

1. NAME OF THE MEDICINAL PRODUCT

Trodely 200 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 200 mg sacituzumab govitecan.

After reconstitution, one mL of solution contains 10 mg sacituzumab govitecan.

Sacituzumab govitecan is a Trop-2-directed antibody-drug conjugate (ADC). Sacituzumab is a humanised monoclonal antibody (hRS7 IgG1κ) that recognises Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a hydrolysable linker. Approximately 7-8 molecules of SN-38 are attached to each antibody molecule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

Off-white to yellowish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Triple-Negative Breast Cancer

Trodely is indicated:

- in combination with pembrolizumab, for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have not received prior systemic therapy for metastatic disease and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (see sections 4.2 and 5.1).
- as monotherapy for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have not received prior systemic therapy for metastatic disease and who are not candidates for PD-1 or PD-L1 inhibitor therapy (see section 5.1).
- as monotherapy for the treatment of adult patients with unresectable or metastatic TNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease (see section 5.1)

HR-Positive, HER2-Negative Breast Cancer

Trodely 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).

4.2 Posology and method of administration

Trodely must only be prescribed and administered to patients by healthcare professionals experienced in the use of anti-cancer therapies and administered in an environment where full resuscitation facilities are available.

Patient Selection

PD-L1 testing for treatment with sacituzumab govitecan in combination with pembrolizumab should be assessed by a CE-marked in vitro diagnostic (IVD) intended for use with pembrolizumab. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1 and 5.1).

Posology

The recommended dose of sacituzumab govitecan as monotherapy or in combination with pembrolizumab 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.

Patients should be administered sacituzumab govitecan before pembrolizumab when given on the same day.

Refer to the pembrolizumab Summary of Product Characteristics (SmPC) for dosing information on pembrolizumab.

Prevention treatment

Prior to each dose of sacituzumab govitecan, treatment for prevention of infusion-related reactions and prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended (see section 4.4).

Prophylaxis for neutropenia

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) should be considered starting in the first cycle in patients at increased risk of febrile neutropenia (see section 4.4).

Dose modifications for adverse reactions for sacituzumab govitecan

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of sacituzumab govitecan. The recommended dose reduction schedule is presented in Table 1 and the recommended dose modifications for adverse reactions are provided in Table 2. The sacituzumab govitecan dose should not be re-escalated after a dose reduction for adverse reactions has been made.

Table 1: Dose reduction schedule

Dose reduction schedule	Dose level
Recommended starting dose	10 mg/kg
First dose reduction	Reduce to 7.5 mg/kg
Second dose reduction	Reduce to 5 mg/kg
Requirement for further dose reduction	Discontinue treatment

Table 2: Recommended dose modifications for adverse reactions

Adverse reactions	Severity	Dose modification
Neutropenia	- Grade 3-4 neutropenia (Absolute Neutrophil Count [ANC]<1000/mm³) - Grade 3-4 febrile neutropenia (ANC<1000/mm³)	- Withhold treatment until resolved to ≤ Grade 1 (ANC ≥ 1500/mm³) for Day 1 dose or Grade 2 (ANC ≥ 1000/mm³) for Day 8 dose (see section 4.4). - Administer G-CSF during treatment as clinically indicated. - For subsequent Grade 3-4 febrile neutropenia events or subsequent prolonged Grade 3-4 neutropenia events, reduce one dose level with each recurrence or discontinue according to Table 1.
Nausea/Vomiting/Diarrhoea	Grade 3-4 nausea, vomiting or diarrhoea due to treatment that is not controlled with antiemetics and anti-diarrheal agents	- Withhold treatment until resolved to ≤ Grade 1 (see section 4.4). - Reduce one dose level with each occurrence or discontinue according to Table 1.
Infusion-related reaction	Grade 1-3 infusion-related reactions	Slow or interrupt the infusion rate of sacituzumab govitecan
	Grade 4 infusion-related reactions	Discontinue treatment
Other Toxicities	Other Grade 3-4 toxicities of any duration despite optimal medical management	- Withhold treatment until resolved to ≤ Grade 1. - Reduce one dose level with each occurrence or discontinue according to Table 1.

Dose modifications for adverse reactions for sacituzumab govitecan in combination with pembrolizumab

When sacituzumab govitecan is administered in combination with pembrolizumab, treatment with one or both medicines should either be interrupted, discontinued or the dose of sacituzumab govitecan should be reduced to manage adverse reactions as appropriate, as described in Table 1 and Table 2. For recommendations for management of adverse reactions of pembrolizumab, refer to the pembrolizumab SmPC.

Special populations

Elderly

No dose adjustment is required in patients ≥ 65 years old. Data from sacituzumab govitecan in patients ≥ 75 years are limited.

Hepatic impairment

No adjustment to the starting dose is required when administering sacituzumab govitecan to patients with mild hepatic impairment (bilirubin ≤ 1.5 upper limit of normal [ULN] and aspartate aminotransferase [AST]/alanine aminotransferase [ALT] < 3 ULN).

The safety of sacituzumab govitecan in patients with moderate or severe hepatic impairment has not been established. Sacituzumab govitecan has not been studied in patients with any of the following: serum bilirubin > 1.5 ULN, or AST or ALT > 3 ULN in patients without liver metastases, or AST or ALT > 5 ULN in patients with liver metastases. The use of sacituzumab govitecan should be avoided in these patients.

Renal impairment

No adjustment to the starting dose is required when administering sacituzumab govitecan to patients with mild or moderate renal impairment.

Sacituzumab govitecan has not been studied in patients with severe renal impairment or end-stage renal disease (Creatinine Clearance [CrCl] < 15 mL/min).

Paediatric population

The safety and efficacy of sacituzumab govitecan in children aged 0 to 18 years have not been established. No data are available.

Method of administration

Sacituzumab govitecan is for intravenous use only. It must be reconstituted and diluted by a healthcare professional experienced in the handling of anti-cancer therapies. It must be administered as an intravenous infusion, not as an intravenous push or bolus.

First infusion: the infusion should be administered over a period of 3 hours.

Subsequent infusions: the infusion should be administered over a period of 1 to 2 hours if prior infusions were tolerated.

Patients have to be observed during each infusion and for at least 30 minutes after each infusion for signs or symptoms of infusion-related reactions (see section 4.4).

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Neutropenia

Sacituzumab govitecan can cause severe or life-threatening neutropenia (see section 4.8). Fatal infections in the setting of neutropenia have been observed in clinical studies with sacituzumab govitecan, primarily in the first two cycles of treatment.

Primary prophylaxis with G-CSF should be considered starting in the first cycle of treatment in patients at increased risk of febrile neutropenia, e.g., older patients (in particular aged 65 years and older), patients with previous neutropenia, poor performance status, organ dysfunction (including renal, liver or cardiovascular dysfunction), or multiple comorbid conditions. Monitor ANC during treatment.

Sacituzumab govitecan should not be administered if the ANC is below 1500/mm³ on Day 1 of any cycle or if the neutrophil count is below 1000/mm³ on Day 8 of any cycle. Sacituzumab govitecan should not be administered in case of neutropenic fever. Dose modifications may be required due to neutropenia or febrile neutropenia. Treat neutropenia with G-CSF and consider prophylaxis in subsequent cycles as clinically indicated (see sections 4.2 and 4.8).

Diarrhoea

Sacituzumab govitecan can cause severe diarrhoea (see section 4.8). Diarrhoea in some cases was observed to have led to dehydration and subsequent acute kidney injury. Sacituzumab govitecan should not be administered in case of Grade 3-4 diarrhoea at the time of scheduled treatment and treatment should only be continued when resolved to $\leq$ Grade 1 (see section 4.2 and 4.8). At the onset of diarrhoea, and if no infectious cause can be identified, treatment with loperamide should be initiated. Additional supportive measures (e.g. fluid and electrolyte substitution) may also be employed as clinically indicated.

Patients who exhibit an excessive cholinergic response to treatment with sacituzumab govitecan (e.g. abdominal cramping, diarrhoea, salivation, etc.) can receive appropriate treatment (e.g. atropine) for subsequent treatments with sacituzumab govitecan.

Hypersensitivity

Sacituzumab govitecan can cause severe and life-threatening hypersensitivity (see section 4.8). Anaphylactic reactions have been observed in clinical studies with sacituzumab govitecan and the use of sacituzumab govitecan is contraindicated in patients with a known hypersensitivity to sacituzumab govitecan (see section 4.3).

Pre-infusion treatment, including antipyretics, H1 and H2 blockers, or corticosteroids (e.g. 50 mg hydrocortisone or equivalent, orally or intravenously), for patients receiving sacituzumab govitecan is recommended. Patients should be closely observed for infusion-related reactions during each sacituzumab govitecan infusion and for at least 30 minutes after completion of each infusion. The infusion rate of sacituzumab govitecan should be slowed down or infusion interrupted if the patient develops an infusion-related reaction. Sacituzumab govitecan should be permanently discontinued if life-threatening infusion-related reactions occur (see section 4.2).

Nausea and vomiting

Sacituzumab govitecan is emetogenic (see section 4.8). Antiemetic preventive treatment with two or three medicinal products (e.g. dexamethasone with either a 5-hydroxytryptamine 3 [5-HT₃] receptor antagonist or a Neurokinin-1 [NK-1] receptor antagonist as well as other medicinal products as indicated) is recommended for prevention of chemotherapy-induced nausea and vomiting (CINV).

Sacituzumab govitecan should not be administered in case of Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and treatment should only be continued with additional supportive measures when resolved to $\leq$ Grade 1 (see section 4.2). Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medicinal products with clear instructions for prevention and treatment of nausea and vomiting.

