Sacituzumab govitecan (Trodelvy®) for the treatment of unresectable or metastatic hormone receptor-positive, HER2-negative breast cancer

General information

Drug description [1]

Sacituzumab govitecan (Trodelvy®, IMMU-132) 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.

Indication [2]

Sacituzumab govitecan (Trodelvy®) as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor positive (HR+), human epidermal growth receptor 2 negative (HER2-) breast cancer who have received endocrine-based therapy, and at least two additional systemic therapies in the advanced setting.

Incidence

In Austria, in 2020, 5,443 women were newly diagnosed with breast cancer. The age-standardised incidence rate[1] in 2020 was 111,4 per 100,000 women [2].

HR+/HER2– disease is the most common subtype of metastatic breast cancer with an age-adjusted rate of 87.2 new cases per 100,000 women, based on 2016–2020 cases [3].

Patients with de novo metastatic breast cancer present with distant sites of disease at initial diagnosis. De novo metastatic breast cancer represents approximately 3% to 6% of new breast cancer diagnoses in high-income countries. This incidence has not declined despite decades of widespread use of population-based mammography screening [4].

Current treatment [5]

For the treatment of HR+ breast cancer, Onkopedia recommends the following:

- For patients with HR+ breast cancer, endocrine-based therapy is the first choice, with exception of vital danger or danger to organ function due to metastatic disease. In this situation, the role of endocrine therapy in combination with CDK 4/6 inhibitors, as compared to chemotherapy, remains unclear.
- Remission rates of endocrine therapy are 20-30%.
- As compared to chemotherapy, there are less adverse effects and a longer duration of remission.
- In patients with HER2+ carcinoma, endocrine therapy is administered in combination with an anti-HER2-therapy.
- In patients with distant metastases, the endocrine therapy is continued until disease progress.
- The occurrence of adverse effects is monitored by anamnesis, clinical examination, laboratory analysis and medical imaging (as appropriate) approximately every 4 weeks.
- Response on systemic therapy is controlled every 2 to 3 months (after 2-3 cycles) by clinical examination, laboratory parameters and targeted medical imaging.
- **Premenopausal patients**
  - In premenopausal patients, ovarian function suppression (GnRH analogues, ovariectomy or – rarely – radiomenolysis), in combination with tamoxifen is the therapy of choice.
  - In case of progress during endocrine therapie, change of medication is necessary.
  - Alternatively, the oestrogen receptor-antagonist fulvestrant can be administered to patients pretreated with endocrine therapy or in case of the occurrence of debilitating adverse effects.
  - Endocrine therapy can be combined with an CD4/6 inhibitor.
  - Recent data shows:
    - Among patients of a subgroup in an approval study, palbociclib leads to prolongation of PFS (HR 0.42, median 6.4 months); there was no prolongation of OS or improvement of remission rate.
    - A randomised trial in premenopausal women showed that ribociclib in combination with GnRH-analogues and either tamoxifen or a non-steroidal aromatase inhibitor leads to a prolongation of PFS (HR 0.553, median 10.8 months) and has positive effects on pain symptoms and QoL. No prolongation of OS was achieved.
- **Postmenopausal patients**

[1] European Standard Population 2013.

