APPLICATIONS FOR CANCER MEDICINES TO THE 25TH EXPERT COMMITTEE ON SELECTION AND USE OF ESSENTIAL MEDICINES - REVIEW OF CANCER MEDICINES

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I. OVERVIEW AND RECOMMENDATIONS[1]

A. Context

Each year, approximately 20 million people are diagnosed with cancer, affecting more than 1 in 6 people during their lifetime.[2] Yet, outcomes from cancer, determined by access to services, is widely inequitable between and within countries, negatively affecting the social and economic well-being of populations. Available evidence suggests that inequalities in cancer care are significant[3], even in well-resourced settings[4], and effects to accelerate access to essential cancer services have not kept pace with the rapid pace of innovation[5], leaving large populations without access behind.

The WHO cancer team in cancer, through its integrated cancer initiatives, are now supporting more than 100 Member States strengthen their national cancer programmes by defining cancer control priorities, as part of universal health coverage[6]; additionally, the WHO cancer 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 is used to inform national planning[7].

As referenced in previous reports submitted by the WHO cancer team to the EML Expert Committee, there are a diverse set of factors impacting access to essential medicines and should be considered when reviewing applications to WHO EML: These four factors impact the feasibility of accessing cancer medicines, in addition to the financing implications, as outlined below.

(1) Diagnostic capacity availability: 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. Recent studies have shown an increase in the percentage

1 The WHO cancer team in the Department of Noncommunicable Diseases (NCD/MND) would like to thank the Expert Committee for the efforts. The cancer team has reviewed the application for the 2025 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 Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today, accessed 20 Apr 2025.

3 Global cancer burden growing, amidst mounting need for services. World Health Organization. Available from https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidst-mounting-need-for-services, accessed 20 Apr 2025.

4 Beating Cancer Inequalities in the EU. OECD. Available from https://www.oecd.org/en/publications/beating-cancer-inequalities-in-the-eu_14fdc89a-en.html, accessed 20 Apr 2025.

5 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

6 As mandated in World Health Assembly Resolution 70.12 (2017)

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

of cancers harbouring predictive biomarker of therapy response, an increase from 8.9% to 31.6% between 2017 and 2022 alone[8]. Yet, this progress must be balanced against the reality that required testing is not available[9,10] or financed in most LMIC settings[11].

(2) Optimal treatment and capacity to manage toxicities: studies have shown relatively poor concordance between treatment guidelines and nEML, particularly related to targeted therapy. In a review of guidelines and nEM[12]. Even when appropriately prescribed systemic therapy still has relatively high rates of adverse events and toxicities, requiring intensive clinical capacity and resources to manage such events, including for example immunotherapy[13]. In the absence of such services, avoidable deaths during treatment increase substantially and jeopardize the delivery of essential cancer medicines.

(3) Inclusivity of LMIC in cancer research: 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[14].

In addition to these factors impacting feasibility, *one major factor impacts accessibility - financing of essential cancer medicines.* A published report[11] on the inclusion of cancer medicines in health benefit packages reveals a general lack of coverage for cancer services. Within the Organisation for Economic Co-operation and Development (OECD) member countries, cancer care accounts for an estimated €449 billion annually, representing about 6% of total health expenditures,[15] and in high-income Asian country, cancer medicines constitute approximately 10–20% of total pharmaceutical spending.[16] Significant value for money can still be achieved, but the overall financing burden is significantly

8 Suehnholz SP, Nissan MH, Zhang H et al. Quantifying the Expanding Landscape of Clinical Actionability for Patients with Cancer. Cancer Discov. 2024 Jan 12;14(1):49-65. doi: 10.1158/2159-8290.CD-23-0467. PMID: 37849038; PMCID: PMC10784742.
9 Trapani D, Lengyel CG, Habeeb BS et al. The global landscape of availability, accessibility and affordability of essential diagnostics and therapeutics for the management of HER2-positive breast cancer: The ONCOLLEGE-001 survey. J Cancer Policy. 2021 Jun;28:100285. doi: 10.1016/j.jcpo.2021.100285. Epub 2021 Apr 26. PMID: 35559914.
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 WHO global survey on the inclusion of cancer care in health-benefit packages, 2020–2021 World Health Organization. Online. https://www.who.int/publications/i/item/9789240088504, accessed 20 Apr 2025.
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 Haanen, J. et al.Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology, Volume 33, Issue 12, 1217 - 1238
14 (Provisional results) International Clinical Trials Registry Platform. https://www.who.int/clinical-trials-registry-platform
15 Tackling the Impact of Cancer on Health, the Economy and Society. OECD. Available from https://www.oecd.org/content/dam/oecd/en/publications/reports/2024/11/tackling-the-impact-of-cancer-on-health-the-economy-and-society_0fe99cb5/85e7c3ba-en.pdf, accessed 20 Apr 2025.
16 Health spending on cancer drugs and unmet patient needs in Asia-Pacific. The Swedish Institute for Health Economics. Online. https://ihe.se/en/rapport/cancer-drug-spending-in-asia-pacific, accessed 20 Apr 2025.

borne by families, causing financial hardship due to high out-of-pocket expenditure for cancer care, up to 50-90% in a many number of LMICs[17].

