Public

May 18, 2021

MSD
INVENTING FOR LIFE

The Secretary
Expert Committee on the Selection and Use of Essential Medicines

Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

To the Secretariat and Members of the 23rd Expert Committee on the Selection and Use of Essential Medicines:

Thank you for the opportunity to comment on several products proposed for changes in the twenty-second revision of the World Health Organization's Model List of Essential Medicines (EML) and the eighth revision of the Model List of Essential Medicines for Children (EMLc).

Merck, Sharp & Dohme (known as Merck in the United States and Canada and MSD elsewhere in the world) supports the inclusion of raltegravir 400 mg tablet in the EMLc and is committed to the supply of the raltegravir pediatric formulations which continue to have an important role in many low and middle-income countries (LMICs).

The proposal to include the NSCLC indications for pembrolizumab merits further evidence-informed discussion because of the requirements to implement biomarker testing and treatment modalities. Such a discussion should assess broader health system readiness and coherency to ensure that the benefits of the treatment outweigh the challenges of implementation.

The proposal for consideration of tislelizumab for inclusion on the EML includes several inaccuracies and unfounded claims which warrant further assessment.

We share the WHO's aim to help countries make the best decisions to meet their unique needs and priorities. For 130 years our mission has been to save and improve lives by bringing forward medicines and vaccines for many of the world's most challenging diseases. In addition, MSD continues to work with our partners to build the capabilities needed to improve healthcare in countries where health system gaps exist. We look forward to our continued partnership in this vital work.

Our comments follow, and we welcome the opportunity to elaborate on any points.

We are respectfully yours,

Eliav Barr, MD
Senior Vice President
Global Medical & Scientific Affairs

Julie Louise Gerberding, MD, MPH
Executive Vice President
Chief Patient Office

Raltegravir (RAL)

In order to update the list of antiretrovirals (ARVs) recommended for treatment of HIV-infected adults and children on the 21st edition of EML and 7th edition of EMLc[1], the Global HIV, Hepatitis and STIs Programs (HHS) suggests below several deletions for the next revision. These recommendations were made to align the EML and EMLc with the 2019 WHO ARV guidelines[2] and the recently revised Optimal Formulary and Limited Use List for Pediatric ARVs (Dec 2020 to be launched in Q1 2021) from the group of partners convened by WHO via the Global Accelerator for Pediatric Formulations (GAP-f) platform. The following deletions are recommended for both EML and EMLc:

- *"RAL 100 mg chewable tablet is proposed for deletion from the EML and EMLc.*
- *RAL 400 mg tablet is proposed for deletion from the EMLc only.*
- *The 100 mg chewable tablet formulation of RAL was replaced by the 25 mg chewable tablet in the 2018 optimal formulary and limited use for children but was retained on the Model Lists in 2019 until availability of the 25 mg formulation was established. It was flagged by the 2019 Expert Committee for deletion in 2021 without further discussion[3].*
- *Due to the very limited use of RAL following dolutegravir availability, deletion of the RAL 400 mg tablet from the EMLc is also recommended. The 25 mg chewable tablet and the 100 mg granules should be maintained*." [4]

MSD has been committed to addressing the challenges of HIV for more than 30 years. Pediatrics is a critical area of unmet needs and continues to be a focus for our company. MSD has had a comprehensive program to develop pediatric formulations for ISENTRESS and has received stringent regulatory approval for chewable tablets (25mg and scored 100mg), oral granules for suspension and film coated 400 mg tablets that allow for dosing of raltegravir from neonates to adolescents living with HIV. We believe with these formulations raltegravir plays a significant role in addressing unmet medical needs, especially in neonates and young children for whom there are limited treatment options.

Pediatric antiretroviral treatment remains an area where multi-sector efforts are needed to accelerate the end of the pediatric AIDS epidemic. To enhance access to these formulations in the areas of greatest need, MSD has committed to making ISENTRESS pediatric formulations available at no-profit pricing in sub-Saharan Africa and in low-income countries. As we announced at the Rome Action Plan meeting in November 2018, MSD is working in partnership with PEPFAR (the President's Emergency Plan for AIDS Relief) and the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) to accelerate the treatment of neonates in Africa.

