CDA-AMC Reimbursement Review

Rapid Provisional Funding Algorithm

Indication: Advanced or metastatic gastric, gastroesophageal junction, or esophageal cancer

This report supersedes the Provisional Funding Algorithm report for advanced or metastatic gastric, gastroesophageal junction, or esophageal cancer dated December 3, 2024.

Please always check Provisional Funding Algorithms to ensure you are reading the most recent algorithm report.

Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.

Background

Following a request from jurisdictions, CDA-AMC will design or update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed "provisional." Publishing of provisional algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions. Please refer to Provisional Funding Algorithm Procedures.

Provisional funding algorithms delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Further, provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CDA-AMC following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions. Note that as per process, implementation advice from panelists and the resulting algorithms cannot contradict prior expert committee (e.g. pERC or FMEC) recommendations or expand target populations beyond what was recommended.

Jurisdictional cancer drug programs requested a rapid provisional funding algorithm on Advanced or metastatic gastric, gastroesophageal junction, or esophageal cancer.

History and Development of the Provisional Funding Algorithm

CDA-AMC developed the first provisional funding algorithm in June 2022 for HER2-negative advanced or metastatic gastric, gastroesophageal junction or esophageal cancer, incorporating recommendations for the following implementation issues:

- Immunotherapy in the advanced or metastatic setting for patients with disease of unknown HER2 status
- Selection of immunotherapy in the advanced or metastatic setting based on disease site and histology
- Sequencing of therapies in second and subsequent lines following first-line immunotherapy in the advanced or metastatic setting

Note that CDA-AMC also published an updated rapid algorithm report in December 2024 to incorporate the following recommendations:

- Pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumours express PD-L1 (combined positive score [CPS] ≥ 1) as determined by a validated test.

- Pembrolizumab 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.

For this rapid algorithm, the purpose is to incorporate the latest pERC recommendations for:

- zolbetuximab 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 gastroesophageal junction adenocarcinoma whose tumours are Claudin 18.2 positive.
- Trastuzumab deruxtecan as monotherapy for the treatment of adult patients with unresectable, locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have receive a prior trastuzumab-based regimen

Table 1: Relevant CDA-AMC Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Trastuzumab deruxtecan (Enhertu)	April 23, 2025 (PC0367-000)	pERC recommends that trastuzumab deruxtecan be reimbursed as monotherapy, for the second-line treatment of adult patients with unresectable, locally advanced, or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior anti–HER2-based regimen for a time-limited period while additional evidence is generated and only if the following conditions are met: **Initiation** 1. Trastuzumab deruxtecan should be initiated as second-line treatment for patients who have all of the following: 1.1. 18 years of age or older 1.2. unresectable, locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma 1.3. received a prior trastuzumab-based regimen in the first-line treatment setting 1.4. good performance status. 2. Patients must not have any of the following: 2.1. symptomatic spinal cord compression 2.2. clinically active CNS metastases 2.3. current ILD or pneumonitis. **Discontinuation** 3. Treatment with trastuzumab deruxtecan should be discontinued upon the occurrence of any of the following: 3.1. objective disease progression 3.2. unacceptable toxicity. **Prescribing** 4. Trastuzumab deruxtecan should only be prescribed by clinicians with experience and expertise in treating gastric or GEJ adenocarcinoma. 5. Trastuzumab deruxtecan should not be reimbursed in combination with other anticancer drugs. **Pricing** 6. A reduction in price. **Time-limited reimbursement**

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		7. A recommendation in favour of reimbursement is time-limited and contingent on a future reassessment of additional evidence that addresses the uncertainty. **Guidance on treatment sequencing (Adapted from Table 2: Responses to Questions from the Drug Programs)** **<u>Considerations for Initiation of therapy</u>** • **Question: Should trastuzumab deruxtecan be considered for third or subsequent lines?** According to the clinical experts consulted by the review team, if reimbursed, trastuzumab deruxtecan is expected to become the standard of care in the second-line setting for patients with HER2-positive gastric and GEJ cancer, and trastuzumab deruxtecan will not be rechallenged in the third line and later settings when there is disease progression. However, the clinical experts consulted by the review team noted that for a small number of patients who are using currently available second line or later lines of therapy and have never received trastuzumab deruxtecan between the present and the time when trastuzumab deruxtecan becomes available in the second-line setting, trastuzumab deruxtecan can be used for these patients in third line and later settings. Patients who have experienced unsuccessful treatment using trastuzumab deruxtecan in previous lines of therapy should not be rechallenged. pERC agreed with the clinical experts. • **Question: Should trastuzumab deruxtecan be considered for patients with advanced HER2-positive esophageal adenocarcinoma who have received prior anti-HER2 targeted therapy?** pERC agreed with the clinical experts consulted by the review team that any patient with esophageal, gastric, or GEJ adenocarcinoma whose tumour is HER2-positive should be eligible for trastuzumab deruxtecan if they otherwise meet the eligibility criteria outlined in this recommendation. The clinical experts noted that the classification of "esophageal" versus "GEJ" is somewhat arbitrary, and that there is no preclinical or clinical rationale to suggest that the biology of HER2-positive disease or the response to HER2-directed therapies differ based on whether the disease is in the esophagus proper or the GEJ. According to the clinical experts consulted by the review team, an estimated 20% of all esophageal cancers (based on clinical experience in Ontario) would consist of adenocarcinomas. The clinical experts additionally noted that the distribution of adenocarcinoma versus squamous cell carcinoma may differ between patient populations with different risk factors (e.g., patients with smoking and/or alcohol exposure are more likely to present with squamous cell carcinoma histology; patients with obesity, reflux, or metabolic syndrome are more likely to present with adenocarcinoma histology).

