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ORIGINAL RESEARCH

Essential cancer medicines: adding feasibility to the magnitude of clinical benefit value chain

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Background: Cancer is a global public health problem, requiring efficient health system investments to deliver sustainable impact on population health. Access to medicines is a critical component of health systems, having a crucial role in delivering therapeutic benefits. Since 1977, the World Health Organization (WHO) has published a Model List of Essential Medicines (EML) that includes key health interventions for the prevention and control of conditions of public health relevance. Essential medicines are selected for inclusion in the EML based on the evidence of efficacy, safety, therapeutic value, and the potential to impact population health. With the rapid changes in the therapeutic landscape of cancer treatment with new medicine approvals, there is a critical need to select and prioritise specific cancer interventions based on their intrinsic value.

Materials and methods: The European Society for Medical Oncology (ESMO) has developed a decisional methodology based on a threshold with a minimum set of technical specifications and a consensus-based procedure for decisions to select candidate cancer medicines to be submitted to the WHO for consideration for the WHO EML.

Results: ESMO recognises the WHO EML as an important reference guide for medicines that all countries should include in their national EMLs. Cancer medicines on the WHO EML are used in the treatment of the majority of cancers, and are recommended in the evidence-based ESMO Clinical Practice Guidelines that medical oncologists use to treat patients. ESMO's submissions to the WHO EML in 2019 and 2021 and their respective outcomes are presented in the manuscript.

Conclusion: Due to the rising costs associated with newly available therapies, structured, reproducible, and field-tested tools to evaluate the added clinical benefit from these therapies need to be implemented in pre-selecting potential candidate medicines to be included in the WHO EML. ESMO is proud to collaborate closely with WHO on this important global public health initiative.

Key words: Global cancer policy, cancer medicines, WHO Model List of Essential Medicines, ESMO-MCBS, value in health

INTRODUCTION

The global burden of cancer continues to rise, along with cancer-related deaths. The recent global estimates from the International Agency for Research on Cancer show that cancer is one of the leading causes of premature death (i.e. death among individuals aged 30-69 years) and a leading cause of death worldwide.[1] A decline in cancer mortality is observed in many high-income countries due to effectively funded public health programmes for cancer control framed across the cancer care continuum.[1] The implementation of evidence-based control strategies of primary and secondary cancer prevention, together with the prioritisation of safe and effective essential cancer treatments, rehabilitation, and palliative care interventions, are crucial elements for success in cancer control.

Investing in cancer treatment has been identified as an accelerator of cancer control that will help in achieving the health-related goals of the 2030 United Nations Sustainable Development Goals (UN SDGs). This is particularly true for the objectives of reducing cancer mortality by one-third by 2030 (SDG target 3.4), and pursuing Universal Health Coverage

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(SDG target 3.8). The latter recognises the importance of prioritising access to 'safe, effective, quality, and affordable essential medicines' for cancer prevention and control.[2]

With regard to the selection of cancer medicines, the World Health Organization (WHO) has been instrumental in recognising those medicines with public health relevance since 1977, by adding them to the WHO Model List of Essential Medicines (EML). The EML provides guidance for countries to prioritise medicines that provide the best payback in terms of important benefits. To set national priorities, countries usually complement WHO recommendations with information on local disease epidemiology, health demands, resources, and to implement and fund effective and impactful health programmes.[3]

Since its first edition in 1977, the EML has been updated every 2 years and includes an increasing number of antineoplastic agents.[4,5] In 2019, the 21st EML added 12 new cancer medicines to the list, including targeted agents and immune-checkpoint inhibitors (ICIs).[6] In 2021, four cancer medicines were added, along with new indications for childhood cancers, and extensions of indication were approved for previously adopted medicines.[7]

The selection process of medicines for consideration in the EML is well structured: stakeholders can submit proposals for medicines to be included in the WHO EML, which will ultimately be discussed by the WHO Expert Committee on the Selection and Use of Essential Medicines for the decision to list them or not. In 2021, as part of the broader dialogue and multistakeholder effort, the WHO received 23 applications for cancer medicines to be added to the EML.

The European Society for Medical Oncology (ESMO) has participated in the identification of potential cancer medicines for consideration for inclusion in the EML, submitting specific proposals in the 2019, 2021, and 2023 updates of the EML.

