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 met virtually on four occasions between February and April 2021 to review the applications received for cancer medicines for the 2021 update of the Model Lists of Essential Medicines and Essential Medicines for Children. This document provides a summary of the Working Group considerations, and the views of the Working Group in relation to the potential listings for cancer medicines.

APPLICATIONS REVIEWED:

A.1 PD-1 and PD-L1 immune checkpoint inhibitors – non-small cell lung cancer – EML
A.3 Azacitidine – acute myeloid leukaemia – EML
A.4 BRAF/MEK inhibitors – metastatic melanoma – EML
A.8 Cyclin-dependent kinase (CDK) 4/6 inhibitors – HR+/HER2+ metastatic breast cancer – EML
A.9 Daratumumab – multiple myeloma – EML
A.11 Enzalutamide – metastatic castration-resistant prostate cancer – EML
A.13 Everolimus – subependymal giant cell astrocytoma – EMLc
A.15 Fulvestrant – metastatic breast cancer – EML
A.19 Ibrutinib – chronic lymphocytic leukaemia with 17p deletion – EML
A.23 Osimertinib – EGFR+ non-small cell lung cancer – EML
A.25 Pertuzumab – HER2+ metastatic breast cancer – EML
A.27 Rasburicase – tumour lysis syndrome – EML and EMLc
A.34 Tislelizumab – Hodgkin lymphoma – EML
A.35 Tislelizumab – urothelial carcinoma – EML
A.39 Zanubrutinib – chronic lymphocytic leukaemia, small lymphocytic lymphoma – EML
A.40 Zanubrutinib – mantle cell lymphoma – EML
I.8 Cancer medicines for children – new indications – EMLc
I.9 Cancer medicines for children – low-grade glioma – EMLc
I.10 Cancer medicines for head and neck cancer – EML
I.11 Doxorubicin – rhabdomyosarcoma – EML and EMLc
I.15 Tyrosine kinase inhibitors – Ph+ acute lymphoblastic leukaemia – EML
I.16 Vinorelbine – rhabdomyosarcoma – EMLc
R.1 CAR-T cell therapy – relapsed/refractory diffuse large B-cell lymphoma

GUIDING PRINCIPLES:

In consideration of the applications, the Working Group recognized the general principles for the consideration of essential cancer medicines, endorsed or recommended by the Expert Committee in 2019[1], namely:

- Consideration of efficacy / benefit
  - A threshold for benefit of at least 4-6 months survival gain;
  - ESMO-MCBS score of A or B (curative setting), or 4 or 5 (non-curative setting) (https://www.esmo.org/guidelines/esmo-mcbs);
- Consideration of types of trials
  - Availability of data from more than one clinical trial;
  - Data from high-quality RCTs are considered the most important; data must be mature in order to assess the impact of the medicine on overall survival; data should show consistent results across trials;
  - Information to inform the deployment of cancer regimens in countries with varying resources and clinical capacity is useful;
  - Trials that define the need for and length of maintenance therapy are of interest (shorter treatment durations that compromise efficacy marginally (or not at all) might substantially reduce outlays and allow more patients access to treatment);
  - Superiority trials are preferred to non-inferiority trials, however non-inferiority trials can be informative in some circumstances;
- Consideration of disease stage and line(s) of therapy.
  - Efficacy is usually less in advanced stages of disease, and when used in advanced lines of treatment. Medicines that are effective in first-line are more clinically meaningful and therefore highly desirable.
- Considerations regarding the indication to be listed
  - Inclusion of a medicine on the Model Lists for a given indication does not imply that it should be considered as essential for other indications.

Other issues considered by the Working Group included:

- Suitability of listing as a pharmacological class (square box), with a representative medicine and specific alternatives.
- Requirements for co-dependent diagnostic testing.
- Other relevant patient and health system issues.