- Therapy of choice in postmenopausal women are steroidal or non-steroidal aromatase inhibitors and, alternatively, tamoxifen or fulvestrant.
- Differential therapy depends on administration of these substances for adjuvant therapy, on when the relapse occurs and the tolerance of the substances if previously administered.
- An extension of therapeutical options is the combination of anti-hormonal drugs with inhibitors of signal-transmission in tumour cells. After treatment failure with a non-steroidal aromatase inhibitor, the combination of exemestane and everolimus leads to a significant prolongation of PFS (but not of OS) as compared to exemestane monotherapy.
- CDK4/6-inhibtors represent a new substance class. They inhibit cell proliferation, act synergistically with other inhibitors and can delay the development of resistances to anti-hormonal therapy. A summary of recent data:
    - In the first-line therapy of postmenopausal patients, palbociclib combined with letrozole leads to a prolongation of PFS (HR 0.58, median 10.3 months); in the second-line therapy, the combination of palbociclib and fulvestrant also prolonged PFS (HR 0.42, median 6.4 months); in premenopausal patients a GnRH-analogue is added. There is no improvement in OS by palbociclib; data is immature. Major adverse effect is neutropenia grade 3 or 4 in approximately 65% of patients.
    - Postmenopausal patients achieve an improvement in PFS with ribociclib combined with a GnRH analogue or an aromatase inhibitor as first-line therapy (HR 0.54, median 10.5 months). Major adverse effect is neutropenia grade 3 or 4 in approximately 60% of patients. Among all patients of the approval study, OS was improved; data is immature.
    - The combination of abemaciclib and letrozole in postmenopausal patients leads to a prolongation of PFS (HR 0.54) and in combination with fulvestrant (HR 0.55, median 7.1 months); in premenopausal patients a GnRH analogue is added. Major adverse effects are neutropenia grade 3 or 4 in approx. 20% of patients and diarrhoea grade 3 or 4 in approx. 10% of patients. Abemaciclib does not improve OS; data is immature.

Regulatory status

EMA [6]	FDA [7, 8]
Approval status for this indication: On 22 June 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Trodelvy®. The CHMP adopted a new indication as follows: ❖ Trodelvy® as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HR+, HER2- breast cancer who have received endocrine-based therapy, and at least two additional systemic therapies in the advanced setting. **Other indications**: ❖ Trodelvy® as monotherapy is indicated 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. ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 3 February 2023, the FDA approved sacituzumab govitecan-hziy (Trodelvy®) for patients with unresectable locally advanced or metastatic HR+, HER2- breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting. **Other indications**: Trodelvy® is indicated for the treatment of adult patients with ❖ Unresectable locally advanced or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, at least one of them for metastatic disease. ❖ Locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 or programmed death-ligand 1 inhibitor (this indication is approved under accelerated approval based on tumour response rate and duration of response).

Manufacturer

Trodelvy® is manufactured by Gilead Sciences, Inc.

Costs

Currently, there is no cost information available.

Posology [8]

- ❖ Do NOT substitute Trodelvy® for or use with other drugs containing irinotecan or its active metabolite SN-38.
- ❖ The recommended dosage of Trodelvy® is 10 mg/kg administered as an intravenous infusion once weekly on days 1 and 8 of 21-day treatment cycles. Continue treatment until disease progression or unacceptable toxicity. Do not administer Trodelvy® at doses greater than 10 mg/kg.
- ❖ Administer Trodelvy® as an intravenous infusion only. Do not administer as an intravenous push or bolus.
- ❖ First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose, for signs or symptoms of infusion-related reactions.

- Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for at least 30 minutes after infusion.
- **Premedication:**
  - Prior to each dose of Trodelvy®, premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting is recommended.
  - Premedicate with antipyretics, H1 and H2 blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions.
  - Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist, as well as other drugs as indicated).

Warnings and precautions [8]

- **Neutropenia**
  - Severe or life-threatening neutropenia may occur.
  - Withhold Trodelvy® for absolute neutrophil count below 1500/mm3 or neutropenic fever. Monitor blood cell counts periodically during treatment.
  - Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.
- **Diarrhoea**
  - Severe diarrhoea may occur.
  - Monitor patients with diarrhoea and give fluid and electrolytes as needed. At the onset of diarrhoea, evaluate for infectious causes and, if negative, promptly initiate loperamide.
  - If severe diarrhoea occurs, withhold Trodelvy® until resolved to ≤ Grade 1 and reduce subsequent doses.
- **Hypersensitivity and infusion-related reactions**
  - Hypersensitivity reactions including severe anaphylactic reactions have been observed. Monitor patients for infusion-related reactions.
  - Permanently discontinue Trodelvy® if severe or life-threatening reactions occur.
- **Nausea/Vomiting**
  - Use antiemetic preventive treatment and withhold Trodelvy® for patients with grade 3 nausea or grade 3-4 vomiting at the time of scheduled treatment.
- **Patients with reduced UGT1A1 activity**
  - Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anaemia following initiation of Trodelvy® treatment.
- **Embryo-foetal toxicity**
  - Trodelvy® can cause foetal harm. Advise patients of potential risk to a foetus and to use effective contraception.

