WHO MODEL LISTS OF ESSENTIAL MEDICINES

CANCER MEDICINES WORKING GROUP

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

INTRODUCTION:

The EML Cancer Medicines Working Group has reviewed the applications received for cancer medicines for the 2023 update of the Model Lists of Essential Medicines (EML) and Essential Medicines for Children (EMLc). Final remarks from the Working Group evolved through several iterations. In 2022 the Working Group met six times in online meetings to review the evidence supporting use of cancer medicines not included in the Model List, discussed controversial issues regarding the selection and use of essential cancer medicines, and refined the list of medicines that could be prioritised for the 2023 update of the Model List of Essential Medicines. This document provides a summary of the Working Group considerations, and the consensus views of the Working Group in relation to the potential listings for cancer medicines.

The following document outlines the assessment of the cancer medicine applications by the Working Group. The statements represent the consensus opinion of the Working Group members. In case of diverging opinions among experts, these are explicitly mentioned in the statements.

APPLICATIONS REVIEWED:

A.5/A.46 PD-1 / PD-L1 immune checkpoint inhibitors – locally advanced and metastatic non-small cell lung cancer (EGFR, ALK, and ROS1 wild type) – EML
A.8 CAR-T cell therapy for relapsed/refractory diffuse large B-cell lymphoma – EML
A.12 Cyclin-dependent kinase 4/6 inhibitors for hormone receptor positive/ HER2-negative advanced breast cancer – EML
A.30 Osimertinib –locally advanced or metastatic non-small cell lung cancer (EGFR mutated) – EML
A.31 Pegfilgrastim – febrile neutropenia prophylaxis – EML and EMLc
A.49 Toripalimab – recurrent and metastatic nasopharyngeal carcinoma and advanced oesophageal, squamous carcinoma – EML
A.52 Zanubrutinib – chronic lymphocytic leukaemia, small lymphocytic lymphoma – EML
I.1/I.2/I.8 Cancer medicines for children – new indications – EMLc
F.2 Pegylated liposomal doxorubicin (PLD) - indication of treating Kaposi's sarcoma in adults and children -EML and EMLc

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SUMMARY OF EML CANCER MEDICINES WORKING GROUP ADVICE

Application	Working Group conclusions / Advice for Expert Committee
General remarks	Among all cancer medicine applications received for the 2023 update of the WHO Model Lists for Essential Medicines, the Working Group considers that the highest priorities for addition are pegfilgrastim for febrile neutropenia prophylaxis and pegylated liposomal doxorubicin for Kaposi sarcoma. The Working Group also supports expansion of the listings of existing medicines on the EMLc for the new indications of anaplastic large cell lymphoma (ALCL) and Langerhans cell histiocytosis (LCH) but does not support inclusion of the new medicines crizotinib (for ALCL) or cladribine (for LCH). The Working Group did not reach a consensus regarding the addition of pembrolizumab and other immune checkpoint inhibitors for non-small cell lung cancer (NSCLC) to the Model List. While the inclusion could be supported based on their clinical efficacy and safety, there are major concerns about financial risks. Overall, the Working Group noted that immune checkpoint inhibitors were potentially more relevant in terms of benefit to patients than other cancer medicines associated with large benefits and considered for this update, namely osimertinib for lung cancer and cyclin-dependent kinase 4/6 inhibitors for breast cancer. For all these medicines the Working Group considered the financial impact associated with use to be unmanageable and unsustainable by most countries. The Working Group also did not consider that the addition of CAR-T therapy for B-cell lymphoma, toripalimab for nasopharyngeal and oesophageal carcinoma, and zanubrutinib for chronic lymphocytic leukaemia and small lymphocytic lymphoma should be prioritized.
A.5 /A.46 PD-1 / PD-L1 immune checkpoint inhibitors – locally advanced and metastatic non-small cell lung cancer (NSCLC) – EML	The Working Group was not able to agree on a final suggestion supporting or not supporting the inclusion of PD-1/PD-L1 immune checkpoint inhibitors on the EML for first-line treatment of selected patients with metastatic NSCLC with PD-L1 expression ≥ 50%, whose tumours do not harbour a targetable alteration such as an epidermal growth factor receptor (EGFR) mutation or an anaplastic lymphoma kinase (ALK) fusion. The Working Group acknowledged a relevant and meaningful survival benefit at a long follow-up and a possible improvement of the quality of life associated with the use of pembrolizumab. It was noted that other PD-1 / PD-L1 immune checkpoint inhibitors for example, cemiplimab and atezolizumab as first-line treatment of selected patients with EGFR-wild type, metastatic NSCLC with PD-L1 expression ≥ 50%, and durvalumab for stage III, locally advanced non-metastatic lung cancer with PD-L1 expression ≥ 1%, after prior chemotherapy and radiation therapy, provide similar benefits although the available trial data for these medicines have a shorter duration of follow up. Several members of the Working Group mentioned ongoing uncertainty related to the implications at the country level of listing immune checkpoint inhibitors on the WHO Model List, including financial risks based on the current costs of procurement, opportunity costs associated with diverting resources from other diseases or treatments, highly limited feasibility related to barriers in the timely access to diagnostics and lack of information about most cost-effective duration of treatment and dose. Predictive biomarkers, such as PD-L1 expression, are key to selecting patients with tumours that are more likely to respond to immune checkpoint inhibitors. Some Working Group members highlighted how, despite the approval of several checkpoint inhibitors, prices for these agents have remained prohibitively high in most settings, discounting is consistently limited by the producing companies and biosimilars cannot be expected to be available in most jurisdictions in the near future. Other Working Group members underscored that a positive recommendation on immune checkpoint inhibitors for the treatment of NSCLC by WHO can guide countries in prioritising these medicines for this specific indication, limiting their use for other cancers in which benefits are less relevant. The Model List can support national decision-making and inform national guidelines for clinical practice and guide the procurement and supply of medicines in the public sector. Working Group members also underscored that price competition should be facilitated among immune