Use in patients with reduced UGT1A1 activity

SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via uridine diphosphate-glucuronosyl transferase (UGT1A1). Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous for UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anaemia and are at increased risk for other adverse reactions following initiation of sacituzumab govitecan treatment (see section 4.8). A higher incidence of Grade 3-4 neutropenia, febrile neutropenia, and anaemia was observed in patients homozygous for the UGT1A1*28 allele and patients heterozygous for the UGT1A1*6 allele compared to patients homozygous for the wild-type allele. Approximately 20% of the Black population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. Approximately 0.2% of the Black population, 0.3% of the White population, and 27% of the East Asian population are heterozygous for the UGT1A1*6 allele. Variants in other alleles potentially associated with reduced UGT1A1 enzyme activities might be

prevalent in certain populations. Patients with known reduced UGT1A1 activity should be closely monitored for adverse reactions. When unknown, no testing of UGT1A1 status is required as the management of adverse reactions including the recommended dose modifications will be the same for all patients.

Embryo-foetal toxicity

Based on its mechanism of action, sacituzumab govitecan can cause teratogenicity and/or embryo-foetal lethality when administered to a pregnant woman. Sacituzumab govitecan contains a genotoxic component, SN-38, and targets rapidly dividing cells. Pregnant women and women of childbearing potential should be informed of the potential risk to the foetus. The pregnancy status of females of reproductive potential should be verified prior to the initiation of sacituzumab govitecan (see section 4.6).

Sodium

This medicinal product will be further prepared for administration with sodium-containing solution (see section 6.6) and this should be considered in relation to the total sodium intake to the patient from all sources per day.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

UGT1A1 inhibitors

Concomitant administration of sacituzumab govitecan with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Sacituzumab govitecan should be used with caution in patients receiving UGT1A1 inhibitors (e.g. propofol, ketoconazole, EGFR tyrosine kinase inhibitors).

UGT1A1 inducers

Exposure to SN-38 may be reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Sacituzumab govitecan should be used with caution in patients receiving UGT1A1 inducers (e.g. carbamazepine, phenytoin, rifampicin, ritonavir, tipranavir).

Based on the limited data available from patients who received UGT1A1 inhibitors (n=15) or inducers (n=7) while being treated with sacituzumab govitecan, free SN-38 exposures in these patients were comparable to those in patients who did not receive UGT1A1 inhibitor or inducer.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential have to use effective contraception during treatment and for 6 months after the last dose.

Male patients with female partners of childbearing potential have to use effective contraception during treatment with sacituzumab govitecan and for 3 months after the last dose.

Pregnancy

There are no available data on the use of sacituzumab govitecan in pregnant women. However, based on its mechanism of action, sacituzumab govitecan can cause teratogenicity and/or embryo-foetal lethality when administered during pregnancy. Sacituzumab govitecan contains a genotoxic component, SN-38, and targets rapidly dividing cells.

Sacituzumab govitecan should not be used during pregnancy unless the clinical condition of the woman requires treatment with sacituzumab govitecan.
The pregnancy status of women of childbearing potential should be verified prior to the initiation of sacituzumab govitecan.
Women who become pregnant must immediately contact their doctor.

Breast-feeding

It is unknown whether sacituzumab govitecan or its metabolites are excreted in human milk. A risk to breastfed newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with sacituzumab govitecan and for 1 month after the last dose.

Fertility

Based on findings in animals, sacituzumab govitecan may impair fertility in females of reproductive potential (see section 5.3). No human data on the effect of sacituzumab govitecan on fertility are available.

4.7 Effects on ability to drive and use machines

Sacituzumab govitecan has minor influence on the ability to drive and use machines, e.g. dizziness, fatigue (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Sacituzumab govitecan as monotherapy

The most common adverse reactions reported in patients treated with sacituzumab govitecan were: neutropenia (67.3%), nausea (62.1%), diarrhoea (59.9%), fatigue (57.4%), alopecia (48.3%), anaemia (40.1%), constipation (36.7%), vomiting (31.3%), and decreased appetite (23.3%).

The most common grade 3 or higher adverse reactions were neutropenia (48.6%), diarrhoea (10.0%), leukopenia (9.6%), anaemia (7.7%), fatigue (5.8%), febrile neutropenia (5.6%), and lymphopenia (3.1%).

The most frequently reported serious adverse reactions in patients treated with sacituzumab govitecan were febrile neutropenia (4.5%), diarrhoea (3.7%), neutropenia (2.9%) and pneumonia (2.1%).

Sacituzumab govitecan in combination with pembrolizumab

Adverse reactions occurring in patients treated with sacituzumab govitecan in combination with pembrolizumab were generally similar to those observed with sacituzumab govitecan or pembrolizumab in breast cancer treatment. The most frequent adverse reactions in patients treated with sacituzumab govitecan in combination with pembrolizumab were diarrhoea (70.1%), nausea (67.9%), neutropenia (62.9%), fatigue (58.4%), alopecia (51.6%), constipation (40.7%), anaemia (36.7%) and vomiting (29.4%), and the most frequent grade 3 or higher adverse reactions were neutropenia (43.0%) and diarrhoea (10.0%).

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

When sacituzumab govitecan is administered in combination with pembrolizumab, refer to the SmPC for the respective combination therapy components prior to initiation of treatment. Adverse reactions known to occur with sacituzumab govitecan or combination therapy components given alone may

occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with combination therapy.

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on pooled data from four clinical studies involving 963 patients who received sacituzumab govitecan 10 mg/kg body weight for the treatment of metastatic TNBC and HR+/HER2- breast cancer. The median exposure to sacituzumab govitecan in this data set was 5.29 months.

The safety of sacituzumab govitecan in combination with pembrolizumab has also been evaluated in a clinical study of 221 patients with metastatic TNBC whose tumours express PD-L1 receiving sacituzumab govitecan 10 mg/kg on Days 1 and 8 and pembrolizumab 200 mg on Day 1 of a 21-day cycle. The median exposure of sacituzumab govitecan in the combination therapy data set was 8.9 months.

Adverse reactions observed in clinical studies of sacituzumab govitecan as monotherapy or in combination with pembrolizumab or reported from post-marketing use of sacituzumab govitecan are listed in Table 3. The adverse reaction frequencies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than sacituzumab govitecan, such as the disease, other medicinal products or unrelated causes. The severity of adverse drug reactions was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE), defining grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, and 5 = death.

Adverse reactions are listed by System Organ Class and frequency category. Frequency categories are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\,000$ to $< 1/100$); rare ($\geq 1/10\,000$ to $< 1/1\,000$); very rare ($< 1/10\,000$); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: List of adverse reactions

System organ class (SOC) and Frequency	Monotherapy	In combination with pembrolizumab
Infections and infestations		
Very common	Urinary tract infection Upper respiratory tract infection	Urinary tract infection Upper respiratory tract infection
Common	Sepsis Pneumonia Influenza Bronchitis Nasopharyngitis Sinusitis Oral herpes	Sepsis Pneumonia Influenza Bronchitis Nasopharyngitis Sinusitis Oral herpes
Blood and lymphatic system disorders		
Very common	Neutropenia ¹ Anaemia ² Leukopenia ³ Lymphopenia ⁴	Neutropenia ¹ Anaemia ² Leukopenia ³
Common	Febrile neutropenia Thrombocytopenia ⁵	Febrile neutropenia Lymphopenia ⁴ Thrombocytopenia ⁵
Immune system disorders		
Very common	Hypersensitivity ⁶	Hypersensitivity ⁶

System organ class (SOC) and Frequency	Monotherapy	In combination with pembrolizumab
Metabolism and nutrition disorders		
Very common	Decreased appetite Hypokalaemia Hypomagnesaemia	Decreased appetite
Common	Dehydration Hyperglycaemia Hypophosphataemia Hypocalcaemia Hyponatraemia	Dehydration Hyperglycaemia Hypokalaemia Hypomagnesaemia Hypophosphataemia Hypocalcaemia Hyponatraemia
Psychiatric disorders		
Common	Insomnia Anxiety	Insomnia Anxiety
Nervous system disorders		
Very common	Headache Dizziness	Headache Dizziness
Common	Dysgeusia	Dysgeusia
Vascular disorders		
Common	Hypotension	Hypotension
Respiratory, thoracic and mediastinal disorders		
Very common	Dyspnoea ⁷ Cough	Cough
Common	Epistaxis Productive cough Rhinorrhoea Nasal congestion Upper airway cough syndrome	Dyspnoea ⁷ Epistaxis Productive cough Rhinorrhoea Nasal congestion
Uncommon		Upper airway cough syndrome
Gastrointestinal disorders		
Very common	Diarrhoea Vomiting Constipation Stomatitis Nausea Abdominal pain	Diarrhoea Vomiting Constipation Stomatitis Nausea Abdominal Pain
Common	Neutropenic colitis ⁸ Colitis Abdominal pain upper Dyspepsia Gastrooesophageal reflux disease Abdominal distension	Colitis Abdominal pain upper Dyspepsia Gastrooesophageal reflux disease Abdominal distension
Uncommon	Enteritis	Neutropenic colitis ⁸ Enteritis
Skin and subcutaneous tissue disorders		
Very common	Alopecia Rash Pruritus	Alopecia Rash Pruritus
Common	Rash maculopapular Skin hyperpigmentation Dermatitis acneiform Dry skin	Rash maculopapular Skin hyperpigmentation Dermatitis acneiform Dry skin
Musculoskeletal and connective tissue disorders		
Very common	Back pain Arthralgia	Back pain Arthralgia
Common	Musculoskeletal chest pain Muscle spasms	Musculoskeletal chest pain Muscle spasms

System organ class (SOC) and Frequency	Monotherapy	In combination with pembrolizumab
Renal and urinary disorders		
Common	Haematuria Proteinuria Dysuria	Haematuria Proteinuria Dysuria
General disorders and administration site conditions		
Very common	Fatigue ⁹	Fatigue ⁹
Common	Pain Chills	Pain Chills
Investigations		
Very common	Blood alkaline phosphatase increased	Weight decreased Blood alkaline phosphatase increased
Common	Weight decreased Activated partial thromboplastin time prolonged Blood lactate dehydrogenase increased	Blood lactate dehydrogenase increased
Injury, poisoning and procedural complications		
Common	Infusion related reaction	Infusion related reaction

1: Includes the following preferred terms: neutropenia; neutrophil count decreased.

