 4	0	0	3 (0.4%)	12 (1.2%)
Grade 3	0	0	2 (0.3%)	7 (0.7%)
Grade 4	0	0	1 (0.1%)	5 (0.5%)
Magnesium (Hypomagnesemia)	260	233	675	1043
Grade 3 or 4	2 (0.8%)	0	5 (0.7%)	8 (0.8%)
Grade 3	0	0	2 (0.3%)	2 (0.2%)
Grade 4	2 (0.8%)	0	3 (0.4%)	6 (0.6%)
Potassium (Hyperkalemia)	263	237	678	1046
Grade 3 or 4	5 (1.9%)	0	11 (1.6%)	19 (1.8%)
Grade 3	3 (1.1%)	0	5 (0.7%)	9 (0.9%)
Grade 4	2 (0.8%)	0	6 (0.9%)	10 (1.0%)
Potassium (Hypokalemia)	263	237	678	1046
Grade 3 or 4	11 (4.2%)	1 (0.4%)	28 (4.1%)	36 (3.4%)
Grade 3	10 (3.8%)	1 (0.4%)	27 (4.0%)	34 (3.3%)
Grade 4	1 (0.4%)	0	1 (0.1%)	2 (0.2%)
Sodium (Hypernatremia)	263	237	678	1046
Grade 3 or 4	0	0	3 (0.4%)	5 (0.5%)
Grade 3	0	0	1 (0.1%)	1 (< 0.1%)
Grade 4	0	0	2 (0.3%)	4 (0.4%)
Sodium (Hyponatremia)	263	237	678	1046
Grade 3 or 4	2 (0.8%)	1 (0.4%)	8 (1.2%)	12 (1.1%)
Grade 3	2 (0.8%)	0	4 (0.6%)	4 (0.4%)
Grade 4	0	1 (0.4%)	4 (0.6%)	8 (0.8%)
Urinalysis				
Protein (Proteinuria [Dipstick])	105	66	255	589
Grade 3 or 4	0	0	0	2 (0.3%)
Grade 3	0	0	0	2 (0.3%)

CTCAE = Common Terminology Criteria for Adverse Events; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SG = sacituzumab govitecan; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

Severity grades were defined by 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. 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.

Grade 3 or 4 laboratory abnormalities with a frequency of 0 are not shown in this table

Source: ISS IA2, Table 14.3.3.6.2.1

The majority of participants had at least 1 graded laboratory abnormality; the incidence of laboratory abnormalities was similar in individual Study IMMU 132 09 SG group, Study IMMU 132 01 HR+/HER2− mBC group, and the 3 ISS pooled populations.

In Study IMMU 132 09, the incidence of Grade 3 or 4 laboratory abnormalities was 64.9% (172 participants) in the SG group and 49.2% (119 participants) in the TPC group. The incidence of Grade 4 laboratory abnormalities was 26.0% (69 participants) in the SG group and 18.6% (45 participants) in the TPC group.

The most commonly reported Grade 3 or 4 haematology laboratory abnormalities in both treatment groups were decreased neutrophils (SG: 52.5%; TPC: 40.2%), decreased leukocytes (SG: 38.1%; TPC: 25.7%), and decreased lymphocytes (SG: 21.1%; TPC: 13.7%) in Study IMMU-132-09.

The percentage of SG-treated participants with Grade 3 or 4 laboratory abnormalities was similar in individual Study IMMU 132 09 SG group, Study IMMU 132 01 HR+/HER2− mBC group, and the 3 ISS pooled populations.

Adverse drug reactions

The analysis of safety from the clinical development of Trodelvy for the treatment of hormone receptor-positive (HR+)/human epidermal growth factor receptor 2 negative (HER2−) metastatic breast cancer (mBC) comprised 6 cohorts as presented in the Integrated Analysis of Safety.

CIOMS frequency provided in the List of Adverse Reactions (Table 66) are that of the frequency observed with the larger pooled population of the Overall Targeted mBC sample size (n=688). The crude frequencies of potential adverse drug reactions (ADRs) were based on all events coded to individual Medical Dictionary for Regulatory Activities (MedDRA) preferred terms with the exception of the terms anaemia, dyspnoea, fatigue, hypersensitivity, leukopenia, lymphopenia, neutropenia, neutropenic colitis, and thrombocytopenia. The counting of these ADRs was based on a defined collection of preferred terms with similar medical concept to attempt to provide a complete and inclusive estimate of crude frequency for these ADRs.

To identify potential new ADRs, the same algorithm was applied to the new Overall Targeted HR+/HER2- mBC that was utilized for the initial Trodelvy EU marketing authorization application:

- TEAEs observed in ≥1.0% of participants in the Overall Targeted mBC pooled population (n=688)

and

- with a ≥2.0% higher frequency in the Overall Targeted HR+/HER2− pooled population (N=322) than the treatment of physician's choice (TPC) group (n=249) of IMMU-132-09 TEAEs meeting this algorithm were considered to be a potential ADR for inclusion in the List of Adverse Reactions.

Table 66: Comprehensive List of Adverse Reactions to support Updates to Product Information

MedDRA System organ class	**All severity grades Frequency**	**All severity grades (%) n=~~366~~ 688**	**Severity grade ≥3 (%) n=~~366~~ 688**
Infections and infestations			
Urinary tract infection	Very common	~~15.3~~ 12.9	~~1.1~~ 1.0
Upper respiratory tract infection	Very common	~~13.1~~ 10.0	~~0.3~~ 0.1
Pneumonia	*Common*	*3.8*	*2.3*

MedDRA System organ class	All severity grades Frequency	All severity grades (%) n=~~366~~ 688	Severity grade ≥3 (%) n=~~366~~ 688
Nasopharyngitis	Common	~~5.2~~ 3.8	0.0
Sinusitis	Common	~~4.4~~ 3.2	0.0
Bronchitis	Common	~~3.8~~ 2.3	~~0.3~~ 0.1
Oral Herpes	Common	~~2.5~~ 1.5	0.0
Influenza	Common	~~2.5~~ 1.3	0.3
Sepsis	*Common*	*1.2*	*1.2*
Blood and lymphatic system disorders			
Neutropenia[1]	Very common	~~64.2~~ 67.6	~~49.5~~ 50.7
Anaemia[2]	Very common	~~43.2~~ 40.6	~~10.1~~ 9.3
Leukopenia[3]	Very common	~~19.4~~ 17.2	~~12.0~~ 10.5
Lymphopenia[4]	Very common	~~10.9~~ 11.2	~~2.5~~ 2.9
Thrombocytopenia[5]	*Common*	*8.6*	*1.5*
Febrile neutropenia	Common	~~6.6~~ 6.1	~~6.6~~ 6.1
Immune system disorders			
Hypersensitivity[6]	Very common	~~36.6~~ 33.0	~~1.9~~ 1.7
Metabolism and nutrition disorders			
Decreased appetite	Very common	~~28.1~~ 25.7	~~1.4~~ 1.3
Hypokalaemia	Very common	~~16.7~~ 15.1	2.5
Hypomagnesaemia	Very common	~~15.0~~ 11.9	~~0.3~~ 0.1
Hyperglycaemia	~~Very c~~Common	~~11.7~~ 8.3	~~1.6~~ 0.9
Hypophosphataemia	Common	~~8.7~~ 8.3	~~5.2~~ 4.2
Dehydration	*Common*	*6.3*	*1.6*
Hypocalcaemia	Common	~~7.1~~ 6.1	~~0.8~~ 0.7
Hyponatraemia	*Common*	*3.8*	*1.6*
Psychiatric disorders			
Insomnia	Very common	~~11.7~~ 10.9	0.0
Anxiety	Common	~~6.3~~ 5.5	~~0.3~~ 0.1
Nervous system disorders			
Headache	Very common	~~19.4~~ 18.6	~~0.8~~ 0.6
Dizziness	Very common	~~13.7~~ 12.4	0.0
Dysgeusia	Common	~~9.0~~ 6.8	0.0
Vascular disorders			
Hypotension	*Common*	*3.8*	*0.4*
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	*Very common*	*22.1*	*3.1*
Cough	Very common	~~22.7~~ 19.2	0.0
Epistaxis	Common	~~5.2~~ 6.8	0.0
Rhinorrhoea	Common	~~6.6~~ 5.7	0.0
Nasal congestion	Common	~~6.0~~ 4.9	0.0

MedDRA System organ class	All severity grades Frequency	All severity grades (%) n=~~366~~ 688	Severity grade ≥3 (%) n=~~366~~ 688
~~Dyspnoea exertional~~	~~Common~~	~~4.1~~	~~0.0~~
Productive cough	Common	~~3.8~~ 2.8	0.0
Upper airway cough syndrome	Common	~~2.7~~ 2.2	0.0
Gastrointestinal disorders			
Nausea	Very common	~~64.2~~ 62.6	~~4.1~~ 2.8
Diarrhoea	Very common	~~64.5~~ 62.5	~~10.7~~ 10.3
Constipation	Very common	~~36.3~~ 36.2	~~0.5~~ 0.4
Vomiting	Very common	~~38.0~~ 33.6	~~3.0~~ 2.5
Abdominal pain	Very common	~~20.8~~ 20.2	~~2.2~~ 2.8
Stomatitis	Common	~~9.6~~ 8.7	~~0.8~~ 0.6
Abdominal pain upper	Common	~~6.8~~ 7.4	~~0.3~~ 0.6
Dyspepsia	*Common*	*6.3*	*0.0*
Gastrooesophageal reflux disease	Common	~~5.7~~ 6.3	0.0
Abdominal distention	Common	~~5.5~~ 5.8	0.0
Colitis	*Common*	*1.9*	*0.9*
Neutropenic colitis[8]	*Common*	*1.0*	*0.9*
Enteritis	*Uncommon*	*0.4*	*0.3*
Skin and subcutaneous tissue disorders			
Alopecia	Very common	~~44.3~~ 45.6	0.0
Rash	Very common	~~15.8~~ 13.2	~~1.1~~ 0.7
Pruritus	Very common	~~12.0~~ 12.1	~~0.0~~ 0.1
Dry skin	Common	~~9.0~~ 8.0	0.0
Rash maculopapular	Common	~~6.8~~ 6.0	~~0.0~~ 0.3
Skin hyperpigmentation	*Common*	*2.5*	*0.0*
Dermatitis acneiform	*Common*	*2.0*	*0.0*
Musculoskeletal and connective tissue disorders			
Back pain	Very common	~~18.3~~ 16.0	~~0.8~~ 1.0
Arthralgia	Very common	~~13.7~~ 15.7	~~0.3~~ 0.6
Musculoskeletal chest pain	Common	~~6.3~~ 5.4	0.0
Muscle spasms	Common	~~5.2~~ 6.1	0.0
Renal and urinary disorders			
Dysuria	Common	~~4.4~~ 3.8	0~~.3~~ 0.1
Haematuria	Common	~~2.7~~ 2.3	0~~.3~~ 0.1
Proteinuria	*Common*	*1.7*	*0.0*
General disorders and administration site conditions			
Fatigue[9]	Very common	~~52.5~~ 61.5	~~5.2~~ 6.8
Pain	Common	~~7.1~~ 7.0	~~0.8~~ 0.7
Chills	Common	~~5.5~~ 5.1	0.0
Investigations			

MedDRA System organ class	All severity grades Frequency	All severity grades (%) n=~~366~~ 688	Severity grade ≥3 (%) n=~~366~~ 688
Blood alkaline phosphatase increased	Common	~~8.5~~ 9.7	~~0.0~~ 1.3
Weight decreased	~~Very c~~Common	~~10.1~~ 8.0	0.0
Blood lactate dehydrogenase increased	*Common*	*3.6*	*0.0*
Activated partial thromboplastin time prolonged	Common	~~4.1~~ 2.6	~~0.5~~ 0.3
Injury, poisoning and procedural complications			
Infusion related reaction	*Uncommon*	*0.9*	*0.0*

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: dyspnoea; hypotension; flushing; erythema; chest discomfort; **rhinitis allergic;** wheezing; oedema; urticaria; anaphylactic reaction; mouth ulceration**;** skin exfoliation; swollen tongue; throat tightness
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

Safety in special populations

Race

Only 19 Black or African American were included (7 participants [2.6%] and 12 participants [4.8%] in the SG vs TPC arm, respectively). All black patients had a neutropenia, 86% nausea and 57% diarrhoea, fatigue, and leukopenia.

