Provisional Funding Algorithm

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

This report supersedes Canada's Drug Agency provisional funding algorithm report for HER2-Negative Gastric, Gastroesophageal Junction, or Esophageal Cancer dated June 21, 2022.

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

Background

Following a request from jurisdictions, Canada's Drug Agency (CDA-AMC) may 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*. The publishing of provisional algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

- CDA-AMC's pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians convened by CDA-AMC concerning the sequencing of drugs in the therapeutic space of interest
- existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

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.

Provisional funding algorithms also 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.

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.

Jurisdictional cancer drug programs requested a CDA-AMC provisional funding algorithm on gastric cancer. However, no outstanding implementation issues were identified, and no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

CADTH 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.

These recommendations are outlined in Table 2. For this rapid algorithm, the purpose is to incorporate the latest pERC recommendations for the following:

- 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.

Table 1: Relevant CDA-AMC Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Pembrolizumab (Keytruda)	October 23, 2024	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 GEJ adenocarcinoma only if the following conditions are met: 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. 4. Treatment should be discontinued upon the occurrence of any of the following: 4.1. Clinical disease progression 4.2. Unacceptable toxicity

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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. 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. 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 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.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		• 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	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 tumours 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: 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. 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. 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. 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

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		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: • 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	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: • Previously untreated, HER2-negative, advanced/metastatic GC/GEJC/EC with histologically confirmed predominant adenocarcinoma • Good performance status • No contraindications to immunotherapy or uncontrolled CNS metastases • Assessment for renewal based on clinical/radiographic evaluation every 2 to 4 months • Maximum of 24 months of treatment • Prescribed in combination with fluoropyrimidine- and platinum- containing chemotherapy • A reduction in price • Feasibility of adoption must be addressed (magnitude of budget impact) Optimal sequencing guidance:

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		• 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 re-treatment 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	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: • Histologically confirmed predominant adenocarcinoma or squamous cell carcinoma of esophagus or GEJ • Completed neoadjuvant CRT • Complete resection of the tumour • Residual pathologic disease with a tumour and node classification status of ypT1 or ypN1, at minimum • Good performance status • Treatment with nivolumab initiated within 4 to 16 weeks of complete resection • Assessed for renewal by treating physician with diagnostic imaging every 3 to 6 months • Maximum of equivalent of 1 year of treatment • Should not be used in combination with other adjuvant anti-cancer drugs • A reduction in price • Feasibility of adoption must be addressed (magnitude of and uncertainty in budget impact) 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

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		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	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 to 5 cm above the gastric cardia) only if the following conditions are met: • 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 GEJ • ECOG performance status of 0 or 1 • 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 (see optimal sequencing guidance below) • Assessment based on clinical/radiographic evaluation every 9 weeks • Maximum of 24 months of treatment • Prescribed in combination with fluoropyrimidine- and platinum- containing chemotherapy • A reduction in price • Feasibility of adoption must be addressed (magnitude of budget impact) 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 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	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

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		up to 1.6 months); however, there remains a large unmet need for more effective therapies.
Trifluridine-Tipiracil (Lonsurf)	March 24, 2020	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; CNS = central nervous system; CPS = combined positive score; 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; SOC = standard of care; ypN1 = pathologic lymph node stage 1; ypT1 = pathologic tumour stage 1.

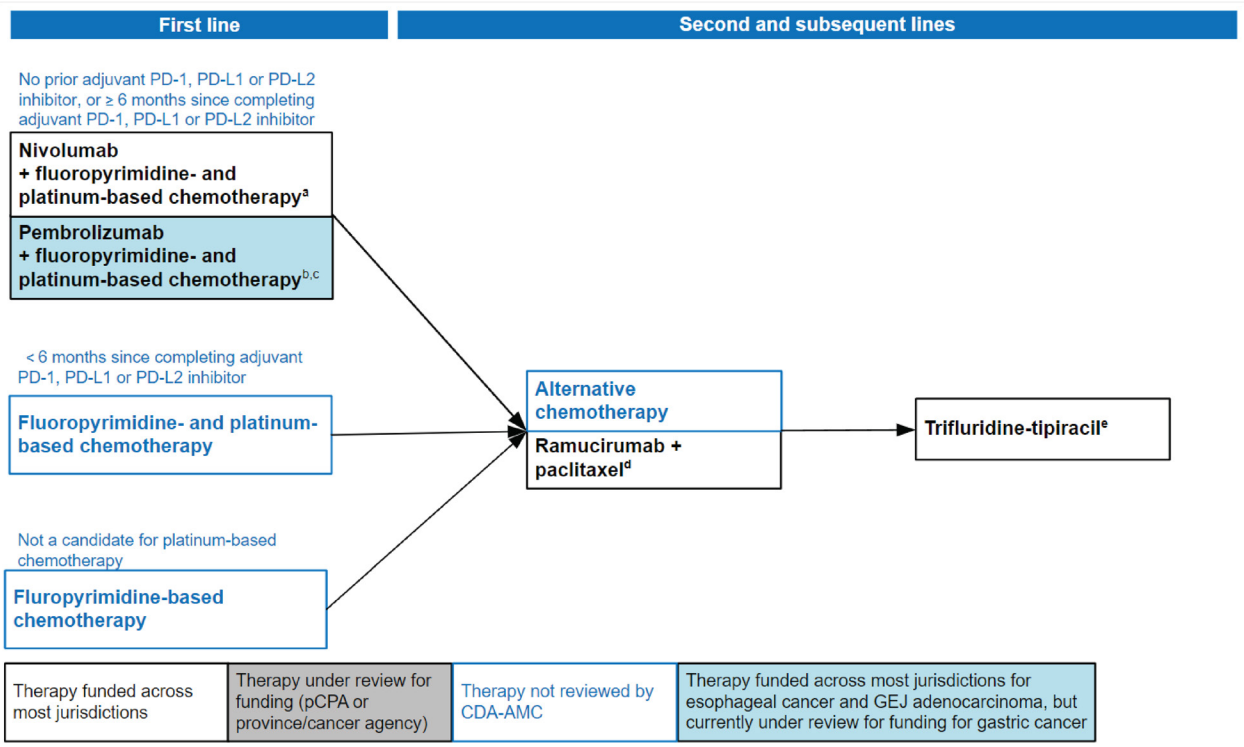
Table 2: CDA-AMC Implementation Advice Panels on HER2-negative Advanced or Metastatic Gastric, GEJ or Esophageal Cancer