2: Includes the following preferred terms: anaemia; haemoglobin decreased; red blood cell count decreased.

3: Includes the following preferred terms: leukopenia; white blood cell count decreased.

4: Includes the following preferred terms: lymphopenia; lymphocyte count decreased.

5: Includes the following preferred terms: thrombocytopenia; platelet count decreased.

6: Hypersensitivity events reported up to the end of the day after treatment was administered. Includes events coded to the following preferred terms: rash, infusion related reaction, hypersensitivity, periorbital oedema, catheter site dermatitis, contrast media reaction, dermatitis allergic, dermatitis contact, eczema, rash erythematous, urticaria, anaphylactic reaction, bronchospasm, conjunctivitis allergic, dermatitis, dermatitis acneiform, dermatitis exfoliative generalised, drug hypersensitivity, infusion related hypersensitivity reaction, rash macular, rash maculo-papular, rash papular, rash pustular, rhinitis allergic, swelling face, swelling of eyelid, swollen tongue, Type IV hypersensitivity reaction, cough with pruritus, cough with rash, dyspnoea with pruritus, dyspnoea with rash, dyspnoea with wheezing and rash, hypotension with dyspnoea

7: Includes the following preferred terms: dyspnoea; dyspnoea exertional

8: Includes the preferred term of neutropenic colitis and events reported as typhilitis

9: Includes the following preferred terms: fatigue, asthenia

Description of selected adverse reactions

The data below reflect information for significant adverse reactions for sacituzumab govitecan as monotherapy in clinical trials (see section 5.1). The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

Neutropenia

The median time to onset of neutropenia (including febrile neutropenia) following the start of the first treatment cycle was 20 days. The median duration of neutropenia was 10 days.

Neutropenia occurred in 67.3% of patients treated with sacituzumab govitecan, including Grade 3-4 neutropenia in 48.6% of patients. Neutropenia was the reason for dose reduction in 14.2% of patients. Neutropenic colitis was observed in 1.3% of patients. Fatal infections secondary to neutropenia (including neutropenic colitis) occurred in 0.6% of patients.

Febrile neutropenia occurred in 5.6% of patients treated with sacituzumab govitecan. Febrile neutropenia was the reason for dose reduction in 2.7% of patients.

Use in patients with reduced UGT1A1 activity

The incidence of Grade 3-4 neutropenia was 59.6% in patients homozygous for the UGT1A1*28 allele, 50.7% in patients heterozygous for the UGT1A1*28 allele, and 44.9% in patients homozygous for the wild-type allele. The incidence of Grade 3-4 febrile neutropenia was 10.6% in patients homozygous for the UGT1A1*28 allele, 5.9% in patients heterozygous for the UGT1A1*28 allele, and 4.3% in patients homozygous for the wild-type allele. The incidence of Grade 3-4 anaemia was

10.6% in patients homozygous for the UGT1A1*28 allele, 6.4% in patients heterozygous for the UGT1A1*28 allele, and 6.3% in patients homozygous for the wild-type allele. For patients heterozygous for the UGT1A1*6 allele, the incidences of Grade 3-4 neutropenia, febrile neutropenia, and anaemia were 53.8%, 7.7%, and 7.7%, respectively.

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.

Diarrhoea

The median time to onset of diarrhoea following the start of the first treatment cycle was 13 days. The median duration of diarrhoea was 7 days.

Diarrhoea occurred in 59.9% of patients treated with sacituzumab govitecan. Grade 3 events occurred in 10.0% of patients. Four of 963 patients (< 1%) discontinued treatment because of diarrhoea.

Hypersensitivity

Hypersensitivity reactions reported up to the end of the day following dosing occurred in 12.8% of patients treated with sacituzumab govitecan. Grade 3 and above hypersensitivity occurred in 0.5% of patients treated with sacituzumab govitecan. The incidence of hypersensitivity reactions leading to permanent discontinuation of sacituzumab govitecan was 0.2%.

Immunogenicity

Across clinical studies in patients treated with sacituzumab govitecan, 13 (1.2%) of 1058 patients developed antibodies to sacituzumab govitecan following administration; 10 of these patients (0.9% of all patients treated with sacituzumab govitecan) had neutralizing antibodies against sacituzumab govitecan. In study ASCENT-04, no treatment-emergent antibodies against sacituzumab govitecan were observed in 207 patients who were evaluable for antibodies against sacituzumab govitecan and received sacituzumab govitecan 10 mg/kg in combination with pembrolizumab.

Special Populations

There was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (8%) compared with younger patients (4%) with metastatic breast cancer. Higher incidence rates of febrile neutropenia and severe diarrhoea were observed in patients aged 65 years or older. A higher incidence rate of fatal infections was observed in patients aged 65 years or older. There was a higher incidence rate of serious adverse events in patients aged 75 years or older (52%) compared to patients aged 65 years or older (35%) and patients younger than 65 years (25%) with metastatic breast cancer.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

Ireland

HPRA Pharmacovigilance

Website: www.hpra.ie

Malta

ADR Reporting Website: <https://medicinesauthority.gov.mt/adrportal>

4.9 Overdose

In clinical studies, doses of up to 18 mg/kg (approximately 1.8 times the maximum recommended dose of 10 mg/kg body weight) led to a higher incidence of severe neutropenia.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, in particular severe neutropenia, and appropriate treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies, and antibody drug conjugates, ATC code: L01FX17.

Mechanism of action

Sacituzumab govitecan binds to Trop-2-expressing tumour cells and is internalised with the subsequent release of SN-38 from a hydrolysable linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death.

Clinical efficacy and safety

Triple Negative Breast Cancer (TNBC)

In Combination with Pembrolizumab in Previously Untreated, Unresectable Locally Advanced or Metastatic TNBC whose tumours express PD-L1 (ASCENT-04)

The efficacy of sacituzumab govitecan in combination with pembrolizumab was evaluated in a multicentre, open-label, randomised study (ASCENT-04) conducted in 443 patients with unresectable locally advanced or metastatic TNBC who had not received prior systemic therapy for advanced disease and whose tumours express PD-L1 (defined using the PD-L1 IHC 22C3 assay as tumours with a CPS ≥ 10) at screening. Patients may have received chemotherapy with or without a PD-1 or PD-L1 inhibitor and/or radiotherapy in early-stage TNBC, however at least 6 months must have elapsed between the completion of curative systemic breast cancer therapy or surgery, whichever occurred last, and first local or distant recurrence. No prior treatment with topoisomerase I inhibitors or antibody drug conjugates containing a topoisomerase inhibitor was allowed.

Patients with active chronic inflammatory bowel disease or gastrointestinal (GI) perforation within 6 months of enrolment or with active serious infections requiring systemic antimicrobial therapy were excluded.

Randomisation was stratified by treatment-free interval (de novo versus disease recurrence within 6 to 12 months from completion of treatment in the curative setting versus disease recurrence > 12 months from completion of treatment in the curative setting), and by geographic region (United State/Canada/Western Europe versus Rest of World), and prior exposure to PD-1 or PD-L1 inhibitor (yes versus no).

Patients were randomised (1:1) to receive either:

- Sacituzumab govitecan 10 mg/kg as an intravenous (IV) infusion on Days 1 and 8 of 21-day cycles and pembrolizumab 200 mg on Day 1 of 21-day cycles. Pembrolizumab was administered for a maximum of 35 cycles (approximately 24 months).
- Pembrolizumab 200 mg on Day 1 of 21-day cycles in combination with nab-paclitaxel 100 mg/m² on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m² on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m² and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days. Pembrolizumab was administered for a maximum of 35 cycles (approximately 24 months).

Patients were treated until blinded independent central review (BICR)-verified disease progression, unacceptable toxicity, death, or consent withdrawal. Tumour imaging was obtained every 8 weeks for the first 18 months followed by every 12 weeks thereafter. Following BICR-verified radiographic

disease progression and study treatment discontinuation, patients who were randomised to treatment of physician's choice (TPC) and pembrolizumab were able to be enrolled in the crossover phase of this study to receive sacituzumab govitecan monotherapy.

The primary efficacy outcome was progression-free survival (PFS) by BICR per RECIST v1.1. Additional efficacy outcomes measures included overall survival (OS) and objective response rate (ORR).

The median age of patients in the study population was 55 years (range: 23-88 years), and 26% of patients were 65 years or over. All patients were female (100%). The majority of patients were White (58%) and Asian (24%); 6% were American Indian or Alaska Native, 5% were Black, and 3% were other race. Thirty-four percent of patients presented with de novo metastatic disease at screening, 18% with recurrent disease within 6 to 12 months from completion of treatment in the curative setting and 48% with recurrent disease > 12 month from completion of treatment in the curative setting. One-point four percent (1.4%) of patients received a prior PD-1 or PD-L1 inhibitor. At study entry, all patients had an ECOG performance status of 0 (70%) or 1 (30%), 36% of patients were pre-menopausal and 64% were post-menopausal. The majority of patients (95%) had metastatic disease at screening, brain metastases were observed in 3% of patients. BRCA mutation analysis by Whole Exome Sequencing was available for 75% of participants, of which 21% of the participants had BRCA1 or BRCA2 mutated tumours.