[1] The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). World Health Organization. https://apps.who.int/iris/handle/10665/330668

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SUMMARY OF EML CANCER MEDICINES WORKING GROUP ADVICE

Application	Working Group conclusions / Advice for Expert Committee
A.1 PD-1 / PD-L1 immune checkpoint inhibitors – locally advanced and metastatic non-small cell lung cancer – EML	The Working Group supports the inclusion of pembrolizumab on the EML for first-line treatment of metastatic NSCLC in selected patients with PD-L1 expression ≥ 50% based on evidence of a relevant and meaningful survival benefit. Considering the other PD-1/PD-L1 monoclonal antibodies, atezolizumab has also shown evidence of benefit in this setting (first-line, PD-L1 expression ≥ 50%), but the data are not as robust as they are for pembrolizumab. Recent meta-analyses suggest, however, similar performance of the different PD-1 /PD-L1 antibodies, so other monoclonal antibodies within the same class could be considered as possible alternatives for selection at country level to provide opportunities for better procurement and tendering. The Working Group does not support listing for PD-1/PD-L1 immune checkpoint inhibitors for use in stage 3 locally-advanced disease, second-line in the metastatic setting, or as maintenance therapy at this time. Regarding cost-effectiveness, the Working Group noted that cost-effectiveness is not proven using the list-price available in countries, but rather at discounted prices negotiated with health system payers. The budget impact of supplying these treatments will be very high in many countries. Weight-based dosing of pembrolizumab (2 mg/kg) may be preferred over fixed dosing due to lower costs, without loss of benefit.
A.3 Azacitidine – acute myeloid leukaemia – EML	The Working Group does not support the inclusion of azacitidine on the EML for the treatment of acute myeloid leukaemia. The Working Group noted that the observed magnitude of benefit for azacitidine in AML in terms of overall survival is modest, and below the threshold for benefit established for EML consideration. The Working Group recognized that AML is a disease with a poor prognosis, and an unmet clinical need exists, particularly for older patients (>60 years). However, use of azacitidine is not a curative treatment option and provides only a small benefit.
A.4 BRAF/MEK inhibitors – metastatic melanoma – EML	The Working Group does not support the inclusion on the EML of BRAF-MEK inhibitors for the treatment of metastatic melanoma. The Working Group acknowledged the relevant benefit associated with BRAF-MEK inhibitors in the second-line treatment setting for metastatic melanoma, and that the primary place in therapy for BRAF-MEK inhibitors for melanoma is in the second-line setting (after failure of immunotherapy), or as first-line in patients for whom immunotherapy is not suitable, or in patients for whom a rapid response is required. However, noting a preference to prioritize inclusion of first-line therapies on the Model List, and the established role of immunotherapy in the first-line setting for melanoma, the Working Group did not support listing of BRAF-MEK inhibitors as this would apply for only the small sub-group of patients for whom first-line immunotherapy is not recommended or rapid response induction would be required and approval might result in inappropriate use outside of this population, with the associated toxicity risks and high cost. The Working Group also noted that the burden of disease of melanoma is highest in high-income countries and regions, with a low burden in many low- and middle-income countries.