Study characteristics [9-12]

Trial name	n	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
TROPiCS-02 NCT03901339	543 (1:1)	sacituzumab govitecan 10 mg/kg IV on days 1 and 8 for every 21-day cycle	chemotherapy of physician's choice (eribulin, capecitabine, gemcitabine, or vinorelbine)	PFS by BICR	10.2 months	**ongoing**[2], open-label, randomised, multicentre phase III study	HR+/HER2-	Gilead Sciences, Inc.	TROPiCS-02 trial [9]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline
❖ ≥18 years with histologically confirmed HR+/HER2- metastatic breast cancer according to ASCO/CAP criteria ❖ Previously treated with ≥2 but ≤4 prior systemic chemotherapy regimens for metastatic breast cancer, including ≥1 prior taxane in any setting, ≥1 anticancer	❖ Prior Topo 1 inhibitors ❖ History of significant cardiovascular disease or a clinically significant ECG abnormality ❖ Active CNS metastases unless stable for at least 4 weeks	❖ Female: 99% vs. 99% ❖ Median age: 55 vs. 57 years ❖ ECOG PS • 0: 43% vs. 46% • 1: 57% vs. 54% ❖ Visceral metastases at baseline: 95% vs. 95%

[2] The TROPiCS-02 trial is ongoing; estimated study completion date is 10/2023.

hormonal treatment and ≥1 CDK4/6 inhibitor in any setting ❖ Disease progression on the most recent therapy documented by CT or MRI and ≥1 measurable target lesion according to RECIST 1.1 is required (patients with bone disease only are not eligible) ❖ Eligibility per investigator for ≥1 of 4 prespecified treatment of physician's choice agents (capecitabine, eribulin, vinorelbine or gemcitabine) ❖ ECOG PS of ≤1 and adequate bone marrow, renal and hepatic function	❖ Active infection requiring intravenous systemic therapy or active chronic inflammatory bowel disease with previous bowel obstruction ❖ Additional concurrent medical or psychiatric conditions that may confound study interpretation or prevent completion of study procedures and assessments	❖ Liver metastases: 84% vs. 87% ❖ De novo metastatic breast cancer: 29% vs. 22% ❖ Median time from initial metastatic diagnosis to random assignment: 48.5 vs. 46.6 months ❖ Prior chemotherapy in the (neo)adjuvant setting: 64% vs. 68% ❖ Prior endocrine therapy in the metastatic setting >6 months: 86% vs. 86% ❖ Prior CDK4/6i ≤12 months: 59% vs. 61% ❖ Median prior chemotherapy regimens in the metastatic setting, no.: 3 vs. 3 ❖ Median prior chemotherapy regimens, no.: 4 vs. 4 ❖ Median prior anticancer regimen, no.: 7 vs. 7