	checkpoint inhibitors by allowing early utilization of more molecules in national markets. The Working Group noted that the applications did not consider camrelizumab, nivolumab/ipilimumab, sintilimab, sugemalimab nor toripalimab. Most have shown comparable improvement in disease control compared to other immune checkpoint inhibitors under consideration. However, only for nivolumab/ipilimumab data on overall survival were mature, with all other molecules tested in clinical trials with incomplete survival data.
A.8 CAR-T cell therapy for relapsed/refractory diffuse large B-cell lymphoma (DLBCL) (REVIEW)	The Working Group does not support the inclusion of CD19- directed CAR-T cell immunotherapy as a therapeutic class or as individual medicines on the EML. The Working Group acknowledged that CAR-T cell therapy (i.e. axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel) is superior to salvage immunochemotherapy in terms of progression free-survival, without evidence of heterogeneity across trials. However, for all medicines proposed, the Working Group noted that long-term trial follow-up is limited, and that the survival benefit observed is currently uncertain, with one study potentially associated with a detrimental effect of CAR-T. In addition, current costs associated with the administration of these medicines are very high, with cost-effectiveness analyses finding these treatments not to be cost-effective in most settings at current prices. Further concerns were raised about the feasibility of administering these treatments and managing adverse effects in low-resource settings. It was noted that CAR-T cell therapy is a rapidly evolving field with a high likelihood the currently available products would be replaced by more advanced constructs in the near future. The Working Group agreed that CAR-T cell therapies for DLBCL, and probably other cancer indications (e.g., acute lymphoblastic leukaemia), are an area of significant interest and therapeutic relevance. The Working Group considered that the evidence base for these therapies should continue to be monitored on an ongoing basis. Costimulatory signalling domains should be also considered as they might have implications for clinical efficacy and in prioritizing one CAR-T cell immunotherapy over others. The Working Group noted that T-cell production modes, other than industry-scaled centralised manufacturing by companies, are now being explored. Decentralised production in academic medical centres and hospitals closer to the patients has the potential to facilitate widespread patient access to CAR T cell therapy. These techniques should be monitored as well by WHO.
A.12 Cyclin-dependent kinase 4/6 inhibitors for hormone receptor positive/ HER2-negative advanced breast cancer	The Working Group does not support the inclusion of palbociclib, ribociclib, or abemaciclib on the EML for the treatment of adult patients with hormone receptor positive / HER2-negative advanced breast cancer. The Working Group noted that the evidence indicates the cyclin-dependent kinase 4/6 inhibitors in combination with endocrine therapy (aromatase inhibitors, tamoxifen or fulvestrant) are associated with meaningful overall survival benefit when compared with placebo / aromatase inhibitors or placebo / fulvestrant. The Working Group acknowledged enduring uncertainties related to dose and duration of therapy, and whether relevant clinical differences exist between agents within the pharmacological class. At the current high price, cyclin-dependent kinase 4/6 inhibitors have not been found to be cost-effective in most settings and would pose serious affordability challenges, especially in low-resource settings. The Working Group noted molecules of this class would be potential candidates for voluntary license mechanisms under the aegis of the Medicines Patent Pool.
A.30 Osimertinib – non-small cell lung cancer – EML	The Working Group does not support the inclusion of osimertinib on the EML for first-line treatment of selected patients with epidermal growth factor receptor (EGFR) mutated locally advanced or metastatic NSCLC. The Working Group noted that the evidence indicates that the third-generation tyrosine kinase inhibitor osimertinib has meaningful overall survival benefit compared with the first- and second-generation tyrosine kinase inhibitors currently listed on the EML (erlotinib, gefitinib and afatinib) when used as monotherapy. However, the Working Group noted the evidence originating from a Phase III randomized control trial in India comparing gefitinib monotherapy versus gefitinib in combination with chemotherapy (Noronha V, Patil VM, Joshi A, et al. Gefitinib Versus Gefitinib

