APPLICATIONS FOR CANCER MEDICINES TO THE 24TH EXPERT COMMITTEE ON SELECTION AND USE OF ESSENTIAL MEDICINES - REVIEW OF CANCER MEDICINES

Table of Content

I. OVERVIEW AND RECOMMENDATIONS[1]

A. Context

Cancer is a major public health threat, reflected in the extent of the disease burden (more than 1 in 6 global deaths[2]) and the profound inequities in access to care between and within countries (less than 15% of low-income countries generally have access to comprehensive cancer treatment compared to more than 90% of high-income countries[3]), greatly affecting the social and economic well-being of populations. Inequalities are worsening as well-resourced settings benefit from the rapid pace of innovation (47% of all pharmaceutical clinical trials are for cancer medicines)[4], leaving large populations without access behind.

The WHO technical team in cancer has been increasingly supporting Member States strengthen their national cancer programmes by defining cancer control priorities, as part of universal health coverage[5]; additionally, the WHO technical team has systematically evaluated the cancer medicine market across the value chain as part of the Global Platform for Access to Childhood Cancer Medicines (detailed below). These activities by the WHO cancer team have re-inforced challenges to access cancer medicines and services including how WHO EML[6] is used to inform national planning[7]:

- *Lack of financing of cancer medicines*: a review of the inclusion of cancer services and products in minimum benefit packages by WHO has demonstrated a general lack of coverage for cancer services. For example, only 25% LIC Member States and 59% lower-middle-income MS included basic outpatient chemotherapy, and coverage rates were even lower for some

[1] The technical team (cancer) in the Department of Noncommunicable Diseases (NCD/MND) would like to thank the Expert Committee for the efforts. The technical team has reviewed the application for the 2023 Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc). The review was made taking into careful consideration detailed analyses of the applications submitted to the Secretariat and the dialogue between EML Cancer Working Group (EML CWG) and the Secretariat, who has convened this Working Group.

[2] WHO. Global Report on cancer (2020): setting priorities, investing wisely and providing cancer care for all. Online. https://apps.who.int/iris/handle/10665/330745

[3] Assessing national capacity for the prevention and control of noncommunicable diseases: report of the 2019 global survey. Geneva: World Health Organization; 2020.

[4] WHO. Technical report: pricing of cancer medicines and its impacts: a comprehensive technical report for the World Health Assembly Resolution 70.12: operative paragraph 2.9 on pricing approaches and their impacts on availability and affordability of medicines for the prevention and treatment of cancer. Online. https://apps.who.int/iris/handle/10665/277190

[5] As mandated in World Health Assembly Resolution 70.12 (2017)

[6] Jenei K, Aziz Z, Booth C, et al. Cancer medicines on the WHO Model List of Essential Medicines: processes, challenges, and a way forward. Lancet Glob Health. 2022 Dec;10(12):e1860-e1866. https://pubmed.ncbi.nlm.nih.gov/36183737/

[7] The comments provided in this section relate to how WHO EML as outlined in EB109/8 (2001): (1) impact on national guidelines for clinical health care practice; (2) guide the procurement and supply of medicines in the public sector; (3) procurement by UN organizations, nongovernmental organizations and international non-profit supply agencies

targeted therapies[8]. The consequences are financial hardship due to high out-of-pocket expenditure for cancer care, reaching 50-90% in a large number of LMICs[9].

- *Limited diagnostic capacity*: unavailable or inaccessible cancer diagnostic services further compromises the appropriate selection, prescribing and use of cancer medicines, particularly those that require advanced in-vitro diagnostics. In one survey of providers from 16 countries, at least one in four patients were affected by varying availability of diagnostic items and that families paid out-of-pocket for essential diagnostic item[10].
- *Limited infrastructure capacity*: In addition to capacity for diagnostics, appropriate national selection and administration of essential medicines is also limited by available infrastructure for management of toxicities, safe administration and surveillance during and after treatment.
- *Lack of research in low- and middle-income countries*: the evidence to inform the inclusion of candidate cancer medicines is generally informed by high-quality clinical trials, supplemented by real-world data generated in high-income countries. An ongoing review of clinical trials registered in International Clinical Trials Registry Platform (ICTRP) is showing that an estimated 90% of clinical trials for cancer medicines include HIC only[11].
- *Limited availability of treatment standards and coherence with national EML*: studies have shown relatively poor concordance between treatment guidelines and nEML, particularly related to targeted therapy. In a review of guidelines and nEML from 17 countries, 8 countries had trastuzumab in national guidelines but not in the national EML[12]. Even in the presence of nEML inclusion of essential anti-neoplastics as defined by WHO EML, access is severely constrained by availability and affordability as well as concerns about quality[13]. Cancer products are the most commonly reported noncommunicable diseases medicines to be reported as substandard or falsified[2].

[8] WHO HTA benefit package survey summary 2020/2021. (https://app.powerbi.com/view?r=eyJrIjoiYzMyZDY4NDEtY2VmOC00YjNhLTgzZWUtMDU0MTlhODNlZmMyIiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9&pageName=ReportSection6010075c0d83085bc926)

[9] Jan S, Laba TL, Essue BM, et al. Action to address the household economic burden of non-communicable diseases. Lancet. 2018 May 19;391(10134):2047-2058. doi: 10.1016/S0140-6736(18)30323-4. Epub 2018 Apr 5. PMID: 29627161.

