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A.22 PD-1/PD-L1 Immune Checkpoint Inhibitors

MSF supports the application from the WHO Collaborating Center on Evidence Synthesis and Evaluation of Novel Cancer Therapies for the inclusion of the six immune checkpoint inhibitors, atezolizumab, cemiplimab, dostarlimab, durvalumab, ipilimumab, and tremelimumab to the Complementary List of the WHO Model List of Essential Medicines (EML), for adult patients with solid cancers in palliative first line setting, and for extension of the indications for nivolumab and pembrolizumab which are currently listed as therapeutic alternatives for the treatment of malignant melanoma.

According to the International Agency for Research on Cancer (IARC), there were 20 million new cancer cases and 9.7 million deaths in 2022. About 1 in 5 people develop cancer in their lifetime, approximately 1 in 9 men and 1 in 12 women die from cancer. A critical concern is the persistently high rate of advanced-stage cancer at initial diagnosis, particularly in low- and middle-income countries (LMICs), where limited access to early screening, treatment and access to effective palliative therapies exacerbates outcomes and survival disparities.

Since the early 2000s, a new therapeutic class has emerged in oncology: immune checkpoint inhibitors (ICIs). Their mechanism of action is based on the recognition of cancer cells by the patient's immune system. Three classes of ICIs are at a more advanced stage of development in oncology: PD-1 inhibitors, PDL-1 inhibitors, and anti-CTLA4. These are monoclonal antibodies administered intravenously.

The development of ICIs began in the management of metastatic melanomas, leading to tumor response rates and durations of response never seen before, resulting in rapid approval for clinical use (as early as 2011). Since then, the indications have continued to expand across the majority of tumor subtypes. ICIs can be used alone (as monotherapy or as a combination of 2 ICIs) or in combination with other therapeutic classes (chemotherapies, anti-angiogenic agents).

The application provides a synthesis of high-quality clinical trial data and systematic reviews supporting the efficacy and safety of ICIs in the first-line palliative setting. It highlights improved overall survival, durable responses, and favorable toxicity profiles compared to standard of care selected patient populations. When ICIs are used alone, most studies also report improvement in quality of life compared to standard of care. Also of interest are the results observed in virus-induced cancers such as hepatocellular carcinoma or cervical cancers, which have a particularly high incidence in LMICs: in all these trials, complete responses were reported. In the event of a complete response, this could be prolonged over time, even after stopping ICIs, eventually leading to cures.

However, these positive outcomes are limited to some subgroups of patients. Indeed, most of these trials selected the patients based on predictive testing. Most of the time, the selection is based on the expression of PDL-1, and it is usually observed that the stronger the expression of PDL-1 is, the better the chance of response. Another predictive test is the identification of “MSI” tumors (MicroSatellite Instability tumors). This is a rare situation, more frequent in colorectal, endometrial and gastric cancers. These MSI tumors are very sensitive to ICIs which should be, nowadays, the

preferred regimen for these patients. Both of these predictive tests are immunohistochemistry tests that could be implemented in LMICs.

The results in first-line metastatic cancers are such that ICIs are now continuing their development in early stages of cancers with very interesting data in terms of overall survival.

According to the application, ICIs such as pembrolizumab and nivolumab have demonstrated significant survival benefits and improved quality of life in a range of advanced solid cancers, including but not limited to non-small cell lung cancer, melanoma, renal cell carcinoma, and head and neck cancers.

MSF would like to draw the attention of the Expert Committee to the following points:

- ICIs represent a significant advance in cancer care but are associated with very high prices, posing serious challenges for health systems, especially in LMICs.
- The potential for biosimilar versions of pembrolizumab and nivolumab to enter the market could reduce the prices, thus development, prequalification, and uptake of biosimilars should be supported.
- The inclusion of ICIs as essential medicines would be an important step towards equitable access, by guiding national policy and procurement, in order to help reduce disparities in cancer care and to support countries in achieving better health coverage for cancer patients.
- ICIs remain very expensive therapies. To enable access to these innovative treatments, a dialogue must be initiated with ministries of health, treatment providers, civil society, and manufacturers to work towards pooled forecasting, coordinated procurement, preferential prices for LMICs, and ultimately, equitable access.

Considering all these elements, MSF urges the 25th Expert Committee on the Selection and Use of Essential Medicines to include atezolizumab, cemiplimab, dostarlimab, durvalumab, ipilimumab, and tremelimumab to the Complementary List of the WHO Model List of Essential Medicines, for adult patients with solid cancers in palliative first line setting, and to extend the indications for nivolumab and pembrolizumab which are currently listed as therapeutic alternatives for the treatment of malignant melanoma.

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