Technology Guidance

Review of cancer drugs

for previously treated advanced gastric cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion for treating patients with unresectable locally advanced or recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma after two or more prior systemic therapies in line with the following criteria:
  - Patients must not have received prior treatment with a PD-1/PD-L1 inhibitor for unresectable locally advanced or recurrent gastric or GEJ cancer; and
  - Nivolumab should be given as a weight-based dose up to a maximum of 240 mg every two weeks or 480 mg every four weeks.

Subsidy status

Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication with effect from 1 September 2022.

MAF assistance **does not** apply to any formulations or strengths of pembrolizumab, ramucirumab, regorafenib or trifluridine/tipiracil when used for previously treated advanced gastric cancer.

Clinical indications, subsidy class and MediShield Life claim limits for all drugs included in the evaluation are provided in the Annex.

Updated: 1 April 2026

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of nivolumab, pembrolizumab, ramucirumab, regorafenib, and trifluridine/tipiracil combination product (Lonsurf) for treating unresectable locally advanced, recurrent or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for all drugs was considered in line with their registered indications and/or specific clinical criteria defined by clinical experts to reflect the use of these drugs in local clinical practice. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE ascertain the clinical value of the drugs under evaluation and provided clinical advice on their appropriate and effective use based on the available clinical evidence.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1. Approximately 540 patients are diagnosed with gastric cancer each year in Singapore. For previously untreated patients with unresectable locally advanced, recurrent or metastatic gastric cancer, the Committee noted that chemotherapy and trastuzumab currently represent standard of care and are already subsidised.

2.2. Patients whose disease progresses after first-line systemic therapy are treated with chemotherapy (irinotecan or a taxane) or ramucirumab (as a single agent or in combination with paclitaxel) in local practice, in line with international clinical practice guidelines.

2.3. For patients whose disease progresses after two or more lines of systemic therapy, the treatment options used in local practice are chemotherapy (irinotecan or a taxane), nivolumab, trifluridine/tipiracil, pembrolizumab and regorafenib. While nivolumab and trifluridine/tipiracil are HSA-approved for this indication, the Committee heard that pembrolizumab and regorafenib have not yet been approved by HSA or a reputable overseas regulatory authority for treating gastric cancer irrespective of biomarker status in this line of therapy.

2.4. While irinotecan and taxanes are currently subsidised, the Committee acknowledged the clinical need to also consider nivolumab, ramucirumab and trifluridine/tipiracil for subsidy to improve treatment affordability and allow flexibility in treatment protocols. Given that pembrolizumab and regorafenib do not have regulatory approval for the indication under review and there are HSA-approved alternatives, the Committee considered that there was low clinical need to consider these drugs for subsidy at this time.

Clinical effectiveness and safety

3.1. Advanced gastric cancer that has progressed after first-line systemic therapy
The Committee reviewed the available clinical evidence from phase III randomised controlled trials (RCTs) for ramucirumab monotherapy (REGARD) and ramucirumab in combination with paclitaxel (RAINBOW). Both trials were conducted in patients with advanced or metastatic gastric or GEJ adenocarcinoma that had progressed after first-line chemotherapy.

3.2. The REGARD trial showed that ramucirumab plus best supportive care (BSC) led to an improvement in median overall survival (OS) of 1.4 months compared to placebo plus BSC. In terms of safety, hypertension was reported more frequently with ramucirumab compared to placebo, but the rates of other adverse events were similar between treatment groups.

3.3. In the RAINBOW trial, ramucirumab plus paclitaxel led to an improvement in median OS of 2.2 months compared to placebo plus paclitaxel. However, ramucirumab plus paclitaxel was associated with more events of grade 3 or 4 neutropenia and leucopenia, and grade 3 hypertension, abdominal pain and fatigue compared to placebo plus paclitaxel.

3.4. Advanced gastric cancer that has progressed after ≥2 lines of systemic therapy
The Committee reviewed the available clinical evidence from phase III RCTs for nivolumab (ATTRACTION-2) and trifluridine/tipiracil (TAGS). Both trials were conducted in patients with advanced or metastatic gastric or GEJ adenocarcinoma that was previously treated with at least two chemotherapy regimens.

3.5. In the ATTRACTION-2 trial, nivolumab led to an improvement in median OS of 1.12 months compared to placebo. The most frequently reported treatment-related adverse events in the nivolumab group were pruritus, diarrhoea, rash and fatigue.

3.6. In the TAGS trial, trifluridine/tipiracil plus BSC led to an improvement in median OS of 2.1 months compared to placebo plus BSC. The most frequently reported adverse events of any cause in the trifluridine/tipiracil group were neutropenia, anaemia, nausea and decreased appetite.

3.7. In view of the heterogeneous trial populations and differences in adverse event profiles between nivolumab and trifluridine/tipiracil, the Committee acknowledged that the comparative effectiveness and safety of the two treatments could not be assessed. In the absence of a head-to-head study showing superiority of one drug over the other, both treatments were considered to be clinically comparable for this indication.

3.8. For pembrolizumab and regorafenib, the Committee noted that the available clinical data from phase II trials was insufficient to determine their clinical effectiveness for this indication at this time.

Cost effectiveness

4.1. The manufacturers of nivolumab, ramucirumab and trifluridine/tipiracil were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration. However, the manufacturer of ramucirumab did not submit a pricing proposal, indicating that they did not wish for the drug to be considered for subsidy.