[10] Lam C, et al. Defining availability of 100 essential diagnostic items for children with cancer and gaps in implementing WHO recommendations: Global CEDx Working Group survey. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(22)00428-4/fulltext

[11] (Provisional results) International Clinical Trials Registry Platform. https://www.who.int/clinical-trials-registry-platform

[12] Trapani D, Douillard JY, Winer EP, et al. The Global Landscape of Treatment Standards for Breast Cancer. J Natl Cancer Inst. 2021 Sep 4;113(9):1143-1155. doi: 10.1093/jnci/djab011. PMID: 33502535. https://academic.oup.com/jnci/article/113/9/1143/6120790?login=false

[13] Cherny NI, Sullivan R, Torode J, Saar M, Eniu A. ESMO International Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in countries outside of Europe. Ann Oncol. 2017 Nov 1;28(11):2633-2647. doi: 10.1093/annonc/mdx521. PMID: 28950323; PMCID: PMC5834140. https://www.annalsofoncology.org/article/S0923-7534(19)34620-4/fulltext

These factors threaten the function of nEML to inform national guidelines for clinical practice and fails to guide the procurement and supply of medicines in the public sector[14,15], further re-inforced by evidence that essential cancer medicines are not being prioritized in nEML or used for selection in minimum benefit packages.

A recent survey of perspectives on what is an essential medicine from oncology providers in 82 countries, working in health systems of all levels of complexity, noted that most health systems are failing to ensure access to essential products, suggesting a greater focus on established medicines contained in WHO EML should be prioritized[16].

Taken together, it is increasingly recognised that essential cancer medicines are generally not accessible to large percentages of populations, particularly those living in countries with weak health systems or who are from vulnerable communities.

B. Recent WHO activities in access to cancer medicines

The technical team has launched three global cancer initiatives in breast[17], cervical[18] and childhood[19] cancers for which access to treatment, including essential medicines, is a core focus. In that regard, the technical team would like to share emerging opportunities and resources that can further support the selection of and access to cancer medicines:

1. Global Platform for Access to Childhood Cancer Medicines: WHO and St Jude Children's Research Hospital announced the Platform in Dec 2021 with the commitment to provide access to essential medicines to all children with cancer in 50 countries by 2027[20], enabled by St Jude's $US 200 million commitment to purchase the medicines and enable the success of the Platform. The initial set of six countries are expected to receive 35 essential medicines (among 53 formulations) by Q4 2023.

[14] Martei YM, Chiyapo S, Grover S, Ramogola-Masire D, Dryden-Peterson S, Shulman LN, Tapela N. Availability of WHO Essential Medicines for Cancer Treatment in Botswana. J Glob Oncol. 2018 Sep;4:1-8. doi: 10.1200/JGO.17.00063. PMID: 30241225; PMCID: PMC6223417. https://pubmed.ncbi.nlm.nih.gov/30241225/

[15] WHO medicines strategy Revised procedure for updating WHO's Model List of Essential Drugs, Report by the Secretariat. https://apps.who.int/gb/archive/pdf_files/EB109/eeb1098.pdf . https://apps.who.int/gb/archive/pdf_files/EB109/eeb1098.pdf

[16] Fundytus A, Sengar M, Lombe D, et al. Access to cancer medicines deemed essential by oncologists in 82 countries: an international, cross-sectional survey. Lancet Oncol. 2021 Oct;22(10):1367-1377. doi: 10.1016/S1470-2045(21)00463-0. https://www.sciencedirect.com/science/article/pii/S1470204521004630

[17] WHO Global Breast Cancer Initiative. https://www.who.int/initiatives/global-breast-cancer-initiative

[18] Cervical Cancer Elimination Initiative. https://www.who.int/initiatives/cervical-cancer-elimination-initiative

[19] Global Initiative for Childhood Cancer. https://www.who.int/initiatives/the-global-initiative-for-childhood-cancer

[20] Global Platform for Access to Childhood Cancer Medicines. https://www.who.int/news/item/13-12-2021-who-and-st.-jude-to-dramatically-increase-global-access-to-childhood-cancer-medicines

This Platform will provide end-to-end support – consolidating global demand to shape the market; assisting countries with the selection of medicines; developing treatment standards; and building information systems to track that effective care is being provided and to drive innovation. As part of this Platform, WHO and St Jude are also evaluating the pipeline of childhood cancer product by reviewing all ongoing clinical trials and will also initiate the Paediatric drug optimization standard procedure (PADO) process[21].

It is relevant to note that only products on WHO EML will be purchased and supplied, and UN procurement support is expected to be used. Offered products are routinely evaluated for facilitated regulatory approval processes, and an initial set of products (provisionally, five or six) will be included in WHO Prequalification Programme.

WHO technical team has further intensified its attention to promote the inclusion of cancer products in WHO EML that are feasible for delivery in countries with weaker health systems and facilities in those countries supported by the Platform.

2. Technical briefs for cancer management: to complement the Platform, WHO cancer team is developing briefs to provide programme managers with guidance on diagnostics and treatment standards. A set of six briefs are being developed for childhood cancer with the plan to expand to additional cancers in the near future. These WHO Technical briefs are systematically gathering, evaluating and summarizing international and national treatment guidelines using GRADE criteria and will provide direct guidance on treatment standards, including recommended medicines, to Member States using a resource-stratified approach, leveraging existing guidelines as requested by Member States in WHA 70.12.

The WHO technical team in cancer will ensure full alignment with WHO EML to provide programme managers with guidance on the accompanying health system requirements (e.g., diagnostic test, staging studies, services to manage toxicities).