Sacituzumab govitecan in combination with pembrolizumab demonstrated a statistically significant improvement in PFS versus TPC in combination with pembrolizumab as assessed by BICR. At the time of the interim analysis of OS, patients had a median follow-up of 22.5 months. The efficacy results are summarized in Table 4, Figure 1 and Figure 2.

Table 4: Efficacy endpoints (ASCENT-04)

	Sacituzumab govitecan 10 mg/kg in combination with Pembrolizumab n=221	TPC in combination with Pembrolizumab n=222
Progression-Free Survival by BICR ¹		
Number (%) of patients with events	109 (49%)	140 (63%)
Median PFS in months (95% CI)	11.2 (9.3, 16.7)	7.8 (7.3, 9.3)
Hazard ratio (95% CI) ²	0.65 (0.51, 0.84)	
p-value ³	0.0009	
Objective Response Rate by BICR ¹		
ORR (95% CI) ⁴	60% (53, 66)	53% (46, 60)
Overall Survival ⁵		
Number (%) of patients with events	97 (43.9%)	106 (47.7%)
Median OS in months (95% CI)	31.21 (25.56, NR)	28.39 (24.44, NR)
Hazard ratio (95% CI) ²	0.915 (0.694, 1.206)	

¹ Based on PFS primary analysis with median follow-up time 14 months (data cut-off 3 March 2025)

² Hazard ratio based on the stratified Cox proportional hazard model

³ Stratified log-rank test adjusted for stratification factors: treatment-free interval (de novo vs recurrent disease within 6 to 12 months vs recurrent disease occurring > 12 months from completion of treatment in the curative setting) and geographic region (US/Canada/Western Europe vs Rest of World)

⁴ Based on 2-sided 95% CIs using the Clopper-Pearson method

⁵ Based on interim OS analysis (data cut-off 16 February 2026)

BICR = Blinded Independent Central Review; CI = Confidence Interval

NR= Not reached

TPC = nab-paclitaxel, paclitaxel, or gemcitabine

Figure 1: Progression free survival by BICR in ASCENT-04

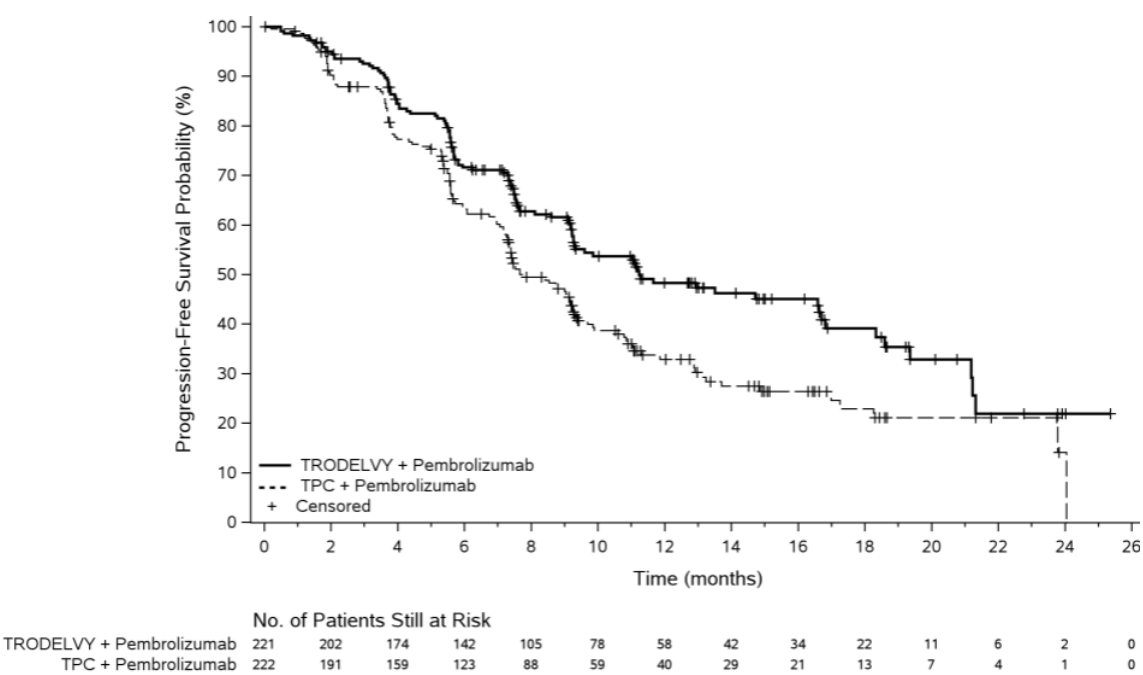
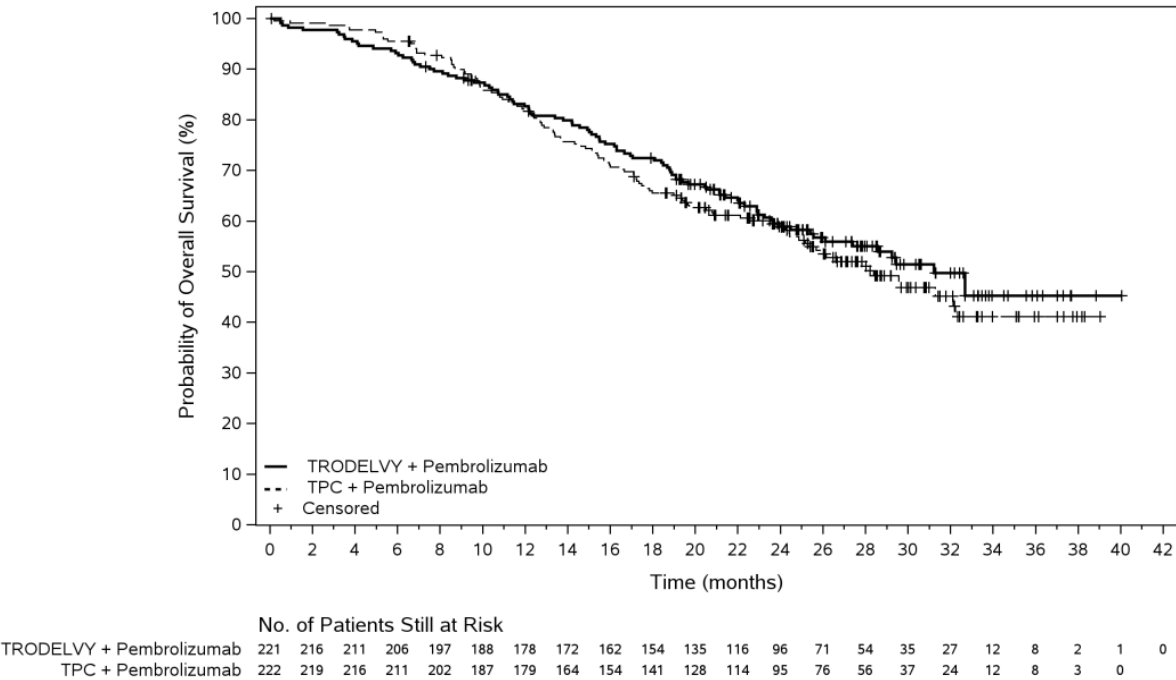


Figure 2: Overall survival in ASCENT-04



Previously Untreated, Unresectable Locally Advanced or Metastatic TNBC in patients who are not candidates for PD-1/PD-L1 inhibitor therapy (ASCENT-03)

The efficacy of sacituzumab govitecan was evaluated in a multicentre, open-label, randomised study (ASCENT-03) conducted in 558 patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who had not received previous systemic therapy for advanced disease and who were not candidates for PD-1 or PD-L1 inhibitor therapy. The study enrolled patients with tumours that are PD-L1 negative (defined as having a tumour CPS < 10 using the IHC 22C3 assay), and patients with tumours that are PD-L1 positive (defined as having a CPS ≥ 10 using the IHC

22C3 assay) if they received a PD-1 or PD-L1 inhibitor in the (neo)adjuvant setting or if they had a comorbidity precluding treatment with PD-1 or PD-L1 inhibitor therapy.

Patients may have received chemotherapy with or without a PD-1 or PD-L1 inhibitor and/or radiotherapy in the early-stage of TNBC, however at least 6 months must have elapsed between the completion of systemic (neo) adjuvant breast cancer therapy or surgery, whichever occurred last, and first local or distant recurrence. No prior treatment with topoisomerase 1 inhibitors or antibody drug conjugates containing a topoisomerase inhibitor was allowed.

Patients were randomised (1:1) to receive sacituzumab govitecan 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day cycle (n=279) or Treatment of Physician's Choice (TPC) (n=279). TPC was determined by the investigator before randomisation from one of the following regimens: gemcitabine and carboplatin, paclitaxel or nab-paclitaxel. Randomisation was stratified by de novo vs recurrent disease within 6 to 12 months from completion of treatment in the curative setting versus recurrent disease > 12 months from completion of treatment in the curative setting, and by geographic region (United States, Canada, Western Europe vs. Rest of World).

Patients were treated until BICR-verified disease progression, unacceptable toxicity, death, or consent withdrawal. Tumour imaging was obtained every 6 weeks for the first year followed by every 12 weeks thereafter. Following BICR-verified objective disease progression and study treatment discontinuation, patients who were randomised to TPC chemotherapy were able to receive sacituzumab govitecan supplied on trial in the crossover phase of this study if eligible.

