NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
OCTOBER 2021

Sacituzumab govitecan for treating HR+/HER2- negative metastatic breast cancer

NIHRIO ID	27164	**NICE ID**	10703
Developer/Company	Gilead Sciences Ltd	**UKPS ID**	662210

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Sacituzumab govitecan is in clinical development for the treatment of adult patients with hormone receptor positive and human epidermal growth factor 2 negative (HR+/HER2-) metastatic breast cancer, whose disease has progressed despite treatment with at least two prior rounds of chemotherapy. Survival outcomes for patients with metastatic breast cancer are poor and current chemotherapy options are associated with adverse side effects so there is a need for additional therapies for these patients.

Sacituzumab govitecan belongs to a class of medicinal products called antibody drug conjugates (ADCs) which are developed by attaching (conjugating) a specific protein, called a monoclonal antibody, to an anti-cancer drug. The monoclonal antibody component of savicituzumab govitecan specifically targets and attaches to a protein, TROP-2, which is found on the surface of cancer cells allowing the entry of the sacituzumab govitecan into the cancer cell. Once inside the cell the anti-cancer drug SN-38 is released resulting in DNA damage that causes death of the cancerous cells. Sacituzumab govitecan is administered by intravenous infusion (IV) and if licensed will offer an additional treatment option for patients with HR+/HER2- metastatic breast cancer whose disease has progressed despite treatment with at least two prior rounds of chemotherapy.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Treatment of adult patients with HR+/HER2- metastatic breast cancer who have failed at least two prior chemotherapy regimens.[1]

TECHNOLOGY

DESCRIPTION

Sacituzumab govitecan (Trodelvy[2], GS-0132, IMMU-132) is an ADC, that specifically targets TROP-2 expressing cancer cells. It is comprised of a humanised monoclonal TROP-2) antibody (RS7) with chemical linkage to the topisomerase 1 inhibitor SN-28, which is a highly potent active metabolite of irinotecan. Sacituzumab govitecan targets cancer cells expressing TROP-2 through the its RS7 component, before subsequently becoming internalized and subsequently hydrolysed to release SN-38, a moderately toxic chemotherapeutic agent, which induces DNA damage-mediated apoptosis of cancer cells.[3,4]

Sacituzumab govitecan is currently in clinical development as a treatment option for HR+/HER2- metastatic breast cancer patients whose disease has progressed following at least two prior chemotherapy regimens. In the phase III clinical trial TROPICS-02 (NCT03901339, 2018-004201-33) participants receive 10mg/kg via IV injection on days 1 and 8 of a 21-day cycle.[1,5]

INNOVATION AND/OR ADVANTAGES

ADCs such as sacituzumab govitecan represent an evolving class of therapeutic agents specifically designed to improve the delivery of chemotherapeutic agents by exploiting the target-selectivity of monoclonal antibodies. The antibody component of the ADC, which binds specific cell surface antigens can be individualised to be more selective to antigens which are more highly expressed on tumour cells compared to normal cells. Specific targeting of tumour cells limits off-target toxicity, thereby reducing the levels of toxicity normally associated with chemotherapy.[6,7]

Further, sacituzumab govitecan has a higher than most drug-to-antibody ratio compared to other ADCs permitting a high site-specific coupling of SN-38 per monoclonal antibody without altering the pharmacokinetics or decusing the therapeutic index of the conjugated antibody. This delivery advantage ensures high concentrations of SN-38 are delivered to cancer cells.[4,7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Sacituzumab govitecan currently has Marketing Authorisation in the EU/UK for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior lines of systemic therapies, at least one of them given for unresectable locally advanced or metastatic disease.[8]

The most common adverse drug reactions (ADRs) (reported at a frequency of ⩾20%) in the overall TNBC population were diarrhoea, nausea, neutropenia, fatigue, alopecia, anaemia, vomiting, constipation, decreased appetite, cough, and abdominal pain. Very common (≥10%)

Copyright © National Institute for Health Research Innovation Observatory (NIHRIO), The University of Newcastle upon Tyne

grade 3 or higher ADRs that were reported included neutropenia, leukopenia, diarrhoea and anaemia.[8]

Sacituzumab is also currently in phase II and/or III development for the treatment of a number of other solid tumour indications including: ovarian cancer, urothelial carcinoma, gastric cancer hepatocellular carcinoma.[9]

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer develops when abnormal cells in the breast, most commonly the cells that line the milk ducts, begin to grow and divide in an uncontrolled manner and eventually form a growth (tumour). Breast cancer predominantly affects women, however some men can also develop breast cancer.[10]