A.8 CDK4/6 inhibitors – HR+/HER2- breast cancer – EML	The Working Group does not support the inclusion of CDK4/6 inhibitors as a therapeutic class or as individual medicines on the EML at this time. 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. A review of the data after longer follow-up could be considered for a future EML update. Based on clinical benefit, only ribociclib meets the EML criteria for first-line survival benefit and ESMO-MCBS score. However, there are concerns about bias in the MONALEESA-7 trial, including high censoring rates, that reduces confidence in the estimates of benefit. In addition, the eligible patient population for these medicines is likely to be very large, current costs are very high with cost-effectiveness analyses finding these treatments not to be cost-effective in most settings at current prices. Treatment duration is long-term and therefore the budget impact to health systems would be significant and unaffordable in many settings.
A.9 Daratumumab – multiple myeloma – EML	The Working Group does not support the inclusion of daratumumab on the EML for treatment of multiple myeloma at this time. The Working Group considered that use of daratumumab would be of greatest value for treatment of patients with newly diagnosed MM (NDMM) who are ineligible for ASCT. However, the Working Group noted that mature, long-term overall survival data for daratumumab are not yet available in any of the three treatment settings proposed (NDMM transplant eligible, NDMM transplant ineligible and relapsed/refractory MM). The Working Group also noted the increased toxicity, and significant high costs associated with daratumumab treatment and toxicity management.
A.11 Enzalutamide - metastatic castration-resistant prostate cancer – EML	The Working Group noted that enzalutamide meets the criteria for survival benefit and ESMO-MCBS score for consideration for EML inclusion and appears to demonstrate comparable efficacy and safety to abiraterone, which is currently included on the EML, however, no direct head-to-head trial data are available. Consideration was given to what the added benefit of including enzalutamide on the EML might be, in the absence of any clinical advantage over abiraterone. There is currently no evidence that having both agents available would results in improved access or cost benefits in terms of market competition. However, having options available may provide opportunities for countries to negotiate better prices as part of their national procurement processes. The Working Group therefore concluded that financial considerations precluded support for inclusion of enzalutamide on the EML. The Working Group also noted the evidence around the use of low-dose abiraterone and considered that this was an area where WHO could advocate for this cost-saving treatment approach.
A.13 Everolimus – subependymal giant cell astrocytoma – EMLc	The Working Group supports the inclusion of everolimus on the EMLc for the treatment of SEGA in children. If recommended by the Expert Committee, it should be very clearly communicated that the recommendation is for this indication alone, and not for other indications where the evidence for everolimus has not been reviewed. The Working Group noted that SEGA is a very rare disease with a genetic component. There is evidence of benefit for everolimus in the treatment of children with SEGA. However, the Working Group held some concerns about the feasibility of use of everolimus in some settings, noting the requirements for specialist diagnosis and monitoring.

A.15 Fulvestrant – metastatic breast cancer – EML	The Working Group does not support the inclusion of fulvestrant on the EML for the treatment of metastatic breast cancer. The Working Group noted that available data for use of fulvestrant in the first-line setting are less consolidated, while use in the second-line setting is more established and data are more consistently reported in the literature. The meta-analysis presented in the application did not differentiate between first- and second-line use. From the meta-analysis presented, the OS benefit for fulvestrant (+ aromatase inhibitor) was modest, but within the threshold of survival gain endorsed by the Expert Committee. However, there was substantial heterogeneity between the included trials, post-progression therapies were unclear, and the benefit not unequivocally accepted. The Working Group also noted the high cost of the medicine, that the eligible patient population is likely to be large, and variable findings in cost-effectiveness analyses.
A.19 Ibrutinib – chronic lymphocytic leukaemia with 17p deletion – EML	The Working Group supports the inclusion of ibrutinib on the EML as first-line treatment for the high-risk sub-group of patients with 17p deleted CLL, recognizing that this population has a significantly poorer prognosis, and an unmet need for effective treatment exists. A broader role for ibrutinib in all patients with CLL, and in the second-line setting is not supported at this time. However, the Working Group noted the significant cardiovascular toxicity associated with ibrutinib, in particular atrial fibrillation and major bleeding, management of which requires specialized care and resources that may not be widely available in some settings. The Working Group also considered the issue of availability of molecular testing to identify patients with 17p deletion most likely to benefit from treatment may be a further limitation, particularly in some resource-limited settings. The Working Group also recognized the high cost of the medicine, the potentially long duration of treatment, and that ibrutinib has not been found to be cost-effective at current prices in multiple analyses. It is hoped that with the emerging availability of generics in some settings, the price will reduce, and treatment will be more affordable.
A.23 Osimertinib – EGFR+ non-small cell lung cancer – EML	The Working Group does not support the inclusion of osimertinib on the EML at this time. The Working Group noted that first-generation TKIs currently listed on the EML for EGFR-mutated NSCLC are available as generics and are more likely to be affordable, accessible treatment options for patients and health systems. The Working Group noted that osimertinib has demonstrated meaningful OS benefit in comparison to first generation TKIs and meets the criteria for ESMO-MCBS score. However, the current cost of osimertinib is prohibitively high for both patients and health systems, and it has not been found to be cost-effective in some analyses. The Working Group also noted the requirement for companion diagnostic testing, which has variable and limited availability in low- and middle-income settings.

