M E M O R A N D U M

From:	Dir/NCD	**To:**	Dir/EML	**Date: 24 May 2021**
Our ref:		**Attention:**		
Your ref:	HQ-2021-DOCS-eMemo-74597	**Through:**		
Originator:		**Subject:**	23rd EXPERT COMMITTEE ON SELECTION AND USE OF ESSENTIAL MEDICINES - COMMENTS ON NCD-RELATED APPLICATIONS: Cancer related medicines	

With reference to the 23rd Expert Committee Meeting on Selection and Use of Essential Medicines scheduled to take place from 21 June to 2 July 2021, please find enclosed the NCD Department comments on Cancer medicines-related applications as requested with the Memorandum HQ-2021-DOCS-eMemo-74597, here attached for ease of reference.

Please note that Application for cancer medicines to WHO Model List of Essential Medicines have been reviewed by the technical team (cancer) in the Department of Noncommunicable Diseases (NCD). Detailed reviews of individual applications are attached to this memorandum.

The technical team notes with appreciation the EML Cancer Working Group (EML CWG) who has provided detailed analyses of the applications and the Secretariat who has convened this Working Group and developed an improved methodology for the systematic and scientific review of applications. The technical team also acknowledge the significant and valued efforts made by entities who have submitted applications with the interest to improve cancer care globally.

The number of applications in cancer and the utility of the EML CWG reflect the rapid pace of innovation in cancer and the need for new approaches to establish what is essential in the light of the variability of what is feasible in a particular national context. Two recent reports by WHO, the 2020 WHO Global report on cancer: Setting priorities, investing wisely and providing cancer care for all[1] and Technical report: pricing of cancer medicines and its impacts[2], present the current status of cancer care including the social and economic value of cancer care, current obstacles to accessing cancer medicines, and the need to develop sustainable approaches to improve the availability and affordability of these products.

ENCLs: (1)

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

[2] 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

These reports further established that: (i) cancer care is generally not accessible to large percentages of the global population and (ii) national responses should be informed by value-based care and evidence-informed priority setting. In line with these findings and as mandated in World Health Assembly Resolution 70.12 (2017), the technical unit remains fully committed to support Member States define priority interventions, including medicines and technologies, as part of universal health coverage.

In that regard, WHO NCD/MND has and is further developing a suite of tools to enable Member States have the data necessary to inform national decision-making on the selection and prioritization of cancer interventions based on health system capacity and in line with the principles of universal health coverage. These products include: (i) a platform to prioritize cancer prevention control interventions, to estimate their feasibility including health system requirements including costs, and to predict their impact including lives saved, allowing for the generation of an investment case, and (ii) normative guidance on established standards in oncologic care, informed by resource-stratified capacities and by current scientific understanding.

WHO NCD would like to highlight five points for considerations:

1) The full list of anti-neoplastic medicines current included in the latest WHO model EML is currently not accessible particularly in low-income countries nor in many middle-income countries. Nonetheless, WHO EML includes clinically-relevant, impactful cancer medicines that can continue to serve important functions for all Member States and other stakeholders. This includes, for example, use of WHO EML to support middle-income country prioritization and enabling improved access through multi-sectoral dialogues, such as informing the selection of products for UN procurement support or WHO biosimilar prequalification programme.

2) The development of a further standardized approach to assessing cancer medicines and to designating what medicines are feasible in different health system contexts is warranted. This includes consideration for appropriate national selection and administration of essential medicines based on available infrastructure including management of toxicities, capacity for diagnostics, safe administration and surveillance during and after treatment.

As previously commented, the technical unit notes that mechanisms have been used by the Secretariat to designate what is essential but are not necessarily affordable for all health systems[3]. It is increasingly noted with concern that a significant portion of total medicine expenditure and cancer management budget is being allocated to cancer medicines and that financial hardship due to high out-of-pocket expenditure on all components of cancer care is common. The advancement of a standardized approach to select medicines that considers feasibility and that provides end-users guidance on how to contextualize WHO EML to national dialogues is needed.

3) Cancer diagnostic capacity is limited in many low- and middle-income countries (LMIC) and must also inform inclusion on WHO EML to avoid inappropriate prescribing of essential medicines. Data from Assessing National Capacity for the Prevention and Control of Noncommunicable Disease demonstrated that only 39% of low-income countries reported that basic pathology services are generally available to their population. While nationally reported information on availability of more advanced molecular

[3] In line with the mandate provided to the Expert Committee in EB109/8 (2001), in Annex 1, paragraph 10. https://apps.who.int/gb/archive/pdf_files/EB109/eeb1098.pdf

diagnostics are not collected globally, data from peer-reviewed publications suggest availability is even more limited then histopathology.