Breast cancers can be categorised according to whether or not they are sensitive to certain hormones in the body and the specific genes that the the tumour cells express.[11] The most common subtype of breast cancer is HR+/HER2-, which is sometimes referred to as luminal A breast cancer. This subtype tends to grow at a slower rate than other types of breast cancer and the tumour cells are characterised by expressing receptors for the hormones estrogen or progesterone, which can promote growth of HR+ tumours, but do not express high levels of the protein HER2.[12,13] Metastatic (stage IV) breast cancer refers to when the cancer has spread beyond the breast to other parts of the body; most commonly the lungs, liver, bones or brain.[14]

The causes of breast cancer are not fully understood but are thought to be a combination of genetic, environmental and lifestyle factors. Risk factors include increasing age; having a family history of breast cancer; having previously had a diagnosis of breast cancer or a benign lump in the breast; having a higher breast density; exposure to higher levels of oestrogen; being overweight or obese; being tall; drinking excess alcohol; exposure to radiation or radiotherapy; and taking hormone replacement therapy.[15]

The first symptom of breast cancer that most women notice is a lump or an area of thickened tissue in their breast. Other signs or symptoms of breast cancer include: a change in the size or shape of one or both breasts; a discharge of fluid from either of the nipples; a lump or swelling in either of the armpits; a change in the look or feel of the skin, such as puckering, dimpling, a rash or redness; a rash (like eczema), crusting, scaling or itchy skin or redness around the nipple; a change in the appearance of the nipple (e.g. becoming sunken into the breast).[16]

CLINICAL NEED AND BURDEN OF DISEASE

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases (2016-2018).[17] Breast cancer is much more common amongst females than males. In England, the European age-standardised incidence rate per 100,000 of the population was 169.2 amongst females and 1.3 amongst males (2016-2018).[18] Breast cancer incidence is strongly related to age, with higher incidence rates observed with increasing age. In the UK, 24% of new breast cancer cases were in people aged 75 and older. The highest incidence rates were observed in those aged 90 years and older amongst females and 85-89 amongst males.[19]

Copyright © National Institute for Health Research Innovation Observatory (NIHRIO), The University of Newcastle upon Tyne

In England and Wales (2020-21) there were 202,340 finished consultant episodes (FCE) for malignant neoplasm of the breast (ICD-10 code C50), of which 955 were for male patients and 201,314 were for female patients. This resulted in 199,266 admissions, 172,062 day cases and 47,613 FCE bed days.[20] In England (2017) there were 2,372 patients diagnosed with stage IV (metastatic) breast cancer. Based on estimates that around 37% of breast cases are the luminal A subtype, it can be approximated that of these patients, 878 patients were diagnosed with this HR+/HER2- metastatic breast cancer.[21,22]

In England and Wales (2017) there were 10,219 deaths where malignant neoplasm of the breast was recorded as the underlying cause; in England (2017) the directly age-standardised registration of death from malignant neoplasm of the breast was 33.3 per 100,000.[23,24] For adult women in England diagnosed with stage IV breast cancer between 2013 and 2017 and followed up to 2018, the 1 year and 5 year age-standardised survival rate was 66.0% and 26.2% respectively.[25]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Breast cancer is managed by a multidisciplinary team and the type of treatment a patient receives will depend on the stage and grade of their cancer, in addition to the general health of the patient and whether or not they have experienced menopause. The main treatments for breast cancer are: surgery, radiotherapy, chemotherapy, hormone therapy and targeted therapy.[26]

CURRENT TREATMENT OPTIONS

For HR+/HER2- locally advanced or metastatic breast cancer, NICE currently recommends the following third-line treatment options:[27]

- Eribulin
- Chemotherapy; single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment)

PLACE OF TECHNOLOGY

If licenced, sacituzumab govitecan will offer an additional treatment option for patients with metastatic HR+/HER2- breast cancer.[1]

CLINICAL TRIAL INFORMATION

Trial	NCT01631552; A Phase I/II Study of IMMU-132 (hRS7-SN38 Antibody Drug Conjugate) in Patients With Epithelial Cancer **Phase III** – Completed **Locations:** United States **Actualy primary completion date:** March 2019
Trial design	Non-randomised, sequential assignment, open-label

Copyright © National Institute for Health Research Innovation Observatory (NIHRIO), The University of Newcastle upon Tyne