Age

Most participants in the SG and TPC groups in Study IMMU 132 09 were < 65 years of age (73.1% and 75.5%, respectively). The incidence of common AEs across the age subgroups was similar in the SG and TPC groups in Study IMMU 132 09. Within the SG group, the most common AEs in the < 65 years of age group were neutropenia (72.4%), nausea (59.7%), and diarrhoea (57.1%). The most common

AEs in the ≥ 65 years of age group were diarrhoea (75.0%), neutropenia (65.3%), and nausea (55.6%).

Table 67: Treatment-Emergent Adverse Events: Overall Summary by Age Group - IMMU-132-09 ISS Populations

	IMMU-132-01 HR+/HER2- mBC (N=54)	IMMU-132-09 SG Treated (N=268)	IMMU-132-09 TPC (N=249)	Overall Targeted HR+/HER2- mBC (N=322)	Overall Targeted mBC (N=688)	All Treated SG(10 mg/kg) (N=1063)
Age Group: >= 65 years	12	72	61	84	152	336
Subjects with Any Treatment-emergent Adverse Events (TEAEs)	12 (100.0%)	72 (100.0%)	61 (100.0%)	84 (100.0%)	152 (100.0%)	334 (99.4%)
Worst CTCAE Grade						
3 or higher	11 (91.7%)	54 (75.0%)	37 (60.7%)	65 (77.4%)	113 (74.3%)	273 (81.3%)
5	0	5 (6.9%)	0	5 (6.0%)	6 (3.9%)	14 (4.2%)
3 or 4	11 (91.7%)	49 (68.1%)	37 (60.7%)	60 (71.4%)	107 (70.4%)	259 (77.1%)
4	4 (33.3%)	20 (27.8%)	9 (14.8%)	24 (28.6%)	41 (27.0%)	81 (24.1%)
3	7 (58.3%)	29 (40.3%)	28 (45.9%)	36 (42.9%)	66 (43.4%)	178 (53.0%)
2	1 (8.3%)	18 (25.0%)	17 (27.9%)	19 (22.6%)	36 (23.7%)	56 (16.7%)
1	0	0	7 (11.5%)	0	3 (2.0%)	5 (1.5%)
Subjects with Treatment-related TEAEs	12 (100.0%)	69 (95.8%)	52 (85.2%)	81 (96.4%)	147 (96.7%)	324 (96.4%)
Worst CTCAE Grade						
3 or higher	11 (91.7%)	50 (69.4%)	31 (50.8%)	61 (72.6%)	106 (69.7%)	233 (69.3%)
5	0	1 (1.4%)	0	1 (1.2%)	1 (0.7%)	1 (0.3%)
3 or 4	11 (91.7%)	49 (68.1%)	31 (50.8%)	60 (71.4%)	105 (69.1%)	232 (69.0%)
4	3 (25.0%)	18 (25.0%)	7 (11.5%)	21 (25.0%)	38 (25.0%)	75 (22.3%)
3	8 (66.7%)	31 (43.1%)	24 (39.3%)	39 (46.4%)	67 (44.1%)	157 (46.7%)
2	1 (8.3%)	18 (25.0%)	15 (24.6%)	19 (22.6%)	37 (24.3%)	76 (22.6%)
1	0	1 (1.4%)	6 (9.8%)	1 (1.2%)	4 (2.6%)	15 (4.5%)

Age Group: >= 65 years	12	72	61	84	152	336
Subjects with Treatment-emergent Serious Adverse Events (SAEs)	5 (41.7%)	31 (43.1%)	11 (18.0%)	36 (42.9%)	51 (33.6%)	139 (41.4%)
Worst CTCAE Grade						
3 or higher	5 (41.7%)	28 (38.9%)	10 (16.4%)	33 (39.3%)	47 (30.9%)	128 (38.1%)
5	0	5 (6.9%)	0	5 (6.0%)	6 (3.9%)	13 (3.9%)
3 or 4	5 (41.7%)	23 (31.9%)	10 (16.4%)	28 (33.3%)	41 (27.0%)	115 (34.2%)
4	1 (8.3%)	7 (9.7%)	0	8 (9.5%)	11 (7.2%)	26 (7.7%)
3	4 (33.3%)	16 (22.2%)	10 (16.4%)	20 (23.8%)	30 (19.7%)	89 (26.5%)
2	0	3 (4.2%)	1 (1.6%)	3 (3.6%)	4 (2.6%)	11 (3.3%)
1	0	0	0	0	0	0
Subjects with Treatment-related Treatment-emergent SAEs	1 (8.3%)	17 (23.6%)	3 (4.9%)	18 (21.4%)	27 (17.8%)	68 (20.2%)
Worst CTCAE Grade						
3 or higher	1 (8.3%)	14 (19.4%)	3 (4.9%)	15 (17.9%)	24 (15.8%)	63 (18.8%)
5	0	1 (1.4%)	0	1 (1.2%)	1 (0.7%)	1 (0.3%)
3 or 4	1 (8.3%)	13 (18.1%)	3 (4.9%)	14 (16.7%)	23 (15.1%)	62 (18.5%)
4	0	5 (6.9%)	0	5 (6.0%)	8 (5.3%)	20 (6.0%)
3	1 (8.3%)	8 (11.1%)	3 (4.9%)	9 (10.7%)	15 (9.9%)	42 (12.5%)
2	0	3 (4.2%)	0	3 (3.6%)	3 (2.0%)	5 (1.5%)
1	0	0	0	0	0	0

	IMMU-132-01 HR+/HER2- mBC (N=54)	IMMU-132-09 SG Treated (N=268)	IMMU-132-09 TPC (N=249)	Overall Targeted HR+/HER2- mBC (N=322)	Overall Targeted mBC (N=688)	All Treated SG(10 mg/kg) (N=1063)
Age Group: >= 65 years	12	72	61	84	152	336
Subjects with TEAEs Leading to Death	0	5 (6.9%)	0	5 (6.0%)	6 (3.9%)	12 (3.6%)
Subjects with Treatment-related TEAEs Leading to Death	0	1 (1.4%)	0	1 (1.2%)	1 (0.7%)	1 (0.3%)
Subjects with TEAEs Leading to Study Drug Adjustment						
TEAEs Leading to Study Drug Withdrawal / Discontinuation	0	12 (16.7%)	3 (4.9%)	12 (14.3%)	14 (9.2%)	39 (11.6%)
TEAEs Leading to Study Drug Dose Reduction	N/A	27 (37.5%)	17 (27.9%)	27/72 (37.5%)	45/121 (37.2%)	81/200 (40.5%)
TEAEs Leading to Study Drug Interruption	8 (66.7%)	49 (68.1%)	27 (44.3%)	57 (67.9%)	89 (58.6%)	192 (57.1%)
Subjects with Treatment-related TEAEs Leading to Study Drug Adjustment						
TEAEs Leading to Study Drug Withdrawal / Discontinuation	0	4 (5.6%)	2 (3.3%)	4 (4.8%)	6 (3.9%)	19 (5.7%)
TEAEs Leading to Study Drug Dose Reduction	N/A	27 (37.5%)	17 (27.9%)	27/72 (37.5%)	45/121 (37.2%)	80/200 (40.0%)
TEAEs Leading to Study Drug Interruption	7 (58.3%)	44 (61.1%)	18 (29.5%)	51 (60.7%)	81 (53.3%)	170 (50.6%)

Within the SG group, the incidence of AEs, Grade 3 or higher AEs, AEs leading to dose reduction, AEs leading to dose interruption, and AEs leading to death were similar across the age subgroups in Study IMMU-132-09. Serious adverse events (SAEs) were observed with SG with increasing age: For patients with age <65 years 21.9% and for the patients of more than 65 years of age, the incidences were 43.1%.

Table 68: Treatment-Emergent Adverse Events: Overall Summary by Age Group (< 50, < 65, ≥ 65, ≥ 75 years) in the IMMU-132-09 SG Treated and Overall Targeted mBC Populations - IMMU-132-09 ISS Populations

	Age Group < 50 years		Age Group < 65 years			Age Group ≥ 65 years		Age Group ≥ 75 years	
	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	IMMU-132-09 SG Treated (N = 268)	IMMU 132 09 TPC (N = 249)	Overall Targeted mBC (N = 688)	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)
N	**70**	**212**	**196**	**536**	**72**	**61**	**152**	**16**	**28**
Participants with Any TEAEs	70 (100.0%)	212 (100.0%)	196 (100.0%)	535 (99.8%)	72 (100.0%)	61(100%)	152 (100.0%)	16 (100.0%)	28 (100.0%)
Participants with TEAEs Grade 3 or higher	49 (70.0%)	155 (73.1%)	144 (73.5%)	393 (73.3%)	54 (75.0%)	37 (60.7%)	113 (74.3%)	13 (81.3%)	23 (82.1%)
Participants with Treatment-related TEAEs	68 (97.1%)	208 (98.1%)	191 (97.4%)	524 (97.8%)	69 (95.8%)	52 (85%)	147 (96.7%)	15 (93.8%)	27 (96.4%)
Participants with Treatment-emergent SAEs	13 (18.6%)	56 (26.4%)	43 (21.9%)	144 (26.9%)	31 (43.1%)	11(18.04%)	51 (33.6%)	10 (62.5%)	15 (53.6%)
Participants with Treatment-related Treatment-emergent SAEs	4 (5.7%)	32 (15.1%)	19 (9.7%)	75 (14.0%)	17 (23.6%)	3 (4.9%	27 (17.8%)	5 (31.3%)	8 (28.6%)
Participants with TEAEs Leading to Death	0	0	1 (0.5%)	2 (0.4%)	5 (6.9%)	0	6 (3.9%)	0	0
Participants with Treatment-related TEAEs Leading to Death	0	0	0	0	1 (1.4%)	0	1 (0.7%)	0	0
TEAEs Leading to Study Drug Withdrawal/Discontinuation	3 (4.3%)	11 (5.2%)	5 (2.6%)	22 (4.1%)	12 (16.7%)	3 (4.9%)	14 (9.2%)	2 (12.5%)	3 (10.7%)
TEAEs Leading to Study Drug Dose Reduction	22 (31.4%)	41/162 (25.3%)	63 (32.1%)	102/405 (25.2%)	27 (37.5%)	17 (27.9%)	45/121 (37.2%)	8 (50.0%)	9/24 (37.5%)
TEAEs Leading to Study Drug Interruption	45 (64.3%)	123 (58.0%)	129 (65.8%)	328 (61.2%)	49 (68.1%)	27 (44.3%	89 (58.6%)	11 (68.8%)	16 (57.1%)
Participants with Treatment-related TEAEs Leading to Study Drug Withdrawal/Discontinuation	1 (1.4%)	4 (1.9%)	3 (1.5%)	10 (1.9%)	4 (5.6%)	2 (3.3%)	6 (3.9%)	1 (6.3%)	2 (7.1%)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ISS = integrated summary of safety; mBC = metastatic breast cancer; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event

The denominator for percentages was the number of participants in each subgroup.

Treatment-emergent AEs are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Treatment-related is defined as events reported as 'Possibly Related', 'Related' or missing; 'Unlikely Related' or 'Not Related' is not included.

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

AEs Leading to Study Drug Dose Reduction were not collected in IMMU-132-01, therefore IMMU-132-01 subjects were excluded from denominator for percentages of TEAEs Leading to Study Drug Dose Reduction.