	Plus Pemetrexed and Carboplatin Chemotherapy in EGFR-Mutated Lung Cancer. J Clin Oncol. 2020;38(2):124-136. doi:10.1200/JCO.19.01154). In this trial the addition of chemotherapy to a first-generation tyrosine kinase inhibitor significantly prolonged overall survival (not reached v 17 months [95% CI, 13.5 to 20.5 months]; hazard ratio [95% CI, 0.31 to 0.65]). Other trials have shown similar results. The Working Group, therefore, considered that the benefit of first-generation tyrosine kinase inhibitors in combination with chemotherapies might provide similar benefits to those associated with use of osimertinib, albeit at a higher risk of toxicity. At the current high price, osimertinib has not been found to be cost-effective and would pose serious affordability challenges, especially in low-resource settings. The Working Group noted the availability of another drug, aumolertinib, which received regulatory approval from the Chinese National Medical Products Administration for the treatment of patients with NSCLC harbouring EGFR T790M mutations who had progressed on or after other EGFR TKI therapy. The approval was based on findings from the open-label phase II APOLLO study [NCT02981108]. Additional support for the efficacy of aumolertinib comes from AENEAS [NCT03849768]. PFS was significantly longer with aumolertinib compared with gefitinib (HR 0.46; 95%CI, 0.36 to 0.60; p<0.0001). Aumolertinib could potentially lead to price competition against osimertinib at least within certain LMICs. The Working Group noted that if a drug for lung cancer were to be added to the Model List, immunotherapy would get a priority higher than that of osimertinib based on overall impact on survival.
A.31 Pegfilgrastim – febrile neutropenia prophylaxis – EML and EMLc	The Working Group supports the inclusion of pegfilgrastim and quality assured biosimilars on the EML and EMLc for the prevention of febrile neutropenia. The available evidence shows that a single dose of pegfilgrastim is an efficacious and safe alternative to daily injections of filgrastim. In clinical practice, particularly in low- and middle-income countries, short-acting filgrastim is associated with increased risks of lower adherence, as it can require daily administration for up to 11-14 days. In low-income countries where cold supply chain capacity for biotherapeutics is often limited outside secondary treatment centres, patients using filgrastim are likely to face longer hospital stays or daily clinic visits. The Working Group noted that in clinical practice, due to these constraints the duration of filgrastim treatment is often shorter than 11 days and often also shorter than 7 days. In some patients reduced duration of filgrastim may be associated with worse outcomes compared with the full cycle of filgrastim or pegfilgrastim. The Working Group acknowledged the high cost of pegfilgrastim but noted that these costs are dropping with the approval of several biosimilars and noted the potential for cost-savings of using single-dose administration over daily dose administration without significantly compromising benefit. The availability of pegfilgrastim biosimilars and improved affordability is likely to correlate with increased use and additional price discounts. The Working Group noted that in patients receiving short chemotherapy intervals, like weekly chemotherapies, although unusual in needing granulocyte colony-stimulating factor (G-CSF) support, filgrastim should be administered for shorter than 11-14 days. In that case filgrastim should be preferred over pegfilgrastim. Despite the support for inclusion of pegfilgrastim in the EML, the Working Group recalled that G-CSF support should not be used if the risk of febrile neutropenia from chemotherapy is limited, consistent with the ASCO Choosing Wisely campaign. The Working Group reiterated the need to not use G-CSF routinely among patients with neutropenia but without fever, or routinely in combination with antibiotics among patients with febrile neutropenia but without other risk factors for poor outcomes.
A.49 Toripalimab – recurrent and metastatic nasopharyngeal carcinoma and	The Working Group does not support the inclusion of toripalimab for nasopharyngeal carcinoma or oesophageal carcinoma at this time, because the absolute benefits are still unclear and data from trials have a short follow-up (i.e., 22 months). The Working Group notes that toripalimab could represent a treatment with potential high therapeutic value for the treatment of patients with nasopharyngeal cancer, a cancer endemic in

