Technology Guidance

# Immune Checkpoint Inhibitors and BRAF/MEK Inhibitors

## for treating advanced malignant melanoma

**Technology Guidance from the MOH Drug Advisory Committee**

## Guidance Recommendations

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

- ✓ Dabrafenib 50 mg and 75 mg capsules and trametinib 0.5 mg and 2 mg tablets;
- ✓ Nivolumab 40 mg/4 mL, 100 mg/10 mL concentrate for solution for infusion;
- ✓ Nivolumab 40 mg/4 mL, 100 mg/10 mL and 240 mg/24 mL concentrate for solution for infusion used in combination with ipilimumab 50 mg/10 mL concentrate for solution for infusion; and
- ✓ Pembrolizumab 100 mg/4 mL solution for infusion

for treating advanced malignant melanoma in line with specific clinical criteria.

### Subsidy status

Dabrafenib 50 mg and 75 mg capsules used in combination with trametinib 0.5 mg and 2 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for treating advanced unresectable or metastatic malignant melanoma in patients with a BRAF V600 mutation with effect from 4 January 2022.

Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion and pembrolizumab 100 mg/4 mL solution for infusion are recommended for inclusion on MAF for:

- adjuvant treatment of completely resected malignant melanoma with lymph node involvement; and
- treating advanced unresectable or metastatic malignant melanoma.

Nivolumab 40 mg/4 mL, 100 mg/10 mL and 240 mg/24 mL concentrate for solution for infusion used in combination with ipilimumab 50 mg/10 mL concentrate for solution for infusion are recommended for inclusion on the MAF for treating advanced unresectable or metastatic malignant melanoma.

MAF assistance for nivolumab, ipilimumab and pembrolizumab will be implemented from 1

**Updated: 1 August 2025**

September 2022. Treatments should be given in line with the dosing regimens outlined in the Annex.

MAF assistance **does not** apply to:

- dabrafenib 50 mg and 75 mg capsules used in combination with trametinib 0.5 mg and 2 mg tablets for adjuvant treatment of completely resected BRAF V600 mutation positive malignant melanoma with lymph node involvement; and
- cobimetinib 20 mg and vemurafenib 240 mg tablets.

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

# Factors considered to inform the recommendations for subsidy

## Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab) and BRAF/MEK inhibitors (cobimetinib, dabrafenib, trametinib, vemurafenib) for treating advanced malignant melanoma. 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 were considered in line with their registered indications. 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 use of ipilimumab, dabrafenib, vemurafenib and trametinib monotherapy, for advanced unresectable or metastatic malignant melanoma was outside the scope of the evaluation following advice from local clinical experts and ODS members who confirmed that there was no clinical need for these indications to be evaluated. The 200 mg strength of ipilimumab was excluded from evaluation as it is not commercially available in Singapore.

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 subsidy considerations.

## Clinical need

2.1. The Committee noted that approximately 60 to 80 patients are diagnosed with malignant melanoma each year in Singapore, of which up to 50% have a BRAF mutation. The Committee noted that immune checkpoint inhibitors and BRAF/MEK inhibitors have improved survival for patients with malignant melanoma compared with chemotherapy and acknowledged that there was a high clinical need to consider them for subsidy to improve treatment affordability and ensure appropriate patient care.

2.2. Adjuvant treatment following tumour resection

The Committee acknowledged that 1-year adjuvant therapy with a PD-1 inhibitor (pembrolizumab or nivolumab) or combination therapy with BRAF/MEK inhibitors for BRAF mutation positive tumours are standard of care for high-risk stage III resected melanoma. The Committee heard that PD-1 inhibitors are generally preferred over combination therapy with BRAF/MEK inhibitors due to their favourable toxicity profile and off-treatment efficacy in advanced disease.

2.3. Treatment of unresectable or metastatic malignant melanoma

In local clinical practice, the Committee heard that PD-1 inhibitor monotherapy is standard of care for treating unresectable or metastatic malignant melanoma while combination therapy with BRAF/MEK inhibitors are reserved for rapidly progressing, BRAF mutation positive tumours.