Source: Adhoc 200092 Table 1.1

UGT1A1 Genotype

Table 69: Treatment Exposure by UGT1A1 Genotype (IMMU-132-09 ISS Populations[1])

	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
UGT1A1 Genotype: *1/*1	103	285	416
Treatment Duration (Months)[2]			
N	103	285	416
Mean (SD)	5.15 (4.243)	5.79 (5.726)	5.54 (5.463)
Median	3.94	4.50	4.21
Min, Max	0.03, 23.03	0.03, 38.44	0.03, 38.44
≥ 3 months	62 (60.2%)	176 (61.8%)	254 (61.1%)

	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
≥ 6 months	37 (35.9%)	104 (36.5%)	148 (35.6%)
≥ 12 months	8 (7.8%)	28 (9.8%)	35 (8.4%)
≥ 24 months	0	6 (2.1%)	8 (1.9%)
≥ 36 months	0	1 (0.4%)	2 (0.5%)
Number of Cycles Received[3]			
N	103	285	416
Mean (SD)	7.59 (5.795)	8.46 (7.762)	8.13 (7.425)
Median	6.00	7.00	6.00
Min, Max	1, 30	1, 52	1, 52
Number of Doses Received			
N	103	285	416
Mean (SD)	14.64 (11.233)	16.44 (15.294)	15.80 (14.683)
Median	12.00	12.00	12.00
Min, Max	1, 51	1, 103	1, 103
Cumulative Dosage (mg/kg)			
N	102	284	415
Mean (SD)	136.51 (100.326)	154.25 (141.412)	146.54 (135.264)
Median	110.09	120.59	118.70
Min, Max	9.88, 405.31	9.88, 976.75	9.24, 976.75
Number of Participants with Treatment Delays > 3 Weeks[4]	4 (3.9%)	13 (4.6%)	17 (4.1%)
Number of Participants with Infusion Interruptions	3 (2.9%)	10 (3.5%)	20 (4.8%)
Number of Participants with Dose Reductions			
Any	26 (25.2%)	69 (24.2%)	114 (27.4%)
1	21 (20.4%)	51 (17.9%)	86 (20.7%)
2	5 (4.9%)	17 (6.0%)	27 (6.5%)
3	0	0	0
> 3	0	1 (0.4%)	1 (0.2%)
Time to First Dose Reduction (Days)			
N	26	69	114
Mean (SD)	66 (69.3)	96 (134.7)	80 (119.7)
Median	36	44	41
Min, Max	15, 323	14, 876	8, 876
Relative Dose Intensity (%)[5]			
N	102	284	415
Mean (SD)	93.86 (10.155)	94.76 (9.728)	93.87 (10.495)
Median	99.40	99.65	99.52
Min, Max	62.32, 106.06	52.31, 106.94	51.33, 107.26
Relative Dose Intensity			
< 70%	5 (4.9%)	10 (3.5%)	18 (4.3%)
70% to < 90%	18 (17.5%)	52 (18.2%)	86 (20.7%)
90% to < 110%	79 (76.7%)	222 (77.9%)	311 (74.8%)
≥ 110%	0	0	0
UGT1A1 Genotype: *1/*28	119	272	420
Treatment Duration (Months)[2]			
N	119	272	420
Mean (SD)	6.77 (6.783)	7.05 (8.005)	6.53 (7.724)
Median	4.83	4.85	4.17
Min, Max	0.03, 30.62	0.03, 62.55	0.03, 62.55
≥ 3 months	75 (63.0%)	169 (62.1%)	252 (60.0%)
≥ 6 months	46 (38.7%)	105 (38.6%)	149 (35.5%)

	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
≥ 12 months	22 (18.5%)	48 (17.6%)	60 (14.3%)
≥ 24 months	4 (3.4%)	13 (4.8%)	17 (4.0%)
≥ 36 months	0	2 (0.7%)	4 (1.0%)
Number of Cycles Received[3]			
N	119	272	420
Mean (SD)	9.91 (9.506)	10.31 (11.170)	9.49 (10.482)
Median	7.00	7.00	6.00
Min, Max	1, 44	1, 90	1, 90
Number of Doses Received			
N	119	272	420
Mean (SD)	19.24 (18.755)	20.08 (22.097)	18.44 (20.762)
Median	13.00	14.00	12.00
Min, Max	1, 87	1, 178	1, 178
Cumulative Dosage (mg/kg)			
N	118	271	419
Mean (SD)	171.94 (165.501)	183.05 (195.250)	166.67 (180.466)
Median	119.57	119.86	110.44
Min, Max	10.00, 868.51	9.16, 1340.92	8.98, 1340.92
Number of Participants with Treatment Delays > 3 Weeks[4]	3 (2.5%)	8 (2.9%)	17 (4.0%)
Number of Participants with Infusion Interruptions	2 (1.7%)	12 (4.4%)	18 (4.3%)
Number of Participants with Dose Reductions			
Any	51 (42.9%)	92 (33.8%)	148 (35.2%)
1	37 (31.1%)	69 (25.4%)	113 (26.9%)
2	12 (10.1%)	20 (7.4%)	31 (7.4%)
3	1 (0.8%)	1 (0.4%)	2 (0.5%)
> 3	1 (0.8%)	2 (0.7%)	2 (0.5%)
Time to First Dose Reduction (Days)			
N	51	92	148
Mean (SD)	81 (91.0)	92 (136.1)	82 (117.7)
Median	49	44	41
Min, Max	7, 588	7, 925	7, 925
Relative Dose Intensity (%)[5]			
N	118	271	419
Mean (SD)	90.85 (12.531)	92.46 (11.647)	91.89 (11.906)
Median	98.30	99.12	98.64
Min, Max	50.00, 102.82	50.00, 107.34	45.32, 107.34
Relative Dose Intensity			
< 70%	9 (7.6%)	17 (6.3%)	26 (6.2%)
70% to < 90%	35 (29.4%)	63 (23.2%)	107 (25.5%)
90% to < 110%	74 (62.2%)	191 (70.2%)	286 (68.1%)
≥ 110%	0	0	0
UGT1A1 Genotype: *28/*28	25	71	112
Treatment Duration (Months)[2]			
N	25	71	112
Mean (SD)	5.13 (6.437)	5.85 (6.187)	5.92 (7.971)
Median	2.79	4.14	3.98
Min, Max	0.03, 29.11	0.03, 29.11	0.03, 61.90
≥ 3 months	12 (48.0%)	44 (62.0%)	65 (58.0%)
≥ 6 months	7 (28.0%)	22 (31.0%)	34 (30.4%)
≥ 12 months	3 (12.0%)	8 (11.3%)	13 (11.6%)

	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
≥ 24 months	1 (4.0%)	2 (2.8%)	4 (3.6%)
≥ 36 months	0	0	1 (0.9%)
Number of Cycles Received[3]			
N	25	71	112
Mean (SD)	7.56 (8.471)	8.41 (7.909)	8.53 (10.863)
Median	5.00	7.00	6.00
Min, Max	1, 39	1, 39	1, 89
Number of Doses Received			
N	25	71	112
Mean (SD)	14.28 (16.131)	16.25 (15.513)	16.49 (21.378)
Median	9.00	12.00	12.00
Min, Max	1, 73	1, 73	1, 176
Cumulative Dosage (mg/kg)			
N	24	70	111
Mean (SD)	126.45 (135.862)	141.62 (127.356)	144.87 (197.941)
Median	82.58	120.40	101.57
Min, Max	10.00, 620.14	10.00, 620.14	9.94, 1757.68
Number of Participants with Treatment Delays > 3 Weeks[4]	0	3 (4.2%)	3 (2.7%)
Number of Participants with Infusion Interruptions	0	3 (4.2%)	4 (3.6%)
Number of Participants with Dose Reductions			
Any	11 (44.0%)	31 (43.7%)	53 (47.3%)
1	8 (32.0%)	24 (33.8%)	43 (38.4%)
2	3 (12.0%)	7 (9.9%)	10 (8.9%)
3	0	0	0
> 3	0	0	0

	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Time to First Dose Reduction (Days)			
N	11	31	53
Mean (SD)	65 (99.0)	55 (65.7)	76 (226.0)
Median	29	35	29
Min, Max	1, 353	1, 353	1, 1647
Relative Dose Intensity (%)[5]			
N	24	70	111
Mean (SD)	85.73 (15.496)	88.03 (15.006)	88.30 (13.851)
Median	93.89	95.39	94.02
Min, Max	60.93, 100.32	47.42, 107.14	47.42, 107.14
Relative Dose Intensity			
< 70%	6 (24.0%)	11 (15.5%)	13 (11.6%)
70% to < 90%	5 (20.0%)	19 (26.8%)	36 (32.1%)
90% to < 110%	13 (52.0%)	40 (56.3%)	62 (55.4%)
≥ 110%	0	0	0

HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; SG = sacituzumab govitecan; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group, Study IMMU-132-09 TPC group, and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

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

[3] Cycles are counted if participant received at least 1 dose in that cycle.

[4] Treatment delay > 3weeks is defined as > 28 days between the first 2 doses of the same cycle or > 35 days between Dose 2 and Dose 1 of the next cycle

[5] Relative Dose Intensity = cumulative dosage received (mg/kg) / total assigned dosage (mg/kg). See details in the statistical analysis plan.

Source: ISS IA2, Table 14.3.1.1.6

Table 70: Treatment-Emergent Adverse Events: Overall Summary by UGT1A1 Genotype in Participants Treated With SG (IMMU-132-09 ISS Populations[1])

	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
UGT1A1 Genotype: *1/*1	103	285	416
Participants with Any TEAEs	103 (100.0%)	285 (100.0%)	415 (99.8%)
Grade 3 or higher	69 (67.0%)	195 (68.4%)	299 (71.9%)
Participants with Treatment-related TEAEs	100 (97.1%)	281 (98.6%)	408 (98.1%)
Grade 3 or higher	57 (55.3%)	170 (59.6%)	244 (58.7%)
Participants with Treatment-emergent SAEs	26 (25.2%)	70 (24.6%)	133 (32.0%)
Participants with Treatment-related Treatment-emergent SAEs	12 (11.7%)	35 (12.3%)	62 (14.9%)
TEAEs Leading to Study Drug Interruption	70 (68.0%)	176 (61.8%)	243 (58.4%)
TEAEs Leading to Study Drug Dose Reduction	26 (25.2%)	46/216 (21.3%)	69/268 (25.7%)
TEAEs Leading to Study Drug Withdrawal/Discontinuation	5 (4.9%)	13 (4.6%)	27 (6.5%)
Participants with TEAEs Leading to Death	1 (1.0%)	1 (0.4%)	7 (1.7%)
Participants with Treatment-related TEAEs Leading to Death	0	0	1 (0.2%)

	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
UGT1A1 Genotype: *1/*28	119	272	420
Participants with Any TEAEs	119 (100.0%)	271 (99.6%)	418 (99.5%)
Grade 3 or higher	89 (74.8%)	204 (75.0%)	320 (76.2%)
Participants with Treatment-related TEAEs	116 (97.5%)	261 (96.0%)	404 (96.2%)
Grade 3 or higher	81 (68.1%)	183 (67.3%)	272 (64.8%)
Participants with Treatment-emergent SAEs	32 (26.9%)	78 (28.7%)	134 (31.9%)
Participants with Treatment-related Treatment-emergent SAEs	18 (15.1%)	41 (15.1%)	61 (14.5%)
TEAEs Leading to Study Drug Interruption	76 (63.9%)	161 (59.2%)	230 (54.8%)
TEAEs Leading to Study Drug Dose Reduction	49 (41.2%)	68/215 (31.6%)	89/270 (33.0%)
TEAEs Leading to Study Drug Withdrawal/Discontinuation	7 (5.9%)	14 (5.1%)	27 (6.4%)
Participants with TEAEs Leading to Death	4 (3.4%)	6 (2.2%)	11 (2.6%)
Participants with Treatment-related TEAEs Leading to Death	1 (0.8%)	1 (0.4%)	2 (0.5%)
UGT1A1 Genotype: *28/*28	25	71	112
Participants with Any TEAEs	25 (100.0%)	71 (100.0%)	112 (100.0%)
Grade 3 or higher	23 (92.0%)	62 (87.3%)	101 (90.2%)
Participants with Treatment-related TEAEs	24 (96.0%)	70 (98.6%)	109 (97.3%)
Grade 3 or higher	21 (84.0%)	56 (78.9%)	89 (79.5%)
Participants with Treatment-emergent SAEs	12 (48.0%)	32 (45.1%)	61 (54.5%)
Participants with Treatment-related Treatment-emergent SAEs	6 (24.0%)	22 (31.0%)	39 (34.8%)
TEAEs Leading to Study Drug Interruption	19 (76.0%)	46 (64.8%)	78 (69.6%)
TEAEs Leading to Study Drug Dose Reduction	10 (40.0%)	22/59 (37.3%)	30/76 (39.5%)
TEAEs Leading to Study Drug Withdrawal/Discontinuation	3 (12.0%)	5 (7.0%)	8 (7.1%)
Participants with TEAEs Leading to Death	1 (4.0%)	1 (1.4%)	2 (1.8%)
Participants with Treatment-related TEAEs Leading to Death	0	0	0

AE = adverse event; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; NA = not available; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group, Study IMMU-132-09 TPC group, and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

The denominator for percentages was the number of patients in each subgroup.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Treatment-related is defined as events reported as “Possibly Related,” “Related,” or missing; “Unlikely Related” or “Not Related” is not included.