3. Collaboration with Medicine Patent Pool (MPP)[22] and ATOM Coalition: WHO is pleased to work with MPP on identifying candidate products for voluntary license and notes with great interest the inclusion of cancer products in Medicines Patent Pool Strategy 2023-2025[23] and the recent announcement of voluntary license for nilotinib[24], done in collaboration with the Access to Oncology

[21] Paediatric drug optimization standard procedure. https://www.who.int/publications/i/item/9789240039520
[22] Medicine Patent Pool (homepage). https://medicinespatentpool.org/
[23] Medicine Patent Pool Strategy 2023-2025. https://medicinespatentpool.org/news-publications-post/launch-of-the-medicines-patent-pool-strategy-2023-2025
[24] Nilotinib. https://medicinespatentpool.org/licence-post/nilotinib

Medicines (ATOM) Coalition[25] of the Union for International Cancer Control. The technical team is pleased to note and engage with, as appropriate, the important advancements by MPP and ATOM.

C. Strategic considerations

Given these emerging opportunities, the WHO technical team would like to highlight considerations for the Expert Committee to inform the methodology used for EML selection and implementation to improve how end users can benefit:

1. Designate products that require higher degrees of specialized care including greater budget impact: cancer products generally meet the criteria for "specialized health care facilities may be needed or which meet all the selection criteria and which are cost-effective within their therapeutic group, but which are not necessarily affordable for all health systems," as detailed in EB109/8 (2001)[26]. In light of this finding, and as further outlined in the review of the products below, designation of these factors can be strongly considered for select cancer medicines to enable their inclusion while noting that such products may not be feasible in countries with weaker health systems or lacking sufficient specialized health care facilities.

It may be worthwhile to note that cost-effectiveness analyses reported in the application process can suffer from incomplete or biased data, lack of standardization in the methods used, and differences in the cost-effectiveness thresholds used across settings. A standardized approach to evaluating what products meet the criteria of requiring specialized facilities and/or affordability can be developed.

2. Present detailed evaluation of efficacy, safety, feasibility, and cost-effectiveness of cancer medicines. To further support guidance in the selection of product in and stakeholder use of WHO EML, additional dimensions can be reported that include efficacy, safety, feasibility, and cost-effectiveness. Providing objective rating across different criteria can enable greater customization in how WHO EML is applied to national context.

This is particularly relevant in cancer, for which such factors should inform decision-making by programme managers and health care professionals. Include designating what products are generally given in combination (i.e., as part of regimen) to ensure essential medicines are appropriately given in combination and chemoprotectants are available. As an example, a products with higher toxicity

[25] ATOM Coalition. https://www.uicc.org/what-we-do/driving-global-impact/new-initiatives/access-oncology-medicines-atom-coalition

[26] Annex 1, paragraph 10 of WHO medicines strategy Revised procedure for updating WHO's Model List of Essential Drugs, Report by the Secretariat. https://apps.who.int/gb/archive/pdf_files/EB109/eeb1098.pdf

rates contribute directly to the large percentage of treatment-related deaths: in childhood cancer, it is estimated to contribute to 5-10% of cancer-related deaths[27].

The WHO technical team (cancer) offers its great appreciation to the EML Expert Committee for their efforts and the opportunity to draw attention to the urgency of these considerations in light of the great inequities in cancer care and the rapid pace of innovative product development in cancer treatment (as reflected in the total number of applications to WHO EML).

[27] Lam CG, Howard SC, Bouffet E, Pritchard-Jones K. Science and health for all children with cancer. Science. 2019 Mar 15;363(6432):1182-1186. doi: 10.1126/science.aaw4892. PMID: 30872518. https://www.science.org/doi/10.1126/science.aaw4892

III. REVIEW OF CURRENT APPLICATIONS: GENERAL OVERVIEW

There were fourteen applications for cancer medicines and/or cancer prevention (sunscreen) to 2023 WHO Model List of Essential Medicines (EML) published on the Expert committee's meeting webpage on the WHO website.

Each application was reviewed by the technical team, with appreciation to the WHO EML Cancer Working Group, with consideration to clinical setting indication (metastatic and/or adjuvant); clinical trial design; efficacy and magnitude of benefit including quality of life and safety; guidelines and regulatory agency review; and cost-effectiveness, cost and feasibility.

Detailed reviews of individual applications are listed below.

IV. REVIEW OF CURRENT APPLICATIONS: ADULT CANCER

1. ANTI-PD1, ANTI-PD-L1 IMMUNE CHECKPOINT INHIBITORS FOR NSCLC

Pembrolizumab, Atezolizumab, Cemiplimab, and Durvalumab are immune checkpoint inhibitors (ICI) that have been submitted for EML evaluation as monotherapy or combined therapy in non-small cell lung cancer (NSCLC), in different settings:

Metastatic NSCLC:

- Pembrolizumab, Atezolizumab, Cemiplimab

Locally Advanced unresectable NSCLC

- Durvalumab

a) *Efficacy*: For these indications, anti-PD1 ICI have evidence of high efficacy and magnitude of benefit (16 months overall survival (OS) benefit, ESMO-MCBS high score (5) and are considered standard of care (recommended ESMO and NCCN Guidelines). Generally, a more favourable toxicity profile compared to existing chemotherapy on WHO EML. However, high frequency and complexity of immune-related toxicities also require trained professionals, and resources to identify and manage them.
b) *Feasibility*: Requires high-skilled molecular diagnostics and services able to exclude driver mutations (nearly 50% of NSCLC host driver mutations and patients with these mutations have better outcomes when treated with targeted therapies). Undiscriminated use of these medicines without adequate diagnostic capacity or expertise may result in harm to cancer patient, loss of benefit for populations and inefficiency in expenditure.

