

WHO EML Cancer Medicines Working Group (CMWG)

Report of the meeting 22 – 23 March 2018

Geneva, Switzerland

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Acronyms and abbreviations

AB	Absolute benefit
ASCO	American Society of Clinical Oncology
ASCO-VF	ASCO Value Framework
EMA	European Medicines Agency
EML	Essential Medicines List
EMLc	Essential Medicines List for Children
EMP	Essential Medicines and Health Products (WHO Department)
ESMO	European Society for Medical Oncology
ESMO-MCBS	ESMO Magnitude of Clinical Benefit Scale
FDA	U.S. Food and Drug Administration
HR	Hazard ratio
IAU	Innovation, Access and Use (WHO Unit)
LMIC	Low- and middle-income countries
MND	Management of Noncommunicable Diseases (WHO Unit)
NVI	Noncommunicable Diseases, Disability, Violence and Injury Prevention (WHO Department)
OS	Overall survival
PFS	Progression-free survival
RB	Relative benefit
RCT	Randomized controlled trial
WHO	World Health Organization

Executive Summary

At the Seventieth World Health Assembly in 2017, World Health Organization (WHO) Member States adopted resolution WHA70.12, Cancer prevention and control in the context of an integrated approach, and WHO was requested to prepare a technical report on pricing approaches for cancer medicines for presentation to the Executive Board. A cancer medicines working group (CMWG) was convened by WHO in March 2018 at the recommendation of the WHO Expert Committee on the Selection and Use of Essential Medicines. The CMWG aims to obtain relevant input from experts to guide the selection of optimal cancer medicines under consideration for inclusion in the Essential Medicines List (EML).

- There was agreement on the usefulness and relevance of current magnitude of benefit scales for cancer medicines (ASCO-VF and ESMO-MCBS): these two scales have promoted the involvement of the oncology community (clinicians, researchers) and cancer patients in discussing the value of new cancer medicines and have fostered better understanding of what it is meant by relevant clinical benefit.
- The discussion on what is a clinically relevant magnitude of benefit was examined comparing ASCO-VF and ESMO-MCBS scales. Data from recent cancer trials were used to evaluate medicines recently approved by FDA and EMA using both scales: only a minority of newly approved medicines provide data on survival and quality of life. Indeed clinically relevant data are often lacking at the registration phase.
- It was noted that for the vast majority (i.e. 75%) of cancer medicines approved over the last 15-20 years, there has been a lack of definitive evidence of substantial clinical benefit for patients at registration.
- The magnitude of benefit of treatment for OS and PFS might differ between one cancer and another (e.g. benefits that are relevant for chronic leukaemia might differ from benefits that are relevant for lung cancer). However, the CMWG agreed that an interval of overall survival benefits could be identified for consideration for inclusion of EML.
- The CMWG recommended WHO endorse the need to have overall survival as the main eligibility criterion of a medicine proposed for EML listing. Further the CMWG recommended endorsement of an interval for overall survival of at least 4-6 months for first-line treatments as a general guiding principle.
- Among the considerations that supported the 4-6 months overall survival interval were:
 - a strong clinical and ethical conviction that for OS less than 3 months, the benefits seem weak, marginal or not relevant (depending on cancer types);
 - a 3-month survival threshold has been endorsed by both ASCO and ESMO scales, with different implications in their respective scales;
 - clinical trials estimates tend to overestimate the benefits because of patient selection, risk of bias and spurious findings. Patients included in clinical trials often differ from those seen in real life settings: benefits in patients seen in everyday practice might be less convincing as compared to those selected in trials. Trials often have important methodological limitations, leading to biased estimates of intervention effectiveness. Single studies are often exposed to type I error. Finally interventions studied in trials might not be directly transferable in LMICs as capacity of centers to deliver essential medicines and manage related toxicity might be diminished.
- In addition to the advantages of considering medicines for inclusion on EML endorsing a reference interval for clinical benefit will support countries in their local selection of cancer medicines most likely to have high impact without investing resources on treatments that provide little benefits.

