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Health Technology Briefing
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Sacituzumab govitecan for urothelial cancer

Company/Developer	Gilead Sciences Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29329	NICE ID: 10707	UKPS ID: 662209

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Sacituzumab govitecan is in clinical development for the treatment of adult patients with metastatic or locally advanced, unresectable urothelial cancer (UC). UC occurs on the lining of the renal pelvis, ureter, bladder and urethra, and other parts of the urinary system. Locally advanced bladder cancer indicates that the cancer has grown through the bladder wall or has spread into lymph nodes, while metastatic UC occurs when the cancer has spread to other parts of the body. Durable responses are rare with current standard of care treatments. Therefore, treatment approaches with longer-term disease control and extending to broader metastatic UC patient populations are needed.

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 sacituzumab 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 metastatic or locally advanced, unresectable UC.

Proposed Indication

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 unavailable to comment.

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Treatment of adults with metastatic or locally advanced, unresectable urothelial cancer (UC).[1,2]

Technology

Description

Sacituzumab govitecan (Trodelvy) is a Trop-2-directed antibody-drug conjugate. Sacituzumab is a humanised antibody that recognises Trop-2.[3] Trop-2, a transmembrane calcium signal transducer, is overexpressed in numerous epithelial cancers, and stimulates cancer-cell growth.[4]
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.[3]

Sacituzumab govitecan is currently in phase II (TROPHY U-01, NCT03547973) and phase III (TROPiCS-04, NCT04527991) clinical development for the treatment of adults with metastatic and locally advanced, unresectable UC respectively. In these trials, sacituzumab govitecan 10mg/kg is administered intravenously on day 1 and day 8 of 21 day cycles.[1,2]

Key Innovation

Sacituzumab govitecan is an antibody-drug conjugate (ADC) which 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 highly expressed on tumour cells. Specific targeting of tumour cells limits off-target toxicity, thereby reducing the levels of toxicity normally associated with chemotherapy.[5,6]

Furthermore, sacituzumab govitecan has a higher 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 disturbing the therapeutic index of the conjugated antibody. This delivery advantage ensures high concentrations of SN-38 are delivered to cancer cells.[6]

Regulatory & Development Status

Sacituzumab govitecan currently has a Marketing Authorisation in the 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.[3]

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, gastric cancer, hepatocellular carcinoma and castration resistant prostate cancer.[7]

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Patient Group

Disease Area and Clinical Need

Urothelial cancer UC, also called transitional cell carcinoma (TCC), begins in the transitional cells that line the renal pelvis, ureters, bladder and urethra, and some other organs . These cells can change shape and stretch without breaking apart.[8] Metastatic urothelial cancer occurs when cancer cells break away from where they began (the primary tumour) and travel through the lymph system or blood to other parts of the body, such as the liver or bones.[9] Locally advanced bladder cancer indicates that the cancer has grown through the bladder wall or has spread into lymph nodes.[10] The main risk factors for bladder cancer include: smoking, bladder infections, medical conditions such as systemic sclerosis, as well as prior bladder cancer and family history, being overweight, and exposure to certain chemicals.[11] The symptoms include blood in the urine, increased frequency/urgency of urine passing, pain or a burning sensation when passing urine, weight loss, back/lower tummy/bone pain, fatigue and illness.[12]

UC is the most common type of bladder cancer.[13] UC accounts for about 90% of all bladder cancers and 12% of kidney cancers (of which 7% begin in the renal pelvis, and 5% in the ureter).[14] In England in 2017, there were 8,686 new registrations for malignant neoplasm of bladder (ICD-10 code C67), 692 for malignant neoplasm of renal pelvis (ICD-10 code C65), and 596 for malignant neoplasm of ureter (ICD-10 code C66).[15] The 2020-2021 Hospital Episodes Statistics for England recorded a total of 56,069 finished consultant episodes (FCE) for malignant neoplasm of bladder, resulting in 52,437 hospital admissions, 73,087 FCE bed days and 30,679 day cases. There were 1,512 FCE for malignant neoplasm of renal pelvis, resulting in 1,385 hospital admissions, 2,572 FCE bed days and 768 day cases. The FCE for malignant neoplasm of ureter were 2,159, resulting in 1,942 hospital admissions, 4,241 FCE bed days and 1,003 day cases.[16]

Recommended Treatment Options

For locally advanced or metastatic urothelial cancer, treatment options may include chemotherapy, immunotherapy or treatment to relieve cancer symptoms. If the cancer is too advanced, palliative care may be offered to manage pain.[17]