Considerations for ICI for the other settings: durvalumab for locally advanced unresectable NSCLC (low cross-over (<25%) and lack of mature data).

General considerations: It is important to note that the majority of evidence in ICIs in NSCLC is from high-income countries. Effective delivery of immunotherapy requires capacity to provide accurate diagnosis (excluding genomic driver mutations) and the appropriate management of toxicities.

WHO NCD department recommendation: it is now well established that there is evidence of meaningful clinical benefit for ICIs in NSCLC, in line with the summary of evidence discussed with the EML CWG. Data on Durvalumab are less mature and require further consideration as such data become available.

There remains significant uncertainty regarding the feasibility of including ICIs in WHO EML and, by extension, national EML, particularly for LMIC, where access to these medicines are generally

inaccessible and are difficult to effectively introduce because of diagnostic test availability, capacity to manage toxicities and overall budget impact. Access to diagnostics in an appropriate timeframe is key to assess PD-L1 expression and to exclude driver mutations. In addition, management of toxicity may require resource intensive and highly specialized services.

Based on these factors and current evidence, the technical team highlights its uncertainty about including of ICIs on this occasion. Further data from LMIC that could test and validate the effectiveness and feasibility of widespread use of ICI would help all stakeholders understand the implications of including this class of medicines in WHO EML. These data can include evaluating ability to safely delivery these medicines and to provide concomitant diagnostic services and management of toxicities.

From a perspective of efficacy only, it is understandable that ICI would be included in WHO EML – this was reinforced in its evaluation as a priority in a convenience sample of oncologists[28]. It is the broader context of health system readiness and feasibility that complicates the decision. Very clear guidance from the Expert Committee to acknowledge health system factors (as summarized in Section 1, above) and diagnostic requirements (i.e., PD-L1 testing) could enable ICI inclusion if and when appropriate.

2. CDK 4/6 INHIBITORS – HR+/HER2- ADVANCED/METASTATIC BREAST CANCER

Palbociclib, ribociclib, abemaciclib are CDK 4/6 inhibitors that have been submitted for EML evaluation as monotherapy or combined therapy in patients with hormone positive, HER-2 negative, metastatic breast cancer.

a) *Efficacy:* variable degrees of efficacy depending on the clinical setting including indication and line of therapy (ESMO MCBS score ranging from 3-5), with evidence that does suggest possible overall survival gain in select studies and with improvements in progression-free survival (PFS) in major trials. In addition to PFS and OS gains, secondary benefits have been reported in trials, such as delayed time to use of chemotherapy (by about a year) and delayed deterioration of quality of life. Toxicities are common (eg, grade 3 or 4 adverse events occur in approximately 55-80%), particularly neutropenia, though they are otherwise well tolerated.
b) *Feasibility*: oral drugs; except for fulvestrant combination. HR and HER2 testing required.

CDK4/6 inhibitors have high rates of toxicity (particularly neutropenia).

Although from an efficacy point of view CDK4/6 inhibitors are useful, the overall survival benefit is limited, in the context that many patients can still have a 4+ year median OS without such treatments

[28] Fundytus A, Sengar M, Lombe D, et al. Access to cancer medicines deemed essential by oncologists in 82 countries: an international, cross-sectional survey. Lancet Oncol. 2021 Oct;22(10):1367-1377. doi: 10.1016/S1470-2045(21)00463-0.

(i.e. products such as AI, tamoxifen and cytotoxic agents can be used for a similar indication with similar efficacy). Though, it can be noted that in select high-income settings, this class of medicines is emerging as 1st-line treatment for ER+ metastatic breast cancer (MBC).

Based on previous recommendation by the Expert Committee, Medicine Patent Pool has evaluated the candidacy of CDK4/6 inhibitors and produced an excellent report[29]. They noted that current access programmes are limited to few LMICs with caps on the number of cycles supported, and that patents on all three CDK 4/6 inhibitors have been filed in several LMICs with the primary patent on Palbociclib expiring in 2023 with secondary patents expiring in 2034. In the short term, the cost of CDK4/6 remains high.

*Summar*y: CDK4/6 inhibitors are effective medications that maintain quality of life, can improve OS, delay time to chemotherapy, and are reasonably well tolerated.

WHO NCD Department recommendation: there are data to support the efficacy of CDK 4/6 inhibitors in overall survival gain and acceptability, the inclusion of this relevant therapeutic class in the WHO EML is uncertain in light of the benefit against the harms.

There are data to support OS gains from CDK4/6 inhibitors, though the magnitude may be relatively minor and less certain because of limited long-term or real-world data. Further limitations to consider include high rates of toxicity (particularly neutropenia) and importance to focus on established first-line therapy (eg, hormone therapies) that is more feasible in systems with weaker health systems.

Continued dialogue with Medicine Patent Pool can create a more favourable balance of benefits and harms as further data emerge on long-term value of these products and evidence from LMICs regarding feasibility.

3. TORIPALIMAB (ANTI-PD1 ICI) FOR OESOPHAGEAL AND NASOPHARYNGEAL CANCER

Toripalimab has been submitted for EML evaluation as monotherapy in advanced Oesophageal and Nasopharyngeal cancer.

a) *Efficacy*: evidence from limited clinical trials has demonstrated Toripalimab provides clinical benefit when compared to chemotherapy in terms of OS and PFS gain and that it offers more favourable toxicity profile. The clinical value for Nasopharyngeal has been rated by MCBS at 3 (oesophageal cancer MCBS score not available).
b) *Feasibility*: access to diagnostics in a decent time is key to assess PD-L1 expression. Rates of adverse events are not significantly higher than chemotherapy but can require specialized care. Cost-effectiveness data are generally not available, though early studies are emerging.