4) Inclusion of second-line medicines for cancer has an impact on equity and accessibility. First-line agents generally have greater value in cancer treatment at the population level. While second- and subsequent-line therapies may have relevant clinical benefit, their inclusion may preclude increasing access to first-line therapy for the general population in line with the principles of progressive realization for universal health coverage. Inclusion of second-line therapy without consideration for accessibility of first-line therapy in a population raises the issue of equity.

5) Need for expanded research agenda for cancer therapies in low- and middle-income countries to assess feasibility. The evidence to inform the inclusion of candidate cancer medicines are generally informed by high-quality clinical trials, supplemented by real-world data generated in high-income countries (HIC). Consideration should also be given for the availability of evidence from countries with weaker health systems and different epidemiological profiles to understand the population impact and feasibility of effectively and appropriately delivering cancer medicines in these settings. Highlighting the need for such data would also further elevate the importance of cancer research in countries of all income levels to advance care with a view toward equity in all settings.

While these considerations are relevant to other disease programmes and application, the technical department recognizes the size of the disease burden (more than 1 in 6 global deaths), inequities in access, and the rapid pace of innovation (47% of all pharmaceutical clinical trials are on cancer medicines[1,2]) increase the urgency for developing cancer medicine policies that can mitigate issues being experienced at country level in relation to the implementation of EML cancer medicine recommendations and access to cancer medicines. The technical team appreciates the opportunity to work with the EML Secretariat and the EML CWG toward this end and anticipates a significant effort to review key EML selection dimensions – costs, availability and feasibility at country level – that are part of the evaluation of the EML Expert Committee in preparation for the 23rd WHO EML in 2023.

We remain available should more information be required.

Thank you,

Dr Bente Mikkelsen

Section 8: Cancer Medicines - Review of current applications

There were 16 applications for new cancer medicines, 6 applications for new indications for existing listed cancer medicines and 1 submission reviewing the available evidence for CAR-T cell therapy. Each application was reviewed by the technical team, with appreciation to the WHO EML EML Cancer Working Group (EML CWG), 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.

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

Pembrolizumab, Nivolumab, Atezolizumab or Durvalumab are the ICI that has been submitted for EML evaluation as monotherapy or combined therapy in different settings:

Metastatic NSCLC:

- 1st Line:
  Pembrolizumab and atezolizumab in metastatic with high levels of PD-L1
  Pembrolizumab and chemotherapy irrespective to PD-L1 expression
- 2nd Line (After 1st line chemotherapy):
  Pembrolizumab (PD-L1 positive >1% and >=50%)
  Nivolumab, Atezolizumab for non-PD-L1 selected patients

Locally Advanced unresectable NSCLC

- Durvalumab for PD-L1 on ≥ 1% tumors* (original RCT included all patients, irrespective to PD-L1 expression)

Efficacy: For these indications, anti-PD1 immune checkpoint inhibitors have evidence of high efficacy and magnitude of benefit and are considered standard of care (16 months overall survival (OS) benefit, ESMO-MCBS high score (5), included in ESMO and NCCN Guidelines recommended). Generally, a more favorable toxicity profile compared to existing chemotherapy on WHO EML. However, high frequency and complexity of immune-related toxicities also require trained professionals, and resources to identify and manage them.

Feasibility: Requires high-skilled molecular diagnostics and services able to exclude driver mutations (nearly 50% of NSCLC host driver mutations). Undiscriminated use of these medicines without adequate diagnostic capacity or expertise may result in harm to cancer patient, loss of benefit for populations and inefficiency in expenditure.

Difference in tumour biology between populations re-inforce the importance of diagnostic capacity; approximately 30% of NSCLC exhibit PD-L1 ≥ 50% in high-income countries (HIC) compared to some studies from low- and middle-income countries (LMIC) with positivity rates as low as 16% (pre analytical and analytical issues vs population phenotype). Pembrolizumab indication in 1st-line setting for PD-L1 high expression (guided by biomarker expression (PD-L1 ≥50%)) has greater impact (and thus more favorable CE ratio) when compared to 2nd-line setting (15.8 months vs 6.7 month OS).

It is important to note that the majority of evidence is from high-income countries with mature health systems. Effective delivery of immunotherapy requires capacity to provide accurate diagnosis (excluding genomic driver mutations) and the appropriate management of toxicities.

Considerations for ICI for the other settings: Pembrolizumab plus chemotherapy irrespective to PD-L1 expression (higher toxicity); 2ND Line Nivolumab: atezolizumab for non-PD-L1 selected

patients (did not comply with WHO EML requirements for inclusion); durvalumab for locally advanced unresectable NSCLC (low cross-over (<25%) and lack of mature data).