Population	N=515; adults aged 18 years and older; histologically or cytologically confirmed epithelial cancers including non-triple negative breast cancer; refractory or relapsed to at least one prior standard therapeutic regemin
Intervention(s)	Sacituzumab Govitecan IV injection
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Percentage of participants experiencing any treatment emergent adverse events (TEAEs) and serious TEAEs. [Time Frame: First dose up to last dose for data cutoff date of 01 March 2019 (maximumum duration: 55.2 months) plus 30 days] *See trial record for full list of outcome measures
Results (efficacy)	At a median follow-up of 11.5 months, the ORR was 31.5% [95% confidence interval (CI), 19.5%–45.6%; 17 partial responses]; median DOR was 8.7 months (95% CI 3.7–12.7), median PFS was 5.5 months (95% CI 3.6–7.6), and median OS was 12 months (95% CI 9.0–18.2).[28]
Results (safety)	At data cut-off (1 March 2019), 12 patients were still alive. Key grade ⩾ 3 treatment-related toxicities included neutropenia (50.0%), anemia (11.1%), and diarrhea (7.4%). Two patients discontinued treatment due to treatment-related adverse events. No treatment-related deaths occurred.[28]

Trial	**TROPiCS-02**, NCT03901339, 2018-004201-33; **Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Versus Treatment of Physician's Choice (TPC) in Subjects With Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer (MBC) Who Have Failed at Least Two Prior Chemotherapy Regimens** **Phase III** – Active, not recruiting **Locations:** 6 EU countries, UK, USA and Canada **Estimated primary completion date:** November 2021
Trial design	Randomised, parallel assignment, open-label
Population	N=543; adults aged 18 years and older; documented evidence of HR+/HER2- metastatic breast cancer; refractory to or relapsed after at least two and no more than four prior systemic chemotherapy regimens
Intervention(s)	Sacituzumab Govitecan IV injection
Comparator(s)	Treatment of physician's choice with one of the following options, dosing as per the national comprehensive cancer network (NCCN) guidelines: • Eribulin (IV) • Capecitabine (oral administration) • Gemcitabine (IV) • Vinorelbine (IV)
Outcome(s)	Primary outcome measure:

Copyright © National Institute for Health Research Innovation Observatory (NIHRIO), The University of Newcastle upon Tyne

	• Progression free survival (PFS) [time Frame: Up to approximately 3 years] *See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The estimated cost of sacituzumab govitecan is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (TA423). December 2016
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). August 2017
- NICE cancer service guideline. Improving outcomes in breast cancer (CSG1). August 2002
- NICE quality standard. Breast cancer. (QS12). June 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO). 5th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 5). 2020.[29]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. 2018.[30]

ADDITIONAL INFORMATION

Copyright © National Institute for Health Research Innovation Observatory (NIHRIO), The University of Newcastle upon Tyne

REFERENCES

1 Clinicaltrials.gov. *Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Versus Treatment of Physician's Choice (TPC) in Subjects With Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer (MBC) Who Have Failed at Least Two Prior Chemotherapy Regimens. Trial ID: NCT03901339*. 2019. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03901339 [Accessed 04 October 2021].

2 Giled. *FDA Approves Trodelvy®, the First Treatment for Metastatic Triple-Negative Breast Cancer Shown to Improve Progression-Free Survival and Overall Survival.* 2021. Available from: https://www.gilead.com/news-and-press/press-room/press-releases/2021/4/fda-approves-trodelvy-the-first-treatment-for-metastatic-triplenegative-breast-cancer-shown-to-improve-progressionfree-survival-and-overall-surviv [Accessed 09 October 2021].

3 DrugBank. *Sacituzumab govitecan.* 2016. Available from: https://go.drugbank.com/drugs/DB12893 [Accessed 04 October 2021].

4 Weiss J, Glode A, Messersmith WA, Diamond J. Sacituzumab govitecan: breakthrough targeted therapy for triple-negative breast cancer. *Expert Review of Anticancer Therapy*. 2019 2019/08/03;19(8):673-9. Available from: https://doi.org/10.1080/14737140.2019.1654378.

5 European Clinical Trial Register. *Phase 3 Study of Sacituzumab Govitecan (IMMU-132) versus Treatment of Physician's Choice (TPC) in subjects with Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer (MBC) who have failed at least two prior chemotherapy regimens. Trial ID: 2018-004201-33*. 2018. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-004201-33/GB [Accessed 05 October 2021].

6 Parslow AC, Parakh S, Lee F-T, Gan HK, Scott AM. Antibody-Drug Conjugates for Cancer Therapy. *Biomedicines*. 2016;4(3):14. Available from: https://doi.org/10.3390/biomedicines4030014.

7 Rugo HS, Bardia A, Tolaney SM, Arteaga C, Cortes J, Sohn J, et al. TROPiCS-02: A Phase III study investigating sacituzumab govitecan in the treatment of HR+/HER2- metastatic breast cancer. *Future Oncology (London, England)*. 2020 Apr;16(12):705-15. Available from: https://doi.org/10.2217/fon-2020-0163.