[29] Medicine Patent Pool. Prioritisation Report. 2021. https://medicinespatentpool.org/uploads/2022/02/Prioritisation_Report_2021.pdf

WHO NCD Department recommendation: in line the findings of the EML CWG, there are insufficient mature data on the efficacy and safety of Toripalimab, though the technical team does note with interest the relevant early findings in oesophageal and nasopharyngeal cancers. Further consideration can be made as additional studies are reported and increased understanding of feasibility is achieved.

4. OSIMERTINIB FOR EGFR+ NON-SMALL CELL LUNG CANCER

Osimertinib is submitted for EML evaluation as an individual medicine in adult patients with metastatic non-small cell lung cancer (NSCLC) with EGFR sensitizing mutations.

a) *Efficacy*: Osimertinib, 3° generation EGFR tyrosine kinase inhibitor (TKI) offers clinical benefits when compared to the first-generation TKI gefitinib and erlotinib in terms of OS gain and more favourable toxicity profile in NSCLC patients with EGFR mutation (MCBS: 4).
b) *Feasibility*: treatment with Osimertinib require access to high-skilled molecular diagnostics and services able to assess the presence of EGFR driver mutations.

First-generation TKIs on the 21st WHO EML (i.e. Erlotinib, gefitinib, afatinib) may have a more favourable cost-effectiveness profile and lower budgetary impact with proven long-term clinical impact. Evidence from select economic analyses suggests that Osimertinib may not be generally cost effective in select settings and ; and if the cost remains so high this would probably reduce health equity.

Based on previous recommendation by the Expert Committee, Medicine Patent Pool has evaluated the candidacy of Osimertinib and produced an excellent report[28]. They noted that current access is limited, and that the primary patent will expire in 2032 with secondary patents expiring in 2035.

WHO NCD Department recommendation: In light of this, and in agreement with the EML CWG, there are insufficient evidence to justify the inclusion of Osimertinib in the EML at this time, though the technical team notes with significant interest the value of Osimertinib in the context of T790M mutation and its evaluation as a priority in a convenience sample of oncologists[27].

Future evaluation of Osimertinib should be considered in light of evolving data, the broader context of accessibility including ongoing dialogue with Medicine Patent Pool and prioritization against other TKIs.

5. ZANUBRUTINIB FOR CHRONIC LYMPHOCYTIC LEUKEMIA /SMALL LYMPHOCYTIC LYMPHOMA

Zanubrutinib is submitted for EML evaluation as an individual medicine in adult patients with treatment naïve (TN) or relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma. Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL).

a) *Efficacy*: Zanubrutinib has been proven to have better efficacy and safety profile in head to head multinational phase 3 clinical trials with lower cost compared with Ibrutinib (added into EML List in 2021 with the indication of R/R chronic lymphocytic leukaemia). In particular, data demonstrate a lower rate of treatment discontinuation and fewer cardiac disorder events, including fewer cardiac events leading to death, in patients treated with Zanubrutinib. Select professional society guidelines recommend zanubrutinib in CLL patients for the treatment of first-line and second-line patients, regardless of whether they have del (17p) or TP53 mutation.
b) *Feasibility*: alternative medicines currently included in WHO EML for the proposed indication(s) are Ibrutinib: R/R CLL; Rituximab: Diffuse large B-cell lymphoma (DLBCL), CLL, Follicular lymphoma (FL); and Bendamustine: CLL, FL.

In summary, Zanubrutinib treatment CLL/SLL is known to reduce mortality, improve QoL and seems to have a favourable safety profile, although more mature data are needed for confirmation. Ongoing evaluation of Zanubrutinib against other BTKis and immunochemotherapies in R/R CLL patients will provide further guidance on the appropriateness and scope of its possible inclusion.

WHO NCD department recommendation: In line with the findings of the EML WG, there is insufficient evidence, at this time, to justify the inclusion of Zanubrutinib for the treatment of CLL/SLL. While there are some data to support its clinical value, there is insufficient mature OS data available to fully justify its inclusion at this time, further reinforced by the need for additional data regarding its toxicity profile and feasibility of delivering in settings with weaker health systems and lack of specialized clinical services. Continued dialogue with Medicine Patent Pool[28] is also warranted.

6. CAR-T CELL THERAPIES FOR DIFFUSE LARGE B CELL LYMPHOMA

CAR-T cell therapies have been submitted for EML evaluation in relapsed/refractory Diffuse large B cell lymphoma (DLBCL).

a) *Efficacy*: CAR-T cell therapies demonstrated better PFS (HR 0.47 95% CI 0.37-0.60) compared to salvage chemo + autolugus stem-cell transplantation in three trials. OS results were immature at data cut-off in all three trials.
b) *Feasibility*: this treatment is technologically demanding requiring upfront large investments and is feasible in tertiary care centres only (highly specialized medical management) and countries with manufacturing and logistic capacity. Unique toxicities to CAR-T cell therapy

require higher levels of specialized care including cardiac complications, delayed cytopenias, acute and chronic Graft versus Host Disease, and tumoral lysis syndrome are recognized as specific potent complications following CAR T-cells infusion.

WHO NCD department recommendation: In line the findings of the EML CWG, there are insufficient mature data on the efficacy (measured by overall survival) and safety of CAR-T cell therapies. Further consideration can be made as additional studies are reported and increased understanding of feasibility is achieved. The WHO technical team concurs with the need to monitor the evidence regarding these therapies and to consider a broader context for access to these therapies with further guidance and inputs to be developed.