## Clinical effectiveness and safety

3.1. Adjuvant treatment following tumour resection

**Pembrolizumab and nivolumab**

The Committee reviewed the available clinical evidence for pembrolizumab and nivolumab (KEYNOTE 054 and CHECKMATE 038 trials) and considered that pembrolizumab and nivolumab demonstrated statistically and clinically significant improvements in recurrence-free survival (RFS) compared with routine surveillance and ipilimumab, respectively. While there was no direct comparison between nivolumab and routine surveillance, the Committee noted that a published indirect comparison by the PBAC (Australia) using ipilimumab as the common reference showed that nivolumab was likely to improve RFS compared to routine surveillance. The Committee noted the uncertainty in the magnitude of the clinical benefit for PD-1 inhibitors due to the immaturity of the overall survival (OS) data and agreed that there was a net clinical benefit for these patients. The Committee also noted that both drugs were generally well-tolerated with no detrimental effects on health-related quality of life.

3.2. **Combination therapy with dabrafenib/trametinib**

The Committee reviewed the available clinical evidence for dabrafenib plus trametinib (COMBI-AD trial) and considered that it demonstrated statistically and clinically significant improvements in RFS compared with placebo. The Committee noted that OS results were immature, and that dabrafenib plus trametinib resulted in more serious adverse events (AEs) compared with placebo.

3.3. Treatment of unresectable or metastatic malignant melanoma

**Pembrolizumab, nivolumab and combination therapy with nivolumab/ ipilimumab**

The Committee reviewed the available clinical evidence for immune checkpoint inhibitors (CHECKMATE 066 and 067 and KEYNOTE 006 trials) comparing a)

nivolumab versus dacarbazine and b) pembrolizumab, nivolumab and nivolumab plus ipilimumab versus ipilimumab alone in patients with unresectable or metastatic malignant melanoma. Patients were either treatment naïve (CHECKMATE trials) or had received at least one prior systemic therapy excluding ipilimumab (KEYNOTE 006). Results showed that nivolumab led to statistically significant PFS and OS gains compared to dacarbazine (CHECKMATE 066); and pembrolizumab, nivolumab and nivolumab plus ipilimumab were superior in PFS and OS compared with ipilimumab (KEYNOTE 006 and CHECKMATE 067). The Committee also noted that while survival gains with nivolumab plus ipilimumab were better than nivolumab monotherapy in CHECKMATE 067, the trial was not statistically powered to detect a difference between these treatments.

3.4. The Committee noted that the safety profiles of pembrolizumab and nivolumab were more favourable than chemotherapy and ipilimumab with fewer grade ≥3 AEs reported. The most commonly reported AEs for pembrolizumab and nivolumab were fatigue, itching, diarrhoea, and rash and nivolumab plus ipilimumab was associated with more AEs compared with nivolumab monotherapy.

3.5. **Combination therapy with dabrafenib/trametinib and vemurafenib/cobimetinib**
The Committee reviewed the available clinical evidence for BRAF/MEK inhibitors (co-BRIM, COMBI-d, COMBI-v trials) comparing a) vemurafenib plus cobimetinib versus vemurafenib and b) dabrafenib plus trametinib versus dabrafenib or vemurafenib in previously untreated, BRAF V600 mutation positive unresectable or metastatic malignant melanoma. The Committee noted that the results showed that both BRAF/MEK inhibitor combinations were superior in both PFS and OS compared to BRAF inhibitor monotherapy.

3.6. The Committee noted that combination therapy with BRAF/MEK inhibitors was generally tolerable with no difference in the incidence of grade ≥3 AEs compared with BRAF inhibitor monotherapy. They heard that combination therapy was associated with a higher incidence of pyrexia, retinopathy, decreased left ventricular ejection fraction and increased creatinine phosphatase levels compared to BRAF inhibitor monotherapy but was associated with fewer skin-related AEs including cutaneous squamous cell carcinoma and keratoacanthomas.

## Cost effectiveness

4.1. The companies of all drugs under evaluation were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration.

4.2. Adjuvant treatment following tumour resection
In the absence of local cost-effectiveness analyses (CEAs), the Committee reviewed results of evaluations from overseas HTA agencies for pembrolizumab and nivolumab compared to routine surveillance and noted the uncertainty in the ICERs. The

Committee also noted that the prices of both PD-1 inhibitors were comparable to overseas reference jurisdictions, and treatment costs were for a fixed 1-year duration. For BRAF mutation positive melanoma, the Committee acknowledged that combination therapy with BRAF/MEK inhibitors was unlikely to be cost-effective compared to pembrolizumab or nivolumab monotherapy.

