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Newcastle University

Health Technology Briefing
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Sacituzumab govitecan for treating previously untreated locally advanced or metastatic triple negative breast cancer with negative PD-L1 status

Company/Developer	Gilead Sciences Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29304	NICE ID: Not available	UKPS ID: 660836

Licensing and Market Availability Plans

Currently in phase III trials

Summary

Sacituzumab govitecan is in clinical development for the treatment of adult patients with previously untreated locally advanced or metastatic triple negative breast cancer (TNBC) with PD-L1- status. TNBC is a rare form of breast cancer where the tumour cells do not have hormone response receptors such as oestrogen or progesterone. PD-L1 is a protein involved in the activation of an immune response. Locally advanced breast cancer is cancer that has progressed locally but has not yet spread outside the breast and local lymph nodes, whereas metastatic breast cancer is cancer that has spread to other areas in the body. Symptoms of TNBC can include a new lump or thickening in the breast or armpit. Established risk factors of breast cancer include age, early onset of menstruation, late menopause, older age at first completed pregnancy, and a family history. Treatment options for TNBC are limited and are often associated with short-lived benefits and higher susceptibility to treatment resistance in the future.

Sacituzumab govitecan is formed of two parts – an antibody (protein) and a chemotherapy drug that can kill cancer cells. Sacituzumab govitecan is administered to the patient via intravenous infusion. Most TNBC cells have too much Trop2 protein on their surface. Trop2 proteins facilitate cancer cell growth. Sacituzumab govitecan attaches to Trop2 proteins, Trop2 signals to the cancer cells. This stops cancer cells from growing. Then, it delivers the chemotherapy component, SN-38, directly to the breast cancer cells and destroys them. By targeting the cancer cells, the chemotherapy causes less harm to healthy cells in the body. If licensed, sacituzumab govitecan would offer an additional treatment option for people with TNBC who have received no previous treatment.

Proposed Indication

Treatment of adults with programmed death-ligand 1 (PD-L1)-negative, triple-negative breast cancer (TNBC) who have received no previous treatment for locally advanced or metastatic disease.[1]

Technology

Description

Sacituzumab govitecan (Trodelvy; SG; GS-0132; IMMU-132) is a tumour-associated calcium signal transducer 2 (Trop-2)-directed antibody-drug conjugate. Sacituzumab is a humanised antibody that recognises Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker. Sacituzumab govitecan binds to Trop-2-expressing cancer cells and is internalised with the subsequent release of SN-38 via hydrolysis of the 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.[2]

Sacituzumab govitecan is in phase III development (ASCENT-03; NCT05382299) for the treatment of TNBC for patients who have received no previous treatment. Sacituzumab govitecan is administered intravenously (IV), at a predetermined dosage per protocol, two days (day 1 and day 8) per 21-day cycle, for 4 cycles.[1]

Key Innovation

TNBC is an aggressive cancer subtype, owing to its high metastatic potential.[3] Personalising therapy in TNBC represents a challenge due to the scarcity of treatment options outside of cytotoxic chemotherapy and limited predictive and prognostic biomarkers to tailor treatment. Recent developments in understanding TNBC biology have sparked interest in exploring treatment optimisation and personalisation. This could limit exposure to cycles of cytotoxic chemotherapy.[4]

Trop-2 is expressed in all breast cancer subtypes and is associated with poor prognosis. Sacituzumab govitecan is a first-in-class Trop-2–directed ADC, with an antibody that is highly specific for Trop-2 and a high drug-to-antibody ratio. Additionally, it has a SN-38 payload, which is more potent than irinotecan, the parent compound.[5] In a previous clinical trial (ASCENT; NCT02574455), progression-free and overall survival were significantly longer with sacituzumab govitecan than with single-agent chemotherapy among patients with metastatic triple-negative breast cancer who were previously treated with at least two systemic chemotherapy regimens for unresectable, locally advanced or metastatic disease.[6,5]Therefore, if licensed, sacituzumab govitecan will offer an additional first line treatment option for patients with TNBC who have received no previous treatment.