- The CMWG recommended using the 4-6 month overall survival interval as a criterion for screening promising medicines proposed for EML listing. Medicines that have limited or no data on survival and are associated with highly relevant PFD/DFS advantages could also be considered by the Expert Committee when these large benefits are validated and consistent across studies.
- The CMWG preferred the ESMO-MCBS to the ACSO-VF. The ESMO-MCBS allows for threshold values in relative and absolute gains. This is consistent with Expert Committee processes, where consideration is given to both relative and absolute effects by the Expert Committee in their evaluation of other medicines for inclusion on the EML
- The CMWG recommended using the ESMO-MCBS as a screening tool to identify candidate medicines that might be potentially suitable for inclusion in EML. Since January 2016 ESMO - a non-governmental organization in official relations with WHO – has been evaluating all newly approved cancer medicines. This exercise was extended to some important previously approved medicines (e.g., trastuzumab). ESMO, in collaboration with the European Haematological Society, will expand the ESMO-MCBS to cover also haematological malignancies and treatments. Medicines that are top ranked by ESMO are strong candidates for evaluation by the EML Expert Committee. This means that WHO can focus its efforts on coordinating applications for top ESMO-MCBS scoring medicines, supporting tough decisions that countries are facing in terms of reimbursement. Applications for medicines that are not top-scoring would be still acceptable.
- The CMWG recommended that medicines that receive an ESMO score equal to 4, 5 or A-B could be eligible to become EML candidates if clinical benefits meet or exceed the 4-6 month survival interval. Among top-scoring medicines using the ESMO-MCBS there might be medicines that have still an uncertain risk to benefit profile since toxicity and therapy discontinuation are not fully considered by this scale. Candidates should always go through a standard application process and be fully examined by the EML Expert Committee.
- The CMWG emphasized the need to comprehensively evaluate all evidence, cumulating results across clinical trials and evaluating their consistency, to identify potential limitations of validity and generalizability at global level. The CMWG also advised to always give full consideration to toxicity data, treatment discontinuation, patient attrition, and selection of settings and patients included in clinical trials as compared to low and middle income settings and real-life populations.
- Ongoing work of the CMWG should involve the development of resource documents to inform and provide guidance to countries in the selection of cancer medicines at national level:
 1. A summary document of the current situations and trends in cancer medicine regulatory approvals with the recommendations of the CMWG on how to screen and select candidates for the WHO EML.
 2. A commissioned report showing the data on magnitude of benefit of all medicines registered in the last 15-20 years. The report will discuss the implications of using different scales to assess magnitude of benefit, the role of the WHO thresholds, and issues in evaluation clinical benefits. Finally the report will give consideration to me-too drugs and biosimilars as important areas to expand access of cancer medicines to patients.
 3. A commissioned report outlining the historical trajectory of clinical trials in oncology (where they were first implemented 40 years ago) and how progressively the trial designs has been modified to better demonstrate small benefits in larger trials, satisfying the interests of commercial sponsors and regulatory agencies. Some additional considerations will be made on the importance of having public funded trials to support public health questions and fill important knowledge gaps.

I. Background

At the Seventieth World Health Assembly in 2017, Member States adopted resolution WHA70.12, Cancer prevention and control in the context of an integrated approach. As part of this resolution, the Director-General was requested “to prepare a comprehensive technical report to the Executive Board at its 144th session that examines pricing approaches, including transparency, and their impact on availability and affordability of medicines for the prevention and treatment of cancer, including any evidence of the benefits or unintended negative consequences, as well as incentives for investment in research and development on cancer and innovation of these measures, as well as the relationship between inputs throughout the value chain and price setting, financing gaps for research and development on cancer, and options that might enhance the affordability and accessibility of these medicines”.

At the 2017 meeting of the WHO Expert Committee on Selection and Use of Essential Medicines, the potential to identify thresholds of benefits for cancer medicines was discussed. The Expert Committee recommended the establishment of the Cancer Medicines Working Group (CMWG) to review selected cancer medicines for the Essential Medicines List (EML - incorporating the Essential Medicines List for Children (EMLc)). The aim was to establish clear principles that can guide the selection of optimal medicines to be considered for EML inclusion and review the available tools and thresholds for clinical and public health relevance of a medicine.

The mandate of this working group is to focus on the benefits and benefit-risk balance associated with new cancer treatments, and to discuss the magnitude of benefit issues, including the values of new treatments. It is important to be mindful of the risk of “selling hope” to patients, given the marginal benefits of some recently approved new medicines and also the consequences of the expenditure for patients and health systems.