The primary efficacy outcome was progression-free survival (PFS) by BICR per RECIST v1.1. Additional efficacy outcomes measures included overall survival (OS) and objective response rate (ORR) by BICR.

The median age of the study population was 55 years (range: 23-86 years), and 26% of patients were 65 years or over; 99.5% of patients were female. The majority of patients were White (64%); 23% were Asian, 3% were Black, and 4% were other race. Thirty-one percent (31%) of patients had de novo disease, 21% of patients had recurrent disease with a disease-free interval (DFI) 6 to 12 months and 48% of patients with DFI > 12 months. Ninety-nine point five percent (99.5%) of patients enrolled had tumours that were PD-L1 negative and 0.5% of patients had tumours that were PD-L1 positive. At study entry, all patients had an ECOG performance status of 0 (66%) or 1 (34%). The majority of patients (97.8%) had metastatic disease at screening; brain metastases were observed in 5% of patients. BRCA 1/2 mutation status was known for 76% of participants, out of which 18% of tested study participants had positive BRCA mutations.

Sacituzumab govitecan demonstrated a statistically significant improvement in PFS versus TPC by BICR. At the time of the first interim OS analysis, patients had a median follow-up of 17.7 months. Efficacy results are summarized in Table 5, Figure 3 and Figure 4.

Table 5. Efficacy endpoints (ASCENT-03)

	Sacituzumab govitecan N=279	TPC N=279
Progression-free survival by BICR ¹		
Number (%) of patients with events	161 (58%)	188 (67%)
Median PFS in months (95% CI)	9.7 (8.1, 11.1)	6.9 (5.6, 8.2)
Hazard ratio (95% CI) ²	0.62 (0.50, 0.77)	
p-value ³	< 0.0001	
Objective response rate by BICR ¹		
ORR, (95% CI) ⁴	48% (42%, 54%)	46% (40%, 52%)
Overall survival ⁵		

	Sacituzumab govitecan N=279	TPC N=279
Number (%) of patients with events	139 (50%)	144 (52%)
Median OS in months (95% CI)	21.5 (18.9, 26.5)	21.3 (18.7, 25.2)
Hazard ratio (95% CI) ²	0.95 (0.75, 1.20)	

1. Based on PFS primary analysis (data cut-off 2 April 2025) with median follow-up time 13.2 months.
 2. Hazard ratio with 95% CIs based on the stratified Cox proportional hazards model adjusted for randomisation stratification factors: disease stratification (de novo vs recurrent disease within 6 to 12 months vs recurrent disease occurring > 12 months from completion of treatment in the curative setting) and geographic region (US/Canada/Western Europe vs rest of the world).
 3. 2-sided p-value based on log-rank test adjusted for randomisation stratification factors: disease stratification (de novo vs recurrent disease within 6 to 12 months vs recurrent disease occurring > 12 months from completion of treatment in the curative setting) and geographic region (US/Canada/Western Europe vs rest of the world)
 4. The 95% CI is based on the Clopper-Pearson exact method.
 5. Based on first interim OS analysis (data cut-off 27 October 2025) with median follow-up time 17.7 months
- BICR = Blinded Independent Central Review; CI = Confidence Interval
TPC = gemcitabine and carboplatin, paclitaxel, or nab-paclitaxel

Figure 3: Progression free survival by BICR in ASCENT-03 (data cut-off date 2 April 2025)

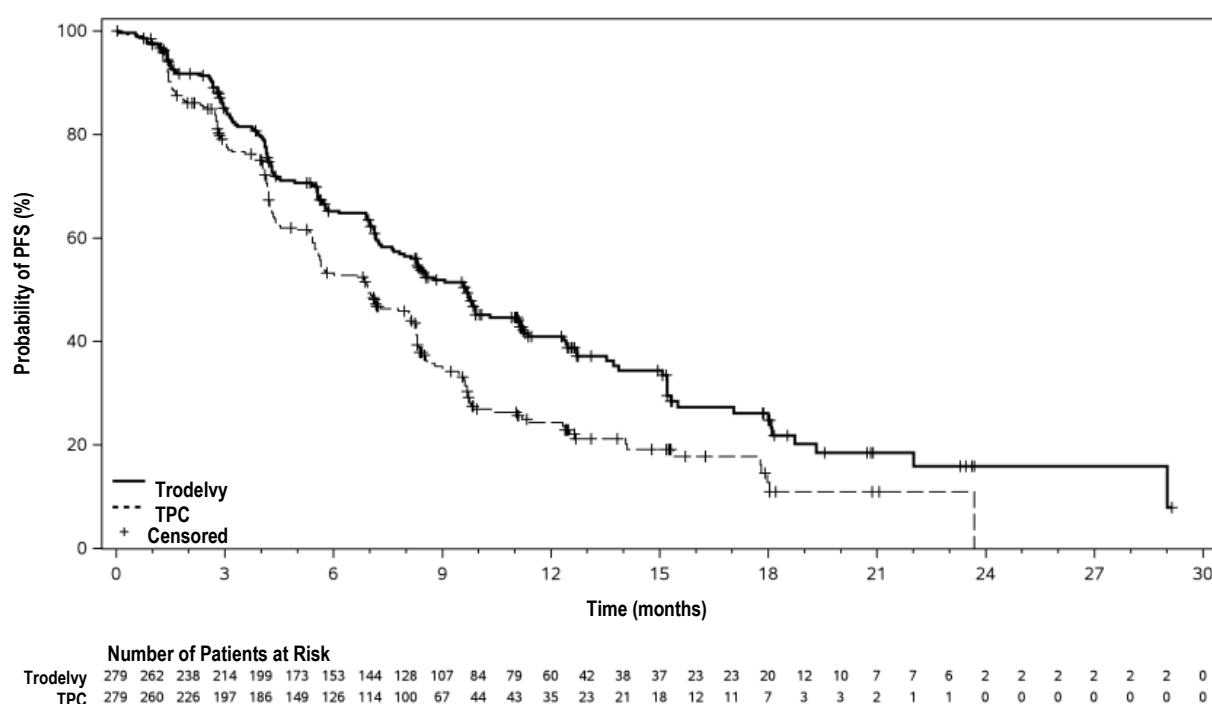
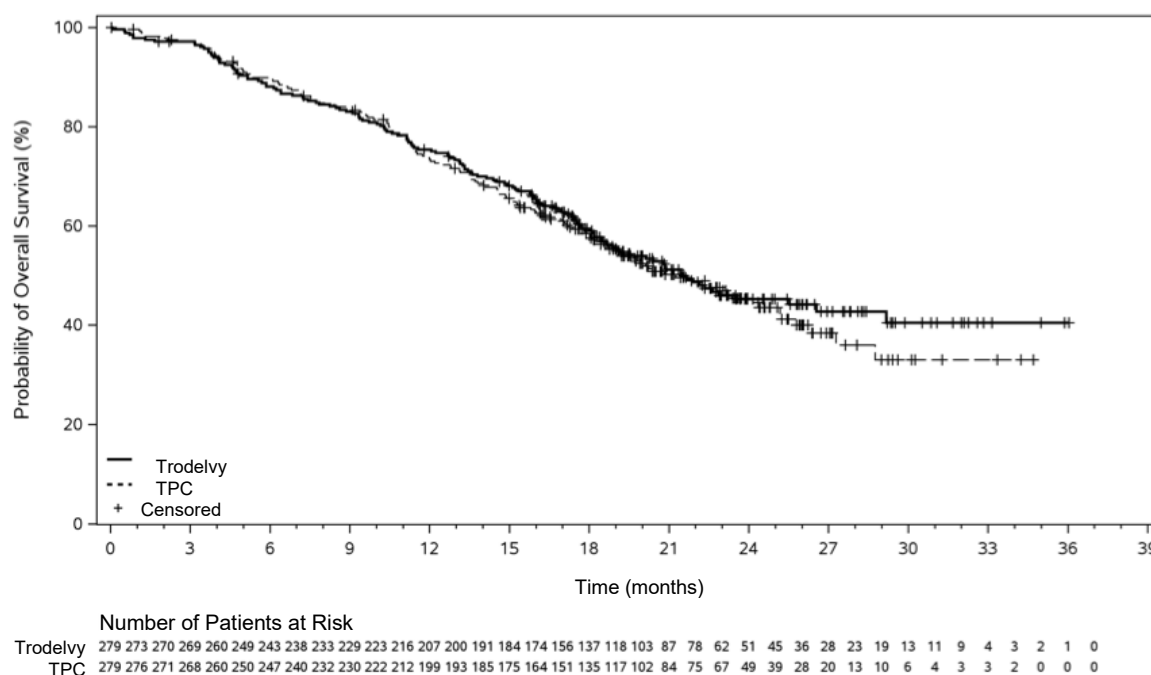


Figure 4: Overall survival in ASCENT-03 (data cut-off date 27 Oct 2025)



Unresectable or metastatic Triple Negative Breast Cancer (ASCENT)

The efficacy and safety of sacituzumab govitecan was assessed in ASCENT (IMMU-132-05), an international Phase 3, multicentre, open-label, randomised study conducted in 529 patients with unresectable locally advanced or metastatic TNBC who had relapsed after at least two prior chemotherapies (no upper limit) for breast cancer. Earlier adjuvant or neoadjuvant therapy for more limited disease qualified as one of the required prior regimens if the development of unresectable, locally advanced or metastatic disease occurred within a 12-month period of time after completion of chemotherapy. All patients received previous taxane treatment in either the adjuvant, neoadjuvant, or advanced stage unless they had a contraindication or were intolerant to taxanes. Poly-ADP ribose polymerase (PARP) inhibitors were allowed as one of the two prior chemotherapies for patients with a documented germline BRCA1/BRCA2 mutation.