In this paper, we aim to: (i) describe the ESMO selection process for candidate cancer medicines for consideration for the WHO EML based on analyses including the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS); (ii) understand the critical elements to address when submitting a new proposal for inclusion in the EML; and (iii) provide summary vignettes of ESMO's applications to the EML, as case studies.

THE ESMO PROCESS

How candidate medicines for the WHO EML are selected based on their intrinsic therapeutic value

The ESMO process to identify cancer medicines proposed for consideration for the WHO EML has been consolidated in recent years. With the development of practice and policy tools, such as the ESMO-MCBS,[8,9] and the participation in the dialogue on global cancer policy, ESMO has developed a decisional methodology based on a threshold with a minimum set of technical specifications and a consensus-based procedure for decisions to select candidate medicines to be submitted to the WHO for consideration for the WHO EML.

The first step of the ESMO selection process of cancer medicines to submit to WHO is the review of data from clinical trials. An extensive literature research is conducted in a systematic, comprehensive way, to contextualise the clinical efficacy—safety data of the candidate medicines, including in real-life settings and low-middle income countries, and as it pertains to 'value for money' and health system implications.[10] The WHO EML Expert Committee indicated the ESMO-MCBS as a screening tool to identify possible cancer medicines to be considered for inclusion in the WHO EML.[11] In addition, the WHO EML Expert Committee established a desirable threshold for the absolute gain of 4-6 months in overall survival (OS) for a first-line treatment based on mature data from clinical trials (i.e. appropriate follow-up and/or final analyses).[11] Finally, these cancer medicines need to have a significant public health relevance.[12] Thus, as a second step, a subset of all medicines with ESMO-MCBS scores of A or B in the curative setting and 4 or 5 in the non-curative setting is submitted to WHO, based on discussions with members of the ESMO Faculty Groups, the ESMO Public Policy Committees, the ESMO-MCBS Working Group, and the ESMO Guidelines Steering Committee. The process includes collaboration with the ESMO Chief Medical Officer and the Scientific Affairs Department, and submissions are approved by the ESMO Executive Board. A schematic representation of this selection process can be seen in Figure 1.

The ESMO-MCBS has been designed in accordance with the 'accountability for reasonableness' ethical framework of fair public policy decision making.[13] The scale facilitates priority-setting to address the implementation of new therapeutic technologies, including pharmaceuticals in the management of cancer, highlighting those treatments providing substantial clinical benefit and distinguishing them from those with lesser or marginal clinical benefit.

How to frame the selection of candidate medicines for the WHO EML in a health system approach

The evaluation of the public health relevance of a medicine is based on its intrinsic value but also on broader considerations of health systems, feasibility, and implementation. To make essential treatments available to the patients who will benefit the most, one needs to consider several variables. For instance, in the case of targeted agents or medicines benefitting only in molecularly selected patients (i.e. the need to account for companion diagnostics), a relevant factor is represented by the assays and procedures for identification of the tumour molecular targets.[14]

Other key aspects are the infrastructures, technologies, and expertise to manage the samples to be tested (e.g. health system requirements and quality assurance), and health care facilities and resources for the management of patients and potential treatment-related toxicities (e.g. health care resource utilisation and capacity to prevent and treat toxicities). Eventually, potential cancer workforce deficiencies across countries and, considerations of health system capacity and the demand for adequate

