Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Recommendation

Reimbursement Recommendation

(Draft)

Zolbetuximab for Injection (Vyloy)

Indication: In combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2-negative gastric or gastroesophageal junction adenocarcinoma whose tumours are Claudin 18.2 positive

Sponsor: Astellas Pharma Canada, Inc.

Recommendation: Reimburse with Conditions

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Recommendation

The CDA-AMC pCODR Expert Review Committee (pERC) recommends that zolbetuximab for injection, in combination with fluoropyrimidine- and platinum-containing chemotherapy, be reimbursed for the first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive only if the conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

Evidence from two randomized, double-masked, placebo-controlled phase III trials (SPOTLIGHT and GLOW) demonstrated that zolbetuximab, when added to fluoropyrimidine- and platinum-containing chemotherapy (mFOLFOX6 or CAPOX) for the first line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive, resulted in added clinical benefit. The SPOTLIGHT trial (N = 565) demonstrated that treatment with zolbetuximab in combination mFOLFOX6 resulted in statistically significant and clinically meaningful improvements in overall survival (OS; hazard ratio [HR] = 0.784; 95% confidence interval [CI], 0.644 to 0.954; P = 0.0075) and progression-free survival (PFS; HR = 0.751; 95% CI, 0.598 to 0.942; P = 0.0066) compared with placebo in combination with mFOLFOX6. The GLOW trial (N = 507) similarly demonstrated that treatment with zolbetuximab in combination with CAPOX resulted in statistically significant and clinically important meaningful improvements in OS (HR = 0.763; 95% CI, 0.622 to 0.936; P = 0.0047) and PFS (HR = 0.687; 95% CI, 0.544 to 0.866; P = 0.0007), compared with placebo in combination with CAPOX. In the pivotal trials, treatment with zolbetuximab in combination with chemotherapy was shown to be associated with an increased risk of nausea, vomiting, and infusion related reactions (IRRS), when compared with chemotherapy alone. However, pERC agreed with the clinical experts that these adverse events (AEs) may be manageable in clinical practice.

The sponsor-submitted indirect treatment comparisons suggested that there was little to no difference between zolbetuximab, nivolumab, and pembrolizumab for improving OS and PFS, when added to chemotherapy. Although the comparisons were not limited to patients whose tumours are CLDN 18.2 positive, pERC agreed that the clinical benefit with zolbetuximab is comparable to the clinical benefit with nivolumab or pembrolizumab for patients for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma. pERC noted that the harms and health-related quality of life (HRQoL) outcomes were not evaluated in the submitted indirect treatment comparisons.

Patients identified the need for new effective therapies that can prolong survival, reduce risk of disease progression, improve quality of life, allow for more convenient administration of therapy, and minimize side effects. pERC concluded that zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy met some of the needs identified by patients because it prolongs survival and delays disease progression.

At the sponsor submitted price for zolbetuximab and publicly listed price for all other drugs zolbetuximab in combination with fluoropyrimidine and platinum-based chemotherapy was more costly than nivolumab in combination with fluoropyrimidine and platinum-based chemotherapy. As zolbetuximab is considered similarly effective as nivolumab, the total drug cost of zolbetuximab when used in combination with fluoropyrimidine and platinum-based chemotherapy should not exceed the total drug cost of the least costly immunotherapy when used in combination with fluoropyrimidine and platinum-based chemotherapy.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Zolbetuximab, in combination with fluoropyrimidine- and platinum-containing chemotherapy could be initiated in patients who have all the following: 1.1. 18 years of age or older 1.2. Previously untreated locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma 1.3. HER2-negative and CLDN18.2 positive tumours	Evidence from the SPOTLIGHT and GLOW trials demonstrated statistically significant OS and PFS benefits in patients who fulfilled the characteristics listed in this condition.	**For condition 1.3:** pERC agreed with the clinical experts consulted during this review on the following: 1. CLDN18.2 positive status should be defined as ≥75% of tumour cells demonstrating moderate to strong membranous CLDN18.2 immunohistochemical staining as determined by a validated test 2. Immunohistochemical testing for CLDN18.2 status could be carried out, as part of routine care, following diagnosis of gastric or GEJ adenocarcinoma, when similar testing for HER2 status is performed. 3. Zolbetuximab may be added on to chemotherapy should there be delay in confirming a patient's biomarker status (e.g. HER2-negative, CLDN18.2 positive)
2. Patients must not have active CNS metastases.	The SPOTLIGHT and GLOW trials excluded patients with a history of CNS metastases.	pERC considered it appropriate to consider patients with controlled CNS metastases for eligibility.
3. Patients must have good performance status.	The SPOTLIGHT and GLOW trials included patients with an ECOG performance status of 0 or 1.	pERC agreed with the clinical experts that patients with an ECOG performance status of more than 1 may be treated at the discretion of the treating physician.
Discontinuation		
4. Treatment should be discontinued upon the occurrence of any of the following: 4.1. Clinical disease progression 4.2. Unacceptable toxicity	Patients in the SPOTLIGHT and GLOW trials discontinued treatment upon progression or unacceptable toxicity, consistent with clinical practice.	—
Prescribing		
5. Zolbetuximab in combination with chemotherapy should be prescribed by clinicians with expertise and experience in treating gastric or GEJ cancers.	This condition is to ensure that treatment is prescribed only for appropriate patients and adverse events are managed in an optimized and timely manner.	Patients should receive treatment with antiemetic prophylaxis (e.g., in accordance with recommendations in the product monograph or as directed by healthcare providers).

Reimbursement condition	Reason	Implementation guidance
The treatment should be delivered in institutions with expertise in systemic therapy delivery and management of immunotherapy-related side effects.		
6. Zolbetuximab should be prescribed in combination with fluoropyrimidine- and platinum-containing chemotherapy.	In SPOTLIGHT and GLOW, zolbetuximab was administered in combination FOLFOX or CAPOX. No evidence was available to support the clinical benefit of zolbetuximab monotherapy.	After treatment initiation, chemotherapy may be discontinued due to intolerance and/or patient-prescriber consensus with zolbetuximab continuing as monotherapy until disease progression or unacceptable toxicity.
Pricing		
7. Zolbetuximab in combination with chemotherapy should be negotiated so that it does not exceed the drug program cost of the least costly immunotherapy in combination with chemotherapy for the treatment of locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma gastric or GEJ cancers.	The results of the network meta-analysis, clinical expert opinion, and the output of the pharmacoeconomic model concluded that OS and PFS is similar between patients receiving treatment with either zolbetuximab, nivolumab, or pembrolizumab (all in combination with chemotherapy). As such, there is insufficient evidence to justify a cost premium for zolbetuximab over nivolumab or pembrolizumab for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma gastric or GEJ cancers.	—
Feasibility of adoption		
8. The feasibility of adoption of zolbetuximab in combination with chemotherapy 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 the CDA-AMC estimate(s).	—
9. Organizational feasibility must be addressed: 9.1. Access to CLDN18.2 testing will be required to identify patients who may be eligible for treatment with zolbetuximab.	CLDN18.2 is a novel biomarker and is not currently assessed in routine clinical practice.	—

CAPOX = capecitabine plus oxaliplatin; CLDN18.2 = claudin-18 splice variant 2; CPS = Combined Positive Score; ECOG = Eastern Cooperative Oncology Group; FOLFOX = fluorouracil plus lurcovorin plus oxaliplatin; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; OS = overall survival; PD-L1 = Programmed cell death-ligand 1; PFS = progression-free survival

