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CADTH Reimbursement Recommendation

Sacituzumab Govitecan (Trodelvy)

Indication: For the treatment of adult patients with unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+, or IHC 2+/ISH−) breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting.

Sponsor: Gilead Sciences Canada, Inc.

Final recommendation: Reimburse with conditions

Summary

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 hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+, or IHC 2+/ISH−) breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Trodelvy should only be covered to treat adult patients with unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer who have been previously treated with at least 1 taxane, at least 1 prior anticancer hormonal treatment, and at least 1 cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor in any setting, have experienced treatment failure after 2 to 4 prior systemic chemotherapy regimens for metastatic disease, and have good performance status.

What Are the Conditions for Reimbursement?

Trodelvy should only be reimbursed if it is prescribed by clinicians with expertise and experience in treating breast cancer in approved centres, and if the price of Trodelvy is reduced.

Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that Trodelvy was better than treatment of physician's choice (TPC) (including eribulin, capecitabine, gemcitabine, or vinorelbine) in allowing patients to live longer and improving quality of life.

Based on CADTH's assessment of the health economic evidence, Trodelvy does not represent good value to the health care system at the public list price. A price reduction is therefore required.

Based on public list prices, Trodelvy is estimated to cost the public drug plans approximately $129 million over the next 3 years. However, the actual budget impact is uncertain and may be lower depending on the initiation criteria required for reimbursement.

Summary

Additional Information

What Is HR-Positive, HER2-Negative Advanced or Metastatic Breast Cancer?

Breast cancer can be classified by proteins (receptors) expressed by the cancer cell. The HR-positive and HER2-negative subtype is the most prevalent breast cancer in Canada. Moreover, a breast cancer is considered unresectable and locally advanced or metastatic when the cancer spreads to other parts of the body or cannot be removed by surgery.

Unmet Needs in HR-Positive, HER2-Negative Advanced or Metastatic Breast Cancer

For many patients, their cancer does not respond to available treatment options. Even in patients whose cancer does respond to treatment, the cancer may still return. Patients with advanced HR-positive, HER2-negative breast cancer who do not benefit from endocrine therapy or additional chemotherapy regimens need other treatments that prevent or delay cancer from returning, prolong survival with an acceptable toxicity profile, and maintain quality of life.

How Much Does Trodelvy Cost?

Treatment with Trodelvy is expected to cost approximately $15,765 per patient per 28-day cycle, assuming a patient weight of 70 kg.

Recommendation

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) recommends that sacituzumab govitecan be reimbursed for the treatment of adult patients with unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (immunohistochemistry [IHC] 0, IHC 1+, or IHC 2+/in situ hybridization [ISH]–) breast cancer who have received endocrine-based therapy and at least 2 additional systemic chemotherapies in the metastatic setting, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 phase III, multicentre, multinational, open-label, randomized trial (the TROPiCS-02 trial; N = 543) demonstrated that treatment with sacituzumab govitecan resulted in added survival benefit for patients with HR-positive, HER2-negative locally advanced breast cancer or metastatic breast cancer (mBC) who had received endocrine-based therapy and a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor in any setting, and at least 2 additional systemic chemotherapies in the metastatic setting. The TROPiCS-02 trial demonstrated that, compared with a treatment of physician's choice (TPC) (i.e., eribulin, capecitabine, gemcitabine, or vinorelbine), sacituzumab govitecan resulted in a statistically significant and clinically meaningful improvement in overall survival (OS) (hazard ratio = 0.789; 97.77% confidence interval [CI] adjusted for multiplicity, [redacted]; P = 0.020), and a statistically significant improvement in progression-free survival (PFS) (hazard ratio = 0.66; 95% CI, 0.53 to 0.83; P = 0.0003). Additionally, data from the TROPiCS-02 trial showed that sacituzumab govitecan may result in an increase in time to deterioration (TTD) in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) domains of global health status quality of life (hazard ratio = 0.75; 95% CI, 0.61 to 0.92; P = 0.006) and fatigue (hazard ratio = 0.73; 95% CI, 0.60 to 0.89; P = 0.002), and a clinically important decrease in TTD in the EORTC QLQ-C30 diarrhea domain ([redacted]). However, pERC acknowledged that there was uncertainty in the results for patient-reported outcomes due to the open-label nature of the trial and a significant amount of missing data. Although there were increased incidences of serious adverse events such as severe neutropenia and diarrhea, pERC considered the safety profile of sacituzumab govitecan to be manageable, as sacituzumab govitecan is expected to be prescribed and administered by clinicians who are experienced with this drug.

Patients identified a need for new and effective treatment options that control disease, improve quality of life, and extend the lives of individuals living with metastatic breast cancer with fewer side effects than currently available treatments. pERC concluded that sacituzumab govitecan met some important needs identified by patients, as it provides improvements in PFS and OS and may maintain quality of life.

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 $506,807 per quality-adjusted life-year (QALY) gained, compared with TPC in adult patients with unresectable locally advanced or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+, or IHC 2+/ISH–) breast cancer who have received

endocrine-based therapy and at least 2 additional systemic chemotherapies in the metastatic setting only. At this ICER, sacituzumab govitecan is not cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained. A price reduction is therefore required.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with sacituzumab govitecan should be initiated in adult patients with unresectable locally advanced or metastatic breast cancer who meet all of the following criteria: 1.1. documented evidence of HR-positive, HER2-negative breast cancer 1.2. previously treated with at least 1 taxane, at least 1 prior anticancer hormonal treatment, and at least 1 CDK4/6 inhibitor in any setting 1.3. refractory or relapsed after 2 to 4 prior systemic chemotherapy regimens for metastatic disease.	Evidence from the TROPiCS-02 trial demonstrated that treatment with sacituzumab govitecan resulted in a survival benefit in patients with these characteristics.	In the TROPiCS-02 trial, HR-positive, HER2-negative patients were identified based on the following criteria: • A tumour was considered HR-positive if at least 1% of the cells examined have estrogen and/or progesterone receptors. • HER2-negative was defined as immunohistochemistry ≤ 2+ or fluorescence in situ hybridization negative. pERC agreed that neoadjuvant or adjuvant therapy for early-stage disease would qualify as 1 of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within a 12-month period of initiation of the therapy. pERC agreed with the clinical experts that patients who have not received taxanes due to a medical contraindication should still be considered eligible for sacituzumab govitecan. pERC agreed that, at the onset of implementation, access to sacituzumab govitecan could be provided to patients who have received more than 4 lines of prior chemotherapy in the metastatic setting and did not have the opportunity to use this drug earlier in their treatment journey, if they maintain a good performance status to receive the treatment.
2. Patients must have good performance status.	Patients enrolled in the TROPiCS-02 trial had an ECOG PS of 0 or 1.	—
3. Patients must not have: 3.1. active CNS metastases and/or carcinomatous meningitis 3.2. received prior treatment with a topoisomerase 1 inhibitor as	The TROPiCS-02 trial excluded patients with these characteristics. CADTH reviewed no evidence to demonstrate a treatment benefit for sacituzumab govitecan in patient	—

Reimbursement condition	Reason	Implementation guidance
a free form or as part of other formulations.	populations that were excluded from the TROPiCS-02 trial.	
Discontinuation		
4. Treatment with sacituzumab govitecan should be discontinued upon the occurrence of any of the following: 4.1. disease progression 4.2. unacceptable toxicity attributed to sacituzumab govitecan.	In the TROPiCS-02 trial, treatment was continued until disease progression as determined by RECIST 1.1, unacceptable toxicity, study withdrawal, or death.	—
5. Assessment of disease progression should be based on clinical and radiographic evaluations as per clinical standard of care.	In the TROPiCS-02 trial, tumour response was assessed by CT or MRI scans every 6 weeks for 54 weeks, and every 12 weeks thereafter, until the occurrence of disease progression requiring discontinuation of further treatment.	—
Prescribing		
6. Sacituzumab govitecan should only be prescribed by clinicians with expertise and experience in treating breast cancer in approved centres for sacituzumab govitecan.	This ensures that sacituzumab govitecan is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
7. A reduction in price.	The ICER for sacituzumab govitecan is $506,807 per QALY gained when compared to TPC. A price reduction of 88% would be required for sacituzumab govitecan 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 estimate(s).	—

CDK4/6 = cyclin-dependent kinase 4 and 6; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; TPC = treatment of physician's choice; TTD = time to deterioration.

Discussion Points

- pERC agreed that there is an unmet need for efficacious treatments in later lines of therapy for patients with HR-positive, HER2 -negative locally advanced breast cancer or mBC due to

the multirefractory drug experience in this setting. The patient groups expressed a need for new treatment options that control disease, improve quality of life, and extend lives of patients living with mBC.