AEs Leading to Study Drug Dose Reduction were not collected in IMMU-132-01, therefore IMMU-132-01 participants were excluded from denominator for percentages of TEAEs Leading to Study Drug Dose Reduction.

Source: ISS IA2, Table 14.3.2.1.1.6

Table 71: Adverse Events Reported in ≥ 10% of Participants in the Study IMMU-132-09 SG Group by UGT1A1 Genotype (IMMU-132-09 ISS Populations[1])

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
UGT1A1 Genotype: *1/*1	103	285	416
Participants with Any Treatment-Emergent Adverse Events	103 (100.0%)	285 (100.0%)	415 (99.8%)
Blood and lymphatic system disorders	85 (82.5%)	226 (79.3%)	323 (77.6%)
Neutropenia	73 (70.9%)	196 (68.8%)	251 (60.3%)
Anaemia	34 (33.0%)	112 (39.3%)	168 (40.4%)
Leukopenia	17 (16.5%)	49 (17.2%)	75 (18.0%)
Lymphopenia	11 (10.7%)	33 (11.6%)	50 (12.0%)
Gastrointestinal disorders	96 (93.2%)	266 (93.3%)	387 (93.0%)
Nausea	62 (60.2%)	183 (64.2%)	268 (64.4%)
Diarrhoea	60 (58.3%)	169 (59.3%)	254 (61.1%)
Constipation	37 (35.9%)	105 (36.8%)	158 (38.0%)
Vomiting	25 (24.3%)	101 (35.4%)	158 (38.0%)
Abdominal pain	21 (20.4%)	64 (22.5%)	102 (24.5%)
General disorders and administration site conditions	72 (69.9%)	215 (75.4%)	311 (74.8%)
Fatigue	37 (35.9%)	134 (47.0%)	206 (49.5%)
Asthenia	22 (21.4%)	44 (15.4%)	56 (13.5%)
Pyrexia	14 (13.6%)	40 (14.0%)	60 (14.4%)
Infections and infestations	40 (38.8%)	129 (45.3%)	194 (46.6%)
Urinary tract infection	12 (11.7%)	36 (12.6%)	57 (13.7%)
Investigations	32 (31.1%)	96 (33.7%)	154 (37.0%)
Aspartate aminotransferase increased	14 (13.6%)	40 (14.0%)	54 (13.0%)
Alanine aminotransferase increased	13 (12.6%)	34 (11.9%)	47 (11.3%)
Metabolism and nutrition disorders	39 (37.9%)	145 (50.9%)	231 (55.5%)
Decreased appetite	21 (20.4%)	75 (26.3%)	124 (29.8%)
Musculoskeletal and connective tissue disorders	46 (44.7%)	129 (45.3%)	193 (46.4%)
Back pain	12 (11.7%)	45 (15.8%)	65 (15.6%)
Arthralgia	14 (13.6%)	35 (12.3%)	55 (13.2%)
Nervous system disorders	43 (41.7%)	140 (49.1%)	184 (44.2%)
Headache	23 (22.3%)	64 (22.5%)	76 (18.3%)
Psychiatric disorders	23 (22.3%)	61 (21.4%)	83 (20.0%)
Insomnia	12 (11.7%)	37 (13.0%)	46 (11.1%)
Respiratory, thoracic and mediastinal disorders	47 (45.6%)	141 (49.5%)	210 (50.5%)
Dyspnoea	20 (19.4%)	50 (17.5%)	74 (17.8%)
Cough	18 (17.5%)	54 (18.9%)	81 (19.5%)
Epistaxis	12 (11.7%)	25 (8.8%)	35 (8.4%)
Skin and subcutaneous tissue disorders	60 (58.3%)	188 (66.0%)	267 (64.2%)
Alopecia	45 (43.7%)	132 (46.3%)	190 (45.7%)
Rash	11 (10.7%)	43 (15.1%)	55 (13.2%)
UGT1A1 Genotype: *1/*28	119	272	420
Participants with Any Treatment-Emergent Adverse Events	119 (100.0%)	271 (99.6%)	418 (99.5%)
Blood and lymphatic system disorders	97 (81.5%)	214 (78.7%)	314 (74.8%)
Neutropenia	86 (72.3%)	184 (67.6%)	265 (63.1%)
Anaemia	43 (36.1%)	106 (39.0%)	156 (37.1%)
Leukopenia	15 (12.6%)	46 (16.9%)	75 (17.9%)
Lymphopenia	16 (13.4%)	32 (11.8%)	41 (9.8%)

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Gastrointestinal disorders	113 (95.0%)	252 (92.6%)	385 (91.7%)
Diarrhoea	77 (64.7%)	171 (62.9%)	271 (64.5%)
Nausea	70 (58.8%)	169 (62.1%)	267 (63.6%)
Constipation	45 (37.8%)	106 (39.0%)	153 (36.4%)
Vomiting	28 (23.5%)	82 (30.1%)	130 (31.0%)
Abdominal pain	23 (19.3%)	50 (18.4%)	85 (20.2%)
Abdominal pain upper	16 (13.4%)	27 (9.9%)	29 (6.9%)
General disorders and administration site conditions	91 (76.5%)	203 (74.6%)	322 (76.7%)
Fatigue	49 (41.2%)	127 (46.7%)	212 (50.5%)
Asthenia	30 (25.2%)	46 (16.9%)	60 (14.3%)
Pyrexia	20 (16.8%)	41 (15.1%)	68 (16.2%)
Oedema peripheral	12 (10.1%)	31 (11.4%)	59 (14.0%)
Mucosal inflammation	14 (11.8%)	26 (9.6%)	27 (6.4%)
Investigations	37 (31.1%)	102 (37.5%)	159 (37.9%)
Aspartate aminotransferase increased	13 (10.9%)	31 (11.4%)	42 (10.0%)
Metabolism and nutrition disorders	55 (46.2%)	144 (52.9%)	239 (56.9%)
Decreased appetite	27 (22.7%)	66 (24.3%)	119 (28.3%)
Hypokalaemia	18 (15.1%)	53 (19.5%)	77 (18.3%)
Musculoskeletal and connective tissue disorders	54 (45.4%)	132 (48.5%)	203 (48.3%)
Arthralgia	19 (16.0%)	51 (18.8%)	71 (16.9%)
Back pain	15 (12.6%)	45 (16.5%)	71 (16.9%)
Nervous system disorders	47 (39.5%)	114 (41.9%)	169 (40.2%)
Headache	16 (13.4%)	39 (14.3%)	50 (11.9%)
Dizziness	12 (10.1%)	35 (12.9%)	55 (13.1%)
Respiratory, thoracic and mediastinal disorders	43 (36.1%)	127 (46.7%)	206 (49.0%)
Dyspnoea	19 (16.0%)	53 (19.5%)	82 (19.5%)
Skin and subcutaneous tissue disorders	80 (67.2%)	171 (62.9%)	266 (63.3%)
Alopecia	64 (53.8%)	128 (47.1%)	195 (46.4%)
Pruritus	17 (14.3%)	33 (12.1%)	56 (13.3%)
UGT1A1 Genotype: *28/*28	25	71	112
Participants with Any Treatment-Emergent Adverse Events	25 (100.0%)	71 (100.0%)	112 (100.0%)
Blood and lymphatic system disorders	23 (92.0%)	66 (93.0%)	100 (89.3%)
Neutropenia	19 (76.0%)	52 (73.2%)	78 (69.6%)
Anaemia	12 (48.0%)	36 (50.7%)	58 (51.8%)
Thrombocytopenia	4 (16.0%)	12 (16.9%)	16 (14.3%)
Cardiac disorders	3 (12.0%)	6 (8.5%)	11 (9.8%)
Tachycardia	3 (12.0%)	4 (5.6%)	6 (5.4%)
Gastrointestinal disorders	23 (92.0%)	67 (94.4%)	103 (92.0%)
Diarrhoea	17 (68.0%)	52 (73.2%)	77 (68.8%)
Nausea	14 (56.0%)	43 (60.6%)	71 (63.4%)
Vomiting	6 (24.0%)	25 (35.2%)	42 (37.5%)
Constipation	6 (24.0%)	21 (29.6%)	39 (34.8%)
Abdominal pain	6 (24.0%)	12 (16.9%)	23 (20.5%)
Stomatitis	4 (16.0%)	10 (14.1%)	13 (11.6%)
Abdominal pain upper	3 (12.0%)	6 (8.5%)	8 (7.1%)
Neutropenic colitis	3 (12.0%)	3 (4.2%)	5 (4.5%)
General disorders and administration site conditions	17 (68.0%)	55 (77.5%)	85 (75.9%)

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Fatigue	8 (32.0%)	32 (45.1%)	54 (48.2%)
Pyrexia	4 (16.0%)	12 (16.9%)	24 (21.4%)
Asthenia	4 (16.0%)	12 (16.9%)	19 (17.0%)
Mucosal inflammation	5 (20.0%)	9 (12.7%)	12 (10.7%)
Infections and infestations	9 (36.0%)	32 (45.1%)	47 (42.0%)
Urinary tract infection	3 (12.0%)	7 (9.9%)	12 (10.7%)
Investigations	12 (48.0%)	30 (42.3%)	53 (47.3%)
Alanine aminotransferase increased	5 (20.0%)	12 (16.9%)	17 (15.2%)
Aspartate aminotransferase increased	3 (12.0%)	12 (16.9%)	17 (15.2%)
Blood alkaline phosphatase increased	3 (12.0%)	9 (12.7%)	15 (13.4%)
Blood bilirubin increased	4 (16.0%)	6 (8.5%)	7 (6.3%)
Gamma-glutamyltransferase increased	3 (12.0%)	4 (5.6%)	4 (3.6%)
Metabolism and nutrition disorders	7 (28.0%)	34 (47.9%)	67 (59.8%)
Decreased appetite	5 (20.0%)	23 (32.4%)	44 (39.3%)
Hypokalaemia	4 (16.0%)	12 (16.9%)	20 (17.9%)
Musculoskeletal and connective tissue disorders	10 (40.0%)	29 (40.8%)	48 (42.9%)
Arthralgia	5 (20.0%)	11 (15.5%)	20 (17.9%)
Back pain	5 (20.0%)	12 (16.9%)	18 (16.1%)
Muscle spasms	3 (12.0%)	4 (5.6%)	4 (3.6%)
Respiratory, thoracic and mediastinal disorders	11 (44.0%)	33 (46.5%)	51 (45.5%)
Cough	4 (16.0%)	17 (23.9%)	24 (21.4%)
Dyspnoea	4 (16.0%)	11 (15.5%)	19 (17.0%)
Epistaxis	3 (12.0%)	7 (9.9%)	7 (6.3%)
Skin and subcutaneous tissue disorders	11 (44.0%)	42 (59.2%)	63 (56.3%)
Alopecia	9 (36.0%)	32 (45.1%)	49 (43.8%)
Vascular disorders	4 (16.0%)	11 (15.5%)	18 (16.1%)
Hypotension	3 (12.0%)	5 (7.0%)	10 (8.9%)

AE = adverse event; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TEAE = treatment-emergent adverse event; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1a

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group, Study IMMU-132-09 TPC group, and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

The denominator for percentages was the number of patients in each subgroup.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Multiple adverse events are counted only once per participant for each SOC and PT. MedDRA Version 25.0 was used for coding.