advanced oesophageal, squamous carcinoma – EML	some low- and middle-income countries with limited therapeutic options. The Working Group noted that multiple immune-checkpoint inhibitors are under development or have been granted approval for the management of advanced oesophageal carcinoma, suggesting similar benefits. A comprehensive evaluation of the landscape is appropriate to identify those immune-checkpoint inhibitors that provide the best payback to health care systems. Regarding cost-effectiveness, the Working Group noted that the lower price of toripalimab compared to other immune checkpoint inhibitors and improvement of the overall survival may result in better cost-effectiveness, although the cost for treatment may be still important from a budget impact perspective.
A.52 Zanubrutinib – chronic lymphocytic leukaemia, small lymphocytic lymphoma – EML	The Working Group does not support the inclusion of zanubrutinib on the EML for treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma at this time. It was noted that while data supported progression free survival gains from zanubrutinib when compared to ibrutinib, another TKI recommended by WHO as an essential medicine, the magnitude of these gains may be limited, and few long-term and real-world data were available. Furthermore, high rates of toxicity (particularly neutropenia), remaining uncertainty on potential better safety profile in bleeding, hypertension and atrial fibrillation, and limited information on prices with uncertain cost–effectiveness (given lower doses that can be used with ibrutinib as compared to those proposed in the application) were acknowledged as limitations for the procurement and use of zanubrutinib.
I.1/I.2/I.8 Cancer medicines for children – new indications – EMLc	The Working Group supports the expansion of the listings on the EMLc for the proposed cancer medicines for the proposed new indications (cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, methotrexate, prednisolone, vinblastine for anaplastic large cell lymphoma; cytarabine, immunoglobulin i.v., 6-mercaptopurine, methotrexate, prednisone, vinblastine, vincristine for Langerhans cell histiocytosis; rituximab for Burkitt lymphoma). These medicines are all used in standard, multi-modal chemotherapy protocols for the proposed indications. Expanding the EMLc indications for these medicines would support the goals of WHO Global Paediatric Cancer initiative and contribute towards the achievement of the best possible cancer care for children. The Working Group acknowledged that the availability of clinical evidence in the paediatric context is limited but considered that obtaining the usual level of evidence required for EML listings was unlikely. In this case, efficacy and safety could be accepted based on of extrapolation of the well-known benefits and harms from use of these medicines in adults, for other indications in children, and as part of standard cancer care in children. The Working Group was divided on the role played by crizotinib in anaplastic large cell lymphoma (ALCL). Crizotinib is not currently listed on the Model Lists for any other cancer. The Working Group noted that crizotinib is associated with benefits like other chemotherapies in first line, and it is considered as a therapeutic option for relapsed or refractory ALK-positive disease. However, crizotinib is associated with potentially severe toxicities. The Working Group commented that brentuximab-based chemotherapy is a new standard of care in adults with ALCL. Brentuximab-based chemotherapy is now studied also in children as it can represent a favourable first line option based on its benefit to harm ratio. The application did not cover brentuximab-based chemotherapy. The Working Group was also divided on the role of cladribine for Langerhans cell histiocytosis given the severe toxicity and the difficulty of managing these in resource limited settings. Cladribine is used as a salvage treatment. Its use is associated with high rates of cure among high-risk patients. However, it is also associated with prolonged hospitalization and increased risk of treatment-related death. The Working Group noted that an international, multicentre, prospective clinical study for paediatric Langerhans Cell Histiocytosis LCH is ongoing (NCT02205762) This study is planned to recruit 1400 patients and might provide data to guide the clinical care of children and young adults.

F.2 Pegylated liposomal doxorubicin (PLD) (& paclitaxel in adults) - indication of treating Kaposi's sarcoma in adults and children -EML and EMLc	The Working Group supports the inclusion of pegylated liposomal doxorubicin (PLD) for the treatment of advanced stage Kaposi's sarcoma in adults and children based on a positive benefit-risk profile. The Working Group noted that PLD is associated with relevant survival benefits for patients and reduced harms when compared to other chemotherapies (gemcitabine, vinorelbine, bleomycin, vinblastine, vincristine, etoposide). The Working Group reiterated the relevance of paclitaxel, a medicine already recommended by WHO for Kaposi sarcoma, as it is associated with benefits like PLD in adults, and it is likely to be better available than PLD in low resource settings. However, paclitaxel is associated with higher toxicity when compared to PLD, particularly neutropenia and sensory neuropathy. While generics of PLD become more available, the Model List must reiterate the relevance of paclitaxel as first-line chemotherapy for adult patients with advanced AIDS-associated Kaposi sarcoma in sub-Saharan Africa.