The objectives of the CMWG meeting were to discuss:

- the magnitude of benefit of new cancer medicines approved in the last 15-20 years;
- recent trends in benefits of medicines approved by regulatory agencies;
- recent trends in how trials evaluating cancer medicines are designed;
- how to discriminate between medicines of marginal value and treatments that offer high value in terms of magnitude of clinical benefit and public health value, addressing both the curative and non-curative treatment settings.

A separate informal advisory group was convened on the availability and affordability of cancer medicines on 4-6 April 2018. The aim of that meeting was to provide expert advice on the scope of the technical report referenced above, the benefits and consequences of various pricing approaches for cancer medicines, and options for improving availability and affordability of cancer medicines. A summary of that meeting is published as a companion to this report.

II. Summary of presentations

The main points raised in presentations made by CMWG participants are summarized below.

1. Essential medicines for cancer on the EML and EMLc

The WHO EML lists the most efficacious, safe and cost-effective medicines for priority conditions. In 2013, the antineoplastic sections of the EML and EMLc contained 30 and 16 medicines, respectively—all off-patent—but did not contain information regarding specific indications for optimal use.

In 2015, there was a full review of cancer medicines on the EML and EMLc. A disease-based approach was taken to analyse the benefits and risks of the medicines. Twenty-seven adult and paediatric diseases were identified where systemic therapies had major benefit, and/or the burden of disease was very high. Sixteen new medicines were added to the previous list of 30 for adults, and 10 were added to the previous list of 16 for children. Six medicines among those proposed in the applications were rejected.

The 2017 EML specifies each medicine's indication, with details on regimens, demonstrated benefit, toxicities, and other information for each indication. Rituximab for lymphoma, trastuzumab for HER2-positive breast cancer, and imatinib, all-trans retinoic acid (ATRA), and bendamustine for various leukaemias were added because of their dramatic contribution to improvements in survival, despite their high cost. The availability of less costly (but less effective) alternatives is controversial, since the choice between different cancer medicines might affect millions of people. Some policy makers and advocates argue that it could be preferable to provide a larger number of people with cheaper treatments that are less effective (or more toxic), than restricting cancer treatments to a smaller number and providing more expensive but more effective or less toxic alternatives. WHO has to date advocated for equitable access to an agreed standard of care across countries.

The medicines rejected by the Expert Committee fell into several categories. In 2015 (and again in 2017) gefitinib and erlotinib were rejected for non-small cell lung cancer because it was considered that many countries would not have the capacity to conduct molecular testing needed to determine which patients might benefit. In 2017, EML listings of enzalutamide and trastuzumab emtansine (TDM-1) were not recommended because of the need to perform a more comprehensive review and evaluation of other available options, while receiving more feedback from countries on health system needs and capacity.

2. Limitations of pivotal registration studies for cancer medicines

While numerous attributes are used to describe efficacy of a cancer medicine, cure or prolongation of life is the most important outcome. To that end, the availability of overall survival (OS) data from efficacy trials with and without active comparators will be considered most valid in selecting medicines that would be potential candidates for listing on the EML. The use of surrogate outcomes, especially progression-free survival (PFS) in diseases where its value as a surrogate is often not established, should be considered inadequate for the purpose of potential listing on the EML unless the magnitude of the PFS is particularly large in comparison with previous treatments.

The actual conduct of randomised trials in cancer includes the problem of censoring and early ascertainment of efficacy and the impact of toxicity will be important. The latter takes on added importance in low and low to middle income countries where the burden and difficulties of managing treatment complications can be especially onerous making toxicity a very important outcome.

Several studies were presented, covering medicines approved by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA), and different time periods (up to January 1995). While the number of cancer medicines approved every year is increasing, all studies are concordant in showing that most cancer medicines that have arrived on the market have come with little evidence that they improve the survival or wellbeing of patients. For instance, 48 cancer medicines were approved by the EMA between 2009 and 2013 for use as treatments in 68 different indications. At the time the therapies

became available there was no conclusive evidence that they improved overall survival in almost two-thirds of the situations for which they were approved. In only 10% of the indications medicines did improve quality of life. Overall, for 57% of approved indications, evidence from pivotal registration trials showed no benefits for either overall survival or quality of life.