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.[18] **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 WHO cancer team launched three global cancer initiatives in breast[19], cervical[20] and childhood[21] cancers for which access to treatment, including essential medicines, is a core focus. In that regard, the WHO cancer 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 launched the Platform in Feb 2025[22] with the commitment to provide access to essential medicines to all children with cancer in 50 countries within the next five years,[23], enabled by St Jude's $US 200 million commitment to purchase the medicines and enable the success of the Platform.

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[24].

17 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.
18 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 .
19 WHO Global Breast Cancer Initiative. https://www.who.int/initiatives/global-breast-cancer-initiative
20 Cervical Cancer Elimination Initiative. https://www.who.int/initiatives/cervical-cancer-elimination-initiative
21 Global Initiative for Childhood Cancer. https://www.who.int/initiatives/the-global-initiative-for-childhood-cancer
22 Closing the Gap: The Global Platform's approach to childhood cancer medicine access. World Health Organization. https://cdn.who.int/media/docs/default-source/ncds/mnd/cancer-programme/gpaccm-closing-the-gaps-draft.pdf, accessed 20 Apr 2025.
23 Downing JR, Ghebreyesus TA. The Global Platform for Access to Childhood Cancer Medicines: addressing inequities in childhood cancer care. Lancet Oncol. 2025 Mar 31:S1470-2045(25)00146-9. doi: 10.1016/S1470-2045(25)00146-9. Epub ahead of print. PMID: 40179919.
24 Paediatric drug optimization standard procedure. https://www.who.int/publications/i/item/9789240039520

It is relevant to note that only products on WHO EML will be purchased and supplied. 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.

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 to provide programme managers with guidance on the accompanying health system requirements (e.g., diagnostic test, staging studies, services to manage toxicities), , aligned with WHO EML and WHO EDL. These WHO Technical briefs have systematically gathering, evaluating and summarizing international and national treatment guidelines using GRADE criteria and use a resource-stratified approach, leveraging existing guidelines as requested by Member States in WHA 70.12. Planned publication of the first brief is scheduled for Q3 2025.

3. Collaboration with Medicine Patent Pool (MPP)[25] 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[26] and the recent announcement of voluntary license for nilotinib[27], done in collaboration with the Access to Oncology Medicines (ATOM) Coalition[28] of the Union for International Cancer Control. The WHO cancer team is pleased to note and engage with, as appropriate, the important advancements by MPP and ATOM.

C. Strategic considerations

Given these emerging opportunities and as previously suggested to the Expert Committee, the WHO cancer team would like to highlight considerations 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)[29]. In light of this finding, and as further outlined in the review of the products below,

25 Medicine Patent Pool (homepage). https://medicinespatentpool.org/
26 Medicine Patent Pool Strategy 2023-2025. https://medicinespatentpool.org/news-publications-post/launch-of-the-medicines-patent-pool-strategy-2023-2025
27 Nilotinib. https://medicinespatentpool.org/licence-post/nilotinib
28 ATOM Coalition. https://www.uicc.org/what-we-do/driving-global-impact/new-initiatives/access-oncology-medicines-atom-coalition
29 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

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.

2. Include **evaluation of efficacy, safety, and feasibility** for selected products in WHO EML to provide guidance in the selection of product in and stakeholder use of WHO EML. 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 and should include: (1) regimens: designating what products are generally given in combination to ensure essential medicines are appropriately given in combination; (2) diagnostic requirements; and (3) essential chemoprotectants.

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3. Comment on **research priorities**, particularly to promote better access to emerging cancer therapies. Many of the applications still include products without mature data and/or for which optimization of dose and schedule are not fully established[30]. Additionally, feasibility of prescribing and administering select products is not well established in LMIC, linked to significant inequalities in access to clinical trials and relevant patient populations (eg, people living with HIV). Defining and promoting such research priorities can signal to research funders, clinical experts and other stakeholders on their value and relevance to inform applications for WHO EML. The WHO cancer team is also working to define such priorities.

The WHO cancer team 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).

[30] The cancer team takes note and appreciate the statement documented by the Expert Committee in its 2023 report that: "…more data are needed regarding the optimal doses and duration of treatment, with some data already suggesting that for several immune checkpoint inhibitors, lower doses and shorter durations may be sufficient."

II. REVIEW OF CURRENT APPLICATIONS: GENERAL OVERVIEW

There were fourteen applications for cancer medicines and/or cancer prevention (sunscreen) to 2025 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 cancer 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.

