Sacituzumab govitecan (Trodelvy®) as monotherapy for the treatment of patients with unresectable or metastatic triple-negative breast cancer (mTNBC)

General information [1]

Drug description	Indication
Sacituzumab govitecan (Trodelvy®) is an antineoplastic agent. It combines a humanised monoclonal antibody, which binds to trop-2-expressing cancer cells, and a linked cytotoxic moiety SN-38 (govitecan), which inhibits topoisomerase I, preventing DNA repair and leading to apoptosis and cell death.	Sacituzumab govitecan (Trodelvy®) as monotherapy is indicated for the treatment of adult patients with unresectable or mTNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease.

Current treatment [2, 3]

- Triple-negative breast cancer is an aggressive type of breast cancer that does not have the usual receptors (targets) which other targeted cancer medicines act on.
- Currently, chemotherapy remains the standard treatment for patients with mTNBC. However, it is estimated that only 10 to 15% of patients with this type of cancer respond to this treatment and the time without their disease worsening is only 2 to 3 months. Therefore, there is a high unmet medical need for new treatments that improve the outlook for patients.
- NICE recommends gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.
- Eribulin is also recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when:
  - it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine),
  - the company provides eribulin with the discount agreed in the patient access scheme.

Regulatory status

EMA [1, 4]

Approval status for this indication: On 14 October 2021, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Trodelvy®. Trodelvy® was reviewed under EMA's accelerated assessment programme.

The full indication is:

- Trodelvy® as monotherapy is indicated for the treatment of adult patients with unresectable or mTNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 22/11/2021

✓ Medicine under additional monitoring

Other indications: none

FDA [5, 6]

Approval status for this indication: On 7 April 2021, the FDA granted regular approval to sacituzumab govitecan (Trodelvy®) for patients with unresectable locally advanced or mTNBC who have received two or more prior systemic therapies, at least one of them for metastatic disease.

- ✓ Priority review
- ✓ Breakthrough designation

In April 2020, sacituzumab govitecan received accelerated approval for patients with mTNBC who have received at least two prior therapies for metastatic disease.

Other indications:

- Trodelvy® is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor (this indication is approved under accelerated approval based on tumour response rate and duration of response).

Costs

Currently, no cost information is available.

Premedication [5]

- 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 [5]

- **Neutropenia and diarrhoea:**
  - 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 a patient with febrile neutropenia without delay.
  - Severe **diarrhoea** may occur. Monitor patients with diarrhoea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhoea of any severity. At the onset of late 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 [7-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ASCENT, IMMU-132-05 NCT02574455; EudraCT number 2017-003019-21	529 (468)[1]	**sacituzumab govitecan** at a dose of 10 mg/ kg of body weight IV on days 1 and 8 of each 21-day cycle	single-agent **chemotherapy** as determined before randomisation[2]	PFS (as determined by BICR) among patients without known baseline brain metastases[3])	global, open-label, randomised, phase 3 trial	-	Immunomedics	[9]

Efficacy (I vs. C)

Efficacy in patients without brain metastases (n=468)

Median PFS as determined by central review: 5.6 months (95% CI, 4.3-6.3) vs. 1.7 months (95% CI, 1.5-2.6); HR for disease progression or death 0.41; 95% CI, 0.32-0.52; p<0.001

PFS by investigator assessments: 5.6 months vs. 1.7 months; HR for disease progression or death 0.35; 95% CI, 0.28-0.44

Median OS: 12.1 months (95% CI, 10.7-14.0) vs. 6.7 months (95% CI, 5.8-7.7) with chemotherapy; HR for death 0.48; 95% CI, 0.38-0.59; p<0.001

PFS in predefined subgroups:

- Patients 65 years of age or older: median, 7.1 vs. 2.4 months

Safety (I vs. C)[4]

Any treatment-related grade 3 AEs: n=117/258 (45%) vs. n=71/224 (32%)

Any treatment-related grade 4 AEs: n=48/258 (19%) vs. n=33/224 (15%)

Treatment-related SAEs: n=39/258 (15%) vs. n=19/224 (8%)

Death due to AEs: n=3/258 (1%) vs. n=3/224 (1%)

[1] A total of 529 patients with TNBC were enrolled. 61 patients had brain metastases at baseline, and 468 patients had no evidence of brain metastases (primary trial population for the analysis of efficacy).