The Working Group agreed that some of the data presented should be further updated and include a 20-year perspective of main regulatory agencies (FDA and EMA) approvals.

3. Regulatory approval and benefit scales for cancer medicines

In the last two decades the design of experimental trials evaluating new cancer treatments have evolved. These trials have become larger to detect small differences between the new agent and the comparator and to increase the statistical power. This is a consequence of preferring surrogate outcomes to final outcomes, and selecting minimally important differences of uncertain clinical value as primary outcomes. This evolving scenario is largely due the preference given to rapid approval of new medicines based on pharmacological activity as opposed to rigorous evaluation of patient outcomes, which would require longer time. The clinical oncology community recently started a discussion on what would be relevant differences in clinical trials, and have been critical of results that meet the threshold for statistical significance but possibly do not meet criteria for clinical relevance. Often pivotal trial endpoints are likely to not be patient-centered.

With the approval of dozens of new cancer medicines with different potential clinical impact, the oncology community has started to develop scales to measure value, with consideration given to clinical benefits and adverse events, and the cost of therapy. The scales of the European Society for Medical Oncology (ESMO) and of the American Society of Clinical Oncology (ASCO) were used to measure the clinical benefits of recently approved cancer medicines for common cancers. The analysis revealed that less than a half of the randomized controlled trials (RCTs) met the criteria for clinical benefit on the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS). Pivotal trials with significant results favouring the experimental group had less consistent scores with ASCO-VF. Moreover, treatments that met the ESMO threshold for benefit had a lower median incremental monthly cost than those that did not.

These new magnitude of benefits scales are important tools in guiding the selection of medicines that provide the best results in terms of clinical benefits. They offer a rational, structured, and consistent approach to stratify benefits associated with cancer medicines in an ordinal framework, with medicines reaching clinically meaningful results classified at the top, and medicines achieving only partial, marginal or no benefit classified at the bottom. In other words, these tools are useful in disentangling statistical significance from clinical relevance. The large majority of cancer trials invariably provide positive findings (i.e. they demonstrate statistically significant differences on pre-specified primary or secondary outcomes in favor the experimental medicines versus standard treatments options). A minority offers clinical benefits and this minority is captured by value frameworks.

4. Research and development, regulatory approval and market entry of ‘me-too’ cancer medicines, generics and biosimilars

Development by several pharmaceutical companies and their approval by regulatory agencies of therapeutics that are often nearly identical is becoming more common. While subtle differences are often claimed as important attributes, for the purposes of the EML, slight variations amongst very similar therapeutics will not render one more important than the next. In theory approval of “me too” medicines might seem to be an advantage insofar as it might introduce price competition for similar benefits, but this has not been demonstrated.

Even at heavily discounted prices, “me-too” medicines cost more than generic medicines. Small differences between me-too and originator medicines are likely to not have clinical relevance, making the selection decisions by doctors and patients overly complex. The real stimulus for price competition is the approval and availability in the market of the first inexpensive generic (or biosimilar) medicine in a class.

However generics and biosimilars are often delayed in their access to market. Lack of competition among cancer agents is a recurring system obstacle. Biosimilars of a therapeutic can be easily included in the EML providing individual countries greater leverage in the procurement of their essential medicines.

Despite claims that research and development activities carried out by pharmaceutical companies are very expensive, and largely lead to failures, there is increasing evidence that these claims are exaggerated. Over the years several pharmaceutical companies have increasingly acquired new medicines by buying smaller biotech firms with promising compounds in their laboratories and pipelines. Prices of new medicines clearly do not reflect the actual cost of research and development. In fact, even where a company has invented and developed the medicine from scratch, there are several factors that used to justify high prices, i.e. the cost of developing all medicines, including those that have been through trials and failed.

The CMWG discussed that maybe one important element limiting access and affordability of essential medicines concerns the granting of exclusive rights to make, use and distribute medicines, excluding generics from the market. Restrictive interpretations of international trade agreements continue to limit the availability of some medicines in developed and developing countries, even when these medicines would respond to primary public health needs. The exclusive rights regime can be very expensive, and inefficient relative to the paucity of the research and development investments that it induces. There are strong economic incentives to invest in similar products within a therapeutic class as these are perceived to be lower risk investments. Pivotal trials are undertaken to meet regulatory requirements rather than inform clinical practice. The proprietary nature of rebate information makes estimating the savings from within-class competition a matter of speculation, especially if generic medicines already exist in the class. Against this background, new policies that de-link research and development costs from product prices could present a solution to expand access to new products.