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		<u>Generalizability</u> **Question: Are the following patients eligible for trastuzumab deruxtecan?** • **ECOG PS > 1** • **Prior treatment with trastuzumab deruxtecan (e.g., for breast cancer)** ECOG PS > 1: The DESTINY-Gastric02 trial included patients with an ECOG PS of 0 or 1. However, pERC agreed with the clinical experts that selected patients with an ECOG PS of more than 1 could be considered for treatment at the discretion of the treating physician. Prior treatment with trastuzumab deruxtecan: According to the clinical experts consulted by the review team, the scenario in which a patient has received trastuzumab deruxtecan for other types of cancer (e.g., breast cancer) and later developed gastric or GEJ cancer is very rare. pERC was unable to comment on the effectiveness of trastuzumab deruxtecan in this scenario, as it did not review any evidence that supported the use of trastuzumab deruxtecan in patients who have a history of previously receiving this treatment for another cancer site. However, pERC agreed with the clinical experts that patients with HER2-positive advanced or metastatic gastric or GEJ adenocarcinoma who discontinue trastuzumab deruxtecan due to disease progression should not be rechallenged with this drug in subsequent lines of treatment. **Questions:** **Should patients currently on another second-line regimen be eligible to switch to trastuzumab deruxtecan?** **Should patients on subsequent lines (after second line) be considered for trastuzumab deruxtecan?** pERC agreed with the clinical experts consulted by the review team that patients who are currently on other treatment regimens in the second or later lines of therapy, and have not previously been treated with trastuzumab deruxtecan, would be considered for treatment with trastuzumab deruxtecan, if they otherwise meet the eligibility criteria outlined in this recommendation. PERC also agreed with the clinical experts that patients who are currently on other treatment regimens in the second line of therapy would be considered, on a limited time basis, to switch to treatment with trastuzumab deruxtecan, especially if they experience serious adverse events on their current treatment in the second line. **<u>Funding algorithm</u>** **Question:**

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		For patients with HER2-positive disease, under what circumstances would trastuzumab deruxtecan be preferred over ramucirumab-paclitaxel and vice versa? **For patients who receive second-line trastuzumab deruxtecan, what therapies would be funded in subsequent lines?** According to the clinical experts consulted by the review team, once reimbursed, trastuzumab deruxtecan will likely become the standard of care in the second-line setting for adult patients with HER2-positive gastric and GEJ adenocarcinoma. The clinical experts anticipated that all therapies currently being used in the second-line setting would be moved to the third line and those currently in the third line to the fourth line, and so on, before considering trifluridine-tipiracil as the last resort. However, pERC noted that no evidence was included in this review to support the comparative efficacy and safety of trastuzumab deruxtecan versus ramucirumab-paclitaxel in the second-line setting for patients with HER2-positive disease. pERC noted that the sponsor is currently conducting a phase III DESTINY-Gastric04 trial that is expected to answer this question. The committee was also unable to comment on the sequencing of the subsequent lines after trastuzumab deruxtecan and considered this issue out of the scope of this review. Nevertheless, pERC agreed with the clinical experts that patients who experience disease progression on trastuzumab deruxtecan in the second line should not be rechallenged with this drug in subsequent lines of treatment. **Care provision issues** **Question:** **Is retesting of the tumour after trastuzumab progression needed to confirm HER2 positivity (IHC3+, IHC2+, and ISH+) to be eligible for trastuzumab deruxtecan?** According to the clinical experts consulted by the review team, a rebiopsy of the tumour after trastuzumab progression to confirm HER2 positivity is typically used to determine trastuzumab deruxtecan is the best available treatment option for a patient; however, retesting should not be considered mandatory to determine eligibility for trastuzumab deruxtecan, especially when there is no safe and easily accessible site to biopsy. pERC agreed with the clinical experts.
Zolbetuximab (Vyloy)	February 14, 2025 (PC0338-000)	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 following conditions are met: **Initiation**

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		1. Zolbetuximab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, could be initiated in patients who have all the following: 1.1. aged 18 years of age or older 1.2. previously untreated locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma 1.3. HER2-negative tumours that test CLDN18.2-positive. 2. Patients must not have active CNS metastases. 3. Patients must have good performance status. **Discontinuation** 4. Treatment should be discontinued upon the occurrence of any of the following: 4.1. clinical disease progression 4.2. unacceptable toxicity. **Prescribing** 5. Zolbetuximab in combination with chemotherapy should be prescribed by clinicians with expertise and experience in treating gastric or GEJ cancers. 6. Zolbetuximab should be prescribed in combination with fluoropyrimidine- and platinum-containing chemotherapy. **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. **Feasibility of adoption** 8. The feasibility of adoption of zolbetuximab in combination with chemotherapy must be addressed. 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. 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 a delay in confirming a patient's biomarker status (e.g. HER2- negative, CLDN18.2 positive) **Guidance on treatment sequencing (Adapted from Table 2: Responses to Questions From the Drug Programs)** • **Recipients of adjuvant nivolumab:** Should patients who have received adjuvant treatment with nivolumab, but who relapse less

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		than 6 months after completing adjuvant treatment, be eligible for treatment with zolbetuximab plus chemotherapy? Patients were eligible for the SPOTLIGHT and GLOW trials if they had received either neoadjuvant or adjuvant immunotherapy as long as it was completed at least 6 months before randomization, but no patients were identified as 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 CLDN18.2 biomarker status, performance status, and would otherwise meet eligibility criteria should be offered the treatment. • **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. • **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. • **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 zolbeltuximab 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.