MSD notes the proposal to remove the raltegravir 100mg chewable tablet from the EMLc. We recognize the need to optimize the number of pediatric formulations available; however, we do believe there is continued value in retaining the 400 mg tablet as a treatment option for appropriate children above 6 years of age that is more cost-effective and convenient than the 25 mg chewable tablet formulation. Moreover, the deletion of the raltegravir 400 mg film coated tablet formulation from the EMLc may have consequences for ongoing treatment regimens. While we understand the objectives of the Pediatric Procurement Working Group, MSD supplied pediatric raltegravir to over 30 low-and-middle income countries in 2020. We are ready and committed to supply even low volume of our raltegravir pediatric formulations which continue to have an important role in many low and middle-income countries (LMICs).

Anti PD-1 immune-checkpoint inhibitors (Pembrolizumab 100 mg/4 mL solution in single-use vial)

MSD welcomes the opportunity to comment on the proposal of European Society for Medical Oncology (ESMO) for consideration of pembrolizumab for inclusion on the EML for the treatment of "non-oncogene-addicted" (EGFR, ALK and ROS1 wild type) advanced non-small cell lung cancer (NSCLC).

Summary

Consistent with our 2019 submission, MSD's comments focus on three aspects of ESMO's proposal:

- Health System Readiness – Significant infrastructure and capabilities are required to diagnose, treat, and monitor patients receiving pembrolizumab for the NSCLC indications that ESMO has proposed. Immunotherapies can be associated with rare but serious adverse events (AEs) that require specialized capabilities, treatments, and facilities to manage. Specialized capabilities, equipment and facilities are also required for the multiple predictive biomarker tests needed to identify the right patients for the proposed indications.

- Coherency – Inclusion of immunotherapy for NSCLC indications on the EML requires assessment of the companion diagnostics for inclusion on WHO's Essential Diagnostics List[5]. Of the molecular tests for oncogene mutations and PD-L1 biomarker tests commonly required for NSCLC, only the test for the EGFR oncogene is currently included on the Essential Diagnostics List. For the NSCLC patients who are tested for immunotherapy but ineligible because their tumors are positive for oncogene biomarkers such as EGFR and ALK, oncogene-targeted therapies should be provided immediately to them. Target therapies that are not on the EML should be considered for inclusion for the NSCLC patients who initiate immunotherapy testing.

- Priority – WHO has recently stressed the importance of investing wisely in cancer control and has encouraged governments to prioritize and sequence interventions that are operationally and economically feasible[6]. It is notable that, in the context of feasibility, the most recently updated National Comprehensive Cancer Network (NCCN) Harmonized Guidelines for Sub-Saharan Africa designate PD-L1 testing (and molecular testing for EGFR & ALK) and immunotherapy for NSCLC[7] as "care that may be costly, technically challenging and/or have a less impact on oncologic outcomes" in Sub-Saharan Africa.

MSD and many other partner organizations continue to work to address the significant gaps in the cancer care continuum in less-resourced settings.[8,9,10,11] Nonetheless, in deciding whether to add pembrolizumab to the Model List of Essential Medicines for the proposed indications, the Expert Committee should weigh the clinical potential of the therapy against the risk of harm to the patient populations treated in settings that may not have the necessary capabilities in diagnostics, treatment, and monitoring.

MSD's commitment to cancer patients

As a leading biopharmaceutical company in oncology, MSD is working to transform the way cancer is prevented and treated. We share ESMO's aspiration to increase meaningful patient uptake of the most beneficial cancer therapies. We also support the WHO's mission to accelerate global cancer control through investing wisely in interventions that have the greatest potential to reduce premature mortality, consistent with the Sustainable Development Goals[12].

MSD is committed to achieving better outcomes for cancer patients, through our research, our efforts to improve the access and uptake of our medicines & vaccines, and our partnerships with stakeholders to strengthen cancer health systems.

