Technology Guidance

Nivolumab

for treating gastroesophageal cancers

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, 100 mg/10 mL and 240 mg/24 mL concentrate for solution for infusion for:
  - Adjuvant treatment of completely resected oesophageal or gastroesophageal junction (GEJ) cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy. Maximum treatment duration is 12 months.
  - Untreated, unresectable advanced or metastatic HER2 negative gastric cancer, GEJ cancer or oesophageal adenocarcinoma when used with fluoropyrimidine and platinum-based chemotherapy. Treatment with nivolumab should be stopped at 2 years, or earlier if disease progresses.
  - Treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy. Patients must not have received prior treatment with a PD-1/PD-L1 inhibitor for this condition in the unresectable advanced, recurrent or metastatic setting.

Funding status

Nivolumab 40 mg/4 mL, 100 mg/10 mL and 240 mg/24 mL concentrate for solution for infusion are recommended for inclusion on the Cancer Drug List (Medication Assistance Fund and MediShield Life monthly claim limit of SG$1800) for the abovementioned indications from 1 September 2022.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of nivolumab for three gastroesophageal cancer indications: (i) adjuvant treatment of completely resected oesophageal or gastroesophageal junction (GEJ) cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy; (ii) untreated, unresectable advanced or metastatic human epidermal growth factor receptor 2 (HER2) negative gastric cancer, GEJ cancer or oesophageal adenocarcinoma when used with fluoropyrimidine and platinum-based chemotherapy; and (iii) treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based combination chemotherapy.

1.2. 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 nivolumab was considered in line with its registered indications. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE ascertain the clinical value of nivolumab and provided clinical advice on its appropriate and effective use based on the available clinical evidence.

1.3. 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.

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

Clinical need

2.1. The Committee noted that approximately 650 patients are diagnosed with gastric, GEJ or oesophageal cancer each year in Singapore. Adenocarcinomas represent over 80% of gastric and GEJ cancers, while squamous cell carcinoma (79%) and adenocarcinoma (16%) are the most common types of oesophageal cancer. Among patients with advanced gastric, GEJ or oesophageal adenocarcinoma, at least 80%

of them have HER2-negative tumours.

2.2. The Committee noted that nivolumab was the only adjuvant treatment approved by the Health Sciences Authority (HSA) for patients with completely resected oesophageal or GEJ cancer who have received neoadjuvant chemoradiotherapy but have residual pathologic disease. Local clinical experts confirmed that prior to regulatory approval of adjuvant nivolumab, patients had limited treatment options and usually underwent routine surveillance without active treatment.

2.3. The Committee heard that patients with untreated, unresectable advanced or metastatic HER2 negative gastric cancer, GEJ cancer or oesophageal adenocarcinoma usually receive chemotherapy (e.g., fluoropyrimidine plus platinum) with or without nivolumab in local practice.

2.4. For patients with unresectable advanced, recurrent or metastatic OSCC whose disease is refractory or who are intolerant to one previous fluoropyrimidine- and platinum-based chemotherapy regimen, the Committee noted that nivolumab monotherapy or chemotherapy (irinotecan or a taxane) are most commonly used.

2.5. The Committee noted that many of the chemotherapies (such as CAPOX, FOLFOX, irinotecan, docetaxel, paclitaxel) used for gastroesophageal cancers were already included on the Cancer Drug List (CDL). However, they acknowledged the clinical need to consider nivolumab for funding to allow flexibility in treatment protocols, improve affordability, and ensure appropriate patient care.

Clinical effectiveness and safety

3.1. <u>Adjuvant treatment of resected oesophageal or GEJ cancer</u>
The Committee reviewed the available clinical evidence from a phase III randomised controlled trial (RCT, CheckMate 577) that compared nivolumab with placebo in patients with completely resected oesophageal or GEJ cancer who had received neoadjuvant chemoradiotherapy and had residual pathological disease. Treatment with nivolumab was given for up to one year or until disease recurrence or unacceptable toxicity.

3.2. At a median follow-up of 24.4 months, nivolumab led to a statistically significant improvement in disease-free survival (DFS) of 11.4 months compared with placebo. An updated analysis at a median follow-up of 32.2 months showed that the DFS benefit with nivolumab was maintained over placebo. The Committee noted that overall survival (OS) data was not yet available, but they agreed with local clinical experts that the DFS results were clinically meaningful in this patient population.

3.3. In terms of safety, nivolumab was associated with a higher incidence of treatment-related adverse events (TRAEs) compared with placebo. The most common TRAEs

reported with nivolumab were fatigue, diarrhoea, pruritus and rash, which were consistent with its known safety profile. Treatment discontinuation due to TRAEs occurred in 9% of patients in the nivolumab group compared with 3% in the placebo group.

3.4. Overall, the Committee considered that nivolumab provided superior efficacy but had an inferior safety profile compared with placebo as an adjuvant treatment for resected oesophageal or GEJ cancer.