- pERC deliberated on the efficacy results from the phase III TROPiCS-02 trial that showed statistically significant improvements in PFS, which was the primary end point (median, 5.5 months versus 4.0 months), and OS (median, 14.4 months versus 11.2 months), when compared to TPC (including eribulin, capecitabine, gemcitabine, or vinorelbine). pERC discussed the magnitude of survival benefit and agreed that a median of 3-month OS improvement with sacituzumab govitecan was considered modest but clinically significant in a multidrug refractory metastatic setting. However, the committee agreed with the clinical experts consulted by CADTH that the observed PFS benefit was relatively short in both groups, and that the clinical meaningfulness of the between-group difference of approximately 1.5 months in median value was uncertain. pERC additionally noted that treatment with sacituzumab govitecan can be associated with an increased objective response rate (odds ratio [OR] = 1.63; 95% CI, 1.03 to 2.56; P = 0.03) and clinical benefit rate (OR = 1.80; 95% CI, 1.23 to 2.63; P = 0.003) when compared to TPC.
- pERC discussed the place of sacituzumab govitecan in therapy and agreed that to be eligible to receive sacituzumab govitecan patients should be previously treated with endocrine-based therapy and a CDK4/6 inhibitor, and have experienced treatment failure on at least 2 systemic chemotherapy regimens in the metastatic setting, as the TROPiCS-02 trial demonstrated survival benefit with sacituzumab govitecan in these patients. pERC further discussed that patients with low HR expression (1% to 10% expression by IHC) for whom endocrine therapy is not advised should be eligible to receive sacituzumab govitecan. However, the committee estimated this subgroup of patients to be relatively small. pERC acknowledged that, based on the recently published CADTH Provisional Funding Algorithm (PH0033-000; December 7, 2023), clinicians may have an option to treat patients with a low hormone receptor expression using treatment options for HR-positive, HER2-negative disease, or options for triple-negative breast cancer, but not both.
- pERC deliberated on the safety profile of sacituzumab govitecan compared to TPC, and noted that there were greater frequencies of diarrhea, neutropenia, febrile neutropenia, leukopenia, anemia, fatigue, and grade 3 or higher infections in patients who received sacituzumab govitecan in the trial. The committee acknowledged that the product monograph for sacituzumab govitecan contains a serious warning related to severe or life-threatening neutropenia and/or severe diarrhea and provides recommendations for the management of adverse events, including withholding the treatment, dose adjustment, patient monitoring, and evaluation for infectious causes before reinitiation.
- pERC discussed the feasibility of implementing a reimbursement recommendation for sacituzumab govitecan, and considered the implementation issues raised by the drug programs. pERC agreed that administration of sacituzumab govitecan will require more nursing resources and chair time than the other available treatment options, due to a longer infusion time and concerns regarding infusion reactions. Additionally, a more complex compounding process for sacituzumab govitecan will increase the pharmacy workload.

- pERC noted that there may be barriers to administration of sacituzumab govitecan in rural and satellite oncology sites due to human resource limitations, monitoring difficulties, potential for adverse reactions, and drug wastage. This may result in disparities for patients living in areas without major treatment centres. pERC recognized that the drug programs may need to address these issues through procedural modifications for administration of sacituzumab govitecan (e.g., by making arrangements for administration of sacituzumab govitecan on specific days, and vial sharing to reduce drug wastage).
- pERC discussed the potential size of the budget impact associated with sacituzumab govitecan. The committee noted that the CADTH analysis was conducted in the Health Canada–indicated population, which allows use in patients who have received an endocrine-based therapy and at least 2 additional systemic therapies. To align with the TROPiCS-02 trial, pERC noted that patients should only be considered for sacituzumab govitecan if they had received an endocrine-based therapy, including a hormone and a CDK4/6 inhibitor, and had experienced treatment failure with 2 systemic chemotherapies. This population is narrower than the Health Canada indication, and therefore it was noted that the budget impact in this population will be smaller than the CADTH estimate. If sacituzumab govitecan is used only after a patient has experienced treatment failure with an endocrine-based therapy and 2 systemic chemotherapies, the CADTH base-case budget impact changes to $68,036,864 over 3 years. At $68 million, the result is still more than double the sponsor's submitted estimate.

Background

Breast cancer is a heterogeneous disease most often originating from epithelial cells lining the ducts, lobules, or other parts of breast tissue. The presence or absence of the expression of HER2, estrogen receptor (ER), or progesterone receptor (PR), impacts the proliferation of the cancer cells, prognosis, treatment response, and recurrence of cancers in patients with breast cancer. HR-positive tumours have both ER and PR receptors, are characterized as slow-growing and low-grade, and have less tendency to spread. However, they are known to recur over the years following treatment completion. An HR-positive, HER2-negative breast cancer is defined as a tumour having more than 1% IHC expression of ER and/or PR, and the lack of HER2 expression, which includes HER2-low expression (i.e., IHC score of 1+ or 2+, confirmed as negative by ISH) and HER2, IHC 0 expression. Breast cancer was the second-most diagnosed cancer in Canada in 2022 and the most prevalent among females, with projected estimates of about 28,900 new cases in the overall population (28,600 in females and 270 in males). The 5-year prevalence of breast cancer in females reported in Canada in 2018 was 110,955 patients, equating to a 5-year prevalence rate of 0.73%. The HR-positive, HER2-negative breast cancer subtypes are the most prevalent in Canada, accounting for more than 70% of all new breast cancer cases. Although the prognosis of HR-positive, HER2-negative breast cancer is generally favourable when diagnosed early, the lifetime risk of developing distant metastases ranges from 22% to 52%, and prognosis worsens with each subsequent line of systemic therapy administered. The number of cases of relapse reported among patients with newly diagnosed HR-positive,

HER2-negative mBC who had received first-line treatment was 71%. The 5-year probability of distant recurrence or death among patients diagnosed with early-stage disease was 17.2%. Survival outcomes following progression on endocrine-based therapies reduces significantly with later lines of single-drug chemotherapy, with the median PFS and OS estimated to be as low as 3 months and 7 months, respectively. HR-positive, HER2-negative mBC also negatively impacts patient quality of life, given that symptoms that manifest are due to progression of disease and treatments administered. Common symptoms reported include pain, fatigue, nausea, vomiting, cognitive problems, depression, hair loss, lymphedema, sleep disturbances, loss of appetite, anxiety, and sexual dysfunction.

In Canada, the treatment algorithm for HR-positive, HER2-negative mBC outlines that standard of care systemic treatment in the first-line setting is endocrine therapy in combination with a CDK4/6 inhibitor. Other first-line options include endocrine monotherapy, everolimus plus exemestane, and chemotherapy. For patients with suspected visceral crisis or whose cancer is unresponsive to endocrine therapy, chemotherapy may also be used to achieve initial adequate response, with follow-up endocrine therapy in combination with a CDK4/6 inhibitor. Following progression on first-line treatment with endocrine therapy and a CDK4/6 inhibitor, second-line options include endocrine monotherapy, chemotherapy, or everolimus plus exemestane. For patients who received endocrine monotherapy in the first-line setting, second-line options include endocrine therapy in combination with a CDK4/6 inhibitor or chemotherapy. Patients are faced with limited treatment options beyond the second line. There is no single standard of care, with chemotherapy recommended once patients have progressed on multiple lines of systemic therapy. Available options for single-drug chemotherapy include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine, platinum complexes, and other drugs. The aligned input from the clinical experts consulted by CADTH regarding options for chemotherapy included capecitabine; paclitaxel; nab-paclitaxel; docetaxel; doxorubicin; epirubicin; vinorelbine; gemcitabine; eribulin; adriamycin and cyclophosphamide; cyclophosphamide, methotrexate, and fluorouracil; gemcitabine and cisplatin; or gemcitabine and carboplatin. Chemotherapy is associated with an unfavourable toxicity profile and poor survival outcomes.

Sacituzumab govitecan underwent a priority review via Project Orbis at Health Canada and received a Notice of Compliance on July 19, 2023, for the treatment of adult patients with unresectable locally advanced or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+, or IHC 2+/ISH−) breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting. Sacituzumab govitecan has been approved by the FDA and the European Medicines Agency for the same indication as the reimbursement request.