Our clinical program in immunotherapy is one of the largest medical research endeavors ever undertaken, covering over 1300 trials across many tumors and treatment settings. Our immunotherapy medicine, pembrolizumab, is registered in over 90 countries, reimbursed in over 50 and has been used to

treat over 700,000 patients in both trials and clinical practice worldwide. MSD is also a major producer of HPV vaccines which are a critical component of the WHO's plan to eliminate cervical cancer. Working with governments, NGOs and industry partners to control cancer is based on 3 pillars:

- Researching and developing new vaccines and treatments to control cancer and supporting vaccination programs and the effective use of immunotherapy, including PD-L1 biomarker testing;[13]
- enabling patient access to our medicines through patient access programs;[14]
- building partnerships to address gaps in the care continuum in lower resourced settings, focusing on cancers affecting women's health.[15]

Past consideration of immunotherapy on the Model List

The WHO's Model List of Essential Medicines has helped countries to prioritize medicines for over forty years. Many cancer medicines have been added to the List in recent revisions, sending a clear signal to countries about their importance and utility.[16] In 2019, the 22nd Expert Committee considered an earlier ESMO proposal for the inclusion of Anti-PD1/PD-L1 Immune checkpoint inhibitors (ICIs), including MSD's pembrolizumab, for early and late-stage melanoma, and 1st and 2nd line NSCLC.[17]

In comments provided on ESMO's proposal to the Expert Committee, the WHO Department of Noncommunicable Diseases (NCDs) did not support the inclusion of ICIs on the Model List, given that:

- more evidence was needed to understand the population-level benefit & safety of ICIs, and
- the biomarker tests & adverse event monitoring that these medicines require may not be feasible in low-resource settings.[18]

In its final recommendation in response to ESMO's proposal, the Expert Committee noted that there were no treatment options currently included in the Model List for metastatic melanoma. The Committee therefore recommended the addition of nivolumab and pembrolizumab for this indication. However, it did not recommend inclusion of ICIs for early melanoma or NSCLC, due to the absence of mature data.

Prioritization and coherency are critical when choosing cancer interventions

In early 2020, the WHO Department of NCDs released the WHO Report on Cancer[6] which shows that cancer control can deliver substantial human and economic returns. The report estimates that 7 million unnecessary deaths from cancer can be avoided by 2030 with the right investments.

To achieve this ambitious goal, the report encourages governments to identify cancer control priorities that are feasible, evidence-based, and can be financed[6]. It further argues that these priorities must be coherent. In other words, they should be formulated holistically within a national cancer control plan, so that all interventions are enabled and consistent with each other and together deliver meaningful clinical outcomes for cancer patients. Investments should be introduced in a stepwise fashion according to impact, cost, and feasibility to ensure equitable, high-quality value-based care.

Prioritization and coherency also inform the process used to update the Model List of Essential Medicines. Applications for inclusion, change or deletion of a medicine on the Model must contain information on disease burden, comparative effectiveness, safety and requirements for diagnosis, treatment and monitoring.[19]

Additional information on immunotherapy treatment details, harms, and listing

ESMO's proposal details the public health burden of its proposed indications and summarizes the efficacy, safety, quality of life (QoL) and cost-effectiveness of pembrolizumab and other anti PD-1/PD-L1 therapies. The proposal is based on data from randomized, controlled clinical trials, ESMO-MCBS v1.1

scoring, and regulatory approvals by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA).

The comments that follow do not revisit any of the specific detail included in ESMO's proposal. Instead, they focus on aspects of the "Information to be included in an application for inclusion on the WHO Model List of Essential Medicines"[17] that the ESMO application does not cover in depth, namely:

- *Dose forms(s) and strength(s) proposed for inclusion*
- *Treatment details: Diagnostic tests*
- *Review of harms and toxicity: Summary of evidence of safety*
- *Treatment details: Monitoring requirement*
- *Treatment details: Skill levels of health care workers*
- *Treatment details: Specialized treatment facilities*
- *Whether listing is requested as individual medicine or representative of a pharmacological class.*

Dose forms(s) and strength(s) proposed for inclusion

Pembrolizumab is now supplied as a 100 mg/4 mL (25 mg/mL) solution in a single-use vial. The 50-mg lyophilized formulation is no longer being manufactured and supplied worldwide.