7. CLADRIBINE (PURINE ANTIMETABOLITE) FOR LANGERHANS CELL HISTIOCYTOSIS (LCH) AND GRANULOMATOUS TYPE CNS-LCH

Cladribine has been submitted for EML evaluation in relapsed and refractory multi-system LCH resistant to standard therapy and granulomatous type CNS-LCH.

a) *Efficacy*: Favour cladribine over historical standard in LCH strata where it was tested: survival in patients with refractory LCH and risk-organ involvement is 30%. Cladribine was shown to improve survival up to 85% in HICs
b) *Feasibility*: Expert pathologist required for LCH diagnosis. Radiological imaging (e.g. CT / MRI scans) is needed for staging. Drug administration requires hospitalitation. Inpatient wards with highly specialized personnel in clinical hematology patients are necessary.

Cladribine appears generally cost-effective: while costs are significant, while outcome appears better than historical control without substantial budget impact.

It is noted that toxicity is a concern. The principal acute toxicity is hematologic: profound pancytopenia; others: infections, septicemia, enteritis, myalgia, tubulopathy, neuropathic pain. Toxicity requires careful management, and Cladribine would be used only in tertiary care centres to be delivered in settings with stronger health systems.

WHO NCD department recommendation: there are early data to support its clinical value and inclusion, though there are insufficient data to evaluate the feasibility of its inclusion. Cladribine requires specialist diagnosis, administration, and monitoring. In particular, the toxicity profile must be considered. These factors directly inform the appropriateness of including Cladribine, particularly as further data emerge on the need for feasibility studies in countries with weaker health systems. (additional comments below in Section V.

V. REVIEW OF CURRENT APPLICATIONS: PAEDIATRIC ONCOLOGY

1. VARIOUS: NEW INDICATIONS FOR ANAPLASTIC LARGE CELL LYMPHOMA (ALCL) FOR VARIOUS CANCER MEDICINES FOR CHILDREN.

Clinical Setting indication: New indications for existing cytotoxic medicines in the previous EMLc 2021 list, for the treatment of Anaplastic Large Cell Lymphoma (ALCL): Cyclophosphamide, Cytarabine, dexamethasone, Doxorubicin, Etoposide, Ifosfamide, Methotrexate, Prednisone and Vinblastine.

Target Population: ALCL represents 15% of all Non-Hodgkin Lymphomas in Children and Adolescents, with an incidence of 10-15 per million under the age of 19 yrs.

a) **Efficacy:** for the current indication, different combination of these medicines has shown to produce high response, as part of multiagent standard protocols for treatment of ALCL, resulting in overall survival of 100% for early stage disease (stage I completed resected) and less that 80% for advance disease.[30]

COPADM: Methotrexate, Cyclophosphamide, Vincristine, Prednisone. 3-yrs Survival 83%
POG-APO arm: Doxorubicin, Vincristine, Prednisone, Methotrexate, 6- Mercaptopurine. 4yrs Survival 80%
EICN-ALCL99: Cyclophosphamide, Cytarabine, Dexamethasone, Doxorubicin, Etoposide, Ifosfamide, Leucovorin, Methotrexate, Hydrocortisone and vinblastine. 10yrs Over-all survival 90%

b) **Feasibility:** the majority of these drugs are already included in the previous Model EMLc and are accessible in low- and middle-income countries. Some combinations as those including high dose methotrexate might be difficult to consider in resource constrained settings where there is no capacity to measure level of the drug and excess toxicity might result due to the lack of appropriate supportive therapy to overcome treatment related toxicity.

WHO NCD Department recommendation*:* Considering that Paediatric Anaplastic Large Cell Lymphoma is a highly curable disease the technical unit supports the inclusion of new indications of previously included medicines in EMLc 2021 to treat this condition, contributing to improve access and quality of care for children and adolescents diagnosed with these conditions aligning with the GICC objectives.

[30] https://touchoncology.com/haematological-malignancies/journal-articles/pediatric-anaplastic-large-cell-lymphoma-a-review/#article

2. INDICATION INCLUSION OF ALK INHIBITOR CRIZOTINIB FOR THE TREATMENT OF RELAPSE OR REFRACTORY ALK-POSITIVE ALCL:

Clinical setting indication: This ALK-specific Tyrosine Kinase Inhibitor has been recently approved by FDA and EMA for the treatment of relapse Paediatric ALK-positive ALCL

a) **Efficacy:** Although there seems to be promising results with complete responses in the order of 83-90% for relapsed ALCL the available data is limited (clinical trials include small number of patient numbers, in high income countries and have short follow-up). There is little data on cost effectiveness of the drug.

b) **Feasibility:** highly skilled professionals and infra-structure capacity for molecular biology diagnosis and managing side effects (Neutropenia, Thrombosis) is required.

WHO NCD Department recommendation: While second and subsequent-line therapies may represent relevant clinical benefit, in the case of ALCL the technical unit considers relevant to prioritize continued access to first-line therapy by incorporating new indication of existing drugs in the EMLc 2021 for the treatment of ALCL in line with the principles of progressive realization for universal health coverage and general principles for the inclusion of essential cancer medicines the technical unit considers more data regarding clinical benefits particularly with the inclusion from data from LMIC would help the technical team to consider its inclusion in the future.

Considering that specific requirements for diagnostic to guide the prescription of Crizotinib may be limited in many resource constrained settings, the technical unit favour the inclusion of new indications for those already ELMc medicines which are effective in first-line standard treatment for ALCL and provide more clinical impact.

