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Dear Dr. Simão,

We would like to thank the WHO Secretariat for sharing the Cancer Medicines Working Group (CMWG) [meeting report](#) and the [technical report](#) on temporal trends in clinical trials and the benefit of new cancer therapies. We recognize the efforts of the CMWG to bring greater transparency around the criteria for inclusion of oncology medicines in the Essential Medicines List (EML), however we are concerned with several of the core pillars outlined in these reports. Therefore, we would like to take this opportunity to address some of these concerns in the points outlined below.

1. Having overall survival (OS) benefit of 4-6 months as the main criterion for inclusion on the EML will potentially leave out many therapies with great clinical value.

The strategy of listing medicines based on the magnitude of their OS benefit in clinical trials should be put into context. Many treatments offer clinical benefits beyond OS, detectable and measurable on the level of novel clinical endpoints (reflecting the specificities of innovative treatments), including, very importantly, patient reported quality of life¹. Nonetheless, as explained below in point 2, many of these results will in fact be translated into real clinical benefit when used in a clinical setting and given the necessary time to generate data.

At the same time, it is important to note that OS can be confounded by crossover therapies and influenced by clinical context, while other endpoints, such as Progression-Free Survival (PFS), are not subject to this same potential bias. There are advantages and disadvantages to all endpoints, so when assessing “the benefit” of a therapy, one should have this in mind.

Specifically, assigning a threshold for magnitude of benefit may seem arbitrary when many trials vary by tumor, line of therapy and overall disease severity. In addition, it is unclear how these criteria will take

¹ Nishijima TF, Shachar SS, Muss HB, Tamura K, The Oncologist, [Patient-Reported Outcomes with PD-1/PD-L1 Inhibitors for Advanced Cancer: A Meta-Analysis](#), 2018



into account the clinical benefit of combination products/immunotherapies as currently the EML has a single product listing approach.

2. The decision to use other endpoints in addition to/instead of OS in clinical trials is based on sound scientific evidence and is, ultimately, of great benefit to patients.

Several endpoints, including PFS, can serve different purposes for example a clinical endpoint that represents clinical benefit for traditional regulatory approval or a surrogate endpoint to support traditional or accelerated regulatory approval. However, this assessment is based on context of use such as specific disease and is dependent on effect size/duration, available therapy, disease setting, location of disease and other specific factors. Weighting in these factors may determine that using surrogate endpoints, such as PFS and others, is not only acceptable, but the most ethical approach in a given setting.

As the technical report notes, there are indeed more and more medicines being approved in accelerated or conditional settings, with PFS and OS endpoints that can be perceived as “incremental” at time of approval. This is not a company-driven phenomenon: it’s driven by patient demand to get faster access to promising innovative therapies. This involves some ‘risk taking’, not on the safety-side, but on the side of clinical benefit inferred from early clinical signals. National regulatory authorities understand the risk of early approvals, but also the ethical implications of delaying access. This is why mechanisms have been put in place that allow applicants to follow up with efficacy data²: after approval, manufacturers are required to conduct studies in the post-marketing setting to verify and describe the actual clinical benefit.

In most cases, incremental improvements in OS or surrogate endpoints within a study are additive across lines of therapy, or lead to a meaningful extension of OS in real clinical settings. As an example, pathological complete response (pCR) has been shown to be a predictor of OS in the neoadjuvant setting, allowing for potential evaluation of novel therapies in a much shorter time frame in a high unmet need population³.

3. The EML should not be used as a tool to diminish the value of any medicine currently approved and deemed safe and effective by national regulatory authorities.

We note with concern that these two reports appear to question the strength and impartiality of national regulatory authorities by questioning the methods and standards set for the approval of medicines – this

² U.S. FDA, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics - Guidance for Industry, 2018 <https://www.fda.gov/downloads/drugsGuidanceComplianceRegulatoryInformation/Guidance/UCM071590.pdf>

³ Rastogi et al. “Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27”, Journal of Clinical Oncology, Volume 26, Number 5, 2008 <http://ascopubs.org/doi/10.1200/JCO.2007.15.0235>



may generate concern among members of the public and patients about the overall efficacy of their medicines in general, potentially creating mistrust in health systems.

It is also important to note that when assessing the “benefit of new cancer treatments”, the technical report does not consider the information used as the basis for regulatory approval of these medicines. In fact, the technical report routinely conflates benefits of cancer medicines presented within the peer-reviewed literature as being that that decides regulatory approval of medicines. A more impartial analysis would be to use the publicly available assessment reports which are the output of the full national regulatory authority review (e.g. the European Public Assessment Report and the US FDA’s Summary Basis of Decision), rather than focusing only on summarized information in publications.