Discussion Points

- **Unmet need in patients with combined positive score (CPS) less than 5:** pERC noted that the regulatory approval and reimbursement for nivolumab for adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma is not limited based on a patients' PD-L1 CPS. The clinical experts noted that there may be uncertainty in the clinical community regarding effectiveness of nivolumab plus chemotherapy in patients with a PD-L1 CPS less than 5 (based on a subgroup analysis from the pivotal CheckMate-649 study that suggested statistically non-significant effect of nivolumab plus chemotherapy in patients with PD-L1 CPS of lower than 5). While the effects of zolbetuximab plus chemotherapy was not assessed based on CPS score in the SPOTLIGHT or GLOW trials, pERC acknowledged that there may be an unmet need for patients with advanced or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive and have a PD-L1 CPS score of 5 or less. pERC agreed that zolbetuximab plus chemotherapy may provide an alternative treatment option with a potential to improve survival outcomes over chemotherapy alone in this patient population with very poor prognosis and significant symptom burden, and those who are not eligible for treatment with immune checkpoint inhibitors plus chemotherapy (e.g., when nivolumab or pembrolizumab are contraindicated).
- **Impact on patient-reported outcomes**: pERC discussed the results of patient-reported outcomes from the pivotal trials and noted that the impact of zolbetuximab, when added to chemotherapy, on HRQoL could not be evaluated due to inconsistencies in the reported results for time-to-deterioration based on changes in HRQoL scales across the SPOTLIGHT and GLOW trials.
- **Gastrointestinal adverse events:** pERC noted that treatment with zolbetuximab in combination with chemotherapy is associated with an increased risk of gastrointestinal AEs compared with chemotherapy alone, owing to the effect of zolbetuximab on gastric mucosal cells that induce nausea and vomiting. The product monograph provides recommendations regarding pretreatment with medications to reduce the risk as well as recommendations for treatment interruption and discontinuation (if required) for those who experience Grade 2, 3, or 4 AEs. The clinical experts consulted during this review indicated that these events may be manageable in clinical practice. Recognizing that these AEs may not limit the usage of zolbetuximab where it may be the preferred option, pERC noted that effective AEs management strategies should be used to mitigate concerns with the gastrointestinal symptom burden in patients treated with this drug.
- **CLDN18.2 and CPS testing:** pERC discussed that, while IHC testing for HER2 is currently widely available and already part of routine care across Canadian jurisdictions for patients with gastric or GEJ adenocarcinoma, IHC testing for CLDN18.2 status is not. pERC noted that according to the clinical experts, implementation of IHC testing for CLDN18.2 is not likely to have a substantial health system impact, but since CPS testing is not currently required to identify candidates for treatment with nivolumab (although it may be performed), the availability of zolbetuximab may increase use of CPS testing as clinicians may preferentially use the treatment for those whose tumours are CLDN18.2 positive and who have a CPS score of less than 5 . pERC discussed that testing uptake and the timing of testing – either sequentially (e.g., CLDN18.2 first followed by CPS) or at the same time (e.g., both CLDN18.2 and CPS reflexively and at diagnosis) – will affect the budget impact of zolbetuximab.
- **Economic evidence:** pERC discussed the economic evidence for zolbetuximab. The CDA-AMC reanalyses suggested that based on the indirect evidence, zolbetuximab was associated with greater costs and quality-adjusted life-years (QALYs) for the indicated population, and that a price reduction of approximately 88% would be required for it be considered cost-effective at a $50,000 per QALY gained willingness to pay threshold. However, pERC considered that there was no robust evidence to support a price premium for zolbetuximab, when used in combination with chemotherapy, compared to the least costly immunotherapy when used in combination with chemotherapy, acknowledging that nivolumab and pembrolizumab were recommended with a maximum duration of treatment (24 months), while zolbetuximab is recommended to be continued until progression or unacceptable toxicity. pERC acknowledged that given the implications associated with testing that were noted in an earlier discussion point and organization feasibility of adoption criteria, zolbetuximab is likely to be associated with an incremental cost to the healthcare system.
- **Feasibility of implementation** - pERC discussed that zolbetuximab will be a more resource intensive therapy for both patients and treatment centres (including clinicians, nurses, and pharmacy staff) as it has a considerably longer infusion time

and significantly longer preparation time than the comparator immunotherapies. pERC additionally noted that the final product stability of zolbetuximab at room temperature is short, and that if the infusion time exceeds 6 hours from the time of preparation, then the infusion bag must be discarded and a new infusion bag prepared. Therefore, pERC noted that jurisdictions will need to consider increased chair time and additional pharmacy and nursing resources for the implementation of a reimbursement recommendation for zolbetuximab.

- **Alignment with prior recommendations:** Nivolumab and pembrolizumab have been recommended by pERC for use in combination with chemotherapy for the treatment of patients first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma. The committee acknowledged the input from the participating drug programs that the alignment of reimbursement conditions across drugs in the same therapeutic space is beneficial from a formulary management perspective and that the clinicians consulted by CDA-AMC also supported aligning conditions.

Background

Zolbetuximab for injection has been approved by Health Canada for use in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN 18.2 positive. It is available as 100 mg single-use vials and the dosage recommended in the product monograph is a loading dose of 800 mg/m^2 administered intravenously (IV) and a maintenance dose of 600 mg/m^2 IV every 3 weeks or 400 mg/m^2 IV every 2 weeks.

Sources of Information Used by the Committee

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

- a review of 2 randomized, double-masked, placebo-controlled phase III trials in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive; and one sponsor-submitted indirect treatment comparison
- patients' perspectives gathered by 1 patient group, My Gut Feeling - Stomach Cancer Foundation of Canada
- input from public drug plans that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with gastric or GEJ adenocarcinoma
- input from 1 clinician group(s), Ontario Health (Cancer Care Ontario) Drug Advisory Committees
- a review of testing procedure considerations for determining CLDN18.2 status as part of establishing eligibility for treatment with zolbetuximab.
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to the call for input and from clinical experts consulted for the purpose of this review.

Patient Input

One patient group provided input for this review. My Gut Feeling - Stomach Cancer Foundation of Canada is a non-profit organization providing support, awareness, education, information, and advocacy to stomach cancer patients, survivors, and caregivers. My Gut Feeling conducted an international online survey of patients and caregivers affected by gastric, esophageal, and/or gastroesophageal cancer. A total of 35 respondents completed the survey, 14.3% of whom were caregivers and 85.7% of whom were patients; the majority of respondents resided in Canada (71.4%) or the United States (25.7%).

Nearly all participants (97.2%) responded that their quality of life was significantly affected by the cancer diagnosis. Specifically, physical and mental health, ability to eat, work, finances, social life, identity, and personal image were all impacted. For example,

respondents expressed the exhaustion of managing adequate daily nutrition and the toll of experiencing weight loss or weight gain, including its impact on body image. Patients and caregivers (particularly those affected by metastatic disease) communicated that the cancer diagnosis and its treatment had negative impacts on their mental health and caused anxiety surrounding finances (e.g., loss of income due to work absenteeism, additional expenses due to travel for medical care and specialized diet). Patients reported feeling anxiety, depression, and/or anger, and that experiencing fatigue greatly impacted their daily activities.

Survey participants stated that many factors are considered when weighing treatment options, such as quality of life, survival benefits, side effects, convenience, and duration of therapy, recognizing that treatments have trade-offs that need to be considered on an individual basis. For example, most respondents (82.9%) would choose a treatment that prolongs life despite side effects. Patients also expressed a preference for the convenience of oral chemotherapy taken at home over IV chemotherapy administered in a hospital setting.

My Gut Feeling indicated that gastric and gastroesophageal cancers are rare in Canada with few treatment options. This group expressed an unmet need for equitable access to therapies that prolong life, improve symptoms, reduce the risk of recurrence, and have improved tolerability. My Gut Feeling strongly supports the use of zolbetuximab in combination with chemotherapy as first-line treatment for patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive and expressed that biomarker testing should be accessible at the onset of disease for all patients in Canada. The patient group believed that there should be a choice in treatment options that are available barrier-free and covered under the universal healthcare system in Canada for the benefit of these cancer patients.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The clinical experts consulted for the purpose of this review emphasized that locally advanced and metastatic HER2-negative gastric or GEJ cancer is associated with considerable unmet needs. Treatment with nivolumab in combination with chemotherapy is the currently available first-line option for locally advanced metastatic HER2-negative gastric or GEJ cancer; however, OS outcome remains poor (median OS 13 to 15 months). The clinical experts suggested that the addition of zolbetuximab to chemotherapy would represent an alternative to combination therapy with nivolumab plus chemotherapy in the first-line metastatic treatment setting for patients with locally advanced and metastatic HER2-negative gastric or GEJ cancer whose tumours are CLDN 18.2 positive. Regulatory approval and reimbursement for nivolumab for patients with gastric or GEJ cancer is not limited based on a patients' PD-L1 CPS; however, the clinical experts noted that there is some uncertainty in the clinical community regarding the effectiveness of nivolumab plus chemotherapy in patients with a PD-L1 CPS less than 5 (e.g., a subgroup analysis from the pivotal CheckMate-649 study suggested a reduced effect of nivolumab in patients with PD-L1 CPS of lower than 5 [HR = 0.94; 95% CI, 0.78 to 1.13]). As such, the clinical experts noted that zolbetuximab plus chemotherapy could be a preferred option for patients with CLDN 18.2 positive tumours and PD-L1 CPS less than 5. For those with both CLDN 18.2 positive tumours and a PD-L1 CPS ≥ 5, it is currently unclear which option could offer the best outcomes for patients.