5. LMIC perspectives

In low- and middle-income countries (LMICs), cancer patients are often diagnosed in later stages of disease, when therapies have less chance of significant benefits, including remission. In these settings, expensive cancer treatments might easily take a large percentage (well above 50%) of the entire budget for medicines. Several countries have limited access to monoclonal antibodies, protein kinase inhibitors or hormone therapies on their national EMLs. This might be changing with the recent introduction of generic and biosimilars, as these medicines are becoming more affordable. However use in late disease stage limits their effectiveness.

Carefully conducted comparative studies in the relevant setting should be required before new cancer medicines are adopted in LMICs, including the added clinical value and their cost-effectiveness.

Population-based studies are of limited value in establishing the comparative magnitude of benefits of new medicines but might represent an important source of information to evaluate the transferability of cancer interventions tested in high income settings to LMIC centers, where supportive care capabilities and resources lag behind those in HICs. For instance in LMICs for some childhood cancers and leukaemias, clinicians might prefer different treatment intensities to avoid overtreatment and treatment-related mortality. Maximum cure rates with less intense schedules might differ from those seen in pivotal trials; it is important to monitor the effectiveness of cancer treatments balancing benefits in disease control by intensifying treatment and increases in treatment related mortality. Transferring treatment protocols designed for HIC levels of supportive care to LMIC centers requires determining which protocol modifications are best suited to a particular LMIC setting, and to monitor patient outcomes to establish the best balance between relapses and treatment related deaths. Outcome monitoring will allow for the gradual evolution of treatment strategies potentially maximising cure rates. Another important function of collection of basic data on patient demographics, disease characteristics, and treatment outcomes, including cause of death, is to monitor the capacity of countries for screening and early diagnosis of cancer patients, as this is essential as providing access to medicines (and other health care services such as surgery and radiotherapy) that might prolong survival or be curative.

Standard chemotherapy agents may be available in most hospitals and reimbursed through health insurance schemes. New therapies (e.g. protein kinase inhibitors) are not equally available, as they pose serious issues in terms of affordability and impact on budget.

The frequency of mutations targeted by new therapies might differ across demographic/clinical subgroups. For instance, in lung adenocarcinoma there is higher mutation frequency in Asian populations compared with Caucasian populations, suggesting that mutation testing could be considered for all patients. Benefits of these medicines might also be more relevant where mutations are more frequent.

Medicines are just one component of care. Treatment of cancer is a multifactorial issue and requires an extensive network of screening, diagnosis, monitoring and different treatment strategies (e.g. surgery, radiotherapy) alongside medicines. There is no evidence to suggest that new medicines (e.g. monoclonal antibodies, protein kinase inhibitors) are associated with benefits when used in LMICs, and they are more resource intensive. Reproducibility of relevant patient outcomes in LMICs is important. Acquiring new therapies without paying adequate attention to their requirements, might not utilize resources in the most efficient manner.

6. Magnitude of benefit of cancer medicines: opportunities

The ESMO Magnitude of Clinical Benefit Scale (ESMO–MCBS) has been introduced with the aim of quantifying the benefits physicians and patients can expect to derive from treatment. The ESMO–MCBS focuses on the magnitude of benefit provided by a treatment while the ASCO–Value Framework (ASCO–VF) also takes the cost of a treatment into consideration. These tools are becoming central in evaluating new agents (or new indications) as these agents are increasingly approved on the basis of evidence from phase II trials, which typically have cohorts of fewer than 100 patients, and for additional indications are often non-comparative designs, or large trials showing benefits on outcomes that are not fully relevant.

The ESMO-MCBS is guided by a dual rule comparing the relative benefit (RB) and the absolute benefit (AB) achieved by the therapy to pre-specified threshold values. Despite ESMO-MCBS and ASCO-VF correlating fairly well (particularly for hard outcomes), ASCO-VF is more prone to score high (favouring) experimental treatments as this system privileges relative risks. In fact ASCO-VF relies heavily on the Hazard Ratio (HR), a unitless value that could be difficult to interpret if time of observation, control rate and censoring are not considered. Thus, it is possible that a large hazard ratio is accompanied by a small absolute gain in survival.