The reasons for the omissions noted above seems to be because the technical report relies heavily on data that is at a minimum of ten years old to data that is more than 40 years old. In one specific instance, the technical report references a patient study that is 20 years old⁴. This is of significant concern given that the conclusions comment on the benefit of “new cancer therapies” but does not include recent information about clinical trials.

4. Industry-sponsored clinical trials are designed and conducted to the highest standards of Good Clinical Practice, and routinely deliver innovative, valuable and safe medicines to patients.

All industry-sponsored studies are conducted to very rigorous standards and comply with international standards for Good Clinical Practice. National regulatory authorities review full and comprehensive clinical study reports containing much more data than what is available in the public domain before approving the realization of these trials. These clinical studies also undergo multiple reviews by independent ethics committees to ensure that the design and conduct of the study meets ethical considerations for patients.

5. The ESMO-MCBS Scale is a clinical decision-making tool, not designed as guidance for societal investment decisions.

Using a scale that measures clinical value to support selection of oncology medicines will help increase transparency and consistency. However, this scale was designed as a tool for helping individual clinicians and patients make decisions, and it does not reflect all potential benefits that a medicine can offer to patients, institutions and society. If misapplied, the scale may create barriers to some of the most innovative advances in cancer treatment, as well as potentially restricting access to innovative treatments by limiting the choice for the oncologist to select the best treatment for the individual patient in a

⁴ See sentence “in a study of patients with advanced lung cancer who had completed chemotherapy, the median survival threshold for accepting chemotherapy was 5-9 months.” Reference: Silvestri, et al., Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. *BMJ* 1998; 317.771-5.



national context. It is unclear what other criteria will be considered when potential medicines for selection fall out of the scope of ESMO-MCBS and how the final decision will be made. Many of these value assessments do not account for patient reported outcomes and surrogate endpoints (such as PFS or event-free survival), nor for other components of the health condition or the intervention, such as total expected costs of care resulting from diagnostic, primary care, hospitalization, specialist visit to the most appropriate site, etc.

As explained previously in point 1, using the median for OS or PFS does not reflect the full potential of a medicine (vs using Hazard Ratio or mean values or rates) and can be especially misleading for cancer immunotherapy ("tail of the curve").⁵ Our understanding is that the ESMO-MCBS is working on this issue currently to better reflect the value of cancer immunotherapy in the value scale.

6. Regulatory processes will rely more and more on the use of Real Word Evidence (RWE), which is beneficial to patients.

The rise of digital technologies and the ability to gather and store considerable amounts of health-related data has been rapidly accelerating. These data hold potential to allow better design and conduct of clinical trials and potentially enable studies in the health care setting aimed at answering questions previously thought infeasible. National regulatory authorities are in the process of evaluating how to leverage RWE on product effectiveness to help support regulatory processes, such as the approval of new indications.

For already approved medicines, there is an opportunity for RWE to demonstrate OS and applicability to a more heterogeneous population than that evaluated in the registration study of a given medicine⁶. Health systems data collected in registries or electronic patient records could be used as historical comparison to better determine clinical benefit/meaningfulness of a new therapy in a specific disease population. As advances in precision oncology make it possible to target small patient populations, such as patients with rare molecular alterations in the tumor, it becomes increasingly important to supplement small datasets from clinical trials with reliable regulatory-grade RWE.

7. Selection of CMWG Experts

We would like to have a better understanding on the criteria of and the process for the selection of experts that participate in informal advisory groups such as the CMWG. For instance, we see no representation from national regulatory authorities, which raises a concern when criterion for selection of oncology treatments is being discussed. For innovative medicines in particular, data submitted to

⁵ Peter J et al. "Which Metrics Are Appropriate to Describe the Value of New Cancer Therapies?," BioMed Research International, vol. 2015, Article ID 865101, 9 pages, 2015. <https://doi.org/10.1155/2015/865101>.

⁶Friends of Cancer Research, Establishing a Framework to Evaluate Real-World Endpoints, 2018 https://www.focr.org/sites/default/files/pdf/RWE_FINAL%207.6.18.pdf



national regulatory authorities for granting marketing authorization is often the most detailed source of information regarding these products' safety and efficacy.

We suggest a broader membership involving all relevant stakeholders with appropriate expertise. National Regulatory Authorities, industry and non-state actors in official relations with WHO should be included formally on the working group or as advisors during the development of guidance/positions in addition to engagement at the public comment phase.

In closing, we appreciate the time and consideration of the WHO Secretariat in reviewing our comments and look forward to hearing your response. Moving forward, we welcome future inclusive dialogue on this topic and recognize that each EML update and its related commentary represents an opportunity to encourage constructive dialogue among all health stakeholders on essential medicines.

Best regards,

Thomas Cueni
Director General

Cc: Nicola Magrini, Secretary of the Expert Committee on the Selection and Use of Essential Medicines