Technology Guidance

Review of cancer drugs

for previously treated advanced hepatocellular carcinoma

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Cabozantinib 20 mg, 40 mg and 60 mg tablets; and
- ✓ Regorafenib 40 mg tablet

for treating advanced unresectable hepatocellular carcinoma in patients with disease progression after one or more prior lines of systemic therapy, and who have adequate liver function as assessed by the Child-Pugh scoring system.

Subsidy status

Regorafenib 40 mg tablet is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication with effect from 4 January 2022.

Cabozantinib 20 mg, 40 mg and 60 mg tablets are recommended for inclusion on the MAF for the abovementioned indication with effect from 1 September 2022.

MAF assistance **does not** apply to any formulations or strengths of ramucirumab, pembrolizumab, nivolumab and ipilimumab when used for previously treated advanced hepatocellular carcinoma.

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

Updated: 19 December 2022

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 cabozantinib, ramucirumab, regorafenib, pembrolizumab, nivolumab monotherapy, and nivolumab plus ipilimumab combination treatment for patients with previously treated advanced hepatocellular carcinoma in 2021. 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.

1.4. Following a negative subsidy recommendation in 2021 due to unfavourable cost-effectiveness, the manufacturer of cabozantinib submitted a revised price proposal, which the Committee considered in May 2022.

Clinical need

2.1. Approximately 740 patients are diagnosed with liver cancer each year in Singapore, and hepatocellular carcinoma (HCC) accounts for about 90% of all cases. For patients with advanced unresectable HCC that has progressed after one or more prior lines of systemic therapy, current treatment options in local practice include cabozantinib, ramucirumab, regorafenib, pembrolizumab or nivolumab monotherapy, and nivolumab plus ipilimumab combination therapy.

2.2. The Committee heard that among the six treatments, cabozantinib, ramucirumab and regorafenib were approved by HSA for treating HCC, while pembrolizumab, nivolumab, and nivolumab plus ipilimumab were only approved by overseas regulatory authorities and were yet to achieve HSA registration at the time of evaluation. Nonetheless, pembrolizumab and nivolumab (PD-1 inhibitors) were used in local practice as they represent treatment options with a different mechanism of action. Lenvatinib or sorafenib may also be considered as a subsequent-line treatment option if they have not been prescribed in an earlier setting. According to local clinicians, nivolumab plus ipilimumab combination therapy is rarely used because it is associated with more adverse drug reactions.

2.3. The Committee noted that HCC typically occurs in patients with cirrhosis and hepatic impairment. Therefore, the treatment approach and prognosis of patients will depend not only on the tumour stage but also on the underlying liver function. In local practice, the use of systemic therapies is limited to patients who have adequate liver function as assessed by the Child-Pugh scoring system.

2.4. The Committee acknowledged the clinical need to consider the HSA-approved treatments (cabozantinib, ramucirumab and regorafenib) and PD-1 inhibitors (pembrolizumab and nivolumab monotherapy) for subsidy to improve treatment affordability and allow flexibility in treatment protocols. Given that nivolumab plus ipilimumab combination therapy is rarely used in local practice, the Committee considered that there was low clinical need to consider it for subsidy at this time.

Clinical effectiveness and safety

3.1. The Committee reviewed the available clinical evidence from phase III randomised, placebo-controlled trials (RCTs) for cabozantinib (CELESTIAL), regorafenib (RESORCE), ramucirumab (REACH-2), and pembrolizumab (KEYNOTE-240), as well as a phase I/II multi-cohort trial (CheckMate-040) for nivolumab monotherapy and nivolumab plus ipilimumab combination therapy.

3.2. The CELESTIAL trial for cabozantinib was conducted in patients with advanced HCC who had received up to two previous systemic anticancer treatments including sorafenib, and who had Child-Pugh liver function class A. The trial results showed that cabozantinib provided a significant improvement in median overall survival (OS) of 2.2 months compared with placebo. In terms of safety, the most common grade 3 or 4 adverse events were palmar-plantar erythrodysesthesia, hypertension, increased aspartate aminotransferase (AST), fatigue and diarrhoea.

3.3. The RESORCE trial for regorafenib was conducted in patients with advanced HCC who had progressed on sorafenib treatment and had Child-Pugh liver function class A. The trial results showed that regorafenib provided a significant improvement in median OS of 2.8 months compared with placebo. The most common clinically relevant grade 3 or 4 treatment-emergent events were hypertension, hand-foot skin reaction, fatigue and diarrhoea.