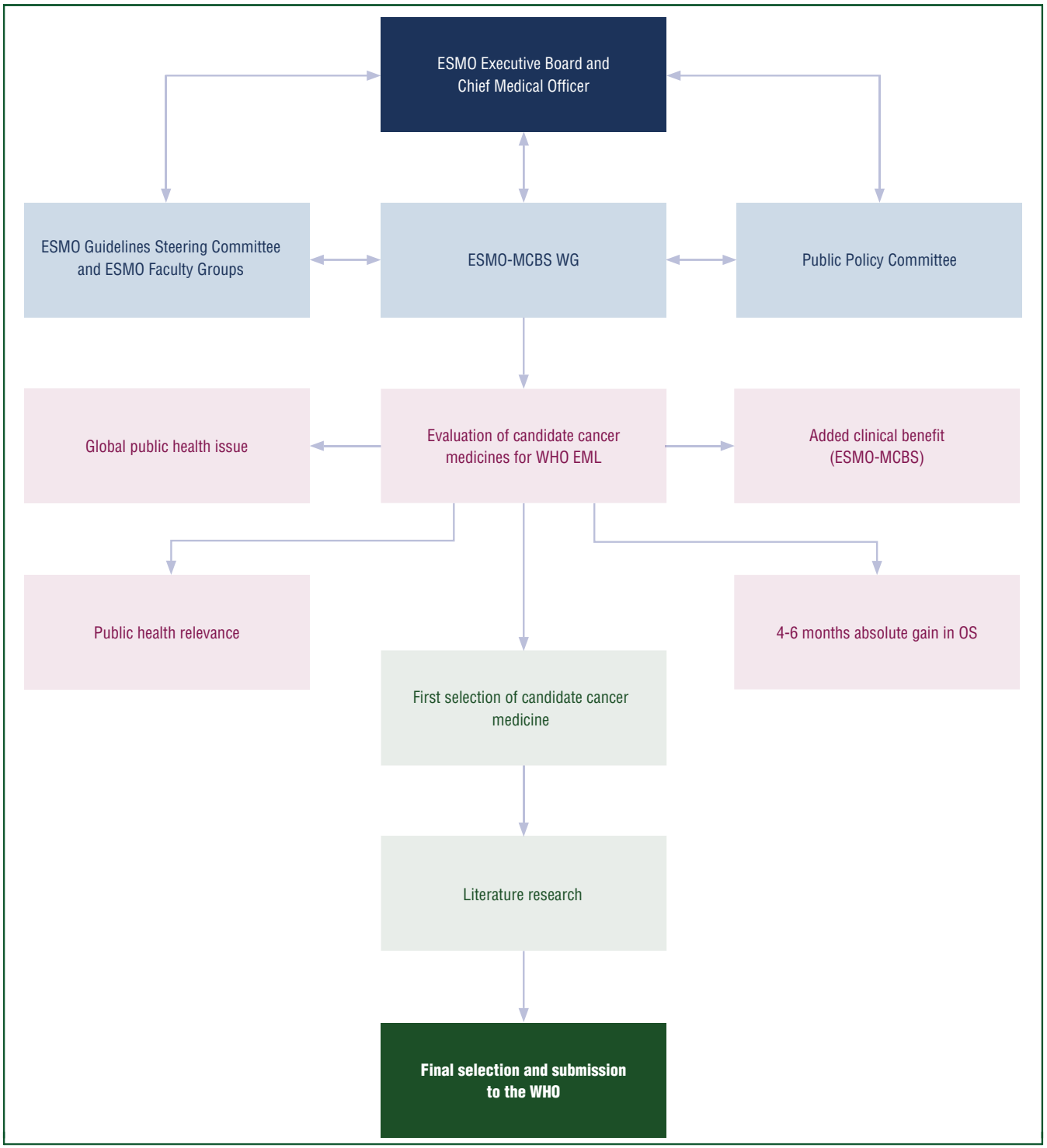

Figure 1. Graphical representation of ESMO selection process of cancer medicines for submission to the WHO Model List of Essential Medicines (EML).
EML, Essential Medicines List; ESMO, European Society for Medical Oncology; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; OS, overall survival; WG, working group; WHO, World Health Organization.

infrastructure, workforce with specific competences and training, and clinical care capacities must be evaluated and highlighted when proposing new medicines intended to be considered for inclusion in the WHO EML.

For concrete examples of the relevance of diagnostic capacity to uptake of new medicines in the continuum of health systems, see Supplementary Appendix 1, available at https://doi.org/10.1016/j.esmoop.2023.101617 with the ESMO applications of the candidate medicines for inclusion in the 2021 WHO EML.

ESMO submissions to the WHO EML in 2019 and 2021 and the respective outcomes

In 2019, and considering the process described above, ESMO submitted the following applications for the 21st WHO EML[11]:

- Anti-programmed death-ligand 1 (PD-L1) and anti-programmed cell death protein 1 (PD-1) ICIs (atezolizumab, nivolumab, and pembrolizumab) for metastatic non-small-cell lung cancer (NSCLC)
- Anti-PD-1 ICIs (nivolumab and pembrolizumab) for early and advanced metastatic melanoma
- Antiemetics (aprepitant) for moderately and high emetogenic chemotherapies