The clinical experts noted the following factors should be used to determine response to treatment: patient reported symptoms and side-effects and response on cross-sectional imaging via CT scans or MRI. The clinical experts suggested that patients should be assessed by a clinician after every 2 to 3 cycles of treatment. Clinician assessment may occur more frequently if the patients report the occurrence of bothersome symptoms or side effects. The clinical experts suggested that patients should undergo CT scans every 2 to 3 months. Tumour markers can be used as per clinical judgement to supplement a fulsome patient assessment. The clinical experts noted that the clinically meaningful end points across all oncology types are OS and QoL and the PFS has limited value in assessing clinical benefit for patients with metastatic disease and a relative short duration of overall survival. The clinical experts suggested that the decision to discontinue treatment with zolbetuximab should be based on patient reported symptoms, patient preference, side-effects and well-being, in combination with assessment of treatment response and disease progression, either radiologic or clinical.

Clinician Group Input

Four clinicians from the Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee (OH-CCO GI DAC) provided a joint clinician group input for this review. Ontario Health (Cancer Care Ontario) drug advisory committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of Cancer Care Ontario's mandate, including the Provincial Drug Reimbursement programs and the Systemic Treatment Program. Regarding current treatments for metastatic HER2-negative gastric cancer, the clinician group providing input stated that standard first-line therapy consists of chemotherapy (typically FOLFOX) combined with immunotherapy (nivolumab, which is currently funded; pembrolizumab, which is approved but not funded). The goals of treatment are to prolong life, delay disease progression, and maintain quality of life. This clinician group expressed that there are currently no approved treatments that specifically target tumours overexpressing CLDN18.2, which represents an unmet need for this population. Clinical experts consulted by CDA-AMC also identified FOLFOX with or without nivolumab as a first line therapy in this population with goals of therapy that were aligned with those identified by the clinician group. These experts identified an unmet need for treatments with other biological targets and for new treatments that will increase survival.

The OH-CCO GI DAC remarked that patients best suited for treatment with zolbetuximab are those with HER2-negative, CLDN18.2-positive advanced gastric or GEJ cancer. This clinician group stated that zolbetuximab would provide an alternative option to nivolumab. For patients with CLDN18.2 overexpression and PD-L1 negative/low disease, the clinician group suspects that zolbetuximab and chemotherapy would be the clear first-line choice of therapy but acknowledges that the best first-line therapy (nivolumab/pembrolizumab or zolbetuximab) for patients with CLDN18.2 overexpression and PD-L1 CPS greater than 5% is unclear. For the latter population of patients, the choice of agent to add (i.e., zolbetuximab, nivolumab, or immunotherapy) would be at the physician's discretion based on comorbidities and toxicity profile and with consideration for maintaining good quality of life.

Drug Program Input

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

Table 2: Responses to Questions from the Drug Programs

Drug program implementation questions	Committee response
Relevant comparators	
No questions identified	Not applicable
Considerations for initiation of therapy	
Recipients of adjuvant nivolumab: Should patients who have received adjuvant treatment with nivolumab, but who relapse less than 6 months after completing adjuvant treatment, be eligible for treatment with zolbetuximab plus chemotherapy? Patients were eligible for SPOTLIGHT and GLOW if they had received either neo-adjuvant or adjuvant immunotherapy as long as it was completed at least 6 months prior to randomization, but no patients were identified has having received prior treatment with nivolumab.	pERC agreed with the clinical experts consulted during this review, who suggested that these patients would be relatively rare in clinical practice and that those who could be considered candidates for zolbetuximab based on CLDN 18.2 biomarker status, performance status, and would otherwise meet eligibility criteria should be offered the treatment.
Performance status: Patients with ECOG performance status 0 or 1 were included in the SPOTLIGHT and GLOW clinical trials. Should patients with ECOG performance status greater than 1 be eligible for zolbetuximab?	pERC agreed with the clinical experts consulted during this review, who noted that patients with an ECOG performance status more than 1 may be treated at the discretion of the treating physician.
Delayed confirmation of HER2 negative status: Patients are required to be HER2-negative to be eligible for zolbetuximab plus chemotherapy. Should patients who have initiated chemotherapy and whose disease has unknown HER2 status be eligible to add on zolbetuximab upon confirmation of HER2 negative status?	pERC agreed with the clinical experts consulted during this review, who noted that patients who have initiated chemotherapy and whose disease has unknown HER2 status should be eligible to add on zolbetuximab upon confirmation of HER2 negative status. It was noted that this already occurs on occasion in routine practice and the patient would receive the initial doses of chemotherapy and subsequently receive

Drug program implementation questions	Committee response
	add-on therapy with nivolumab upon confirmation of HER2 negative status.
Unknown HER2 status: Should patients be eligible for zolbetuximab if they meet the criteria for CLDN18.2 expression, but their HER2 status cannot be determined?	pERC agreed with the clinical experts consulted during this review, who noted that this would be a small minority of patients and that the unknown HER2 status (e.g., due to insufficient tissue for testing) should not prevent access to zolbetuximab if the patient has been confirmed as meeting the criterion for CLDN18.2 expression.
Consistency with prior recommendations: The participating drug programs noted that nivolumab plus chemotherapy and pembrolizumab plus chemotherapy have previously been recommended for reimbursement by CDA-AMC for use as a first-line option in patients with gastric or GEJ adenocarcinoma. The drug programs noted that consistency with initiation criteria in the same therapeutic space can be beneficial from a formulary management perspective.	For consideration by expert committee. The clinical experts consulted during this review did not identify any issues or concerns with the existing criteria that have been recommended by pERC for treatment regimens indicated for use in the treatment of gastric or GEJ cancer.
Chemotherapy ineligible: The Health Canada-approved indication for zolbetuximab states that the drug should be provided in combination with fluoropyrimidine- and platinum-containing chemotherapy. Should patients be eligible for treatment with zolbetuximab if they are not able to receive concomitant chemotherapy?	pERC agreed with the clinical experts consulted during this review, who noted that patients who are unable to initiate treatment with chemotherapy would be unlikely to be considered candidates for zolbetuximab. pERC additionally noted that it did not review any evidence to support the efficacy of monotherapy with zolbetuximab in the patient population under review.
Considerations for discontinuation of therapy	
Discontinuation of chemotherapy: The product monograph states that cytotoxic drugs were shown to increase CLDN18.2 expression in cancer cells and improve zolbetuximab-induced antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. Can zolbetuximab be continued if chemotherapy must be stopped due to intolerance?	pERC agreed with the clinical experts consulted during this review, who noted that all patients will eventually have to discontinue chemotherapy due to toxicity and that these patients should still be considered candidates for treatment with zolbetuximab provided they are continuing to benefit from the therapy and have not demonstrated disease progression.
Considerations for prescribing of therapy	
Switching (clinical preference): If reimbursed by the public drug programs, should patients who are currently receiving treatment with nivolumab plus chemotherapy be eligible to switch to zolbetuximab plus chemotherapy?	pERC agreed with the clinical experts consulted during this review, who noted that patients who are currently receiving treatment with nivolumab plus chemotherapy should be considered eligible to switch to zolbetuximab plus chemotherapy in the first line setting upon confirmation of CLDN 18.2 status.
Switching to zolbetuximab (due to intolerance): If reimbursed by the public drug programs, should patients who have unacceptable toxicity to nivolumab plus chemotherapy be eligible to switch to zolbetuximab plus chemotherapy?	pERC agreed with the clinical experts consulted during this review, who noted that patients who receive treatment with nivolumab plus chemotherapy and experience severe toxicities attributable to nivolumab should be considered eligible to switch to zolbetuximab plus chemotherapy in the first line setting upon confirmation of CLDN 18.2 status provided that there is no disease progression.
Switching to nivolumab (due to intolerance): If reimbursed by the public drug programs, should patients who have unacceptable toxicity to zolbetuximab plus chemotherapy be eligible to switch to nivolumab plus chemotherapy?	pERC agreed with the clinical experts consulted during this review, who noted that patients who receive treatment with zolbetuximab plus chemotherapy and experience severe toxicities attributable to zolbetuximab should be considered eligible to switch to nivolumab plus chemotherapy, or pembrolilzumab plus chemotherapy,in the first line setting