III. REVIEW OF CURRENT APPLICATIONS: ADULT CANCER

1. PANITUMUMAB for KRAS wild type metastatic colorectal cancer

Panitumumab is an anti-epidermal growth factor (EGFR) antibody used in the treatment of KRAS/NRAS wild-type metastatic colorectal cancer.

a) *Efficacy*: completed randomized clinical trials evaluating relevant indications conclude limited efficacy and magnitude of benefit, while noting that overall survival in the PRIME study exceeded 6 months compared with the control (ie, FOLFOX4). The listed ESMO-MCBS high score ranges from 2-4, depending on the indication and comparator. Panitumumab does not have substantive impact on quality of life. While it is emerging as an accepted therapy for KRAS wild-type metastatic colorectal cancer, exact indications (eg, left-side vs right-side cancers; performance vs cetuximab that is not currently included in WHO EML, timing and duration of therapy) are still emerging.
b) *Feasibility*: Requires high-skilled molecular diagnostics and services for BRAF mutation testing (BRAF V600E mutation can make panitumumab less effective). Cost-effectiveness varies depending on the context and comparison group but may not be cost-effective at standard willingness-to-pay thresholds (specific findings depend on factors like the patient population, the comparator, and health system).

WHO NCD department recommendation: while there is select data on the clinical benefit of panitumumab, the therapeutic benefit from the totality of available trials and extent of real-world data (including clinical practice) is insufficient to justify its inclusion in WHO EML at this time, also noting that cetuximab is not currently included in WHO EML. Accordingly, WHO NCD department does not recommend its inclusion at this time.

2. PD1/PD-L1 immune checkpoint inhibitors for multiple solid cancers

PD1/PD-L1 that have been submitted for EML evaluation as monotherapy for multiple solid cancers, for the treatment of 12 adult cancer entities in the non-curative first line setting. The cancer team also notes previous Expert Committee assessments of immune checkpoint inhibitors (ICI) including its statement in the 2023 report that: “the opportunity costs of providing treatment with immune checkpoint inhibitors would be substantial for many health systems and would divert limited available resources from other public health programmes.”

Accordingly, the WHO cancer team agrees that ICI should be evaluated for specific indications to promote optimal prescribing and use in settings for which select indications may be appropriate and blanket indications risk undermining health system-specific standards of care.

The WHO cancer team has participated in the meetings of the EML cancer working group and notes with great appreciation its report that outlines 12 adult cancer entities for ICI in the non-curative first-line setting, focusing on indications that are relevant to diverse populations, particularly the needs in low- and middle-income countries.

For the purposes of its review, the WHO cancer team will focus on specific indications while noting the assessment of the EML cancer working group (WG).

(1) **Biliary tract cancers**: WHO cancer team agrees with the evaluation by the EML cancer WG, noting that the survival benefit is insufficient to meet criteria as essential, also acknowledging the limited therapeutic gain for other ICI in first-line treatment of locally advanced or metastatic biliary tract cancers. It is noted the limited number of emerging therapies for biliary tract cancer and limited number of available studies.

(2) **Cervical cancer**: WHO cancer team agrees with the suggested **inclusion of pembrolizumab**, combined with chemotherapy and without bevacizumab, on EML for ≥1% PD-L1 expression (CPS ≥1), based on survival gain and the deficiencies in innovative therapies for cervical cancer. Given WHO's prioritization of cervical cancer through its WHO Cervical Cancer Elimination Initiative and the accompanying Global Strategy endorsed by Member States, it further re-inforces the importance of access to emerging therapies. The cancer team also notes the importance of further research for use of ICI in immunocompromised populations living with HIV.

(3) **Colorectal cancer**: WHO cancer team appreciates the volume of evidence to support the inclusion of ICI for colorectal cancer is substantial, particularly related to MSI-H/dMMR metastatic CRC, with robust evidence supporting efficacy. The WHO cancer team does note concerns raised by the Expert Committee in its previous reports and by the EML cancer WG on access to ICI and does further agree on the deficits in diagnostic capacity as reference above (pg 2). Additionally, there are emerging data on use of ICI for MSS CRC and appropriateness of combination therapies, currently under active investigation to update the scope of ICIs in CRC treatment. Given constraints related to feasibility in colorectal cancer (particularly diagnostic capacity and overall budget impact/opportunity costs) and higher priority indications that will inform the implementation of WHO EML for ICI beyond the current narrow scope of melanoma, a decision can be deferred to a future review.