Treatment details: Diagnostic tests

The treatment decision with pembrolizumab is based on biomarker testing, including several requirements such as testing infrastructure, imaging processes and professionals such as trained pathologists. It is indicated only in patients with NSCLC who are EGFR, ALK and ROS1 negative. Early data suggest that, even in patients with high PD-L1 expression who harbor EGFR mutations, responses to pembrolizumab are limited.[20] Currently, the WHO Essential Diagnostics List does not include the PD-L1 biomarker test or ALK or ROS1 genomic tumor aberration tests (EGFR was added in 2021).[5] In addition, the availability of EGFR and other molecular testing may be limited in low-resource settings.[21]

ESMO[22] and other guidelines[23] recommend the identification of these driver mutations. Equally important, patients whose tumors harbor these mutations (and are therefore precluded from pembrolizumab monotherapy) should have access to and receive the most appropriate first-line targeted therapy for these types of advanced NSCLC.

Some indications for pembrolizumab are defined by specific biomarkers such as PD-L1 expression levels.[24] The accurate measurement of PD-L1 expression depends critically on adherence to good clinical and laboratory practice during pre-analytical and analytical phases of tissue sample collection, processing, and test interpretation. Suboptimal sample collection or immunohistochemistry (IHC) processing may lead to underestimates of PD-L1 expression, which will reduce the number of patients eligible for treatment.

In the pre-analytical phase, expertise of clinicians is essential in deciding which biopsy tissue samples are best suited for immunohistochemistry (IHC) processing. PD-L1 is particularly sensitive to the time taken to fix samples in formalin (fixing should take no less 6 hours and no longer than 48 hours).[25, 26] This may be an issue when the tissue collection site is located a long distance from the pathology center or when biopsies are performed the day prior to a weekend.

Well-trained and accredited pathologists are also required to process samples and determine the PD-L1 expression level. Accreditation will include considerations of the pre-analytical, analytical, and post-analytical parameters and the quality controls that ensure reliable testing.

In the case of NSCLC, most patients are diagnosed at an advanced stage in both high-resource and low-resource settings. Staging and histologic diagnoses are more challenging in settings with lower access to

specialists & diagnostic imaging and may result in further delays in treatment. In some settings, endemic pulmonary tuberculosis and other infectious disease may result in misdiagnosis and improper treatment with antimicrobials.[27]

Review of harms and toxicity: Summary of evidence of safety

Pembrolizumab and other ICIs are associated with a range of AEs related to their immune mechanism of action. The frequency and timing of immune-related adverse events (irAEs) differ between ICIs, dosing schedules, regimens, and cancer types. Overall, the most frequent irAEs are those affecting the skin, endocrine system, GI tract, and lung. More rarely, neurologic, ocular, cardiovascular, hematologic, and renal irAEs can occur.

Most irAEs may have life-threatening or fatal outcomes. In some cases, the less common toxicities may be life-threatening or fatal and therefore require prompt diagnosis and treatment, particularly because initial presentation may be mild, with nonspecific symptoms such as fatigue, headache, and electrolyte disturbance. Furthermore, irAEs related to ICIs may sometimes present similarly to those related to chemotherapy (e.g., diarrhea and colitis) and may require different diagnostic procedures, additional workup, and different management. Overall, timely and proper diagnosis and management of irAEs requires significant specialized training and knowledge on the part of the oncologist, as well as the availability of adequate diagnostic capabilities and a multi-disciplinary care team[28]. For the full list of side effects and restrictions with pembrolizumab, please see the risk management plan[29] and the product information[30] as referenced.

Pembrolizumab is still under “additional monitoring” by the regulators in the EU[31] and carries a black triangle. The black triangle simply indicates that additional monitoring is required compared to other medicines because generally the medicine is new to the market or long-term data are limited. It does not mean that such medicines are unsafe when the necessary infrastructure and patient management plans are in place.