Sacituzumab govitecan was previously reviewed by CADTH for another indication in the mBC setting, which was different from the current reimbursement request. On February 11, 2022, a recommendation for reimbursement was issued 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.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 randomized, open-label, active-controlled, phase III trial in patients with unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting
- patients' perspectives gathered by patient groups: Canadian Breast Cancer Network (CBCN), Rethink Breast Cancer (Rethink), and a joint input from Breast Cancer Canada (BCC) and the McPeak-Sirois Group (MPSG)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise in the diagnosis and management of patients with breast cancer
- input from 2 clinician groups, including the medical oncologists of the Saskatoon Cancer Centre, and the Ontario Health (Cancer Care Ontario) (OH-CCO) Breast Cancer Drug Advisory Committee (DAC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Input from CBCN, Rethink, and a joint input from BCC and MPSG were submitted for this review. Information from the CBCN group was sourced from 3 online surveys: the CBCN 2022 Triple-Negative Breast Cancer Patient Survey, 2017 Metastatic Breast Cancer Patient Survey, and 2012 Metastatic Breast Cancer Patient and Caregiver Survey Report. Information submitted by the joint input from BCC and MPSG was sourced from a survey that ran from July 6, 2023, to July 21, 2023, distributed via email to patients and caregivers living with recurrent mBC. Information from Rethink was sourced from meetings held with patients with breast cancer, including a consultation with the Metastatic Breast Cancer Advisory Board conducted in July 2023, an online survey with 78 patients living with mBC (which ran from September 2018 to April 2019), and a review of a survey conducted in July 2021.

The patient groups consulted expressed that metastatic disease poses a significant or debilitating impact on patients' quality of life. Breast cancer significantly affects younger patients — especially those diagnosed in their 20s, 30s, and early 40s — as they face age-specific issues such as fertility or family-planning challenges, diagnosis during pregnancy, child care, impact on relationships, body image, dating and sexuality, feeling isolated from peers who do not have cancer, career hiatuses, and financial insecurity. There is an unmet need for treatments in later lines due to the multirefractory drug experience in the metastatic setting. The patient groups expressed a desire for new options that control disease and extend lives of patients living with mBC. Patients highlighted key factors such as treatment effectiveness, availability of treatments that improve quality of life, side effect management, cost, and accessibility as influencing decisions around treatment choice. Patients also expressed the need for personal choice and autonomy in choosing treatments.

Input from 2 patients with mTNBC who had experience with sacituzumab govitecan for a different indication was gathered in the CBCN survey; interviews with 11 patients with prior experience with sacituzumab govitecan (recurrent HR-positive, HER2-negative mBC [n = 6] and prior authorized mTNBC [n = 5]) were summarized in the joint input from BCC and MPSG; and 1 patient diagnosed with ER-positive, HER2-negative mBC and 2 patients diagnosed with mTNBC that had received sacituzumab govitecan were interviewed for the Rethink input. Overall, patients reported manageable side effects as well as positive and meaningful experiences after receiving sacituzumab govitecan. Common side effects reported included hair loss, nausea, fatigue, diarrhea, rash, and headache. All respondents reported that they experienced benefits from receiving sacituzumab govitecan and would recommend the drug to other patients.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The experts identified multiple unmet needs that include: not all patients respond to available treatment, patients become refractory to current treatment options, no treatments are available to reverse the course of disease, treatments are needed that are better tolerated once patients move past endocrine therapy, and therapies are needed to improve convenience and feasibility (e.g., less frequent hospital visits, and less frequent monitoring with imaging scans). The experts indicated that sacituzumab govitecan would fit into the current treatment paradigm for patients who have received prior endocrine-based therapy, including CDK4/6 inhibitors and 2 to 4 prior chemotherapy regimens in the metastatic setting; and as (neo) adjuvant therapy for early-stage disease, qualified as 1 of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within 12 months of therapy (early relapse). The experts emphasized that patients must have previously received at least 1 taxane to be considered for treatment with sacituzumab govitecan. The experts noted that patients with or without visceral metastases, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2, and with expected survival longer than 3 months (patients with brain metastases should have stable brain lesions for at least 4 weeks) are most likely to respond to treatment with sacituzumab govitecan. According to the clinical experts, treatment should be in a hospital setting or specialty clinic that has expertise and staffing to administer systemic therapy and monitor as well as manage treatment-related toxicities; treatment responses are determined with periodic clinical assessment; serial biochemical and radiographic assessment; and are based on symptoms, laboratory markers, and radiographic scans and tumour measurements, with scans usually performed at least every 3 months initially (1 staging scan).

Clinician Group Input

Two clinician groups, including medical oncologists from the Saskatoon Cancer Centre, affiliated with Saskatchewan Cancer Agency, and the OH-CCO Breast Cancer DAC provided input for this review. Input from the Saskatoon Cancer Centre was sourced from discussions held at multidisciplinary rounds, educational sessions, and email communications. Input from the OH-CCO Breast Cancer DAC was gathered via videoconferencing.

The most important treatment goals highlighted by both groups included: prolonging life, improving PFS, improving OS rates, delaying disease progression, maintaining quality of life, minimizing treatment-related

toxicities, and managing disease-related symptoms effectively. Current treatment paradigms for metastatic HR-positive breast cancer include a combination of drug and nondrug therapies. CDK4/6 inhibitors with an aromatase inhibitor are used in the first line, while endocrine therapy (fulvestrant, tamoxifen), chemotherapy (capecitabine, paclitaxel), targeted therapy (alpelisib for *PIK3CA* mutation, olaparib for germline *BRCA* mutation), or clinical trial drugs (if patients are eligible) are available in the second line and beyond for patients with known progression. Both clinician groups highlighted that sacituzumab govitecan would be a valuable option for later lines (third line and beyond) for patients that have exhausted other options. Patients best suited for treatment with sacituzumab govitecan would be those who have undergone prior endocrine therapy and multiple lines of chemotherapy as indicated, similar to the inclusion criteria for the trial, according to both clinician groups. Patients with poor performance status and those who have not received prior chemotherapy (at least 2 lines) would be less suitable to receive treatment, according to the clinician groups. Both groups highlighted that end points assessed in the trial, such as OS, ORR, clinical benefit rate (CBR), DOR, PFS, patient-reported outcomes, and safety, are clinically meaningful and would be used to assess treatment effectiveness in practice. The groups also noted that treatment would be discontinued if disease progression is observed upon radiographic imaging (tumour growth or new lesions), or if there is unacceptable toxicity or undue toxicity, or per patient preference. Sacituzumab govitecan would be best administered under the guidance of a medical oncologist in an outpatient oncology clinic, or in settings with clinicians who have expertise administering systemic therapy to patients with advanced disease.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs (Table 2).

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
Issues with the choice of comparator in the submitted trial(s) Comparators in the TROPiCS-02 trial included single-drug chemotherapy of physician's choice (capecitabine, eribulin, vinorelbine, or gemcitabine). These are relevant comparators. Other comparators depend on what prior therapies were administered for early and recurrent disease, and could include anthracycline- and taxane-based regimens. In addition, trastuzumab deruxtecan used in later lines may be a relevant comparator for HER2-low patients.	The clinical experts agreed with the statement. The clinical experts pointed out that there are no data available on trastuzumab deruxtecan when used as a comparator to sacituzumab govitecan; therefore, it is uncertain whether the outcomes would be similar if it were used in the comparator arm.
Considerations for initiation of therapy	
Disease diagnosis, scoring, or staging for eligibility The trial inclusion criteria required at least 2 but no more than 4 prior systemic chemotherapy regimens for metastatic disease. (Neo) adjuvant therapy for	The experts noted that these patients were included in the study as the inclusion criteria was "HR positive (a tumour is considered HR positive if at least 1% of the cells examined have estrogen and/or progesterone receptors)." In real-world practice, HR-low cancers are likely to behave like HR-negative breast cancers.

