cadth | Reimbursement Review

Provisional Funding Algorithm

Indication: HER2-negative advanced or metastatic gastric, gastroesophageal junction, or esophageal cancer

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

Key Messages

- When human epidermal growth factor receptor 2 (HER2) status cannot be determined, patients should be eligible for first-line chemotherapy plus immunotherapy.
- While awaiting HER2 test results, chemotherapy can be started alone, and immunotherapy can be added once HER2-negative status is confirmed.
- Patients with gastric adenocarcinoma should only be eligible for nivolumab, patients with esophageal squamous cell carcinoma should only be eligible for pembrolizumab, and patients with esophageal or gastroesophageal junction (GEJ) adenocarcinoma should be eligible for either nivolumab or pembrolizumab.
- The addition of immunotherapy to chemotherapy in the first line should not impact the sequencing of subsequent lines of therapy.

Background

The provisional funding algorithm process is used to provide advice when the drug programs have indicated that there is need to establish an appropriate place in therapy for the drug under review relative to alternative treatments that are currently reimbursed by the drug programs, including the impact on the appropriate sequencing of treatments for the purposes of reimbursement. The creation of a new provisional funding algorithm or update of an existing provisional funding algorithm is typically initiated following the issuance of a new pERC recommendation when there are potential implications regarding the funding sequence of drugs within a therapeutic area. CADTH will only initiate work on a provisional funding algorithm at the request of the CADTH Provincial Advisory Group (PAG).

The following item are considered by the expert panels when advising the jurisdictions on the provisional algorithm for the relevant indication:

- unmet therapeutic need for patients (particularly those in understudied populations)
- evidence supporting a particular sequence of therapies (if available)
- clinical experience and opinion that support a particular sequence of therapies
- clinical practice guidelines
- variability across jurisdictions regarding the reimbursement status of existing treatment options
- affordability and sustainability of the health care system
- implementation considerations at the jurisdictional level.

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. Most 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 CADTH website for more details.

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.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CADTH following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Cancer drug programs from federal and provincial jurisdictions requested supplemental implementation advice along with a CADTH provisional funding algorithm on HER2-negative advanced or metastatic gastric, GEJ, or esophageal cancer. See Appendix 1 for a list all past CADTH advice and recommendations relevant for this therapeutic area.

Implementation Issues

At the request of the participating drug programs, CADTH convened a panel of Canadian clinical experts to provide advice for addressing the outstanding implementation issues as follows:

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

Consultation Process and Objectives

The implementation advice panel comprised 4 specialists in Canada with expertise in the diagnosis and management of patients with gastric, GEJ, and esophageal cancer, representatives from public drug programs, and a panel chair. The objective of the panel was to provide advice to the participating drug programs regarding the implementation issues noted in the Background section. A consensus-based approach was used, and input from stakeholders was solicited using questionnaires. Stakeholders including patient and clinician groups and pharmaceutical manufacturers, and public drug programs were invited to provide input in advance of the meeting.

The advice presented in this report has been developed based on the experience and expertise of the implementation advice panel members and, as such, represents experience-informed opinion; it is not necessarily based on evidence.

Advice on Funding Algorithm

Summary of Implementation Advice

Implementation advice regarding the optimal sequencing of treatments is summarized in Table 1. For each implementation issue, a summary of the relevant panel discussion is provided for additional context.

Table 1: Summary of Advice for Addressing Implementation Issues

Issue	Advice	Rationale
Immunotherapy in the advanced or metastatic setting for patients with disease of unknown HER2 status	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.	In the CheckMate 649 trial of nivolumab plus chemotherapy, the eligibility criteria excluded patients with known HER2-positive status. Approximately 40% of the study population had a cancer with unknown HER2 status, balanced across treatment arms.[1] Based on observations in clinical practice, patients with unknown HER2 status are most likely to be HER2-negative (approximately 20% HER2 positivity rate). The panel noted that patients with unrecognized HER2-positive disease may benefit from the addition of immunotherapy. The preliminary results of the phase III KEYNOTE-811 trial, which compares pembrolizumab to placebo in patients with HER2-positive metastatic gastric and GEJ cancer, indicated that the addition of pembrolizumab to chemotherapy and trastuzumab was associated with an increased objective response rate.[2]
Selection of immunotherapy in the advanced or metastatic setting based on disease site and histology	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	The CheckMate 649 trial for nivolumab included patients with gastric, GEJ (regardless of Siewert type), and esophageal adenocarcinoma.[1] The KEYNOTE-590 trial for pembrolizumab included patients with esophageal carcinoma and GEJ adenocarcinoma (Siewert type I only).[3]

Issue	Advice	Rationale
	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.	
Sequencing of therapies in second and subsequent lines following first-line immunotherapy in the advanced or metastatic setting	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.	At the biological level, immunotherapy checkpoint inhibition and vascular endothelial growth factor inhibition can work synergistically via multiple possible mechanisms.