A.25 Pertuzumab – HER2+ metastatic breast cancer – EML	The Working Group acknowledged that the updated data from CLEOPATRA and additional evidence presented from PERUSE and PUFFIN trials, demonstrated relevant benefit in overall survival of pertuzumab (in combination with trastuzumab) in the metastatic breast cancer setting. The Working Group considered that the inclusion of pertuzumab on the EML for treatment of metastatic HER2+ breast cancer, in combination with trastuzumab and a taxane, could be supported from a clinical perspective. However, the Working Group acknowledged that combination therapy with trastuzumab and pertuzumab, both highly-priced medicines, would present significant financial challenges to patients and health systems and access in many settings would be limited. The Working Group also noted that affordability and access to trastuzumab (already listed on the EML model list since 2015) remains very limited in many resource-constrained settings, and the addition of another highly-priced biological medicine would likely compound this problem. In addition, the Working Group noted the diagnostic molecular tests for determining HER2 status (immunohistochemistry and in-situ hybridisation) require highly specialized laboratories and skilled technicians which may not be widely available and affordable in many low- and middle-income settings, and this represents a significant barrier to appropriate use of anti-HER2 therapies that should be addressed. Increasing the availability of biosimilars will also be critical to improve affordability and access. The Working Group therefore concluded that despite pertuzumab demonstrating meaningful clinical benefit in metastatic HER2+ breast cancer, the issues of cost and limited access to trastuzumab and companion diagnostics in many settings precluded support for its inclusion on the EML at this time. In addition, the Working Group highlighted that future consideration should be given to the optimal duration of pertuzumab treatment of patients with metastatic breast cancer. Clinical data to inform this question are currently lacking and should be supported as a research priority by research funding agencies.
A.27 Rasburicase – tumour lysis syndrome – EML and EMLc	The Working Group supports the inclusion of rasburicase on the EML and EMLc for the treatment and prevention of tumour lysis syndrome. The available evidence shows rasburicase to be more efficacious than allopurinol for reducing plasma uric acid levels, and it can be used for treatment as well as prevention of TLS (allopurinol only for prevention). Evidence for benefit in terms of clinical outcomes is less clear (eg, mortality, renal failure), but in this context the benefit of use of rasburicase is undisputed for reducing uric acid (e.g. a surrogate outcome considered reasonably likely, based on therapeutic and pathophysiologic evidence) to predict clinical benefit and avoiding clinical sequalae. Treating TLS once it occurs is very resource intensive so effective preventative measures are desirable. In terms of safety, of particular concern is risk of severe haemolysis, and rasburicase should not be given to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency - testing to identify patients with G6PD needs to be a consideration. In emergency settings, where G6PD deficiency cannot be determined, rasburicase should be used only when haemodialysis is available. Careful patient selection to limit use of rasburicase in patients most likely to benefit (e.g. at high-risk), and less likely to experience adverse effects (e.g. G6PD deficiency) will also be important at country level. The Working group acknowledged the high cost rasburicase, and also noted the potential for cost-savings of using single-dose administration over daily dose administration without significantly compromising benefit.
A.34 Tislelizumab – Hodgkin lymphoma – EML	The Working Group does not support the inclusion of tislelizumab on the EML for treatment of relapsed/refractory Hodgkin lymphoma at this time, noting that the available data for efficacy and safety are very limited (early phase trials, with small patient numbers and with short follow-up), high cost and unknown cost-effectiveness.