Drug program implementation questions	Committee response
	upon confirmation of CLDN 18.2 status provided that there is no disease progression.
Generalizability	
No issues identified	Not applicable
Funding algorithm (oncology only)	
Provisional funding algorithm: The participating drug programs noted that gastric and GEJ is a complex and evolving therapeutic space with multiple lines of therapy, subpopulations, and emerging therapies. If recommended for reimbursement, the implementation of a recommendation for zolbetuximab may require an updated provisional funding algorithm from CDA-AMC.	For information to inform expert committee, patient groups, and clinician groups.
Care provision issues	
Increased nursing and chair time: The product monograph states that zolbetuximab should be administered over a minimum of 2 hours; whereas the administration of nivolumab and pembrolizumab (2 relevant comparators for this review) occurs over 30 minutes. As such, zolbetuximab would require additional nursing resources and chair time.	For consideration in economic evaluations and feasibility of adoption.
Increased preparation time: Zolbetuximab is available in 100 mg vials and must be reconstituted with 5 mL of diluent. The dose is then drawn up and added to an infusion bag. Nivolumab and pembrolizumab are available as a solution; therefore, zolbetuximab will take more time for health care professionals to prepare. In addition, there will be the requirement to use: • 12 or more vials for the loading dose • 9 or more vials for the 600 mg/m^2 dose • 6 or more vials for the 400 mg/m^2 dose. This also adds significant additional preparation time when compared to nivolumab (3 to 6 vials, depending on dose) and pembrolizumab (2 to 4 vials, depending on dose).	For consideration in economic evaluations and feasibility of adoption.
Shorter stability: Once reconstituted, the vial stability is 5 hours at room temperature. There is no preservative. The final preparation in infusion bag is stable for 6 hours at room temperature or 24 hours in the refrigerator (including time for infusion). If the infusion time exceeds 6 hours from time of preparation, then the infusion bag must be discarded and a new infusion bag prepared.	For consideration in economic evaluations and feasibility of adoption.
System and economic issues	
None identified	Not applicable

CLDN18.2 = CLDN18.2 isoform; ECOG = Eastern Cooperative Oncology Group; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2

Clinical Evidence

Systematic Review

Description of Studies

The systematic review included two multinational, double-masked, placebo-controlled randomized studies of zolbetuximab in combination with fluoropyrimidine and platinum-based chemotherapy compared with placebo in combination with fluoropyrimidine and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma whose tumours are CLDN18.2 positive (SPOTLIGHT [N = 565] and GLOW [N = 507]). In both trials, patients were randomized in a 1:1 ratio to zolbetuximab or placebo groups, with randomization stratified by region (Asia versus non-Asia), number of organs with metastatic sites (0 to 2 versus ≥3), prior gastrectomy (Yes or No). The chemotherapy backbone was mFOLFOX6 in SPOTLIGHT and CAPOX in GLOW.

The primary objective in both SPOTLIGHT and GLOW was to assess the PFS benefit of zolbetuximab plus chemotherapy compared to placebo plus chemotherapy. Key secondary objectives were to evaluate OS and time to confirmed deterioration (TTCD) using European Organization for Research and Treatment of Cancer (EORTC) global health status/quality of life (GHS/QoL), physical functioning (PF), and the oesophago-gastric questionnaire on abdominal pain and discomfort (OG-25). Additional secondary objectives were to evaluate objective response rate (ORR) and duration of response (DOR), safety and tolerability, and additional patient-reported outcomes (PROs).

Efficacy Results

Table 3 summarizes results for the efficacy end points from the SPOTLIGHT and GLOW trials. The data cut-offs used in the report were from the primary analysis of PFS (September 9, 2022, and October 7, 2022, for SPOTLIGHT and GLOW, respectively) and from the final analysis of OS (September 8, 2023, and January 12, 2024, for SPOTLIGHT and GLOW, respectively).

- **OS:** In SPOTLIGHT, the final analysis of OS demonstrated that treatment with zolbetuximab plus mFOLFOX6 demonstrated a statistically significant improvement in OS compared with placebo plus mFOLFOX6 treatment (HR = 0.784; 95% CI, 0.644 to 0.954; P = 0.0075). Median OS was 18.2 months (95% CI, 16.1 to 20.6) in the zolbetuximab plus mFOLFOX6 arm and 15.6 (95% CI, 13.7 to 16.9) in the placebo plus mFOLFOX6 arm. In GLOW, the final analysis of OS demonstrated that treatment with zolbetuximab plus CAPOX was associated with a statistically significant improvement in OS compared with placebo plus CAPOX (HR 0.763; 95% CI, 0.622 to 0.936, P = 0.0047).

- **PFS:** In SPOTLIGHT, treatment with zolbetuximab plus mFOLFOX6 showed a statistically significant improvement in PFS compared with placebo plus mFOLFOX6 (HR = 0.751; 95% CI, 0.598 to 0.942; 1-sided P = 0.0066). The median PFS was 10.61 (95% CI, 8.90 to 12.48) months and 8.67 (95% CI, 8.21 to 10.28) months in the zolbetuximab plus mFOLFOX6 and placebo plus mFOLFOX6 groups, respectively. In GLOW, treatment with zolbetuximab plus CAPOX demonstrated a statistically significant improvement in PFS compared with placebo plus CAPOX (HR = 0.687; 95% CI, 0.544 to 0.866; 1-sided P = 0.0007). The median PFS was 8.21 (95% CI, 7.46 to 8.84) months and 6.80 (95% CI, 6.14 to 8.08) months in the zolbetuximab plus CAPOX and placebo plus CAPOX groups, respectively.

- **ORR:** There was no statistically significant difference between the zolbetuximab plus mFOLFOX6/CAPOX and placebo plus mFOLFOX6/CAPOX groups in both SPOTLIGHT and GLOW. In SPOTLIGHT, the ORR was 47.7% (95% CI, 41.76 to 53.70) in the zolbetuximab plus mFOLFOX6 group and 47.5% (95% CI: 41.56 to 53.52) in the placebo plus mFOLFOX6 group. In GLOW, the ORR per IRC was 42.5% (95% CI, 36.36 to 48.85) in the zolbetuximab plus CAPOX group and 40.3% (95% CI: 34.22, 46.64) in the placebo plus CAPOX group.

- **DCR:** Similar to ORR, there was no statistically significant difference in DCR between the zolbetuximab plus mFOLFOX6/CAPOX and the placebo plus mFOLFOX6/CAPOX groups in both SPOTLIGHT and GLOW.

- **DOR:** There was no statistically significant difference in DOR between the zolbetuximab plus mFOLFOX6/CAPOX and the placebo plus mFOLFOX6/CAPOX groups in either the SPOTLIGHT (HR = 0.876; 95% CI, 0.623 to 1.233; P = 0.2218) or GLOW trials (HR = 0.758; 95% CI, 0.527 to 1.089; P = 0.0673).
- **TTP:** In SPOTLIGHT, the median TTP was 17.81 months in the zolbetuximab plus mFOLFOX6 arm and 12.52 months in the placebo plus mFOLFOX6 arm (P = 0.0133). In GLOW, the median TTP according to IRC was 11.99 (95% CI: 8.84 to 20.80) months in the zolbetuximab plus CAPOX arm and 8.31 (95% CI: 8.11 to 9.95) months in the placebo plus CAPOX arm (P = 0.0002).
- **PFS2:** In SPOTLIGHT, treatment with zolbetuximab plus mFOLFOX6 was associated with reduced risk of a PFS2 event compared with placebo plus mFOLFOX6 treatment (HR = 0.782; 95% CI, 0.637 to 0.961). The median (95% CI) PFS2 was 14.23 (12.12, 16.82) months in the zolbetuximab plus mFOLFOX6 group and 11.99 (95% CI, 11.20 to 13.40) months in the placebo plus mFOLFOX6 group. In GLOW, treatment with zolbetuximab plus CAPOX demonstrated a reduced risk of PFS2 event compared with placebo plus CAPOX treatment (HR = 0.708; 95% CI, 0.575 to 0.871). The median PFS2 was 11.01 (95% CI, 10.02 to 13.11) months in the zolbetuximab plus CAPOX group and 9.03 (95% CI, 8.28 to 9.89) months in the placebo plus CAPOX group.