8 Electronic Medicines Compendium (EMC). *Trodelvy 180 mg powder for concentrate for solution for infusion.* 2021. Available from: https://www.medicines.org.uk/emc/product/12880/smpc [Accessed 05 October 2021].

9 Clinicaltrials.gov. *Search for sacituzumab govitecan clinical studies: Phase II and III.* 2021. Available from: https://clinicaltrials.gov/ct2/results?intr=sacituzumab+govitecan&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 05 October 2021].

10 Cancer Research UK. *What is breast cancer?* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/about [Accessed 05 October 2021].

11 Macmillan Cancer Support. *Breast cancer types: What your type means.* 2020. Available from: https://www.mayoclinic.org/diseases-conditions/breast-cancer/in-depth/breast-cancer/art-20045654 [Accessed 05 October 2021].

12 National Cancer Institute. *Cancer Stat Facts: Female Breast Cancer Subtypes.* 2021. Available from: https://seer.cancer.gov/statfacts/html/breast-subtypes.html [Accessed 05 October 2021].

13 Cancer Treatment Centers of America. *Breast cancer molecular types.* 2021. Available from: https://www.cancercenter.com/cancer-types/breast-cancer/types/breast-cancer-molecular-types [Accessed 05 October 2021].

14 National Breast Cancer Foundation. *Metastatic Breast Cancer.* 2021. Available from: https://www.nationalbreastcancer.org/metastatic-breast-cancer [Accessed 05 October 2021].

15 NHS Inform. *Causes and risk factors of breast cancer.* 2021. Available from: https://www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/breast-cancer-female#causes-and-risk-factors-of-breast-cancer [Accessed 05 October 2021].

16 National Health Service (NHS). *Breast Cancer: Symptoms.* 2019. Available from: https://www.nhs.uk/conditions/breast-cancer/symptoms/ [Accessed 05 October 2021].

17 Cancer Research UK. *Breast cancer incidence (invasive).* 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero [Accessed 05 October 2021].

Copyright © National Institute for Health Research Innovation Observatory (NIHRIO), The University of Newcastle upon Tyne

18 Cancer Research UK. *Breast cancer incidence by sex and UK country*. 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Zero [Accessed 05 October 2021].
19 Cancer Research UK. *Breast cancer incidence by age*. 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-One [Accessed 05 October 2021].
20 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Downloaded 16 September 2021].
21 Pandit P, Patil R, Palwe V, Gandhe S, Patil R, Nagarkar R. Prevalence of Molecular Subtypes of Breast Cancer: A Single Institutional Experience of 2062 Patients. *European Journal of Breast Health*. 2020;16(1):39-43. Available from: https://doi.org/10.5152/ejbh.2019.4997.
22 National Cancer Registration and Analysis Service (NCRAS). *Stage breakdown by CCG 2017*. 2017. Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 07 October 2021].
23 Office for National Statistics (ONS). *Deaths registered in England and Wales – 21st century mortality*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset [Downloaded 01 July 2020].
24 Office for National Statistics (ONS). *Cancer Registration Statistics - England (2017)*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 08 October 2021].
25 Office for National Statistics (ONS). *Cancer Survival in England: adults diagnosed between 2013 and 2017 and followed up to 2018*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Downloaded 12 August 2019].
26 National Health Service (NHS). *Breast cancer in women: Treatment Overview*. 2019. Available from: https://www.nhs.uk/conditions/breast-cancer/treatment/ [Accessed 08 October 2021].
27 National Institute for Health and Care Excellence (NICE). *Advanced breast cancer - everything NICE says in an interactive flowchart: Hormone receptor-positive and HER2-negative disease*. 2021. Available from: https://pathways.nice.org.uk/pathways/advanced-breast-cancer#path=view%3A/pathways/advanced-breast-cancer/managing-advanced-breast-cancer.xml&content=view-node%3Anodes-hrpos-and-her2neg [Accessed 08 October 2021].
28 Kalinsky K, Diamond JR, Vahdat LT, Tolaney SM, Juric D, O'Shaughnessy J, et al. Sacituzumab govitecan in previously treated hormone receptor-positive/HER2-negative metastatic breast cancer: final results from a phase I/II, single-arm, basket trial. *Annals of Oncology*. 2020 2020/12/01/;31(12):1709-18. Available from: https://doi.org/https://doi.org/10.1016/j.annonc.2020.09.004.
29 Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Annals of Oncology*. 2020 Dec;31(12):1623-49. Available from: https://doi.org/10.1016/j.annonc.2020.09.010.
30 Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw*. 2018 01 Mar. 2018;16(3):310-20. Available from: https://doi.org/10.6004/jnccn.2018.0012.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

Copyright © National Institute for Health Research Innovation Observatory (NIHRIO), The University of Newcastle upon Tyne