(4) **Endometrial cancer**: there is evidence of meaningfully clinical benefit of dostarlimab combined with chemotherapy and pembrolizumab combined with chemotherapy on the EML as combination treatments for endometrial cancer dMMR/MSI-H. As noted with colorectal cancer above, concerns about diagnostic capacity/exact indications, availability of backbone chemotherapy and health system feasibility to sustainably provide ICI are re-inforced. The WHO cancer team agrees that while available data are robust, mature overall survival data are not yet fully conclusive, particularly for durvalumab, and that ongoing studies are exploring different combination therapies including with other agents like PARP inhibitors. This is a reasonable justification to defer to a future review. Select randomized clinical trials have shown substantial clinical benefit, raising the likelihood for a positive future consideration.

(5) **Gastric or gastro-esophageal junction adenocarcinoma**: WHO cancer team acknowledges the emerging evidence for the use of ICI for gastric and/or gastro-esophageal junction adenocarcinoma., though highlights concerns related to the limited overall survival gain, significant increases in adverse events, and ongoing studies to further define cohorts who will most likely to benefit from ICIs. Given these factors, the WHO cancer team, agreeing with the assessment of the EML cancer WG, does not support the inclusion of ICI combined with chemotherapy for gastric or gastro-esophageal junction adenocarcinoma.

(6) **Head and neck squamous cell carcinoma**: The WHO cancer team notes the survival improvements with the use of ICI for head and neck squamous cell carcinoma with ESMO-MCBS score ranging from 3-4, depending on the therapeutic indication. To date, there is insufficient evidence of sustained, substantive benefit for the use of ICI in head and neck squamous cell carcinomas, though studies are ongoing to evaluate optimal treatment approaches that consider combination therapies and strategies to reduce adverse events, among other factors.

(7) **Hepatocellular carcinoma**: The WHO cancer team notes recent positive ICI studies in the management of hepatocellular carcinoma. The team also notes the variability in therapy test and comparator, making it more difficult to establish a preferred therapeutic approach or cohort most likely to benefit. The WHO cancer team agrees with the EML cancer WG that as further studies are conducted and clarity emerges on an optimal treatment approach, follow-up consideration for ICI in hepatocellular carcinoma can be made.

(8) **Malignant melanoma**: The WHO cancer team appreciates the justification from the EML cancer WG for continued listing of ICI as monotherapy for malignant melanoma and also notes with the evidence for sustained survival benefit with combination therapy. At this time, there is insufficient feedback on the listing for nivolumab and pembrolizumab in WHO EML, the implications in LMIC and ability to manage treatment-related adverse events. Future consideration should be given to re-

assess combination therapy for malignant melanoma and use of ICI for malignant melanoma in children.

(9) **Non-small cell lung cancer**: The WHO cancer team agrees with the EML cancer WG in their comprehensive analysis and **support the inclusion of pembrolizumab, atezolizumab, and cemiplimab as monotherapy for oncogenic-driver wild-type non-small cell lung cancer ≥50% PD-L1 expression**. The WHO cancer team does acknowledge strong consideration for the inclusion of tislelizumab combined with chemotherapy for oncogenic-driver wild-type non-small cell lung cancer ≥50% PD-L1 expression with no EGFR-positive mutations or ALK-positive re-arrangements, that can be viewed favourably as evidence emerges for its use in different population groups.

The WHO cancer team also agrees with the preference for inclusion of ICI for non-small lung cancer ≥50% PD-L1 expression as monotherapy, noting the need for explicit guidance on monotherapy over combination therapy and the prioritization of ≥50% PD-L1 expression over all patients (including the guidance to rule out EGFR-positive mutations or ALK-positive re-arrangements), to enable greater access in settings where budgetary constraints may require prioritization of greatest clinical impact.

(10) **Renal cell carcinoma**: The WHO cancer team notes with interest the evidence for improved survival in the use of ICI for renal cell carcinoma while also acknowledging the inconsistencies in available data and uncertainty regarding the duration of benefit and optimal treatment approach. Accordingly, further evaluation for the use of ICI in renal cell carcinoma can be considered as more mature data are generated and real-world evidence becomes available.

(11) **Squamous cell carcinoma of the esophagus**: The WHO cancer team agrees with the EML cancer WG that the magnitude of clinical benefit is insufficient in extent – with survival gains that approximate 6 months – and inconsistent in magnitude to justify the inclusion of ICI for esophageal squamous cell carcinoma. It can also be noted that the uncertainty in optimal treatment protocol and role of predictive biomarkers further underpin the rationale not to include ICI for esophageal squamous cell carcinoma at this time.

(12) **Triple-negative breast cancer**: The WHO cancer team notes that while a significant number of studies have been conducted to evaluate ICIs in breast cancer (both curative and non-curative settings), there is a general lack of robust on its optimal use for select indications. The team acknowledges emerging clarity on the use of ICI in select cohorts (eg, PD-L1-positive TNBC or tumors with high tumor mutational burden), though highlights that cross-trial comparisons are limited because of, among other factors, different assays and thresholds. Triple-negative breast cancer is constituted by multiple subtypes with variable immunogenicity, raising uncertainty about ICI effectiveness in different cohorts. Finally, it is also noted that confirmatory trials may still be needed

to more conclusively demonstrate sustained clinical benefit. Further consideration can be made in future applications as additional studies are conducted.