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		• **Switching (clinical preference):** If reimbursed by the public drug programs, should patients who are currently receiving treatment with nivolumab plus chemotherapy or pembrolizumab plus chemotherapy be eligible to switch to zolbextuximab 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 or pembrolizumab plus chemotherapy should be considered eligible to switch to zolbetuximab plus chemotherapy in the first-line setting upon confirmation of CLDN18.2 status. • **Switching to zolbetuximab (due to intolerance):** If reimbursed by the public drug programs, should patiets who have unacceptable toxicity to nivolumab plus chemotherapy or pembrolizumab 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 or pembrolizumab plus chemotherapy and experience severe toxicities attributable to nivolumab or pembrolizumab should be considered eligible to switch to zolbetuximab plus chemotherapy in the first-line setting upon confirmation of CLDN18.2 status if 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 zolbeltuximab plus chemotherapy be eligible to switch to nivolumab plus chemotherapy or pembrolizumab 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 pembrolizumab plus chemotherapy, in the first-line setting upon confirmation of CLDN18.2 status if there is no disease progression.
Pembrolizumab (Keytruda)	October 23, 2024 (PC0356-000)	pERC recommends that pembrolizumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, be reimbursed for adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2) negative gastric or gastroesophageal junction (GEJ) adenocarcinoma only if the following conditions are met: **Initiation**

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		1. Treatment with pembrolizumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy should be initiated in patients who have all of the following: 1.1 18 years of age or older 1.2 Previously untreated HER2 negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma 2. Patients must not have: 2.1 Active CNS metastases 2.2 History of therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy, in the advanced or metastatic setting 3. Patients must have good performance status. **Discontinuation** 4. Treatment should be discontinued upon the occurrence of any of the following: 4.1 Clinical disease progression 4.2 Unacceptable toxicity 4.3 Completion of 24 months of treatment (e.g., 35 cycles at a dose of 200 mg every 3 weeks) 5. One component of the treatment can be discontinued at the discretion of the treating physician in case of adverse events. **Prescribing** 6. Pembrolizumab in combination with and chemotherapy should be prescribed by clinicians with expertise and experience in treating gastric or GEJ cancers. The treatment should be delivered in institutions with expertise in systemic therapy delivery and management of immunotherapy-related side effects. 7. Pembrolizumab should be prescribed in combination with fluoropyrimidine- and platinum-containing chemotherapy. **Pricing** 8. Pembrolizumab in combination with chemotherapy should be negotiated so that it does not exceed the drug program cost of treatment with nivolumab in combination with chemotherapy. • For condition 2, pERC agreed with the clinical experts that it may be reasonable to re-treat patients who received prior adjuvant therapy with a PD-1, PD-L1, or PDL2 inhibitor with pembrolizumab plus chemotherapy in the advanced or metastatic setting, if there was a disease-free interval of 6 months or greater after completion of adjuvant therapy. • For condition 3, pERC agreed with the clinical experts that patients with an ECOG Performance Status more than 1 may be treated at the discretion of the treating physician. • For condition 4, pERC agreed with the clinical experts that it would be reasonable to readminister pembrolizumab at the time of recurrence (up to 17 additional every-3-week doses, or 12 months) at the discretion of the treating physician for patients who have discontinued pembrolizumab upon the completion of 2 years of

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		treatment and before any disease progression, or after achieving a complete response. **Optimal sequencing guidance:** • The sponsor-submitted indirect treatment comparisons suggested that there may to be little to no difference in efficacy outcomes between pembrolizumab in combination with chemotherapy and nivolumab in combination with chemotherapy in the patient population under review. pERC agreed that the choice between pembrolizumab and nivolumab will be determined by the treating physician's preference. • Patients with squamous cell or undifferentiated gastric cancer were excluded from the KEYNOTE-859 trial. pERC agreed with the clinical experts that, while it is relatively rare for patients with gastric cancers to present with squamous cell and undifferentiated histology, it would be reasonable for these patients to be considered eligible for treatment with pembrolizumab. • pERC agreed with the clinical experts that eligibility to receive pembrolizumab plus chemotherapy should not be tied to a patient's PD-L1 combined positive score or dMMR or MSI-H status. pERC noted that this would be aligned with the eligibility criteria for combination therapy with nivolumab in the patient population under review. • pERC further discussed that chemotherapy may be initiated pending results of HER2 testing and pembrolizumab added upon confirmation of HER2-negative status. If HER2 status cannot be determined (e.g., insufficient tissue for testing), patients may be considered for the treatment with pembrolizumab plus chemotherapy. • pERC agreed with the clinical experts that in the event pembrolizumab is discontinued after the initial 24 months of treatment, for reasons other than disease progression or intolerability, it would be reasonable to readminister pembrolizumab at the time of recurrence (up to 12 months) at the discretion of the treating physician. pERC agreed with the clinical experts that re-treatment with pembrolizumab, alone or in combination with chemotherapy, should be based on a joint decision-making process between the oncologist and patient, considering disease burden, residual treatment side effects, and patient symptoms, values, and preferences.
Pembrolizumab (Keytruda)	June 26, 2024 (PC0343-000)	pERC recommends that pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, be reimbursed for adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2) positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumors express programmed cell death-ligand 1 (PD-L1) (combined positive score [CPS] ≥ 1) as determined by a validated test, only if the following conditions are met: **Initiation**

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		1. Treatment with pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy should be initiated in patients who have all of the following: 1.1 18 years of age or older 1.2 Previously untreated HER2 positive locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma 1.3 Tumour PD-L1 expression (CPS ≥ 1) 2. Patients must not have: 2.1 Active CNS metastases 2.2 History of therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 drug in the advanced or metastatic setting 3. Patients must have good performance status. **Discontinuation** 4. Treatment should be discontinued upon the occurrence of any of the following: 4.1 Clinical disease progression 4.2 Unacceptable toxicity 4.3 Completion of 24 months of treatment (e.g., 35 cycles at a dose of 200 mg every 3 weeks) 5. One or more treatment components can be discontinued at the treating physician's discretion in case of adverse events. **Prescribing** 6. Pembrolizumab, in combination with trastuzumab and chemotherapy, should be prescribed by clinicians with expertise and experience in treating gastric or GEJ cancers. The treatment should be delivered in institutions with expertise in systemic therapy delivery and management of immunotherapy-related side effects. 7. Pembrolizumab should be prescribed in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy. **Pricing** 8. A reduction in price. • For condition 3, pERC agreed with the clinical experts that patients with an ECOG performance status of 2 may be treated at the treating physician's discretion. • For condition 4, pERC agreed with the clinical experts that it would be reasonable to readminister pembrolizumab at the time of recurrence (up to 17 additional every-3-week doses, or 12 months) at the discretion of the treating physician for patients who have discontinued pembrolizumab upon the completion of 2 years of treatment and before any disease progression, or after achieving a complete response. **Optimal sequencing guidance:**