The toxicity profile of immunotherapies generally differs from those of more traditional therapies, like chemotherapies and molecularly targeted therapies. Preclinical and clinical data demonstrate improved and durable responses in the combination of immunotherapies with chemotherapy, which are correlated to synergism between the drugs’ mechanisms of action. However, consideration for the combination of AEs from both therapies must also be recognized.

It is critical to identify which compound in combination therapy may be responsible for a specific AE, enabling the right course of action to be taken. Decisions regarding AE management is made based on the patient’s medical history, clinical status, and the treating healthcare professional’s experience. Routine laboratory monitoring and training on irAEs, including which specific questions to ask about symptoms, will be needed at all levels of the multidisciplinary team.[32, 33]

Treatment details: Monitoring requirement

For irAEs, prompt recognition, treatment, and careful monitoring are essential to ensure patient safety. Advanced capabilities in diagnostic imaging, sub-specialist care, and access to inpatient hospitalization are essential when caring for patients on pembrolizumab who experience irAEs. For example, serial cross-sectional CT scanning is recommended for diagnosis and to monitor treatment for suspected immune-related pneumonitis.[34] Chest radiography may miss up to 25% of cases of pneumonitis.[35] For severe cases of pneumonitis, prompt hospitalization and administration of intravenous steroids (and potentially other immunosuppressive medications) is required.[36]

Managing AEs in the immune-oncology setting requires the multidisciplinary team to maintain knowledge of potential irAEs and understand how diverse grading evolves over time. An early and prompt reaction to AEs may enable the patient to continue ICI therapy. Although most AEs will happen early in treatment,

some AEs, e.g., diabetes mellitus, hypophysis alterations, and skin reactions, may appear during well-advanced treatment and have the potential to be permanent and require lifelong supportive therapy. Use of immunotherapy-based combinations may also require additional monitoring and parameters for dose adjustment due to adverse events.

The care of patients with irAEs requires a multi-disciplinary care team with expertise in diagnosis and management of these events. This multi-disciplinary team may include physician specialists (e.g., endocrinologists), nurses, and pharmacists, among others. This is especially important in the setting of endemic infectious diseases, which may make diagnosis of immune-related toxicities more challenging.

Treatment details: Specialized treatment facilities

The site-validation checklists that MSD provides for pembrolizumab treatment as part of a clinical trial include the following specialized treatment facilities. This may be instructive in considering the infrastructure necessary for general clinical treatment in resource-constrained settings:

- access to an imaging center or imaging department;
- ability to perform CT scans of diagnostic quality (with oral and IV contrast) and MRI and provide DICOM images within 48 hours to a central imaging vendor, preferably using electronic transfer;
- ability to perform local laboratory assessments PT/INR and PTT/aPTT, CBC with differential, comprehensive chemistry, thyroid labs, urinalysis, serum or urine pregnancy test, HIV, Hepatitis B/C;
- refrigerator stable at 2-8°C and freezers stable at -20°C and -70/-80°C with daily temperature measurements (min/max thermometer required) for drug and lab sample storage, with a back-up power source and alarm system;
- ability to perform 12-lead ECG with QTc measurement;
- facilities and personnel for collecting, processing, storing and shipping DNA, biopsy and/or RNA samples as required by protocol, which may be shipped to MSD and/or a central laboratory;
- IATA Certified Site Personnel for shipment of biologic specimens; and ability to source electronic infusion pumps and (100mL or 250mL) saline bags.