WHO NCD department recommendation: the inclusion of pembrolizumab has significant implications for WHO EML and access to cancer medicines globally. There is strong merit to its inclusion based on its clinical impact, ability to address major disease burden at the population level, and quality of existing clinical data. Yet, a framework is needed to better inform its selection in national EML given the negative implication its inclusion may have on access including inability to safely delivery, diversion of resources away from other essential medicines, and financial hardship experienced by patients who must make out-of-pocket payments. Further data from LMIC would help the technical team and Expert Committee understand the feasibility and implications of its approval and selection. While its inclusion may be merited, strong consideration should be given to such a framework in this review cycle or in 2023 as referenced above.

2) BRAF-MEK INHIBITORS – METASTATIC MELANOMA

Clinical Setting Indication: Metastatic melanoma with driver mutation (BRAF mutation)

Efficacy: Higher response rates, as compared to chemotherapy or immunotherapy (50 – 68% TKI vs 6-9% dacarbazine vs approximately 30% immunotherapy monotherapy) with long-term OS benefit (34% (95% CI, 30 to 38%) at 5 years for Dabrafenib plus Trametinib). ESMO-MCBS 4-5.

Feasibility: Demand highly skilled professionals and infra-structure capacity for molecular biology diagnosis, and for managing side the effects. Frequent dose reductions occur due to toxicity. Close monitoring is required. Feasibility must also be considered in terms of diagnostic capacity, side-effects management, and affordability.

WHO NCD Department recommendation: given comparisons to immunotherapy for melanoma and as well articulated by the EML CWG, the balance does not strongly favour adopting the class of BRAF-MEK inhibitors at this time.

3) IBRUTINIB – CHRONIC LYMPHOCYTIC LEUKAEMIA

Clinical Setting Indication: CLL patients with 17p deletion, IgHV wild-type. Relapsed CLL. 1ST line

Efficacy: as raised by EML CWG, there is need for further consideration of survival benefit specifically in the 17p- first-line sub-group before finalizing WG decision.

WHO NCD Department recommendation: at the current time, there is not a strong justification for its inclusion. There is one a specific indication for which there may be merit (the 17p deletion); however, given the health system requirements including diagnostic complexities of identifying the appropriate cohort of patients (and balanced against the risks of inappropriate prescribing or use), the high relative risk for relevant side effects, and the absence of QoL gain, there is not sufficient data to merit its inclusion at this time. More data regarding clinical benefit in the del 17p/p53mutation may strengthen the application before considering the inclusion of this medicine in the WHO EML.

4) ZANUBRUTINIB – CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) / SMALL LYMPHOCYTIC LYMPHOMA

Clinical Setting Indication: CLL / small lymphocytic lymphoma

WHO NCD Department recommendation: In line with the findings by the EML CWG, at this time, there is insufficient data to support inclusion of zanubrutinib in WHO EML because of the lack of mature data substantiating a significant clinical impact and concerns about toxicity profile (particularly rates of severe infections).

5) ZANUBRUTINIB – MANTLE CELL LYMPHOMA

Clinical Setting Indication: relapsed / refractory mantle cell lymphoma (MCL)

WHO NCD Department recommendation: In line with the findings by the EML CWG, at this time, there is insufficient data to support inclusion of zanubrutinib in WHO EML because of the lack of mature data substantiating a significant clinical impact and concerns about toxicity profile (particularly rates of severe infections), similar to the review completed for CLL above.

6) RASBURICASE – TUMOUR LYSIS SYNDROME PREVENTION AND TREATMENT (TLS)

Clinical Setting Indication: tumour lysis syndrome prevention and treatment for child and adults with cancer

WHO NCD Department recommendation: inclusion of rasburicase as it offers significant clinical value in all settings, has broad population value (approximately 5% of cancer patients) and has been well validated. The use of rasburicase is particularly relevant in countries where late diagnosis and higher volume of disease might increase the likelihood of TLS.

Considerations should be articulated regarding safety (capacity to manage toxicities of rasburicase) and strategies to improve accessibility (eg, dosing frequency).

7) CDK 4/6 INHIBITORS – HR+/HER2- ADVANCED/METASTATIC BREAST CANCER

Clinical Setting Indication: Hormone positive, HER-2 negative, metastatic breast cancer

WHO NCD Department recommendation: at this time, there is insufficient evidence to support the inclusion of CDK4/6 inhibitor in the WHO EML, either as a therapeutic class or individual medicine. Considerations to substantiate this position is the unfavourable balance of benefit and limitations. There are data to support minor OS gains from CDK4/6 inhibitors, though the magnitude may be limited and there is limited long-term or real-world data. Limitations to consider include diagnostic requirements and high rates of toxicity (particularly neutropenia) while also acknowledging the feasibility of use as first line therapy given the budgetary impact / cost-effectiveness.