3.5. Untreated advanced HER2 negative gastric cancer, GEJ cancer or oesophageal adenocarcinoma

The Committee reviewed the available clinical evidence for nivolumab from two phase III RCTs (CheckMate 649 and ATTRACTION-4). Treatment with nivolumab was given until disease progression or unacceptable toxicity in both trials, and for a maximum of two years in the CheckMate 649 trial.

3.6. Patients enrolled in CheckMate 649 had untreated, unresectable advanced or metastatic HER2 negative gastric, GEJ or oesophageal adenocarcinoma. At a minimum follow-up of 12.1 months, nivolumab plus chemotherapy (CAPOX or FOLFOX) led to a statistically significant improvement in OS of 2.2 months compared with chemotherapy alone in the intention-to-treat (ITT) population.

3.7. An updated analysis at a minimum follow-up of 24.0 months showed that the OS benefit with nivolumab plus chemotherapy was maintained. A longer progression-free survival (PFS) was also observed with nivolumab plus chemotherapy compared with chemotherapy alone.

3.8. ATTRACTION-4 enrolled patients from Asia with untreated, unresectable advanced or recurrent HER2 negative gastric or GEJ cancer, but did not include patients with oesophageal adenocarcinoma. Results showed that nivolumab plus chemotherapy (CAPOX or SOX) significantly improved PFS, but not OS, compared with placebo plus chemotherapy in the ITT population. The Committee considered that the OS results may have been confounded given that more patients in the placebo plus chemotherapy group received subsequent treatment with an immune checkpoint inhibitor compared with the nivolumab plus chemotherapy group.

3.9. In terms of safety, both trials showed that the addition of nivolumab to chemotherapy resulted in more Grade 3 - 4 TRAEs as well as adverse events leading to treatment discontinuation. Nonetheless, the Committee noted that the safety profile of nivolumab plus chemotherapy was consistent with the known safety profiles of the individual treatments and no new safety signals were observed.

3.10. Overall, the Committee considered that nivolumab plus chemotherapy provided superior efficacy but had an inferior safety profile compared with chemotherapy alone in patients with untreated advanced HER2 negative gastric cancer, GEJ cancer or oesophageal adenocarcinoma.

3.11. Previously treated advanced OSCC
The Committee reviewed the available clinical evidence from a phase III RCT (ATTRACTION-3) that compared nivolumab with chemotherapy (docetaxel or paclitaxel) in patients with unresectable advanced, recurrent or metastatic OSCC whose disease was refractory or who were intolerant to one previous fluoropyrimidine and platinum-based chemotherapy regimen. Treatment was continued until disease progression or unacceptable toxicity.

3.12. At a minimum follow-up of 36 months, nivolumab significantly improved OS by 2.4 months compared with chemotherapy. The Committee acknowledged that although the Kaplan-Meier curves for OS showed an initial advantage with chemotherapy, the curves crossed at around five months and showed sustained separation in favour of nivolumab.

3.13. In terms of safety, nivolumab was associated with fewer TRAEs (any grade and Grade 3 - 4) compared with chemotherapy. The incidence of TRAEs leading to treatment discontinuation was similar in both groups.

3.14. Overall, the Committee considered that nivolumab was superior in terms of efficacy and safety compared with chemotherapy in patients with previously treated advanced OSCC.

Cost effectiveness

4.1. The company of nivolumab was invited to submit a value-based pricing (VBP) proposal for funding consideration for the three gastroesophageal cancer indications under review. In the absence of local cost-effectiveness studies, the Committee noted that the company of nivolumab offered a pricing proposal that was competitive compared with overseas reference jurisdictions. Therefore, the Committee agreed that nivolumab was likely to represent a cost-effective treatment in the local setting for the three gastroesophageal cancer indications under review.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system in the first year of including nivolumab on the CDL for each indication was estimated to be:

- less than SG$1 million for adjuvant treatment of resected oesophageal or GEJ cancer;
- between SG$1 million to less than SG$3 million for untreated advanced HER2 negative gastric cancer, GEJ cancer or oesophageal adenocarcinoma; and
- less than SG$1 million for previously treated advanced OSCC.

Recommendations

6.1. Based on available evidence, the Committee recommended nivolumab 40 mg/4 mL, 100 mg/10 mL and 240 mg/24 mL concentrate for solution for infusion be included on the CDL (Medication Assistance Fund and MediShield Life monthly claim limit of SG$1800) for the following three indications in view of clinical need, and acceptable clinical and cost effectiveness:

- Adjuvant treatment of completely resected oesophageal or GEJ cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy. Maximum treatment duration is 12 months.
- Untreated, unresectable advanced or metastatic HER2 negative gastric cancer, GEJ cancer or oesophageal adenocarcinoma when used with fluoropyrimidine and platinum-based chemotherapy. Treatment with nivolumab should be stopped at 2 years, or earlier if disease progresses.
- Treatment of unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy. Patients must not have received prior treatment with a PD-1/PD-L1 inhibitor for this condition in the unresectable, advanced recurrent or metastatic setting.