Drug program implementation questions	Clinical expert response
early-stage disease can be considered as 1 of the required prior chemotherapy regimens if unresectable locally advanced or metastatic disease occurs within 12 months of therapy. Should patients who are considered ER-low or PR-low (IHC 1% to 10%), who may be considered "functionally hormone-receptor negative," be eligible?	Sacituzumab govitecan is already approved for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer. The clinical experts indicated that if the sample for HR-positive mBC is < 10%, then ER–low positive would be favoured by the clinical experts to be considered eligible (as was the case in the study). Otherwise, the clinical experts would be concerned over inadvertently excluding patients with IHC 1% to 10% positive, even though biologically they would be expected to benefit. pERC acknowledged that, based on the recently published CADTH Provisional Funding Algorithm (PH0033-000; December 7, 2023), clinicians may have an option to treat patients with a low HR (more specifically, ER) expression using treatment options for HR-positive HER2-negative disease, or those for triple-negative breast cancer, but not both.
Prior therapies required for eligibility Prior endocrine therapy was an eligibility criterion, as well as at least 2 lines of systemic therapy for metastatic disease. Does endocrine therapy need to be administered in the metastatic setting as part of the lines of therapy in order for a patient to be eligible for sacituzumab govitecan?	According to the clinical experts consulted by CADTH, endocrine therapy does not need to be administered in the metastatic setting as part of the lines of therapy in order for a patient to be eligible for sacituzumab govitecan. However, patients who have not received endocrine therapy in the metastatic setting need to have been exposed to endocrine therapy in the adjuvant setting. As per the patient eligibility criteria in the TROPiCS-02 trial, the patient needs to have received prior endocrine therapy and a CDK4/6 inhibitor in any setting, and 2 to 4 additional systemic chemotherapies in the metastatic setting. If a patient rapidly progresses on adjuvant CDK4/6 inhibitors, they should not be excluded from consideration for sacituzumab govitecan. PERC also acknowledged that, at the onset of implementation, there may be a small proportion of patients who have received more than 4 lines of prior chemotherapy in the metastatic setting. pERC agreed that a time-limited opportunity to access sacituzumab govitecan should be available for those few patients who did not have the opportunity to use this drug earlier in their treatment journey, if they maintain a good performance status to receive the treatment.
Should the following patients be considered for sacituzumab govitecan? • Patients with ECOG PS > 1 • Patients who have not been treated with a taxane due to a contraindication	The clinical experts noted that they would consider patients with ECOG PS 2 to receive sacituzumab govitecan, but not those with a ECOG PS of 3 or 4. pERC agreed with the clinical experts that if taxanes were not used due to a medical contraindication, then the patient should still be eligible for sacituzumab govitecan.
Considerations for discontinuation of therapy	
Definition of loss of response, absence of clinical benefit, or disease progression In the TROPiCS-02 trial, patients in the sacituzumab govitecan group could continue the drug beyond the initial RECIST progression if the investigator believed that the patient was still receiving clinical benefit and was clinically stable and tolerating the drug. What should the discontinuation criteria be?	The experts indicated the discontinuation criteria for sacituzumab govitecan include progression (as per RECIST criteria on scan), clinical deterioration, unacceptable toxicities, or treatment withdrawal by the patient. pERC agreed with the clinical experts that treatment with sacituzumab govitecan should be discontinued upon disease progression.

Drug program implementation questions	Clinical expert response
Considerations for prescribing of therapy	
Dosing, schedule or frequency, and dose intensity Sacituzumab govitecan dosing is 10 mg/kg on days 1 and 8, every 21 days. The preparation of sacituzumab govitecan is labour intensive for pharmacy staff. It requires multiple vial reconstitutions per dose, swirling of vials for up to 15 minutes to dissolve powder, and volume adjustments for final product concentration. Compared to other chemotherapy options used in the TROPiCS-02 trial, sacituzumab govitecan requires the longest compounding time for pharmacy staff.	Comment from the drug programs to inform pERC deliberations. The clinical experts agreed with the suggested considerations. The experts pointed out that this may also impact satellite administration sites that may not be able to accommodate all patient requests.
Drug administration Compared to other chemotherapy options used in the TROPiCS-02 trial, sacituzumab govitecan requires the longest infusion times for treatment rooms and patients.	Comment from the drug programs to inform pERC deliberations. The clinical experts agreed with the suggested consideration.
Generalizability	
Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review Is there a time-limited need to consider patients who may not have received a prior CDK4/6 inhibitor and are no longer eligible for it?	The experts pointed out that, although this population is likely small, there may be patients who previously progressed on endocrine therapy and were not able to access CDK4/6 inhibitors before they became covered, and are currently on chemotherapy. Ideally, if these patients are well enough, they can be considered for sacituzumab govitecan. pERC agreed with the experts that consideration should also be given to patients who could not tolerate a CDK4/6 inhibitor or were not able to take it due to medical contraindications. These individuals should not be excluded from consideration for sacituzumab govitecan if they are otherwise fit to receive it. pERC also agreed with the clinical experts that patients who may not have received a prior CDK4/6 inhibitor and are no longer eligible for it should be considered for a time-limited opportunity to receive sacituzumab govitecan. Acknowledging that the TROPiCS-02 trial excluded patients who received prior treatment with a topoisomerase 1 inhibitor, pERC agreed that considerations should be given to patients who experienced intolerance or severe toxicity to a prior topoisomerase inhibitor.
Funding algorithm (oncology only)	
Drug may change place in therapy of comparator drugs.	Comments from the drug programs to inform pERC deliberations.
Drug may change place in therapy of drugs reimbursed in previous lines.	
Drug may change place in therapy of drugs reimbursed in subsequent lines.	
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	

Drug program implementation questions	Clinical expert response
Care provision issues	
Drug preparation, storage, administration, or dispensing The preparation of sacituzumab govitecan is labour intensive for pharmacy staff. It requires multiple vial reconstitutions per dose, swirling of vials for up to 15 minutes to dissolve powder, and volume adjustments for final product concentration. Compared to other chemotherapy options used in the TROPiCS-02 trial, sacituzumab govitecan requires the longest compounding time for pharmacy staff.	Comment from the drug programs to inform pERC deliberations.
Other care provision issues Drug wastage is likely, as the dosing is 10 mg/kg on days 1 and 8, every 21 days, and the vial size is 180 mg.	Comment from the drug programs to inform pERC deliberations.
System and economic issues	
Concerns regarding the anticipated budget impact and sustainability Budget impact seems to assume that use will be mainly in the fourth-line setting.	Comment from the drug programs to inform pERC deliberations.
Additional costs to be considered (other than related to care provision as detailed previously) Significant relative increases for chair time, patient and caregiver time at treatment centres, and pharmacy and nursing resources will be required for administration and preparation of sacituzumab govitecan vs. current comparators in this patient population.	Comment from the drug programs to inform pERC deliberations.
Presence of confidential negotiated prices for comparators Comparators used in the TROPiCS-02 trial are either generic and/or have confidential prices.	Comment from the drug programs to inform pERC deliberations

BICR = blinded independent central review; CDK4/6 = cyclin-dependent kinase 4 and 6; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hormone receptor; mBC = metastatic breast cancer; NA = not applicable; NR = not reported; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; RECIST = Response Evaluation Criteria in Solid Tumours; TPC = treatment of physician's choice; vs. = versus.

Clinical Evidence

Systematic Review

Description of Studies

One multicentre, multinational, open-label, randomized phase III trial (the TROPiCS-02 trial) comparing sacituzumab govitecan with TPC in patients with unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer who received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting was included. To be eligible for the trial, patients must have had evidence of HR-positive (at least 1% of the cells examined had estrogen and/or progesterone receptors) and HER2-

negative (IHC ≤ 2+ or fluorescence ISH-negative) mBC confirmed by a local laboratory; been refractory to or relapsed after 2 to 4 prior systemic chemotherapy regiments for metastatic disease ([neo] adjuvant therapy for early-stage disease qualified as 1 of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within a 12-month period of time of the therapy); and been previously treated with at least 1 taxane, at least 1 prior anticancer hormonal treatment, and at least 1 CDK4/6 inhibitor in any setting. Eligible patients (N = 543) were randomized in a 1:1 ratio to either sacituzumab govitecan (n = 272) (10 mg/kg, administered as an IV infusion once weekly on days 1 and 8 of a 21-day treatment cycle) or TPC (n = 271) (one of eribulin, capecitabine, gemcitabine, and vinorelbine, by investigators' choice) groups. Patients were treated until progression requiring discontinuation of further treatment, unacceptable toxicity, study withdrawal, or death. Measures of survival (PFS, OS), tumour response to treatment (ORR, CBR, DOR), patient-reported outcomes (TTD in the EORTC QLQ-C30 domains of global health status/quality of life, fatigue, pain, and diarrhea), and time to treatment discontinuation were compared. Harms were also reported.