System organ classes are presented alphabetically and PTs within SOC are presented by descending order of the total frequencies.

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.

Source: ISS IA2, Table 14.3.2.2.1.6

Table 72: Grade 3 or Higher Adverse Events Reported in ≥ 5% in Any UGT1A1 Genotype in Participants Treated With SG (Overall Targeted mBC and All Treated SG Populations)

Overall Targeted mBC

System Organ Class Preferred Term	*1/*1 (N = 285)	*1/*28 (N = 272)	*28/*28 (N = 71)
Participants with Any Grade 3 or Higher TEAEs	195 (68.4%)	204 (75.0%)	62 (87.3%)
Blood and lymphatic system disorders	150 (52.6%)	158 (58.1%)	53 (74.6%)
Neutropenia	140 (49.1%)	144 (52.9%)	43 (60.6%)
Leukopenia	25 (8.8%)	33 (12.1%)	10 (14.1%)
Anaemia	23 (8.1%)	20 (7.4%)	11 (15.5%)
Febrile neutropenia	13 (4.6%)	16 (5.9%)	10 (14.1%)
Lymphopenia	8 (2.8%)	6 (2.2%)	5 (7.0%)
Thrombocytopenia	2 (0.7%)	2 (0.7%)	4 (5.6%)
Gastrointestinal disorders	34 (11.9%)	51 (18.8%)	21 (29.6%)
Diarrhoea	19 (6.7%)	34 (12.5%)	13 (18.3%)
General disorders and administration site conditions	20 (7.0%)	29 (10.7%)	5 (7.0%)
Fatigue	9 (3.2%)	18 (6.6%)	3 (4.2%)
Metabolism and nutrition disorders	32 (11.2%)	38 (14.0%)	9 (12.7%)
Hypophosphataemia	16 (5.6%)	8 (2.9%)	2 (2.8%)

AE = adverse event; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TEAE = treatment-emergent adverse event; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

Denominator for percentages was big N.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Multiple adverse events are counted only once per participant for each SOC and PT. MedDRA Version 25.0 was used for coding.

System organ classes are presented alphabetically and PTs within SOC are presented by descending order of the total frequencies.

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.

Source: ISS IA2, Table 14.3.2.6.2.2

All Treated SG

System Organ Class Preferred Term	*1/*1 (N = 416)	*1/*28 (N = 420)	*28/*28 (N = 112)
Participants with Any Grade 3 or Higher TEAEs	299 (71.9%)	320 (76.2%)	101 (90.2%)
Blood and lymphatic system disorders	212 (51.0%)	230 (54.8%)	84 (75.0%)
Neutropenia	180 (43.3%)	204 (48.6%)	65 (58.0%)
Anaemia	39 (9.4%)	41 (9.8%)	24 (21.4%)
Leukopenia	40 (9.6%)	53 (12.6%)	19 (17.0%)
Febrile neutropenia	23 (5.5%)	22 (5.2%)	16 (14.3%)
Lymphopenia	17 (4.1%)	11 (2.6%)	9 (8.0%)
Gastrointestinal disorders	66 (15.9%)	82 (19.5%)	33 (29.5%)
Diarrhoea	34 (8.2%)	49 (11.7%)	17 (15.2%)
General disorders and administration site conditions	34 (8.2%)	51 (12.1%)	12 (10.7%)

System Organ Class Preferred Term	*1/*1 (N = 416)	*1/*28 (N = 420)	*28/*28 (N = 112)
Fatigue	19 (4.6%)	36 (8.6%)	7 (6.3%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TEAE = treatment-emergent adverse event; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

Denominator for percentages was big N.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Multiple adverse events are counted only once per participant for each SOC and PT. MedDRA Version 24.0 was used for coding.

System organ classes are presented alphabetically and PTs within SOC are presented by descending order of the total frequencies.

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.

Source: ISS IA2, Table 14.3.2.6.2.1

Table 73: Serious Adverse Events Reported in ≥ 4 Participants Treated With SG by UGT1A1 Genotype (Overall Targeted mBC and All Treated SG Populations)

Overall Targeted mBC

System Organ Class Preferred Term	*1/*1 (N = 285)	*1/*28 (N = 272)	*28/*28 (N = 71)
Participants with Any Treatment-Emergent SAEs	70 (24.6%)	78 (28.7%)	32 (45.1%)
Blood and lymphatic system disorders	16 (5.6%)	21 (7.7%)	18 (25.4%)
Febrile neutropenia	11 (3.9%)	12 (4.4%)	8 (11.3%)
Neutropenia	4 (1.4%)	9 (3.3%)	5 (7.0%)
Anaemia	2 (0.7%)	0	5 (7.0%)
Gastrointestinal disorders	22 (7.7%)	24 (8.8%)	12 (16.9%)
Diarrhoea	8 (2.8%)	13 (4.8%)	5 (7.0%)
Vomiting	5 (1.8%)	5 (1.8%)	2 (2.8%)
Abdominal pain	4 (1.4%)	3 (1.1%)	3 (4.2%)
Nausea	4 (1.4%)	2 (0.7%)	2 (2.8%)
General disorders and administration site conditions	11 (3.9%)	7 (2.6%)	1 (1.4%)
Pyrexia	4 (1.4%)	2 (0.7%)	1 (1.4%)
Infections and infestations	21 (7.4%)	21 (7.7%)	9 (12.7%)
Pneumonia	4 (1.4%)	8 (2.9%)	1 (1.4%)
Metabolism and nutrition disorders	4 (1.4%)	7 (2.6%)	0
Dehydration	2 (0.7%)	4 (1.5%)	0
Respiratory, thoracic and mediastinal disorders	13 (4.6%)	10 (3.7%)	3 (4.2%)
Dyspnoea	4 (1.4%)	1 (0.4%)	1 (1.4%)
Pleural effusion	4 (1.4%)	2 (0.7%)	0

AE = adverse event; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SG = sacituzumab govitecan; SOC = system organ class; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

Denominator for percentages was big N.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Multiple adverse events are counted only once per participant for each SOC and PT. MedDRA Version 25.0 was used for coding.

System organ classes are presented alphabetically and PTs within SOC are presented by descending order of the total frequencies.

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.

Source: ISS IA2, Table 14.3.2.5.2.2

All Treated SG

System Organ Class Preferred Term	*1/*1 (N = 416)	*1/*28 (N = 420)	*28/*28 (N = 112)
Participants with Any Treatment-Emergent SAEs	133 (32.0%)	134 (31.9%)	61 (54.5%)
Blood and lymphatic system disorders	30 (7.2%)	28 (6.7%)	25 (22.3%)
Febrile neutropenia	20 (4.8%)	17 (4.0%)	13 (11.6%)
Neutropenia	8 (1.9%)	10 (2.4%)	6 (5.4%)
Anaemia	4 (1.0%)	1 (0.2%)	6 (5.4%)
Gastrointestinal disorders	41 (9.9%)	39 (9.3%)	24 (21.4%)
Diarrhoea	16 (3.8%)	17 (4.0%)	8 (7.1%)
Vomiting	7 (1.7%)	5 (1.2%)	3 (2.7%)
Abdominal pain	7 (1.7%)	4 (1.0%)	4 (3.6%)
Nausea	6 (1.4%)	4 (1.0%)	3 (2.7%)
Colitis	4 (1.0%)	3 (0.7%)	3 (2.7%)
Small intestinal obstruction	1 (0.2%)	5 (1.2%)	2 (1.8%)
Neutropenic colitis	0	3 (0.7%)	5 (4.5%)
General disorders and administration site conditions	16 (3.8%)	13 (3.1%)	4 (3.6%)
Pyrexia	5 (1.2%)	4 (1.0%)	3 (2.7%)
Infections and infestations	40 (9.6%)	41 (9.8%)	13 (11.6%)
Pneumonia	7 (1.7%)	14 (3.3%)	1 (0.9%)
Urinary tract infection	7 (1.7%)	7 (1.7%)	2 (1.8%)
Sepsis	7 (1.7%)	2 (0.5%)	2 (1.8%)
Metabolism and nutrition disorders	6 (1.4%)	8 (1.9%)	1 (0.9%)
Dehydration	2 (0.5%)	5 (1.2%)	1 (0.9%)
Psychiatric disorders	3 (0.7%)	4 (1.0%)	1 (0.9%)
Mental status changes	0	4 (1.0%)	0
Respiratory, thoracic and mediastinal disorders	21 (5.0%)	20 (4.8%)	4 (3.6%)
Dyspnoea	7 (1.7%)	4 (1.0%)	1 (0.9%)
Pleural effusion	4 (1.0%)	5 (1.2%)	0
Respiratory failure	1 (0.2%)	4 (1.0%)	2 (1.8%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SG = sacituzumab govitecan; SOC = system organ class; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

Denominator for percentages was big N.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Multiple adverse events are counted only once per participant for each SOC and PT. MedDRA Version 25.0 was used for coding.

System organ classes are presented alphabetically and PTs within SOC are presented by descending order of the total frequencies.

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.

Source: ISS IA2, Table 14.3.2.5.2.1

Adverse Events Leading to Discontinuation of Study Drug

Adverse events leading to discontinuation of study drug were reported in a higher percentage of participants who were homozygous for the UGT1A1*28 allele compared with participants who were

either heterozygous or homozygous for the UGT1A1*1 allele (12.0% vs 5.9% and 4.9%, respectively) in Study IMMU-132-09.

Febrile neutropenia was the only AE leading to discontinuation in > 1 participant; it was reported in 2 participants (1.8%) with the UGT1A1*28/*28 allele and 1 participant (0.2%) with the UGT1A1*1/*1 allele in the All Treated SG pooled population

Adverse Events Leading to Dose Reduction

Adverse events leading to dose reduction were reported in a higher percentage of participants who were either homozygous or heterozygous for the UGT1A1*28 allele compared with participants who were homozygous for the UGT1A1*1 allele (40.0% and 41.2% vs 25.2%, respectively) in Study IMMU-132-09

Adverse Events Leading to Study Drug Interruption

Adverse events leading to study drug interruption were reported in a higher percentage of participants who were homozygous for the UGT1A1*28 allele compared with participants who were either heterozygous or homozygous for the UGT1A1*1 allele (76.0% vs 63.9% and 68.0%, respectively) in Study IMMU-132-09.