Whether listing is requested as an individual medicine or as representative of a pharmacological class

It is important to consider the molecular differences among monoclonal antibodies used in immunotherapy, even those directed against the same pathway. These biologic drugs are highly complex molecules with key characteristics that can change at any stage of a multi-step manufacturing process. For example, the binding affinity (the strength of the binding interaction between a single molecule to its ligand/binding partner) is different. Each molecule exhibits distinct binding epitope coverage[37,38,39,40] e.g., pembrolizumab binds to a different area on the PD-1 receptor than nivolumab. In addition, as with all therapeutic proteins, there is a potential for immunogenicity. Pembrolizumab's antidrug antibody (ADA) rate is 2.1%.[41] The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and across drug comparisons should be made with caution. Therefore, one cannot assume that any one of these molecules is representative of the entire therapeutic group, and the molecular difference is likely correlated with the different clinical trial results for these molecules when they were studied in similar settings. This is important because other ICI molecules cannot claim to be biosimilar or interchangeable - the distinctive structure and amino acid sequence of pembrolizumab carries a high degree of difficulty to duplicate without clinical impact.[42]

Conclusion

To ensure that patients benefit from pembrolizumab, various criteria have to be met as outlined above. Due to large differences among health systems, the inclusion in the EML merits further discussion before a decision is taken. This is in line with the WHO Report on Cancer which argues that cancer control be implemented "by ensuring that all the necessary facilities, equipment, personnel, information systems and

financing are in place to deliver the cancer plan… If one link in the chain is missing, the patient suffers, and resources are wasted."[6]

Diagnostic and treatment capacities vary widely between and within countries, therefore we ask that the Expert Committee weigh the clinical potential of pembrolizumab, as monotherapy or in combination therapy, against the risk of harm to the patient populations diagnosed and treated in less resourced settings. We further ask that the potential impact of implementing immunotherapy and associated investments in such settings be considered against that of the other investments recommended by the WHO.

MSD is committed to achieving better outcomes for cancer patients, through our research, our efforts to improve the access and uptake of our medicines & vaccines, and our partnerships with stakeholders to strengthen cancer health systems. We look forward to continuing our collaboration in support of the WHO's mission to accelerate global cancer control.

Tislelizumab – urothelial carcinoma and classical Hodgkin lymphoma

We observed several inaccuracies as well as questionable interpretation of the data profile of pembrolizumab in the applications for the inclusion of tislelizumab on the EML for treatment of urothelial cancer and classical Hodgkin lymphoma (cHL). These are important considerations and can have significant impact on the actual magnitude of benefits to cancer patients.

Urothelial Carcinoma

Within the urothelial carcinoma application, the claim of superior efficacy (versus pembrolizumab) in Section 9.3.2[43] is simply invalid and unwarranted given the lack of head-to-head trials and comparative studies (i.e., no formal statistical comparison). Many trials included in Table 9-1[43] were from earlier disease settings, making such comparison irrelevant. Furthermore, data are inconsistent with the product labels and/or the latest publication of pembrolizumab[44,45]. The statement in Section 11.2.2[43] on cost-effectiveness of tislelizumab versus other ICIs is unjustified, considering that no cost-effectiveness analysis has been conducted for tislelizumab per the applicant; an attempt to justify cost effectiveness of tislelizumab by association with pembrolizumab is inappropriate.

Classical Hodgkin's Lymphoma (cHL)

Within the cHL application, the binding epitope of pembrolizumab on PD-1[46] is inaccurately described in the data cited, leading to the erroneous conclusion that the binding characteristics of pembrolizumab are inferior to those reported for tislelizumab. The statements that compare nonclinical pharmacology between pembrolizumab and tislelizumab are based on experiments performed by BeiGene without the consideration of the nonclinical data that Merck has published. Moreover, the PFS and OS data cited for pembrolizumab are incorrect in Reference 29, Table 9-2[47].

There may be value in seeking input from other companies whose products are referenced in the two applications to confirm whether their data are reflected accurately. There could be further benefit in having the data and claims included in the two applications assessed by independent clinical experts.