Harms Results

In the pooled analysis of safety from the SPOTLIGHT and GLOW trials, the AEs that were reported for at least 20% of patients in either group included (zolbetuximab versus placebo, respectively): nausea (75.8% versus 55.8%), vomiting (66.8% versus 33.4%), decreased appetite (44.3% versus 33.6%), anemia (35.6% versus 37.0%), diarrhea (35.6% versus 39.5%), neutrophil count decreased (31.0% versus 28.5%), peripheral sensory neuropathy (30.4% versus 33.0%), neutropenia (28.5% versus 24.5%), constipation (25.9% versus 31.1%), fatigue (21.0% versus 25.2%), aspartate aminotransferase (AST) increased (21.0% versus 22.0%), abdominal pain (20.1% versus 25.8%), asthenia (20.1% versus 18.2%) and platelet count decreased (18.9% versus 20.7%). SAEs were reported in 245 (46.0%) patients in the combined zolbetuximab group and 245 (46.5%) patients in the combined placebo group. SAEs reported in at least 4% of patients in either group included (zolbetuximab versus placebo, respectively): vomiting (7.1% versus 4.6%), nausea (5.6% versus 3.2%) and malignant neoplasm progression (3.6% versus 4.7%). AEs leading to permanent discontinuation of zolbetuximab or placebo were reported in 106 (19.9%) patients and 66 (12.5%) patients, respectively. The most frequent AEs leading to permanent discontinuation of zolbetuximab or placebo (present in ≥2% of patients in either combined group) were vomiting (3.8% versus 0.6%) and nausea (3.4% versus 0.4%), respectively.

Critical Appraisal

Baseline and demographic characteristics were generally well balanced across the zolbetuximab and placebo groups in both SPOTLIGHT and GLOW. The clinical experts consulted during this review had no concerns regarding the baseline characteristics of the SPOTLIGHT and GLOW trial populations. Both SPOTLIGHT and GLOW were double-masked clinical trials. Patients who received zolbetuximab more commonly reported AEs of nausea and vomiting as well as infusion site reactions. The clinical experts consulted during this review noted that the AE profile in the trial could potentially allow some patients and investigators to infer the allocated treatment group. The objective endpoints (e.g., PFS, OS, and ORR) would not be subject to bias in the event treatment groups could be inferred as a result of AEs; however, the HRQoL that require subjective reporting could potentially be biased. The primary and secondary endpoints of the SPOTLIGHT and GLOW trials were aligned with those recommended by regulatory authorities for gastric cancer trials in the metastatic setting. The clinical experts consulted by CDA-AMC noted that PFS is not a particularly useful endpoint in the context of metastatic disease where survival is typically limited to one year. However, the inclusion of final analyses showing an improvement in overall survival were considered demonstrative of a clinically meaningful benefit in comparison with chemotherapy alone.

The clinical experts consulted during this review noted that the baseline and demographic characteristics for the SPOTLIGHT and GLOW trials are a reasonable reflection of the target patient population in Canada. There are no other drugs specifically indicated for use in the treatment of patients with CLDN18.2 G/GEJ in Canada; therefore, the choice of placebo plus mFOLFOX6/CAPOX was considered to be appropriate by regulatory authorities. However, the clinical experts consulted during this review noted that the comparator used in SPOTLIGHT and GLOW (i.e., placebo plus mFOLFOX6 or CAPOX) is not reflective of routine practice in

Canada where patients would typically be offered nivolumab plus chemotherapy as the preferred treatment option. The SPOTLIGHT and GLOW trials initiated in 2018, which predated the regulatory approval of nivolumab plus chemotherapy for gastric and GEJ cancer (e.g., approved in Canada in October 2021); however, nivolumab plus chemotherapy remains the most relevant comparator for the current review. In the absence of a direct comparison against nivolumab plus chemotherapy, the sponsor has provided an indirect comparison which was reviewed by CDA-AMC. In October 2024, pembrolizumab received a recommendation in favour of reimbursement from pERC for use in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma.

SPOTLIGHT and GLOW involved the following zolbetuximab dosage regimen (single loading dose of 800 mg/m2 IV; followed by 600 mg/m2 IV Q3W maintenance dosing). This is likely reflective of how zolbetuximab would be used in Canadian practice for patients receiving it combination with CAPOX (which is administered Q3W), but not when administered in combination with mFOLFOX6 (which is administered Q2W). As such, the product monograph recommends the following regimen when zolbetuximab is used in combination with mFOLFOX6 (800 mg/m^2 loading dose followed by 400 mg/m^2 every 2 weeks). This was based on population pharmacokinetic modelling that predicted the 400 mg/m2 Q2W maintenance dosage would have similar exposure to the 600 mg/m2 Q3W regimen.

Zolbetuximab is the first drug to specifically target CLDN18.2. Routine screening for CLDN18.2 is not currently performed in Canada for patients with G/GEJ (or any other cancer). The SPOTLIGHT and GLOW trials enrolled patients who had CLDN18.2-positive tumours defined as at least 75% of tumour cells demonstrating moderate to strong membranous CLDN18 staining based on central IHC assessment using the companion diagnostic test (i.e., the CLDN18 RxDx Assay). The clinical experts consulted during this review supported the use of a 75% threshold for concluding that a patient harbours CLDN18.2-positive tumours. The experts further noted that they would not anticipate any challenges with interpreting the results of the CLDN18 RxDx Assay (e.g., diagnosis would likely be consistent across different centers in Canada).

GRADE Summary of Findings and Certainty of the Evidence

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:

Table 3: Summary of Findings for Zolbetuximab Versus Placebo for Patients

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	What happens
		Placebo + Chemotherapy	Zolbetuximab + Chemotherapy	Difference		
Overall Survival (SPOTLIGHT; mFOLFOX6 chemotherapy)						
Probability of survival at 12 months **Median follow-up (months):** Zolbetuximab: 33.28 Placebo: 31.38	1 RCT (N = 565)	60.65 per 100 (54.57 to 66.19 per 100)	67.36 per 100 (61.36 to 72.64 per 100)	6.71 more per 100 ([redacted])	Moderate[a]	The addition of zolbetuximab to chemotherapy likely results in a clinically important increase in OS when compared to placebo plus chemotherapy at 12 months.
Probability of survival at 36 months **Median follow-up (months):** Zolbetuximab: 33.28 Placebo: 31.38	1 RCT (N = 565)	13.72 per 100 (9.12 to 19.26 per 100)	20.92 per 100 (15.53, 26.87 per 100)	7.20 more per 100 ([redacted])	Moderate[a]	The addition of zolbetuximab to chemotherapy likely results in a clinically important increase in OS when compared to placebo plus chemotherapy at 12 months.
Overall Survival (GLOW; CAPOX chemotherapy)						
Probability of survival at 12 months **Median follow-up (months):** Zolbetuximab: 31.70 Placebo: 32.95	1 RCT (N = 507)	50.44 per 100 (43.89 to 56.61 per 100)	56.68 per 100 (50.08 to 62.75 per 100)	6.24 more per 100 ([redacted])	Moderate[a]	The addition of zolbetuximab to chemotherapy likely results in a clinically important increase in OS when compared to placebo plus chemotherapy at 12 months.
Probability of survival at 36 months **Median follow-up (months):** Zolbetuximab: 31.70 Placebo: 32.95	1 RCT (N = 507)	7.88 per 100 (4.41 to 12.63 per 100)	18.30 per 100 (12.95 to 24.39 per 100)	10.42 more per 100 ([redacted])	Moderate[a]	The addition of zolbetuximab to chemotherapy likely results in a clinically important increase in OS when compared to placebo plus chemotherapy at 12 months.
Progression-Free Survival per RECIST v1.1 by IRC (SPOTLIGHT; mFOLFOX6 chemotherapy)						
Probability of PFS at 6 months **Median follow-up (months):** Zolbetuximab: 12.94 Placebo: 12.65	1 RCT (N = 565)	71.95 per 100 (66.03 to 77.03 per 100)	78.05 per 100 (72.43 to 82.67 per 100)	6.1 more per 100 ([redacted])	Moderate[a]	The addition of zolbetuximab to chemotherapy likely results in an increase in PFS when compared to placebo plus chemotherapy at 6 months. The clinical importance of the increase is unclear.
Probability of PFS at 12 months **Median follow-up (months):** Zolbetuximab: 12.94 Placebo: 12.65	1 RCT (N = 565)	35.04 per 100 (28.45 to 41.69 per 100)	48.86 per 100 (41.92 to 55.43 per 100)	13.8 more per 100 ([redacted])	High	The addition of zolbetuximab to chemotherapy results in an increase in PFS when compared to placebo plus chemotherapy at 12 months. The clinical importance of the increase is unclear.
Probability of PFS at 30 months **Median follow-up (months):** Zolbetuximab: 12.94 Placebo: 12.65	1 RCT (N = 565)	13.01 per 100 (7.07 to 20.82 per 100)	24.41 per 100 (17.36 to 32.13 per 100)	11.4 more per 100 ([redacted])	High	The addition of zolbetuximab to chemotherapy results in an increase in PFS when compared to placebo plus chemotherapy at 30 months. The clinical importance of the increase is unclear.
Progression-Free Survival per RECIST v1.1 by IRC (GLOW; CAPOX chemotherapy)						
Probability of PFS at 6 months **Median follow-up (months):**	1 RCT (N = 507)	61.47 per 100 (54.82 to 67.45 per 100)	70.20 per 100 (63.42 to 75.96 per 100)	8.7 more per 100 ([redacted])	Moderate[b]	The addition of zolbetuximab to chemotherapy results in an increase in PFS when compared to

