Technology Guidance

[GUIDANCE IS OUTDATED AND HAS BEEN WITHDRAWN ON 31 AUGUST 2022. PLEASE REFER TO GUIDANCE ON *UPDATE OF MOH LIST OF SUBSIDISED DRUGS TO INCLUDE TREATMENTS FOR VARIOUS CANCER CONDITIONS* FOR UP TO DATE SUBSIDY INFORMATION ON THIS TOPIC].

Tyrosine Kinase Inhibitors, Immune Checkpoint Inhibitors and Everolimus

for treating advanced renal cell cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Ipilimumab 50 mg/10 mL concentrate for solution for infusion;
- ✓ Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion; and
- ✓ Pazopanib 200 mg and 400 mg tablets

for treating advanced renal cell cancer (RCC) in line with specific clinical criteria.

Subsidy status

Pazopanib 200 mg and 400 mg tablets are recommended for inclusion on the MOH Standard Drug List (SDL) for treating advanced RCC with effect from 4 January 2022.

Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion and ipilimumab 50 mg/10 mL concentrate for solution for infusion used as combination therapy are recommended for inclusion on the Medication Assistance Fund (MAF) for untreated intermediate- or poor-risk advanced RCC. Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion is recommended for inclusion on the MAF as monotherapy for previously treated advanced RCC.

MAF assistance will be implemented from 1 September 2022.

SDL subsidy and MAF assistance **does not** apply to axitinib 1 mg and 5 mg tablets, avelumab 200 mg/10 mL concentrate for solution for infusion, cabozantinib 20 mg, 40 mg and 60 mg

capsules, everolimus 2.5 mg, 5 mg and 10 mg tablets, lenvatinib 4 mg and 10 mg capsules, pembrolizumab 100 mg/4 mL solution for infusion and sunitinib 12.5 mg, 25 mg, 37.5 mg and 50 mg capsules when used to treat advanced RCC.

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 tyrosine kinase inhibitors (TKIs; axitinib, cabozantinib, lenvatinib, pazopanib, sunitinib), immune checkpoint inhibitors (avelumab, ipilimumab, nivolumab, pembrolizumab) and everolimus for treating advanced renal cell cancer (RCC). Of these drugs, pazopanib and sunitinib were previously considered by the Committee for first-line treatment of advanced RCC in 2018. 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 bevacizumab in combination with interferon alfa-2a and temsirolimus for untreated advanced RCC; and the use of sorafenib for advanced RCC in patients who have failed or are unsuitable for prior systemic therapy were outside the scope of the evaluation following advice from local clinical experts and ODS members 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 acknowledged that RCC is the most common type of kidney cancer among adults in Singapore with approximately 160 patients diagnosed with advanced and/or metastatic RCC each year. The Committee noted that only 20% of patients with stage IV disease live for up to 5 years and acknowledged that there was a high clinical need to consider treatments for subsidy to improve affordability and ensure appropriate patient care.

2.2. Untreated advanced RCC

In local clinical practice, the Committee noted that TKIs and immune checkpoint inhibitors are standard of care for treating newly diagnosed, advanced and/or metastatic RCC, in line with international clinical practice guidelines. None of these treatments are currently included in the MOH List of Subsidised Drugs, representing a therapeutic gap.

2.3. Previously treated advanced RCC

The Committee heard from clinical experts that 50-60% of patients will have progressive disease following first-line treatment. Considering these patients had limited treatment options and poor prognoses, the Committee agreed there was a high clinical need to provide them with a subsidised treatment. They noted that nivolumab monotherapy is routinely used for patients who have received prior TKI therapy, while TKIs are generally prescribed for patients who have received prior immune checkpoint inhibitor therapy.

Clinical effectiveness and safety

3.1. Untreated advanced RCC

Sunitinib and pazopanib

The Committee considered the clinical evidence for sunitinib and pazopanib and noted that sunitinib only demonstrated a marginal overall survival (OS) benefit compared to interferon alfa-2a (HR=0.821, 95% CI 0.673 to 1.001; p=0.051) in the pivotal trial. No other clinical trials demonstrated an OS benefit for either sunitinib or pazopanib compared to any other first-line treatments for RCC. With respect to progression-free survival (PFS), results indicated that sunitinib and pazopanib were both statistically significantly superior to interferon alfa-2a and placebo, respectively (sunitinib: median PFS gain of 11 months versus 5 months for interferon alfa-2a; HR 0.539, 95% CI 0.451 to 0.643, p<0.001; pazopanib: median PFS of 11.1 months versus 2.8 months for placebo; HR 0.40, 95% CI 0.27 to 0.60, p<0.0001).