8) DARATUMUMAB – NEWLY DIAGNOSED AND RELAPSED/REFRACTORY MULTIPLE MYELOMA

Clinical Setting Indication: Multiple Myeloma Transplant-Eligible, Multiple Myeloma Transplant non Eligible, Relapsed-refractory Multiple Myeloma

WHO NCD Department recommendation: while there are some data to support its clinical value, there is insufficient mature OS data available to fully justify its inclusion. Furthermore, the toxicity profile must also be considered.

9) FULVESTRANT – Hormone receptor positive (HR+) METASTATIC BREAST CANCER
Clinical Setting Indication: Metastatic HR+ breast cancer

Efficacy and magnitude of benefit: median OS gain of 5.8 months (1st and 2nd line included; low-certainty evidence; ESMO-MCBS score 2)

WHO NCD Department recommendation: in line with the recommendation from EML CWG, there is insufficient evidence of significant clinical impact in comparison to existing EML listed.

10) PERTUZUMAB – HER-2+ METASTATIC BREAST CANCER
Clinical Setting Indication: Metastatic HER-2 + breast cancer

WHO NCD Department recommendation: it is established that there is evidence of clinical benefit for pertuzumab, in line with the summary of evidence discussed with the EML CWG. It remains uncertain regarding the feasibility of its inclusion in WHO EML and national EML, particularly for LMIC, when access to trastuzumab remains limited because of costs and diagnostic capacity. The addition of pertuzumab, in light of the increased focus and availability of trastuzumab biosimilar, has an opportunity cost that may further limit inclusion of HER-2+ targeted therapies in national EML and benefit packages as part of universal health coverage.

There also remains uncertainty regarding the duration of therapy, which may also impact its accessibility in LMIC. Given these considerations, increasing access to trastuzumab, including through WHO Prequalification, should be considered a priority before re-visiting the candidacy of pertuzumab on WHO EML.

11) TISLELIZUMAB – RELAPSED/REFRACTORY HODGKIN LYMPHOMA
Clinical Setting Indication and therapeutic class: Relapsed/refractory lymphoma; PD-1 inhibitor (humanized IgG4 monoclonal antibody)

WHO NCD Department recommendation: in line with the findings from the EML CWG, there are insufficient data demonstrating sufficient clinical benefit to be included at this time.

12) Enzalutamide for metastatic prostate cancer
Clinical Setting Indication and therapeutic class: metastatic castration-resistant prostate cancer

WHO NCD Department recommendation: The 21st WHO EML includes abiraterone for the metastatic castration-resistant prostate cancer. As noted by the EML CWG, abiraterone has favourable access characteristics. The addition of enzalutamide does not offer significant

additional clinical benefit in terms of OS gains, QoL or other parameter, but its inclusion may improve market access.

12) Osimertinib for EGFR+ non-small cell lung cancer (ESMO)
Clinical Setting Indication: metastatic non-small cell lung cancer with EGFR sensitizing mutations

WHO NCD Department recommendation: evidence suggests that osimertinib does offer clinical value when compared to the first-generation TKI gefitinib and erlotinib in terms of OS gain and more favourable toxicity profile. There are concerns regarding the accessibility of first-generation TKIs on the 21st WHO EML, which may also have a more favourable cost-effectiveness profile and lower budgetary impact. In light of this, and as noted by the EML CWG, this may limit consideration of osimertinib at this time. Future evaluation of osimertinib should be considered in light of evolving data and the broader context of accessibility and prioritization.

13) Tislelizumab for urothelial carcinoma
Clinical Setting Indication: PD-L1 (>= 25% EXPRESSION) locally advanced or metastatic urothelial carcinoma (anti-PD-1) who have failed platinum-containing chemotherapy.

WHO NCD Department recommendation: In line the findings of the EML CWG, there are insufficient mature data on the efficacy and safety of tislelizumab. Further consideration can be made as additional studies are reported and increased understanding of feasibility is achieved.

14) TYROSINE KINASE INHIBITORS – Ph+ ACUTE LYMPHOBLASTIC LEUKAEMIA
Clinical Setting Indication: ALL (Ph+) (TKI included in WHO EML for gastrointestinal stromal tumor and Chronic Myeloid Leukemia)

WHO NCD Department recommendation: in line with the findings of the EML CWG, there is sufficient evidence to justify the inclusion of TKI for the treatment of ALL (Ph+) given its clinical impact and the established feasibility and increasing availability of TKI for other cancer related indications. TKI/imatinib treatment for ALL (Ph+) is known to reduce mortality, improve QoL and possess a favourable safety profile. Data for other TKI's (dasatinib/ponatinib) are less mature and require further consideration as such data become available.