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	What happens
		Placebo + Chemotherapy	Zolbetuximab + Chemotherapy	Difference		
Zolbetuximab: 12.62 Placebo: 12.09						placebo plus chemotherapy at 6 months. The clinical importance of the increase is unclear.
Probability of PFS at 12 months **Median follow-up (months):** Zolbetuximab: 12.62 Placebo: 12.09	1 RCT (N = 507)	19.13 per 100 (13.50 to 25.51 per 100)	34.86 per 100 (27.75 to 42.05 per 100)	15.7 more per 100 ([redacted])	High[c]	The addition of zolbetuximab to chemotherapy results in an increase in PFS when compared to placebo plus chemotherapy at 12 months. The clinical importance of the increase is unclear.
Probability of PFS 30 months **Median follow-up (months):** Zolbetuximab: 12.62 Placebo: 12.09	1 RCT (N = 507)	7.28 per 100 (2.99 to 14.16 per 100)	Not reached	NE	NA	The addition of zolbetuximab to chemotherapy results in an increase in PFS when compared to placebo plus chemotherapy at 30 months. The clinical importance of the increase is unclear.
Time to first confirmed deterioration in health-related quality of life scales (SPOTLIGHT; mFOLFOX6 chemotherapy)						
Time to deterioration of 13 points in the Physical Functioning scale	1 RCT (N = 565)	Median time to event: 12.32 months	Median time to event: 10.71 months	Absolute differences not reported by sponsor	Cannot evaluate[d]	Based on relative estimates of effect, the evidence is uncertain about the effect of zolbetuximab added to chemotherapy on time to first confirmed deterioration based on the physical functioning, OG25-Pain scale, or GHS/QoL scale.
Time to deterioration of 16.7 in the OG25-Pain scale	1 RCT (N = 565)	Median time to event: 8.48 months	Median time to event: 6.83 months			
Time to deterioration of 13 points in GHS/QoL scale	1 RCT (N = 565)	Median time to event: 11.83 months	Median time to event: 15.44 months			
Time to first confirmed deterioration in health-related quality of life scales Health-related quality of life (GLOW; CAPOX chemotherapy)						
Time to deterioration of 13 points in the Physical Functioning scale	1 RCT (N = 507)	Median time to event: 7.92 months	Median time to event: 8.31 months	Absolute differences not reported by sponsor	Cannot evaluate[d]	Based on relative estimates of effect, the evidence is uncertain about the effect of zolbetuximab added to chemotherapy on time to first confirmed deterioration based on the physical functioning, OG25-Pain scale, or GHS/QoL scale.
Time to deterioration of 16.7 in the OG25-Pain scale	1 RCT (N = 507)	Median time to event: 12.94 months	Median time to event: 19.81 months			
Time to deterioration of 13 points in GHS/QoL scale	1 RCT (N = 507)	Median time to event: 7.49 months	Median time to event: 9.69 months			
Harms						
Nausea	2 RCTs (N = 1060)	55.8 per 100	75.8 per 100	NR	High	The addition of zolbetuximab to chemotherapy results in an increased risk of nausea, vomiting, and IRR when compared to placebo plus chemotherapy. The clinical experts consulted during this review noted that these events are manageable in clinical practice.
Vomiting	2 RCTs (N = 1060)	33.4 per 100	66.8 per 100	NR	High	
IRR	2 RCTs (N = 1060)	11.0 per 100	40.3 per 100	NR	High	

[a] Rated down 1 level for serious imprecision. Although the point estimate suggests a clinically important benefit (exceeding the 5 to 10% threshold suggested by the clinical experts consulted on this review), the lower bound of the 95% CI is compatible with little to no difference in clinical benefit.

[b] Rated down 1 level for serious imprecision as the lower bounds of the 95% CI were compatible with little to no difference in clinical benefit.

[c] The clinical experts consulted on this review indicated a lack of clarity about a threshold of clinical importance therefore the null was used. Although the certainty of evidence was not rated down or serious indirectness, there were concerns about the clinical importance of PFS.

[d] Certainty of evidence cannot be evaluated, as the sponsor did not report the absolute difference between groups and was not able provide this information upon request. In the absence of a reported absolute difference, CDA-AMC was unable to determine an appropriate target of the certainty assessment under the GRADE framework since the reported relative effects for these endpoints were not considered suitable for inferring whether a clinically meaningful difference was observed for these endpoints. Likewise, the ability to assess the imprecision of any target of the certainty assessment would have been limited if it were based on relative effect estimates alone. Although the certainty for these endpoints cannot be assessed, the results for these endpoints were noted to have a potential risk of bias as the sponsor reported that the results of the analyses are immature to derive thresholds for clinically meaningful deterioration.

Long-Term Extension Studies

Not applicable.

Indirect Comparisons

In the absence of direct head-to-head trials evaluating the comparative efficacy of zolbetuximab versus relevant comparators for first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN 18.2 positive, a review of indirect evidence was undertaken and submitted by the sponsor.[64] The objective of this section is to summarize and critically appraise the sponsor-submitted ITC, and to inform the pharmacoeconomic model.

Description of Studies

In the sponsor conducted systematic review, [redacted] publications reporting on [redacted] studies were included. After applying the NMA inclusion and exclusion criteria, [redacted] RCTs, including GLOW and SPOTLIGHT, were deemed relevant for the sponsor's NMA, including 14 unique treatment regimens. After removal of one study that did not include subgroup analysis based on CPS score, [redacted] studies were included in the analysis. The sponsor reported that the inclusion and exclusion criteria, including disease stage, age, and performance status, were generally consistent across trials. The sample size across trials ranged from [redacted] patients to [redacted] patients, and the median follow-up ranged from [redacted] months. Half of the included trials were only conducted in Asian countries and the dosing schedule of the majority of treatment regimens appears to be consistent across studies with some variation for fluorouracil-based regimens and S-1 based regimens. OS and PFS were analyzed in the NMA, and the definitions were reported as mainly consistent across the trials.

Efficacy Results

The NMA was constructed using a fixed effects model and the sponsor reports that the trace and density plots, the Gelman-Rubin plots, and the Gelman-Rubin diagnostics showed that convergence of the results was generally achieved. For OS, results from the NMA are consistent with results of the pivotal evidence, where zolbetuximab combined with CAPOX is superior to CAPOX alone [redacted], and zolbetuximab combined with FOLFOX is superior to FOLFOX alone ([redacted]). The HR for cross-comparisons with CAPOX and FOLFOX are also consistent, however the wide CrIs may indicate heterogeneity between studies that used CAPOX vs FOLFOX. CrIs for the comparisons between zolbetuximab plus chemotherapy versus nivolumab or pembrolizumab plus chemotherapy did not favour either comparator in OS, however the HR was consistently higher with zolbetuximab plus FOLFOX compared to zolbetuximab plus CAPOX. For PFS, results are again consistent with results of the pivotal evidence, where zolbetuximab combined with CAPOX is superior to CAPOX alone ([redacted], and zolbetuximab combined with FOLFOX is superior to FOLFOX alone ([redacted]). The HR for cross-comparisons with CAPOX and FOLFOX are also consistent, however the wide CrIs may indicate heterogeneity between studies that used CAPOX vs FOLFOX. CrIs for the comparisons between zolbetuximab plus chemotherapy versus nivolumab or pembrolizumab plus chemotherapy did not favour either comparator in OS, however the HR was consistently higher with zolbetuximab plus FOLFOX compared to zolbetuximab plus CAPOX

Harms Results

Harms outcomes were not evaluated in the NMA.