Patients were randomised (1:1) to receive sacituzumab govitecan 10 mg/kg as an intravenous infusion on Day 1 and Day 8 of a 21-day treatment cycle or TPC which was dosed based on body surface area and per the approved product information. TPC was determined by the investigator before randomisation from one of the following single-agent regimens: eribulin (n = 139), capecitabine (n = 33), gemcitabine (n = 38), or vinorelbine (except if patient had $\geq$ Grade 2 neuropathy, n = 52). Patients with stable brain metastases (pre-treated, non-progressive, without anti-seizure medicinal products and on stable corticosteroid dose for at least 2 weeks) were eligible. Magnetic resonance imaging (MRI) to determine brain metastases was required only for patients with known or suspected brain metastases. Patients with known Gilbert's disease, bone-only disease, known history of unstable angina, myocardial infarction, or congestive heart failure, active chronic inflammatory bowel disease or gastrointestinal (GI) perforation, human immunodeficiency virus (HIV), active hepatitis B or C infection, live vaccine within 30 days, or who have previously received irinotecan were excluded.

Patients were treated until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS in patients without brain metastases at baseline (i.e. BMNeg) as measured by a BICR group of radiology experts using RECIST v1.1 criteria. Secondary efficacy endpoints included PFS by BICR for the overall population, including all patients with and without brain metastases, overall survival (OS), objective response rate (ORR) and duration of response (DOR).

The primary analysis included 235 BMNeg patients in the sacituzumab govitecan group and 233 BMNeg patients in the TPC group. The analysis of the overall population included 267 patients in the sacituzumab govitecan group and 262 patients in the TPC group.

The demographics and baseline characteristics of the overall population (n = 529) were: median age of 54 years (range: 27–82 years) and 81% < 65 years; 99.6% female; 79% White; 12% Black; median number of prior systemic therapies was 4; 69% had previously received 2 to 3 prior chemotherapies; 31% had previously received > 3 prior chemotherapies; 42% had hepatic metastases; 12% had present or a history of brain metastases. 8% were BRCA1/BRCA2 mutational status positive; BRCA status was available for 339 patients. At study entry, all patients had an ECOG performance status of 0 (43%) or 1 (57%). The median time from diagnosis of Stage 4 to study entry was 16.2 months (range: -0.4 to 202.9 months). The most frequent prior chemotherapies were cyclophosphamide (83%), anthracycline (83%) including doxorubicin (53%), paclitaxel (78%), carboplatin (65%), capecitabine (67%), gemcitabine (36%), docetaxel (35%), and eribulin (33%). Overall, 29% of patients had received prior PD-1 or PD-L1 therapy. Thirteen percent of patients in the sacituzumab govitecan group in the overall population received only 1 prior line of systemic therapy in the metastatic setting.

The efficacy results in the BMNeg population showed a statistically significant improvement of sacituzumab govitecan over TPC in PFS and OS with hazard ratios (HR) of 0.41 (n=468; 95% CI: 0.32, 0.52; p-value: <0.0001) and 0.48 (n=468; 95% CI: 0.38, 0.59; p-value: <0.0001), respectively. The median PFS was 5.6 months vs 1.7 months; the median OS was 12.1 months vs 6.7 months, in patients treated with sacituzumab govitecan and TPC, respectively.

The efficacy results in the overall population were consistent with the BMNeg population in the pre-specified final analysis (11 March 2020 cut-off date) and are summarised in Table 6.

Table 6: Efficacy endpoints (overall population) - pre-specified final analysis (ASCENT)

	Pre-specified Final Analysis (11 March 2020 cut-off date)	
	Sacituzumab govitecan n=267	Treatment of physician’s choice (TPC) n=262
Progression-free survival ¹		
Number of events (%)	190 (71.2)	171 (65.3)
Median PFS in months (95% CI)	4.8 (4.1,5.8)	1.7 (1.5, 2.5)
Hazard ratio (95% CI)	0.43 (0.35, 0.54)	
p-value ²	<0.0001	
Overall survival		
Number of deaths (%)	179 (67.0)	206 (78.6)
Median OS in months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.7)
Hazard ratio (95% CI)	0.51 (0.41, 0.62)	
p-value ²	<0.0001	
Overall response rate (ORR)		
Number of responders (%)	83 (31)	11 (4)
Odds ratio (95% CI)	10.99 (5.66, 21.36)	
p-value ³	<0.0001	
Complete response, n (%)	10 (4)	2 (1)
Partial response, n (%)	73 (27)	9 (3)
Duration of response (DOR)		
Median DOR in months (95% CI)	6.3 (5.5, 9.0)	3.6 (2.8, NE)

1 PFS is defined as the time from the date of randomization to the date of the first radiological disease progression or death due to any cause, whichever comes first.

2 Stratified log-rank test adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.

3 Based on Cochran-Mantel-Haenszel test.

CI = Confidence Interval

In an updated efficacy analysis (final database lock 25 February 2021), results were consistent with the pre-specified final analysis. The median PFS by BICR was 4.8 months vs 1.7 months, in patients treated with sacituzumab govitecan and TPC, respectively (HR of 0.41; 95% CI: 0.33, 0.52). The median OS was 11.8 months vs 6.9 months, respectively (HR of 0.51; 95% CI: 0.42, 0.63). Kaplan-Meier curves for updated PFS by BICR and OS are presented in Figures 5 and 6.

Figure 5: Progression free survival (overall population; final database lock 25 February 2021) by BICR in ASCENT

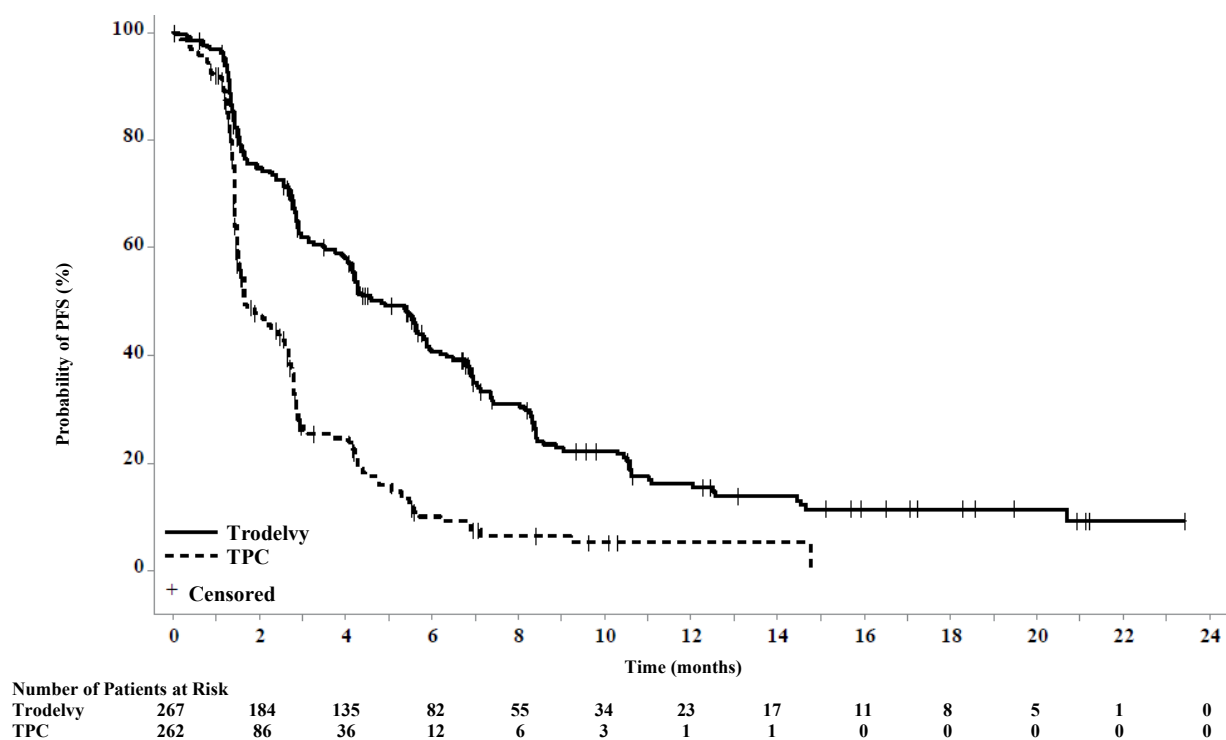
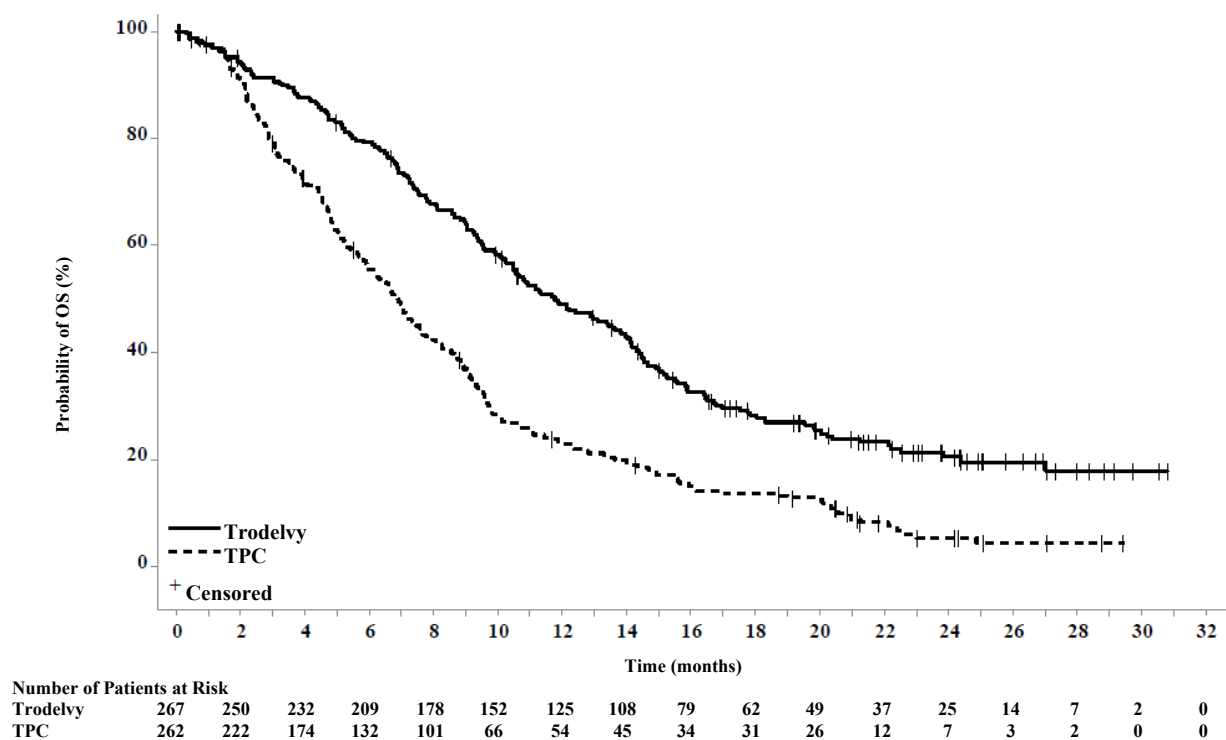