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		• pERC agreed with the clinical experts that patients with HER2 positive gastric or GEJ adenocarcinoma who receive nivolumab in the adjuvant setting, can be considered eligible to receive pembrolizumab in the first line advanced or metastatic setting, if there was a disease-free interval of 6 months or greater after completion of adjuvant therapy with nivolumab. • pERC agreed with the clinical experts that results from the KEYNOTE-811 trial could be generalized to patients with esophageal adenocarcinomas that are HER2 positive. The clinical experts noted that, and that generalizing results patients with gastric or GEJ adenocarcinoma to patients with esophageal adenocarcinoma has been done for other treatments, such as trastuzumab and trifluridine-tipiracil. • pERC agreed with the clinical experts that addition of pembrolizumab to current SOC treatment regimen is appropriate for those who are currently on platinum- plus fluoropyrimidine-based chemotherapy. • pERC agreed with the clinical experts that, for patients who have already initiated chemotherapy, pembrolizumab and trastuzumab can be added to the treatment regimen once HER2 positive and PD-L1 CPS status is confirmed. • pERC agreed with the clinical experts that in the event pembrolizumab is discontinued after the initial 24 months of treatment for reasons other than disease progression or intolerability, it would be reasonable to readminister pembrolizumab at the time of recurrence (up to 12 months) at the discretion of the treating physician. The clinical experts noted that re-treatment should be based on a joint decision-making process between the oncologist and patient, considering disease burden, residual treatment side effects, and patient symptoms, values, and preferences.
Nivolumab (Opdivo)	March 22, 2022 (PC0259-000)	The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy be reimbursed for the first-line treatment of adult patients with HER2- negative advanced or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma only if the following conditions are met: **Initiation** 1. Treatment with nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy should only be reimbursed in adult patients who have all of the following: 1.1. Previously untreated, HER2-negative, advanced/metastatic GC/GEJC/EC with histologically confirmed predominant adenocarcinoma 1.2. Good performance status 2. Patients should not have either of the following: 2.1. No contraindications to immunotherapy 2.2. uncontrolled CNS metastases **Renewal**

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		3. Assessment for renewal based on clinical and radiographic evaluation every 2 to 4 months. 4. Treatment with nivolumab may be reimbursed for a maximum of 24 months. **Prescribing** 5. Treatment should be prescribed by clinicians with expertise and experience in treating GC, GEJC, or EC. The treatment should be supervised and delivered in outpatient specialized oncology clinics with expertise in systemic therapy delivery and management of immunotherapy-related side effects. 6. Nivolumab should be prescribed only in combination with fluoropyrimidine- and platinum-containing chemotherapy. **Pricing** 7. A reduction in price 8. Feasibility of adoption must be addressed (magnitude of budget impact) **Optimal sequencing guidance:** • For patients whose disease has unknown HER2 status, pERC considered it appropriate for these patients to begin chemotherapy alone and add nivolumab upon confirmation of HER2-negative status. • pERC noted that for the treatment of advanced or metastatic gastroesophageal cancers, only pembrolizumab would be used for squamous cell cancers and only nivolumab would be used for gastric cancers. • pERC did not expect the place in therapy for drugs currently reimbursed in subsequent lines to be affected by reimbursement of nivolumab for this indication, aside from a small percentage of patients who may receive retreatment with nivolumab. The CheckMate-649 trial excluded patients with a history of receiving an anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy, or an agent directed to another co-inhibitory T-cell receptor. pERC agreed with the clinical experts that it may be reasonable to re-treat patients who received prior adjuvant therapy with a PD-1, PD-L1, or PDL2 inhibitor with nivolumab plus chemotherapy in the advanced or metastatic setting, if there was a disease-free interval of 6 months or greater after completion of adjuvant therapy.
Nivolumab (Opdivo)	January 26, 2022 (PC0253-000)	pERC recommends that nivolumab be reimbursed for the adjuvant treatment of completely resected esophageal or GEJ cancer in patients who have residual pathologic disease following prior neoadjuvant chemoradiotherapy only if the following conditions are met: **Initiation** 1. Adjuvant treatment with nivolumab should only be initiated in adult patients who have all of the following: 1.1. Histologically confirmed predominant adenocarcinoma or squamous cell carcinoma of esophagus or GEJ 1.2. Completed neoadjuvant CRT 1.3. Complete resection of the tumour