Overall WHO NCD department recommendation on ICI: it is now well established that there is evidence of meaningful clinical benefit for ICIs for indications specified above, in line with the summary of evidence discussed with the EML cancer WG. The WHO cancer team agrees that **prioritized indications can be included**.

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. In addition, management of toxicity may require resource intensive and highly specialized services.

The WHO cancer team calls for further data from routine use of ICI in LMIC that to validate the effectiveness and feasibility of widespread use of ICI. These data can include evaluating ability to safely and effectiveness of delivering these medicines. Because of their demonstrable efficacy, ICI can be included in WHO EML. 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 (eg, PD-L1 testing) could enable ICI inclusion if and when appropriate.

The WHO cancer team also notes with appreciation the suggested strategies to improve access to ICI, particularly in LMIC, including the interchangeability of ICI, and the need for better data regarding treatment duration and intensity (including awaiting results from ongoing trials to evaluate reduced dosing or prolonged dosing intervals). WHO highlights recommendations on pricing approaches as previously published[31] and also acknowledges ongoing efforts to promote access to essential cancer medicines.

Finally, WHO cancer team particularly emphasizes the need for the formulation, implementation and monitoring of national treatment standards for cancer after approvals by health technology assessors and appraisers. In WHO cancer team's work providing technical support to governments, particularly

[31] 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

upper-middle-income countries, it is increasingly common that products are prescribed inconsistent with national standards established best practices, off-label, and/or inappropriately – particularly when there is a stockout of a related product or backbone for a regimen. The WHO cancer team, working with partners, has developed a methodology to enable forecasting, supply planning, guideline development, training of health professionals and monitoring of guideline implementation. WHO EML can promote appropriate prescribing by explicitly designated indications/appropriate use of listed EML products while noting that others are not approved (eg, PD-L1 levels).

3. TISLELIZUMAB for oesophageal squamous cell carcinoma

Tislelizumab has been submitted for EML evaluation in advanced oesophageal squamous cell carcinoma.

WHO NCD Department recommendation: The above sections provide an assessment of ICI for oesophageal squamous cell carcinoma. In brief, WHO cancer team agrees on the inconclusive and potentially limited clinical efficacy of ICI oesophageal squamous cell carcinoma.

4. TORIPALIMAB for Nasopharyngeal carcinoma, oesophageal squamous cell carcinoma

Toripalimab (anti-PD1 ICI) has been re-submitted for EML evaluation as monotherapy in advanced Oesophageal and Nasopharyngeal cancer and notes the previous conclusion of the Expert Committee that "…toripalimab plus chemotherapy compared to chemotherapy alone might meaningfully improve survival, however the available evidence was still preliminary with only a short follow-up."

The above sections provide an assessment of ICI for head and neck squamous cell carcinoma and oesophageal squamous cell carcinoma. The WHO cancer team notes the expanded availability of toripalimab outside of China, the review by other regulatory authorities and the emerging favourable cost-effectiveness (though again acknowledging the limitations of such studies).

WHO NCD Department recommendation: in line the findings of the EML CWG, there are emerging data yet still insufficiently mature data on the overall survival benefit from toripalimab, particularly among different cancer types. The cancer team does note with interest the relevant findings particularly for nasopharyngeal cancers and concludes that further consideration can be made as additional studies are reported.

5. ZANUBRUTINIB FOR CHRONIC LYMPHOCYTIC LEUKEMIA /SMALL LYMPHOCYTIC LYMPHOMA

Zanubrutinib is re-submitted for EML evaluation for Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL). The cancer team notes the previous assessment of the Expert Committee in which "…the magnitude of these gains may be limited, and that few long-term data were available…and also noted important toxicity concerns (particularly neutropenia). The Committee considered that at the current high price, zanubrutinib would neither be considered cost-effective nor affordable in most low- and middle-income settings." The application considers interval studies, outlined in the application and EML cancer WG.

Interval studies have shown possible progression free survival difference between zanubrutinib versus ibrutinib as well as possible differences in safety profiles. Evidence for overall survival gains have not been published.

WHO NCD department recommendation: In line with the findings of the EML cancer WG, the inclusion of zanubrutinib can be deferred for further review given the possibility of an equivalent or more favouable survival benefit and/or safety profile.

IV. REVIEW OF CURRENT APPLICATIONS: PAEDIATRIC ONCOLOGY

The 25TH Expert Committee for the selection and use of Cancer Medicine Candidates to the 2025 Model Lists of Essential Medicines received a total of two submissions for new cancer medicines to be considered for addition for the EMLc, Temozolomide and Blinatumomab. A detailed assessment of each submission, including clinical evidence, public health relevance, and implementation considerations, is outlined below.

