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CADTH Reimbursement Recommendation

# Sacituzumab Govitecan (Trodelvy)

**Indication:** For the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer who have received 2 or more prior therapies, with at least 1 of them for metastatic disease

**Sponsor:** Gilead Sciences Canada, Inc.

**Final recommendation:** Reimburse with conditions

CADTH

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**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

# Summary

CADTH

## What Is the CADTH Reimbursement Recommendation for Trodelvy?

CADTH recommends that Trodelvy should be reimbursed by public drug plans for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior therapies, at least 1 of them for metastatic disease if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Trodelvy should only be covered to treat patients with triple-negative breast cancer that has spread to other parts of the body or cannot be removed by surgery, and who have received 2 or more prior treatments, including at least 1 treatment for metastatic disease; and have good performance status.

### What Are the Conditions for Reimbursement?

Trodelvy should only be reimbursed if it is prescribed by a clinician who is experienced in treating cancer. The price of Trodelvy must be lowered to be cost-effective and affordable.

### Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that Trodelvy was better than treatment of physician's choice (TPC; i.e., eribulin, capecitabine, gemcitabine, or vinorelbine) in delaying the spread of triple-negative breast cancer and allowing patients to live longer.

Based on public list prices, Trodelvy is not considered cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY) for patients included in the indication approved by Health Canada, relative to TPC. Economic evidence suggests that the price of Trodelvy needs to be reduced by at least 87% for it to be cost-effective at a $50,000 per QALY threshold.

Based on public list prices, Trodelvy is expected to cost the public drug plans at least $72 million over 3 years.

## Additional Information

### What is Triple-Negative Breast Cancer?

Breast cancer can be classified by proteins (receptors) expressed by the cancer cell. Some breast cancers do not have estrogen and progesterone hormone receptors and do not have much HER2 receptors. This is called triple-negative breast cancer and is considered unresectable locally advanced or metastatic when the cancer spreads to other parts of the body or cannot be removed by surgery.

### Unmet Needs in Triple-Negative Breast Cancer

There are no effective treatments available for patients with triple-negative breast cancer. Many patients do not respond to available treatment options. Even for patients who do respond, the cancer may still return and spread in the breast or to another part of the body.

### How Much Does Trodelvy Cost?

Treatment with Trodelvy was estimated to cost approximately $12,478 per patient per cycle.

## Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that sacituzumab govitecan be reimbursed for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior therapies, at least 1 of them for metastatic disease, only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

One phase III, randomized, open-label, multi-centre study (ASCENT) demonstrated that treatment with sacituzumab govitecan resulted in added survival benefit for patients with unresectable locally advanced or mTNBC who have received 2 or more prior therapies, at least 1 of them for metastatic disease (N = 529). ASCENT demonstrated that, compared with chemotherapy (TPC [i.e., eribulin, capecitabine, gemcitabine, or vinorelbine], sacituzumab govitecan was associated with statistically significant and clinically meaningful improvements in progression-free survival [PFS]; hazard ratio [HR] = 0.409; 95% confidence interval [CI], 0.323 to 0.519; P < 0.0001 in the brain-metastases negative [BM-Neg] population and HR = 0.433; CI, 0.347 to 0.541; P < 0.0001 in the intent-to-treat [ITT] population) and overall survival [OS] (HR = 0.476; 95% CI, 0.383 to 0.592; P < 0.0001 in the BM-Neg population and HR = 0.508, 95% CI, 0.414 to 0.624; P < 0.0001 in the ITT population). Although health-related quality of life (HRQoL) was an exploratory analysis in the ASCENT study, results suggested that HRQoL was maintained during treatment with sacituzumab govitecan. Sacituzumab govitecan was associated with a manageable toxicity profile.

Patients expressed a need for treatments that control disease progression, prevent recurrence, extend survival, maintain HRQoL, reduce disease symptom severity, and have a manageable side effect profile. Given the totality of the evidence, pERC concluded that sacituzumab govitecan met the needs identified by patients as it provides improvement in PFS, and OS, maintained quality of life, and has a manageable side effect profile.

Using the sponsor submitted price for sacituzumab govitecan and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for sacituzumab govitecan was $375,333 per QALY compared with TPC. At this ICER, sacituzumab govitecan is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for adults with either locally advanced or mTNBC who were either refractory or had relapsed after at least 2 prior therapies. A reduction in price of at least 87% is required for sacituzumab govitecan to be considered cost-effective at a $50,000 per QALY threshold.

## Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason |
|---|---|
| **Initiation** | |
| 1. Treatment with sacituzumab govitecan should be initiated only in adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior therapies, at least 1 of them for metastatic disease (including a taxane regardless of disease stage) | No evidence was reviewed to support a clinical benefit of sacituzumab govitecan in patients without prior exposure to a taxane.<br>In the ASCENT study, patients must have been previously treated with a taxane regardless of disease stage (adjuvant, neoadjuvant or advanced). |
| 2. Patient must have good performance status | Patients enrolled in the ASCENT study had an ECOG PS of 0 or 1. pERC acknowledged that clinicians may consider using sacituzumab govitecan for patients with a higher ECOG PS at their discretion. |
| 3. Patient must have all of the following:<br>3.1. Adequate blood counts and organ function<br>3.2. Stable brain metastases or no brain metastases<br>3.3. No Gilbert disease | No evidence was reviewed to support a clinical benefit of sacituzumab govitecan in patients with impaired hematology parameters and organ dysfunction, brain metastases that were not considered stable CNS disease at baseline, and Gilbert disease.<br>The ASCENT study enrolled patients with adequate hematology parameters and organ function, and patients with no brain metastases at baseline as well as patients with stable CNS disease for at least 4 weeks at baseline.<br>The ASCENT study excluded patients with Gilbert disease. |
| **Renewal** | |
| 4. Assessment for renewal of sacituzumab govitecan should be based on clinical and radiographic evaluation performed every 6 to 9 weeks for the first 9 months after treatment initiation | In the ASCENT study, tumour response was assessed by CT or MRI scans every 6 weeks for 36 weeks and then every 9 weeks thereafter until the occurrence of disease progression requiring discontinuation of further treatment. |
| **Discontinuation** | |
| 5. Treatment with sacituzumab govitecan should be discontinued upon the occurrence of any of the following:<br>5.1. documented radiographic disease progression<br>5.2. unacceptable toxicity attributed to sacituzumab govitecan<br>5.3. clinical deterioration | In the ASCENT study, the primary PFS analysis considered clinical progression with documented radiographic progression.<br>Patients who are unable to complete treatment with sacituzumab govitecan due to unacceptable toxicity would likely not be able to receive further treatment with sacituzumab govitecan.<br>Patients with symptomatic deterioration indicating treatment failure in the absence of clinical benefit, and patients with significant change in performance status and in quality of life would likely not be able to receive further treatment with sacituzumab govitecan. |
| **Prescribing** | |
| 6. Sacituzumab govitecan should only be prescribed by clinicians with expertise and experience in treating breast cancer in approved centres for sacituzumab govitecan | To ensure that sacituzumab govitecan is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner. |

| Reimbursement condition | Reason |
|---|---|
| **Pricing** | |
| 7. A reduction in price | The ICER for sacituzumab govitecan is $375,333 per QALY when compared with TPC; a weighted basket of eribulin, capecitabine, gemcitabine, and vinorelbine).<br>A price reduction of 87% would be required for sacituzumab govitecan to be able to achieve an ICER of $50,000 per QALY compared to TPC. |
| **Feasibility of adoption** | |
| 8. The feasibility of adoption of sacituzumab govitecan must be addressed | At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's reanalyses. |

CT = computed tomography; CNS = central nervous system; ECOG PS= Eastern Cooperative Oncology Group performance status; MRI = magnetic resonance imaging; PFS = progression-free survival, QALY = quality-adjusted life-year; TPC = treatment of physician's choice

## Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by pERC and the drug plans are summarized in Table 2.

### Table 2: Implementation Guidance From pERC

| Condition no. from Table 1 | Implementation considerations and guidance |
|---|---|
| 1 | pERC recognized that patients without previous taxane exposure due to contraindications would not have been eligible for the ASCENT study. pERC also noted that patients who are intolerant to a taxane would have had exposure to a taxane, and therefore would meet the inclusion criteria for the ASCENT study. pERC agreed with the clinical experts that it would be reasonable to offer sacituzumab govitecan to patients who did not receive a previous taxane due to contraindications or are intolerant to a taxane. |
| 3.3 | pERC acknowledged that while the ASCENT study excluded patients with Gilbert disease, as per Health Canada product monograph, Gilbert disease was not an absolute contraindication for sacituzumab govitecan, rather the use of sacituzumab govitecan in patients harbouring a UGT1A1 polymorphism is cautioned. As a result, pERC felt it may be reasonable to offer dose reduced sacituzumab govitecan to patients with increased bilirubin due to Gilbert disease. The precise dose reduction in this patient population is not known. |
| 4 | pERC noted that assessment of treatment response occurred more frequently in the ASCENT study compared to current clinical standards. Clinical experts indicated that response to treatment should be assessed at each follow-up visit with serial imaging typically performed on an 8- to 12-week interval, with toxicity and safety assessments done more often during early treatment (every 2 to 4 weeks) or as needed. The assessment for renewal of sacituzumab govitecan should align with current clinical standards. |