ESMO-MCBS is more selective discriminating those trials that have demonstrated clinically relevant benefits from those that detected initial benefits on surrogate outcomes, which might lead to little or no additional benefits. The ESMO-MCBS scale is to be applied to individual studies and could thus result in different scores for different indications/studies.

ESMO-MCBB is being applied to all new cancer medicines approved by EMA since January 2016. Trastuzumab and imatinib, recently selected as essential medicines, were both scored highly with the ESMO-MCBS. Other cancer drugs such as bevacizumab were also scored using ESMO-MCBS.

The Working Group noted the intention for the ESMO-MCBS to be expanded to apply to medicines for haematological cancers in the forthcoming months (through collaboration with EHS).

7. Methodological issues in magnitude of benefit assessment

Applying a magnitude of benefit assessment, for example the ESMO-MCBS, in health technology assessment at country level would support the choice of medicines that provide meaningful clinical benefits (e.g. prolonged overall survival) over medicines that do not provide similar advantages.

Retrospective assessments using ESMO-MCBS led to 20% of all newly approved cancer medicines (n=70) being categorized in the group associated with meaningful clinical benefits. An adapted version of the same scale, in which point estimates were used in preference to the lower limit of the confidence interval,

and with downgrading for serious adverse events, further decreased the percentage of medicines associated with meaningful clinical benefits to 10%.

8. An ethical perspective

Cancer medicines should be considered not only within the context of clinical trials but also within the context of clinical practice settings. The facilities and resources available for the care of cancer patients vary among centers. However it is key to identify some characteristics that define the capacity of centers to deliver specific essential medicines. Even basic settings should aim at having the minimal requirements for treating patients with curative intent. More advanced settings should have increased access to diagnostic and supportive care facilities, using all essential cancer medicines, and should be associated with higher cure rates. The professional standard includes interventions that may not be the very best when compared to available alternatives, but are nonetheless professionally recognised as a reasonable option (for example, as evidenced in treatment guidelines). It is important to consider if and how oncologists value cancer medicines outside the research context: as medicine focuses on surrogate outcomes and patients without comorbidities, the applicability of the data produced by RCTs to the clinical context will come under intensified and longer scrutiny.

Understanding if RCTs address issues of genuine significance to medical doctors enables evaluation of RCTs more critically and effectively. There should be a stronger involvement from patient representatives and civil society groups in the evaluation of new cancer medicines, as has been seen for HIV.

It has been asserted that contributing to sustainable improvements in health by progressively increasing the standard of care, including access to medicines, is an ethical obligation of health care systems. Post-trial access to medicines or treatments is an important dimension, and costs associated with this should be considered. An evaluation of risks, benefits and costs at both individual and societal levels, is also important in determining the ethical value of treatment.

III. Summary of CMWG Discussions

The CMWG considered that overall survival is a metric with several advantages including:

- Objective and easily measurable
- Protects against performance and detection bias
- Encompasses both benefits and harms
- Important to patients and public health systems
- Can be easily communicated

There was substantial agreement among the CMWG on the low contribution that progression-free survival makes in discriminating between high and low impact medicines. However, it was noted that most RCTs exploring the efficacy/effectiveness of new medicines, even at the longest follow up, report OS findings in the order of weeks. These improvements, despite being statistically significant, are not relevant particularly in settings in which resources are scarce. The most common tool used by countries to screen cancer medicines for clinical and economic value, for reimbursement or access, are HTA reports. However these reports require access to the necessary skills and require time to be completed, and often come to conclusions of uncertain value as evidence is incomplete or immature. Furthermore the transferability of results of trials done in tertiary care settings in developed countries is uncertain, and estimates of toxicity and treatment discontinuation given the highly selected populations included in clinical trials can also be biased in comparison to real-life populations.

Acknowledging that identifying a fixed threshold for OS benefit is difficult as its relevance is highly subjective, the CMWG considered that a conservative threshold - quantified as 4-6 months - for OS could provide a clear and easily communicable message to decision makers about medicines that provide relevant survival gains. The Working Group noted that all new cancer medicines listed in the EML since 2015 have met this criterion: trastuzumab, rituximab, imatinib, dasatinib, nilotinib, and ATRA.