Table 74: Overall Summary of treatment-emergent adverse events of the pooled all treated SG patient population by genotype

	UGT1A1 Genotype: *1/*1 All SG Treated (N = 416)	UGT1A1 Genotype: *1/*28 All SG Treated (N = 420)	UGT1A1 Genotype: *28/*28 All SG Treated (N = 112)
Participants with Any TEAEs	415 (99.8%)	418 (99.5%)	112 (100.0%)
Grade 3 or higher	299 (71.9%)	320 (76.2%)	101 (90.2%)
Participants with Treatment-related TEAEs	408 (98.1%)	404 (96.2%)	109 (97.3%)
Grade 3 or higher	244 (58.7%)	272 (64.8%)	89 (79.5%)
Participants with Treatment-emergent SAEs	133 (32.0%)	134 (31.9%)	61 (54.5%)
Participants with Treatment-related Treatment-emergent SAEs	62 (14.9%)	61 (14.5%)	39 (34.8%)
TEAEs Leading to Study Drug Interruption	243 (58.4%)	230 (54.8%)	78 (69.6%)
TEAEs Leading to Study Drug Dose Reduction	69/268 (25.7%)	89/270 (33.0%)	30/76 (39.5%)
TEAEs Leading to Study Drug Withdrawal/Discontinuation	27 (6.5%)	27 (6.4%)	8 (7.1%)
Participants with TEAEs Leading to Death	7 (1.7%)	11 (2.6%)	2 (1.8%)
Participants with Treatment-related TEAEs Leading to Death	1 (0.2%)	2 (0.5%)	0

Discontinuation due to adverse events

Table 75: Adverse Events Leading to Discontinuation of Study Drug in ≥ 2 Participants by System Organ Class[2] and Preferred Term

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs Leading to Discontinuation of Study Drug	17 (6.3%)	11 (4.4%)	36 (5.2%)	78 (7.3%)
Blood and lymphatic system disorders	3 (1.1%)	3 (1.2%)	5 (0.7%)	12 (1.1%)
Neutropenia	2 (0.7%)	0	3 (0.4%)	6 (0.6%)
Leukopenia	1 (0.4%)	0	1 (0.1%)	2 (0.2%)
Thrombocytopenia	0	2 (0.8%)	1 (0.1%)	1 (< 0.1%)
Febrile neutropenia	0	0	0	3 (0.3%)
Gastrointestinal disorders	4 (1.5%)	0	6 (0.9%)	17 (1.6%)
Diarrhoea	1 (0.4%)	0	3 (0.4%)	6 (0.6%)
Colitis	1 (0.4%)	0	1 (0.1%)	2 (0.2%)
General disorders and administration site conditions	4 (1.5%)	1 (0.4%)	10 (1.5%)	16 (1.5%)
Asthenia	2 (0.7%)	0	2 (0.3%)	4 (0.4%)
Fatigue	0	1 (0.4%)	3 (0.4%)	6 (0.6%)
General physical health deterioration	2 (0.7%)	0	2 (0.3%)	2 (0.2%)
Infections and infestations	3 (1.1%)	1 (0.4%)	6 (0.9%)	11 (1.0%)
Pneumonia	1 (0.4%)	1 (0.4%)	3 (0.4%)	6 (0.6%)
Sepsis	0	0	1 (0.1%)	3 (0.3%)
Investigations	1 (0.4%)	0	1 (0.1%)	3 (0.3%)
Alanine aminotransferase increased	1 (0.4%)	0	1 (0.1%)	2 (0.2%)
Aspartate aminotransferase increased	1 (0.4%)	0	1 (0.1%)	2 (0.2%)
Nervous system disorders	1 (0.4%)	3 (1.2%)	1 (0.1%)	1 (< 0.1%)
Polyneuropathy	0	2 (0.8%)	0	0
Reproductive system and breast disorders	0	0	1 (0.1%)	3 (0.3%)
Breast pain	0	0	1 (0.1%)	2 (0.2%)
Respiratory, thoracic, and mediastinal disorders	2 (0.7%)	1 (0.4%)	4 (0.6%)	9 (0.8%)
Pneumonitis	0	1 (0.4%)	1 (0.1%)	2 (0.2%)
Skin and subcutaneous tissue disorders	0	1 (0.4%)	1 (0.1%)	5 (0.5%)
Pruritus	0	0	0	3 (0.3%)

AE = adverse event; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ISS = Integrated Summary of Safety; mBC = metastatic breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SG = sacituzumab govitecan; SOC = system organ class; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

[1] The ISS populations called the Study IMMU-132-01 HR+/HER2− mBC group and Overall Targeted HR+/HER2− mBC pool are not presented in the table.

[2] This table presents only those PTs that occurred in ⩾ 2 participants in the ISS groups shown. In the source table, the frequencies of the SOCs are based on all PTs under the SOC, not only the PTs of TEAEs leading to discontinuation of study drug reported in ⩾ 2 participants.

Denominator for percentages was big N.

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date.

Multiple adverse events are counted only once per participant for each SOC and PT. MedDRA Version 25.0 was used for coding.

System organ classes were presented alphabetically and PTs within SOC were presented by descending order of the total frequencies.

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.

Source: ISS IA2, Table 14.3.2.9.3.1

Table 76: Adverse Events Leading to Dose Reduction of Study Drug Reported in ≥ 1% of Participants in Selected ISS Populations[1] by System Organ Class[2] and Preferred Term

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs Leading to Dose Reduction of Study Drug	90 (33.6%)	82 (32.9%)	147/526 (27.9%)	205/661 (31.0%)
Blood and lymphatic system disorders	50 (18.7%)	52 (20.9%)	80/526 (15.2%)	103/661 (15.6%)
Neutropenia	42 (15.7%)	44 (17.7%)	65/526 (12.4%)	80/661 (12.1%)
Febrile neutropenia	8 (3.0%)	3 (1.2%)	15/526 (2.9%)	19/661 (2.9%)
Anaemia	3 (1.1%)	1 (0.4%)	6/526 (1.1%)	9/661 (1.4%)
Thrombocytopenia	0	7 (2.8%)	1/526 (0.2%)	1/661 (0.2%)
Gastrointestinal disorders	27 (10.1%)	6 (2.4%)	44/526 (8.4%)	61/661 (9.2%)
Diarrhoea	21 (7.8%)	0	34/526 (6.5%)	49/661 (7.4%)
Nausea	2 (0.7%)	3 (1.2%)	7/526 (1.3%)	9/661 (1.4%)
Vomiting	4 (1.5%)	2 (0.8%)	5/526 (1.0%)	6/661 (0.9%)
General disorders and administration site conditions	13 (4.9%)	7 (2.8%)	24/526 (4.6%)	36/661 (5.4%)
Fatigue	8 (3.0%)	3 (1.2%)	13/526 (2.5%)	25/661 (3.8%)
Asthenia	3 (1.1%)	3 (1.2%)	8/526 (1.5%)	8/661 (1.2%)
Investigations	0	7 (2.8%)	2/526 (0.4%)	5/661 (0.8%)
Aspartate aminotransferase increased	0	3 (1.2%)	1/526 (0.2%)	1/661 (0.2%)
Nervous system disorders	4 (1.5%)	14 (5.6%)	5/526 (1.0%)	6/661 (0.9%)
Neuropathy peripheral	1 (0.4%)	7 (2.8%)	1/526 (0.2%)	1/661 (0.2%)
Skin and subcutaneous tissue disorders	1 (0.4%)	3 (1.2%)	2/526 (0.4%)	5/661 (0.8%)
Palmar-plantar erythrodysaesthesia syndrome	0	3 (1.2%)	0/526 (0.0%)	0/661 (0.0%)

Table 77 Adverse Events Leading to Treatment Interruption of Study Drug Reported in ≥ 1% of Participants

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Participants with Any TEAEs Leading to Interruption of Study Drug	178 (66.4%)	109 (43.8%)	417 (60.6%)	615 (57.9%)
Blood and lymphatic system disorders	143 (53.4%)	71 (28.5%)	326 (47.4%)	450 (42.3%)
Neutropenia	134 (50.0%)	59 (23.7%)	304 (44.2%)	408 (38.4%)
Leukopenia	9 (3.4%)	5 (2.0%)	32 (4.7%)	48 (4.5%)
Anaemia	9 (3.4%)	2 (0.8%)	27 (3.9%)	49 (4.6%)

System Organ Class Preferred Term	IMMU-132-09 SG Treated (N = 268)	IMMU-132-09 TPC (N = 249)	Overall Targeted mBC (N = 688)	All Treated SG (10 mg/kg) (N = 1063)
Thrombocytopenia	4 (1.5%)	7 (2.8%)	10 (1.5%)	11 (1.0%)
Febrile neutropenia	1 (0.4%)	5 (2.0%)	10 (1.5%)	17 (1.6%)
Eye disorders	0	0	3 (0.4%)	4 (0.4%)
Eye pain	0	0	1 (0.1%)	1 (< 0.1%)
Gastrointestinal disorders	19 (7.1%)	8 (3.2%)	50 (7.3%)	92 (8.7%)
Diarrhoea	8 (3.0%)	3 (1.2%)	25 (3.6%)	37 (3.5%)
Nausea	2 (0.7%)	2 (0.8%)	9 (1.3%)	20 (1.9%)
Abdominal pain	6 (2.2%)	1 (0.4%)	8 (1.2%)	11 (1.0%)
Vomiting	2 (0.7%)	2 (0.8%)	7 (1.0%)	17 (1.6%)
General disorders and administration site conditions	10 (3.7%)	13 (5.2%)	36 (5.2%)	70 (6.6%)
Fatigue	3 (1.1%)	2 (0.8%)	7 (1.0%)	24 (2.3%)
Pyrexia	0	3 (1.2%)	10 (1.5%)	15 (1.4%)
Asthenia	3 (1.1%)	2 (0.8%)	6 (0.9%)	9 (0.8%)
Mucosal inflammation	3 (1.1%)	0	3 (0.4%)	4 (0.4%)
Oedema peripheral	0	0	1 (0.1%)	2 (0.2%)
Swelling face	0	0	1 (0.1%)	1 (< 0.1%)
Infections and infestations	26 (9.7%)	11 (4.4%)	66 (9.6%)	103 (9.7%)
Upper respiratory tract infection	2 (0.7%)	0	9 (1.3%)	16 (1.5%)
COVID-19	5 (1.9%)	2 (0.8%)	7 (1.0%)	7 (0.7%)
Urinary tract infection	2 (0.7%)	3 (1.2%)	4 (0.6%)	10 (0.9%)
Pneumonia	1 (0.4%)	1 (0.4%)	6 (0.9%)	11 (1.0%)
Clostridium difficile infection	0	0	3 (0.4%)	4 (0.4%)
Investigations	5 (1.9%)	14 (5.6%)	10 (1.5%)	24 (2.3%)
Alanine aminotransferase increased	2 (0.7%)	9 (3.6%)	2 (0.3%)	4 (0.4%)
Aspartate aminotransferase increased	2 (0.7%)	3 (1.2%)	2 (0.3%)	6 (0.6%)
Metabolism and nutrition disorders	2 (0.7%)	4 (1.6%)	13 (1.9%)	29 (2.7%)
Dehydration	1 (0.4%)	2 (0.8%)	4 (0.6%)	13 (1.2%)
Nervous system disorders	2 (0.7%)	6 (2.4%)	7 (1.0%)	15 (1.4%)
Peripheral sensory neuropathy	0	3 (1.2%)	0	1 (< 0.1%)
Respiratory, thoracic, and mediastinal disorders	9 (3.4%)	5 (2.0%)	27 (3.9%)	41 (3.9%)
Dyspnoea	6 (2.2%)	2 (0.8%)	15 (2.2%)	17 (1.6%)

Post marketing experience

As of 28 June 2022, the cumulative post-marketing exposure is estimated to be 10,837 patients.

There have been no newly identified adverse reactions for SG based on the post-marketing data available to date.

2.5.1. Discussion on clinical safety

Safety data has been provided for 688 patients that received SG 10 mg/kg in the breast cancer pool (BC pool: HR+/HER2- BC (proposed indication) and TNBC patients (approved indication)). The other safety population of interest are patients from the pivotal study IMMU-132-09 (HR+/HER2- breast cancer; n=268 who received SG). The size of the safety data available on breast cancer patients who have received SG at the proposed dose of 10 mg/kg Q3W is considered acceptable. The median treatment duration of SG in study IMMU-132-09 and the mBC pool were 4.11 months and 4.63 months, respectively. A total of 37% of the patients in the mBC pool, which includes the SG-treated patients from study IMMU-132-09, had an exposure of SG for more than 6 months and 13% were exposed for more than 12 months, which is acceptable and considered a relevant exposure for the safety assessment.