At baseline, the mean age was [redacted] years (standard deviation [SD] = [redacted]) in the sacituzumab govitecan group and [redacted] years (SD = [redacted]) in the TPC group. Nearly all patients were female (99.1%). The study participants were categorized in the following groups for ethnicity: Asian (2.9%), Black (3.9%), white (66.7%), and other or not reported (26.5%). Most patients were from the US (42.0%), France (25.2%), and Spain (12.7%), among the other countries in North America and Europe. All patients had progressive disease and extensive prior systemic treatment in the metastatic setting (median prior lines of chemotherapy = 3; 96% with 2 or more prior chemotherapies) and had received a prior CDK4/6 inhibitor, reflecting standard of care and allowing assessment of efficacy post–CDK4/6 inhibitor treatment. Overall, most patients (95%) had visceral metastases at baseline, which are associated with particularly poor outcomes. The percentage of patients who had received at least 1 concomitant medication was similar in the sacituzumab govitecan ([redacted]) and TPC ([redacted]) groups. Most used concomitant medications including analgesics ([redacted] in the sacituzumab govitecan group versus [redacted] in the TPC group), antiemetics and antinauseants ([redacted] versus [redacted]), and drugs for acid-related disorders ([redacted] versus [redacted]). At any time during the study, 54.1% (145 of 268 in the safety population) of patients in the sacituzumab govitecan group and 34.1% (85 of 249 in the safety population) in the TPC group used granulocyte colony-stimulating factor (G-CSF), of which 35.4% (n = 95) versus 21.7% (n = 54) used G-CSF as prophylaxis for neutropenia, and [redacted] versus [redacted] for the management of neutropenia in the 2 groups, respectively.|

Efficacy Results

The key efficacy results from the TROPiCS-02 trial are summarized in Table 3. The intention-to-treat (ITT) population dataset (including all randomized patients in the group to which they were randomized), which is the same as the full analysis set in this study (272 in the sacituzumab govitecan group and 271 in the TPC group), was used for the survival and tumour response to treatment outcomes. The health-related quality of life (HRQoL)-evaluable population datasets (subsets of the ITT population, including patients with a baseline assessment and at least 1 postbaseline assessment) were used for the patient-reported outcomes.

Survival Outcomes

The primary efficacy end point of the TROPiCS-02 trial was PFS per blinded independent central review (BICR) at the first interim analysis (data cut-off: January 3, 2022; median duration of follow-up = 10.22 months; range, 0.03 to 27.93). The median PFS per BICR was 5.5 months (95% CI, 4.2 to 7.0) for patients treated with sacituzumab govitecan and 4.0 months (95% CI, 3.1 to 4.4) for patients treated with TPC (hazard ratio = 0.66; 95% CI, 0.53 to 0.83; P = 0.0003). The Kaplan-Meier (KM) estimates of the probability of PFS in the sacituzumab govitecan versus TPC groups, respectively, were 66.0% (95% CI, 59.6% to 71.6%) versus 57.8% (95% CI, 50.8% to 64.1%) at 3 months, 46.1% (95% CI, 39.4% to 52.6%) versus 30.3% (95% CI, 23.6% to 37.3%) at 6 months, 32.5% (95% CI, 25.9% to 39.2%) versus 17.3% (95% CI, 11.5% to 24.2%) at 9 months, 21.3% (95% CI, 15.2% to 28.1%) versus 7.1% (95% CI, 2.8% to 13.9%) at 12 months, and 13.3% (95% CI, 7.8% to 20.4%) versus 7.1% (95% CI, 2.8% to 13.9%) at 18 months, as of January 3, 2022. At the final analysis (exploratory; data cut-off: December 1, 2022; median duration of follow-up = 12.75 months [range, 0.03 to 38.05]), the median PFS per BICR in the sacituzumab govitecan versus TPC groups, respectively, was 5.5 months (range, 4.2 to 6.9) versus 4.0 months (range, 3.0 to 4.4) (hazard ratio = 0.65; 95% CI, 0.53 to 0.81; P = 0.0001). The KM estimates of the probability of PFS for the sacituzumab govitecan versus TPC groups, respectively, were 45.6% (95% CI, 38.9% to 52.0%) versus 29.4% (95% CI, 22.9% to 36.2%) at 6 months, 21.7% (95% CI, 15.8% to 28.3%) versus 8.4% (95% CI, 4.2% to 14.5%) at 12 months, and 14.4% (95% CI, 9.1% to 20.8%) versus 4.7% (95% CI, 1.3% to 11.6%) at 18 months, as of December 1, 2022.

One of the secondary end points was OS per BICR at the second interim analysis (data cut-off: July 1, 2022; median duration of follow-up = 12.48 months (range, 0.03 to 35.48). The median OS per BICR was 14.4 months (95% CI, 13.0 to 15.7) for patients treated with sacituzumab govitecan versus 11.2 months (95% CI, 10.1 to 12.7) for patients treated with TPC (hazard ratio = 0.789; [redacted]; P = 0.020). The KM estimates of the probability of OS in the sacituzumab govitecan versus TPC groups, respectively, were 60.8% (95% CI, 54.6% to 66.4%) versus 47.3% (95% CI, 41.1% to 53.2%) at 12 months, 38.9% (95% CI, 32.8% to 44.9%) versus 32.4% (26.7 to 38.2) at 18 months, and 24.6% (95% CI, 18.8% to 30.7%) versus 21.4% (95% CI, 16.0% to 27.3%) at 24 months, as of July 1, 2022. At final analysis (exploratory; data cut-off: December 1, 2022), the median OS per BICR in the sacituzumab govitecan versus TPC groups, respectively, was 14.5 months (95% CI, 13.0 to 16.0) versus 11.2 months (95% CI, 10.2 to 12.6) (hazard ratio = 0.788; 98.21% CI, 0.627 to 0.990; P = 0.0133). The KM estimates of the probability of survival for sacituzumab govitecan versus TPC, respectively, were 60.9% (95% CI, 54.8% to 66.4%) versus 47.1% (95% CI, 41.0% to 53.0%) at 12 months, 39.2% (95% CI, 33.4% to 45.0%) versus 31.7% (95% CI, 26.2% to 37.4%) at 18 months, and 25.7% (95% CI, 20.5% to 31.2%) versus 21.1% (95% CI, 16.3% to 26.3%) at 18 months, as of December 1, 2022.

Tumour Response to Treatment

At the second interim analysis (data cut-off: July 1, 2022), ORR (complete response [CR] or partial response [PR]) per BICR was 21% (57 of 272) in the sacituzumab govitecan group and 14% (38 of 271) in the TPC group (OR = 1.63; 95% CI, 1.03 to 2.56; P = 0.03). CBR (CR, PR, or stable disease ≥ 6 months) per BICR was 34% (92 of 272) and 22% (60 of 271) in the sacituzumab govitecan and TPC groups, respectively (OR = 1.80; 95% CI, 1.23 to 2.63; P = 0.003). Both ORR and CBR were secondary end points.

Median DOR per BICR (secondary end point) was 8.1 months (95% CI, 6.7 to 9.1) in the sacituzumab govitecan group and 5.6 months (95% CI, 3.8 to 7.9) in the TPC group (hazard ratios and their respective 95% CIs were not reported), based on the data from 57 responders (CR or PR) in the sacituzumab govitecan group and 38 responders in the TPC group, as of July 1, 2022.

Patient-Reported Outcomes

Patient-reported outcomes included the TTD in EORTC QLQ-C30 global health status or quality of life (QoL), fatigue, pain, and diarrhea domains at the second interim analysis (data cut-off: July 1, 2022) in the HRQoL-evaluable population.

The median TTD in the EORTC QLQ-C30 global health status or QoL domain (secondary end point) was 4.3 months (95% CI, 3.1 to 5.7) in the sacituzumab govitecan group and 3.0 months (95% CI, 2.2 to 3.9) in the TPC group (hazard ratio = 0.75; 95% CI, 0.61 to 0.92; P = 0.006), based on the available data from 234 patients (86%) in the sacituzumab govitecan group (272 patients at baseline) and 207 patients (76%) in the TPC group (271 patients at baseline).

The median TTD in the EORTC QLQ-C30 fatigue domain (secondary end point) was 2.2 months (95% CI, 1.6 to 2.8) and 1.4 months (95% CI, 1.1 to 1.9) in the sacituzumab govitecan and TPC groups, respectively (hazard ratio = 0.73; 95% CI, 0.60 to 0.89; P = 0.002), based on the available data from 234 patients (86%) in the sacituzumab govitecan group and 205 patients (76%) in the TPC group.

The median TTD in the EORTC QLQ-C30 pain domain (secondary end point) was 3.8 months (95% CI, 2.8 to 5.0) in the sacituzumab govitecan group and 3.5 months (95% CI, 2.8 to 5.0) in the TPC group (hazard ratio = 0.918; 95% CI, 0.748 to 1.126; P = 0.415), based on the available data from 229 patients (84%) in the sacituzumab govitecan group and 202 patients (75%) in the TPC group.

The median TTD in the EORTC QLQ-C30 diarrhea domain (exploratory end point) was [redacted] in the sacituzumab govitecan group and TPC group, respectively ([redacted]), based on the available data from 232 patients (85%) in the sacituzumab govitecan group and [redacted] patients in the TPC group.