## Discussion Points

- pERC acknowledged that there is an unmet treatment need for patients with locally advanced or mTNBC who have received 2 or more prior systemic treatments, including at least 1 systemic treatment for metastatic disease, because there is an absence of clinically effective alternative options. The clinical experts noted that current standard treatments are not effective in relapsed or refractory triple-negative breast cancer (TNBC) patients.
- pERC noted that the Health Canada–approved indication for sacituzumab govitecan does not stipulate prior taxane exposure, whereas for the ASCENT, study prior treatment with a taxane, regardless of disease stage, was an eligibility criterion. pERC agreed with the clinical experts that the majority of patients who have received 2 or more prior systemic treatments for locally advanced or mTNBC, at least 1 systemic treatment for metastatic disease would have received a taxane. pERC acknowledged that a small subset of patients who have contraindications to taxanes would not have had prior experience with a taxane and agreed with the clinical experts that it would be reasonable to offer sacituzumab govitecan to this subset of patients.
- pERC discussed the penetration of sacituzumab govitecan into the central nervous system (CNS) and deliberated on the clinical effectiveness of sacituzumab govitecan in patients with brain metastases. Given that the ITT population in the ASCENT study included patients with stable CNS metastases and excluded patients with CNS metastases that were not considered stable at baseline, pERC agreed that reimbursement of sacituzumab govitecan should include patients with stable brain metastases and patients without brain metastases.
- Notable adverse drug reactions associated with sacituzumab govitecan included diarrhea and neutropenia. pERC acknowledged that despite the high rates of Grade 3 diarrhea, this adverse effect was consistent with currently available locally advanced or mTNBC treatments. Overall, pERC agreed with the clinical experts and evidence from patient groups that the adverse effects associated with sacituzumab govitecan were significant but manageable.
- pERC discussed that administration of sacituzumab govitecan with UGT1A1 inhibitors and UGT1A1 inducers should be exercised with caution given that the Health Canada product monograph advises to exercise caution when administering UGT1A1 inhibitors with sacituzumab govitecan due to theoretical risk of increased SN-38 exposure; and when administering UGT1A1 inducers due to theoretical risk of decreased SN-38 exposure.
- pERC noted that in the ASCENT study, G-CSF was administered for primary and secondary prophylaxis of neutropenia and that a high number of patients in the sacituzumab govitecan group received G-CSF. pERC discussed the availability of G-CSF in Canada and noted that public access varies across jurisdictions. The clinical experts highlighted that there is limited access to G-CSF in Canada in the metastatic setting, and that typical clinical practice would include dose reduction and if necessary, treatment discontinuation in patients with severe or persistent neutropenia or febrile neutropenia. As a result, pERC concluded that in jurisdictions with limited access to G-CSF, the relative dose intensity for both sacituzumab govitecan and TPC in the ASCENT study may not align with clinical practice and the impact of dose intensity on clinical efficacy is uncertain.
- pERC also discussed that the budget impact of reimbursing sacituzumab govitecan is likely to be greater than that estimated by CADTH, given that the costs associated with chair time, pharmacy and nursing resources, and potential concomitant G-CSF use were not accounted for in the CADTH reanalyses. Additionally, pERC also discussed that the

number of patients receiving of sacituzumab govitecan may be initially greater than estimated in the analyses.

## Background

Sacituzumab govitecan has a Health Canada indication for the treatment of adult patients with unresectable locally advanced or mTNBC who have received 2 or more prior therapies, with at least 1 of them for metastatic disease. Sacituzumab govitecan is an antibody-drug conjugate directed against human trophoblast cell-surface marker 2 (Trop-2), a transmembrane protein involved in calcium signal transduction that is overexpressed in many epithelial cancers including TNBC. Sacituzumab govitecan is administered at a dose of 10 mg/kg as an IV infusion on days 1 and 8 of a 21-day treatment cycle.

