A.22 PD-1 / PD-L1 immune checkpoint inhibitors – EML

Reviewer summary	☒ Supportive of the proposal (partly) ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Cancer is a growing societal, public health, and economic problem, responsible for almost one in six deaths worldwide. In 2022 there were almost 20 million new cases of cancer (including nonmelanoma skin cancers) and 9.7 million deaths from cancer (including NMSC), suggesting that 1:5 people may develop cancer during a lifetime. The death-related proportions according to sex are 1:9 men and 1:12 women. Lung cancer was the most frequently diagnosed, (approximately 2.5 million new cases), or 12.4% of all cancers globally, followed by: female breast cancer (11.6%), colorectum (9.6%), prostate (7.3%), and stomach (4.9%). There were an estimated 1.8 million deaths (18.7%) from lung cancer followed by colorectal (9.3%), liver (7.8%), female breast (6.9%), and stomach (6.8%) cancers. Incidence rates (including NMSC) varied from four-fold to five-fold across world regions, 507.9 per 100,000 in Australia/ New Zealand to 97.1 per 100,000 in Western Africa, among men, and 410.5 per 100,000 in Australia/New Zealand to close to 103.3 per 100,000 in South-Central Asia among women[1]. There are several causes for high incidence and mortality in LMICs: barriers to healthcare access, late diagnosis - including late-stage presentation, and low availability and high prices of cancer medicines. Data from high-income countries (HICs), shows that advanced stage at first presentations, part of the phenotype of some aggressive cancers, also remains substantial. From a global perspective, the risk of developing cancer tends to increase with increasing human development index (HDI) level[1]. Upper middle-income countries show the largest proportion of cancer deaths, with estimated 4.11 million in 2022 rising to 7.6 million in 2050. These countries are doubly burdened with problems of LMIC and of HIC. Immune Checkpoint Inhibitors (ICIs) are monoclonal antibodies targeting specific receptors and ligands in immune regulation, including cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), programmed cell death ligands 1 and 2 (PD-L1/PD-L2), and lymphocyte activation gene 3 protein (LAG-3). Unlike cytotoxic treatment regimens that directly attack and destroy rapidly dividing cells, ICIs modulate the host immune system to target tumour cells. They may enhance tolerability of anti-cancer treatment for certain populations, while introducing immune-mediated adverse events. The application was submitted by two entities (WHO Collaborating Center on Evidence Synthesis and Evaluation of Novel Cancer Therapies and Institute of Public Health, Medical Faculty and University Hospital Cologne University of Cologne, Germany), and focuses on Immune Checkpoint Inhibitors; ICI as individual medicines, pairing with other ICIs and other antineoplastic medicines in various regiments for various types of cancers. The application applied prioritization criteria, in the following order: approval by EMA (atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, ipilimumab, nivolumab, pembrolizumab, tislelizumab, tremelimumab, relatlimab and 76 EMA approvals of ICI-containing treatment regimens for 21 cancer indications); palliative first-line treatment setting; ESMO-magnitude of clinical benefit score ≥ 4, focusing on approvals based on RCTs. The WHO Cancer Experts Committee (WHO CC) has revised the application and recommended some of the indications, while not supporting others[2]. Recommendations by the WHO CC have been added to this review for further insight. WHO CC supports the inclusion of PD-1 and PD-L1 monotherapy (pembrolizumab, atezolizumab and cemiplimab) for non-small cell lung cancer ≥50% PD-L1 expression, pembrolizumab monotherapy for colorectal cancer (deficient mismatch repair/microsatellite instability-high - dMMR/MSI-H), as well as pembrolizumab combined with chemotherapy for cervical cancer (CPS ≥1). There is evidence of effectiveness and less so for safety for these medicines/indications; there is some variation in quality of evidence for two of these medicines/indications (for atezolizumab in NSCLC and for pembrolizumab monotherapy for colorectal cancer, although for the latter, very new evidence suggests important increases in OS and in PFS).