The ESMO application proposed ICIs (pembrolizumab and nivolumab) for both early and advanced stage in melanoma. Based on the safety profile, the added clinical benefit, and cost-effectiveness, the EML Expert Committee recommended ICIs only for the advanced setting of care, stating that 'these medicines demonstrated highly relevant increases in OS and represent the first medicines on the EML for metastatic melanoma'.[11]

Aprepitant was also added to the EML and the WHO Essential Medicines for Children (EMLc) as part of the best supportive care practices to deliver improved patient-centred outcomes. Positive factors that contributed to the decision for inclusion by the WHO Expert Committee on Selection and Use of Essential Medicines were the clinical benefit risk-based profile—it has been shown to be more effective than standard antiemetics, generics, and has a greater worldwide availability.[15]

Despite recognition of the expected clinical benefit, the application for the adoption of ICIs in NSCLC was unsuccessful due to a lack of mature data confirming the duration of expected benefit at that time.[15] The Expert Committee did not recommend the ICI application stating that 'their place in therapy for this condition is still evolving and more data with longer follow-up are needed to better demonstrate estimates of their actual magnitude of benefit'.[11] The WHO recommended a revision of the application in 2021, which ESMO prepared and submitted.

ESMO also submitted an application request for the recognition of quality-assured biosimilars for trastuzumab and rituximab, which was granted by the WHO due to their potential to increase affordability and availability of these medicines.[11]

In 2021, ESMO proposed the inclusion of the following cancer medicines for the 22nd WHO EML[16]:

1. PD-1/PD-L1 ICIs for the treatment of 'non-oncogene-addicted' locally advanced and metastatic NSCLC (atezolizumab, nivolumab, durvalumab, and pembrolizumab)
2. Osimertinib for first-line treatment of epidermal growth factor receptor (EGFR)-mutated locally advanced or metastatic NSCLC
3. BRAF-mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors for unresectable or metastatic melanoma with a BRAFV600 mutation (dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib)
4. Cyclin-dependent kinase (CDK) 4/6 inhibitors for hormone receptor (HR) positive/human epidermal growth factor receptor 2 (HER2)-negative advanced and metastatic breast cancer (palbociclib, ribociclib, and abemaciclib).

None of the cancer medicines proposed by ESMO in 2021 were included in the 22nd WHO EML.[17] The main considerations of the WHO EML Committee for non-inclusion of these medicines in the EML were that costs, affordability, and feasibility played a significant role against their inclusion. A summary is presented in Table 1.

In particular, the EML Expert Committee noted the following:

- The ICIs are associated with a relevant median OS benefit as first-line treatment (well above the EML threshold of 4-6 months) and have substantially improved outcomes for the treatment of NSCLC, but in practice the greatest benefits are reported in the population of patients whose tumours have high ($\geq$50%) PD-L1 expression.[16] The addition of PD-1/PD-L1 ICIs to conventional chemotherapy was associated with modest increases in toxicity, which may require highly specialised management in selected cases.[16] Thus, despite a favourable benefit/risk ratio, the listing was not recommended because (i) at current prices these medicines for this indication would result in unsustainable expenditures for many patients and health systems, (ii) the need for diagnostic testing to identify patients most likely to benefit is challenging, and (iii) uncertainties about the optimal duration of treatment, the significant disease burden, and the likely large eligible patient population.[16]
- For osimertinib, despite evidence that indicates its meaningful OS benefit compared with the first- and second-generation tyrosine kinase inhibitors (TKIs) currently listed on the EML (erlotinib, gefitinib, and afatinib), the available data are currently immature, limiting confidence in the actual magnitude of benefit.[16] In addition, at the current high price, osimertinib has not been found to be cost-effective and would pose serious affordability challenges, especially in low-resource settings.[16] Additionally, the Committee considered whether osimertinib could be included as a therapeutic alternative under the current listing for erlotinib but decided against this option due to the risk of considerable additional expenditure at the country level when the currently listed TKIs are likely to be more affordable and accessible, with some generics currently available.
- BRAF/MEK inhibitor combinations are associated with important gains in terms of OS, but the magnitude of benefit is not as large as that seen with immunotherapies such as nivolumab and pembrolizumab, which are currently listed and remain the preferred therapy for metastatic melanoma.[16] The Committee also noted that the limited availability of genomic testing to identify patients with tumours carrying the BRAF V600 mutation could be a potential barrier to access and appropriate use in many settings.
- CDK 4/6 inhibitors appear to be associated with a positive benefit/risk ratio, but survival data, while promising, are currently immature - in particular in the first-line it was not confirmed whether the improvements in progression-free survival will translate