## Sources of Information Used by pERC

To make their recommendation, pERC considered the following information:

- A review of 1 phase III, randomized, open-label, multi-centre study (ASCENT) in adult patients with locally advanced or mTNBC previously treated with at least 2 systemic chemotherapy regimens (including 1 taxane in the adjuvant, neoadjuvant, or advanced setting).
- Patients' perspectives gathered by patient groups, Rethink Breast Cancer (RBC) and the Canadian Breast Cancer Network (CBCN).
- Input from public drug plans and cancer agencies that participate in the CADTH review process.
- Two clinical specialists with expertise diagnosing and treating patients with breast cancer.
- Input from 3 clinician groups, including Ontario Health-Cancer Care Ontario (OH-CCO) Breast Cancer Drug Advisory Committee (3 medical oncologists and 1 pharmacist), The Ottawa Hospital Cancer Centre (TOHCC) Breast Medical Oncology group (4 medical oncologists), and the RBC Scientific Advisory Committee (6 medical oncologists from across Canada).
- A review of the pharmacoeconomic model and report submitted by the sponsor

## Stakeholder Perspectives

### Patient Input

Input was provided by 2 patient groups for this review, RBC and the CBCN. RBC conducted an online patient survey in June and July 2021; among 30 respondents with mTNBC (22 from the US and 6 from Canada), 4 with direct experience with sacituzumab govitecan, participated in telephone interviews. CBCN distributed online surveys in 2012 and 2017 to patients living with breast cancer registered in the membership databases of CBCN and other patient

organizations; among 157 respondents, data from 14 patients with mTNBC were captured in the input, and 1 Canadian patient with direct experience with sacituzumab govitecan participated in a telephone interview.

Patients highlighted the negative impacts of mTNBC including spread to the bone, liver, lungs, and brain. Symptoms frequently included pain, fatigue, and insomnia and imposed significant financial burdens and limitations on patients' ability to work, caregiving responsibilities, physical activity, and ability to spend time with loved ones. Patients highlighted the limited treatment options for mTNBC and their experiences with prior therapies (chemotherapy and immunotherapy), including their limited effectiveness in delaying progression, managing symptoms, and maintaining HRQoL as well as their side effects (e.g., nausea and/or vomiting, fatigue, hand and foot syndrome). Twenty patients contacted by RBC and 1 patient contacted by CBCN had direct experience with sacituzumab govitecan. Patients felt that the drug was effective in controlling disease, extending survival, maintaining HRQoL, and reducing mTNBC symptoms (e.g., Jacksonian marches, bone pain, neuropathy) and noted that side effects (e.g., fatigue, alopecia, diarrhea, neutropenia) were manageable although not all patients were currently able to access the drug.

Patients with mTNBC identified an important unmet need for treatments that control disease progression, prevent recurrence, and extend survival. Other needs identified by patients were treatments that maintain HRQoL, reduce disease symptom severity, and have a manageable side effect profile.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

Two clinical experts with expertise in the diagnosis and management of mTNBC highlighted the poor outcomes in patients with mTNBC and limited effective treatment options for later-line therapy (single-drug chemotherapy, optimal sequencing undefined). Objective response rates (ORRs) by objective tumour imaging are low for lines of therapy beyond anthracyclines and taxanes, many patients become refractory to treatment, and many treatments are poorly tolerated. The main goals of therapy are to extend survival and delay progression with minimal toxicity while maintaining or improving HRQoL. Sacituzumab govitecan would be administered for later-line treatment after at least 2 prior lines of chemotherapy (at least 1 taxane in the adjuvant, neoadjuvant, or advanced setting and at least 1 therapy in the metastatic setting), where it may cause a shift in the current treatment paradigm by providing an option for targeted therapy. Any patients with mTNBC who have received at least 2 prior lines of systemic therapy with adequate performance status, adequate hematological/organ function and stable CNS disease would be a candidate for sacituzumab govitecan. Treatment would be initiated in suitable patients by the primary treating physician based on pathology or biomarker assessment and imaging/biopsy results. Response to treatment is assessed by serial imaging showing stable or shrinking disease (objective responses), laboratory markers, clinical assessment, and maintained or improved HRQoL and cancer symptoms. Treatment would be discontinued in patients with progressive disease (PD) or with significant worsening of symptoms, performance status or HRQoL, as well as in patients with significant and persistent side effects (especially diarrhea).

### Clinician Group Input

Three clinician groups provided input for this review: TOH-CCO Breast Cancer Drug Advisory Committee (3 medical oncologists and 1 pharmacist), TOH-CCO Breast Medical Oncology

group (4 medical oncologists), and the RBC Scientific Advisory Committee (6 medical oncologists from across Canada). No major contrary views were presented; clinical groups echoed the lack of effective options for later-line therapy of mTNBC. Sacituzumab govitecan may change the treatment paradigm and be used before vinorelbine-gemcitabine or reuse of doxorubicin.

## Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for sacituzumab govitecan:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues
- potential need for a provisional funding algorithm (oncology only).