3.4. The Committee heard that PBAC (Australia) had reviewed an indirect treatment comparison of cabozantinib versus regorafenib and considered that the two drugs were non-inferior in terms of OS and their safety profiles were likely to be comparable in clinical practice.

3.5. For ramucirumab, the REACH-2 trial was conducted in patients with advanced HCC who were previously treated with sorafenib and had Child-Pugh liver function class A. The patients also had increased serum alpha-fetoprotein (AFP) concentrations of ≥400 ng/mL at baseline, which could be indicative of a biologically distinct subtype of HCC that was associated with poor prognosis. The trial results showed that ramucirumab provided a significant improvement in median OS of 1.2 months compared with placebo. Hypertension and hyponatraemia were the most common grade ≥3 treatment-emergent adverse events that occurred in ≥5% of patients and at a higher frequency in the ramucirumab group compared to the placebo group.

3.6. The KEYNOTE-240 trial for pembrolizumab was conducted in patients with advanced HCC who were previously treated with sorafenib and had Child-Pugh liver function class A. The trial results showed that pembrolizumab did not achieve the prespecified statistical significance for the co-primary endpoints of OS and progression-free survival (PFS) when compared to placebo. In terms of safety, the grade ≥3 adverse events that occurred more frequently with pembrolizumab than placebo were increased AST, blood bilirubin and alanine aminotransferase (ALT) levels.

3.7. In the phase I/II non-comparative CheckMate-040 trial, nivolumab monotherapy and nivolumab plus ipilimumab combination therapy were studied in separate cohorts of patients with advanced HCC**.** Given the absence of an appropriate comparator arm in the trial, the Committee acknowledged that the results for both treatments could not be interpreted in a clinically meaningful manner.

3.8. Overall, the Committee agreed that there was sufficient clinical evidence to support the use of cabozantinib, regorafenib and ramucirumab for treating HCC. However, in the absence of head-to-head studies, a recommendation on the superiority of one drug over another could not be concluded.

3.9. The Committee noted that the pivotal trials of cabozantinib, regorafenib and ramucirumab had specifically enrolled patients who were previously treated with sorafenib. Nonetheless, they considered that it was appropriate for any subsidy listing of these agents to be extended to patients who were previously treated with other systemic therapies to allow flexibility in treatment protocols.

3.10. The Committee agreed that the use of pembrolizumab for treating HCC was not supported as the pivotal trial did not meet its primary endpoints. For nivolumab monotherapy and nivolumab plus ipilimumab combination therapy, the Committee considered that their clinical benefit versus placebo and the HSA-approved treatments was uncertain based on the available evidence from a non-comparative trial.

Cost effectiveness

4.1. The manufacturers of cabozantinib, ramucirumab and regorafenib 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, nivolumab and ipilimumab, no VBP proposals were requested from the manufacturers as these products have not been approved by HSA for treating HCC. Given that the clinical effectiveness of these treatments was uncertain, the Committee did not assess their cost-effectiveness in this indication.

4.3. For cabozantinib, ramucirumab and regorafenib, no local cost-effectiveness studies in patients with HCC were identified. Hence, the Committee reviewed evaluations from overseas HTA agencies for cabozantinib and regorafenib. No overseas evaluations for ramucirumab were identified.

4.4. Based on the evaluations by CADTH (Canada), cabozantinib and regorafenib were not cost-effective versus best supportive care (BSC). However, the results were not considered generalisable to the Singapore context as the drug prices used in the analyses were higher than local proposed prices. In the evaluations by PBAC (Australia) and NICE (UK), the drug prices were not published or had included confidential discounts from the manufacturers, thus it was unknown whether their prices were comparable to those in Singapore and if the results were generalisable.

4.5. The Committee acknowledged that the price proposed for regorafenib was comparable to prices in overseas reference jurisdictions, thus it was likely to represent a cost-effective treatment for HCC in the local setting. When compared with regorafenib, the monthly treatment cost of cabozantinib was higher based on the prices proposed in 2021. Hence, cabozantinib was not cost-effective versus regorafenib on a cost-minimisation basis.

4.6. In May 2022, following a revised price proposal from the manufacturer, the Committee agreed that the treatment cost of cabozantinib was reasonable and could be considered an acceptable use of healthcare resources.