Table 1. Summary of cancer medicines submitted by ESMO for inclusion in the 21st and 22nd WHO EML and respective outcomes

Cancer medicine	Indication	Outcome	Reasons for the outcome
21st WHO EML			
PD-1/PD-L1 antibodies (nivolumab, pembrolizumab)	Early and advanced stage melanoma	Recommended—only for the advanced setting	No alternatives available, clinical benefit
Antiemetics (aprepitant)	Moderately and high emetogenic chemotherapies	Recommended	Positive risk-based profile
PD-1/PD-L1 antibodies (atezolizumab, nivolumab, pembrolizumab)	Locally advanced or metastatic NSCLC (non-oncogene addicted)	Not recommended	Waiting for mature data for survival gain
22nd WHO EML			
Osimertinib	First-line EGFR-mutated locally advanced or metastatic NSCLC	Not recommended	• Health expenditure at country level • TKIs enlisted are likely to be more affordable and accessible • Generics currently available (TKIs other than osimertinib)
PD-1/PD-L1 antibodies (atezolizumab, nivolumab, pembrolizumab)	Locally advanced or metastatic NSCLC (non-oncogene addicted)	Not recommended	Unstainable expenditures for many patients and health systems
CDK 4/6 kinase inhibitors (palbociclib, ribociclib and abemaciclib)	HR+/HER2− advanced and metastatic breast cancer	Not recommended	• High prices • Risk to compromise affordability, especially in low-resource settings
BRAF-MEK inhibitors (dabrafenib + trametinib, vemurafenib + cobimetinib and encorafenib + binimetinib)	Unresectable or metastatic melanoma with a BRAF V600 mutation	Not recommended	Genomic testing to identify patients with BRAF V600 mutation tumours could be a potential barrier to access and appropriate use

CDK4/6, cyclin-dependent kinases 4 and 6; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; MEK, mitogen-activated extracellular signal-regulated kinase; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitors; WHO EML, World Health Organization Model List of Essential Medicines.

to an OS benefit in the long term.[16] There is also uncertainty about optimal dose and duration of therapy and use in early-stage disease, and whether relevant clinical differences exist between agents within the pharmacological class. Finally, the Committee noted that at the current high prices, these medicines have not been found to be cost-effective and would pose serious affordability challenges, especially in low-resource settings.

However, for osimertinib and CDK 4/6 inhibitors applications, the Committee has welcomed a resubmission, with updated survival data at its next meeting in 2023.[16]

Following on the WHO Expert Committee recommendations from the 2021 meeting, in 2023 ESMO proposed the lung cancer and breast cancer indications (numbers 1, 2, 4 above) for inclusion in the 23rd WHO EML.[18-21] The applications were based on the previous ESMO applications for the 22nd Essential Medicines List (released in 2021) considering the clinical benefit after updated and revised quality-of-life data, economic analysis, and more mature OS data. These medicines were identified as priority interventions with tangible health benefits in patients with cancer, and therefore prioritised in the ESMO dialogue on cancer control.

WHY DOES ESMO SUBMIT APPLICATIONS FOR CANCER MEDICINES TO BE INCLUDED IN THE WHO EML

ESMO recognises the WHO EML as an important reference guide for medicines that all countries should include in their national EMLs. Cancer medicines on the WHO EML are used in the treatment of most cancers and are recommended in the evidence-based ESMO Clinical Practice Guidelines[22] that medical oncologists use to treat patients.

ESMO is actively engaged in advocating for improved and increased access to, and availability of, quality and high-value cancer medicines, that meet patients' needs for optimal cancer care.[23] The recommendations by the Economist Intelligence Unit (EIU), a report supported by ESMO, urge countries to use the WHO EML as a guide when creating or updating their national essential medicines list.[24] In addition, countries should put in place a process to ensure those medicines are never in short supply.

Weaknesses in access to cancer medicines regard both the shortages of traditional chemotherapy agents and the unaffordability of high-priced medicines. As a result, ESMO supports the continuous update of the WHO EML, as a normative guidance for all countries to set treatment standards and ensure essential cancer care to all patients.