Time to Treatment Discontinuation

The analysis of time to treatment discontinuation was not prespecified by the sponsor; however, it was requested by the CADTH for the purpose of the certainty of evidence appraisal. Analysis on time to treatment discontinuation was performed at the final analysis (data cut-off: December 1, 2022; median duration of follow-up = [redacted] months (range, [redacted])]. The median (95% CI) time to treatment discontinuation was [redacted] in the sacituzumab govitecan group compared with [redacted] in the TPC group ([redacted]). The 18-month event-free rate was [redacted] and [redacted] for patients treated with sacituzumab govitecan and TPC, respectively.

Harms Results

The key harm results from the TROPiCS-02 trial at the second interim analysis (data cut-off: July 1, 2022) are summarized in Table 3. The safety population dataset (all patients who received at least 1 dose of the

study drug, analyzed per the treatment received; 268 in the sacituzumab govitecan group and 249 in the TPC group) was used for all the safety outcomes.

As of July 1, 2022, adverse events (AEs) were reported in 100% and 96.0% of patients in the sacituzumab govitecan and TPC groups, respectively. The most-reported AEs by treatment group were neutropenia (70.5%), diarrhea (61.9%), and nausea (58.6%) in the sacituzumab govitecan group, and neutropenia (54.6%), nausea (34.9%), and fatigue (32.9%) in the TPC group.

The incidence of serious adverse events (SAEs) was 27.6% in the sacituzumab govitecan group compared with 19.3% in the TPC group. The most-reported SAEs were diarrhea (4.9%), febrile neutropenia (4.1%), and neutropenia (3.0%) in the sacituzumab govitecan group, and febrile neutropenia (4.0%), pneumonia (2.0%), nausea (2.0%), and dyspnea (1.6%) in the TPC group. The incidence of AEs leading to study drug discontinuation was 6.3% in the sacituzumab govitecan group and 4.4% in the TPC group. No trends in AEs leading to study drug discontinuation were identified in either group. AEs leading to study drug discontinuation that were reported for more than 1 patient were neutropenia, asthenia, and general physical health deterioration in the sacituzumab govitecan group, and thrombocytopenia and polyneuropathy in the TPC group. Six patients (2.2%) in the sacituzumab govitecan group versus no patients in the TPC group had AEs leading to death. One patient experienced an AE leading to death that was assessed by the investigator to have been treatment-related (septic shock due to neutropenic colitis with large intestine perforation). The AEs leading to death in the other 5 patients were assessed by the investigator as not related or unlikely related to sacituzumab govitecan. Upon detailed review of the AEs leading to death, no patterns were identified by the investigator regarding specific mechanism or etiology. The most-reported grade 3 or higher AEs were neutropenia in 51.5% of patients treated with sacituzumab govitecan and 39.0% of those treated with TPC, leukopenia (8.6% and 6.0%, respectively), “infections+” (9.7% and 4.8%), diarrhea (10.1% and 1.2%), anemia (7.5% and 3.6%), febrile neutropenia (6.0% and 4.4%), fatigue (6.0% and 3.6%), “neuropathy+” (2.6% and 3.6%), “hypersensitivity+” (1.5% and 0.8%), and “pulmonary events+” (0 and 0.4%), with “+” indicating that the outcome consists of grouped AE term. Specifically, “infection+” consists of infections and infestations by system organ class; “neuropathy+” consists of gait disturbance, hypoesthesia, muscular weakness, neuropathy peripheral, paresthesia, and peripheral sensory neuropathy; “hypersensitivity+” consists of hypersensitivity Standardized MedDRA Query (SMQ) (broad and narrow) and anaphylactic reactions SMQ (broad and narrow), and “pulmonary events+” refers to interstitial lung disease SMQ (narrow).

Critical Appraisal

Randomization methods in the TROPiCS-02 trial were appropriate. There was an imbalance in the proportion of patients who were randomized but not treated (1.5% versus 8.1% in the sacituzumab govitecan and TPC groups, respectively). The presence and extent of any bias that may have been introduced could not be determined because baseline demographic and disease characteristics of these patients were unavailable. The clinical experts commented that most of the concomitant medications were likely for management of AEs, and the imbalances in some of them likely reflected the different incidences of AEs related to the treatments and were less likely to impact the effect estimates in the TROPiCS-02 trial. The proportion of patients with no baseline images or no postbaseline evaluable assessment was higher in the TPC group

(13.7%) than the sacituzumab govitecan group (2.9%), mainly due to the imbalance in patients who were randomized but never treated. Furthermore, for ORR and CBR, the proportion of patients who were not evaluable was higher in the TPC group (18.8%) than the sacituzumab govitecan group (5.5%), mainly due to the imbalance in patients who were randomized but never treated, and an imbalance across groups in the proportion of patients who withdrew consent. The reasons for patients being randomized but never treated were not reported. As such, it is not possible to determine whether the results would be biased, as it is not known whether there were imbalances in prognostic characteristics of these patients relative to those who were randomized and treated (or those who did or did not withdraw consent). The TROPiCS-02 trial had an open-label study design, which could potentially increase the risk of bias due to deviations from the intended interventions and measurement of the outcomes, particularly for outcomes with a subjective nature, including the patient-reported outcomes (TTD in the self-reported domains on the EORTC QLQ-C30) and some AEs (e.g., nausea, rash, diarrhea, neuropathy, and fatigue). Response outcomes (i.e., PFS, CR, CBR, DOR) were assessed via BICR; therefore, the risk of bias was mitigated for the measurement of these outcomes. OS and some AEs (e.g., neutropenia, febrile neutropenia, leukopenia, and anemia) were objective measures with standardized criteria, and/or they relied on objective clinical or laboratory examination. As such, the risk of bias in the measurement of these outcomes is low. For the 4 domains from the EORTC QLQ-C30, data were analyzed for approximately 80% of the total study population for those who had baseline scores with room for at least a 10-point deterioration among the HRQoL-evaluable population. The impact of the missing data is unclear. The TROPiCS-02 trial was powered on its primary outcome. The statistical tests were appropriate using a hierarchical testing approach to control for type I error. The stratified Cox proportional-hazards model was used for the survival outcomes. Generally, multiplicity control appeared adequate. In the time-to-event analysis for PFS, OS, DOR (among 95 responders), and time to treatment discontinuation ([redacted] observations were excluded from the analyses due to not receiving treatment), all patients were included in the evaluation irrespective of event occurrence. In general, censoring was balanced between the groups for OS, PFS, DOR, and TTD outcomes.

According to the clinical expert, no major issues were identified with respect to the generalizability of the TROPiCS-02 trial, although the patients who did not meet the inclusion and exclusion criteria in the TROPiCS-02 trial might be eligible for treatment with sacituzumab govitecan in Canadian clinical practice (e.g., it is reasonable to include patients with an ECOG PS of 2 or with brain metastases [after treatment for those metastases], and those have not been treated with taxanes due to a medical contraindication).

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (i.e., internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: PFS; OS; ORR; CBR; DOR; EORTC QLQ-C30 global health status or QoL; fatigue; pain and diarrhea domains; time to treatment discontinuation; and grade 3 or higher AEs including diarrhea, neutropenia, febrile neutropenia, leukopenia, anemia, fatigue, infections+, neuropathy+, hypersensitivity+, and pulmonary events+.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for PFS; OS; ORR; CBR; DOR; EORTC QLQ-C30 global health status or QoL domain; EORTC QLQ-C30 fatigue domain; EORTC QLQ-C30 pain domain; EORTC QLQ-C30 diarrhea domain; time to treatment discontinuation; and grade 3 or higher AEs including diarrhea, neutropenia, febrile neutropenia, leukopenia, anemia, fatigue, infections+, neuropathy+, hypersensitivity+, and pulmonary events+, due to the lack of a formal MID estimate.

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for sacituzumab govitecan versus TPC in adult patients with unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer who received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting.