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

## Table 3: Responses to Questions From the Drug Programs

| Implementation issues | Response |
|---|---|
| **Relevant comparators** | |
| How does sacituzumab govitecan compare to other chemotherapy agents used in triple-negative breast cancer regimens (other than eribulin, gemcitabine, capecitabine and vinorelbine)? | pERC agreed with the clinical experts in those treatments that are not represented in the ASCENT study were likely used in an earlier line of therapy. Comparison of sacituzumab govitecan with other chemotherapies (e.g., carboplatin) would likely show similar benefits. |
| **Considerations for initiation of therapy** | |
| Should patients with ECOG PS of 2 or greater be eligible for sacituzumab govitecan? | Patients enrolled in the ASCENT study had an ECOG PS of 0 or 1. pERC acknowledged that clinicians may consider using sacituzumab govitecan for patients with a higher ECOG PS at their discretion. |
| In the ASCENT study, inclusion criteria included previous exposure to taxanes. If patients did not receive a previous taxane due to contraindications or intolerance: are they eligible for treatment with sacituzumab govitecan? | pERC acknowledged the clinical experts' response (i.e., yes, in the real world, patients would likely still be offered sacituzumab govitecan although this situation would be rare for third- or further-line therapy).<br>pERC felt that if a patient was intolerant to a taxane, they were exposed to a taxane and therefore would meet the inclusion criteria (as there was no stipulation for duration of taxane treatment); and that if a patient had a contraindication (e.g., peripheral neuropathy), pERC agreed it would be reasonable to offer sacituzumab govitecan. |

| Implementation issues | Response |
|---|---|
| **Considerations for prescribing of therapy** | |
| In comparison with currently available treatments, would you expect that sacituzumab govitecan will require more nursing resources and chair time? | The clinical experts stated yes. Although the dosing schedules for sacituzumab govitecan and chemotherapy are similar, the first infusion of sacituzumab govitecan is approximately 3 hours with subsequent infusions being 1 to 2 hours. This is due to concerns regarding infusion reactions that are mitigated by premedication (e.g., antihistamines, steroids). Comparator chemotherapies require much shorter chair times than sacituzumab govitecan.<br>In rural oncology satellite sites, sacituzumab govitecan may not be initially accessible due to human resource limitations, monitoring difficulties, potential for adverse reactions, and drug wastage concerns. However, additional sites are likely to be added over time and with additional experience with the drug.<br>pERC agreed with the clinical experts and acknowledged that the infusion time is similar to taxanes where often the first dose is given at a tertiary cancer centre and if tolerated, then it is given a satellite site. |
| **Generalizability** | |
| Should patients with ECOG PS of 2 or greater be eligible for sacituzumab govitecan? | Patients enrolled in the ASCENT study had an ECOG PS of 0 or 1. pERC acknowledged that clinicians may consider using sacituzumab govitecan for patients with a higher ECOG PS at their discretion. |
| **Funding algorithm (oncology only)** | |
| Do you expect that sacituzumab govitecan would impact the treatment paradigm such that administration of comparator chemotherapy regimens, previous lines of therapy, and subsequent lines of therapy will be impacted? Is there a certain subpopulation that would be mainly impacted? | pERC agreed with the clinical experts that if sacituzumab govitecan is available, most patients will use it in the second- or third-line setting; and if eligible, patients will likely use it as early as possible according to the indication. pERC also agreed with the clinical experts that the impact on the treatment paradigm is not clear yet. |
| **Care provision issues** | |
| Sacituzumab govitecan is supplied as a 180 mg vial of lyophilized powder. The dosage of sacituzumab govitecan is 10 mg/kg intravenously on days 1 and 8 of a 21-day treatment cycle. Do you expect drug wastage to occur? | pERC acknowledged the resource impact and recognized the challenges of vial sharing as a result of the limited product stability of sacituzumab govitecan. |
| The preparation of sacituzumab govitecan requires a sterile compounding pharmacy, and the final product stability is also very short (4-hour storage at 4 to 8°C with administration within 4 hours including infusion time according to the FDA; 4- hour storage at 2 to 8°C with administration within 6 hours including infusion time according to Health Canada product monograph). In your opinion, which settings in Canada would be able to administer sacituzumab govitecan successfully? | The clinical experts noted that any site in Canada with the capacity to mix and administer IV chemotherapy, such as major cancer centres, would be able to successfully administer sacituzumab govitecan. The situation for rural and satellite sites is less certain. Administration by smaller sites could exacerbate drug wastage. Procedural modifications for administration may be needed depending on how long sacituzumab govitecan takes to prepare, local human resource constraints, and potential for vial sharing. For example, some centres may be able to arrange for administration of all sacituzumab govitecan on specific days.<br>pERC acknowledged and agreed with the clinical experts' response. |