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		1.4. Residual pathologic disease with a tumour and node classification status of ypT1 or ypN1, at minimum 2. Patients should have a good performance status. 3. Treatment with nivolumab should be initiated within 4 to 16 weeks of complete resection. **Renewal** 4. Patients should be assessed by the treating physician with diagnostic imaging conducted every 3 to 6 months. 5. Nivolumab can be continued for an equivalent of 1 year of treatment; i.e., a maximum of: 5.1. 17 cycles if administered at a dose of 240mg over 30 minutes every 2 weeks for 16 weeks, followed by 480mg over 30 minutes every 4 weeks beginning at week 17 5.2. 13 cycles if administered at a dose of 480 mg over 30 minutes every 4 weeks for 16 weeks, followed by 480 mg over 30 minutes every 4 weeks beginning at week 17. **Prescribing** 6. Nivolumab should be prescribed by clinicians with experience and expertise in treating advanced esophageal or GEJ cancer. The treatment should be supervised and delivered in outpatient specialized oncology clinics with expertise in systemic therapy and immunotherapy delivery. 7. Nivolumab should not be used in combination with other adjuvant anti-cancer drugs. **Pricing** 8. A reduction in price **Feasibility of adoption** 9. The feasibility of adoption of nivolumab must be addressed. **Optimal sequencing guidance:** • The clinical experts consulted by CADTH highlighted that nivolumab would represent the new standard of care for adjuvant therapy for patients who do not achieve a pathologic complete response following neoadjuvant chemoradiotherapy, as nivolumab is the first adjuvant therapy based on phase III trial evidence that has demonstrated a significant disease-free survival benefit. pERC agreed with the clinical experts that the future treatment paradigm will be impacted if pembrolizumab and/or nivolumab are funded in the first-line metastatic setting. pERC agreed with the clinical experts that patients who receive nivolumab in the adjuvant setting may be rechallenged or retreated with a PD-1 or PD-L1 inhibitor in the locally advanced or metastatic setting if the patient experiences a disease recurrence after a disease-free interval of 6 months or greater after completion of adjuvant therapy.
Pembrolizumab (Keytruda)	December 20, 2021 (PC0250-000)	pERC recommends that pembrolizumab in combination with platinum and fluoropyrimidine–based chemotherapy be reimbursed for the first-line treatment of adult patients with locally advanced unresectable or metastatic carcinoma of the esophagus or HER2- negative adenocarcinoma of the esophagogastric junction (tumour centre 1 cm

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		to 5 cm above the gastric cardia) only if the following conditions are met: **Initiation** 1. Treatment with pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy should be initiated only in adult patients who have all of the following: 1.1. Histologically or cytologically confirmed locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus, or advanced or metastatic Siewert type I adenocarcinoma of the esophagogastric junction 1.2. ECOG performance status of 0 or 1 2. Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy should be initiated in patients with no history of receiving anti-PD-1, anti-PD-L1, or anti-PD-L2 therapies, or an agent directed to another co-inhibitory T-cell receptor. **Renewal** 3. Assessment for renewal of pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy should be based on clinical and radiographic evaluation every 9 weeks (2 months). 4. Treatment with pembrolizumab may be reimbursed for a maximum of 24 months (i.e., complete of 35 administrations). **Discontinuation** 5. Treatment with pembrolizumab should be discontinued upon the occurrence of any of the following: 5.1. documented disease progression as per RECIST 1.1 5.2. unacceptable toxicity **Prescribing** 6. Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy should only be administered under the supervision of clinicians experienced in the treatment of cancer. 7. Pembrolizumab should be prescribed in combination with platinum and fluoropyrimidine-based chemotherapy for eligible patients. **Pricing** 8. A reduction in price **Feasibility of adoption** 9. The feasibility of adoption of pembrolizumab must be addressed. **Optimal sequencing guidance:** pERC agreed with the clinical experts consulted by CADTH that adding pembrolizumab in the first-line setting would not cause a shift in the sequencing of therapies because pembrolizumab is not standard of care in Canada. KEYNOTE-590 excluded patients with a history of receiving anti– PD-1, anti–PD-L1, or anti–PD-L2 therapies. pERC agreed with the clinical

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		experts consulted by CADTH that it may be reasonable to re-treat patients who received prior adjuvant therapy with a PD-1, PD-L1, or PD-L2 inhibitor with pembrolizumab plus platinum and fluoropyrimidine–based chemotherapy in the locally advanced or metastatic setting, if there was a disease-free interval of 6 months or greater after completion of adjuvant therapy.
Ramucirumab (Cyramza)	October 29, 2015 (PC0059-000)	pERC recommends funding ramucirumab in combination with paclitaxel, conditional on its cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma with ECOG PS of 1 or 2 and with disease progression following first-line chemotherapy. **Optimal sequencing guidance:** pERC noted that first-line treatment of advanced or metastatic gastric cancer or GEJ adenocarcinoma includes chemotherapy, typically with a fluoropyrimidine and a platinum. After failure of first- line therapy in patients who maintain an ECOG performance status of 0 to 2, the Committee noted that, based on the opinion of the Clinical Guidance Panel, treatment with taxanes (docetaxel, paclitaxel) and irinotecan-based chemotherapy has demonstrated modest improvements in survival when compared with best supportive care (i.e., difference in median overall survival up to 1.6 months); however, there remains a large unmet need for more effective therapies.
Trifluridine-Tipiracil (Lonsurf)	March 24, 2020 (PC0197-000)	pERC recommends funding trifluridine-tipiracil (Lonsurf) in combination with best supportive care for the treatment of adult patients with metastatic gastric cancer or adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least 2 prior lines of chemotherapy including a fluoropyrimidine, a platinum, and either a taxane or irinotecan and if appropriate, with HER2/ neu-targeted therapy, conditional on cost-effectiveness being improved to an acceptable level. Optimal sequencing guidance: • pERC agreed with the CGP that the mechanisms of action are different and prior immunotherapy should not influence safety or efficacy of trifluridine-tipiracil. Thus, the results can be applied to patients treated with prior immunotherapy. pERC agreed with the CGP that data reflecting the optimal sequencing of trifluridine-tipiracil and immunotherapy is limited. If patients with High levels of MicroSatellite Instability or deficient MisMatch Repair can access immunotherapy, it should not preclude them from treatment with trifluridine-tipiracil if they are deemed suitable for ongoing treatment given the different mechanisms of action of these treatments.