4.3. Treatment of unresectable or metastatic malignant melanoma

**Pembrolizumab, nivolumab and combination therapy with nivolumab/ipilimumab**

In March 2021, the Committee reviewed results of evaluations from overseas HTA agencies for pembrolizumab and nivolumab monotherapy compared to ipilimumab and agreed that they were likely to be generalisable to the local context. The Committee noted that at the local proposed prices, the monthly treatment cost of nivolumab plus ipilimumab was much higher than PD-1 inhibitors and agreed it was unlikely to represent a cost-effective treatment.

4.4. In July 2022, the Committee considered that the company's revised proposal provided more certainty in ensuring the cost-effective use of healthcare resources for nivolumab plus ipilimumab.

4.5. **Combination therapy with dabrafenib/trametinib and vemurafenib/cobimetinib**

In the absence of local CEAs, the Committee reviewed results of evaluations from overseas HTA agencies for BRAF/MEK inhibitor combination therapy compared to BRAF inhibitor monotherapy and agreed that they were likely to be generalisable to the local context. The Committee acknowledged that the local proposed prices for dabrafenib and trametinib were comparable with overseas reference jurisdictions. Hence, they considered that dabrafenib in combination with trametinib was likely to represent a cost-effective treatment in the local context.

4.6. The Committee agreed that vemurafenib plus cobimetinib was not cost-effective versus dabrafenib plus trametinib on a cost-minimisation basis at the prices proposed by the company.

## Estimated annual technology cost

5.1. Adjuvant treatment following tumour resection

The Committee noted that the annual cost impact for pembrolizumab and nivolumab was estimated to be less than SG$1 million in the first year of listing on MAF based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions.

5.2. Treatment of unresectable or metastatic malignant melanoma

Based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions, the annual cost impact for each drug in the first year of listing

on MAF for treating unresectable or metastatic malignant melanoma was estimated to be:

- Dabrafenib plus trametinib (MAF): less than SG$1 million;
- Nivolumab (MAF): less than SG$1 million;
- Nivolumab plus ipilimumab (MAF): less than SG$1 million; and
- Pembrolizumab (MAF): less than SG$1 million.

## Recommendations

6.1. Adjuvant treatment of resected malignant melanoma with lymph node involvement
Based on available evidence, the Committee recommended listing nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion and pembrolizumab 100 mg/4 mL solution for infusion on the MAF for the adjuvant treatment of resected malignant melanoma with lymph node involvement, in view of the current therapeutic gap in the MOH List of Subsidised Drugs and acceptable clinical and cost-effectiveness at the prices proposed by the companies.

6.2. The Committee recommended not listing dabrafenib and trametinib combination therapy on MAF because of low clinical need and unfavourable cost-effectiveness compared with PD-1 inhibitors.

6.3. Treatment of unresectable or metastatic malignant melanoma
In March 2021, based on available evidence, the Committee recommended listing nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion, pembrolizumab 100 mg/4 mL solution for infusion and dabrafenib 50 mg and 75 mg capsules plus trametinib 0.5 mg and 2 mg tablets combination therapy on the MAF for treating unresectable or metastatic malignant melanoma, in view of the current therapeutic gap in the MOH List of Subsidised Drugs, favourable clinical effectiveness and acceptable cost effectiveness at the prices proposed by the companies.

6.4. In July 2022, following an acceptable revised proposal from the company, the Committee recommended nivolumab 40 mg/4 mL, 100 mg/10 mL and 240 mg/24 mL concentrate for solution for infusion used in combination with ipilimumab 50 mg/10 mL concentrate for solution for infusion be listed on the MAF for treating unresectable or metastatic malignant melanoma.

6.5. At the prices proposed by the company, vemurafenib plus cobimetinib combination therapy was not recommended for listing on the MAF due to unfavourable cost-effectiveness compared with dabrafenib plus trametinib combination therapy.