[1] https://www.who.int/selection_medicines/committees/expert/22/applications/raltegravir/en/
[2] https://www.who.int/selection_medicines/committees/expert/22/applications/s6.4.2_ARV-formulations-deletion.pdf?ua=1
[3] World Health Organization. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization. (WHO Technical Report Series, No. 1021); 2019
[4] https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-deletion-of-medicines-formulations/d.1_arv-deletions.pdf?sfvrsn=4ad596c3_4
[5] World Health Organization. The selection and use of essential in vitro diagnostics. WHO Technical Report Series, No. 1031, 2021 https://www.who.int/publications/i/item/9789240019102
[6] World Health Organization. Report on Cancer. 2020. https://www.who.int/publications/i/item/who-report-on-cancer-setting-priorities-investing-wisely-and-providing-care-for-all
[7] NCCN Harmonized Guidelines for Sub-Saharan Africa for Non-Small Cell Lung Cancer, Version 6.2020 https://www.nccn.org/professionals/physician_gls/pdf/nscl_harmonized-africa.pdf
[8] Mathew, A. Global Survey of Clinical Oncology Workforce. Journal of Global Oncology. 2018. 10.1200/JGO.17.00188 - published online February 8, 2018
[9] Jamison, D. T., H. Gelband, S. Horton, P. Jha, R. Laxminarayan, C. N. Mock, and R. Nugent, editors. Disease Control Priorities: Improving Health and Reducing Poverty. Disease Control Priorities (third edition). 2018. Volume 9. Washington, DC: World Bank. doi:10.1596/978-1-4648-0527-1. License: Creative Commons Attribution CC BY 3.0 IGO – pages 217-219
[10] Funk L M, Weiser T G, Berry W R, Lipsitz S R, Merry A F et al. "Global Operating Theatre Distribution and Pulse Oximetry Supply: An Estimation from Reported Data." Lancet. 2010. 376 (9746): 1055–61
[11] IAEA (International Atomic Energy Authority). 2013. "Radiotherapy Availability." Programme of Action for Cancer Therapy (PACT), Programme Office. http://cancer.iaea.org/agart.asp
[12] https://sdgs.un.org/goals/goal3
[13] Dietel, M, Savelov N, Salanova R et al. Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non–small-cell lung cancer: The global, multicenter EXPRESS study. Lung Cancer. 2019. 134:174-179 https://doi.org/10.1016/j.lungcan.2019.06.012
[14] https://www.msdresponsibility.com/access-to-health/oncology/
[15] For example through the City Cancer Challenge https://www.uicc.org/what-we-do/convening/ccan-2025-city-cancer-challenge and through the Alliance to Advance Patient Centered Cancer Care https://cancercarealliance.org/
[16] Robertson, Jane & Barr, Ronald & Shulman, Lawrence & Forte, Gilles & Magrini, Nicola. Essential medicines for cancer: WHO recommendations and national priorities. Bulletin of the World Health Organization. 94. 2016. 735-742. 10.2471/BLT.15.163998
[17] World Health Organization. The Selection and Use of Essential Medicines. WHO Technical Report Series - 1021 2019. https://www.who.int/publications/i/item/9789241210300
[18]https://www.who.int/selection_medicines/committees/expert/22/applications/s8.1_antiPD1_NVIcomments.pdf?ua=1
[19] World Health Organization. INFORMATION FOR APPLICANTS 2021 WHO Expert Committee on the Selection and Use of Essential Medicines. 2020. https://cdn.who.int/media/docs/default-source/essential-medicines/expert-committees/expcom23-information-for-applicants_f2b1574d-0842-4de2-833b-442004c46389.pdf?sfvrsn=414e533c_4
[20] Lisberg A, Cummings A, Goldman JW, Bornazyan K, N Reese et al. A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC. Journal of Thoracic Oncology 2018; 13: 1138-1145
[21] Carbonnaux M, Souquet PJ, Meert AP, Scherpereel A, Peters M et al. Inequalities in lung cancer: a world of EGFR. Eur Respir J. 2016 May;47(5):1502-9