CGP = clinical guidance panel; CLDN18.2 = Claudin 18.2; CNS = central nervous system; CRT = chemoradiotherapy; ECOG = Eastern Cooperative Oncology Group; EC = esophageal cancer; GC = gastric cancer; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor; pERC = pCODR Expert Review Committee; pCODR = pan-Canadian Oncology Drug Review; PD-L1 = programmed death-ligand 1; PD-L2 = programmed death-ligand 2; PD-1 programmed cell death protein 1; ypN1 = pathologic lymph node stage 1; ypT1 = pathologic tumour stage 1.

Table 2: CDA-AMC Implementation Advice from Previous Panel Provisional Funding Algorithms on Gastric Cancer

Date of publication	Implementation Advice
June 21, 2022	• The panel noted that some patients with advanced or metastatic gastroesophageal cancer, especially those with esophageal adenocarcinoma not involving the GEJ and those with recurrent disease, may have disease with unknown HER2 status. While awaiting patients' HER2 test results, the panel advised that chemotherapy can be started alone, and immunotherapy can be added upon confirmation of HER2-negative status. If HER2 status cannot be determined (e.g., rare occurrence that sufficient tissue cannot be obtained for HER2 testing), the panel advised that patients with unknown HER2 status should be eligible for concurrent immunotherapy. • The panel advised that patients with gastric adenocarcinoma should only be eligible for nivolumab. The panel advised that patients with esophageal squamous cell carcinoma should only be eligible for pembrolizumab. The panel advised that patients with esophageal or GEJ adenocarcinoma should be eligible for either nivolumab or pembrolizumab. The panel indicated that the Siewert classification can be difficult to ascertain in routine clinical practice and advised that Siewert classification should not have to be reported to access immunotherapy for GEJ adenocarcinoma. The panel noted that the addition of immunotherapy to chemotherapy for the first-line treatment of advanced or metastatic gastric adenocarcinoma, GEJ adenocarcinoma, or esophageal carcinoma should not impact the sequencing of subsequent lines of therapy.

GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2.

Consultation Process and Objectives

A rapid algorithm is undertaken when an expert committee (e.g., pERC, FMEC) recommendation can be directly incorporated into an existing provisional funding algorithm without supplemental advice from clinical specialists. Eligible patient, clinician and industry groups were invited to provide input on the proposed scope and feedback on the draft report. Input is sought before the project is initiated to help shape the direction and / or the scope of the funding algorithm, whereas feedback is collected when the funding algorithm is near completion for refinement. For transparency, this report includes a summary of input on the proposed scope and a summary of feedback on the draft report. Please refer to the appropriate sections of the report.

Summary of Input on the Proposed Scope

Note that the submission received prior to September 3, 2024 (e.g. zolbetuximab) followed an earlier version of the provisional funding algorithm where input was not available for the provisional funding algorithm.

Pertaining to the review with trastuzumab deruxtecan, two inputs were received on the proposed scope of the rapid provisional funding algorithm: one from a patient group from My Gut Feeling – Stomach Cancer Foundation of Canada and another from an industry group from AstraZeneca Canada. Note that the full

submissions received are available on the project landing page in the consolidated document. <insert hyperlink or citation to project landing page>.

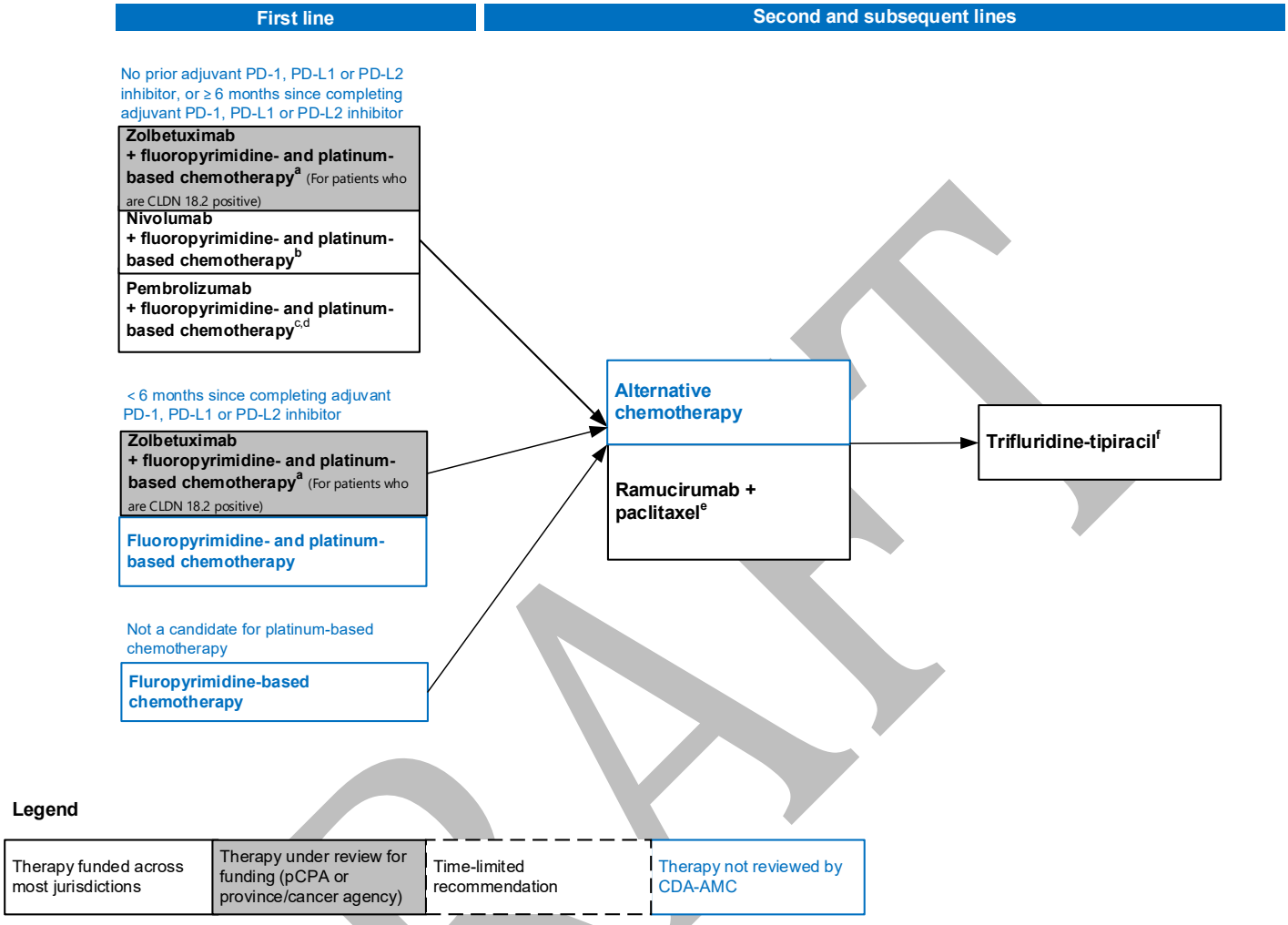
Stomach Cancer Foundation of Canada emphasized the lack of second or later-line therapy options for HER2+ GEJ/esophageal cancer patients. This group highlighted that trastuzumab deruxtecan has fewer side effects and could be a viable alternative for patients not suitable for standard later-line treatments. This group emphasized the need for multiple therapeutic options given the heterogeneity of the cancer and disease characteristics.