	Generalizability of effects may be limited due to selective indications, no participation in trials of certain groups and, more importantly, lack of head-to-head comparisons. However, the experts reiterate that ICIs should be perceived as a class, with class effect, which suggests that although pembrolizumab is the most employed, other ICIs may have the same profile. ICIs are all under patent and will remain so at least until 2028 at the soonest or 2036 at the latest, if no actions as to patent renewal by pharmaceutical companies are successful. Cost of treatment is very high, and cost-effectiveness may only be reached with significant (from 21-95%) price reduction, depending on substance. Several diagnostic requirements as to patient probable response status are critical for effectiveness of ICIs and may substantially limit use in low or middle-income settings. Access is therefore, far from ideal, although approved regulatory status is advancing in several jurisdictions. Cancer incidence is rising worldwide, while oncology drugs have been plagued by shortages and stockouts effectively impeding implementation of treatments. New drugs, although very expensive, show important trade-offs in effectiveness outcomes. Because of this scenario and the role represented by the class in these indications, I support the addition of pembrolizumab and cemiplimab PD-L1 ≥ 50% (for NSCLC), pembrolizumab dMMR/MSI-H (for colorectal carcinoma) and of pembrolizumab-based treatment PD-L1 CPS ≥1 (for cervical cancer) in the EML. Additionally, as Experts suggest, the use of a square box listing with pembrolizumab representative of the class.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? Nivolumab (and pembrolizumab as square box) for metastatic melanoma (2019) (8.2.3 Immunomodulators) Given the dominant role of pembrolizumab in the therapeutic landscape for malignant melanoma and other cancers, the WHO Cancer Experts advised nivolumab to be listed as a therapeutic alternative to pembrolizumab instead, reversing the current listing in the EML.	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? WHO CC supports the following indications based on effectiveness outcomes (Overall survival, progression-free survival, health-related quality of life). Across indications, the largest body of evidence proving a beneficial effect for multiple ICI-based treatments was identified for oncogenic-driver wild-type NSCLC. Quality of life improvements, even though statistically significant in several trials, only reached a level of clinically noticeable difference (i.e., minimal clinically important difference) in the case of pembrolizumab monotherapy for NSCLC with high PD-L1 expression or colorectal carcinoma with dMMR/MSI-H, and the combination of dostarlimab with chemotherapy in endometrial carcinoma with dMMR/MSI-H. However, due to relatively low participant numbers in studies of cancers with mismatch-repair protein deficiency, the certainty in the body of evidence was low for this outcome. Single-agent pembrolizumab (a PD-1 inhibitor) is currently the standard-of-care as monotherapy in patients with PD-L1 expression >= 50%, either alone or in combination with chemotherapy when PD-L1 expression is less than 50%. The WHO CC Experts highlighted that atezolizumab monotherapy and cemiplimab monotherapy are also EMA-approved for the first-line treatment of non-small cell lung cancer (PD-L1 ≥50%), offer important gains in overall survival, and may be used as therapeutic alternatives to pembrolizumab monotherapy for that indication. However, for atezolizumab overall quality of evidence was inferior. The combination of first-line PD-1/PD-L1 inhibitors with anti-CTLA-4 antibodies has also been shown to improve survival compared to platinum-based chemotherapy in advanced NSCLC, particularly in people with high tumour mutational burden (TMB)[3]. In the PD-L1 expression >= 50% group single-agent ICI probably improved OS compared to platinum-based chemotherapy (hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.60 to 0.76, 6 RCTs, 2111 participants, moderate-certainty evidence). In this group, single-agent ICI also may improve PFS (HR: 0.68, 95% CI 0.52 to 0.88, 5 RCTs, 1886 participants, low-certainty evidence) and ORR (risk ratio (RR):1.40, 95% CI 1.12 to 1.75, 4 RCTs, 1672 participants, low-certainty evidence). HRQoL data were available for only one study including only people with PDL1 expression E 50%, which suggested that single-agent ICI may improve HRQoL at 15 weeks compared to platinum-based chemotherapy (RR: 1.51, 95% CI 1.08 to 2.10, 1 RCT, 297 participants, low-certainty evidence)[3]. Double-ICI treatment probably prolonged OS compared to platinum-based chemotherapy in people with PD-L1 expression ≥ 50% (HR: 0.72, 95% CI 0.59 to 0.89 2 RCTs, 612 participants, moderate-	☒ Yes ☒ No ☐ Not applicable

certainty evidence)[3]. For 65 yrs and older the addition of ICIs to platinum-based chemotherapy probably increased overall survival compared to platinum-based chemotherapy alone (hazard ratio (HR) 0.78, 95% confidence interval (CI) 0.70 to 0.88; 8 studies, 2093 participants; moderate-certainty evidence). The addition of ICIs to platinum-based chemotherapy probably improves progression-free survival (HR 0.61, 95% CI 0.54 to 0.68; 7 studies, 1885 participants; moderate-certainty evidence). However, these effects diminish with increasing age[4].