All patients experienced at least one **adverse event** (AE) in the pivotal study IMMU-132-09 and the most frequently observed adverse events in the SG arm vs the TPC arm were neutropenia (70.5% vs 54.6%), diarrhoea (61.9% vs 22.9%), nausea (58.6% vs 34%) and alopecia (47.8% vs 18.5%).

Treatment-related AEs (ADRs) with SG vs TPC were also neutropenia (70.1% vs 23.8%), diarrhoea (56.7% vs 16.9%) and nausea (55.2% vs 30.9%). Hematotoxicity and gastrointestinal toxicity was markedly increased with SG vs TPC and clinically significantly more commonly observed.

Grade ≥3 AEs in the SG arm vs the TPC arm were neutropenia (51.5% and 39.0%), diarrhoea (10.1% vs 1.2%), leukopenia (8.6% vs 6.0%), anaemia (7.5% and 3.6%), febrile neutropenia (6.0% vs 4.4%) and fatigue (6.0% vs 3.6%). Treatment-related grade ≥3 adverse events were more frequent in the SG arm (64.6% vs. 51.4%).

Adverse events of special interest included neutropenia, febrile neutropenia, infections, diarrhoea, hypersensitivity, pulmonary events and neuropathy, which are important identified risks of treatment with SG. **Neutropenia** was as expected commonly observed in both the pivotal study IMMU-132-09 (72.8%) and in the BC pool (62.5%) and these events were most often of grade 3 or higher (54.9% vs 53.3%). The majority of these events were assessed to be treatment-related and often led to study drug interruptions and reductions. **Febrile neutropenia** was observed as grade 3 or higher and the incidences were similar in the SG arm and the BC pool, 6% vs 6.3% respectively. Section 4.2 of the SmPC has been updated to reflect the need to administer G-CSF as soon as clinically indicated in case of severe neutropenia, which is considered more conservative and supported. Section 4.4. has also been updated to reflect that fatal infections in the setting of neutropenia have been observed in clinical studies with sacituzumab govitecan.

Adverse events and treatment-related AEs of **diarrhoea** occurred in a higher percentage of participants in the SG group (61.9% and 56.7% of participants, respectively) than in the TPC group (22.9% and 16.9% of participants, respectively) in Study IMMU 132 09. 10.1% had grade 3 or higher events. One participant (0.4%) discontinued SG treatment in Study IMMU 132-09 because of diarrhoea. Incidences and severity of diarrhoea are similar in the SG arm compared to the mBC pool. The SmPC section 4.4 has been updated to reflect that diarrhoea in some cases was observed to have led to dehydration and subsequent acute kidney injury.

Serious Adverse events (SAEs) were observed with 27.6% in SG arm, which was similar to the incidences observed in the mBC pool (28.3%) but considerably higher compared to the TPC arm (19.3%). The most commonly observed SAEs in the BC pool and the SG arm were diarrhoea in 4.1% vs 4.9%, respectively, febrile neutropenia (4.8% vs 4.1%) and neutropenia (2.4% vs 3.0%). Remarkably, approximately 10 % of SAEs were infections and infestations and approximately 2% experienced a sepsis or a septic shock. In the TPC arm, the most common SAEs were febrile neutropenia (4.0%), nausea and pneumonia (2 % each).

Serious infections secondary to neutropenia and severe diarrhoea are currently important identified risk for sacituzumab govitecan. The observed high incidences and frequencies do not warrant any additional updates to the RMP.

In the SG arm, 70.1% had **died,** 63.4% of disease progression and 3.0% of an adverse event. In comparison, more patients had died in the TPC arm, 66.3% of disease progression and no patients died from an adverse event. Hence, treatment with SG carries more severe toxicity, which could be outweighed by fewer cases of disease progression and death compared to standard of care (TPC). Only one out of ten fatal AEs was classified as possibly related to SG treatment. This is considered unlikely, as there were no fatal AEs in the TPC arm. In addition, all, but one patient who died of an AE were at least heterozygous for the UGT1A1*28 allele (patient who died was homozygous for the UGT1A1*28 allele). Considering that this genomic disposition could lead to less tolerability of SG, the higher deaths rates in the SG arm are probably not coincidental. Adequate warnings on the use in patients with reduced UGT1A1 activity are already included in the SmPC section 4.4 (see discussion below on UGT1A1 *28 allele).

In Study IMMU-132-09, 6.3% of the patients in the SG arm **discontinued treatment** due to adverse events, which was only little higher compared to the TPC arm (4.4%) and in line with the rate for the SG-BG pool. Discontinuations rates appeared low taken the high SAE rates into consideration.

Dose reductions of SG were common, and the rates were similar in both SG arm (33.6%) and the TPC arm (32.9%). Most frequent AEs leading to dose reductions were neutropenia and diarrhoea, which is consistent with the known safety profile of SG.

Dose interruptions were even more common and higher the SG arm (66.4%) and the TPC arm (43.8%). Most frequent AEs leading to dose interruptions were neutropenia, leukopenia, and anaemia. The rate of dose reductions and interruptions with SG were high but acceptable considering the targeted non-curative setting.

Regarding **laboratory findings**, the level of haematological toxicity with SG was high, also compared to the haematotoxic TPC (eribulin, vinorelbine, gemcitabine or capecitabine). Regarding shifts in chemistry, the most grade 3 or 4 events in the SG vs the TPC arm were decreased potassium (4.2% vs 0.4%), increased bilirubin (2.3% vs 0.8%) and decreased creatinine (2.3% vs 1.3%). This is considered acceptable. Overall, laboratory findings were in line with the reported AEs.

The incidence of **ADAs** was low in participants who received SG (see clinical pharmacology). Overall, safety was similar between participants with or without ADAs to SG across individual studies and pooled populations. There was no clear impact of ADA on safety.

Data on the **elderly population** are limited. Although there was no difference in discontinuation rate due to adverse events in patients aged 65 years or older compared with younger patients with mTNBC, there was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (14%) compared with younger patients (3%) with HR+/HER2- metastatic breast cancer. There was a higher incidence rate of serious adverse events in patients aged 75 years or older (67%) compared to patients aged 65 years or older (43%) and patients younger than 65 years (24%) with HR+/HER2- metastatic breast cancer (see SmPC section 4.8). Overall, increasing toxicity of SG could be observed with increasing age regarding serious adverse events (SAEs) both in the IMMU-132-09 study and the mBC pool. In addition, all but two patients who died of an adverse event were older than 65 years old, which could be indicating that SG is not tolerable for elderly patients. Section 4.8 of the SmPC has been updated to reflect the increased toxicity observed with age in patients with HR+/HER2- metastatic breast cancer.

An overall summary of TEAEs by race suggested comparable safety profile, so far. Overall, the most common TEAEs reported with SG treatment occurred at a similar incidence rate between Black and White participants in the Overall Targeted mBC and the All Treated SG 10 mg/kg populations. However, interpretation of safety results by racial subgroups was hampered by the small number of participants who were Asian or Black or African American. Given the fact that approximately 20% of the Black or African American population is homozygous for the UGT1A1*28 allele, limited data in this subgroup are of concern (see discussion below on UGT1A1 *28 allele).

SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via UGT1A1. The **UGT1A1 *28 allele** is associated with decreased rates of transcription, initiation, expression, and enzyme activity of UDP-glucuronosyltransferase 1-1 (see EPAR Trodelvy). No significant differences in SG or free SN-38 exposure were observed in participants with the UGT1A1*28/*28 genotype compared with participants with the UGT1A1*1/*1 or UGT1A1*1/*28 genotype. Incidences of AES were high in patients regardless of genotype, however, Grade 3 or higher AEs were reported in a significant higher percentage of participants who were homozygous for the UGT1A1*28 allele (92.0%) compared with participants who were either heterozygous (74.8%) or were homozygous for the UGT1A1*1 allele (67.0%). This applies also to the serious AEs which were reported in half of participants who were homozygous for the UGT1A1*28 allele (48.0%) compared with participants who were either heterozygous (26.9%) or homozygous for the UGT1A1*1 allele (25.2%). This refers also to the 'all SG treated group', were more than 54% of the patients experienced a SAE. Furthermore, compared to patients homozygous for the wild-type allele, earlier median onset of neutropenia and anaemia was observed in patients homozygous for the UGT1A1*28 allele and in patients heterozygous for the UGT1A1*28 allele.

In study IMMU-132-09 this correlation was even more pronounced. Although data are limited (n=25 for the UGT1A1*28/*28 genotype), data suggested that SG could be not tolerable for those patients. Almost all patients (92%) experienced AEs Grade 3 or higher, 48 % an SAE and 1 patient died. 75% of these patients had dose interruptions and 12% discontinued the study due to AEs.

In the approved TNBC population only slightly elevated Grade 3-4 AEs and SAEs were described. With the present variation, the incidences of AEs in patients with reduced UGT1A1 activity have been updated in section 4.8 of the SmPC. The SmPC adequately reflects that individuals who are homozygous for UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anaemia and other adverse reactions following initiation of sacituzumab govitecan treatment. Patients with known reduced UGT1A1 activity should be closely monitored for adverse reactions (see SmPC section 4.4).

The overall toxicity observed with SG mg/kg is considered manageable and in line with what has previously been observed in other clinical trials and the incidences reflected in the BC pool. No new toxicities were observed in the pivotal study. Adequate warnings and recommendations in the SmPC are considered sufficient to mitigate the risks. No additional pharmacovigilance activities are considered necessary, as the risks are sufficiently characterised.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics. The frequencies of the existing ADRs in the approved Trodelvy product information were updated with the frequencies of treatment emergent adverse events (TEAEs) observed in the Overall Targeted mBC pooled population (n=688) which is acceptable.

No new safety concerns have been identified and no changes are made to the pharmacovigilance plan, which is agreed. There is currently one category 3 study ongoing to determine an appropriate starting

dose for patients with moderate to severe hepatic impairment, already agreed at the initial marketing authorisation, which is also considered relevant for the proposed indication (see section 2.6).

As part of the present variation, the MAH has also proposed the removal of 500 mL limit for the infusion bags and specific instruction for patient whose body weight exceeds 170 kg from section 6.6 of the SmPC based on low risk of endotoxin exposure from Trodelvy. The endotoxin acceptance limit of Trodelvy is at 0.05 EU/mg, therefore, the maximum endotoxin exposure introduced from the drug product (at a dose of 10mg/kg) would be 0.5 EU/kg patient weight, which is ≤ 10% of the compendial limit of 5 EU/kg patient weight per hour. As the endotoxin from Trodelvy is significantly low (10% compendial limit of 5 EU/kg), 500 mL limit for the infusion bags and the patient weight limit were removed to allow hospitals to choose appropriate size bags based on the site practices and preference as long as product concentration is within 1.1 – 3.4 mg/mL. Accordingly, the MAH proposed not to include a statement regarding specific instruction for obese patients. This is considered acceptable.

2.5.2. Conclusions on clinical safety

The safety profile of SG is considered rather unfavourable mainly due to high rates of haematological events (severe neutropenia) and gastrointestinal disorders (severe diarrhoea). Nonetheless, toxicities can be regarded as manageable by support with GCS-factor and dose modifications and overall acceptable in the proposed indication of advanced HR+Her2-BC. Given the generally high rates of AEs, Grade 3 AEs, SAEs and deaths, the SmPC has been updated to adequately reflect the tolerability of SG in the fragile elderly population and in the population wit UGT1A1*28 allele.