Regulatory & Development Status

Sacituzumab govitecan currently has Marketing Authorisation in the UK for the treatment of adult patients with unresectable locally advanced or metastatic TNBC, who have received two or more prior lines of systemic therapies, at least one of them given for unresectable locally advanced or metastatic disease.[2,7]

Sacituzumab govitecan is in phase III/II clinical development for: [8]

- cervical cancer
- ovarian cancer
- endometrial carcinoma
- breast cancer with brain metastasis

- prostate cancer
- glioblastoma
- salivary gland cancer
- bladder cancer
- solid tumours
- lung cancers
- urothelial carcinoma
- epithelial cancer
- oesophageal cancer

Patient Group

Disease Area and Clinical Need

Breast cancer occurs when abnormal cells in the breast grow and divide in an uncontrolled way and eventually form a tumour.[9] TNBC is a rare form of breast cancer where the tumour cells do not have receptors for the hormones oestrogen and progesterone, or the HER2 protein. Some women with TNBC also have a breast cancer type 1 or type 2 (BRCA1, BRCA2) gene fault. BRCA1 is one of the gene faults that can increase the risk of breast cancer within families. PD-L1 is a protein that acts as a kind of "brake" to keep the body's immune responses under control. When PD-L1 binds to another protein called PD-1 (a protein found on T cells), it keeps T cells from killing the PD-L1-containing cells, including the cancer cells.[10] Locally advanced cancer is cancer that has spread from where it started to nearby tissue or lymph nodes.[11] Metastatic cancer is cancer that has spread from the primary site to other places in the body.[12] Symptoms of TNBC include: a new lump or thickening in the breast or armpit, a change in size, shape or feel of the breast and skin changes in the breast.[13,14] Established risk factors of breast cancer include age, early onset of menstruation, late menopause, older age at first completed pregnancy, and a family history. Additional risk factors can include obesity and alcohol consumption, and in men the risk factors are not fully understood but the condition is rare.[15]

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases (2016-2018).[16] The age standardised incidence rate of breast cancer in England is 1.3 and 169.2 per 100,000 amongst males and females respectively.[17] Around 8 in 10 (80.6%) women in England diagnosed with breast cancer between ages 15-44 survive their disease for ten years or more, compared with almost 6 in 10 (57.1%) women diagnosed aged 75-99 (2013-2017); ten-year survival is highest in women aged 55-64 (87.2%) (2013-2017). [16] In England (2022-23), there were 259,866 finished consultant episodes (FCE) and 256,441 admissions for malignant neoplasm of breast (ICD-10 code C50) which resulted in 233,521 day cases and 61,787 bed days.[18] Based on estimates that around 15% of breast cancer cases are the TNBC subtype, it can be approximated that there were 389,79 FCE and 38,466 admissions for TNBC, which results in 35,028 day cases and 9,268 bed days.[18]

Recommended Treatment Options

There is no treatment option recommended by the National Institute for Health and Care Excellence (NICE) for TNBC that does not express PD-L1.

Other treatment options for TNBC include: chemotherapy, lumpectomy, mastectomy, and radiation therapy.[19]

Clinical Trial Information

Trial	**ASCENT-03;** NCT05382299; Phase 3 Study of Sacituzumab Govitecan Versus Treatment of Physician's Choice in Patients With Previously Untreated, Locally Advanced, Inoperable or Metastatic Triple-Negative Breast Cancer Whose Tumors Do Not Express PD-L1 or in Patients Previously Treated With Anti-PD-(L)1 Agents in the Early Setting Whose Tumors Do Express PD-L1 **Phase III** – Active, not recruiting **Location**: 13 EU countries, UK, USA, Canada, and other countries **Primary completion date**: May 2027
Trial Design	Randomised, open label, parallel assignment.
Population	N=540; aged 18 years and older; subjects with histologically confirmed diagnosis of locally advanced, inoperable or metastatic breast cancer with PD-L1 negative status, previously untreated
Intervention(s)	Participants will receive sacituzumab govitecan 10 mg/kg on Days 1 and 8 of a 21-day cycle (i.e., 2 weekly doses plus 1 week without treatment) until progressive disease (PD), death, unacceptable toxicity, or another treatment discontinuation criterion is met.
Comparator(s)	Participants in the active comparator arm of the study will receive treatment of physician's choice,which comprises of the following options: • Paclitaxel 90 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle • Nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle • Gemcitabine 1000 mg/m^2 + carboplatin area under the curve (AUC) 2 on Days 1 and 8 of a 21-day cycle
Outcome(s)	Primary outcome measure: - Progression-free Survival (PFS) as Assessed by Blinded Independent Central Review (BICR) per Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Sacituzumab govitecan is already marketed in the UK for the treatment of unresectable triple-negative advanced breast cancer after 2 or more therapies. A 180mg vial costs £793.[20]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Capivasertib with paclitaxel for untreated metastatic triple-negative breast cancer (TA11411). Expected publication date: to be confirmed
- NICE clinical guideline. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (CG164). November 2019
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). February 2009

- NICE quality standard. Breast cancer (QS12). September 2011

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)-European Society for Medical Oncology (ESMO) Advanced Breast Cancer (ABC) Clinical Practice. 5th ESO-ESMO International Consensus Guidelines for ABC (ABC 5). 2020. [21]
- Insights: Breast Cancer, Version 4.2023 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. 2023.[22]

Additional Information

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