| Implementation issues | Response |
|---|---|
| Hormone receptor status and HER2 are standard tests done in jurisdictions for metastatic breast cancer. | pERC acknowledged that these are standard tests performed at diagnosis. |
| **System and economic issues** | |
| The manufacturer estimates a 3-year pan-Canadian budget of $44M, based on a market uptake of [redacted] in years 1 to 3 respectively. PAG is concerned that market uptake may be underestimated since sacituzumab govitecan may represent the new standard of care for patients who meet the ASCENT study criteria. | pERC agreed with the clinical experts that the uptake would likely be higher in practice than estimated by the sponsor; and noted that CADTH's re-analysis was based on greater uptake. pERC considered that despite the alternate uptake assumptions by CADTH, the potential uptake may be underestimated. |
| Chair time and additional pharmacy and nursing resources will be required for administration and preparation of sacituzumab govitecan. | pERC acknowledged that chair time and additional pharmacy and nursing resources would be required for administration and preparation of sacituzumab govitecan. pERC noted that CADTH indicated the administration impact was underestimated, but that the re-analysis was unable to address this limitation. |
| Comparators used in the ASCENT study are generic or have confidential prices. | pERC acknowledged the confidential nature of drug prices. |

ECOG PS = Eastern Cooperative Oncology Group Performance Status; FDA = Food and Drug Administration; PAG = Provincial Advisory Committee; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

# Clinical Evidence

## Description of Study

One phase III, randomized, open-label (OL), multi-centre study (ASCENT, N = 529)[11,12] was included in the systematic review. The primary objective of the study was to compare the efficacy of sacituzumab govitecan (10 mg/kg as an IV infusion on days 1 and 8 of a 21-day treatment cycle) with chemotherapy (TPC selected from 1 of the following: eribulin, capecitabine, gemcitabine, or vinorelbine) in prolonging PFS among adult patients with locally advanced or mTNBC previously treated with at least 2 systemic chemotherapy regimens (including 1 taxane in the adjuvant, neoadjuvant, or advanced setting). Of note, the study enrolled a small number of patients (approximately 3%) with locally advanced mTNBC who had not received prior therapy in the metastatic setting. According to the sponsor and clinical experts consulted for this review, the treatment approach for unresectable locally advanced and mTNBC is the same, and patients with unresectable locally advanced TNBC who had been treated previously in the same manner as a metastatic patient and received at least 2 lines of systemic therapy would be eligible to receive sacituzumab govitecan in accordance with the Health Canada indication.

Patients with acceptable performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1) and organ function were randomized 1:1 to receive sacituzumab govitecan or TPC; randomization was stratified by the number of prior therapies (2 to 3 versus more than 3), baseline brain metastases (BM) status, and region (North America versus rest of world). Most patients (88.5%) were BM-negative (BM-Neg) while 11.5% were BM-positive (BM-Pos). The mean (standard deviation [SD]) age of patients was 54.0 (11.5) years and most were White (79.0%), not Hispanic/Latino (87.0%), and from North America (65.6%; nearly all from the US). The mean number of prior systemic therapies was 4.5 (2.1); nearly all patients had received

prior breast cancer-related surgery (94.9%), most had received prior non-brain radiotherapy (81.1%), and approximately 1 quarter had received prior programmed cell death protein-1 (PD-1)/programmed death ligand-1 (PD-L1) therapy (28.9%).

Patients were treated until PD or unacceptable toxicity and were followed up for survival. Crossover was not permitted. The primary outcome was PFS by blinded independent review committee (IRC) assessment in the BM-Neg population, while PFS in the ITT set, OS in the BM-Neg population and ITT set, ORR in the BM-Neg population and the ITT set, and HRQoL were secondary outcomes.