3.2. The Committee further acknowledged that pazopanib was noninferior to sunitinib for PFS in a head-to-head (COMPARZ) trial (HR: 1.05, 95%CI: 0.90 to 1.22), and both drugs had a different safety profile. Sunitinib was associated with more fatigue, hand-foot syndrome and thrombocytopenia while pazopanib was associated with more liver

impairment.

3.3. **Cabozantinib**
The Committee reviewed the available clinical evidence for cabozantinib (CABOSUN, a phase II study) and acknowledged that while the trial showed improved PFS with cabozantinib versus sunitinib, the magnitude of the benefit was uncertain given the small sample size and high risk of bias of the clinical trial (e.g. open-label design and substantial differences in the investigator-assessed and IRC analyses of PFS). The Committee also noted that there was no statistically significant difference with respect to OS or adverse events between the drugs. The Committee also noted similar conclusions were made by overseas HTA agencies.

3.4. **Nivolumab plus ipilimumab and axitinib plus either pembrolizumab or avelumab**
The Committee reviewed the available clinical evidence for the immune checkpoint inhibitors (CHECKMATE 214, KEYNOTE 426 and JAVELIN Renal 101) for previously untreated advanced RCC and acknowledged that nivolumab plus ipilimumab led to superior OS compared to sunitinib. The Committee noted that statistically significantly longer PFS compared to sunitinib was only observed in the intermediate- and poor-risk subgroups (primary efficacy population). For axitinib plus either pembrolizumab or avelumab, the Committee noted that OS data remained immature, although PFS for these combinations was statistically significantly longer than sunitinib.

3.5. The Committee also acknowledged results from indirect evidence by Monteiro et al 2020 which suggested that all three checkpoint inhibitor combinations were comparable in clinical efficacy with no significant difference in improved survival compared with sunitinib.

3.6. <u>Previously treated advanced RCC</u>
Cabozantinib, nivolumab, lenvatinib plus everolimus, axitinib and everolimus
The Committee reviewed five pivotal trials (METEOR, CHECKMATE 025, Study 205, AXIS, and RECORD-1) in patients with previously treated advanced and/or metastatic RCC and noted that cabozantinib, nivolumab and lenvatinib plus everolimus led to statistically significantly longer OS compared with everolimus, while axitinib did not improve OS compared with sorafenib. The Committee also noted that the results for lenvatinib plus everolimus were based on a small-scale, open-label phase 2 trial (Study 205) with a high risk of bias.

3.7. The Committee acknowledged results from indirect evidence considered by NICE (UK) which suggested that nivolumab and cabozantinib were comparable in clinical efficacy and superior to everolimus in terms of OS. The Committee also noted that local experts considered TKIs to be clinically comparable.

Cost effectiveness

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

4.2. Untreated advanced RCC

The Committee noted that at the 2018 meeting, sunitinib and pazopanib were not considered to be cost-effective, with base-case incremental cost-effectiveness ratios (ICERs) of >$105,000 per QALY gained compared to interferon alfa. In 2021, following revised price proposals from both manufacturers, the Committee agreed that the revised cost of pazopanib, which was comparable with overseas reference jurisdictions, was reasonable and could be considered an acceptable use of healthcare resources. Sunitinb remained at a higher cost compared with pazopanib and was not considered cost-effective.

4.3. The Committee considered the economic evaluation conducted by ACE and noted that nivolumab plus ipilimumab was associated with a favourable base-case ICER of <SG$15,000 per QALY gained compared with sunitinib.

4.4. The Committee also noted that the local proposed prices for axitinib and cabozantinib were higher than overseas reference jurisdictions and the average monthly treatment costs of axitinib plus pembrolizumab, axitinib plus avelumab, and cabozantinib were higher than nivolumab plus ipilimumab. Hence, the Committee agreed that these treatments were not likely to represent cost-effective treatments for RCC in the local context.

4.5. Previously treated advanced RCC

In the absence of local cost-effectiveness evaluations, the Committee reviewed published economic analyses of drugs used in previously treated advanced RCC from overseas HTA agencies. The Committee noted that the price of nivolumab was comparable to prices in overseas reference jurisdictions. At the local proposed prices, its monthly treatment cost was also lower than that of cabozantinib, lenvatinib plus everolimus, axitinib and everolimus.

4.6. The Committee agreed that nivolumab was likely to represent a cost-effective treatment for previously treated advanced RCC, while cabozantinib or other TKIs were not considered to be cost-effective versus nivolumab on a cost-minimisation basis.