1. TEMOZOLOMIDE for high-grade glioma, Ewing sarcoma and neuroblastoma

Temozolomide is a cytotoxic imidazotetrazine second-generation alkylating agent proposed for inclusion in the WHO Model List of Essential Medicines for children for the treatment of high-grade gliomas, recurrent and progressive Ewing Sarcoma and relapsed or refractory Neuroblastoma, including its use in palliative care settings for these conditions.

a) Efficacy: Evidence supporting the efficacy of temozolomide as a single agent in these relapsed paediatric cancers is limited. For high-grade gliomas (HGG), modest improvements in survival have been observed when temozolomide is used in combination with radiotherapy, as reported by the International European collaborative HIT-HGG2007 Clinical Trial[32], however, findings from the Children's Oncology Group study ACNS0126 did not demonstrate a survival benefit, highlighting the inconsistency in outcomes across studies for children with high grade gliomas.[33]

In the setting of relapsed or refractory Ewing Sarcoma, monotherapy data are sparse, combination regimens of temozolomide with irinotecan have demonstrated objective response rates up to 28% and a one-year overall survival of approximately 55% in retrospective studies.[34]

In the case of relapsed neuroblastoma one of the largest phase II multicentre European collaborative clinical trials involving the Société Française des Cancers de l'Enfant and United Kingdom Children Cancer Study Group showed clinical activity and response in 20% of the patients included. Significant haematological toxicity (Grade 3 and 4 thrombocytopenia) was present in 24% of the administered

32 Kwiecien, R., Gielen, G. H., Benesch, M., Perwein, T., Nussbaumer, G., Sturm, D., W Jones, D. T., Pfister, S. M., Eyrich, M., Rutkowski, S., Fleischhack, G., Karremann, M., Kortmann, D., Hagel, C., Calaminus, G., Faldum, A., Bison, B., Pietsch, T., Hoffmann, M., . . . Kramm, C. M. (2022). HGG-16. Final analysis of the HIT-HGG-2007 trial (ISRCTN19852453): Significant survival benefit for pontine and non-pontine pediatric high-grade gliomas in comparison to previous HIT-GBM-C/-D trials. Neuro-Oncology, 24(Suppl 1), i63. https://doi.org/10.1093/neuonc/noac079.231

33 Cohen KJ, Pollack IF, Zhou T, Buxton A, Holmes EJ, Burger PC, Brat DJ, Rosenblum MK, Hamilton RL, Lavey RS, Heideman RL. Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. Neuro Oncol. 2011 Mar;13(3):317-23. doi: 10.1093/neuonc/noq191. PMID: 21339192; PMCID: PMC3064602.

34 Salah S, To YH, Khozouz O, Ismail T, Yaser S, Alnsour A, Shahin O, Sultan I, Abuhijlih R, Halalsheh H, Abuhijla F, Lewin J. Irinotecan and temozolomide chemotherapy in paediatric and adult populations with relapsed Ewing Sarcoma. Clin Transl Oncol. 2021 Apr;23(4):757-763. doi: 10.1007/s12094-020-02466-9. Epub 2020 Aug 5. PMID: 32761317.

cycles requiring dose reduction and resulting in treatment delays. No significant survival benefits were observed as all responders experienced a median progression free survival of 8 months (range, 3.7 to14.7 months) and ultimately died due to disease progression.[35]

b) Feasibility: Although there is modest evidence documenting clinical activity of temozolomide in combination with other cancer medicines as Irinotecan and Topotecan in relapse and refractory paediatric solid tumours[36] in heavily treated patients with refractory or relapsed solid tumours,[37] the treatment is associated with moderate haematological toxicity, requiring continuous laboratory monitoring of WBC which might not be feasible in resource-constrained settings.

WHO NCD Department cancer team recommendation: In light of the above findings, the cancer team at this time suggests **deferring a decision to include temozolomide as a single agent for the proposed indications or for use in the palliative care setting until more mature data on the efficacy of combination regimens becomes available**. Future consideration can also be made for high risk neuroblastoma and other refractory solid tumours. Future submission could be reconsidered for temozolomide in combination regimens which will be particularly relevant for resource-limited settings, where access to high-dose chemotherapy with autologous stem cell transplantation or targeted therapies is often unavailable. In such contexts, temozolomide, when used as part of a combination regimen alongside appropriate symptom management and comprehensive palliative care, may represent a valuable treatment option for children with otherwise limited alternatives and poor prognoses.

2. BLINATUMOMAB for acute lymphoblastic leukemia

Blinatumomab, a bispecific T-cell engager immunotherapy, is currently submitted for inclusion in EMLc as treatment for frontline and relapsed/refractory (R/R) setting for paediatric patients with CD19-positive B-lineage acute lymphoblastic leukemia (B-ALL).