## Efficacy Results

The primary outcome was PFS in the BM-Neg population. Median (95% confidence interval [CI]) OS was statistically significantly longer in patients treated with sacituzumab govitecan versus TPC (12.1 [10.7 to 14.0] months versus 6.7 (5.8 to 7.7) months in the BM-Neg population; 11.8 [10.5 to 13.8] months versus 6.9 [5.9 to 7.7] months in the ITT set) (P < 0.0001). The hazard ratio (HR) (95% CI) for death among patients treated with sacituzumab govitecan relative to TPC was 0.476 (0.383 to 0.592) in the BM-Neg population and 0.508 (0.414 to 0.624) in the ITT set. Median (95% CI) PFS by blinded IRC assessment was statistically significantly longer in patients treated with sacituzumab govitecan versus TPC (5.6 [4.3 to 6.3] months versus 1.7 (1.5 to 2.6) months in the BM-Neg population; 4.8 [4.1, 5.8] months versus 1.7 [1.5 to 2.5] months in the ITT set) (P < 0.0001 in both the BM-Neg population and the ITT set). The HR (95% CI) for progression or death among patients treated with sacituzumab govitecan relative to TPC was 0.409 (0.323 to 0.519) in the BM-Neg population and 0.433 (0.347 to 0.541) in the ITT set. Median (95% CI) time to progression in the sacituzumab govitecan arm compared with the TPC arm was 5.8 (4.8 to 6.9) months versus 2.1 (1.5, 2.7) months in the BM-Neg population and 5.6 (4.3 to 6.2) months versus 2.1 (1.5, 2.8) months in the ITT set. The ORR (95% CI) in the sacituzumab govitecan arm compared with the TPC arm was 34.9% (28.8% to 41.4%) versus 4.7% (2.4% to 8.3%) in the BM-Neg population and 31.1% (25.6% to 37.0%) versus 4.2% (2.1% to 7.4%) in the ITT set. Mean (standard deviation [SD]) time to response for patients receiving sacituzumab govitecan and TPC was 2.67 (1.91) months versus 1.86 (0.92) months in the BM-Neg population and 2.66 (1.91) months versus 1.85 (0.92) months in the ITT set. Subgroup analyses were not adjusted for multiplicity and were not powered to evaluate differences in the treatment effects of sacituzumab govitecan in patients with and without *BRCA1 and/or BRCA2* mutations, patients who had received 2 to 3 or more than 3 prior lines of therapy, or BM-Pos and BM-Neg patients. Nevertheless, the clinical experts consulted for this review felt that the results of the trial were generalizable for all of these subgroups.

## Harms Results

Adverse events (AEs) occurred in almost all patients treated with both sacituzumab govitecan and TPC (99.6% versus 97.8%). Serious AEs (SAEs) and withdrawal due to AEs (WDAEs) occurred in similar proportions of sacituzumab govitecan- and TPC-treated patients (26.7% versus 28.1% and 4.7% versus 5.4%, respectively). Deaths due to AEs occurred in 1 (0.4%) sacituzumab govitecan-treated patient and 3 (1.3%) TPC-treated patients.

Neutropenia/febrile neutropenia occurred more frequently in patients treated with sacituzumab govitecan versus TPC (65.1% versus 44.2%), including Grade 3 neutropenia (48.4% versus 29.0%), Grade 4 neutropenia (17.8% versus 13.4%), and serious neutropenia (7.4% versus 2.7%). Diarrhea occurred more frequently in patients treated with sacituzumab govitecan versus TPC (65.1% versus 17.0%), including Grade 3 diarrhea (11.2% versus 0.9%)

and serious diarrhea (3.5% versus 0%). Only 1 patient discontinued sacituzumab govitecan due to a notable harm (diarrhea) although 10.9% and 4.7% of patients required sacituzumab govitecan dose reduction due to neutropenia and diarrhea, respectively.

### Critical Appraisal

Most of the notable limitations of the ASCENT study were tied to its OL design. Although outcome assessment of PFS and OS was conducted by a blinded IRC, patient-reported HRQoL and harms outcomes may have been influenced to some degree by knowledge of treatment allocation. The decision to discontinue patients from therapy was made by investigators based on unblinded review of local imaging results and/or clinical assessments and biased decision-making could have altered exposure to sacituzumab govitecan and/or TPC. Higher proportions of patients randomized to the TPC arm discontinued the study before receiving protocol therapy, during treatment, and during survival follow-up, and more PFS events were censored in the TPC arm due to initiation of other anti-cancer therapy and missed assessments. In addition, the magnitude of bias due to screening failures of unknown cause could not be evaluated as these data were not provided on a per-patient basis. The absence of formal statistical comparison and high amounts of missing HRQoL data (due to deaths and drop-outs) limited the interpretation of potentially important changes in this end point.

The demographic and disease characteristics of the ASCENT study population were broadly reflective of the Canadian population with mTNBC. Of note, the study enrolled small numbers of patients with locally advanced disease who had not received prior therapies in the metastatic setting (approximately 3%). According to the sponsor and the clinical experts consulted for this review, the treatment approach for unresectable locally advanced and mTNBC is the same, and patients with unresectable locally advanced TNBC who had been treated previously in the same manner as a metastatic patient and received at least 2 lines of systemic therapy would be eligible to receive sacituzumab govitecan in accordance with the Health Canada indication. Thus, enrolment of these patients in the trial would not impact generalizability. A potentially important issue limiting generalizability to Canadian patients with mTNBC was the use of G-CSF to counteract neutropenia in approximately half of the patients in the sacituzumab govitecan arm. According to the clinical experts, limited access to G-CSF in Canada may mean that dose reductions would be required in more patients; the potential impact on efficacy is unclear. Generalizability to patients not included in the study (e.g., ECOG performance status 2, patients who have not previously received taxanes, earlier lines of therapy) could not be evaluated.