AstraZeneca noted that in clinical practice setting of Canada, clinicians often aim to exhaust the use of available second-line treatment options before moving to trifluridine-tipiracil. Given the changing landscape in this therapeutic space, not all second-line options should be considered in subsequent settings. This industry group supports shifting the funded sequence to later line considerations if applicable. This industry group also suggest to consider applying evidence across those with similar disease sites such as across gastric, GEJ, and esophageal cancer.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for HER2-Negative Advanced or Metastatic Gastric, GEJ, or Esophageal Cancer

Alt Text: A flow diagram depicting the therapies that are funded or under review for funding across most jurisdictions for patients with HER2-negative advanced or metastatic gastric, GEJ, or esophageal cancer across adjuvant, first line, second and subsequent lines. Full description can be found in the text.



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- Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. All drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the cited sources of information on the CDA-AMC website for more details.

Footnotes:

[a] Zolbetuximab for injection, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is recommended to be reimbursed 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 may also offer an alternative treatment for patients with the same condition who have a PD-L1 CPS < 5 and are ineligible for immune checkpoint inhibitors

[b] For HER2-negative gastric, gastroesophageal, and esophageal adenocarcinoma, nivolumab is indicated in the first line.

[c] For HER2-negative gastric, gastroesophageal, and esophageal adenocarcinoma, as well as for esophageal squamous cell carcinoma, pembrolizumab is indicated in the first line.

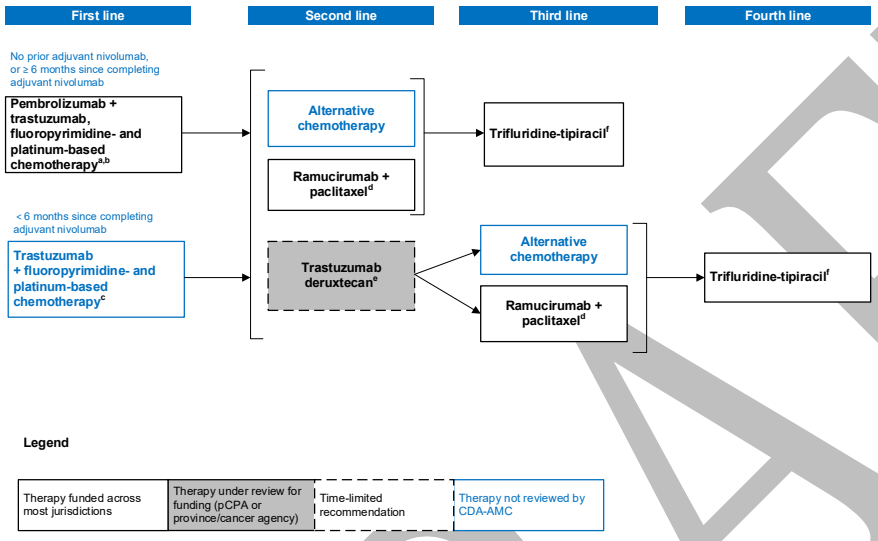
[d] Re-treatment with pembrolizumab, alone or in combination with chemotherapy, allowed for up to 1 additional year if stopped after the initial 24 months of treatment for reasons other than disease progression or intolerance.

[e] Ramucirumab plus paclitaxel is indicated for gastric cancer or GEJ adenocarcinoma after prior chemotherapy.

[f] Trifluridine- tipiracil is indicated for gastric cancer or GEJ adenocarcinoma previously treated with at least 2 prior lines of chemotherapy including a fluoropyrimidine, a platinum, and either a taxane or irinotecan.

Figure 2: Provisional Funding Algorithm Diagram for HER2-Positive Advanced or Metastatic Gastric, GEJ, or Esophageal Cancer

Alt Text: A flow diagram depicting the therapies that are funded or under review for funding across most jurisdictions for patients with HER2-positive advanced or metastatic gastric, GEJ, or esophageal cancer across adjuvant, first line, second and subsequent lines. Full description can be found in the text.



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Footnotes:

[a] The addition of pembrolizumab to trastuzumab in combination with fluoropyrimidine- and platinum-based chemotherapy is for patients with previously untreated HER2-positive locally advanced unresectable or metastatic gastric, gastroesophageal, and esophageal adenocarcinoma with tumour PD-L1 expression (CPS ≥ 1).