The current treatment option recommended by NICE for locally advanced or metastatic UC in adults who have had platinum-containing chemotherapy is atezolizumab.[18]

Clinical Trial Information

Trial	NCT04527991; 2020-002964-29; A Randomized Open-Label Phase III Study of Sacituzumab Govitecan Versus Treatment of Physician's Choice in Subjects With Metastatic or Locally Advanced Unresectable Urothelial Cancer **Phase III** – Recruiting **Location(s):** EU, UK, USA, Canada, Australia and China **Primary completion date:** June 2023
Trial Design	Randomised, open label, parallel assignment

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Population	N=600 (estimated); Subjects aged 18 and over with histologically documented metastatic or locally advanced unresectable UC; progression or recurrence following platinum-containing regimen and anti PD-1/PD-L1 therapy
Intervention(s)	10 mg/kg of sacituzumab govitecan-hziy intravenously on Day 1 and Day 8 of 21-day cycles
Comparator(s)	Choice of either paclitaxel, docetaxel, or vinflunine at standard of care (SOC) doses of 175, 75, and 320 mg/m^2 respectively, every 3 weeks on Day 1 of 21-day cycles
Outcome(s)	**Primary outcome measure:** Overall Survival (OS) [Time Frame: Up to 3.5 years] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT03547973; 2018-001167-23; A Phase II Open Label, Study of IMMU-132 in Metastatic Urothelial Cancer After Failure of Platinum-Based Regimen or Anti-PD-1/ PD-L1 Based Immunotherapy **Phase II –** Recruiting **Location(s):** USA and France **Primary completion date:** October 2022
Trial Design	Non-Randomised, open label, parallel assignment
Population	N=321 (estimated); Subjects aged 18 and over with histologically confirmed UC
Intervention(s)	**Cohort 1 & 2**: 10 mg/kg of sacituzumab govitecan-hziy intravenously on Days 1 and 8 of a 21-day cycle **Cohort 3**: 10 mg/kg of sacituzumab govitecan-hziy intravenously on Days 1 and 8 of a 21-day cycle and 200mg of pembrolizumab only on Day 1 of a 21-day cycle **Cohort 4**: Cisplatin (either at 70 mg/m^2 on Day 1 of a 21-day cycle or at a split dose of 35 mg/m^2 on Days 1 and 8 of a 21-day cycle with a maximum body surface area of 2) and sacituzumab govitecan-hziy with maximum dose of 10 mg/kg intravenously on Days 1 and 8 of a 21-day cycle for up to 6 cycles. Participants who do not progress receive maintenance therapy of avelumab 800mg every 2 weeks beginning on cycle 1, day 1 and every 2 weeks thereafter and sacituzumab govitecan-hziy 10mg/kg on days 1 and 8 every 21 days **Cohort 5**: Cisplatin (either at 70 mg/m^2 on Day 1 of a 21-day cycle or at a split dose of 35 mg/m^2 on Days 1 and 8 of a 21-day cycle with a maximum body surface area of 2) and sacituzumab govitecan-hziy RP2D determined in Cohort 4 on Days 1 and 8 of a 21-day cycle, and 800 mg of avelumab every 2 weeks beginning on Cycle 1, Day 1 and every 2 weeks

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Comparator(s)	-
Outcome(s)	**Primary outcome measure:** Overall Response Rate (ORR) Based on Central Review by Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) Criteria. [Time Frame: Up to Survival Follow-up Visit (maximum of 2 years after Safety Follow-up Visit (30 days after last dose date))] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Sacituzumab govitecan is already marketed in the UK. A 180mg vial costs £793.[19]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Durvalumab with tremelimumab and chemotherapy for treating unresectable or advanced urothelial cancer (GID-TA 10748). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated unresectable or metastatic urothelial cancer when cisplatin is unsuitable (GID-TA 10826). Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA692). April 2021.
- NICE technology appraisal guidance. Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy (TA530). July 2018.
- NICE technology appraisal guidance. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA525). June 2018.
- NICE technology appraisal guidance. Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (TA272). Jan 2013.
- Nice guidance. Bladder cancer: diagnosis and management (NG2). February 2015.

NHS England (Policy/Commissioning) Guidance

- NHS England. Specialised kidney, bladder and prostate cancer services (Adults). Service Specification (170114S). February 2019.
- 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

- Powles T, Bellmunt J, Comperat E, et al., Bladder cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. 2021.[20]

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- European Association of Urology. Guidelines on muscle-invasive and metastatic bladder cancer. 2020.[21]

Additional Information

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