Figure 6: Overall survival (overall population; final database lock 25 February 2021) in ASCENT



Sub-group analysis

In subgroup analyses, improvements in PFS and OS in patients treated with sacituzumab govitecan compared to TPC were consistent across patient subgroups irrespective of age, race, BRCA status, prior number of systemic therapies overall (2 and >2, 2-3 and >3) and in the metastatic setting (1 and >1), prior therapy with anthracycline or PDL1, and liver metastases.

Brain metastases

An exploratory analysis of PFS and OS in patients with previously treated, stable brain metastases showed a stratified HR of 0.65 (n=61; 95% CI: 0.35, 1.22) and 0.87 (n=61; 95% CI: 0.47, 1.63), respectively. The median PFS was 2.8 months vs 1.6 months; the median OS was 6.8 months vs 7.5 months, in patients treated with sacituzumab govitecan and TPC, respectively.

Trop-2 expression

Additional subgroup analyses were conducted to evaluate the efficacy by tumour Trop-2 expression levels and the results were consistent across the different scoring methods used. In patients with low Trop-2 levels using membrane H-score by quartiles, benefit of sacituzumab govitecan over TPC was shown for both PFS (HR 0.64; 95% CI: 0.37, 1.11) and OS (HR of 0.71; 95% CI: 0.42, 1.21).

HR-Positive, HER2-Negative Breast Cancer

Unresectable or metastatic HR-positive/ HER2-negative breast cancer (TROPiCS-02)

The efficacy of sacituzumab govitecan was evaluated in a multicentre, open-label, randomised study TROPiCS-02 (IMMU-132-09) conducted in 543 patients with unresectable locally advanced or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+, or IHC 2+/ISH-) breast cancer whose disease has progressed after the following in any setting: a CDK 4/6 inhibitor, endocrine therapy, and a taxane; patients received at least two prior chemotherapies in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if progression or recurrence occurred within 12 months of completion of the chemotherapy). Patients with bone-only disease, active chronic inflammatory bowel disease and known history of bowel obstruction, known history of unstable angina or myocardial infarction or congestive heart failure or active hepatitis B or C infection were excluded from the study.

Patients were randomised (1:1) to receive sacituzumab govitecan 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day cycle (n=272) or TPC (n=271). TPC was determined by the investigator before randomisation from one of the following single-agent regimens: eribulin (n=130), vinorelbine (n=63), gemcitabine (n=56), or capecitabine (n=22). Randomisation was stratified based on prior chemotherapy regimens for metastatic disease (2 vs. 3-4), visceral metastasis (yes vs. no), and endocrine therapy in the metastatic setting for at least 6 months (yes vs. no).

Patients were treated until disease progression or unacceptable toxicity. The primary efficacy outcome measure was PFS as determined by BICR per RECIST v1.1. Additional efficacy outcome measures were OS, ORR by BICR, and DOR by BICR.

The median age of the study population was 56 years (range: 27-86 years), and 26% of patients were 65 years or over. Almost all patients were female (99%). The majority of patients were White (67%); 4% were Black, 3% were Asian, and 26% were of unknown race. Patients received a median of 7 (range: 3 to 17) prior systemic regimens in any setting and 3 (range: 0 to 8) prior systemic chemotherapy regimens in the metastatic setting. 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. Most patients received endocrine therapy in the metastatic setting for ≥ 6 months (86%). Patients had an ECOG performance status of 0 (44%) or 1 (56%). Ninety-five percent of patients had visceral metastases; 4.6% of patients had stable, pre-treated brain metastases.

Sacituzumab govitecan demonstrated a statistically significant improvement in PFS by BICR and OS versus TPC. The improvement in PFS by BICR and OS was generally consistent across pre-specified subgroups. Efficacy results are summarized in Table 7.

Table 7. Efficacy endpoints – Pre-specified final analysis (TROPiCS-02)

	Sacituzumab govitecan n=272	TPC n=271
Progression-free survival by BICR ¹		
Number of events (%)	170 (62.5%)	159 (58.7%)
Median PFS in months (95% CI)	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)
Hazard ratio (95% CI)	0.661 (0.529, 0.826)	
p-value ²	0.0003	
PFS rate at 12 months, % (95% CI)	21.3 (15.2, 28.1)	7.1 (2.8, 13.9)
Overall survival ³		
Number of events (%)	191 (70.2%)	199 (73.4%)
Median OS in months (95% CI)	14.4 (13.0, 15.7)	11.2 (10.1, 12.7)
Hazard ratio (95% CI)	0.789 (0.646, 0.964)	
p-value ²	0.0200	
Objective response rate by BICR ³		
Number of responders (%)	57 (21.0%)	38 (14.0%)
Odds ratio (95% CI)	1.625 (1.034, 2.555)	
p-value	0.0348	

¹ PFS is defined as the time from the date of randomisation to the date of the first radiological disease progression or death due to any cause, whichever comes first (data cut-off 3 January 2022).

² Stratified log-rank test adjusted for stratification factors: prior chemotherapy regimens for metastatic disease (2 vs. 3-4), visceral metastasis (yes vs. no), and endocrine therapy in the metastatic setting for at least 6 months (yes vs. no).

³ Based on second interim OS analysis (data cut-off 1 July 2022).

BICR = Blinded Independent Central Review; CI = Confidence Interval

In an updated efficacy analysis with a median duration of follow-up of 12.8 months (data cut-off 1 December 2022), results were consistent with the pre-specified final analysis. The median PFS by BICR was 5.5 months vs 4.0 months, in patients treated with sacituzumab govitecan and TPC, respectively (HR of 0.65; 95% CI: 0.53, 0.81). The median OS was 14.5 months vs 11.2 months, respectively (HR of 0.79; 95% CI: 0.65, 0.95). Kaplan-Meier curves for updated PFS by BICR and OS are presented in Figures 7 and 8.

Figure 7: Progression free survival by BICR (data cut-off 1 December 2022) in TROPiCS-02