Table 3: Summary of Findings for SG vs. TPC for Adult Patients With Unresectable Locally Advanced or Metastatic HR-Positive, HER2-Negative Breast Cancer

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			TPC	SG	Difference		
Progression-free survival (data cut-off: January 3, 2022)							
PFS per BICR Follow-up, median: • SG: 11.25 months • TPC: 9.79 months	543 (1 RCT)	PFS events (progression or death) at data cut-off: • SG: 625 per 1,000 • TPC: 587 per 1,000 • Stratified hazard ratio (95% CI) = 0.66 (0.53 to 0.83) Median (95% CI) PFS at data cut-off, months • SG: 5.5 (4.2 to 7.0) • TPC: 4.0 (3.1 to 4.4)				High[a,b,c]	SG results in an increase in PFS when compared with TPC. The clinical importance of the increase is uncertain.
Overall survival (data cut-off: July 1, 2022)							
OS per BICR Follow-up, median: • SG: 13.80	543 (1 RCT)	OS events (deaths) at data cut-off: • SG: 702 per 1,000 • TPC: 734 per 1,000				High[a,b,c]	SG results in a clinically important increase in OS when compared with TPC.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			TPC	SG	Difference		
months • TPC: 10.68 months		• Stratified hazard ratio (97.77% CI) = 0.789 ([redacted]) Median (95% CI) OS at data cut-off, months • SG: 14.4 (13.0 to 15.7) • TPC: 11.2 (10.1 to 12.7)					
Tumour response to treatment (data cut-off: July 1, 2022)							
ORR (CR or PR) per BICR, % Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	536 (1 RCT)	OR = 1.625 (1.034 to 2.555)	140 per 1,000	210 per 1,000 (163 to 263 per 1,000)	70 more per 1,000 (NR)	Moderate[a,b,d,e]	SG likely results in an increase in objective response rate when compared with TPC. The clinical importance of the increase is uncertain.
CBR (CR, PR, or stable disease ≥ 6 months) per BICR, % Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	536 (1 RCT)	OR = 1.796 (1.227 to 2.628)	221 per 1,000	338 per 1,000 (282 to 398 per 1,000)	117 more per 1,000 (NR)	Moderate[a,b,d,e]	SG likely results in an increase in clinical benefit rate when compared with TPC. The clinical importance of the increase is uncertain.
DOR per BICR Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	95 (1 RCT)	DOR events at data cut-off: • SG: 579 per 1,000 • TPC: 579 per 1,000 • Stratified hazard ratio (95% CI): NR (NR) Median (95% CI) DOR at data cut-off, months • SG: 8.1 (6.7 to 9.1) • TPC: 5.6 (3.8 to 7.9)				Low[a,b,f]	SG may result in an increase in duration of response when compared with TPC. The clinical importance of the increase is uncertain.
HRQoL (data cut-off: July 1, 2022)							
Time to deterioration in EORTC QLQ-C30 Global Health Status or QoL domain (0 [worst] to 100 [best]) defined as having a ≥ 10-point deterioration	441 (1 RCT)	Deterioration events at data cut-off: • SG: 897 per 1,000 • TPC: 894 per 1,000 • Stratified hazard ratio (95% CI) = 0.751 (0.612 to 0.922) Median (95% CI) time to deterioration at data cut-off, months • SG: 4.3 (3.1 to 5.7) • TPC: 3.0 (2.2 to 3.9)				Low[a,b,c,g]	SG may result in an increase in time to deterioration in EORTC QLQ-C30 Global Health Status or QoL domain when compared with TPC. The clinical importance of the increase is uncertain.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			TPC	SG	Difference		
from baseline Follow-up, median: • SG: 13.80 months • TPC: 10.68 months							
Time to deterioration in EORTC QLQ-C30 fatigue domain (0 [best] to 100 [worst]) defined as having a ≥ 10-point deterioration from baseline Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	439 (1 RCT)	Deterioration events at data cut-off: • SG: 932 per 1,000 • TPC: 932 per 1,000 • Stratified hazard ratio (95% CI) = 0.732 (0.598 to 0.894) Median (95% CI) time to deterioration at data cut-off, months • SG: 2.2 (1.6 to 2.8) • TPC: 1.4 (1.1 to 1.9)				Low[a,b,c,h]	SG may result in an increase in time to deterioration in EORTC QLQ-C30 fatigue domain when compared with TPC. The clinical importance of the increase is uncertain.
Time to deterioration in EORTC QLQ-C30 pain domain (0 [best] to 100 [worst]) defined as having a ≥ 10-point deterioration from baseline Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	431 (1 RCT)	Deterioration events at data cut-off: • SG: 904 per 1,000 • TPC: 891 per 1,000 • Stratified hazard ratio (95% CI) = 0.918 (0.748 to 1.126) Median (95% CI) time to deterioration at data cut-off, months • SG: 3.8 (2.8 to 5.0) • TPC: 3.5 (2.8 to 5.0)				Very low[a,b,i,j]	The evidence is very uncertain about the effect of SG on EORTC QLQ-C30 pain domain when compared with TPC.
Time to deterioration in EORTC QLQ-C30 diarrhea domain (0 [best] to 100 [worst]) defined as having a	440 (1 RCT)	Deterioration events at data cut-off: [redacted] Median (95% CI) time to deterioration at data cut-off, months [redacted]				Low[a,b,c,k]	SG may result in a clinically important decrease in time to deterioration in EORTC QLQ-C30 diarrhea domain when compared with TPC.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			TPC	SG	Difference		
≥ 10-point deterioration from baseline Follow-up, median: • SG: 13.80 months • TPC: 10.68 months							
Treatment discontinuation (data cut-off: December 1, 2022)							
Time to treatment discontinuation [l] Follow-up, median: • SG: 14.39 months • TPC: 10.97 months	517 (1 RCT)	Treatment discontinuation events at data cut-off: [redacted] Median (95% CI) time to treatment discontinuation at data cut-off, months [redacted]				High[a,b,c]	SG results in an increase in time to treatment discontinuation when compared with TPC. The clinical importance of the increase is uncertain.
Harms (grade 3 or higher adverse events, data cut-off: July 1, 2022)							
Diarrhea, n (%) Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	517 (1 RCT)	NR	12 per 1,000	101 per 1,000 (NR)	89 more per 1,000 (NR)	Low[a,b,m,n]	SG may result in an increase in neutropenia of grade 3 or higher when compared with TPC. The clinical importance of the increase is uncertain.
Neutropenia, n (%) Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	517 (1 RCT)	NR	390 per 1,000	515 per 1,000 (NR)	125 more per 1,000 (NR)	Moderate[a,b,e,m]	SG likely results in an increase in neutropenia of grade 3 or higher when compared with TPC. The clinical importance of the increase is uncertain.
Febrile neutropenia, n (%) Follow-up, median: • SG: 13.80 months	517 (1 RCT)	NR	44 per 1,000	60 per 1,000 (NR)	16 more per 1,000 (NR)	Low[a,b,m,n]	SG may result in an increase in febrile neutropenia of grade 3 or higher when compared with TPC. The clinical importance of the increase is uncertain.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			TPC	SG	Difference		
• TPC: 10.68 months							
Leukopenia, n (%) Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	517 (1 RCT)	NR	60 per 1,000	86 per 1,000 (NR)	26 more per 1,000	Low[a,b,m,n]	SG may result in an increase in leukopenia of grade 3 or higher when compared with TPC. The clinical importance of the increase is uncertain.
Anemia, n (%) Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	517 (1 RCT)	NR	36 per 1,000	75 per 1,000 (NR)	39 more per 1,000	Low[a,b,m,n]	SG may result in an increase in anemia of grade 3 or higher when compared with TPC. The clinical importance of the increase is uncertain.
Fatigue, n (%) Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	517 (1 RCT)	NR	36 per 1,000	60 per 1,000 (NR)	24 more per 1,000 (NR)	Low[a,b,m,n]	SG may result in an increase in fatigue of grade 3 or higher when compared with TPC. The clinical importance of the increase is uncertain.
Infections+, n (%) Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	517 (1 RCT)	NR	48 per 1,000	97 per 1,000 (NR)	49 more per 1,000 (NR)	Low[a,b,m,n]	SG may result in an increase in infections+ of grade 3 or higher when compared with TPC. The clinical importance of the increase is uncertain.
Neuropathy+, n (%) Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	517 (1 RCT)	NR	36 per 1,000	26 per 1,000 (NR)	10 fewer per 1,000 (NR)	Low[a,b,m,n]	SG may result in little to no difference in neuropathy+ of grade 3 or higher when compared with TPC.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			TPC	SG	Difference		
Hyper-sensitivity+, n (%) Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	517 (1 RCT)	NR	8 per 1,000	15 per 1,000 (NR)	7 more per 1,000 (NR)	Low[a,b,m,n]	SG may result in little to no difference in hypersensitivity+ of grade 3 or higher when compared with TPC.
Pulmonary events+, n (%) Follow-up, median: • SG: 13.80 months • TPC: 10.68 months	517 (1 RCT)	NR	4 per 1,000	0	4 fewer per 1,000 (NR)	Low[a,b,m,n]	SG may result in little to no difference in pulmonary events+ of grade 3 or higher when compared with TPC.