[2] Eribulin 1.4 mg per m² of BSA (North America) or 1.23 mg per m² (Europe) IV on days 1 and 8 of a 21-day cycle, vinorelbine 25 mg per m² IV on day 1 weekly, capecitabine 1000 to 1250 mg per m² orally twice daily on days 1 to 14 of a 21-day cycle, or gemcitabine 800 to 1200 mg per m² IV on days 1, 8, and 15 of a 28-day cycle.

[3] Measured by computed tomography or magnetic resonance imaging according to RECIST, version 1.1.

[4] The safety population consisted of the 482 patients who received at least one treatment dose (258 in the sacituzumab govitecan group and 224 in the chemotherapy group).

- Patients with more than 3 previous therapies: 5.6 vs. 2.5 months
- Patients with previous use of PD-1 or PD-L1 inhibitors: 4.2 vs. 1.6 months
- Patients with triple-negative breast cancer at initial diagnosis: 5.7 vs. 1.6 months
- Patients without triple-negative breast cancer at initial diagnosis: 4.6 vs. 2.3 months
- Patients with liver metastases: 4.2 vs. 1.5 months

ORR: 35% vs. 5% with chemotherapy
Median duration of response: 6.3 months (95% CI, 5.5-9.0) vs. 3.6 months (95% CI, 2.8-could not be estimated); HR 0.39; 95% CI, 0.14-1.07
Median time to response: 1.5 months (range, 0.7-10.6) vs. 1.5 months (range, 1.3-4.2)

Efficacy in the full population (n=529)
Median PFS among all randomly assigned patients (with or without brain metastases): 4.8 months (95% CI, 4.1-5.8) vs. 1.7 months (95% CI, 1.5-2.5); HR for disease progression or death 0.43; 95% CI, 0.35-0.54
Median OS: 11.8 months (95% CI, 10.5-13.8) vs. 6.9 months (95% CI, 5.9-7.7); HR 0.51; 95% CI, 0.41-0.62, p<0.0001

HRQoL [11]:
- The HRQoL analysis included 419 patients.
- Mean QLQ-C30 subscale scores at baseline were similar between treatment arms.
- **Sacituzuman govitecan showed significantly and meaningfully greater improvement than chemotherapy** in global health status (0.7 vs. -3.4), physical (1.3 vs. -4.4) and emotional functioning (3.3 vs. -0.5), and lower symptomatic impact of fatigue (2.0 vs. 7.1), pain (-8.9 vs. -1.9), dyspnea (-3.8 vs. 4.0), and insomnia (-4.7 vs. 0.3).[5]
- Of all symptoms, only diarrhea was significantly and meaningfully worse with Sacituzumab govitecan (14.1 vs. -1.3).
- Sacituzumab govitecan not only prolonged PFS and OS but also improved HRQoL vs. chemotherapy.
- Although symptoms of diarrhea were worse with sacituzumab govitecan, this did not seem to translate to an adverse impact on patients´global health score or functioning.

Deaths that were deemed to be treatment-related: n=0 vs. n=1/224 (0.4% neutropenic sepsis)
Discontinuation[6]: n=12/258 (5%) vs. n=12/224 (5%)

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 months	OS: +4.9 months	HR 0.51 (0.41-0.62)	HR≤ 0.65 AND gain ≥3 months	4	-	-	-	4
Adapted	NC	2a	≤12 months	OS: +4.9 months	HR 0.51 (0.41-0.62)	HR≤ 0.65 AND gain ≥3 months	4	+13% treatment-related grade 3 AEs	-	-1	3

Risk of bias (RCT) [13]

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	-	no, open-label	yes	yes[7]	high

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[5] Due to missing p-values indicating statistically significant QoL improvements in the intervention group, these result were not considered for the ESMO-MCBS assessment.
[6] Discontinuation due to AE(s).
[7] The sponsor team, including former and current employees, designed and conducted the trial and gathered data in collaboration with the trial investigators. Trial oversight was provided by the trial steering committee and an independent data and safety monitoring committee. The data analysis was performed by the sponsor, with statistical service rendered by Covance. The first author, with members of the steering committee and sponsor, guided the initial manuscript draft after an agreement to publish with editorial assistance from professional medical writers funded by the sponsor.

Abbreviations: AE=adverse event, AJ=adjustment, BICR=Blinded independent central review, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DNA=deoxyribonucleic acid, EMA=European Medicines Agency, 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-CSF=granulocyte-colony stimulating factor, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, Int.=intention, IV=intravenous, MG=median gain, mTNBC=metastatic triple-negative breast cancer, n=number of patients, NA=not available, NICE=National Institute for Health and Care Excellence, ORR=objective response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QLQ-C30= QLQ-C30 = Quality of Life Questionnaire C30, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, ST=standard treatment

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