3. NEW INDICATION OF RITUXIMAB FOR THE TREATMENT OF MATURE B CELL NEOPLASMS (BURKITT LYMPHOMA AND MATURE B CELL LEUKAEMIA).

Clinical setting indication: According to the IARC Global Cancer Observatory the incidence of Burkitt Lymphoma in 2020 was 5 cases/million.[31] One in four children diagnosed with Burkitt Lymphoma present with advanced disease in HIC while in LMIC the percentage of advanced disease can be as high as 60% of newly diagnosed cases.

https://gco.iarc.fr/today/online-analysis-multi-bars?v=2020&mode=cancer&mode_population=co

a) **Efficacy**: For the current indications the target therapy with Rituximab (Anti-CD20) has demonstrated significant efficacy in reducing early death and improving survival when added to standard regimens for the treatment of mature B malignancy without adding increased toxicity[32].[33] [34]This represent an excellent opportunity particularly in Low- and middle-income settings (LMIC) were patients present with advanced disease and high rates of toxic death related to inadequate supportive care to treat severe comorbidities (malnutrition, infections) and treatment related complications.

b) **Feasibility:** Although this target therapy is included in the current EMLc 2021, unfortunately its high cost limits the possibility of delivering this medicine in such settings. Limited cancer diagnostic capacity represents also an important barrier for the inclusion of Rituximab in the modified or adapted treatment regimens used effectively in LIMC settings.

WHO NCD Department recommendation: Although there is strong merit to extend its indication for the treatment of Mature B cell malignancies (Burkitt Lymphoma/Leukaemia) based on its clinical impact, decreasing early death and improving survival for advance disease (Stage III and IV Mature-B malignancies), feasibility must also be considered in terms of diagnostic capacity, side-effects management, and affordability. The emerging WHO-St Jude Platform to access childhood cancer medicines would play an important role in increasing access to this target therapy in LMIC settings; in that context, the technical unit generally favours the inclusion of this new indications for a product already on ELMc.

4. **LISTING OF A NEW ENTITY, LANGERHANS CELL HISTIOCYTOSIS (LCH), NEW INDICATIONS FOR VARIOUS CANCER MEDICINES IN EMLc2021 AND INCLUSION OF NEW MEDICINES, CLADRIBINE (2-CDA), FOR ITS TREATMENT**:

Clinical setting indication: Inclusion of a new entity, **Langerhans Cell Histiocytosis** (LHC), which is a rare multisystemic disease, that affects mainly children less than 10 years of age but can present at any age. It has an estimated incidence of 1/50,000.[35] Treatment varies according to the extension of disease and compromise of risk organs. Systemic Chemotherapy is indicated in cases with involvement of risk organs (Liver, spleen, lungs, bone marrow Central nervous system).

1. Inclusion of new indication for the treatment of multisystemic LCH with existing cancer medicines in the EMLc2021 is proposed:
    - Cytarabine

[32] Rituximab for High-Risk, Mature B-Cell Non-Hodgkin's Lymphoma in Children PubMed (nih.gov)
[33] Rituximab with chemotherapy in children and adolescents with central nervous system and/or bone marrow-positive Burkitt lymphoma/leukaemia: A Children's Oncology Group Report PubMed (nih.gov)
[34] https://doi.org/10.1182/bloodadvances.2020002178
[35] https://www.sciencedirect.com/science/article/pii/S108387910900531X

- 6-Mercpatopurine
- Methotrexate
- Prednisone
- Vinblastine
- Vincristine
- Intravenous Immunoglobulin

a) Efficacy: several combinations of the above medicines have been effective in the treatment of multifocal disease, and Central nervous system involvement[36] Standard treatment is based on the experience of sequential trials of the Histiocyte Society. Standard therapy with Prednisone and vinblastine regimens have yielded overall survival of 84% for patients with high risk disease[37]. Randomized studies from the LCH-III protocol for high risk patients (organ involvement) treated with either Prednisone, Vinblastine and 6-Mercaptopurine do as good as with the other randomized arm including intravenous or oral methotrexate during induction. Treatment with intravenous immunoglobulin resulted in stabilization of the disease but no significant difference in symptom improvement.

b) Feasibility: the majority of these drugs are included in the previous Model list EMLc (2021) and are accessible in many low- and middle-income countries.

WHO NCD Department recommendation*:* Considering that high risk LCH has shown excellent response rates and overall survival greater that 80% in patients with high risk characteristics when treated with systemic chemotherapy according to international standards (Histiocyte Society Protocols), the technical unit supports the inclusion of new the indications of previously included medicines in EMLc 2021 for the treatment of LCH.

2. Inclusion of Cladribine for the treatment of refractory multisystemic Langerhans cell Histiocytosis

a) Efficacy: Although Cladribine in the treatment of recurrent high-risk LCH in children has shown promising results due to its dual effect providing cytoreductive component and its immunosuppressive activity, achieving remission rates greater than 70%, there is limited data to support its population value to be considered for EML inclusion.

b) Feasibility: The need for high-skilled histopathological diagnosis and capacity to identify and manage immune-related toxicity (grade 3 and 4 neutropenia described) may limit its access in most LMIC.

[36] https://onlinelibrary.wiley.com/doi/epdf/10.1002/pbc.26784

[37] https://www.hematologyandoncology.net/archives/february-2019/pediatric-langerhans-cell-histiocytosis-state-of-the-science-and-future-directions/

WHO NCD Department recommendation: although there is some data to support its clinical value in a limited subset of patients (high risk refractory LHC) issues related to feasibility and safety described above, the technical unit does not support the inclusion of Cladribine into the EMLc at this moment.