Estimated annual technology cost

5.1. Based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions, the total annual cost impact in the first year of listing cabozantinib and regorafenib on the MAF for previously treated advanced HCC was estimated to be less than SG$1 million.

Recommendations

6.1. In 2021, the Committee recommended regorafenib 40 mg tablet be listed on MAF for previously treated advanced HCC in view of clinical need, and favourable clinical and cost-effectiveness at the price proposed by the manufacturer.

6.2. The Committee did not recommend cabozantinib and ramucirumab for listing on MAF due to unfavourable cost-effectiveness compared with regorafenib, and in view that the manufacturer of ramucirumab did not want their product considered for subsidy.

6.3. The Committee did not recommend pembrolizumab, nivolumab, and nivolumab plus ipilimumab combination therapy for listing on MAF due to uncertain clinical effectiveness.

6.4. In May 2022, the Committee recommended cabozantinib 20 mg, 40 mg and 60 mg tablets be listed on MAF for previously treated advanced HCC following an acceptable price proposal from the manufacturer which improved its 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)
Regorafenib 40 mg tablet	Treatment of advanced unresectable hepatocellular carcinoma in patients with disease progression after 1 or more prior lines of systemic therapy, and who have adequate liver function as assessed by the Child-Pugh scoring system.	MAF (4 Jan 2022)	$1800 (1 Sep 2022)
Cabozantinib 20 mg, 40 mg and 60 mg tablets	Treatment of advanced unresectable hepatocellular carcinoma in patients with disease progression after 1 or more prior lines of systemic therapy, and who have adequate liver function as assessed by the Child-Pugh scoring system.	MAF (1 Sep 2022)	$1800 (1 Sep 2022)
Ramucirumab 100 mg/10 mL and 500 mg/50 mL concentrate for solution for infusion	Treatment of advanced unresectable hepatocellular carcinoma in patients with disease progression after 1 or more prior lines of systemic therapy, and who have serum alpha-fetoprotein (AFP) of ≥400 ng/mL, and have adequate liver function as assessed by the Child-Pugh scoring system.	Not recommended for subsidy	$1800 (1 Sep 2022)
Pembrolizumab 100 mg/4 mL solution for infusion	Treatment of advanced unresectable hepatocellular carcinoma (HCC) in patients with disease progression after 1 or more prior lines of systemic therapy, and who have adequate liver function as assessed by the Child-Pugh scoring system. Patients must not have received prior treatment with a PD-1/PD-L1 inhibitor for advanced unresectable HCC. Treatment with pembrolizumab should be stopped at 2 years, or earlier if disease progresses.	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 advanced unresectable hepatocellular carcinoma (HCC) in patients with disease progression after 1 or more prior lines of systemic therapy, and who have adequate liver function as assessed by the Child-Pugh scoring system. Patients must not have received prior treatment with a PD-1/PD-L1 inhibitor for advanced unresectable HCC. 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. Treatment with nivolumab should be stopped at 2 years, or earlier if disease progresses.‡	Not recommended for subsidy	$1800 (1 Sep 2022)

Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion	Nivolumab in combination with ipilimumab for treatment of advanced unresectable hepatocellular carcinoma (HCC) in patients with disease progression after 1 or more prior lines of systemic therapy, and who have adequate liver function as assessed by the Child-Pugh scoring system. Patients must not have received prior treatment with a PD-1/PD-L1 inhibitor for advanced unresectable HCC. The doses of nivolumab and ipilimumab should not exceed: 1 mg/kg nivolumab and 3 mg/kg ipilimumab every 3 weeks for 4 doses, followed by nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks as a single agent. Treatment with nivolumab should be stopped at 2 years, or earlier if disease progresses. Re-induction with ipilimumab is not allowed.	Not recommended for subsidy	$1800 (1 Sep 2022)

Abbreviations: MAF, Medication Assistance Fund; PD-1/PD-L1, Programmed Cell Death 1/ Programmed Cell Death Ligand 1

‡revised clinical indication with effect from 1 Feb 2023.

VERSION HISTORY

Guidance on review of cancer drugs for previously treated advanced hepatocellular carcinoma

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 extend MAF listing to cabozantinib**
   Date of Publication 12 Jul 2022

3. **Guidance updated to revise the clinical indication for nivolumab regarding weight-based dosing**
   Date of Publication 19 Dec 2022

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, 2 July 2021, 20 May 2022 and 2 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

Chief HTA Officer
Agency for Care Effectiveness
Email: ACE_HTA@moh.gov.sg