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

In addition to the previously outlined advice, the panel indicated that because an improvement in cost-effectiveness was a condition for reimbursement in each of the recommendations related to the drugs in scope, implementation of any advice herein should be contingent upon ensuring that the relevant treatments are affordable to public payers.

Panel Discussion

Immunotherapy in the Advanced or Metastatic Setting for Patients With Disease of Unknown HER2 Status

The panel described the circumstances in which HER2 testing is conducted in the advanced or metastatic setting. It was noted that reflexive HER2 testing is not consistently available for all gastroesophageal cancers at initial diagnosis, particularly for esophageal cancers and earlier stages of cancer. For some patients with recurrent disease, HER2 testing must be requested.

The panel discussed the benefit of reflexive HER2 testing of all stages of gastroesophageal cancer at initial diagnosis. There was concern among the panellists about delays associated with testing, in which immunohistochemistry could take approximately 10 business days, and equivocal findings from immunohistochemistry testing would require additional time for fluorescence in situ hybridization (FISH) testing. The panel shared some observations from routine clinical practice to support reflexive testing at all stages. First, the rate of subsequent disease recurrence in this cancer type when treated in the curative intent setting is generally 50% or higher. Second, many patients with advanced or metastatic gastroesophageal cancer have a significant symptom burden and are at risk of rapid clinical deterioration. There also may be some cases in which testing is not feasible (e.g., diagnostic tissue sample is insufficient for HER2 testing and there is no appropriate way to obtain further tissue).

The panel agreed that it would be reasonable to start chemotherapy alone while waiting for HER2 testing results and add immunotherapy upon confirmation of HER2-negative status. There was also consensus among the panellists that there is evidence to support the use of immunotherapy in patients waiting for HER2 status confirmation or with disease of unknown HER2 status. The panel cited evidence from the pivotal study of nivolumab, the CheckMate 649 trial, to support the use of immunotherapy in patients with disease of unknown HER2 status. First, in the CheckMate 649 trial of nivolumab plus chemotherapy, the eligibility criteria specified that patients were eligible if they had "no known HER2-positive status."[1] As a result, approximately 40% of the study population had disease of unknown or unreported HER2 status and this population was balanced across treatment arms.[1] Because the population with disease of unknown HER2 status was included and studied in this trial, the panel considers patients with disease of unknown HER2 status eligible for concurrent nivolumab in routine clinical practice. To further support the use of immunotherapy in patients with disease of unknown HER2 status, the panel also discussed that patients with disease of unknown HER2 status are more likely to be HER2-negative than positive (approximately 20% HER2 positivity rate).

In the event the patient has unrecognized HER2-positive disease, the panel noted that this group of patients would likely still clinically benefit from immunotherapy. The panel cited the preliminary results of the phase III KEYNOTE-811 trial, which compares pembrolizumab to placebo in patients with HER2-positive metastatic gastric and GEJ cancer. The addition of pembrolizumab to chemotherapy and trastuzumab was associated with a 22.7% (95% confidence interval, 11.2% to 33.7%; P = 0.00006) increase in objective response rate, an improved disease control rate, and an improved complete response rate.[2]

If patients were to be eligible to receive immunotherapy while waiting for HER2 test results, the panel would be concerned about losing access to trastuzumab therapy for patients with HER2-positive disease. Additionally, the panel showed concern over the potential difficulty of switching therapies without progression and the possibility of limiting treatment options in the future.

Selection of Immunotherapy in the Advanced or Metastatic Setting Based on Disease Site and Histology

Patients with squamous cell carcinoma of the esophagus should be eligible for pembrolizumab and not nivolumab because only the pembrolizumab pivotal trial (KEYNOTE-590) included patients with squamous cell carcinoma of the esophagus. The panel agreed that patients with gastric adenocarcinoma should be eligible for nivolumab and not pembrolizumab because only the nivolumab pivotal trial (CheckMate 649) included patients with gastric adenocarcinoma.

Citing the pivotal trials, the panel agreed that there is no evidence to support the use of pembrolizumab or nivolumab over the other in patients with esophageal or GEJ adenocarcinoma, aside from Siewert type II and III GEJ adenocarcinomas being studied in the pivotal nivolumab trial (CheckMate 649) only. Patients with esophageal

adenocarcinoma or GEJ adenocarcinoma should be eligible for either pembrolizumab or nivolumab.

There was concern among the panellists about using the Siewert classification to determine eligibility for immunotherapy. The Health Canada indication and the CADTH recommendation for pembrolizumab in this setting specify Siewert type I GEJ adenocarcinomas. Per the panel, an accurate Siewert classification can only be made on gross pathological assessment of a surgical resection specimen; for patients with intact primary cancers, the information available to a medical oncologist based on radiography and upper endoscopy operative reports may make it impossible to determine the exact Siewert classification of a GEJ cancer. Given the difficulty of ascertaining Siewert classification and the inclusion of patients with GEJ adenocarcinoma with all Siewert types in the pivotal nivolumab trial (CheckMate 649)[1], the panel indicated that it may be prudent to use nivolumab in patients with GEJ adenocarcinoma. However, the panel confirmed that in terms of the funding algorithm, it is appropriate for patients with GEJ adenocarcinoma to be eligible for either pembrolizumab or nivolumab based on the clinical judgment of the treating physician.