[b] Re-treatment with pembrolizumab allowed for up to 1 additional year if stopped after the initial 24 months of treatment for reasons other than disease progression or intolerance.

[c] Patients who are not candidates for platinum-based chemotherapy may be treated with trastuzumab plus fluoropyrimidine-based chemotherapy

[d] For patients with gastric cancer or GEJ adenocarcinoma, ramucirumab with paclitaxel is indicated in the second and subsequent lines.

[e] Trastuzumab deruxtecan received a time-limited recommendation in favour of reimbursement contingent on a future reassessment of additional evidence that addresses uncertainty.

[f] Trifluridine-tipiracil is only indicated for gastric cancer or metastatic GEJ adenocarcinoma who have been previously treated with at least two prior lines of chemotherapy including a fluoropyrimidine, a platinum, and either a taxane or irinotecan, and if appropriate, with HER2/neu-targeted therapy.

Description of the Provisional Funding Algorithm

Options for HER2-Negative Advanced or Metastatic Gastric, GEJ, or Esophageal Cancer

First-Line Setting

HER2-negative patients who have not received prior adjuvant PD-1, PD-L1 or PD-L2 inhibitor therapy or have completed adjuvant PD-1, PD-L1 or PD-L2 inhibitor 6 or more months ago may receive nivolumab or pembrolizumab in combination with fluoropyridine- and platinum-based chemotherapy, depending on the disease site and histology. Pembrolizumab is indicated for esophageal squamous cell carcinoma. Both pembrolizumab and nivolumab are indicated for esophageal, GEJ, and gastric adenocarcinoma.

Adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive may receive zolbetuximab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment. Zolbetuximab is currently under review for funding for this indication.

Patients who completed adjuvant treatment with a PD-1, PD-L1, or PD-L2 inhibitor less than 6 months ago may receive first-line treatment with zolbetuximab plus chemotherapy if they meet eligibility criteria, have an appropriate CLDN 18.2 biomarker status and performance status, or with fluoropyrimidine- and platinum-based chemotherapy.

Patients who are not candidates for platinum-based chemotherapy may be treated with fluoropyrimidine-based chemotherapy in the first-line.

Second and Subsequent Settings

Patients who receive treatment in the first-line setting as described previously can receive ramucirumab with paclitaxel or an alternative chemotherapy in the second-line setting. Ramucirumab and paclitaxel in the second-line is only indicated for patients with gastric cancer or GEJ adenocarcinoma.

In subsequent lines, trifluridine-tipiracil is indicated for patients with gastric cancer or metastatic GEJ adenocarcinoma who have been previously treated with at least 2 prior lines of chemotherapy, including a fluoropyrimidine, a platinum, and either a taxane or irinotecan.

Options for HER2-Positive Advanced or Metastatic Gastric, GEJ, or Esophageal Cancer

First-Line Setting

In the first-line setting, patients with HER2-positive gastric, GEJ or esophageal adenocarcinoma whose tumours express PD-L1 (CPS ≥1) and who have not received prior adjuvant nivolumab or have completed adjuvant nivolumab 6 or more months ago may receive pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-based chemotherapy.

Patients who are within less than 6 months since completing adjuvant nivolumab, and patients whose tumours express PD-L1 CPS<1 may be treated with trastuzumab plus fluoropyrimidine- and platinum-based chemotherapy in the first-line.

Patients who are not candidates for platinum-based chemotherapy may be treated with trastuzumab plus fluropyrimidine-based chemotherapy.

Second and Subsequent Settings

Patients who have been previously treated with a trastuzumab-based regimen in the first-line setting can receive trastuzumab deruxtecan in the second line. Trastuzumab deruxtecan is currently under review for funding for adult patients with gastric cancer or metastatic GEJ, or esophageal adenocarcinoma. Trastuzumab deruxtecan received a time-limited recommendation in favour of reimbursement from pERC that is contingent on a future reassessment of additional evidence that addresses the uncertainty.

Another option in the second-line setting is ramucirumab with paclitaxel or an alternative chemotherapy. Ramucirumab and paclitaxel in the second line is only indicated for patients with gastric cancer or GEJ adenocarcinoma.

In the third-line setting, trifluridine-tipiracil is indicated for patients with gastric cancer or metastatic GEJ adenocarcinoma who have been previously treated with at least 2 prior lines of chemotherapy, including a fluoropyrimidine, a platinum, and either a taxane or irinotecan and, if appropriate, with HER2/neu-targeted therapy.

Third-line treatment options also include alternative chemotherapy or ramucirumab with paclitaxel if the patient's disease has progressed on trastuzumab deruxtecan. Trifluridine-tipiracil may be considered as a fourth-line option once prior treatment criteria have been met.

Additional Remarks

During panel deliberations on June 21, 2022 for HER2-negative advanced or metastatic gastric, GEJ, or esophageal cancer, the panellists emphasized programmed death-ligand 1 (PD-L1) combined positive score (CPS) cut-offs should not guide access to nivolumab and pembrolizumab. The panel agreed there are not sufficient data to preclude any patient from receiving therapy based on CPS, and CPS should only be used in consultations with the patients if it is available and at the discretion of the treating clinician. In the KEYNOTE-590 and CheckMate 649 trials, overall survival was statistically significantly improved with the addition of immunotherapy regardless of PD-L1 expression. In CheckMate 649, the results showed the population with a CPS of less than 5 did not gain an overall survival benefit from nivolumab, but this was an unplanned post hoc exploratory analysis, thus only hypothesis generating.

Summary of Feedback on the Draft Report

<Available for final report only>. Note that the full submissions received are available on the project landing page in the consolidated document. <insert hyperlink or citation to project landing page>.