Efficacy (I vs. C)	**Safety** (I vs. C)
Data cutoff date (3 January 2022) **PFS:** 34% reduction in risk of progression or death (HR 0.66; 95% CI, 0.53-0.83; p=.0003; 329 events) **Median PFS by BICR**: 5.5 months (95% CI, 4.2-7.0) vs. 4.0 months (95% CI, 3.1-4.4) **Reduction in risk of progression or death was consistent with local investigator assessment** (HR 0.73; 95% CI, 0.60-0.88; p=.001) **PFS rate at 6 months**: 46% vs. 30% **PFS rate at 12 months**: 21% vs. 7% **Median OS** (first planned interim analysis): 13.9 months (95% CI, 12.7-15.4) vs. 12.3 months (95% CI, 10.8-14.2); HR for death 0.84; 95% CI, 0.67-1.06; p=.14[3] **ORR by BICR:** 21% vs. 14% with chemotherapy (of these, CR in 1% vs. 0%) **Clinical benefit rate**: 34% vs. 22% **Median time to response**: 2.9 months (range, 1.2-11.3) vs. 2.7 months (range, 1.2-10.5) **Median duration of response**: 7.4 months (95% CI, 6.5-8.6) vs. 5.6 months (95% CI, 3.8-7.9) **UPDATE: Second interim OS analysis (data cut-off 1 July 2022) [1]:** Median OS: 14.4 months (95% CI, 13.0-15.7) vs. 11.2 months (95% CI, 10.1-12.7); HR 0.789 (95% CI, 0.646-0.964); p-value=0.0200 **UPDATE: Efficacy analysis (median duration of follow-up of 12.8 months; data cut-off 1 December 2022) [1]:** Median PFS by BICR: 5.5 months vs. 4.0 months; HR 0.65; 95% CI, 0.53-0.81) Median OS: 14.5 months vs. 11.2 months; HR 0.79; 95% CI, 0.65-0.95)	**Serious treatment-related AEs:** n=37/268 (14%) vs. 25/249 (10%) **AEs leading to study treatment discontinuations:** n=17/268 (6%) vs. n=11/249 (4%) **AEs leading to death:** n=6/268[4] vs. 0

Patient-reported outcomes (Abstract data) [13]
❖ The analysis included 446 patients (n=236 vs. n=210) ❖ The EORTC QLQ-C30 completion rate was ≥85% up to day 1 in cycle 13 in both treatment arms ❖ Mean HRQoL scores at baseline were generally similar for both treatment groups ❖ The sacituzumab govitecan arm showed a trend of improvement in most HRQoL domains

[3] These results are not yet mature; further follow-up is ongoing.

[4] 1 patient had a treatment-related AE leading to death (septic shock because of neutropenic colitis); the AEs leading to death in the remaining 5 patients included (n=1 each) arrhythmia, COVID-19 pneumonia, pulmonary embolism, pneumonia, and nervous system disorder.

- A significantly greater improvement in physical functioning and dyspnoea was observed for I vs. C and greater worsening in diarrhoea
- EORTC QLQ-C30 least-square mean change from baseline:
  - Global health status/QoL (I vs. C): 2.4 (95& CI, -0.7-5.5)
- Despite the association with worsening diarrhoea, sacituzumab govitecan demonstrated an overall HRQoL benefit in heavily pretreated patients with HR+/HER2- metastatic breast cancer.

ESMO-MCBS version 1.1 [14]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 months	OS: +3.2 months	0.789 (0.646-0.964)	HR ≤0.65 AND gain ≥3 months	4	-	-	-	4
Adapted	NC	2a	≤12 months	OS: +3.2 months	0.789 (0.646-0.964)	HR >0.70 OR gain <1.5 months	1	-	-	-	1

Risk of bias (RCT) [15]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no[5] high risk	unclear[6] unclear risk	yes[7] high risk	**unclear**

Ongoing trials [16]

NCT number/trial name	Description	Estimated study completion date
NCT03901339/ TROPiCS-02	Please see above.	10/2023
NCT04639986	A phase 3 Asian study of sacituzumab govitecan vs. treatment of physician's choice in subjects with HR+/HER2- metastatic breast cancer who have failed ≥2 prior chemotherapy regimens.	03/2024
NCT05840211/ASCENT-07	A randomised, open-label, phase 3 study of sacituzumab govitecan vs. treatment of physician's choice in patients with HR+/HER2- inoperable, locally advanced, or metastatic breast cancer and have received endocrine therapy.	12/2028
NCT04595565/SASCIA	Phase 3 post neoadjuvant study evaluating sacituzumab govitecan, an antibody drug conjugate in primary HER2- breast cancer patients with high relapse risk after standard neoadjuvant treatment.	03/2029