VI. REVIEW OF CURRENT APPLICATIONS: ADULT AND PEDIATRIC CANCER

1. INCLUSION OF PEGFILGRASTIM ON THE EML FOR THE SAME INDICATIONS OF FILGRASTIM:

a) Efficacy: The value of administration of Granulocyte colony stimulating factors (G-CSF) as primary prophylaxis to reduce myelotoxicity associated with multidrug regimens in children with cancer has been documented. Available data has demonstrated similar efficacy and safety of Pegfilgrastim[38] [39] when compared to Filgrastim. Limited data is available for infants and children with lower body weight (< 45kg).

b) Feasibility: Although the higher cost of Pegfilgrastim as compared to filgrastim might condition availability and feasibility at country level in resource constrained settings, other factors should be taken into consideration such as the potential favourable impact of one single injection vs multiple injections on the indirect cost of cancer treatment (housing expenses while in the hospital, transportation expenses disruption of the child's and family quality of life) and the availability since 2018 of biosimilar products (less expensive).

WHO NCD Department recommendation*:* Considering the similar efficacy and safety of Pegfilgrastim as compared to filgrastim in the paediatric setting and the potential cost-benefits one single dose vs multiple doses can have on the indirect cost of cancer treatment plus additional benefits to the child's and family quality of life, the technical unit favours the inclusion of Pegfilgrastim on the EML.

2. DOXORUBICIN PEGYLATED: ADDITION OF NEW FORMULATION TO EML AND EMLC FOR THE TREATMENT OF KAPOSI SARCOMA

Clinical setting indication: Addition of new formulation for the treatment of Kaposi Sarcoma

Pegylated doxorubicin (PLD), constitutes a new formulation of conventional doxorubicin with reduced cardiotoxicity and improved pharmacokinetic properties (longer effect, higher levels of drug concentration and less frequency administration). It has been approved for the treatment of ovarian cancer, multiple myeloma and AIDS related Kaposi Sarcoma.[40]

[38] https://doi.org/10.1080/16078454.2023.2172292

[39] Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: a meta-analysis of randomized controlled trials - PubMed (nih.gov)

[40] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/050718s051lbl.pdf

Kaposi Sarcoma represents the most common childhood cancer in eastern and central Africa. ART in combination with multisystemic chemotherapy (Vincristine and Bleomycin, ABV and/or Paclitaxel) have been used to treat Paediatric Kaposi Sarcoma but the data is limited as no large controlled randomized clinical trials have been undertaken. Most standard therapies rely on expert's consensus[41].[42] In all regimens where anthracycline is indicated the cumulative doses of conventional doxorubicin should not exceed 300mg/m^2. Estimated cardiotoxicity in cumulative doses of 300-400 mg/ m^2 is around 3-20%

a) *Efficacy:* treatment regimens containing Liposomal pegylated doxorubicin have not shown significant difference in reducing disease progression as compared to conventional regimens, and non-statistically significant overall mortality benefit from liposomal doxorubicin as compared to conservative management consisting of either bleomycin plus vinblastine, vincristine or single-agent antiretroviral therapy alone .[43] The majority of the data comes from few published adults trials.

b) *Feasibility*: access to PLD is limited in many resource constrained settings, shortages reported in 2011 have not allowed its wider use in ongoing clinical trials in LMIC settings.[44] In these setting consideration should be given to improving cancer diagnostic and therapeutic infrastructure including increasing access to adequate supportive therapy to handle significant morbidity and mortality associated to conventional chemotherapy toxicity in these populations.

***WHO NCD Department recommendation*:** while there are some data to support its clinical value with reduced toxicity (including cardiotoxicity), there is insufficient mature overall survival data available to fully evaluate its candidacy, particularly given that alternate, established regimens are already included in WHO EML. Nonetheless, it should be noted that acceptability may be greater due to a more favourable dosing schedule.

3. SUNCREEN FOR PERSONS WITH ALBINISM, XERODERMA PIGMENTOSUM

This submission is made in support of the inclusion of broad-spectrum sunscreen on the core EML and EMLc for persons with albinism, whose condition results in greatly increased risk of the harmful effects of ultraviolet radiation on unprotected skin.

[41] The management of children with Kaposi sarcoma in resource limited settings - Molyneux - 2013 - Pediatric Blood & Cancer - Wiley Online Library
[42] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9121366/
[43] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4174344/
[44] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7236082/pdf/nihms-1576120.pdf

Sunscreen is proposed not for treatment, but for prevention of Malignant neoplasms involving the skin and Chronic effects of ultraviolet radiation on the skin in the target population.

Efficacy: Extensive research has shown the benefits of using sunscreen in reducing the incidence of skin cancer in all groups of people including in persons with albinism. Use of sunscreen has been shown to reduce the incidence of both melanoma and non-melanoma skin cancers.

General considerations: Sunscreens are available as personal care products or over the counter medicines in most middle- and upper-income level countries. Availability and affordability in lower income countries will need to be supported by government programs. Adding sunscreen to the EML/EMLc can contribute to ensuring free or reduced cost of sunscreen for person with albinism, who are disproportionately affected by poverty, particularly in developing and least developed countries.

WHO NCD Department recommendation: Based on the available evidence the technical unit favour the inclusion of topical sunscreen in multiple possible dosage forms, as proposed in the current application, to the EML and EMLc to reduce the risk of skin cancer in the target population.