Critical Appraisal

The sponsor submitted NMA was based on studies identified from a systematic literature review of relevant evidence, based on a PICO defined a priori. While the risk of bias of the comparator trials was assessed, it was not reported how many reviewers conducted the quality assessment and the risk of bias was not assessed per outcome. The sponsor conducted two primary analyses: with CAPOX and FOLFOX as separate comparators and then with the two regimens combined as a single comparator. This was based on the sponsor's assumption that CAPOX and FOLFOX were of equivalent efficacy, an assumption that was also supported by the clinical experts consulted for this review. The results of the primary NMA analysis that keeps the comparators separate, however, do not support combining these comparators as there are wide CrIs in the cross-comparisons between both treatments, indicating systematic heterogeneity between studies that used CAPOX versus those that used FOLFOX. Therefore, the results of both analyses must be interpreted with caution.

The clinical experts consulted during this review have noted that proactive screening for gastrointestinal cancers is more common in some Asian countries and that this tends to contribute to more favourable outcomes for some patients. Thus, this heterogeneity in the trial populations across the network likely introduced bias in the comparisons across the network. The sponsors conducted sensitivity analyses excluding the Asia-only trials or focusing on Asia-only trials/Asian subgroup of global trials, and findings were similar to those of the primary NMA analysis, however this sensitivity analysis was only conducted in the second primary analysis with CAPOX/FOLFOX combined and in which we have noted greater heterogeneity across studies.

The sponsor reports that differences in median follow-up (and therefore data maturity) could introduce bias as HRs tend to wane with longer follow-up time yet they were unable to account for differences in data maturity in their analysis. With regards to patient baseline characteristics, the sponsor noted variations across trial in the median age, performance status, tumour location and tumour type, disease stage and number of metastatic sites, mutation status, and prior surgery, however they noted that they did not adjust for these variations in their analysis. Specifically for the tumour location, the clinical experts noted that trial data does not show benefits for patients with GEJ tumours, so heterogeneity across the network in tumour location could be an important source of bias for these NMAs.

There were variations in the collecting and reporting of mutation status across trials, therefore the sponsor did not adjust for HER2 or CLDN 18.2 expression status. The clinical experts that were consulted for this review have noted that, while zolbetuximab + chemotherapy could be a preferred option for patients with CLDN 18.2 positive tumours and PD-L1 CPS less than 5, it is unclear which option would be best for patients with both CLDN 18.2 positive tumours and a PD-L1 CPS ≥ 5. In this NMA, the sponsors conducted 2 subgroup analyses with CPS ≥ 5 and CPS <5 in the 5 trials that reported CPS scores, however these analyses only used CPS-specific HRs from the nivolumab and pembrolizumab trials and did not utilize the subgroup-specific data from SPOTLIGHT and GLOW. The clinical review team considered this approach to be at risk for severe bias due to the existing evidence that has established CPS testing as a potential effect modifier in this disease area. Therefore, this subgroup analysis has significant limitations, and no definitive conclusions could be drawn for this subpopulation of patients.

NMA results were presented only for OS and PFS; harms outcomes and other outcomes of relevance to patients (e.g., HRQoL) were not reported. Treatment effects measured by HRs of OS or PFS assumed proportional hazards, which were held in 3 trials but not reported in most included studies. The consistency test performed in the primary analysis using CAPOX and FOLFOX as combined suggested evidence of inconsistency in the PFS network.

Studies Addressing Gaps in the Evidence from the Systematic Review

Not applicable.

Testing Procedure Considerations

In locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma, the CLDN18.2 isoform may become exposed and detectable in 38% of patients. To be eligible for treatment with zolbetuximab, confirmation of CLDN18.2 positivity could be carried out at the time of metastatic diagnosis. The clinical experts consulted by the review team agreed that the optimal time for testing could be at the time of metastatic diagnosis, when HER2 status is also determined by IHC testing.

Key considerations and relevant information available from materials submitted by the sponsor, input from the clinical experts, and sources from the literature were validated by the review team when possible and are summarized in Table 4.

Table 4: Considerations for IHC Testing for CLDN18.2 Status to Establish Treatment Eligibility for Zolbetuximab in Adult Patients With Locally Advanced Unresectable or Metastatic HER2-Negative Gastric or GEJ Adenocarcinoma

Consideration	Criterion	Available Information
Health System	Number of individuals in Canada expected to require the test (e.g., per year)	The adult population eligible for CLDN18.2 testing was estimated to be 3,645 per year. The sponsor estimated that testing uptake would reach a maximum of 85.4% of eligible adult patients in the first 3 years following implementation, meaning that not all those eligible for testing would receive it. Of note, the clinical experts indicated that the availability of zolbetuximab may also increase use of CPS testing to inform treatment decisions between zolbetuximab and a PD-1 inhibitor.
	Availability and reimbursement status of the testing procedure in jurisdictions across Canada	IHC testing for HER2 status is currently part of the standard of care for gastric and GEJ adenocarcinoma, and therefore IHC testing is widely available across Canadian jurisdictions. However, IHC testing for CLDN18.2 status is not currently a funded test across the provincial and territorial health systems in Canada. The sponsor has proposed needs assessment activities and ongoing educational initiatives to support the implementation of IHC testing across Canada for CLDN18.2 status in gastric and GEJ adenocarcinoma to establish eligibility for treatment with zolbetuximab.
	Testing procedure as part of routine care	The CLDN18.2 testing procedure is not currently performed as part of routine care for locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma.
	Repeat testing requirements	The clinical experts indicated that the optimal time for CLDN18.2 testing could be at the time of metastatic diagnosis, when testing for HER2 status is performed, and because it is currently understood that CLDN18.2 status is likely to remain stable across time, repeat testing is not expected.
	Impact on human and other health care resources by provision of the testing procedure	The clinical experts indicated that implementation of IHC testing for CLDN18.2 status is unlikely to have substantial health system impact; however, some impacts may be expected, such as increased workload for pathologists, lab technicians, bioinformaticians, and oncologists. There is unlikely to be a substantial impact on currently available testing infrastructure because IHC testing is currently part of routine care, although new assays will need to be selected or developed to support testing for CLDN18.2 status.
Patient-oriented	Accessibility of the testing procedure in jurisdictions across Canada	There may be some inconsistencies in access to testing for CLDN18.2 status during the initial phases of implementation; however, because IHC testing is currently part of routine care for gastric and GEJ adenocarcinoma, most patients are expected to have access within the first few years following implementation.
	Expected turnaround times for the testing procedure	IHC testing for CLDN18.2 status is expected to be feasible using previously collected tissue samples in most cases. The clinical experts indicated that the turnaround times for IHC testing in gastric and GEJ adenocarcinoma may be delayed by the introduction of CLDN18.2 testing, but that these delays would be expected to be minimal and time-limited.

Consideration	Criterion	Available Information
	Burden associated with the testing procedure for patients, families, and/or caregivers	The clinical experts consulted for the review indicated it is unlikely that any additional procedure(s) or tissue collection would be necessary to process the test for CLDN 18.2 status and would not impose additional burden for patients and/or families if zolbetuximab were to be approved for funding.
Clinical	Clinical utility of the testing procedure	Studies have demonstrated the clinical utility of CLDN18.2 testing in locally advance unresectable or metastatic gastric and GEJ adenocarcinoma by generating a clinically meaningful benefit of the CLDN18.2-targeted therapy, zolbetuximab, as compared to chemotherapy alone. Of note, if zolbetuximab were to be approved for funding, there may be impacts on clinical decision-making regarding optimal therapy between zolbetuximab and a PD-L1 inhibitor for patients with CLDN 18.2 positive tumours who have a CPS greater than or equal to 5.
	Risks of harm associated with the testing procedure	Because testing for CLDN18.2 can be done using tissue samples that are currently collected as part of routine care, as well as using previously collected samples in most cases, there is no additional risk of harm associated with the testing as part of establishing treatment eligibility.
Cost	Projected cost of the testing procedure	The unit cost of IHC testing for CLDN18.2 was estimated at $100; however, the clinical experts indicated that this estimate may be low. The estimated cost of identifying 1 patient with CLDN18.2 positivity eligible for treatment with zolbetuximab was $260.63, based on the estimated number needed to test of 3. Notably, any variability in the unit cost per test would accordingly impact the estimated cost.