A.35 Tislelizumab – urothelial carcinoma – EML	The Working Group does not support the inclusion of tislelizumab on the EML for treatment of urothelial carcinoma at this time, noting that the available data for efficacy and safety are very limited (early phase trials, with small patient numbers and with short follow-up), high cost and unknown cost-effectiveness.
A.39 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, noting that the available data are very limited (early phase trials, with small patient numbers and with short follow-up), significant toxicity concerns, high cost and unknown cost-effectiveness.
A.40 Zanubrutinib – mantle cell lymphoma – EML	The Working Group does not support the inclusion of zanubrutinib on the EML for treatment of relapsed/refractory MCL at this time, noting that the available data are very limited (early phase trials, with small patient numbers and with short follow-up), significant toxicity concerns, high cost and unknown cost-effectiveness.
I.8 Cancer medicines for children – new indications – EMLc	The Working Group supports the expansion the listings on the EMLc for the proposed cancer medicines for the proposed new indications. 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.
I.9 Cancer medicines for children – low-grade glioma – EMLc	The Working Group supports the expansion the listings on the EMLc for carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine to include the indication of low-grade glioma. The Working Group recognized that the evidence presented is not from randomized controlled trials, but that the treatment protocols are associated with relevant benefits and are recognized as the standard of care for treatment of paediatric LGG and this supports their inclusion on the EMLc. Noting that the EMLc lists medicines for the treatment of children up to 12 years of age, and that LGG also affects older children and adolescents, the Working Group also supports inclusion of these medicines on the EML for this indication. Expanding the EMLc indications for these medicines would also support the goals of WHO's Global Initiative for Childhood Cancer 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.
I.10 Cancer medicines for head and neck cancer - EML	Concomitant chemotherapy-radiotherapy using cisplatin or carboplatin is standard of care for the treatment of head and neck cancers. Both agents are effective radiosensitizers, cisplatin is more active, but also more toxic than carboplatin. The available evidence suggests that there are no significant differences between agents in terms of survival. The Working Group therefore supports the inclusion of carboplatin on the Model List as an alternative treatment option to cisplatin for concomitant chemo-radiation therapy of head and neck cancers in patients unable to tolerate cisplatin.

I.11 Doxorubicin – rhabdomyosarcoma – EML and EMLc	The Working Group noted that the addition of doxorubicin to standard chemotherapy for non-metastatic rhabdomyosarcoma was not associated with increased survival benefit and was associated with increased harms. For this reason, it was not proposed for inclusion on the Model Lists by the applicants. However, the Working Group also considered that single-agent doxorubicin is nevertheless considered to be an effective treatment option for non-metastatic rhabdomyosarcoma and may have a place in cases where standard chemotherapy regimens are not available. As such, it was considered a valuable treatment alternative. Therefore, the Working Group supports the inclusion of doxorubicin on the Model Lists, for use as a single agent in the treatment of rhabdomyosarcoma when standard chemotherapy triplet regimens (IVA, VAC) are not available/affordable.
I.15 Tyrosine kinase inhibitors – Ph+ acute lymphoblastic leukaemia – EML	The Working Group supports the inclusion of imatinib on the EML and EMLc for the treatment of adults and children with Ph+ acute lymphoblastic leukaemia based on evidence of relevant improvement in survival, significantly reduced risk of death and acceptable safety. Imatinib is now off-patent, and generic brands are widely available at lower prices. Despite also being associated relevant survival benefit, the available data for other TKIs (dasatinib, ponatinib) are less mature. There is little evidence supporting their use in children and their global availability (including generics) is more limited. Therefore, the Working Group does not support the inclusion of TKIs as a therapeutic class at this time.
I.16 Vinorelbine – rhabdomyosarcoma – EMLc	The Working Group supports the addition of oral and intravenous vinorelbine to the EMLc for the maintenance treatment of rhabdomyosarcoma. Vinorelbine, used in combination with oral cyclophosphamide, demonstrates relevant survival benefits in children with RMS, with a manageable toxicity profile. The Working Group noted that use of vinorelbine in RMS is now established in current European and American treatment protocols and is considered the standard of care. Noting that RMS also affects older children and adolescents, the Working Group also supports inclusion of vinorelbine on the EML for this indication.
R.1 CAR-T cell therapy for relapsed/refractory diffuse large B-cell lymphoma (REVIEW)	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. It was noted that the currently available data are promising but have significant limitations at this time: small trial sizes (only three trials with more than 100 patients), with heterogenous inclusion criteria (lines of prior therapy, histology), immature outcome data, and modest certainty of evidence. Limited toxicity data are available, and toxicities other than cytokine release syndrome and neurotoxicity are not as well reported. It was recognized by the Working Group that the delivery of CAR-T cell therapies requires a comprehensive health system approach, which extends well beyond any potential future inclusion on the Essential Medicines List, noting that these therapies are not medicines per se. A health system approach is similarly required for other complex treatment interventions such as bone marrow transplantation. The Working Group considered that there is a strong need and opportunity for WHO to have a leadership and advocacy role to facilitate affordable and equitable access to these important treatment interventions.