Estimated annual technology cost

5.1. Treatment of advanced RCC

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 SDL or MAF for treating advanced RCC was estimated to be:

- Pazopanib (SDL): less than SG$1 million;
- Nivolumab (MAF): between SG$1 million to less than SG$3 million; and

- Ipilimumab (MAF): less than SG$1 million;

Recommendations

6.1. Untreated advanced RCC

Based on available evidence, the Committee recommended:

- pazopanib 200 mg and 400 mg tablets be listed on SDL; and
- nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion used in combination with ipilimumab 50 mg/10 mL concentrate for solution for infusion be listed on MAF for untreated intermediate- or poor-risk advanced RCC

in view of the therapeutic gap in the MOH List of Subsidised Drugs and favourable clinical and cost-effectiveness.

6.2. The Committee recommended not listing axitinib in combination with either pembrolizumab or avelumab, cabozantinib or sunitinib on the MAF due to unfavourable cost-effectiveness compared with subsidised alternatives.

6.3. Previously treated advanced RCC

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 previously treated advanced RCC, in view of the therapeutic gap in the MOH List of Subsidised Drugs and favourable clinical and cost-effectiveness.

6.4. The Committee recommended not listing axitinib, cabozantinib, everolimus or lenvatinib used in combination with everolimus on the MAF in view of the low clinical need and unfavourable cost-effectiveness compared with subsidised alternatives.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy Class (implementation date)	MediShield Life claim limit per month (implementation date)
Advanced renal cell cancer			
Pazopanib 200 mg and 400 mg tablets	Treatment of advanced renal cell carcinoma.	SDL (4 Jan 2022)	$1600 (1 Sep 2022)
Sunitinib 12.5 mg, 25 mg, 37.5 mg and 50 mg capsules	Treatment of advanced renal cell carcinoma.	Not recommended for subsidy	$1600 (1 Sep 2022)
Advanced renal cell cancer (previously untreated)			
Cabozantinib 20 mg, 40 mg, 60 mg capsules	For untreated intermediate- or poor-risk advanced renal cell carcinoma.	Not recommended for subsidy	$1800 (1 Sep 2022)
Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion in combination with ipilimumab 50 mg/10 mL concentrate for solution for infusion^	For untreated intermediate- or poor-risk advanced renal cell carcinoma. The doses of nivolumab and ipilimumab should not exceed: 3mg/kg nivolumab and 1mg/kg ipilimumab every 3 weeks for 4 doses. Re-induction with ipilimumab is not allowed.	MAF (1 Sep 2022)	$5200 (1 Sep 2022)
Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion	For untreated intermediate- or poor-risk advanced renal cell carcinoma, following induction treatment with nivolumab in combination with ipilimumab. The dose of nivolumab should not exceed 3mg/kg every 2 weeks. Treatment with nivolumab should be stopped at 2 years, or earlier if disease progresses.	MAF (1 Sep 2022)	$1800 (1 Sep 2022)
Pembrolizumab 100 mg/4 mL solution for infusion in combination with axitinib 1 mg and 5 mg tablets	For untreated advanced renal cell carcinoma. Treatment with PD-1/PD-L1 inhibitor should be stopped at 2 years, or earlier if disease progresses.	Not recommended for subsidy	$1800 (1 Sep 2022)
Avelumab 200 mg/ 10 mL concentrate for solution for infusion in combination with axitinib 1 mg and 5 mg tablets	For untreated advanced renal cell carcinoma. Treatment with PD-1/PD-L1 inhibitor should be stopped at 2 years, or earlier if disease progresses.	Not recommended for subsidy	$1800 (1 Sep 2022)

Advanced renal cell cancer (previously treated)			
Cabozantinib 20 mg, 40 mg, 60 mg capsules	For previously treated advanced renal cell carcinoma.	Not recommended for subsidy	$1800 (1 Sep 2022)
Nivolumab 40 mg/4 mL and 100 mg/10 mL concentrate for solution for infusion	For previously treated advanced renal cell carcinoma (RCC). Patients must not have received prior treatment with a PD-1/PD-L1 inhibitor for RCC. The dose of nivolumab should not exceed 3mg/kg every 2 weeks. Treatment with nivolumab should be stopped at 2 years, or earlier if disease progresses.	MAF (1 Sep 2022)	$1800 (1 Sep 2022)
Axitinib 1 mg and 5 mg tablets	For previously treated advanced renal cell carcinoma.	Not recommended for subsidy	$1600 (1 Sep 2022)
Lenvatinib 4 mg and 10 mg capsules in combination with everolimus 2.5 mg, 5 mg and 10 mg tablets	For previously treated advanced renal cell carcinoma.	Not recommended for subsidy	$1200 (1 Sep 2022)
Everolimus 2.5 mg, 5 mg and 10 mg tablets	For previously treated advanced renal cell carcinoma.	Not recommended for subsidy	$1200 (1 Sep 2022)

Abbreviations: SDL, Standard Drug List; MAF, Medication Assistance Fund.
^ipilimumab 200 mg/40 mL concentrate for infusion for solution is not marketed in Singapore

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. 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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