4.2. For pembrolizumab and regorafenib, no VBP proposals were requested from the manufacturers as the drugs did not have HSA approval for the indication under review.

4.3. Advanced gastric cancer that has progressed after first-line systemic therapy
In the absence of local cost-effectiveness studies, the Committee reviewed the evaluations of overseas HTA agencies for ramucirumab as monotherapy and in combination with paclitaxel. However, given that the drug prices used in the evaluations were not published or had included confidential discounts from the manufacturer, it was unknown whether the prices were comparable to those in Singapore and if the results were generalisable.

4.4. The Committee noted that the current price of ramucirumab in local public healthcare institutions was higher than the prices in overseas reference jurisdictions. The monthly treatment cost of ramucirumab was also substantially higher compared to chemotherapy (irinotecan and taxane). Hence, the Committee considered that it was unlikely that ramucirumab would be a cost-effective treatment for gastric cancer at the current price.

4.5. Advanced gastric cancer that has progressed after ≥2 lines of systemic therapy
No local cost-effectiveness studies were identified for the drugs under review for this indication. The Committee noted an evaluation by CADTH (Canada), which concluded that trifluridine/tipiracil plus BSC was not cost-effective versus BSC alone, with an incremental cost-effectiveness ratio (ICER) estimate of CA$174,465 per quality-adjusted life year (QALY) gained. These results were considered to be generalisable to the Singapore setting given that the price of trifluridine/tipiracil used in the analysis was similar to the proposed price in Singapore. For nivolumab, pembrolizumab and regorafenib, no economic evaluations by overseas HTA agencies were identified.

4.6. The Committee noted that the proposed price of trifluridine/tipiracil was considerably higher than overseas prices and its monthly treatment cost was also higher than nivolumab, which was competitively priced compared with overseas reference jurisdictions. Therefore, the Committee agreed that nivolumab was likely to represent a cost-effective treatment, while trifluridine/tipiracil was not considered to be cost-effective versus nivolumab on a cost-minimisation basis.

Estimated annual technology cost

5.1. Based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions, the annual cost impact in the first year of listing nivolumab on MAF was estimated to be less than SG$1 million for treating advanced gastric cancer that has progressed after two or more lines of systemic therapy.

Recommendations

6.1. Advanced gastric cancer that has progressed after first-line systemic therapy
Based on available evidence and in view that the manufacturer did not want their product considered for subsidy, the Committee did not recommend ramucirumab for listing on MAF for advanced gastric cancer after progression on first-line systemic therapy, due to unfavourable cost-effectiveness.

6.2. Advanced gastric cancer that has progressed after ≥2 lines of systemic therapy
Based on available evidence, the Committee recommended nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion be listed on MAF for advanced gastric cancer that has progressed after two or more lines of systemic therapy, in view of clinical need and acceptable clinical and cost-effectiveness.

6.3. The Committee did not recommend trifluridine/tipiracil for listing on MAF due to unfavourable cost-effectiveness compared to nivolumab at the proposed prices.

6.4. The Committee did not recommend pembrolizumab and regorafenib for listing on MAF due to uncertain clinical and cost-effectiveness.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Ramucirumab 100 mg/10 mL and 500 mg/50 mL concentrate for solution for infusion	Ramucirumab as monotherapy for patients with unresectable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.	Not recommended for subsidy	$1800 (1 Sep 2022)
	Ramucirumab in combination with chemotherapy for patients with unresectable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.^	Not recommended for subsidy	$1800 (1 Sep 2022)
Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion	Treatment of patients with unresectable locally advanced or recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma after 2 or more prior systemic therapies. Patients must not have received prior treatment with a PD-1/PD-L1 inhibitor for unresectable locally advanced or recurrent gastric or GEJ cancer. Nivolumab should be given as a weight-based dose up to a maximum of 240 mg every two weeks or 480 mg every four weeks.‡	MAF (1 Sep 2022)	$1800 (1 Sep 2022)
Trifluridine/ tipiracil 15 mg/6.14 mg and 20 mg/8.19 mg tablets	Treatment of patients with unresectable locally advanced or recurrent gastric or gastroesophageal junction adenocarcinoma after 2 or more prior systemic therapies.	Not recommended for subsidy	$1800 (1 Sep 2022)
Pembrolizumab 100 mg/4 mL solution for infusion	Treatment of patients with unresectable locally advanced or recurrent gastric or gastroesophageal junction adenocarcinoma after 2 or more prior systemic therapies.	Not recommended for subsidy	Not recommended for MediShield Life claims
Regorafenib 40 mg tablet	Treatment of patients with unresectable locally advanced or recurrent gastric or gastroesophageal junction adenocarcinoma after 2 or more prior systemic therapies.	Not recommended for subsidy	Not recommended for MediShield Life claims

Abbreviation: MAF, Medication Assistance Fund.
‡revised clinical indication with effect from 1 Feb 2023.
^revised clinical indication with effect from 1 Apr 2026.

VERSION HISTORY

Guidance on review of cancer drugs for previously treated advanced gastric cancer

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1.	**Publication of guidance**	
	Date of Publication	4 Jan 2022
2.	**Guidance updated to revise the clinical indication for nivolumab regarding weight-based dosing**	
	Date of Publication	7 Dec 2022
3.	**Guidance updated to revise the clinical indication for ramucirumab**	
	Date of Publication	1 Apr 2026