35 Cramer SL, Reddy AT, Minard CG, Voss S, Fox E, Liu X, Denic K, Reid JM, Weigel BJ. A Phase 1 Study of ABI-009 (Nab-sirolimus) in Combination With Temozolomide and Irinotecan in Pediatric Patients With Recurrent or Refractory Solid Tumors, Including CNS Tumors-A Children's Oncology Group Pediatric Early Phase Clinical Trial Network Study ADVL1514. Cancer Med. 2024 Nov;13(21):e70376. doi: 10.1002/cam4.70376. PMID: 39487711; PMCID: PMC11533328.

36 Rubie H, Geoerger B, Frappaz D, Schmitt A, Leblond P, Ndiaye A, Aerts I, Le Deley MC, Gentet JC, Paci A, Chastagner P, Dias N, Djafari L, Pasquet M, Chatelut E, Landman-Parker J, Corradini N, Vassal G. Phase I study of topotecan in combination with temozolomide (TOTEM) in relapsed or refractory paediatric solid tumours. European Journal of Cancer 2010; 43(15): 2763-2770. doi.org/10.1016/j.ejca.2010.05.004.

37 Brahmi M, Toulmonde M, Winter S, De Percin S, Valentin T, Corradini N, Gantzer J, Marec-Berard P, Gouin F, Claude L, Ducassou A, Gaspar N, Tlemsani C, Berlanga P, Ostéosarcome et sarcome d'Ewing récurrents ou réfractaires – Directives françaises des groupes FSG/NETSARC et GroupOs, Bulletin du Cancer 2025. doi.org/10.1016/j.bulcan.2024.03.010.

a) Efficacy: Blinatumomab has demonstrated significant clinical efficacy in relapsed/refractory (R/R) settings for the treatment of B-AL and more recently studies have documented improved rates of MRD-negativity, gains in OS, and fewer acute adverse effects (Grade 3 cytokine release syndrome in 0.3% and seizures in 0.7% of first courses) when incorporated into frontline treatment regimens for B-ALL.[38,39,40]

b) Feasibility: Although Blinatumomab has shown promising efficacy in the treatment of frontline and relapsed or refractory B-cell acute lymphoblastic leukaemia (B-ALL), its administration presents significant feasibility challenges in low- and middle-income countries (LMICs). The drug requires continuous intravenous infusion and adequate infrastructure in specialized childhood cancer facilities and high-skilled and trained health professional to monitor and manage adverse events associated, such as cytokine release syndrome and neurotoxicity. Ensuring safe and effective delivery of blinatumomab would likely require substantial health system strengthening and resource allocation, which may not be immediately achievable in all contexts.

WHO NCD Department cancer team recommendation: In light of the above findings, **the cancer team supports the Cancer Expert Committee's decision to include blinatumomab in the EMLc 2025**. While its clinical efficacy in treating frontline and relapsed or refractory B-cell acute lymphoblastic leukaemia is well established, the team emphasizes the importance of also addressing the infrastructure and health system requirements necessary for its safe and effective use. Increased access to this effective therapy could be facilitated through the development of partnership models that support pooled procurement and coordinated supply strategies. The inclusion of blinatumomab in the WHO EMLc presents a valuable opportunity to enhance sustainable and equitable access, particularly through access to medicines initiatives such as the Global Platform to Access Childhood Cancer Medicines. Such collaborations can play a critical role in strengthening childhood cancer care in low- and middle-income countries by addressing affordability, availability, and implementation challenges.

38 von Stackelberg A, Locatelli F, Zugmaier G, Handgretinger R, Trippett TM, Rizzari C, Bader P, O'Brien MM, Brethon B, Bhojwani D, Schlegel PG, Borkhardt A, Rheingold SR, Cooper TM, Zwaan CM, Barnette P, Messina C, Michel G, DuBois SG, Hu K, Zhu M, Whitlock JA, Gore L. Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. J Clin Oncol. 2016 Dec 20;34(36):4381-4389. doi: 10.1200/JCO.2016.67.3301. Epub 2016 Oct 31. PMID: 27998223.

39 Hunger SP et al. Blinatumomab Added to Chemotherapy Improves Disease-Free Survival in Newly Diagnosed NCI Standard Risk Pediatric B-Acute Lymphoblastic Leukemia: Results from the Randomized Children's Oncology Group Study AALL1731. *Blood* (2024) 144 (Supplement 1): 1. doi.org/10.1182/blood-2024-207450.