AE = adverse event; BICR = blinded independent central review; CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRQoL = health-related quality of life; KM = Kaplan-Meier; NA = not applicable; NR = not reported; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RCT = randomized controlled trial; SG = sacituzumab govitecan; TPC = treatment of physician's choice; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. The "+" sign indicates that the adverse event of special interest consists of grouped AE terms, and the following terms were mapped: "neutrophil count decreased" was grouped into neutropenia; "white blood cell count decreased" was grouped into leukopenia; "lymphocyte count decreased" was grouped into lymphopenia; "hemoglobin decreased" and "red blood cell count decreased" were grouped into anemia; and "platelet count decreased" was grouped into thrombocytopenia.

[a]Although the CADTH review team noted that the proportion of patients with no baseline images or no postbaseline evaluable assessment was higher in the TPC group (37 patients, 13.7%) than the SG group (8 patients, 2.9%), mainly due to patients categorized as "randomized but never treated" (4 [50.0%] of the patients categorized as having no baseline images or no postbaseline evaluable assessment in the SG group and 21 [56.8%] in the TPC group), the certainty of evidence was not rated down because whether these patients differed in prognostic characteristics compared with those who were evaluated was not known, so the presence and direction of potential bias on the effect estimate was uncertain.

[b]Indirectness was not rated down. Differences between the patients in the 1 RCT informing the evidence (who must have had stable brain metastasis for at least 4 weeks, with an ECOG PS of 0 or 1, and who had not received a live vaccine within 30 days of randomization, among the other patient inclusion and exclusion criteria) and the patients in clinical practice were noted but were not considered serious enough to result in important differences in the observed effect, according to the clinical experts consulted by CADTH. The TPC comparator was considered directly relevant to Canadian clinical practice by the clinical experts consulted by CADTH.

[c]Imprecision was not rated down. In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of imprecision was based on the 95% CI for the hazard ratio using the null as the threshold. The clinical importance of the between-group difference was judged based on the difference in median time to event and the input of the clinical experts consulted by CADTH for the review.

[d]For CRR and CBR, although the CADTH review team noted that the proportion of patients who were not evaluable was higher in the TPC group (51 patients, 18.8%) than the SG group (15 patients, 5.5%), mainly due to the "randomized but never treated" category (4 [26.7%] of the not evaluable patients in the SG group and 22 (43.1%) in the TPC group) and the "informed consent withdrawn" category (3 [20.0%] of the not evaluable patients in the SG group and 14 [27.5%] in the TPC group), the certainty of evidence was not rated down because whether these patients differed in prognostic characteristics compared with those who were evaluated was not known, so the presence and direction of potential bias on the effect estimate was uncertain.

[e]Rated down 1 level for serious imprecision due to the small number of events. The 95% CI of the absolute effect was not available.

[f]Rated down 2 levels for very serious imprecision due to the small sample size. The 95% CI of the absolute effect was not available.

[g]Rated down 2 levels for very serious risk of bias due to the open-label nature of the study and the subjective nature of the outcome. The impact of the missing outcome data (18.8% of the total patients) is unclear.

[h]Rated down 2 levels for very serious risk bias of due to the open-label nature of the study and the subjective nature of the outcome. The impact of the missing outcome data (19.2% of the total patients) is unclear.

[i]Rated down 2 levels for very serious risk bias of due to the open-label nature of the study and the subjective nature of the outcome. The impact of the missing outcome data (20.6% of the total patients) is unclear.

[j]Rated down 1 level for serious imprecision. In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of imprecision was based on the 95% CI for the hazard ratio using the null as the threshold. The 95% CI of the hazard ratio included the "no effect" threshold

of 1. The clinical importance of the between-group difference was judged based on the difference in median event rates and the input of the clinical experts consulted by CADTH for the review.

[k]Rated down 2 levels for very serious risk bias of due to the open-label nature of the study and the subjective nature of the outcome. The impact of the missing outcome data (19.0% of the total patients) is unclear.

[l]The analysis of time to treatment discontinuation was not prespecified by the sponsor; however, it was requested by the CADTH for the purpose of the certainty of evidence appraisal.

[m]Risk of bias was not rated down. Possible subjectiveness in the judgment of grade 3 or higher for these adverse events was noted but was not considered serious enough to result in important differences in the observed effect, from the assessment of the CADTH review team.

[n]Rated down 2 levels for very serious imprecision due to very small number of events. The 95% CI of the absolute effect was not available.

Source: TROPiCS-02 Clinical Study Report (Interim Analysis 1), TROPiCS-02 Clinical Study Report (Interim Analysis 2), sponsor's submissions.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partition survival model
Target population	Adults with unresectable locally advanced or metastatic hormone receptor HR-positive, HER2-negative (IHC 0, IHC 1+, or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting.
Treatment	Sacituzumab govitecan
Dose regimen	10 mg/kg administered as an IV infusion once weekly on days 1 and 8 of a 21-day treatment cycle
Submitted price	180 mg, vial for injection: $1,478.00 per vial
Treatment cost	$15,765 per 28 days assuming a weight of 70 kg
Comparator	TPC, consisting of a weighted basket of single-drug chemotherapy regimens: eribulin, capecitabine, gemcitabine, vinorelbine
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	10 years
Key data source	TROPiCS-02 trial (a pivotal phase III, multicentre, randomized, open-label trial)
Submitted results	ICER = $341,152 per QALY gained when compared to TPC (incremental costs: $101,369; incremental QALYs: 0.30)
Key limitations	• Long-term OS predicted by the model is likely overestimated. The sponsor assumes after approximately 12 months, mortality rates for patients receiving TPC or sacituzumab govitecan will decrease over time. This results in optimistic estimates of OS with some patients living beyond 10 years. Clinical experts consulted by CADTH noted that very few patients would be alive at 5 years and that mortality rates are not expected to decrease over time, especially as most patients will have experienced progression after 2 years. • Resource use associated with treatment administration, monitoring, and concomitant medications is underestimated. Based on feedback elicited for this review, sacituzumab govitecan requires substantial time to administer intravenously relative to other IV treatments in this setting. • Treatment costs associated with sacituzumab govitecan are uncertain. The sponsor estimated the RDI from the trial data; however, it is uncertain what impact a lower dose will have on drug costs and whether

Component	Description
	RDI double counts the impact from dose delay. • Uncertainty was not properly characterized in survival curves. The sponsor used KM data up to 14.4 months before using parametric survival curves to extrapolate long-term survival for OS, PFS, and time to treatment discontinuation. When analyzing the uncertainty associated with KM curves, data from the trial (such as patient numbers and censored events) were not used to inform uncertainty. CADTH notes this limitation has a minor impact on the results.
CADTH reanalysis results	• CADTH incorporated the following changes to address the identified limitations for the base case: using a gamma distribution to extrapolate long-term OS; assuming higher administration costs; assuming an additional vial of sacituzumab govitecan would not be used if the received dose fell within 5% of the recommended dose; including costs associated with G-CSF to be co-administered with sacituzumab govitecan; using parametric fits for all survival curves. • In the CADTH base case, sacituzumab govitecan is associated with an ICER of $506,807 per QALY gained (incremental QALYS: 0.19; incremental costs: $101,369) when compared to TPC. • At this ICER, an 88% price reduction is required to achieve cost-effectiveness at a $50,000 per QALY gained threshold.

G-CSF = granulocyte colony-stimulating factor; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; ISH = in situ hybridization; KM = Kaplan-Meier; LY = life-year; PSM = partitioned survival model; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RDI = relative dose intensity; TPC = treatment of physician's choice.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the size of the prevalent population was likely overestimated, eligible patients in the third-line setting were inappropriately excluded, the proportion of patients receiving later lines of therapy in the metastatic space was underestimated, patients with an ECOG PS of 2 were excluded, the cost of sacituzumab govitecan was underestimated, the market uptake of sacituzumab govitecan is uncertain, and concomitant medication costs were not considered.

CADTH reanalysis included correcting the sponsor's assumption that sacituzumab govitecan would only be offered in a fourth-line setting; aligning the attrition rates for the second-line, third-line, and fourth-line settings with clinical expert input; changing the cost of sacituzumab govitecan; assuming patients with an ECOG PS of 2 will be eligible for sacituzumab govitecan; and correcting the sponsor's estimates used to determine the prevalent population size. CADTH reanalyses suggest that the reimbursement of sacituzumab govitecan for the requested reimbursement population (adult patients with unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting) would be associated with an overall budgetary increase of $129,191,759 (year 1: $42,125,294; year 2: $40,020,849; year 3: $47,045,615).

CADTH noted that the budget impact will decrease if the patient is required to have experienced treatment failure with an endocrine-based therapy and 2 systemic chemotherapies, rather than an endocrine-based therapy and any 2 systemic therapies.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: December 6, 2023

Regrets: One expert committee member did not attend.

Conflicts of interest: One expert committee member did not participate due to conflict-of-interest considerations.

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