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HEALTH TECHNOLOGY BRIEFING
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Sacituzumab govitecan for metastatic or unresectable locally advanced triple-negative breast cancer – third line

NIHRIO ID	9546	**NICE ID**	9806
Developer/Company	Gilead Sciences / Immunomedics	**UKPS ID**	659617

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

SUMMARY

Sacituzumab govitecan is in clinical development for the treatment of adult patients with metastatic or unresectable locally advanced triple-negative breast cancer (TNBC) who have received at least two prior therapies. TNBC patients tend to have worse clinical outcomes than non-TNBS groups due to its high-risk biological characteristics and lack of effective treatments.

Sacituzumab, a type of molecule called a monoclonal antibody, targets the Trop-2 protein; which is found in more than 90% of TNBCs. Sacituzumab govitecan is an antibody-drug conjugate. The linking compound attaches (conjugates) the monoclonal antibody sacituzumab to the SN-38 chemotherapy. Sacituzumab govitecan is administered as an intravenous infusion. If licensed, sacituzumab govitecan will offer an additional treatment option for adult patients with metastatic or unresectable locally advanced TNBC who have received at least two prior therapies.

PROPOSED INDICATION

Treatment of adult patients with metastatic or unresectable locally advanced triple-negative breast cancer who have received at least two prior therapies.[a]

TECHNOLOGY

DESCRIPTION

Sacituzumab govitecan (Trodelvy) is an antibody-drug conjugate containing the humanized monoclonal antibody, hRS7, against tumour-associated calcium signal transducer 2 (TACSTD2 or TROP2) and linked to the active metabolite of irinotecan, 7-ethyl-10-hydroxycamptothecin (SN-38), with potential antineoplastic activity. The antibody moiety of sacituzumab govitecan selectively binds to TROP2. After internalization and proteolytic cleavage, SN-38 selectively stabilizes topoisomerase I-DNA covalent complexes, resulting in DNA breaks that inhibit DNA replication and trigger apoptosis. TROP2, also known as epithelial glycoprotein-1 (EGP-1), is a transmembrane calcium signal transducer that is overexpressed by a variety of human epithelial carcinomas; this antigen is involved in the regulation of cell-cell adhesion and its expression is associated with increased cancer growth, aggressiveness and metastasis.[1]

The recommended dose of sacituzumab govitecan is 10 mg/kg administered as an intravenous infusion once weekly on days 1 and 8 of 21-day treatment cycles. The treatment should be continued until disease progression or unacceptable toxicity.[b]

INNOVATION AND/OR ADVANTAGES

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 antibody-drug conjugate (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.[2]

The majority of patients with TNBC have disease progression after receiving first line therapy showing very poor outcomes. Standard chemotherapy is associated with low response rates (10 to 15%) and short progression-free survival (2 to 3 months) among patients with pretreated metastatic triple-negative breast cancer.[3]

Sacituzumab govitecan was associated with a significant improvement in progression-free survival and overall survival for previously treated patients with metastatic triple-negative breast cancer (TNBC) versus standard single-agent chemotherapy, show phase 3 study data.[4,5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Sacituzumab govitecan does not currently have Marketing Authorisation in the EU/UK for any indication.

[a] Information provided by Gilead Sciences Ltd on UK PharmaScan
[b] Information provided by Gilead Sciences Ltd on UK PharmaScan

Sacituzumab govitecan is in phase II and III development for:[6]

- Metastatic non-small cell lung carcinoma
- Head and neck squamous cell carcinoma
- Endometrial cancer
- Solid tumour
- Metastatic malignant neoplasm in the brain
- Prostate cancer
- Glioblastoma
- Urothelial cancer
- Epithelial cancer
- Ovarian cancer

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer is the most common type of cancer in the UK. Most women diagnosed with breast cancer are over the age of 50, but younger women can also get it.[7] Though breast cancer mostly affects women, men can get it too. Breast cancer starts in the breast tissue, most commonly in the cells that line the milk ducts of the breast.[8] TNBC is cancer that tests negative for oestrogen receptors, progesterone receptors, and excess HER2 protein.[9]

Unlike other types of breast cancer, TNBC is more likely to be diagnosed in people younger than 50. Other risk factors include being Black and Hispanic woman, and having BRCA1 mutation.[9] The symptoms of TNBC are similar to other types of breast cancer, such as: swelling of all or part of a breast, skin dimpling, breast or nipple pain, nipple retraction, nipple or breast skin that is red, dry, flaking or thickened, nipple discharge, and swollen lymph nodes.[10]