Available assessments

- An assessment to appraise the clinical and cost effectiveness of sacituzumab govitecan within its marketing authorisation for treating HR+ and HER2- metastatic breast cancer after ≥2 therapies is currently in progress by NICE [17].
- An efficacy assessment for sacituzumab govitecan in patients with HR+, HER2-breast cancer who had received at least 3 prior therapies will be published by G-BA in November 2023 [18].
- A reimbursement recommendation by CADTH is awaited for 2024 [19].
- No assessment was identified via ICER

Other aspects and conclusions

- In June 2023, the **CHMP adopted a new indication** for sacituzumab govitecan (Trodelvy®) as monotherapy for the treatment of adult patients with unresectable or metastatic HR+, HER2- breast cancer who have received endocrine-based therapy, and ≥2 additional systemic therapies in the advanced setting. In February 2023, the **FDA approved** Trodelvy® for patients with unresectable locally advanced or metastatic HR+, HER2- breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.
- **TROPiCS-02 trial** is a randomised, open-label phase III study, aiming to compare sacituzumab govitecan with physician's choice chemotherapy in endocrine-resistant, chemotherapy-treated HR+/HER2– locally recurrent inoperable or metastatic breast cancer. Eligible patients had histologically locally confirmed measurable HR+/HER2– metastatic breast cancer and 2-4 prior systemic chemotherapy regimens for metastatic disease. Patients were included if they had previously received ≥1 taxane, ≥1 anticancer hormonal treatment, and ≥1 CDK4/6i, reflecting

[5] TROPiCS-02 is an open-label trial.
[6] Since the TROPiCS-02 trial is currently ongoing and final analysis data is not available, selective outcome reporting cannot be ruled out. ORR was originally stated as a primary endpoint; it is listed as a secondary endpoint in the final protocol. At the time of protocol amendment 6 in January 2021, the interim analysis of ORR was removed.
[7] The study is industry-funded and was designed through a collaboration of the sponsor and the lead investigator.

standard clinical practice. Patients were excluded if they had received prior Topo 1 inhibitors or have a history of significant cardiovascular disease, a clinically significant ECG abnormality, active CNS metastases, active infection requiring intravenous systemic therapy or active chronic inflammatory bowel disease with previous bowel obstruction.

- PFS, the **primary endpoint**, was met with a 34% reduction in risk of progression or death (HR 0.66, 95% CI, 0.53-0.83; p=.0003). The **median PFS** was 5.5 months (95%CI, 4.2-7.0) with sacituzumab govitecan and 4.0 months (95%CI, 3.1-4.4) with chemotherapy.
- In physical functioning and dyspnoea, a significantly greater improvement was achieved with sacituzumab govitecan vs. chemotherapy; in contrast, greater worsening was observed in diarrhoea.
- The original and adapted **ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit of 4 and 1, respectively.
- Since the TROPiCS-02 trial is currently **ongoing** and final analysis data is not available yet, **the risk of bias was considered unclear**. However, the risk of bias is increased by the open-label design of the trial, the change of ORR from primary to secondary endpoint during the trial and the involvement of the sponsor in the trial design.
- Beside the ongoing TROPiCS-02 trial, another 3 phase III trials, assessing the role of sacituzumab govitecan in patients with HER2- breast cancer, were identified.
- Final analysis data from the TROPiCS-02 trial and additional, robust phase III data is required to provide and efficient and safe treatment option for heavily pretreated breast cancer patients.

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Abbreviations: AE=adverse event, AJ=adjustment, ASCO=American Society of Clinical Oncology, BICR=blinded independent central review, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CAP=College of American Pathologists, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CT=computed tomography, DoR=duration of response, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EMA=European Medicines Agency, EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer quality of life of cancer patients core questionnaire version 3.0 ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HER2=human epidermal growth factor receptor 2, HR-=hormone receptor-negative, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, MG=median gain, MRI=magnetic resonance imaging, n=number of patients, NICE=National Institute for Health Care Excellence, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, ULN=upper limit of normal

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