THE IMPORTANCE OF NATIONAL ESSENTIAL MEDICINES LISTS

At the national level, the WHO recommends the use of global standards that can assist countries so that national formularies (national EMLs or NEMLs) reflect the public health value of medicines for their citizens. NEML can assist decision makers in managing their health care system sustainability by helping them identify priority medicines to meet their country's health needs. NEMLs represent a government-approved list of medicines that potentially guide the procurement, supply, and reimbursement of medicines, according to each country's value-chain model.

To make the WHO EML more accessible, the WHO has published an electronic version of the WHO EML (eEML).[25] Most countries have NEMLs, but they may differ from the WHO list. To allow countries to compare their NEMLs to the WHO EML, the WHO supported the development of an online 'Global Essential Medicines Dashboard'.[26] The dashboard consists of an interactive map which shows the number of medicines on a country's NEML and how many of them are also on the WHO EML. The WHO has also published a user guide entitled 'Selection of essential medicines at country level: using the WHO model list of essential medicines to update a national essential medicines list' which outlines actions to guide policymakers responsible for the national medicines and reimbursement lists.[27] This WHO Guide for national decision makers incorporates the use of ESMO-MCBS as part of WHO's guiding principles for inclusion of cancer medicines on the WHO EML. It also stresses that NEMLs are a fundamental tool for achieving Universal Health Coverage.

For modifications to NEML, the WHO recommends consultation with relevant stakeholders in charge of developing national clinical practice guidelines for patient treatment. For medicines that the WHO has never evaluated, national authorities should submit a request for evaluation to the WHO EML Secretariat. The application process is described in the WHO 'Information for Applicants Preparing a Submission for the 2023 Meeting of the WHO Expert Committee on Selection and Use of Essential Medicines'.[12]

A CONCRETE EXAMPLE OF LINKING NATIONAL ESSENTIAL MEDICINES LISTS AND CANCER PROTOCOLS TO PRIORITISE CANCER MEDICINES

ESMO has developed a methodology to empower health systems globally to make efficient spending decisions allowing comprehensive coverage of cancer services for entire populations.[28-30] The generalisable model was originally developed to help the country of Kazakhstan update and rationalise its national list of essential cancer medicines and treatment protocols.[28-30] In a four-phase approach, a comprehensive list of all anticancer medicines used in Kazakhstan was created and cross-checked against the WHO EML, therapeutic indications from the European Medicines Agency (EMA) database and, where available, scores on the ESMO-MCBS were provided, cross-correlated with recommendations from the ESMO Clinical Practice Guidelines, and an expert review was conducted for all cancer medicines not on the WHO Model List of Essential Medicines and the country treatment protocols.[28-30]

The ESMO-MCBS scoring of medicines according to their actual clinical benefit and the ESMO Guidelines' focus on evidence-based practice enabled the prioritisation of high-value treatments to ensure the highest treatment standards and deliver patient-centred positive outcomes. Additionally, this methodology has the advantage of using open-access, evidence-based references such as the WHO EML, which serves as a model for countries to develop their own national lists and to facilitate sustainable, equitable access to medicines and diagnostics tests, and to promote their appropriate use.[28-30]

FUTURE PERSPECTIVES

The principles guiding the decisions for including cancer medicines in the WHO EML list remain fundamental. Due to the rising costs associated with newly available therapies, structured, reproducible, and field-tested tools to evaluate the added clinical benefit from these therapies must be implemented in pre-selecting potential candidate medicines to be included in the WHO EML. The ESMO-MCBS is a robust, validated tool to carry out such an evaluation, and its use has been endorsed and recommended by the WHO EML Expert Committee. However, other considerations, namely public health relevance, health care system capacity, feasibility, field implementation, and economic implications, along with the costs associated with cancer treatment, and not only with cancer therapies, need to be considered. Population health impact can only be sustainably and durably achieved through health investments of high intrinsic clinical value and substantial value for money. NEMLs that include safe, effective, quality, affordable essential cancer medicines that are protected against shortages facilitate optimal care delivery. ESMO is proud to collaborate closely with WHO on this important global public health initiative, joining the efforts to deliver with impact, and framed as part of the collaboration under the SDGs, to reduce cancer mortality by one-third by 2030 and ensure universal health care to all in need.[29]

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