Compared with non-TNBC group, TNBC patients tend to have worse clinical outcomes due to its high-risk biological characteristics, high rate of visceral metastasis and lack of effective treatments (eg, endocrine and target therapies).[11,12] Although there is little evidence regarding the quality of life (QoL) of TNBC survivors, some studies show that TNBC is associated with a higher level of anxiety, depression, cancer worry and lower coping capacity which would negatively influence their QoL.[13-15]

CLINICAL NEED AND BURDEN OF DISEASE

Around 15% of all breast cancers are triple negative in the UK.[16] In England in 2017, it was estimated that there were 46,109 newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50).[17] This brings the estimate, according to the figure above, of newly diagnosed cases of TNBC to 6,916 in 2017, in England. The direct age-standardised rate per 100,000 was 166.7 among females and 1.3 among males (ICD-10 code C50).[17] Age-standardised Incidence rates are projected to rise by 2.24% for women in the UK between 2014 and 2035.[18] Approximately 20–40% of patients with early-stage TNBC develop metastatic disease.[19]

In England, in 2017, there were 10,219 deaths with malignant neoplasm of breast (ICD-10 code C50) recorded as the underlying cause for males and females (72 and 10,147

respectively).[20] The latest published data on breast cancer survival for women in England (2018, patients diagnosed 2013-2017) indicate 95.8% survival rate after 1 year, and 85% after 5 years (age-standardised).[21]

In terms of hospital admissions, in England, in 2018-19, there were 215,644 due to malignant neoplasm of breast (ICD-10 code C50), of which 183,828 were day cases. As for finished consultant episodes (FCE), there were 219,885 of them, and 80,435 FCE bed days.[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main treatments for TNBC are surgery, radiotherapy and chemotherapy. The treatment is subject to: where the cancer is, the size of the cancer and whether it has spread (the stage), how abnormal the cells look under the microscope (the grade) and general health of the patient.[23]

Surgery can either be breast-conserving, where the cancerous lump (tumour) is removed, or mastectomy, where the whole breast is removed.[24] After breast conserving surgery radiotherapy usually follows to the rest of the breast tissue. Chemotherapy can be before and after surgery; before: to shrink the tumour, and after: to reduce the risk of the cancer coming back.[23]

CURRENT TREATMENT OPTIONS

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.[25]

Eribulin is also recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when:[25]

- 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.

PLACE OF TECHNOLOGY

If licensed, sacituzumab govitecan will offer a more effective treatment option for adult patients with metastatic or unresectable locally advanced triple-negative breast cancer who have received at least two prior therapies.

CLINICAL TRIAL INFORMATION

Trial	ASCENT; NCT02574455; Phase III Study of Sacituzumab Govitecan (IMMU-132) in Refractory/Relapsed Triple-Negative Breast Cancer **Phase III** – Completed

	Locations: EU (inc. UK), USA and Canada **Actual study completion date:** December 2020
Trial design	Randomised, parallel assignment, open label
Population	- N= 529 (actual enrollment) - Histologically or cytologically confirmed TNBC based on the most recent analyzed biopsy or other pathology specimen - Female or male patients, ≥18 years of age
Intervention(s)	Sacituzumab govitecan (10 mg/kg on Days 1 and 8 of 21-day cycles)
Comparator(s)	- Eribulin (1.4 mg/m2 IV on Days 1 and 8 of a 21-day cycle) - Capecitabine (1000-1250 mg/m2 orally twice daily on Days 1-14 of a 21-day cycle) - Gemcitabine (800-1200 mg/m2 IV on Days 1, 8 and 15 of a 28-day cycle) - Vinorelbine (25 mg/m2 IV on Day 1 weekly)
Outcome(s)	Progression-Free Survival (PFS): [Time Frame: 3 years] See trial record for full list of other outcomes.
Results (efficacy)	Median progression-free survival was 5.6 months with sacituzumab govitecan vs 1.7 months with physician's choice of single-agent chemotherapy (hazard ratio [HR] = 0.41; P < .0001), which met the study's primary endpoint of progression-free survival in the 468 patients without brain metastases on blinded review. Median overall survival was 12.1 months vs 6.7 months (HR = 0.48; P < .0001). An improvement in progression-free survival for the full population was also significant (HR = 0.43; P < .0001).[26]
Results (safety)	The most common adverse events of any grade included neutropenia, diarrhea, nausea, alopecia, fatigue, and anemia. Common grade 3 or 4 toxicities in the experimental vs control arms were neutropenia (51% vs 33%), leukopenia (10% vs 5%), diarrhea (10% vs < 1%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%). Dose reductions were necessary in about one-quarter of patients in each arm. One treatment-related death was due to sepsis in the chemotherapy arm.[26]

ESTIMATED COST

The cost of sacituzumab govitecan is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

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

- Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro M, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). 2020.[27]
- Gradishar WJ, Anderson BO, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. 2020.[28]

ADDITIONAL INFORMATION

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