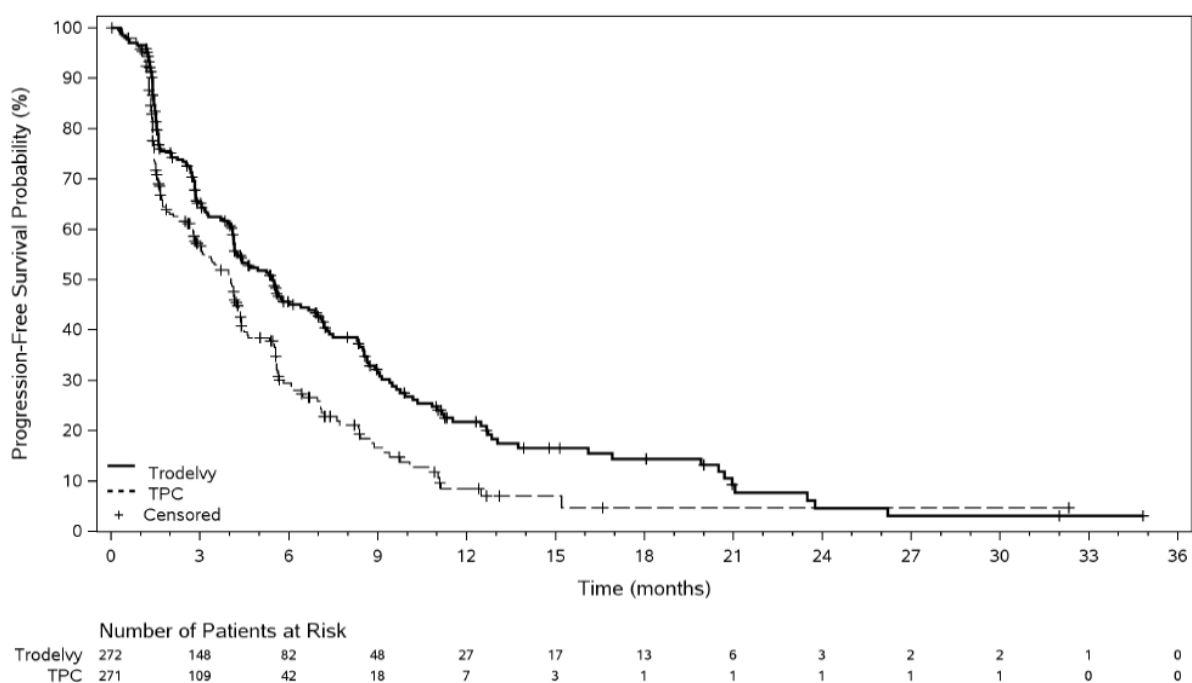
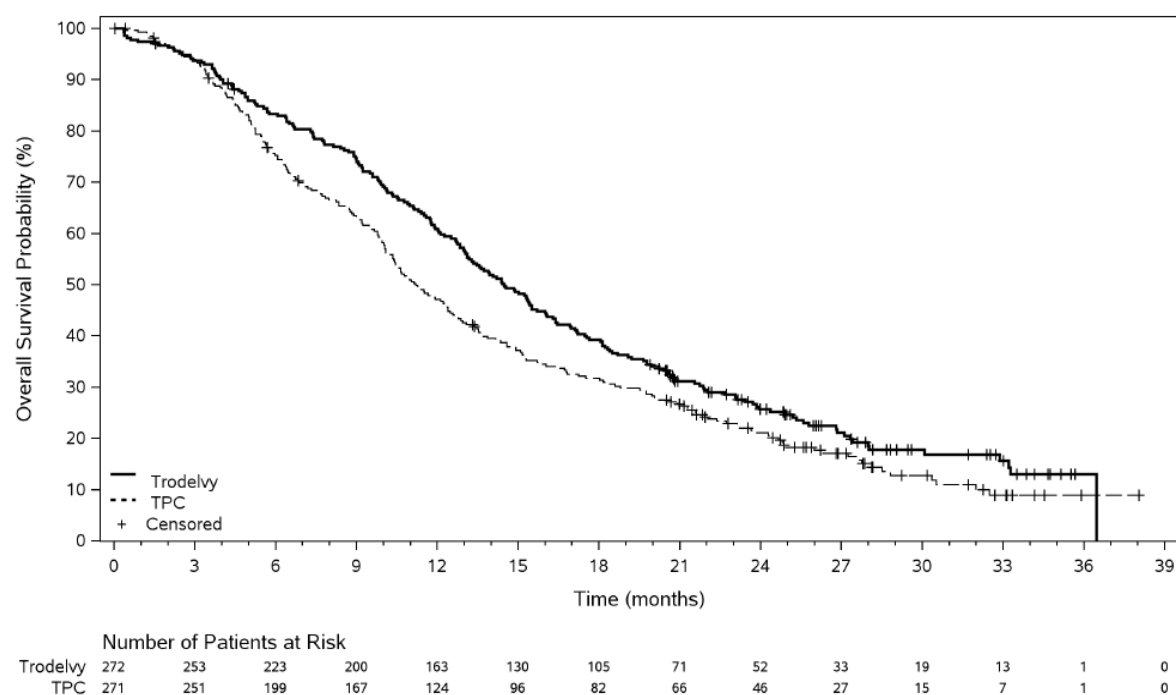


Figure 8: Overall Survival (data cut-off 1 December 2022) in TROPiCS-02



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with sacituzumab govitecan in all subsets of the paediatric population for the treatment of breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The serum pharmacokinetics of sacituzumab govitecan and SN-38 were evaluated in patients with metastatic breast cancer (mBC) who received sacituzumab govitecan at a dose of 10 mg/kg as monotherapy or in combination with pembrolizumab. The pharmacokinetic parameters of sacituzumab

govitecan and free SN-38 when administered as monotherapy or in combination with pembrolizumab are presented in Table 8.

There was no impact of pembrolizumab coadministration on pharmacokinetics of sacituzumab govitecan or SN-38.

Table 8: Summary of mean PK parameters (CV%) of sacituzumab govitecan and free SN-38

	Sacituzumab govitecan	Free SN-38
C_{max} [ng/mL]	258378 (17%)	97 (41%)
AUC_{0-168} [ng*h/mL]	12285980 (19%)	3120 (62%)

*Parameters estimated based on population PK analyses

C_{max} : maximum serum concentration from 0-168 hours after the first dose

AUC_{0-168} : area under serum concentration curve through 168 hours after the first dose

Distribution

Based on population pharmacokinetic analyses, the steady state volume of distribution of sacituzumab govitecan when administered as monotherapy or in combination with pembrolizumab was 4.79 L.

Biotransformation

No metabolism studies with sacituzumab govitecan have been conducted.

SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via UGT1A1.

Elimination

The median elimination half-life ($t_{1/2}$) of sacituzumab govitecan and free SN-38, based on population pharmacokinetic analysis, in patients who received sacituzumab govitecan as monotherapy or in combination with pembrolizumab, was 170 and 21.4 hours, respectively. The estimated mean (%CV) clearance of sacituzumab govitecan is 0.129 L/h (21%).

Special populations

Pharmacokinetic analyses in patients treated with sacituzumab govitecan did not identify an effect of age, race, and mild or moderate renal impairment on the pharmacokinetics of sacituzumab govitecan.

Renal impairment

Renal elimination is known to contribute minimally to the excretion of SN-38, the small molecule moiety of sacituzumab govitecan. 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).

Hepatic Impairment

The exposure of sacituzumab govitecan is similar in patients with mild hepatic impairment (bilirubin $\leq$ ULN and AST $>$ ULN, or bilirubin > 1.0 to ≤ 1.5 ULN and AST of any level;) to patients with normal hepatic function (bilirubin and AST $\leq$ ULN;).

There is limited data on sacituzumab govitecan and free SN-38 exposures in patients with moderate or severe hepatic impairment.

5.3 Preclinical safety data

SN-38 was clastogenic in an *in vitro* mammalian cell micronucleus test in Chinese hamster ovary cells and was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay.

In a repeat-dose toxicity study in cynomolgus monkeys, intravenous administration of sacituzumab govitecan resulted in endometrial atrophy, uterine hemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells at doses ≥ 60 mg/kg (1.9 times the human recommended

dose of 10 mg/kg based on body weight allometric scaling).

Non-clinical data for the novel excipient MES reveal no special hazard for humans based on conventional repeated dose toxicity and genotoxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

2-(*N*-morpholino)ethane sulfonic acid (MES)
Polysorbate 80 (E433)
Trehalose dihydrate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years.

After reconstitution

The reconstituted solution should be used immediately to prepare the diluted solution for infusion. If not used immediately, the infusion bag containing diluted solution can be stored in a refrigerator (2°C to 8°C) for up to 24 hours protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I colourless, clear glass 50 mL vial, with an elastomeric butyl stopper and sealed with an aluminum flip-off overseal containing 200 mg of sacituzumab govitecan.

Each pack contains one vial.

6.6 Special precautions for disposal and other handling

Trodelvy is a cytotoxic medicinal product. Applicable special handling and disposal procedures have to be followed.

Reconstitution

- Calculate the required dose (mg) of Trodelvy based on the patient's body weight.
- Using a sterile syringe, slowly inject 20 mL of sodium chloride 9 mg/mL (0.9%) solution for injection into each vial. The resulting concentration will be 10 mg/mL.

- Gently swirl vials and allow to dissolve for up to 15 minutes. Do not shake. The product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be free of visible particulates, clear and yellow. Do not use the reconstituted solution if it is cloudy or discoloured.
- Use immediately to prepare a diluted solution for infusion.

Dilution

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to the patient's body weight.
- Determine the final volume of the infusion solution to deliver the appropriate dose at a sacituzumab govitecan concentration range of 1.1 mg/mL to 3.4 mg/mL.
- Withdraw and discard a volume of sodium chloride 9 mg/mL (0.9%) solution for injection from the final infusion bag that is equivalent to the required volume of the reconstituted solution.
- Withdraw the calculated amount of the reconstituted solution from the vial(s) using a syringe. Discard any unused portion remaining in the vial(s).
- To minimize foaming, slowly inject the required volume of reconstituted solution into a polyvinyl chloride, polyolefin (polypropylene and/or polyethylene) or ethylene vinyl acetate infusion bag. Do not shake the contents.
- If necessary, adjust the volume in the infusion bag as needed with sodium chloride 9 mg/mL (0.9%) solution for injection, to obtain a concentration of 1.1 mg/mL to 3.4 mg/mL. Only sodium chloride 9 mg/mL (0.9%) solution for injection should be used since the stability of the reconstituted product has not been determined with other infusion-based solutions.
- If not used immediately, the infusion bag containing diluted solution can be stored refrigerated 2°C to 8°C for up to 24 hours protected from light. Do not freeze. After refrigeration, administer the diluted solution at room temperature up to 25°C within 8 hours (including infusion time).

Administration

- Administer Trodelvy as an intravenous infusion. Protect the infusion bag from light. The infusion bag should be covered during administration to the subject until dosing is complete. It is not necessary to cover the infusion tubing or to use light-protective tubing during the infusion.
- An infusion pump may be used.
- Do not mix Trodelvy, or administer as an infusion, with other medicinal products.
- Upon completion of the infusion, flush the intravenous line with 20 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1592/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2021

Date of latest renewal: 23 July 2026

10. DATE OF REVISION OF THE TEXT

08/2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.