CLDN18.2 = Claudin 18.2; CPS = combined positive score; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry

Economic Evidence

Cost and Cost-Effectiveness

Table 5: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Patients with locally advanced unresectable or metastatic HER2-negative CLDN18.2-positive G/GEJ adenocarcinoma.
Treatment	Zolbetuximab plus mFOLFOX6[a]
Dose regimen	• Zolbetuximab: 800 mg/m^2 on day 1 of cycle 1 followed by 600 mg/m^2 every 3 weeks or 400 mg/m^2 every 2 weeks IV until disease progression or unacceptable toxicity. • mFOLFOX6: 85 mg/m^2 of oxaliplatin every 2 weeks (up to 24 weeks), 400 mg/m^2 of folinic acid every 2 weeks, 400 mg/m^2 of 5-fluorouracil (bolus) every 2 weeks, and 2,400 mg/m^2 of 5-fluorouracil (infuser) every 2 weeks.
Submitted price	Zolbetuximab: $638.00 per 100 mg vial
Submitted treatment cost	Assuming a maintenance dose of 600 mg/m^2 every 3 weeks for zolbetuximab, the sponsor estimated drug acquisition costs per 21-day cycle for zolbetuximab plus mFOLFOX6 as $10,091 in cycle 1, $7,887 in cycles 2 to 8, and $7,724 thereafter (first year: $142,250, subsequent years: $131,542).
Comparators	• mFOLFOX6[a] • Nivolumab plus mFOLFOX6[a]

Component	Description
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (17 years)
Key data sources	• Efficacy inputs for zolbetuximab plus mFOLFOX6 and nivolumab plus mFOLFOX6 were informed by a sponsor-submitted unpublished NMA. In the NMA, efficacy for zolbetuximab plus mFOLFOX6 was informed by SPOTLIGHT (final data cut, 8 September 2023), a global, phase 3, randomized, and double-blinded clinical trial; efficacy for nivolumab plus mFOLFOX6 was informed by CHECKMATE 649 (data cut off: May 27, 2020) trials • Efficacy for mFOLFOX6 was informed by SPOTLIGHT (final data cut, September 8, 2023)
Key limitations	• The comparative efficacy of zolbetuximab plus mFOLFOX6 relative to nivolumab plus mFOLFOX6 is uncertain owing to a lack of head-to-head trials and limitations with the sponsor's NMA. Indirect evidence submitted by the sponsor suggests that the comparisons between zolbetuximab plus mFOLFOX6 versus nivolumab plus mFOLFOX6 results in little-to-no difference in OS or PFS. However, there are sources of clinical and methodological heterogeneity across trials in the NMA that may bias the effect estimates, but the magnitude and direction of potential bias cannot be predicted. • The sponsor assumed that the treatment effect of zolbetuximab plus mFOLFOX6 is maintained, regardless of time on treatment. There is no robust evidence for persistence of effect, and clinical expert input noted that treatment efficacy typically declines over time for targeted therapies such as zolbetuximab. Clinical expert input suggested that the treatment effect of zolbetuximab plus mFOLFOX6 is likely to be reduced in relation to mFOLFOX6 after 3 to 5 years of treatment. • The sponsor assumed nivolumab was administered at a fixed dose of 240 mg Q2W. CCO lists the recommended dose as 3 mg/kg, up to a maximum of 240 mg Q2W. As a result, drug acquisition costs for nivolumab were likely overestimated. • The sponsor assumed zolbetuximab would be administered every 3 weeks (600 mg/m^2) as opposed to every 2 weeks (400 mg/m^2). Clinical expert input noted that zolbetuximab will likely be administered every 2 weeks, aligned with the treatment schedule for mFOLFOX6 to reduce the hospital visit burden for the patients. Furthermore, the sponsor did not consider all relevant administration costs (i.e., nursing resources, pharmacist resources, and chair time). Zolbetuximab is more resource intensive compared to nivolumab in terms of treatment preparation and administration. As a result, drug acquisition and administration costs for zolbetuximab were underestimated. • The derived utility values from the SPOTLIGHT trial signaled there was little difference in terms of QoL between those who have not yet progressed on treatment and those who have progressed disease which did not align with clinical expert expectations. Clinical experts found the utility values from the CHECKMATE 649 trial to be more reflective of QoL for the indicated population.
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by adopting: a weight-based dose for nivolumab; an every 2 week maintenance dosing schedule for zolbetuximab; utility values from the CHECKMATE 649 trial; full parametric survival analysis curves for OS, PFS, and DOT; and, assuming the treatment effect of zolbetuximab plus mFOLFOX6 reduces in relation to mFOLFOX6 after 5 years of treatment. Additionally, CDA-AMC corrected the drug unit price for oxaliplatin and assumptions of drug wastage for folic acid and fluorouracil. • In the CDA-AMC base case, in sequential analysis, zolbetuximab plus mFOLFOX6 was associated with an ICER of $1,611,078 per QALY gained compared to nivolumab plus mFOLFOX6 (incremental costs = $56,474; incremental QALYs = 0.035). The results were sensitive to assumptions concerning treatment waning. • There is insufficient clinical evidence to suggest that zolbetuximab should be priced higher than currently available immunotherapies for adult patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma. To ensure cost-effectiveness, zolbetuximab should be priced no more than the lowest cost immunotherapy that is funded for the first-line therapy of adult patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma.

CLDN18.2 = Claudin18.2; CCO = Cancer Care Ontario; DOT = duration of therapy; mFOLFOX6 = folinic acid, 5-fluorouracil, and oxaliplatin; G/GEJ = gastric or gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; ICER = incremental cost-effectiveness ratio; IV = intravenous; LY = life-year; NMA =

network meta-analysis; OS = overall survival; PCPA = pan-Canadian Pharmaceutical Alliance; PERC = pCODR Expert Review Committee; PFS = progression-free survival; PD-1L = programmed death-ligand 1; Q2W = every 2 weeks; Q3W = every 3 weeks; QALY = quality-adjusted life-year; QoL = quality of life; WTP = willingness-to-pay.

[a] The sponsor also considered analyses using costs associated with CAPOX. The ITC included clinical evidence for different backbone treatment individually and combined. For the purposes of the economic evaluation, the sponsor considered mFOLFOX6 to be equivalent to CAPOX in terms of efficacy.

[b] All modelled treatments (i.e., mFOLFOX6, nivolumab plus mFOLFOX6, zolbetuximab plus mFOLFOX6) were on the cost-effectiveness frontier.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the drug acquisition and administration costs are uncertain, the number of eligible patients is uncertain, the market shares are uncertain, and the market uptake of zolbetuximab is uncertain.

The CDA-AMC BIA base case was derived by adopting a weight-based dose for nivolumab and correcting the drug unit price for oxaliplatin and assumptions of drug wastage for folic acid and fluorouracil. The CDA-AMC BIA base case suggests the 3-year budget impact of reimbursing zolbetuximab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative, CLDN18.2-positive G/GEJ adenocarcinoma to be $6,410,018 (Year 1: $597,683; Year 2: $2,554,931; Year 3: $3,257,404), which is higher than the sponsor's estimated budget impact. Including CLDN 18.2 testing costs, the total 3-year budget impact of reimbursing zolbetuximab is estimated to be $6,715,459.

CDA-AMC was unable to address the key issues with the sponsor's approach to incorporating drug costs and testing costs, but notes that the budget impact of zolbetuximab is underestimated in both the sponsor's and CDA-AMC's estimates.

pERC Information

Members of the Committee:

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villneuve, and Danica Wasney.

Meeting date: December 4, 2024

Regrets:

One expert committee member did not attend.

Conflicts of interest:

None