15) VINORELBINE – RHABDOMYOSARCOMA
Clinical Setting Indication: rhabdomyosarcoma (1st-line therapy)

WHO NCD Department recommendation: in line with the recommendation from the EML CWG, vinorelbine meets criteria for inclusion in WHO EML. It is inclusion is further in line with the WHO Global Initiative for Childhood Cancer that seeks to improve childhood patients survival up to 60% by 2030 with access to essential medicines as a major pillar of the Initiative. To this end, the OS benefit (12.8% absolute gain, HR 0.52) and the feasibility of delivering in diverse health systems support its inclusion. Consideration should be given to patient selection (high-risk disease), and toxicity management capacity (haematological and infections rate), what does not preclude this submission.

16) Azacytidine for acute myeloid leukaemia
Clinical Setting Indication: Acute Myeloid Leukemia

WHO NCD Department recommendation: in line with the recommendation from the EML CWG, there are insufficient evidence to justify the inclusion of azacytidine at this time given the existence of an alternate regimen already listed (cytarabine and daunorubicin), lower clinical benefit and superior feasibility considerations.

17) Everolimus for subependymal giant cell astrocytoma
Clinical Setting Indication: treatment of SEGA in children

WHO NCD Department recommendation: in line with the findings from the EML CWG, everolimus has well-established and clinically relevant efficacy for the treatment of SEGA in children. It is important to note, however, that such treatment requires specialist diagnosis (that may include use of MRI and specialized in-vitro diagnostic tests such as immunohistochemistry and FISH) and specialist monitoring. Furthermore, SEGA is a rare condition mainly affecting children with tuberous sclerosis. These factors may ultimately influence the decision to include everolimus according to thresholds of population impact, feasibility and disease burden generally used by WHO EML Expert Committee.

18) Cancer medicines for low-grade glioma
Clinical Setting Indication: Inclusion of Carboplatin, Cisplatin, Cyclophosphamide, Vincristine, and Vinblastine as adjuvant therapy for Low grade gliomas.

WHO NCD Department recommendation: in line with the recommendation from the EML CWG, the inclusion of the indication of low-grade glioma for carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine on EMLc is appropriate. These medicines and accompanying treatment protocols are well established, recognized as the standard of care and associated with clinical benefits including improved survival as well as reducing the long term sequelae related alternate treatment modalities. As above, the extension of these new EMLc indications also support the effort the WHO Global Initiative for Childhood Cancer with LGG as one of the six priority cancers.

19) Doxorubicin for Rhabdomyosarcoma
Clinical Setting Indication: Non-metastatic rhabdomyosarcoma

WHO NCD Department recommendation: in line with the recommendation from the EML CWG, the inclusion of doxorubicin in the cEML for rhabdomyosarcoma is justified given that it addresses a cancer type of public health relevance (rhabdomyosarcoma is the most frequent soft tissue sarcoma in children) and has potential benefits as more feasible in weaker health systems (in which standard chemotherapy regimens are not accessible).

20) Review of medicines for head and neck cancer
Clinical Setting Indication: Platinum based chemotherapy for early and advanced head and neck cancers – carboplatin and cisplatin.

Efficacy and magnitude of benefit: The clinical benefit of adding cisplatin to concomitant radiotherapy is acknowledged by WHO EML - added to the complementary list of the EML for use as a radio-sensitizer in treatment protocols for head and neck cancer – following TRS994. Currently the medicine is used in treatment of squamous oropharynx and nasopharynx cancers.

WHO NCD Department recommendation: The data presented during the technical unit meeting is supported by systematic reviews and lead us to the conclusion that carboplatin provides similar clinical benefit that cisplatin, with different safety profile and more favorable side-effects, reason why the indication addresses "patients unable to tolerate cisplatin".
Considering the public relevance, 6th more incident neoplasm, lack of cost constraints, and the aforementioned benefit, we strongly agree on the technical unit. Of note, the indication for squamous cell head and neck cancers indications for platinum compounds includes not only oropharynx, but other head and neck sites, as such as: oral cavity, larynx, hypopharynx.

21) CAR-T cell therapies

The WHO NCD agrees with the EML CWG with the need to monitor the evidence regarding these therapies and to consider a broader context for access to these therapies with further guidance and inputs to be developed.