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 version 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 3.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3.0 with the following content:

Safety concerns

Table 78: Summary of Safety Concerns

Important Identified Risks	Serious infections secondary to neutropenia
	Severe diarrhoea
	Hypersensitivity
Important Potential Risks	Embryo-foetal toxicity

Missing Information	Use in patients with moderate or severe hepatic impairment
	Immunogenicity

Pharmacovigilance plan

Table 79. 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 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	To identify the safe starting dose of SG in 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.	Use in patients with moderate or severe hepatic impairment	Protocol finalised	30-Oct-2020
			First subject enrolled	Apr-2021
			Last subject completed	Jun-2023
			CSR filing	Dec-2023

CSR= clinical study report; SG=sacituzumab govitecan; PK=pharmacokinetics

Risk minimisation measures

Table 80: Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important identified risks		
Serious infections secondary to neutropenia	Routine risk minimisation measures: • Dose modifications based on severity and occurrence in SmPC section 4.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Warnings of severe or life-threatening neutropenia, including fatal infections in the setting of neutropenia observed in clinical studies, 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	Additional pharmacovigilance activities: • None
Severe diarrhoea	Routine risk minimisation measures: • Dose modifications based on severity and occurrence in SmPC section 4.2 • Warning of severe diarrhoea, including cases observed to have led to dehydration and subsequent acute kidney injury, and recommendation for medication/supportive measures in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • 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
Hypersensitivity	Routine risk minimisation measures: • Guidance and warning for patient monitoring in SmPC sections 4.2 and 4.4, respectively	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Contraindication in SmPC section 4.3 and PL section 2 • Warning for severe hypersensitivity in SmPC section 4.4 • Warning that pre-infusion treatment is recommended in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • Warning in PL section 2 • Side effect in PL section 4 • Restricted medical prescription Additional risk minimisation measures: • None	• None
Important potential risk		
Embryo-foetal toxicity	Routine risk minimisation measures: • Warning and information of the risk of teratogenicity and/or embryo-foetal lethality in SmPC sections 4.4 and 4.6, respectively • Warning and recommendation to verify the pregnancy status of women of childbearing potential prior to use in SmPC sections 4.4 and 4.6, respectively • Recommendation in the case of pregnancy to immediately contact the doctor in SmPC section 4.6 • Recommendation for use of effective contraception during treatment and for up to 6 months after the last dose for female patients and up to 3 months after the last dose for male patients with female partners of childbearing potential in SmPC section 4.6 • Information that SN-38 was clastogenic in SmPC section 5.3 • Warning that TRODELVY should not be used during pregnancy in PL section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Warning to use effective contraception in PL section 2 • Restricted medical prescription Additional risk minimisation measures: • 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 • Restricted medical prescription Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study IMMU-132-15
Immunogenicity	Routine risk minimisation measures: • Available clinical data on SG immunogenicity in 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 result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet (PL) is updated accordingly. The MAH has also taken the opportunity to introduce minor modifications related to the QRD Template and SmPC guideline.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet or a focus test with target patient groups on the updated package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The package leaflet (PL) has been amended with minimal wording to include a new indication for 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.

Therefore, the updates to the PL in this variation consequential to the extension of indication are slight. The key safety messages as well as the design and layout of the package leaflet are not significantly affected. Overall, there seems no negative impact on the readability.

A full user consultation was provided with the dossier of the initial marketing authorisation which demonstrates the success criteria.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication is as follows: "Trodelvy as monotherapy is indicated 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 (see section 5.1)."

HR+/HER2− breast cancer, characterized by hormone receptor positivity (> 1% IHC ER and/or PR) and lack of HER2 expression (IHC score of 0, 1+, or 2+/FISH−), is the most commonly diagnosed breast cancer type.

3.1.2. Available therapies and unmet medical need

Endocrine therapy combined with a CDK 4/6 inhibitor is the current standard of care for patients with newly diagnosed HR+/HER2− metastatic BC (mBC). Subsequent treatment options include sequential alternative endocrine regimens as a single agent or in combination with targeted agents including mTOR inhibitors and PI3K inhibitors, depending on PI3K mutation status.

Treatment options for endocrine resistant/refractory disease include single-agent chemotherapy. PARP inhibitor monotherapy is an option for a subset of patients (< 10%) with HR+/HER2− mBC and BRCA1/2 mutations.

Trastuzumab deruxtecan was approved in January 2023 for the treatment of HER2-low breast cancer (IHC score of 1+ or 2+/ISH−) who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

In metastatic disease stage, HR+/HER2− has the second worst prognosis after metastatic TNBC with a 5-year survival rate of 30%, so there remains an unmet medical need for endocrine-resistant, chemotherapy experienced HR+/HER2- mBC patients.

3.1.3. Main clinical study

Study IMMU-132-09 is an ongoing, open-label, randomized, global Phase 3 study to compare SG versus treatment physician's choice (single-agent treatment of eribulin, capecitabine, gemcitabine or vinorelbine) in participants with 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 treatment regimens for metastatic disease. The primary endpoint was progression free survival (PFS) as determined by BICR using RECIST v1.1. Secondary endpoints in the hierarchical testing procedure for multiplicity adjustment included overall survival, objective response rate (ORR) as determined by BICR using RECIST v1.1 and time to deterioration (TTD) in QOL assessments.

3.2. Favourable effects

The open-label, randomized Phase 3 study IMMU-132-09 evaluated the efficacy of SG versus TPC as control in 543 participants with metastatic HR+/HER2− breast cancer (SG n=272; TPC n=271). As of the data cutoff date (01 July 2022, OS IA2), the median follow-up duration was 12.48 months (13.80 months [range: 0.03-35.48] in the SG arm and 10.68 months [range: 0.03-33.15] in the TPC arm). The data cutoff date for primary PFS analysis was 03-Jan-2022.

Statistically significant improvements in the SG group vs the TPC group were observed in:

- PFS per BIRC (HR 0.66; 95% CI 0.53, 0.83; *P* = 0.0003);
  Median 5.5 vs 4.0 months (at primary PFS analysis; 03 Jan 2022)
- OS (HR 0.79; 95% CI 0.65, 0.96; *P* = 0.02), significant at nominal α=0.0223),
  Median 14.4 vs 11.2 months (at OS IA2; 01 Jul 2022)
- ORR per BICR (21% vs 14%; OR 1.63; 95% CI 1.03, 2.56, *P* = 0.0348)

3.3. Uncertainties and limitations about favourable effects

Highly variable efficacy results were observed for subgroups by TPC chemotherapy agents that remain difficult to interpret. Overall, it has to be acknowledged that the heterogeneous subgroup results do not appear to be plausible and the sample sizes are too small to draw reliable conclusions on a differential effect of SG.

Only a low proportion of patients with brain metastasis (4.6%) and age ≥ 75 years (4.4%) were recruited; thus, no valid conclusions on efficacy can be drawn in these subgroups. These limitations are reflected in the SmPC.

Efficacy endpoints (PFS, ORR, OS, DOR, CBR) were analyzed according to Trop-2 expression to identify any potential correlation with clinical outcome-related endpoints (selected exploratory endpoints). Conclusions on efficacy by Trop-2 expression is hampered by the retrospective/explorative testing and deficiencies regarding analytical and clinical validation (see section 3.7.3).

3.4. Unfavourable effects

Almost all of the patients experienced **adverse events** in the pivotal study and both safety pools and most adverse events were treatment-related. Common AEs were neutropenia (70.5%), diarrhoea (61.9%), nausea (58.8%), fatigue and alopecia (47.8%) anaemia (39.5%). Neutropenia was the most common Grade ≥ 3 AE; other Grade ≥ 3 AEs occurring in at least 5% of patients were: diarrhoea, leukopenia, anaemia, febrile neutropenia and fatigue.

Events of special interest included diarrhoea, neutropenia, febrile neutropenia, infections, neuropathy hypersensitivity and interstitial lung disease.

Serious adverse events (SAEs) were observed with a frequency of 27.6% in the SG arm. The most common (>2%) SAEs in the SG arm were febrile neutropenia (4.1%), neutropenia (3.0%) and diarrhoea (4.9%).

Overall, 70.1% had died, 63.4% of disease progression and 3.0% of an adverse event, mostly occurring more than 30 days after last study drug administration.

The percentage of patients with an AE leading to permanent discontinuation of study drug was low (6.3%). Asthenia and neutropenia (0.7% each) were the only AEs leading to permanent discontinuation of study drug that occurred in more than 1 patient in the SG group in Study IMMU-132-09.

3.5. Uncertainties and limitations about unfavourable effects

Only a low proportion of patients with age ≥ 75 years (4.4%) were recruited; therefore, no firm conclusions can be drawn based on these limited numbers. However available data suggest worse tolerability and increased SAEs in elderly patients with HR+/HER2- metastatic breast cancer. This is reflected in the SmPC.

Safety according to the UGT1A1 genotype was provided indicating a decreased tolerability in patients with UGT1A1*28 allele. Adequate information and warnings are included in the SmPC.

3.6. Effects Table

Table 81: Effects Table for Trodelvy (SG) for the treatment of unresectable or metastatic HR+/HER2- BC after prior endocrine-based therapy, and at least two additional systemic therapies in the advanced setting (data cut-off: 03-Jan-2022 for primary PFS analysis and 01-Jul-2022 for OS IA2 and other endpoints)

Effect	Short description	Unit	SG	TPC	Uncertainties / Strength of evidence
Favourable Effects in ITT population					
PFS, median	Based on BICR per RECIST 1.1	months	5.5	4.0	Highly variable efficacy results were observed for subgroups by TPC chemotherapy agents Low proportion of patients with brain metastasis and age ≥ 75 years
		HR, 95% CI	0.66 (0.53, 0.83)		
OS, median	Time from randomization until death	months	14.4	11.2	
		HR, 95% CI	0.79 (0.65, 0.96)		

Unfavourable Effects					
Safety and Tolerability	Drug-related AEs	%	97.0	87.1	Patients with UGT1A1*28 allele are at increased risk (see SmPC sections 4.4 and 4.8) Safety in elderly is limited and probably unfavourable (see SmPC section 4.8)
	G 3-5 AEs	%	73.9	60.2	
	SAEs	%	27.6	19.3	
	Death due to drug-related AEs	%	0.4	0	
	Discontinuation due to drug-related AEs	%	6.3	4.4	
Drug-related AEs	Neutropenia	%	70.5	54.6	
	Diarrhoea	%	61.9	22.9	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Sacituzumab govitecan demonstrated statistically significant improvements in PFS and OS over an acceptable comparator of TPC with single agent chemotherapies in heavily pre-treated patients with HR+/HER2− metastatic breast cancer. The overall data package supports a clinically relevant benefit of SG in this advanced disease setting.

The safety profile of SG is considered rather unfavourable compared to the chemotherapeutic agents of the control arm, mainly due to high rates of haematological events (severe neutropenia) and gastrointestinal disorders (severe diarrhoea). Nonetheless, toxicities can be regarded as manageable by support with GCS-factor and dose modifications.

3.7.2. Balance of benefits and risks

The observed improvement of 3.2 months in median overall survival in this advanced patient population can be considered a clinically relevant benefit which outweighs the increased toxicities compared to standard chemotherapy options in the overall study population.

3.7.3. Additional considerations on the benefit-risk balance

Overall, Trop-2 expression data suggest an association of Trop2 expression with efficacy of SG, but the evidence of the provided data is not considered valid enough to determine a cutoff of Trop-2 expression below that patients would certainly not derive any benefit from SG. Thus, a restriction of the indication to a subgroup of patients with higher Trop-2 tumor expression is not considered justified. It has however to be emphasized that any conclusions on efficacy by Trop-2 expression is hampered by the retrospective/explorative testing and the described deficiencies regarding analytical and clinical validation.

3.8. Conclusions

The overall B/R of Trodelvy as monotherapy 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 is

considered 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 - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include 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 based on final results from study IMMU-132-09 (TROPiCS-02); this is an open-label, randomized, multicenter phase 3 study of sacituzumab govitecan (IMMU-132) versus treatment of physician's choice (TPC) in subjects with hormonal receptor-positive (HR+) human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer (mBC) who have failed at least two prior chemotherapy regimens. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet (PL) is updated accordingly. Version 3.0 of the RMP is approved. The MAH has also taken the opportunity to introduce minor modifications to the product information related to the QRD Template and SmPC guideline.

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.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Trodelvy-H-C-5182-II-20'