## Indirect Comparisons

No indirect evidence was identified for this review.

## Other Relevant Evidence

No other relevant evidence was identified for this review.

# Economic Evidence

## Table 4: Cost and Cost-Effectiveness

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis<br>Partitioned survival model |
| **Target population** | Adults with either locally advanced or mTNBC who were either refractory or had relapsed after at least 2 prior standard-of-care chemotherapy regimens |
| **Treatment** | Sacituzumab govitecan, 10 mg/kg IV on days 1 and 8 every 21 days |
| **Submitted price** | Sacituzumab govitecan, 180 mg, vial for injection: $1,478.00 per vial |
| **Treatment cost** | At the sponsor submitted price of $1,478 per vial, the per-21-day cycle cost was estimated to be $12,478 based on the sponsor's assumption of a 94% dose intensity and average patient weight of 71.1 kg. |
| **Comparators** | TPC comprised of weighted single-agent chemotherapy regimens:<br>• Eribulin<br>• Capecitabine<br>• Gemcitabine<br>• Vinorelbine |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcomes** | QALYs, LYs |
| **Time horizon** | 5 years |
| **Key data source** | The ASCENT study, a phase III, multi-centre, randomized, trial |
| **Key limitations** | • Although the clinical data were considered mature, there was uncertainty regarding extrapolations beyond the trial period. Clinical experts noted that the sponsor's chosen OS and PFS curves for the extrapolated period were optimistic leading to overestimation of total life-years and QALYs. Of particular concern, were the long tails of the OS and PFS KM curves in the ASCENT study.<br>• Feedback from clinical experts indicated that the assumed TTD data for SG and TPC is uncertain and may be more closely correlated with progression than estimated by the sponsor.<br>• The sponsor incorporated treatment-specific health state utility values, on top of which disutilities associated with AEs were also incorporated, which does not reflect Canadian economic evaluation guidelines.<br>• The relative use of each single-agent chemotherapy in the TPC basket does not align with the use in Canadian clinical practice.<br>• The relative dosing intensity was considered uncertain. It is unclear whether treatments to mitigate discontinuation or treatment dosing changes due to AEs will be available in the Canadian setting as they were in the clinical trial. |

| Component | Description |
|---|---|
| **CADTH re-analysis results** | • CADTH conducted a re-analysis which included: selecting the Weibull distributions for the OS of SG and TPC; selecting the Gamma and Log-logistic distributions for the PFS of SG and TPC; selecting the Gamma and Weibull distribution for the TTD of SG and TPC; applying a single utility value to patients in the progression-free state despite treatment; and, revising the relative dosing intensity for patients who received SG to reflect a full dose.<br>• Based on CADTH reanalyses, the ICER for SG vs. TPC is $375,333 per QALY gained. A price reduction of at least 87% is required for SG to be considered cost-effective at a WTP threshold of $50,000 per QALY gained. |

AE = adverse events; KM = Kaplan-Meier; LY = life year; mTNBC = metastatic triple-negative breast cancer QALY = quality-adjusted life-year; OS = overall survival; PFS = progression-free survival; SG = sacituzumab govitecan; TPC = treatment of physician's choice TTD = time to treatment discontinuation; WTP = willingness to pay.

### Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the anticipated market uptake of SG was underestimated; limitations were identified with several inputs used to estimate the population size eligible for treatment with SG, leading to an underestimation of the population size; and adjustment of treatment costs by updating the pricing of comparators (i.e., vinorelbine and gemcitabine) to reflect Canadian pricing of available products, their dosing regimens to align with the dosing used in the ASCENT study, and alternate usage assumptions. CADTH estimated a revised base case, which included revising the anticipated market share uptake of SG in the new drug scenario and updating the pricing of comparator treatments (i.e., vinorelbine and gemcitabine) and dosing-related inputs (i.e., patient weight and body surface area). Based on the CADTH reanalyses, the estimated budget impact from the reimbursement of SG would be $11,173,751 in year 1, $22,573,305 in year 2, $39,132,475 in year 3, for a total incremental budget impact of $72,879,531 over the 3-year time horizon. CADTH was unable to address limitations related to the uncertainty around the estimated population size eligible for SG. Significant changes in population size would be associated with changes in the budget impact, as shown in a scenario analysis assessing the proportion of patients assumed to progress and receive second-line or third-line treatment comprised of those who did or did not receive systemic therapy before metastasis. A small change in the duration of treatment will have a large effect on budget impact.

## pERC Information

### Members of the Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan, Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

**Meeting date**: December 1, 2021

**Regrets**: None

**Conflicts of interest**: None