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.

Provisional Funding Algorithm

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



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

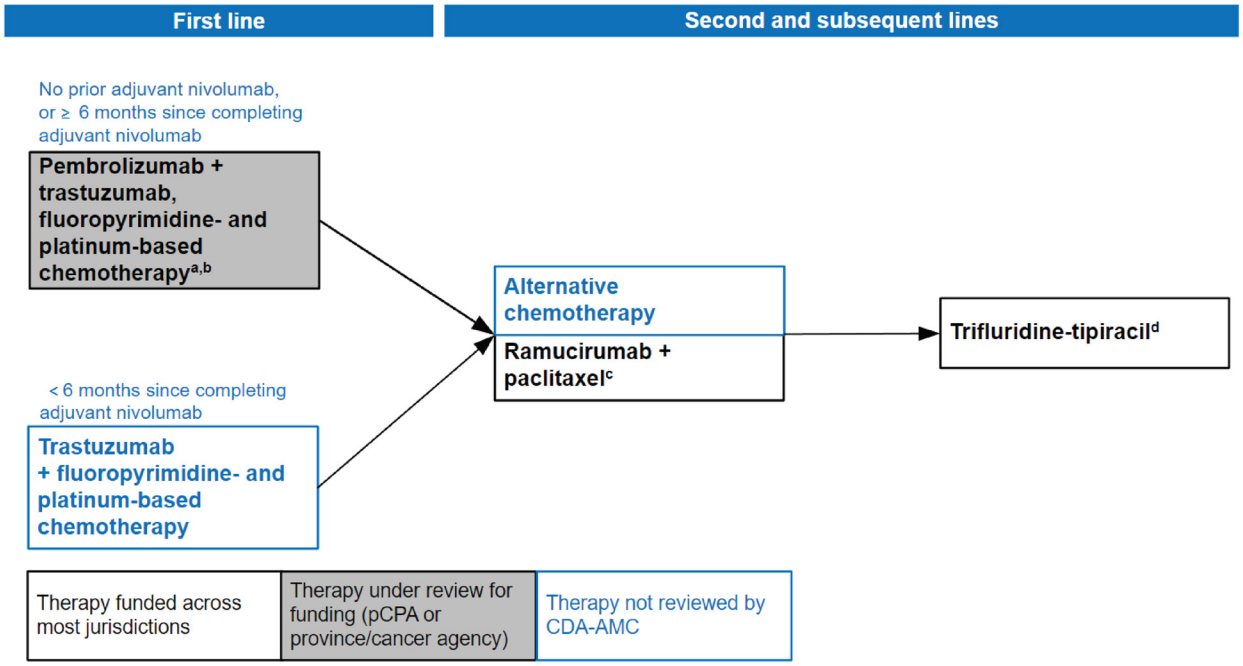
[b]For HER2-negative gastric, gastroesophageal, and esophageal adenocarcinoma, as well as for esophageal squamous cell carcinoma, pembrolizumab is indicated in the first line.

[c]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.

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

[e]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



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

[d]Trifluridine-tipiracil is only indicated for 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.

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. Pembrolizumab is currently under review for funding for gastric adenocarcinoma.

Patients who are within fewer than 6 months since completing adjuvant PD-1, PD-L1 or PD-L2 inhibitor may be treated with fluoropyrimidine- and platinum-based chemotherapy in the first-line.

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. Pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-based chemotherapy is under review for funding

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.

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. The combination of ramucirumab plus 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 and if appropriate, with HER2/neu-targeted therapy.

Additional Remarks

During panel deliberations for HER2-negative advanced or metastatic gastric, GEJ, or esophageal cancer, the panellists emphasized programmed death-ligand 1 (PD-L1) CPS cut-offs should not guide access to nivolumab and pembrolizumab. The panel agreed there are insufficient 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 but this was an unplanned post hoc exploratory analysis, thus only hypothesis generating.

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