A clear cut-off for benefit could be used to discriminate potential candidates for the EML. The CMWG agreed that medicines that might be considered as future candidates for the EML using this criterion alone are:

- Bortezomib, lenalidomide and thalidomide for multiple myeloma (MM);
- arsenic trioxide (ATO) for acute promyelocytic leukaemia (for use in combination with all-trans retinoic acid (ATRA));
- cladribine for hairy cell leukaemia.

For solid cancers, enzalutamide and abiraterone for prostate cancer, and trastuzumab emtansine (TDM-1) for breast cancer demonstrate benefits large enough to be suitable for full evaluation by the Expert Committee through a comprehensive approach evaluating all available options. However it was noted that the Expert Committee is required to evaluate not only potential benefits but also other dimensions (feasibility, costs, etc.).

There was strong agreement from the Working Group to recommend that WHO use a structured and systematic approach that can discriminate between cancer medicines of higher and lower impact.

The ESMO-MCBS and ASCO-VF scales were both considered suitable by the CMWG for assisting in the efficient and appropriate selection and use of those medicines that provide effective care to cancer patients. The intent of the two frameworks differ. The ESMO-MCBS was developed to frame the appropriate use of limited public and personal resources to deliver cost-effective and affordable cancer care. ASCO-VF was designed to assist shared decision-making with patients about clinical benefits and costs of different treatment options. The ESMO-MCBS allows for threshold values in relative and absolute gains, as well as the difference in absolute gain in OS/PFS in comparison to the control arm. The ASCO-VF scores the experimental regimen compared to the control arm, but there are no threshold values, and the ASCO-VF is not intended to be used to compare therapies across trials and types of cancer.

Between the two scales, the CMWG considered the ESMO-MCBS to be preferable, as its use better aligns to EML selection. Thus, while for each cancer there may be several marginally effective treatment options, prioritizing just a few is recommended. Use of the ESMO-MCBS can assist the prioritization and selection process. Such an approach is consistent with the selective nature of the EML, the objective being to provide prescribers and policy makers with a limited number of agents that could be considered optimal choices across cancer as they are associated with highly relevant benefits.

ESMO-MCBS could be adopted as a screening tool to identify treatments that have little or no value (being classified with a rate of 1, 2 or 3 or C). These medicines should not be prioritized as candidates to the EML. 60 to 70% of recently approved medicines are classified in these low/no value categories, meaning that following the ESMO-MCBS scale they do not provide any substantial benefit (i.e. marginal or nil benefits), based on actual trial data.

A score of 4 or 5 on the ESMO-MCBS would support a medicine being evaluated for inclusion in the EML by the Expert Committee, especially when associated with large benefits (over 4-6 months OS, depending on the cancer). Medicines associated with moderate benefits (below 4 months) might receive a positive evaluation and be highlighted as potential choices for countries, but may not be included on the EML. In other words these medicines have some value as they provide some benefits without reaching the thresholds for being considered essential medicines. Thus they might be excluded from the EML, but their benefits would be recognised. However, it is important to note that the Expert Committee does not make its recommendations on the basis of benefit and harm alone, and that other criteria must be taken into account.

The CMWG discussed two other situations. In cancers that are common in LMICs (e.g. renal cancer) and for which there are no highly effective treatments, alternatives with moderate benefits can be considered by countries, when prices are affordable. An example is the potential use of sorafenib in kidney and liver cancers, diseases that are more prevalent in LMICs: generics are often available at reasonable prices, making these medicines a sustainable option. However the EML should be kept selective and medicines that do not meet the proposed survival threshold (over 4-6 months depending on cancer) should not be considered for inclusion unless they are associated with other clear and relevant advantages. Medicines that are supported by early (immature) data on surrogate outcomes (e.g. PFS) may be considered. However attention should be paid to the validity of PFS as a surrogate end point in various disease settings. The question of whether PFS can be considered an acceptable surrogate end point should be evaluated considering formal validation studies, standardized definition and unbiased ascertainment of disease progression in clinical trials. In several cancers (e.g. advanced breast cancer), formal validation of PFS as a surrogate for OS has so far been unsuccessful.

Annex: List of participants

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