[22] Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, Volume 29, Issue Supplement_4, 1 October 2018, Pages iv192–iv237
[23] Hanna N, Johnson D, Temin S, Baker S, Brahmer J et al. Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer Update. Journal of Clinical Oncology 35, 3484-3515
[24] Lindeman NI, Cagle PT, Beasley, MB et al. Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors: Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. Arch Pathol Lab Med. 2013; 137, 828 – 860
[25] Tsao MS. IASLC Atlas of PD-L1 Immunohistochemistry Testing in Lung Cancer. 2017. 1st ed. Editorial Rx Press, Aurora, CO
[26] Lantuejoul S, Tsao M, Cooper W, Girard N et al. PD-L1 Testing for Lung Cancer in 2019: Perspective from the IASLC Pathology Committee. Journal of Thoracic Oncology. 2019. 15. 10.1016/j.jtho.2019.12.107
[27] Singh VK, Chandra S, Kumar S, Pangtey G, Mohan A et al. A Common Medical Error: Lung Cancer Misdiagnosed as Sputum Negative Tuberculosis. Asian Pacific J Cancer Prev 2009; 10, 335-338
[28] Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology 2018 36:17, 1714-1768
[29] https://www.ema.europa.eu/en/documents/rmp-summary/keytruda-epar-risk-management-plan-summary_en.pdf
[30] https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf
[31] https://youtu.be/qzM4NKPoovM
[32] Grünwald V et al. Axitinib plus immune checkpoint inhibitor: evidence- and expert-based consensus recommendation for treatment optimisation and management of related adverse events. British Journal of Cancer. 2020. volume 123, pages 898–904
[33] Wood LS et al. Toxicity Management of Front-Line Pembrolizumab Combined With Axitinib in Clear Cell Metastatic Renal Cell Carcinoma: A Case Study Approach. JCO Oncology Practice. 2020. 16:2_suppl, 15s-19s
[34] Chuzi S, Tavora F, Cruz M, Costa R, Chae YK et al. Clinical features, diagnostic challenges, and management strategies in checkpoint inhibitor-related pneumonitis. Cancer Manag Res. 2017; 9: 207–213
[35] Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti–programmed death-1/programmed death ligand 1 therapy. J Clin Oncol. 2017;35(7):709–717
[36] Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. JAMA Oncol. 2016;2(10):1346–1353
[37] Lepir T et al. Medicine (Baltimore). 2019;98(2):e13804
[38] Tan S et al. Protein Cell. 2018;9(1):135–139
[39] Tan S et al. Nat Comm. 2017;8:14369
[40] Lee JY et al. Nat Comm. 2016;7:13354
[41] KEYTRUDA (pembrolizumab). Prescribing information; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Revised November 2018
[42] Hutchins B et al. In Vivo Pharmacokinetics and Toxicology in Nonhuman Primates of the Anti-PD-1 Antibody Pembrolizumab. Mol Cancer Ther. 2020 Jun;19(6):1298-1307. doi: 10.1158/1535-7163.MCT-19-0774. Epub 2020 Mar 30
[43] https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.35_tislelizumab_uc.pdf?sfvrsn=3c99d0a7_4
[44] Necchi A, F.Y., Bullmunt J, et al., Three-Year Follow-Up From the Phase 3 KEYNOTE-045 Trial: Pembrolizumab Versus Investigator's Choice (Paclitaxel, Docetaxel, or Vinflunine) in Recurrent, Advanced Urothelial Cancer, in European Society for Medical Oncology. Annals of Oncology (2019) 30 (suppl_5): v356-v402. 10.1093/annonc/mdz249
[45] Merck Sharp & Dohme Corp, Inc. KEYTRUDA (pembrolizumab) Prescribing Information. 2021 [cited 2021 7 May]; Available from: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

[46] Hutchins B, Starling GC, McCoy MA, Herzyk D, Poulet FM, Dulos J, Liu L4, Kang SP, Fayadat-Dilman L, Hsieh M, Andrews CL, Ayanoglu G, Cullen C, De Waal Malefyt R, Kastelein RA, Le Saux S, Lee J, Li S, Malashock D, Sadekova S, Soder G, van Eenennaam H, Willingham A, Yu Y, Streuli M, Carven GJ, van Elsas A. Mol Cancer Ther 19(6): 1298-1307 2020

[47] https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.34_tislelizumab_hl.pdf?sfvrsn=7b82eac2_4