Sequencing of Therapies in Second and Subsequent Lines Following First-Line Immunotherapy in the Advanced or Metastatic Setting

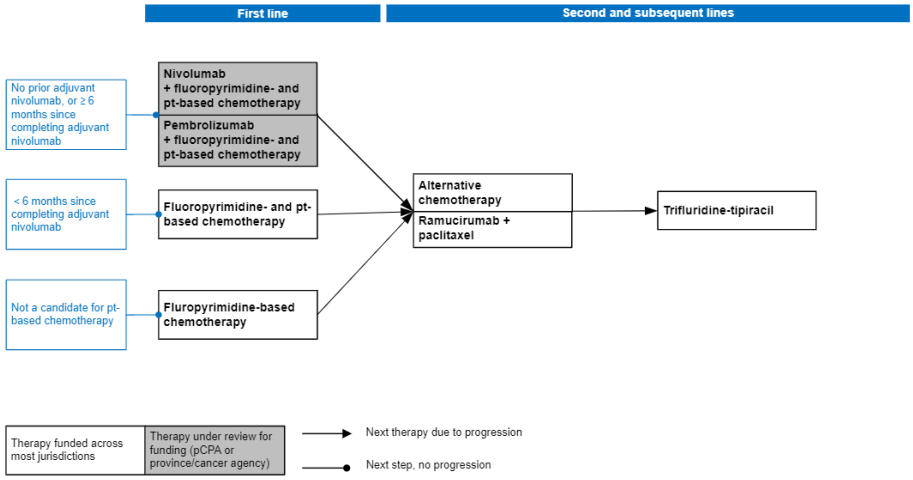
The panel indicated there would be no downstream impact on sequencing of therapies in subsequent lines as the mechanism of action of immunotherapy does not overlap with the downstream options. Aligning with the stakeholder feedback, the panellists agreed that there were emerging data to suggest that patients who receive ramucirumab and paclitaxel may have better outcomes if they received prior treatment with an immune checkpoint inhibitor.[4,5] The panel considered these data to be consistent with the expectation that, at a biologic level, vascular endothelial growth factor inhibition and immunotherapy checkpoint inhibition can work synergistically via multiple possible mechanisms.

Other Remarks

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 but this was an unplanned post hoc exploratory analysis, thus only hypothesis generating.

Provisional Funding Algorithm

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



GEJ = gastroesophageal junction; pCPA = pan-Canadian Pharmaceutical Alliance; pt = platinum.

Note: For gastric cancer, nivolumab is the only immunotherapy indicated in the first line. For squamous cell carcinoma of the esophagus, pembrolizumab is the only immunotherapy indicated in the first line. Ramucirumab plus paclitaxel is indicated for gastric cancer or GEJ adenocarcinoma after prior chemotherapy. 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 1 depicts the provisional funding algorithm proposed by the panel. Note that this diagram is a summary representation of the drug funding options for the condition of interest. It is not a treatment algorithm; it is neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagram may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain provinces. All drugs are subject to explicit funding criteria, which may also vary between provinces. Readers are invited to refer to the individual drug entries on the CADTH website for more details.

First-Line Setting

In the first-line setting, both nivolumab and pembrolizumab are under review for funding. HER2-negative patients who have not received prior adjuvant nivolumab or have completed adjuvant nivolumab 6 or more months ago may receive nivolumab or pembrolizumab in combination with fluoropyridine- and platinum-based chemotherapy when funded, depending on the disease site and histology. Nivolumab is the only immunotherapy indicated for gastric adenocarcinoma, and pembrolizumab is the only

immunotherapy indicated for esophageal squamous cell carcinoma. Both pembrolizumab and nivolumab are indicated for esophageal and GEJ adenocarcinoma.

Patients who are within less than 6 months since completing adjuvant nivolumab 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.

Appendix 1: Past CADTH Advice and Recommendations

Table 2: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation[a]
Nivolumab (Opdivo) PC0259	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:** • 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.

Generic name (brand name)	Date of recommendation	Recommendation[a]
Nivolumab (Opdivo) PC0253	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 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) PC0250	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

Generic name (brand name)	Date of recommendation	Recommendation[a]
		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) PC0059	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 up to 1.6 months); however, there remains a large unmet need for more effective therapies.
Trifluridine-Tipiracil (Lonsurf) PC0197	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

Generic name (brand name)	Date of recommendation	Recommendation[a]
		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; 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.

[a] Summaries of the reimbursement conditions are provided; for the complete recommendations refer to the final recommendations posted on the CADTH website.

References

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