## ANNEX

**Recommendations by the MOH Drug Advisory Committee**

| Drug preparation | Clinical indications | Subsidy class (implementation date) | MediShield Life claim limit per month (implementation date) |
|---|---|---|---|
| **Adjuvant treatment of resected malignant melanoma** | | | |
| Pembrolizumab 100 mg/4 mL solution for infusion | Treatment of completely resected malignant melanoma in patients with lymph node involvement. Treatment must commence within 12 weeks of complete resection (either 12 weeks after resection or 12 weeks prior to resection). Maximum duration of treatment: 12 months.╬ | MAF (1 Sep 2022) | $1800 (1 Sep 2022) |
| Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion | Adjuvant treatment of completely resected malignant melanoma in patients with lymph node involvement. 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. Maximum duration of treatment: 12 months.‡ | MAF (1 Sep 2022) | $1800 (1 Sep 2022) |
| Dabrafenib 50 mg & 75 mg capsules plus trametinib 0.5 mg & 2 mg tablets | Dabrafenib in combination with trametinib for the adjuvant treatment of completely resected malignant melanoma in patients with BRAF V600 mutation-positive disease and lymph node involvement. Maximum duration of treatment: 12 months. | Not recommended for subsidy | $3800 (1 Sep 2022) |
| **Unresectable or metastatic malignant melanoma** | | | |
| Pembrolizumab 100 mg/4 mL solution for infusion | Treatment of advanced unresectable or metastatic malignant melanoma. Patients must not have received a PD-1 inhibitor or ipilimumab for advanced unresectable or metastatic melanoma. | MAF (1 Sep 2022) | $1800 (1 Sep 2022) |
| Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion | Monotherapy for advanced unresectable or metastatic malignant melanoma. Patients must not have received prior treatment with a PD-1 inhibitor or ipilimumab for advanced unresectable or metastatic malignant melanoma. 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) |
| Nivolumab 40 mg/4 mL, 100 mg/10 mL and 240 mg/24 mL concentrate for | Nivolumab in combination with ipilimumab for the treatment of advanced unresectable or metastatic malignant melanoma. The doses of nivolumab and ipilimumab should not exceed: 1 mg/kg | MAF (1 Sep 2022) | $7800† (1 Sep 2022) |

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|---|---|---|---|
| solution for infusion plus ipilimumab 50 mg/10 mL concentrate for solution for infusion^ | nivolumab and 3 mg/kg ipilimumab every 3 weeks for 4 doses. | | |
| Nivolumab 40 mg/4 mL, 100 mg/10 mL and 240 mg/24 mL concentrate for solution for infusion | Treatment of advanced unresectable or metastatic malignant melanoma, following induction treatment with nivolumab in combination with ipilimumab. 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) |
| Dabrafenib 50 mg and 75 mg capsules plus trametinib 0.5 mg and 2 mg tablets | Dabrafenib in combination with trametinib for the treatment of advanced unresectable or metastatic malignant melanoma in patients with a BRAF V600 mutation. Patients must not have received prior treatment with a BRAF/MEK inhibitor for metastatic melanoma. | MAF (4 Jan 2022) | $3800 (1 Sep 2022) |
| Vemurafenib 240 mg tablet plus cobimetinib 20 mg tablet | Vemurafenib in combination with cobimetinib for the treatment of advanced unresectable or metastatic malignant melanoma in patients with a BRAF V600 mutation. Patients must not have received prior treatment with a BRAF/MEK inhibitor for metastatic melanoma. | Not recommended for subsidy | Not recommended for MediShield Life claims |

Abbreviations: SDL, Standard Drug List; MAF, Medication Assistance Fund.
^ipilimumab 200 mg/40 mL concentrate for infusion for solution is not marketed in Singapore.
‡revised clinical indication with effect from 1 Feb 2023.
†change in MSHL claim limit with effect from 1 Feb 2023.
╬revised clinical indication with effect from 1 Aug 2025 .

# VERSION HISTORY

Immune checkpoint inhibitors and BRAF/MEK inhibitors for treating advanced malignant melanoma

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 with the following changes:**
   - extension of MAF listing to nivolumab plus ipilimumab for advanced malignant melanoma
   - clinical criteria for pembrolizumab and nivolumab (in Annex) revised to remove stopping criteria for advanced malignant melanoma

   Date of Publication 31 Aug 2022

3. **Guidance updated with the following changes:**
   - revised clinical criteria for nivolumab regarding weight-based dosing
   - MSHL claim limit for nivolumab plus ipilimumab increased from $5200/month to $7800/month

   Date of Publication 7 Dec 2022

4. **Guidance updated to revise clinical indication for pembrolizumab**

   Date of Publication 1 Aug 2025

Agency for Care Effectiveness - ACE  Agency for Care Effectiveness (ACE)

**About the Agency**

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 16 March 2021, 13 July 2022, 2 November and 11 November 2022. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

*Find out more about ACE at www.ace-hta.gov.sg/about*



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