40 Canichella M, De Fazio L, Molica M. Integrating Blinatumomab in the Frontline Treatment in B-Cell Acute Lymphoblastic Leukemia: A New Era in Therapeutic Management. J. Clin. Med. 2025, 14, 2055. https://doi.org/10.3390/ jcm14062055

VI. REVIEW OF CURRENT APPLICATIONS: ADULT AND PEDIATRIC CANCER

1. Erythropoiesis stimulating agents for chemotherapy induced anaemia (I.5)

The current WHO model list of essential medicines includes the erythropoiesis stimulating agents (ESAs): epoetin alfa, beta, theta and darbepoetin alfa for the management of anaemia for adults and children, and methoxy polyethylene glycol-epoetin beta indicated for adults.

a) Efficacy: For the indication of chemotherapy induced anaemia (CIA) in patients without curative intent several meta-analysis and systematic reviews as well as evidenced-based guidelines, have demonstrated clinical benefit with the administration of ESAs when hemoglobin declines to less than 10 g/dL. In this setting, ESAs have been shown to reduce the need for red blood cell transfusions (RBC) and to improve quality of life.[41,42] However, for patients undergoing chemotherapy with curative intent, the evidence is more conflicted, with concerns regarding the potential increased risk of venous thromboembolism. Most studies emphasize the importance of carefully weighing the benefits and risks in these cases.[43] Recently the 2024 supportive care guidelines from the Italian Association of Medical Oncology recommends individualizing the indication of ESAs taking into consideration key factors including type and stage of the cancer, the degree of anaemia, the patient's life expectancy, the environment in which the patient is treated and the patient's preferences.[44] In children there is limited data on the benefit of ESAs in reducing blood transfusion requirements.[45]

b) Feasibility: In LMICs settings where blood transfusion infrastructure can be limited or unreliable, availability of ESAs biosimilars could contribute to reduce number of transfusions in specific group of patients including patients with advance disease receiving chemotherapy with palliative intent, and women receiving platinum-based chemotherapy who have symptoms associated with anaemia[46]. Adherence to evidence-based guidelines is recommended when evaluating indications of ESAs for the management of CIA in adults.

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41 Bohlius J, Bohlke K, Castelli R, Djulbegovic B, Lustberg MB, Martino M, Mountzios G, Peswani N, Porter L, Tanaka TN, Trifirò G, Yang H, Lazo-Langner A. Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update. J Clin Oncol. 2019 May 20;37(15):1336-1351. doi: 10.1200/JCO.18.02142. Epub 2019 Apr 10. PMID: 30969847.

42 Ross SD, Allen IE, Henry DH, Seaman C, Sercus B, Goodnough LT. Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: a systematic review of the literature. Clin Ther. 2006 Jun;28(6):801-31. doi: 10.1016/j.clinthera.2006.06.003. Erratum in: Clin Ther. 2007 May;29(5):985-6. Erratum in: Clin Ther. 2007 May;29(5):985-986. doi: 10.1016/j.clinthera.2007.05.009. PMID: 16860166.

43 Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, Hyde C, Engert A, Bohlius J. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev. 2012 Dec 12;12(12):CD003407. doi: 10.1002/14651858.CD003407.pub5. PMID: 23235597; PMCID: PMC8145276.

44 Associazzione Italiana di Oncologia Medica. 2024 Linea Guida Gestione de la Tossicitá Ematopoietica in Oncologia.

45 Kronberger, M., Fischmeister, G., Poetschger, U., Gadner, H., & Zoubek, A. (2002). REDUCTION IN TRANSFUSION REQUIREMENTS WITH EARLY EPOETIN ALFA TREATMENT IN PEDIATRIC PATIENTS WITH SOLID TUMORS: A Case-Control Study. Pediatric Hematology and Oncology, 19(2), 95–105. https://doi.org/10.1080/08880010252825687

46 https://www.nice.org.uk/guidance/ta323/chapter/2-Clinical-need-and-practice

WHO NCD Department cancer team recommendation: ESAs' biosimilars availability has increased access and affordability particularly for the management of anaemia associated with chronic renal disease. Chemotherapy induced anaemia is generally managed by adjusting the cancer treatment regimen, with administration of iron supplements and, with RBC transfusion in cases of severe anaemia. While current evidence indicates that ESAs can reduce the need for RBC transfusions, studies consistently emphasize the importance of evaluating the risk–benefit profile, particularly due to potential adverse effects such as thromboembolic events. Although data do not currently support a survival benefit from ESA use alongside chemotherapy or radiotherapy, their use may be justified in selected patients to reduce RBC transfusions and improve quality of life.

In light of the above findings, **the cancer team supports the extension of ESAs for the management of CIA in a carefully defined subset of patients** adhering to established supportive care standards and under the close supervision of trained healthcare professionals to ensure safe and effective use.

2. SUNCREEN, BROAD SPECTRUM for Prevention of skin cancer in people with albinism

The cancer team notes with appreciation the feedback from the Expert Committee on the need for "…details of specific active ingredients and their concentration, and the range of sun protection factor rating." The updated submission includes updated relevant details.

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.

WHO NCD Department recommendation: With additional details providing in the application, 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.