A.22 PD-1 / PD-L1 immune checkpoint inhibitors – EML

Reviewer summary

☒ Supportive of the proposal (in part)

☐ Not supportive of the proposal

Justification (based on considerations of the dimensions described below):

The solid tumors amenable to effective but non-curative therapy using immune checkpoint inhibitors (ICIs) represent major causes of rising burdens with respect lives lost and costs of management in LMICs. The case for inclusion of ICIs on the EML has already been made for the treatment of metastatic melanoma, where indeed therapy can be curative. The major barriers to use of ICIs in LMICs is cost of acquisition and ability to provide sufficient supportive care when severe immune-mediated toxicities emerge.

The application provides an excellent compilation of data for 8 ICIs, and proposes listing for 26 ICI and disease indication pairings. It summarizes the issues around testing for PD-L1 to assess whether expression exceeds arbitrary levels for many indications, including the fact that regulatory approval is often based on such parameters. It also addresses the advantages and disadvantages of considering these agents as monotherapies or in combinations with other drugs, which themselves may or may not be listed on the EML.

The opinions of the Cancer Expert Committee also provide important factors for consideration, as do the issues raised in the paper about financial impact and how this is subject to a changing patent landscape and other mechanisms by which cost of acquisition may change over the next 5 – 10 years. The responses of the sponsors also provided important context, including reinforcing some of the points made in the financial impact document.

This reviewer notes that the Cancer Expert panel preferred to prioritise drug:indication pairs where the weight of evidence strongly favored the ICI both with respect overall survival and common, significant toxicity. Consequently, monotherapy indications were elevated in their recommendations over combination therapies where a trade-off between additional efficacy and additional significant toxicity would typically occur. Such an approach is compelling as it provides the route with the highest chance of concentrating expenditure into areas with the most favorable incremental gain in efficacy:toxicity ratio. As a way of more broadly introducing these drugs into the health system for diseases other than metastatic melanoma, this is supported. However, this should not be to the exclusion of combination therapy where that has the greatest evidence eg endometrial cancer with dMMR or MSI-H. In metastatic melanoma, there is strong evidence of a beneficial effect of nivolumab combined with ipilimumab over single ICI on survival, at the cost of additional toxicity and great expense. The Cancer Expert panel's advice to deprioritise this regimen until single agent nivolumab or pembrolizumab have substantial uptake is persuasive.

Options for considering whether different ICIs have sufficiently similar efficacy and safety to allow formation of therapeutic group(s) have been considered and not recommended by the applicant, nor by the Cancer Expert panel, nor by sponsors. This is an option that could be reconsidered in future years after some key gaps in evidence are closed.

This reviewer is persuaded that the evidence supports recommendations for listing on the EML:

Indication	ICIs
Non-small cell lung cancer, without oncogenic driver, and PD-L1 expression ≥50%	Pembrolizumab, Cemiplimab, Atezolizumab
Colorectal cancer (deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H))	Pembrolizumab
Cervical cancer with PD-L1 expression >1%	Pembrolizumab (with chemotherapy)
Endometrial cancer (dMMR/MSI-H)	Dostarlimab combined with chemotherapy

	It is important that several ICIs and several indications are included in the EML to enable these breakthrough medicines to become more readily available for the majority of patients with responsive cancers / indications in the world.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval?	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable