EXPERT CONSULTATION MEETING ON CANCER MEDICINE CANDIDATES FOR THE 2025 MODEL LISTS OF ESSENTIAL MEDICINES, 23-24 JANUARY 2025

Evaluations and Advice for the Expert Committee on the Selection and Use of Essential Medicines

Contents

INTRODUCTION:

Over the past decade, each update to the Model List of Essential Medicines (EML) and Essential Medicines for Children (EMLc) has seen many applications focusing on medicines against cancer being proposed for evaluation. This trend is consistent with the fact that more than half of new medicines entering the market are cancer medicines, which can be differentiated by the magnitude of benefit they provide (e.g., small versus large) (1-3). The 2025 EML update is not an exception, with a large proportion of medicines targeting cancers.

The WHO Department of Health Product Policies and Standards, in collaboration with the Department of Non-Communicable Diseases, solicited expert views on considerations about the clinical value and feasibility related to the cancer medicines proposed for addition to the EML. The goals of the Cancer Experts consultation were to review the evidence on benefits supporting the use of cancer medicines not included in the Model Lists, prioritize cancers for which the medicines were associated with the best outcomes in terms of survival, and anticipate controversial issues regarding the selection and use of the selected cancer medicines. The Cancer Experts propose a list of medicines that could be prioritized for the 2025 update of the Model Lists and offer several strategies to improve access and affordability.

Final remarks from the Cancer Experts evolved through several iterations. First, the Cancer Experts reviewed the applications received for cancer medicines for the 2025 update of the EML and EMLc. The Cancer Experts also reviewed selection principles for recommending cancer medicines, based on patient-important outcomes, which considered a minimum overall survival benefit of 4-6 months, with improvement in quality of life or lower toxicity compared to standard treatment. The Cancer Experts met online four times (9 July 2024, 23 September 2024, 25 November 2024, and 5 March 2025) and in-person one time for a two-day meeting in Geneva (23-24 January 2025).

This document provides a summary of the Cancer Experts' considerations and the consensus views of the Cancer Experts regarding the potential listings for cancer medicines, including potential strategies to increase the number of patients who could have access to these high-priced medicines.

The following section outlines the assessment of the cancer medicine applications by the Cancer Experts. The statements represent the consensus opinion of the Cancer Experts. Cases of diverging opinions among Cancer Experts are explicitly mentioned.

APPLICATIONS REVIEWED:

The cancer medicine applications the Cancer Experts reviewed are listed below and published in full online. The list of proposals made in the applications is reported below.

A.5 Blinatumomab – CD19-positive frontline, relapsed or refractory B-lineage acute lymphoblastic leukemia – EMLc
A.21 Panitumumab – KRAS/NRAS wild-type metastatic colorectal cancer – EML
A.22 PD-1 / PD-L1 immune checkpoint inhibitors – 12 cancer entities – EML

- Pembrolizumab – cervical cancer / colorectal cancer / endometrial cancer / gastric or gastro-esophageal junction adenocarcinoma / head and neck squamous cell carcinoma / non-small cell lung cancer / esophageal squamous cell carcinoma / renal cell carcinoma / triple-negative breast cancer (9 tumor types)
- Nivolumab combined with ipilimumab – colorectal cancer / malignant melanoma / non-small cell lung cancer / esophageal squamous cell carcinoma / renal cell carcinoma (5 tumor types)
- Durvalumab – biliary tract cancer / endometrial cancer / hepatocellular carcinoma (3 tumor types)
- Nivolumab – gastric or gastro-esophageal junction adenocarcinoma / esophageal squamous cell carcinoma (2 tumor types)
- Atezolizumab – hepatocellular carcinoma / non-small cell lung cancer (2 tumor types)
- Durvalumab combined with tremelimumab – hepatocellular carcinoma / non-small cell lung cancer (2 tumor types)
- Cemiplimab – non-small cell lung cancer (1 tumor type)
- Dostarlimab – endometrial cancer (1 tumor type)
- Tislelizumab – non-small cell lung cancer (1 tumor type)
- Sugemalimab – non-small cell lung cancer (1 tumor type)

A.26 Temozolomide – high-grade glioma / Ewing sarcoma / neuroblastoma / palliative care – EMLc
A.27 Tislelizumab – esophageal squamous cell cancer – EML
A.28 Toripalimab – esophageal squamous cell cancer / nasopharyngeal carcinoma – EML*
A.32 Zanubrutinib – chronic lymphocytic leukemia / small lymphocytic leukemia – EML*

* Resubmission

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SUMMARY OF CANCER EXPERTS' ADVICE:

General Remarks

Among all cancer medicine applications received for the 2025 update of the Model Lists, the Cancer Experts indicated that the highest priorities for addition are:

EML

- Pembrolizumab monotherapy for colorectal cancer (deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H)) and non-small cell lung cancer (PD-L1 ≥50%).
- Pembrolizumab combined with chemotherapy for cervical cancer (CPS ≥1).
- Atezolizumab monotherapy for non-small cell lung cancer (PD-L1 ≥50%).
- Cemiplimab monotherapy for non-small cell lung cancer (PD-L1 ≥50%).

EMLc

- Blinatumomab for CD19-positive frontline, relapsed, or refractory B-lineage acute lymphoblastic leukemia.

The Cancer Experts noted that this advice for immune checkpoint inhibitors reflects on-label use as per the European Medicines Agency (EMA).

The Cancer Experts noted that pembrolizumab has been listed on the WHO EML since 2019 for malignant melanoma (as a therapeutic alternative to nivolumab for this indication). Therefore, the Cancer Experts' advice relates to the expansion of the listing for pembrolizumab to the new indications for cervical cancer (CPS ≥1), colorectal cancer (dMMR/MSI-H), and non-small cell lung cancer (PD-L1 ≥50%).

The Cancer Experts highlighted that atezolizumab monotherapy and cemiplimab monotherapy are also EMA-approved for the first-line treatment of non-small cell lung cancer (PD-L1 ≥50%), offer important gains in overall survival, and may be used as therapeutic alternatives to pembrolizumab monotherapy for that indication. The Cancer Experts placed more value on reducing treatment-limiting toxicities, therefore favoring first-line monotherapy over the combination of immune checkpoint inhibitors with chemotherapy.

The Cancer Experts did not agree on a final decision to support or not support the following cancer medicines at this time:

- Tislelizumab combined with chemotherapy for non-small cell lung cancer (PD-L1 ≥50%).
- Dostarlimab combined with chemotherapy for endometrial cancer (dMMR/MSI-H).
- Pembrolizumab combined with chemotherapy for endometrial cancer (dMMR/MSI-H).
- Toripalimab combined with chemotherapy for nasopharyngeal carcinoma.

The Cancer Experts considered that an updated search (i.e., extending the period of the search to the second half of 2024, not previously included) of the EMA register presented in

application A.22 identified tislelizumab combined with chemotherapy for non-small cell lung cancer (PD-L1 ≥50%). The Cancer Experts considered positively the relatively lower price and higher availability of tislelizumab in China and outside China, but did not agree on whether to prioritize immune checkpoint inhibitors approved as first-line combination therapy, in addition to monotherapy, for this indication. The Cancer Experts noted as an important limitation the absence of trials that have tested tislelizumab as first-line monotherapy. Instead, trials that have tested tislelizumab as second-line monotherapy are available, yielding similar results to those of pembrolizumab and atezolizumab in this setting.

For endometrial cancer, the Cancer Experts noted that dostarlimab combined with chemotherapy resulted in large and long-term gains in overall survival, and overall survival data for pembrolizumab combined with chemotherapy were promising but immature. Some Cancer Experts raised concerns over the price of dostarlimab and pembrolizumab, and the lack of access to established backbone chemotherapy in low-resource settings. They considered that paclitaxel plus carboplatin, as standard first-line chemotherapy for endometrial cancer, should be prioritized for addition to the WHO EML instead.

The Cancer Experts acknowledged the burden of nasopharyngeal carcinoma, especially in lower middle-income countries (LMICs) and low-income countries (LICs). Some Cancer Experts flagged the limited benefit in overall survival with toripalimab and how the maturation of additional data from other approved immune checkpoint inhibitors will be pivotal in refining judgments on whether to include immunotherapy in the WHO EML for the treatment of nasopharyngeal carcinoma in the future.

The Cancer Experts do not currently support the addition of the following candidate medicines:

- Panitumumab for KRAS/NRAS wild-type metastatic colorectal cancer.
- Pembrolizumab for gastric or gastro-esophageal junction adenocarcinoma, head and neck squamous cell carcinoma, non-small cell lung cancer (irrespective of PD-L1 expression), esophageal squamous cell carcinoma, renal cell carcinoma, and triple-negative breast cancer.
- Nivolumab combined with ipilimumab for colorectal cancer (dMMR/MSI-H), malignant melanoma, non-small cell lung cancer (irrespective of PD-L1 expression), esophageal squamous cell carcinoma, and renal cell carcinoma.
- Durvalumab for biliary tract cancer, endometrial cancer (dMMR/MSI-H), and hepatocellular carcinoma.
- Nivolumab for gastric or gastro-esophageal junction adenocarcinoma, and esophageal squamous cell carcinoma.
- Atezolizumab for hepatocellular carcinoma.
- Cemiplimab for non-small cell lung cancer (irrespective of PD-L1 expression).
- Camrelizumab for nasopharyngeal carcinoma.
- Durvalumab combined with tremelimumab for hepatocellular carcinoma and non-small cell lung cancer (irrespective of PD-L1 expression).
- Temozolomide for the treatment of children with high-grade glioma, Ewing sarcoma, neuroblastoma, and in the palliative care setting (for the above-mentioned indications).
- Tislelizumab for esophageal squamous cell cancer and nasopharyngeal carcinoma.
- Toripalimab for esophageal squamous cell cancer.
- Sugemalimab for non-small cell lung cancer (irrespective of PD-L1 expression).
- Zanubrutinib for chronic lymphocytic leukemia and small lymphocytic leukemia.

The Cancer Experts judged that the high price of these new cancer medicines could not be justified given their trivial to modest gains in overall survival for these cancer indications. This negative cost-benefit ratio was underscored as the main reason for exclusion.

The Cancer Experts noted that even narrowing the indications and selection of immune checkpoint inhibitors to those that offer the greatest cost-benefit profile, immune checkpoint inhibitors are likely not affordable and indeed acceptable to several countries and health systems, especially those in LMICs and LICs, due to high price, need for companion diagnostics and the risk of diverting resources at the expense of other essential medicines. Despite this, the Cancer Experts considered that Member States can apply their own affordability criteria in determining which medicines from the Model Lists are to be incorporated into national EMLs and reimbursement schemes. In addition, the Cancer Experts considered that large resources are already being invested by health systems and patients to purchase these medicines (of the order of tens of billions of dollars), so it is critical to identify those cancers for which the use of these medicines offers the best value for health outcomes.

The Cancer Experts considered multiple price-reduction strategies, including optimization of dose and schedule, tendering of medicines in the same class with evidence of therapeutic equivalence, and high and timely uptake of biosimilars. Some of these strategies, such as dose reduction, have the merit of being immediately implementable and substantially improving access to these medicines. These strategies are detailed later in the report. Briefly, the Cancer Experts noted that clinical evidence supporting dose reduction for immune checkpoint inhibitors is rapidly growing. The salient point relates to the large decrease in price that can be achieved through dose reduction while maintaining efficacy levels that are likely to be superior to alternative therapies. The Cancer Experts emphasized the need for further research on dose-optimization strategies to ensure the best balance between efficacy, safety, and financial sustainability. The Cancer Experts also noted that biosimilar entry for pembrolizumab is anticipated in the next 3 to 5 years (2028 to 2030). Because of this and its dominant role in several critical indications, the Cancer Experts signaled that pembrolizumab has the largest potential for price reduction, and that payer price reduction strategies could prioritize pembrolizumab in the immediate future.

The Cancer Experts considered positively that new evidence will be rapidly available regarding possible benefits related to more immune checkpoint inhibitors and the broadening of indications to other cancers. In the absence of differences in the risk-benefit profile of the more recently approved molecules (e.g., cemiplimab) compared with their predecessors (e.g., pembrolizumab), the advantage of me-too medicines in this area is fundamentally related to price reductions and caps on the prices. These should be necessary conditions to make these medicines eligible for reimbursement. However, the Cancer Experts noted that more recently approved immune checkpoint inhibitors are applying strategies that match or are superior to competitors with the primary intent of positioning molecules in niche market segments (e.g., cancers with low prevalence). This strategy limits competition between molecules. The Cancer Experts emphasized that price reductions and price caps should not be evaluated on a per-indication basis, but overall, for all indications, as the price of a vial is the same between indications.

A.5 Blinatumomab – CD19-positive frontline, relapsed or refractory B-lineage acute lymphoblastic leukemia – EMLc

The Cancer Experts support the inclusion of blinatumomab on the complementary list of the EMLc for the treatment of pediatric patients with CD19-positive frontline, relapsed, or refractory B-lineage acute lymphoblastic leukemia (B-ALL) based on a positive benefit-risk profile.

The Cancer Experts considered the burden of B-ALL in LMICs and LICs to be greatest as compared to high-income countries (HICs). The number of years of life lost is substantial, and cure rates are much lower compared to HICs. The Cancer Experts noted the superiority of blinatumomab in achieving clinical cure, prolonging overall survival, eradicating minimal residual disease (MRD), and reducing adverse events (Grade ≥3) when compared to steroids and multiple chemotherapy regimens (e.g., vincristine, cyclophosphamide, daunorubicin/doxorubicine, ifosfamide, cytarabine, L-asparaginase, methotrexate, 6-mercaptopurin), which are associated with substantial risks of myelosuppression, infection, and secondary malignancies. The Cancer Experts highlighted that blinatumomab-specific adverse events, such as cytokine release syndrome and neurological events, can be managed effectively with corticosteroids and neurotoxicity prophylaxis (e.g., progressive dose escalation over the course of the first week of therapy).

The Cancer Experts raised concerns over the feasibility of implementing blinatumomab treatment in LMICs and LICs because of its route of administration and duration of therapy – continuous intravenous infusion via central venous access over a 28 days-period per cycle, and typically up to five treatment cycles. However, the Cancer Experts noted that the development of a subcutaneous formulation is underway and could potentially mitigate these concerns.

The Cancer Experts acknowledged price and access barriers to blinatumomab in LMICs and LICs; however, given its curative potential, it may be proven cost-effective with multisectoral support (4), including access programs, such as those that have already provided blinatumomab in some LMICs (5). The Cancer Experts also highlighted ongoing efforts of the WHO's Global Initiative for Childhood Cancer, which aims to increase access to life-saving cancer medicines and improve the survival of children with cancer globally (6).

Recognizing that blinatumomab is recommended for B-ALL in most frontline regimens, and in all relapsed/refractory settings by authoritative guidelines in both children and adults, the Cancer Experts suggested that an application should be sought for the inclusion of blinatumomab for adults on the EML in the future.

A.21 Panitumumab – KRAS/NRAS wild-type metastatic colorectal cancer – EML

The Cancer Experts do not support the inclusion of the anti-epidermal growth factor (EGFR) antibody panitumumab on the EML for the treatment of KRAS/NRAS wild-type metastatic colorectal cancer.

The Cancer Experts noted results from pivotal randomized trials evaluating panitumumab in wild-type metastatic colorectal cancer. The median overall survival gains were 4.4 months for panitumumab combined with chemotherapy compared to chemotherapy alone in the first-line setting, 2.0 months for panitumumab combined with chemotherapy compared to chemotherapy

alone in the second-line setting, and 2.6 months for panitumumab combined with best supportive care compared to best supportive care alone in the third-line setting. It was also noted that four of five studies addressing quality of life among patients using anti-EGFR monoclonal antibodies (mAbs) showed no clinically relevant improvement in quality of life.

The Cancer Experts judged that the magnitude of the overall survival gains in the second- and third-line settings was limited, especially when considering the WHO EML Expert Committee recommended threshold for benefit of at least 4-6 months overall survival gain to be considered a candidate for inclusion on the WHO EML. For the first-line setting, the Cancer Experts considered the moderate gain in median overall survival in patients with KRAS/NRAS wild-type metastatic colorectal cancer in the context of the need for KRAS/NRAS testing. Excluding patients with RAS (KRAS or NRAS) mutations is essential, given that the addition of panitumumab to chemotherapy in this population has been shown to have a detrimental effect – a decrease in median overall survival by 3.7 months when compared to chemotherapy alone (7). Access to this diagnostic testing is limited in less-resourced settings and is likely to be a barrier to the appropriate use of panitumumab.

A.22 PD-1 / PD-L1 immune checkpoint inhibitors – 12 cancer entities – EML

This application addresses immune checkpoint inhibitors for the treatment of 12 adult cancer entities in the palliative (non-curative) first-line setting.

This application expands on the applications made in 2019, 2021, and 2023 for the inclusion of PD-1/PD-L1 immune checkpoint inhibitors on the EML for the treatment of locally advanced and metastatic non-small cell lung cancer. On each occasion, inclusion was not recommended. However, the favorable benefit-risk ratio of pembrolizumab as evidenced by consolidated data in multiple randomized trials, was recognized in both 2021 and 2023 by previous Expert Committees. The reason for not listing pembrolizumab in 2021 and 2023 was therefore primarily economic (i.e., related to the high price and lack of strategies to increase access).

This application presents a comprehensive review of the evidence for immune checkpoint inhibitors in the treatment of multiple cancers. These cancer entities were prioritized based on their global health relevance, including cancers that are highly prevalent in LMICs and LICs. Where available, evidence was presented for monotherapy and combination therapy across different EMA-approved on-label indications (e.g., based on mutational burden and PD-L1 expression). Key information on the potential to provide the best returns to healthcare systems was reported across all cancers and molecules, following a standard approach.

- *Biliary tract cancer*

The Cancer Experts do not support the inclusion of durvalumab combined with chemotherapy for the first-line treatment of biliary tract cancer, irrespective of PD-L1 expression, at this time. The Cancer Experts judged, based on available evidence, that the increase in median overall survival was small (3.6 months more, 95% confidence interval (CI) 1.1 more to 6.4 more) and did not meet the WHO EML Expert Committee recommended threshold for benefit of at least 4-6 months overall survival gain to be considered a candidate for inclusion on the WHO EML (3).

- *Cervical cancer*

The Cancer Experts support the inclusion of pembrolizumab combined with chemotherapy, without bevacizumab, on the EML as a combination treatment for cervical cancer ≥1% PD-L1 expression (CPS ≥1) based on long-term (median follow-up of 39.1 months) and large gains in median overall survival (11 months more, 95% CI 5.8 more to 17.2 more).

The Cancer Experts considered that the subgroup analysis comparing overall survival in patients with or without concomitant bevacizumab found no difference (hazard ratio (HR) 0.63, 95% CI 0.47 to 0.87 and HR 0.74, 95% CI 0.53 to 1.04, respectively) (8). The Cancer Experts considered additional evidence that showed bevacizumab combined with chemotherapy had limited benefit in advanced cervical cancer – below the WHO EML Expert Committee recommended threshold for benefit of at least 4-6 months overall survival gain to be considered a candidate for inclusion on the WHO EML. In the absence of a synergistic effect, the Cancer Experts opted to support the inclusion of pembrolizumab combined with chemotherapy treatment without concomitant bevacizumab.

The Cancer Experts noted the global distribution of cervical cancer and the disproportionate burden in sub-Saharan Africa, where HIV prevalence is also high. The Cancer Experts considered real-world evidence that found no statistically significant difference in PD-L1 expression between squamous cervical carcinomas of Mozambican women living with and without HIV (9). In these areas, the cancer is often diagnosed at an advanced stage, leaving most patients without curative treatment options. As a result, management typically relies on palliative care through chemotherapy and/or radiotherapy, though many patients either develop resistance or experience recurrence. The Cancer Experts highlighted that both women without and with HIV could benefit from pembrolizumab. The Cancer Experts also noted data demonstrating the safety of immune checkpoint inhibitor use in people living with HIV, where there is viral suppression through antiretroviral therapy (10). Therapeutic effects in this immunocompromised population could be confirmed via randomized trials in HIV endemic settings.

- *Colorectal cancer*

The Cancer Experts support the inclusion of pembrolizumab on the EML as monotherapy for dMMR/MSI-H colorectal cancer based on long-term (median follow-up of 44.5 months) and large gains in median overall survival (12.89 months more, 95% CI 1.07 fewer to 32.55 more). They highlighted additional benefits: pembrolizumab monotherapy may result in a slight increase in health-related quality of life and a moderate decrease in adverse events compared to chemotherapy. The Cancer Experts flagged potential barriers to accessing relevant diagnostics (e.g., next generation sequencing to identify tumors with high MSI) whose use may currently be limited to countries with greater resources.

The Cancer Experts also considered additional evidence for nivolumab combined with ipilimumab. The Cancer Experts raised concerns about the price associated with two immune checkpoint inhibitors when compared to one PD-1 checkpoint inhibitor or chemotherapy, and the additional burden of procuring and administering multiple medicines. Furthermore, the added value of ipilimumab to nivolumab might be limited (11). Therefore, Cancer Experts ultimately judged not to support the inclusion of nivolumab combined with ipilimumab.

- *Endometrial cancer*

The Cancer Experts did not agree on a final decision to support or not support the inclusion of dostarlimab combined with chemotherapy and pembrolizumab combined with chemotherapy on the EML as combination treatments for endometrial cancer dMMR/MSI-H, but agreed not to support the inclusion of durvalumab combined with chemotherapy for this indication.

Based on mature overall survival data, the Cancer Experts judged the calculated increase in median overall survival for dostarlimab combined with chemotherapy compared to chemotherapy alone to be extremely large (66.7 months more, 95% CI 18.4 more to 153.3 more). In terms of health-related quality of life, the Cancer Experts noted that the dostarlimab-based treatment may result in a slight improvement; however, the originator price and duration of dostarlimab-based treatment (i.e., 3 years) raised concerns over price, which would be prohibitively high in most settings.

The Cancer Experts considered additional evidence for durvalumab combined with chemotherapy and pembrolizumab combined with chemotherapy, which was judged as limited due to the lack of mature overall survival data. The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) non-curative scores of 3 for durvalumab combined with chemotherapy and 4 for pembrolizumab combined with chemotherapy in dMMR endometrial cancer were based on progression-free survival data, not overall survival. Further, the magnitude of benefit based on progression-free survival gain was substantially smaller for durvalumab combined with chemotherapy (0.6 months) compared to pembrolizumab combined with chemotherapy (12 months). Similarly to dostarlimab, concerns over price and long treatment duration were raised for durvalumab and pembrolizumab. Therefore, the Cancer Experts ultimately decided not to support the inclusion of durvalumab combined with chemotherapy at this time. However, they emphasized the importance of more mature overall survival data for durvalumab- and pembrolizumab-based treatment that builds on progression-free survival data.

The Cancer Experts agreed that dostarlimab combined with chemotherapy resulted in extremely large and long-term gains in overall survival, and overall survival data for pembrolizumab combined with chemotherapy were promising but immature. However, some Cancer Experts raised concerns over the lack of access to established backbone chemotherapy in their settings. They considered that paclitaxel plus carboplatin, as standard first-line chemotherapy for endometrial cancer, offers meaningful gains in overall survival and should be prioritized for addition to the WHO EML before considering immune checkpoint inhibitors for this indication.

- *Gastric or gastro-esophageal junction adenocarcinoma*

The Cancer Experts do not support the inclusion of pembrolizumab combined with chemotherapy and nivolumab combined with chemotherapy for the first-line treatment of erythroblastic oncogene B (ErbB) 2-negative gastric/gastro-esophageal junction adenocarcinoma with ≥1% PD-L1 expression and ErbB2-negative, gastric/gastro-esophageal junction adenocarcinoma with ≥5% PD-L1 expression, respectively. The Cancer Experts considered whether benefits might be greater in MSI-H patients; however, the decision not to support inclusion was ultimately based on affordability concerns, the limited gains in median overall survival (3.17 months more for pembrolizumab-based treatment and 4.76 months more

for nivolumab-based treatment), trivial to no difference in health-related quality of life, and possible increases in adverse events (CTCAE ≥ 3).

- *Head and neck squamous cell carcinoma*

The Cancer Experts do not support the inclusion of pembrolizumab combined with chemotherapy for the first-line treatment of head and neck squamous cell carcinoma. They considered that the magnitude of benefit, in terms of overall survival gain, while within the accepted EML threshold of at least 4-6 months, was moderate (6 months more). The Cancer Experts also considered that patients often have worse performance status outside of clinical trials (i.e., Eastern Cooperative Oncology Group (ECOG) 2/3). In these patients, the addition of pembrolizumab to chemotherapy is likely to be associated with less pronounced improvements in overall survival (12).

- *Hepatocellular carcinoma*

The Cancer Experts do not support the inclusion of atezolizumab combined with bevacizumab, durvalumab monotherapy, and durvalumab combined with tremelimumab for the first-line treatment of hepatocellular carcinoma, irrespective of PD-L1 expression.

The Cancer Experts considered evidence from multiple trials that compared different immune checkpoint inhibitors to sorafenib, a tyrosine kinase inhibitor (TKI), at different lengths of follow-up. They considered that sorafenib, which is not recommended as an essential medicine, might not represent the best treatment option and thus may not be the appropriate comparator in some trials. The Cancer Experts noted that the largest effect on overall survival was observed in the randomized trial addressing atezolizumab combined with bevacizumab, which also had the shortest follow-up (median overall survival 6.9 months longer based on a median follow-up of 15.6 months). The magnitude of effect was below the EML threshold of 4-6-month overall survival gain after long-term follow-up of patients randomized to durvalumab monotherapy (median overall survival 2.25 months more based on a median follow-up of 47.9 months) and durvalumab combined with tremelimumab (median overall survival 3.9 months more based on a median follow-up of 48.2 months). The Cancer Experts considered that the duration of follow-up and gains in overall survival varied across immune checkpoint inhibitors. This heterogeneity was interpreted as a factor limiting the generalizability of a benefit.

- *Malignant melanoma*

The Cancer Experts do not support the inclusion of nivolumab combined with ipilimumab for the first-line treatment of malignant melanoma irrespective of PD-L1 expression or BRAF V600-mutation.

The Cancer Experts judged that combination therapy with nivolumab combined with ipilimumab, when compared to monotherapy (ipilimumab or nivolumab), had long-lasting and large benefits in overall survival in patients with malignant melanoma, irrespective of PD-L1 expression (median 12.8 months more overall survival based on a median follow-up of 34.6 months). However, concerns were raised over the increased price and adverse events with combination therapy when compared to monotherapy with nivolumab or pembrolizumab. The Cancer Experts also highlighted that only a minority of settings have the resources to promptly recognize and address treatment-related adverse events.

The Cancer Experts noted that nivolumab and pembrolizumab (as a therapeutic alternative to nivolumab) have been listed on the Model List for malignant melanoma as monotherapies since 2019. The adoption of immune checkpoint inhibitors is still in its infancy in many countries. Despite being beneficial, the addition of another immune checkpoint inhibitor to be used in combination with nivolumab would present a further challenge in several settings, confounding the priorities that should remain the large-scale adoption of nivolumab or pembrolizumab.

Given the dominant role of pembrolizumab in the therapeutic landscape for malignant melanoma and other cancers, the Cancer Experts advised nivolumab to be listed as a therapeutic alternative to pembrolizumab instead, reversing the current listing in the EML. The Cancer Experts also suggested that an application addressing pembrolizumab and nivolumab for the treatment of malignant melanoma in children be sought for inclusion in the EMLc in the future.

The Cancer Experts considered evidence on nivolumab combined with ipilimumab compared to BRAF/MEK inhibitors for BRAF v600-mutant malignant melanoma in the first-line metastatic setting to be very uncertain (HR 0.73, 95% CI 0.42 to 1.27; median follow-up of 32.2 months). Therefore, the Cancer Experts also did not support the inclusion of nivolumab combined with ipilimumab for BRAF v600-mutant malignant melanoma.

- *Non-small cell lung cancer*

The Cancer Experts support the inclusion of pembrolizumab, atezolizumab, and cemiplimab as monotherapy for oncogenic-driver wild-type non-small cell lung cancer ≥50% PD-L1 expression, which reflects EMA-approved on-label use.

The Cancer Experts did not agree on a final decision to support or not support the inclusion of tislelizumab combined with chemotherapy for oncogenic-driver wild-type non-small cell lung cancer ≥50% PD-L1 expression.

The Cancer Experts do not support the inclusion of cemiplimab combined with chemotherapy, durvalumab combined with tremelimumab combined with chemotherapy, nivolumab combined with ipilimumab combined with chemotherapy, pembrolizumab combined with chemotherapy, and sugemalimab combined with chemotherapy for the first-line treatment of oncogenic-driver wild-type non-small cell lung cancer irrespective of PD-L1 expression.

The Cancer Experts noted the meaningful gains in overall survival with immune checkpoint inhibitors in treating non-small cell lung cancer in the first-line setting. They emphasized the magnitude of benefit from monotherapy. Cemiplimab monotherapy increased median overall survival by 8 months (95% CI 4.1 more to 12.6 more; median follow-up of 35 months), pembrolizumab monotherapy increased median overall survival by 6.3 months (95% CI 3.9 more to 9.2 more; median follow-up of 61 months) and atezolizumab monotherapy increased median overall survival by 3.7 months (95% CI 1.1 fewer to 11.8 more; median follow-up of 35.6 months). The Cancer Experts noted that the gain in median overall survival with atezolizumab monotherapy might be underestimated, given that a proportion of trial participants received immune checkpoint inhibitors in the subsequent treatment line. Furthermore, the Cancer Experts acknowledged that atezolizumab is one of the few immunotherapies tested in a phase 3 international trial including patients with advanced non-small cell lung cancer who were ineligible for platinum-based chemotherapy due to poor performance status, advanced age, or comorbidities (13). While overall survival is poor

irrespective of therapy (atezolizumab, vinorelbine, or gemcitabine), atezolizumab was associated with less severe toxicities.

The Cancer Experts considered additional evidence on tislelizumab combined with chemotherapy for non-small cell lung cancer ≥50% PD-L1 expression with no EGFR or anaplastic lymphoma kinase (ALK) positive mutations in the first-line setting. The combination treatment received an ESMO-MBS non-curative score of 4, in part due to a demonstrated improvement in the quality of life. The Cancer Experts flagged that evidence and regulatory approval for tislelizumab monotherapy for non-small cell lung cancer ≥50% PD-L1 expression is lacking, and did not agree on a final decision to support or not support the inclusion of this combination therapy. The experts recognized that tislelizumab, with a reimbursed price in China of about 43,500 Chinese yuan (USD $6,170) per year, could be an important therapeutic option also outside China (14).

The decision to support the inclusion of monotherapy over combination therapy was ultimately based on the strong biological rationale that patients with increased PD-L1 expression are likely to benefit more and the potential to avoid cytotoxic effects from chemotherapy. The Cancer Experts highlighted that pembrolizumab monotherapy probably results in a large reduction in adverse events (risk ratio 0.49, 95% CI 0.37 to 0.66) and may result in a meaningful improvement in health-related quality of life. The addition of chemotherapy may compromise such improvements in safety and health-related quality of life. The Cancer Experts pondered the role of indirect evidence showing that tislelizumab as monotherapy is associated with overall survival benefits when used as second- or third-line treatment in non-small cell lung cancer (15). In this setting, tislelizumab's overall survival benefit was considered relevant when compared to docetaxel (median 17.2 versus 11.9 months) (16).

The Cancer Experts raised concerns over feasibility in LICs related to the need for companion diagnostic tests to identify patients with ≥50% PD-L1 expression and rule out patients with tumors that harbor a targetable alteration, such as an EGFR mutation or ALK rearrangements. However, the scenario is more variable in middle-income countries, where searching for molecular alterations is more readily available, and the price associated with tests is a small fraction of the price associated with treatment.

Several Cancer Experts emphasized that immune checkpoint inhibitors for non-small cell lung cancer are likely not cost-effective in most settings, especially in low-resource settings, and risk diverting resources at the expense of other essential medicines. However, Cancer Experts also underscored that supporting the inclusion of immune checkpoint inhibitor monotherapy in patients with ≥50% PD-L1 expression over combination therapy in all patients, irrespective of PD-L1 expression, can guide countries in prioritizing these medicines for the indications in which the benefits would be the largest. They offered further advice on prioritization, supporting the inclusion of pembrolizumab monotherapy as the class representative for this indication on the WHO EML and highlighting that atezolizumab monotherapy and cemiplimab monotherapy may be used as therapeutic alternatives.

- *Esophageal squamous cell cancer*

The Cancer Experts do not support the inclusion of pembrolizumab combined with chemotherapy for first-line treatment of esophageal squamous cell carcinoma ≥10% PD-L1 expression, nor nivolumab combined with chemotherapy, nor nivolumab combined with

ipilimumab and chemotherapy for the first-line treatment of esophageal squamous cell carcinoma ≥1% PD-L1 expression.

It was noted that pembrolizumab combined with chemotherapy, nivolumab combined with chemotherapy, and nivolumab combined with ipilimumab combined with chemotherapy were three of five immune checkpoint inhibitor treatments considered for the front-line treatment of esophageal squamous cell cancer. Against the backdrop of this comprehensive evaluation of immune checkpoint inhibitors, the Cancer Experts considered that pembrolizumab, nivolumab, and nivolumab combined with ipilimumab are likely the least cost-effective options when compared to tislelizumab and toripalimab, which are covered in separate applications.

The Cancer Experts noted evidence from a network meta-analysis addressing the comparative effectiveness of immune checkpoint inhibitors for esophageal squamous cell cancer, which found consistent magnitudes of relative effects on overall survival between the medicines (17). The Cancer Experts noted that the absolute effects calculated in the current application were also comparable. The median increases in overall survival were 6.6, 6.3, and 5.6 months for pembrolizumab combined with chemotherapy, nivolumab combined with chemotherapy, and nivolumab combined with ipilimumab and chemotherapy, respectively.

The Cancer Experts judged the gains in overall survival from pembrolizumab combined with chemotherapy, nivolumab combined with chemotherapy and nivolumab combined with ipilimumab and chemotherapy to be moderate in size, but that these benefits were offset by the price, uncertainty in response durability, unclear role of PD-L1 expression as a predictive biomarker, potential for increased harms associated with poorer prognosis at baseline, and lack of long-term data across the immune checkpoint inhibitors.

- *Renal cell carcinoma*

Given the heterogeneity in results addressing immune checkpoint inhibitors for renal cell carcinoma and concerns over cost-effectiveness outside of HICs, the Cancer Experts do not support the inclusion of nivolumab combined with ipilimumab and pembrolizumab-based treatments (pembrolizumab combined with axitinib and pembrolizumab combined with lenvatinib) for the first-line treatment of renal cell carcinoma irrespective of PD-L1 expression. Nor do they support the inclusion of nivolumab combined with cabozantinib as well as avelumab combined with axitinib, for which additional evidence was presented during the in-person meeting.

The Cancer Experts judged the increase in median overall survival for patients randomized to nivolumab combined with ipilimumab versus sunitinib to be large (13 months more, 95% CI 6.5 more to 20.8 more) but that the benefit was not justified given the increased price associated with treatment based on two immunotherapy drugs when the price of one immunotherapy drug is already prohibitively high in most settings.

When compared to sunitinib, the Cancer Experts noted that the pooled estimate from the meta-analysis of two randomized trials – one evaluating pembrolizumab combined with lenvatinib and the other pembrolizumab combined with axitinib – demonstrated a meaningful benefit (HR for death 0.83, 95% CI 0.72 to 0.94). However, the Cancer Experts flagged that there was heterogeneity in the results of the individual trials, which decreased their certainty of the magnitude of the pooled estimate. The Cancer Experts flagged additional uncertainty around optimal immune checkpoint inhibitor and TKI positioning (e.g., in sequence or in combination).

The Cancer Experts also considered additional evidence from trials addressing nivolumab combined with cabozantinib and avelumab combined with axitinib – both of which randomized patients to sunitinib in the control arm. Based on ESMO-MCBS scorecards, Cancer Experts judged that nivolumab combined with cabozantinib and avelumab combined with axitinib resulted in limited benefit (non-curative scores of 1 and 3, respectively).

The Cancer Experts highlighted that nivolumab combined with ipilimumab may reduce adverse events compared to sunitinib; however, adding a TKI partner to pembrolizumab probably increases adverse events slightly. Thus, the Cancer Experts considered that immunotherapy alone may be better tolerated than TKIs, but not when used with a partner TKI.

The Cancer Experts noted that the price of sunitinib is lower than other TKIs included as immunotherapy partners, and if used with immunotherapy instead of lenvatinib, axitinib or cabozantinib, it has the potential to reduce the price of immunotherapy combined with TKI combination treatments.

- *Triple-negative breast cancer*

The Cancer Experts do not support the inclusion of pembrolizumab combined with chemotherapy for the first-line treatment of advanced triple-negative breast cancer CPS ≥10 because of heterogeneity in results and concerns over cost-effectiveness outside of HICs and feasibility due to diagnostic requirements. The Cancer Experts judged the benefit in median overall survival with pembrolizumab-based treatment to be moderate (6 months more, 95% CI 0.8 to 13.2 months more). However, they also considered additional evidence from a phase 3 trial of chemotherapy with or without atezolizumab for early relapsing unresectable locally advanced or metastatic triple-negative breast cancer, which found no benefit in overall survival with atezolizumab-based treatment (18).

A.26 Temozolomide – high-grade glioma / Ewing sarcoma / neuroblastoma / palliative care – EMLc

The Cancer Experts do not support the inclusion of temozolomide on the EMLc for the treatment of high-grade glioma, Ewing sarcoma, and neuroblastoma, nor for the treatment in the palliative care setting (for the above-mentioned indications).

The Cancer Experts noted that temozolomide is administered orally. However, the Cancer Experts judged that those benefits from oral administration for feasibility and equity, including patient compliance and quality of life in the palliative care setting, would be offset by the increased risk of severe hematological toxicity and the need for monitoring of adverse events in the hospital.

Finally, the Cancer Experts considered that data for overall survival – the outcome the WHO EML Expert Committee recommended listing decisions for cancer medicines be based on – were only available from two studies for high-grade glioma (one in adults and one in children) and thus, are limited.

A.27 Tislelizumab – esophageal squamous cell cancer – EML

The Cancer Experts do not support the inclusion of tislelizumab (or any other immune checkpoint inhibitor) on the EML for the treatment of esophageal squamous cell cancer. It was noted that tislelizumab was one of five immune checkpoint inhibitor treatments considered for the frontline treatment of esophageal squamous cell cancer. Against the backdrop of the comprehensive evaluation of immune checkpoint inhibitors (application A.22) and the separate application for toripalimab (application A.28), the Cancer Experts considered that tislelizumab is likely a more cost-effective option when compared to pembrolizumab, nivolumab and nivolumab combined with ipilimumab, but not toripalimab, which Cancer Experts considered to likely be the most cost-effective.

The Cancer Experts noted evidence from a network meta-analysis addressing the comparative effectiveness of immune checkpoint inhibitors for esophageal squamous cell cancer (17). The study found consistent magnitudes of effect on overall survival between the medicines, suggesting these molecules could be considered therapeutic alternatives.

The Cancer Experts judged these gains in overall survival to be moderate in size. The benefit of these gains was offset by the unclear role of PD-L1 expression as a predictive biomarker, the potential for increased harm associated with poorer prognosis at baseline, and the lack of long-term data across the immune checkpoint inhibitors.

A.28 Toripalimab – esophageal squamous cell cancer / nasopharyngeal cancer – EML*

The Cancer Experts acknowledged that the application proposing the inclusion of toripalimab on the EML for the treatment of nasopharyngeal cancer and esophageal squamous cell cancer is a re-submission.

The Cancer Experts did not agree on a final decision to support or not support the inclusion of toripalimab combined with chemotherapy on the EML for the treatment of nasopharyngeal cancer. The same non-conclusiveness also extends to the following section.

Several Cancer Experts highlighted that nasopharyngeal cancer has limited therapeutic options and is co-endemic with Epstein-Barr virus (EBV) in some LMICs and LICs. Based on comparative price data presented in the application and their own experience, several Cancer Experts emphasized the lower price of toripalimab compared to pembrolizumab. Others noted that the magnitude of the long-term overall survival benefit was limited and reflected by an ESMO-MCBS non-curative score of 3.

The Cancer Experts also considered additional evidence for tislelizumab- and camrelizumab-based treatments, for which overall survival data are immature. Therefore, some Cancer Experts underscored how the maturation of additional data, especially concerning overall survival and quality of life, will be pivotal in refining judgements on whether to include toripalimab, tislelizumab, and/or camrelizumab on the WHO EML in the future.

The Cancer Experts highlighted that nasopharyngeal cancer is highly chemosensitive and radiosensitive, and that carboplatin, cisplatin, fluorouracil, and paclitaxel, but not gemcitabine, are already listed on the WHO EML as chemotherapy for malignant neoplasms of the nasopharynx. During the meeting, the Cancer Experts considered additional evidence focusing

on the role of gemcitabine as part of first-line chemotherapy regimens. A randomized trial of 362 patients demonstrated increased median overall survival in patients treated with gemcitabine combined with cisplatin (22.1 months, 95% CI 19.2 to 25.0 months) compared to fluorouracil combined with cisplatin (18.6 months, 95% CI 15.4 to 21.7 months) (19). They noted that gemcitabine is a global standard for frontline therapy in the metastatic setting for nasopharyngeal cancer, is listed on the WHO EML for malignant neoplasms in the ovary, bronchus and lung, and that 3-year overall survival results from a meta-analysis showed similar overall survival between gemcitabine combined with cisplatin and fluorouracil combined with cisplatin (risk ratio 1.07, 95% CI 0.89 to 1.29) (20). Therefore, the Cancer Experts supported the inclusion of gemcitabine in the WHO EML and the use of fluorouracil combined with cisplatin as a therapeutic alternative.

The Cancer Experts do not support the inclusion of toripalimab (or any other immune checkpoint inhibitor) on the EML for the treatment of esophageal squamous cell cancer.

It was noted that toripalimab was one of five immune checkpoint inhibitor treatments considered for the frontline treatment of esophageal squamous cell cancer. Against the backdrop of the comprehensive evaluation of immune checkpoint inhibitors (application A.22), the Cancer Experts considered that toripalimab likely represents the most cost-effective option when compared to other immune checkpoint inhibitors.

The Cancer Experts noted evidence from a network meta-analysis addressing the comparative effectiveness of immune checkpoint inhibitors for esophageal squamous cell cancer, which found consistent magnitudes of effect on overall survival between the medicines (17).

The Cancer Experts judged these gains in overall survival to be moderate in size. The benefit of these gains was offset by the unclear role of PD-L1 expression as a predictive biomarker, the potential for increased harm associated with poorer prognosis at baseline, and the lack of long-term data across the immune checkpoint inhibitors.

A.32 Zanubrutinib – chronic lymphocytic leukemia / small lymphocytic leukemia – EML*

The Cancer Experts acknowledged that the application proposing inclusion of zanubrutinib on the EML for the treatment of chronic lymphocytic leukemia and small lymphocytic leukemia is a re-submission.

The Cancer Experts do not support the inclusion of zanubrutinib on the EML for the treatment of chronic lymphocytic leukemia and small lymphocytic leukemia. The Cancer Experts noted that treatment for lymphocytic leukemia is a rapidly evolving field, and new studies evaluating combination regimens with zanubrutinib (e.g., triplet combination of zanubrutinib combined with venetoclax and obinutuzumab) are ongoing. Data supported better progression free survival gains with zanubrutinib when compared to ibrutinib – another TKI recommended by WHO as an essential medicine. However, data on overall survival – the outcome that the WHO EML Expert Committee recommended listing decisions for cancer medicines be based on – were unconvincing. Two pivotal randomized trials evaluated overall survival in patients randomized to zanubrutinib. After a median 42.5 months of follow-up, there was no significant difference in overall survival when zanubrutinib was compared to ibrutinib (HR for death 0.77, 95% CI 0.55 to 1.06). Median overall survival was not reached in either group (21). Similarly,

the randomized trial comparing zanubrutinib to a combination of bendamustine and rituximab found no significant difference in overall survival (HR 1.07, 95% CI 0.51 to 2.22) (22).

Finally, the Cancer Experts considered the improved safety profile with zanubrutinib to be the effect of the approved dose of the comparator. It was noted that post-approval studies suggest that lower ibrutinib doses are as effective, and that ibrutinib was therefore used at a dose that was too high, likely leading to an overestimate of the difference in adverse events between zanubrutinib and ibrutinib in the reported results.

Strategies to improve access to cancer medicines with focus on immune checkpoint inhibitors

The Cancer Experts noted that immune checkpoint inhibitors are likely not acceptable treatment options for the proposed indications to most countries, especially those in LMICs and LICs, due to high price, the need for companion diagnostics, and the risk of eroding the financial viability of health systems and diverting resources at the expense of other essential medicines.

The Cancer Experts emphasized the importance of strategies to improve access to cancer medicines. They considered the potential for pharmacological class effect and interchangeability of immune checkpoint inhibitors, reduced intensity dosing and overall treatment duration, vial sharing, biosimilars, pooled procurement, and licensing strategies to improve access to cancer medicines and reduce global inequities.

- *Interchangeability of immune checkpoint inhibitors*

In the absence of head-to-head randomized trials, the Cancer Experts considered strong biological rationale and indirect evidence (e.g., magnitude of benefit compared across randomized trials that have the same reference arm) supporting the potential for recommending different PD-1 and PD-L1 immune checkpoint inhibitors as therapeutic alternatives and PD-1 and PD-L1 as therapeutically equivalent, to set up tendering mechanisms for procurement agencies and hospitals (23, 24).

The Cancer Experts considered that PD-L1 and PD-1 inhibitors act to prevent the same immunological interaction that occurs between the PD-1 receptor on T-cells and the PD-L1 protein on tumor cells, which otherwise suppresses the immune system's ability to attack tumor cells (25). In relation to metastatic non-small cell lung cancer, they reiterated the effects of pembrolizumab, cemiplimab and atezolizumab on long-term overall survival, and any differences in randomized trial results (e.g., magnitude of effect on overall survival) may be attributed to differences in the study design (e.g., length of follow-up) and population (e.g., performance status of included patients), and not inherent differences between the immune checkpoint inhibitors (26-29). Therefore, the Cancer Experts agreed to support the inclusion of PD-1 and PD-L1 monotherapy for non-small cell lung cancer ≥50% PD-L1 expression, suggesting the use of a square box listing with pembrolizumab representative of the class. The Cancer Experts noted that when pembrolizumab, cemiplimab, and atezolizumab for non-small cell lung cancer with ≥50% PD-L1 expression are not available or cannot be afforded, other quality-assured PD-1/PD-L1 inhibitors may be considered at the country-level. It was highlighted that tislelizumab monotherapy has not been evaluated in a randomized trial for non-small cell lung cancer ≥50% PD-L1 expression, but considered that it acts on the same immunological pathway as the PD-1 and PD-L1 inhibitors supported for inclusion on the WHO

EML as monotherapy for this indication. It is important that countries identify the different immune checkpoint inhibitors as therapeutically equivalent and set up competitive mechanisms for procurement (including tendering) in light of overall available evidence to improve access. Since 2020, tislelizumab has been included in the national reimbursement drug list, allowing this molecule to be reimbursed by China's public insurance programmes (30). The national drug price negotiation that preceded the decision to reimburse tislelizumab led to a price reduction of about 80%.

While there may be evidence of similar clinical performance within the same pharmacological class, the magnitude of clinical benefit might not be sufficiently compelling, or there could be factors limiting use across immune checkpoint inhibitors (e.g. use in combination with chemotherapy). For instance, indirect evidence from a network meta-analysis addressing the comparative effectiveness of pembrolizumab, nivolumab, toripalimab, and tislelizumab for esophageal squamous cell cancer found relatively consistent magnitudes of effect on overall survival between the PD-1 inhibitors (17). Although this provides further evidence of a potential pharmacological class effect across PD-1 inhibitors, the magnitude of benefit was considered limited in this cancer, and below the WHO EML Expert Committee recommended threshold to be considered a candidate for inclusion on the WHO EML (3). For non-small cell lung cancer ≥50% PD-L1 expression, tislelizumab has not been approved as monotherapy, unlike pembrolizumab, cemiplimab and atezolizumab. The clinical benefit of tislelizumab has instead been demonstrated in combination with chemotherapy. This caveat is a limitation of the available evidence on the interchangeability of immune checkpoint inhibitors for non-small cell lung cancer ≥50% PD-L1. Therapeutic equivalence may therefore be restricted to cancer medicines and indications in which the magnitude of benefit and level of evidence are large and mature, respectively. These should be prioritized for procurement.

The Cancer Experts highlighted the urgent need for improving current standards for approval and suggested comparative adaptive trials as the new standard to prove equivalence and interchangeability among the various immune checkpoint inhibitors. This research should include head-to-head randomized trials – as recently suggested by the FDA – to reduce heterogeneity in study designs and enable comparisons (31). In general, the inclusion, when possible, of an adjuvant-only monotherapy arm could provide important insights into the actual best role of these immunotherapies for which preferred regimens are still to be defined. It was noted that post-approval studies in patients usually excluded from trials because of performance status, age, or comorbidities, and adoption of a "near-equivalence" approach over widely used non-inferiority trials (25).

The Cancer Experts noted that such trials are unlikely to be supported by the pharmaceutical industry and suggested that the WHO EML Expert Committee, together with the WHO Department of Noncommunicable Diseases, provide strong input on this being a priority for independent collaborative research, where WHO could support development of a research platform serving primarily trial needs of LMICs and LICs, similar to the European Organisation for Research and Treatment of Cancer platform in Europe. The Cancer Experts considered that governments and charitable organizations should be encouraged to support such trials. The PERLA trial is one example of a head-to-head randomized trial that provided evidence for similar efficacy of dostarlimab combined with chemotherapy to pembrolizumab combined with chemotherapy in previously untreated metastatic non-squamous non-small cell lung cancer (32). With indirect evidence, heterogeneity in techniques and tests measuring levels of predictive biomarkers limits confidence in indirect comparisons of immune checkpoint

inhibitors. Finally, post-approval studies can provide critical information related to optimal treatment doses, schedules, duration, and positions (e.g., first-line vs second-line) (25).

- *Reduced intensity treatment*

The Cancer Experts acknowledged growing evidence for immune checkpoint inhibitors that supports the use of reduced intensity treatment. The potential reduction in intensity while maintaining important benefits seems to be an option that extends to many molecules used to treat several types of cancer (33). Within immune checkpoint inhibitors, substantial evidence indicates that much lower doses of both nivolumab and pembrolizumab provide maximal binding to their receptors, and that such binding is maintained for considerably longer than the registered dosing intervals of 2 or 4 weeks for nivolumab and 3 or 6 weeks for pembrolizumab. Relevant evidence for these medicines is summarized below.

Nivolumab: Topalian et al. studied the binding of nivolumab to receptors on circulating T-cells at 8 weeks after a range of doses (0.1-10 mg/kg given every 2 weeks) and found no significant difference in receptor occupancy. The doses evaluated in cohorts of 10-20 patients were 3.3%, 10%, 33%, 100%, and 330% of the clinically approved dose used in clinical trials evaluating the medicine, with only one outlier among 11 patients having reduced binding at the very lowest dose of 0.1 mg/kg (34).

In a study led by researchers at the University of Washington (available only in poster form at the time of writing this report), Tachiki et al. collected 122 serial peripheral blood mononuclear cell (PBMC) samples at multiple time points from 19 patients receiving nivolumab at different doses and at varying frequencies (every 4 to 12 weeks). They measured receptor occupancy on CD4+ and CD8+ T-cells at 4, 8, and 12 weeks after doses of 40 mg, 240 mg, and 480 mg, and found no consistent differences in receptor binding either as a function of dose or time. They also measured serum nivolumab concentration as a function of time after these doses, and although serum concentrations were higher with higher doses, even after 40 mg (1/12 of the dose approved to be given at 4-week intervals) the median serum concentration remained above the minimal effective concentration of 1.5 µg/ml for 3 months (35).

The above pharmacokinetic/pharmacodynamic studies are supported by clinical findings. In a large phase 2 study, 168 patients with advanced renal cell cancer were randomized to receive nivolumab doses of 0.3 mg/kg, 2 mg/kg, and 10 mg/kg every 3 weeks. There was no significant difference in response rate, progression-free survival, or overall survival between these groups, yet the dose taken forward for phase 3 trials was 3 mg/kg every 2 weeks, 15x the lowest dose used in this study (36). A randomized trial conducted in India compared low-dose nivolumab (20 mg flat dose once every 3 weeks) combined with chemotherapy to chemotherapy alone for the treatment of advanced head and neck squamous cell carcinoma in 151 patients. The on-label dose for this cancer is 240 mg every 2 weeks, thus having every 6 weeks an intensity reduction between the on-label and low-dose of approximately 94% (40 mg versus 720 mg). The median overall survival at one-year was 10.1 months (95% CI 7.4 to 12.6) and 6.7 months (95% CI 5.8 to 8.1), respectively (37). The consistent results of the target binding, pharmacokinetic, and clinical studies provide substantial evidence in support of an alternative dosing strategy for nivolumab, especially important in settings where full-dose treatment is not attainable (e.g., due to out-of-pocket costs) (37).

Pembrolizumab: The approved doses of pembrolizumab are 2 mg/kg (or a flat dose of 200 mg) every 3 weeks, or double those doses given every 6 weeks. In a phase 1 study, an ex-vivo IL-

2 PD-1 receptor modulation assay was used to study receptor engagement after doses of 1.0 mg/kg, 3.0 mg/kg, or 10.0 mg/kg every 2 weeks: PD-1 target engagement in patients remained high during multiple courses of therapy and independent of dose (38). Studies reported in the original FDA application by the company have shown that the half maximal inhibitory concentration of pembrolizumab is between 500 pM and 1 nM (39). Intra-patient escalating doses from 0.005 mg/kg were given to patients in the phase 1 trial, and with a terminal half-life of 2-3 weeks, measurements of serum concentration suggest that receptor inhibition would be maintained for at least 2 months after doses as low as 0.3 mg/kg (38).

Multiple trials are ongoing to evaluate reduced dosing or prolonged dosing intervals (40). But there have been fewer clinical studies evaluating much lower than approved doses of pembrolizumab than for nivolumab. A pre-planned interim analysis from the NVALT-30 trial evaluating lower dose pembrolizumab (300 mg Q6W or 100 mg Q3W with or without chemotherapy) and standard dose (400 mg Q6W or 150-200 mg Q3W) for treatment of stage IV non-small cell lung carcinoma found a non-significant difference in one-year overall survival between the arms and met the predetermined criterion for continuing the trial (41).

Weight-based doses instead of fixed doses were shown to maintain treatment effectiveness while reducing treatment costs for non-small cell lung cancer in two retrospective cohort studies and have been implemented in several countries (42-44). It is noteworthy that the initial trials that established efficacy of immunotherapies in melanoma and lung cancer utilized weight-based dosing (45, 46).

Reduced intensity treatment strategies include dose reduction, rounding and banding, longer intervals between administrations, and shorter duration of treatment (40, 47). Cancer Experts considered that promising data were largely available for pembrolizumab and nivolumab based on dose-finding phase 1 and 2 studies (36-38, 48, 49), and pharmacokinetic and pharmacodynamic studies (34, 35, 47, 50-54), but were limited in terms of demonstrating similarity with registered doses based on long-term overall survival from comparative randomized trials, as well as for other immune checkpoint inhibitors. Cancer Experts highlighted >10 ongoing randomized trials, addressing early cessation, extended dosing intervals, and lower doses as reduced intensity treatment strategies (40, 47). The Cancer Experts emphasized that reduced intensity treatment has the potential to significantly reduce the cost of treatment with immune checkpoint inhibitors, and that the cost reduction is much greater than the possible reduction in efficacy. Cost reduction through reduced dose intensity, achieving relevant patient outcomes, is valid across all income settings. The Cancer Experts recommended that emerging evidence from ongoing and future pragmatic dose-optimization trials should be closely monitored.

- *Vial size and sharing*

The immune checkpoint inhibitors are typically provided in single-use vials with fixed concentrations, and unused portions often go to waste if the entire vial is not needed for a specific patient's dose. It can be important to decide on an immune checkpoint inhibitor based on the optimal vial size for the patient. In addition, vial sharing is a practical approach to cutting costs and improving access. Vial sharing allows for precise doses to be administered without wastage, particularly in weight-based regimens (55). Some regions have strict rules regarding the sharing of single-use vials due to contamination risks. However, controlled hospital settings with proper aseptic techniques can mitigate these concerns. It may also require coordination in

scheduling and pharmacy preparation to ensure vials are used efficiently across multiple patients, within stability timeframes.

- *Biosimilars, pooled procurement and licensing strategies*

The Cancer Experts emphasized the need for immediate action to reduce the price of and increase access to cancer medicines, especially immune checkpoint inhibitors. They reiterated the findings from an external report addressing the financial implications of PD-1 and PD-L1 immune checkpoint inhibitors (56), particularly pembrolizumab and nivolumab:

  - "...biosimilar entry is anticipated in the next 3 to 5 years (2028 to 2030)."
  - "...it is anticipated that upon biosimilar entry, the cost of pembrolizumab will decrease up to 60%, while nivolumab may see a more moderate reduction."
  - "Given pembrolizumab's dominant role in critical indications such as advanced melanoma and non-small cell lung cancer, prioritizing efforts to ensure affordable access in these areas could maximize cost-effectiveness and expand access to the largest patient populations."
  - "Despite these anticipated price reduction predictions, achieving prices that meet specific cost-effectiveness criteria will likely require additional strategies beyond the introduction of biosimilars. Strategies to reduce costs and increase affordability of immune checkpoint inhibitors include fostering a biosimilar-friendly policy landscape, leveraging pooled procurement mechanisms, and making use of voluntary and compulsory licensing mechanisms to overcome patent barriers."

The Cancer Experts noted pooled procurement among other strategies in the report, which identified pooled procurement as strengthening "... the collective bargaining position of the purchasing authorities in order to consolidate demand and facilitate access to quality affordable medicines." It was highlighted that pooled procurement by way of the Pan American Health Organization's Strategic Fund and the National Cancer Grid Network in India "... has shown to be effective when applied to oncology mAbs, where bulk purchasing resulted in significant price reductions." Specifically, savings from pooled procurement through the National Cancer Grid Network in India, based on a 2023 study, "...ranged from 23% to 99% (median, 82%) when compared to the maximum retail price..." of included cancer medicines (57). The Cancer Experts noted how several countries rely on the procurement of anti-cancer medicines using centralized healthcare hubs. The efficiency of these hubs is increased by purchasing a limited number of formulations that cover all doses required, or by making selective purchases and limiting the use of alternative formulations to treat the largest number of indications, thereby achieving the best tendering prices. Several suggestions in this report align well with a mechanism that favors the procurement of fewer, highly effective, quality-assured medicines.

The Cancer Experts aligned with the conclusion of the report that stated "...inclusion of immune checkpoint inhibitors on the WHO Model List of Essential Medicines serves as a foundation to legitimize immune checkpoint inhibitor cost-reduction measures, attract global funding and stimulate further investment into immune checkpoint inhibitor biosimilar development" and reinforced the immediate need for "...a multifaceted approach, including biosimilars, procurement mechanisms, and tiered licensing strategies..." to achieve price reductions and greater access to immune checkpoint inhibitors, particularly pembrolizumab, in the short to medium term.

- *Alternative models for stimulating medicine innovation*

The far too high prices of all new cancer medicines are not justified by production costs (that are similar to other monoclonals in other areas of therapeutics) nor by disease rarity, since cancer is a highly frequent disease. The second striking feature of high-priced cancer medicines is their similar price when the benefits are marginal or modest, and when the benefits are large (58, 59). This is particularly striking now when shown using internationally validated scales of clinical benefits such as ESMO-MCBS (60) The sum of these issues – high prices across cancer medicines regardless of the magnitude of clinical benefit – almost invariably leads to restrictions on access in general, and particularly harsh outcomes for persons living in countries with lower average incomes. Efforts to leverage the collective purchasing power through negotiations with public or private procurement or reimbursement authorities, or through price controls, have had, until now, limited success in moderating excessive prices and disparities in access.

In 2009, the governments of Bangladesh, Bolivia, and Suriname made a proposal concerning the possible use of prizes as a new incentive mechanism for innovation in new cancer treatments that separates rewards to innovation from the price of the products in developing countries (61). The proposal aimed to facilitate rapid entry by generic suppliers, offering in return a system of rewards for originators of cancer treatments that is based on a fixed percentage of the national budget for cancer treatments. The 2011 WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual property (GSPA-PHI) recognizes "the price of medicines is one of the factors that can impede access to treatment" and recommended, among other measures, that states explore "new thinking on innovation and access to medicines," including, "where appropriate, the delinking of the costs of research and development and the price of health products." (62) More recently, a U.S. Congress 2024 bipartisan Congressional proposal called for a study by the national academies of science on "alternative models for directly funding, or stimulating investment in, biomedical research and development that delink research and development costs from the prices of drugs, including the progressive replacement of patents and regulatory exclusivities on new drugs with a combination of expanded support for research and innovation prizes to reward the successful development of drugs or achievement of related milestones." (63)

Additional remarks

In consideration of the therapeutic potential of immune checkpoint inhibitor treatment for other cancer indications, the Cancer Experts advised that based on clinical relevance, the following cancer indications could be the subject of future applications for EML evaluation:

- cutaneous squamous cell carcinoma
- basal-cell carcinoma
- Merkel cell carcinoma
- classical Hodgkin lymphoma

The Cancer Experts identified a clinical need to expand the current listing of gemcitabine – a chemotherapeutic drug already listed on the Model List for the treatment of epithelial ovarian

cancer and non-small cell lung cancer. The Cancer Experts support expanding the listing of gemcitabine to include malignant neoplasms of the nasopharynx.

The Cancer Experts acknowledged ongoing efforts of the Department of Health Products Policy and Standards to update the Anatomical Therapeutic Chemical (ATC) classification system and to develop Defined Daily Doses (DDDs) for cancer medicines and the importance of this methodology to help monitor the use of cancer medicines moving forward.

Given the need to identify cancer patients most likely to benefit from immune checkpoint inhibitors (e.g., based on PD-L1 expression), the Cancer Experts support the inclusion of companion diagnostic tests on the Essential Diagnostics List (EDL) that align with the cancer medicines added to the Model Lists. The Cancer Experts also highlighted the importance of developing mechanisms to align the EML and EDL moving forward.

The Cancer Experts commended the WHO Technical Unit on Noncommunicable Diseases: Cancers for their workstream to provide direct support to Member States in prioritizing and accessing cancer medicines.

Finally, the Cancer Experts indicated their support for a formal review of cancer medicines on the Model Lists against available dose-optimization evidence and creation of a subcommittee to the WHO Expert Committee on the Selection and Use of Essential Medicines focused on cancer medicines. They noted that a priority for this formal review could be ibrutinib, which is included on the complimentary EML for the treatment of adolescents and adults with chronic lymphocytic leukemia or small lymphocytic lymphoma. They considered that overdosing with ibrutinib leads to increased adverse events and costs. The Cancer Experts noted that a subcommittee could facilitate the review of the rapidly evolving cancer medicine evidence base, including novel immunotherapies.

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ANNEX 1: MEETING AGENDA.

Expert Consultation Meeting on Cancer Medicine Candidates for the 2025 Model Lists of Essential Medicines

Geneva, 23-24 January 2025
WHO HQ, M Building – Room M505

<table>
<tr><th colspan="3">Day 1 – 23 January 2025</th></tr>
<tr><th>Time</th><th>Agenda item</th><th>Chair/Facilitator</th></tr>
<tr><td>8:45 – 9:00</td><td>Arrival coffee and greetings</td><td></td></tr>
<tr><td>9:00 – 9:10</td><td>Welcome - Introductory remarks</td><td>Deus Mubangizi</td></tr>
<tr><td>9:10 – 9.30</td><td>Declarations of Interests
Expected outcomes:
Brief overview of 2025 EML applications to be reviewed over the two days
Introduction to the review of the EML update process and role of cancer
Broadening inputs by the cancer experts beyond essential medicines</td><td>Lorenzo Moja</td></tr>
<tr><td colspan="3">EML 2025 Applications review</td></tr>
<tr><td rowspan="3">9:30 – 10.30</td><td colspan="2">Comprehensive review of proposed indication and ICI-containing treatment pairings (I)
Pembrolizumab</td><td rowspan="3">Rapporteur for each disease
(5 minutes to present per rapporteur)
All</td></tr>
<tr><td></td><td>Indication: Oncogenic-driver wild-type non-small cell lung cancer with ≥ 50% PD-L1 expression
Therapeutic alternative(s): cemiplimab; atezolizumab
Treatment type: Monotherapy
Rapporteur: Tito Fojo</td></tr>
<tr><td></td><td>Indication: Oncogenic-driver wild-type non-small cell lung cancer, irrespective of PD-L1 expression
Therapeutic alternative(s): cemiplimab; ipilimumab + nivolumab; tremelimumab + durvalumab
Treatment type: Combination therapy
Rapporteur: Tito Fojo</td></tr>
</table>

	Indication: Head and neck squamous cell carcinoma with ≥ 1% PD-L1 expression Therapeutic alternative(s): NA Treatment type: Mono- or combination therapy Rapporteur: Richard Sullivan	
	Indication: Renal cell carcinoma, irrespective of PD-L1 expression Therapeutic alternative(s): ipilimumab + nivolumab Treatment type: Mono- or combination therapy Rapporteur: Ian Tannock	
	Indication: Cervical cancer with ≥ 1% PD-L1 expression Therapeutic alternative(s): NA Treatment type: Combination therapy Rapporteur: Dorothy Lombe	
	Indication: Triple-negative breast cancer with ≥ 10% PD-L1 expression Therapeutic alternative(s): NA Treatment type: Combination therapy Rapporteur: Ian Tannock	
	Indication: Colorectal cancer with mismatch-repair protein deficiency (dMMR/MSI-H) Therapeutic alternative(s): NA Treatment type: Monotherapy Rapporteur: Christopher Booth	
	Indication: HER-2 negative, gastric/gastro-oesophageal junction adenocarcinoma (PD-L1 ≥ 1%) Therapeutic alternative(s): NA Treatment type: Combination therapy Rapporteur: Zeba Aziz	
	Nivolumab Indication: HER-2 negative, gastric/gastro-oesophageal junction adenocarcinoma (PD-L1 ≥ 5%) Therapeutic alternative(s): NA Treatment type: Combination therapy Rapporteur: Zeba Aziz	

10:30 – 11:00	**Coffee Break**	
EML 2025 Applications review - continuing		
11:00 – 13:00	**Comprehensive review of proposed indication and ICI-containing treatment pairings (II) - continued** **Nivolumab** Indication: Oesophageal squamous cell carcinoma (PD-L1 ≥ 1%) Therapeutic alternative(s): ipilimumab + nivolumab Treatment type: Combination therapy Rapporteur: Dario Trapani **Pembrolizumab** Indication: Oesophageal squamous cell carcinoma (PD-L1 ≥ 10%) Therapeutic alternative(s): NA Treatment type Combination therapy Rapporteur: Dario Trapani **Durvalumab** Indication: Hepatocellular carcinoma, irrespective of PD-L1 expression Therapeutic alternative(s): tremelimumab + durvalumab; bevacizumab + atezolizumab Treatment type: Mono- or combination therapy Rapporteur: Bishal Gyawali Indication: Biliary tract cancer, irrespective of PD-L1 expression Therapeutic alternative(s): NA Treatment type: Combination therapy Rapporteur: Bishal Gyawali **Dostarlimab** Indication: Endometrial carcinoma with mismatch-repair protein deficiency (dMMR/MSI-H) Therapeutic alternative(s): NA Treatment type: Combination therapy Rapporteur: Tito Fojo **Ipilimumab + nivolumab** Indication: Malignant melanoma, irrespective of PD-L1 expression Therapeutic alternative(s): nivolumab, pembrolizumab Treatment type: Mono- or combination therapy Rapporteur: Zeba Aziz	Rapporteur for each disease **(5 minutes to present per rapporteur)** All

13:00 – 14:00	**Lunch**	
Dose duration and class effect review		
14:00 – 15:30	• Dose and duration of cancer regimens including immune checkpoint inhibitors, class effect and interchangeability: evidence, uncertainty, and country experiences. • Potential role of the EML	Ian Tannock (off label recommendations on essential medicines) Daniel Goldstein (remote, class effect scenarios) Manju Sengar (India case study) Zeba Aziz (Pakistan case study) Elisabeth de Vries (Netherlands case study) All
15:30 – 16:00	**Coffee break**	
Cancer Medicines Economics		
16:00 - 17:30	• Financial impacts of expanding access to ICIs for treating advanced NSCLC • Prices and patents landscape associated with ICIs • Market dynamics	Kiu Tay Giulia Segafredo (MPP) Arianna Schouten (KEI) All
EML 2025 Applications review - continuing		
17:30 - 18:30	Other EML applications – childhood cancer* • Blinatumomab CD19-positive frontline, relapsed, or refractory B-lineage acute lymphoblastic leukemia – EMLc Rapporteur: Andrea Biondi • Temozolomide – high grade glioma, Ewing sarcoma, neuroblastoma – EML and EMLc Rapporteur: Francesco Ceppi * There is a possibility that this session will move to the next day in case there is delay/fatigue in previous sessions.	Rapporteur for each disease **(5 minutes to present per rapporteur)** All
18:30 – 18:40	Summary and next steps	Elisabeth de Vries Lorenzo Moja

Day 2 – 24 January 2025, Room: 505		
Time	**Agenda item**	**Presenter**
8:30 – 8:45	Introduction and summary of day 1	Elisabeth de Vries
EML 2025 Applications review - continuing		
8:45 – 9.45	Other EML applications • Panitumumab – KRAS wild-type metastatic colorectal cancer – EML Rapporteur: Christopher Booth • Tislelizumab – oesophageal squamous cell cancer – EML Rapporteur: Dario Trapani • Toripalimab – oesophageal squamous cell cancer – EML* Rapporteur: Dario Trapani • Zanubrutinib – chronic lymphocytic leukaemia/small lymphocytic leukaemia – EML* Rapporteur: Maria Elena Cabrera *Resubmission	Rapporteur for each disease **(7 minutes to present per rapporteur)** All
Executive board EML report by DG		
9:45 – 10:30	Revising the procedures for updating WHO's model lists of essential medicines Role of cancer in the new EML procedure Medicines prioritization mechanisms for next EML update	Lorenzo Moja Bernadette Cappello Christopher Booth All
10:30 – 11.00	**Coffee Break**	
Country support to better prioritize cancer medicines		
11:00 – 12.30	Access to cancer medicines: WHO cancer team workstreams including country support • Comprehensive approach to accessing cancer medicines • Validation and review of cancer medicines: a tool for rational use • Upstream pipeline activities and market shaping	Andre Ilbawi

12:30 – 13:30	**Lunch**	
Monitoring cancers and products for cancer		
13:30 – 14:30	WHO Global Status Report on cancer in 2025: highlights on cancer medicines and clinical trials	Raffaella Casolino
14:30 – 15:30	Defined Daily Dose for cancer medicines in collaboration with ATC/DDD International Working Group and WHO Collaborating Centre on Drug Statistics Methodology Harmonizing EML and Essential In-Vitro Diagnostics List (EDL) recommendations	EML and INN Secretariat EML and EDL Secretariat
15:30 – 16.00	**Summary of day 2, timeline for next steps and closing of the meeting**	EML Secretariat / NCD