For cervical cancer, WHO CC supports the inclusion of pembrolizumab combined with chemotherapy, for cervical cancer ≥1% PD-L1 expression (CPS ≥1) based on median follow-up of 39.1 months. There are reported large gains in median overall survival (11 months more, 95% CI 5.8 more to 17.2 more). Also of note is the compatibility of treatment with HIV infection, prevalent in Sub-Saharan Africa, with no difference in PD-L1 expression. Women with and without HIV could benefit from pembrolizumab.

For cutaneous melanoma, compared to chemotherapy, anti-PD1 monoclonal antibodies (immune checkpoint inhibitors) improved overall survival (HR 0.42, 95% CI 0.37 to 0.48, 1 study, 418 participants; high-quality evidence) and probably improved progression-free survival (HR 0.49, 95% CI 0.39 to 0.61, 2 studies, 957 participants; moderate-quality evidence). Anti-PD1 monoclonal antibodies performed better than anti-CTLA4 monoclonal antibodies in terms of overall survival (HR 0.63, 95% CI 0.60 to 0.66, 1 study, 764 participants; high-quality evidence) and progression-free survival (HR 0.54, 95% CI 0.50 to 0.60, 2 studies, 1465 participants; high-quality evidence)[5].

As for colorectal cancer, pembrolizumab monotherapy (dMMR/MSI-H) shows important gains in OS and in PFS[6] and is considered standard-of-care.

The last column of Box 1 (below) complements information with WHO CC recommendations. Of the five recommendations from WHO CC (bright green, teal and blue), two show some level of conflicting quality of evidence data (teal and blue). However, as was pointed out, evidence suggests important gains in OS and in PFS[6] (teal). Light green signifies adequate criteria for application but no recommendation by WHO CC. Pink are medicines/indications not compliant with criteria and peach-coloured medicines/indications showing low quality of evidence without WHO CC recommendation. Orange shows proposal for reorganization of square box listing.

Box 1. Information synthesis of application/WHO CC recommendations.

Medicine (CANCER TYPE AND # trials)	Setting	ESMO score	Requirements	Evidence strength	WHO CC
Non-Small Cell Lung Cancer (11 trials)					
Pembrolizumab monotherapy	P1	5	PD-L1 ≥ 50%	MODERATE-LOW	YES
Atezolizumab monotherapy	P1	5	PD-L1 ≥ 50% (TC), ≥ 10% (IC)	LOW	YES
Cemiplimab monotherapy	P1	4	PD-L1 ≥ 50%	MODERATE-LOW	YES
Cemiplimab-based treatment	P1	4	PD-L1 ≥ 1%	MODERATE-HIGH	NO
Pembrolizumab-based treatment	P1	4	NR	MODERATE-HIGH	NO
Durvalumab/tremelimumab-based treatment	P1	4	NR	LOW	NO
Ipilimumab/nivolumab-based treatment	P1	4	NR	LOW	NO
Head and Neck Squamous Cell Carcinoma (1 trial)					
Pembrolizumab-based treatment	P1	4	NR	MODERATE	NO
Malignant melanoma (5 trials)					
Ipilimumab/nivolumab***	P1	4	NR	MODERATE	NO
Renal Cell Carcinoma (4 trials)					
Ipilimumab/nivolumab				LOW	NO
Pembrolizumab-containing combination regimens				LOW	NO
Hepatocellular carcinoma (2 trials)					
Atezolizumab-based treatment regimens				VERY LOW	NO
Durvalumab monotherapy				LOW	NO
Durvalumab/tremelimumab				MODERATE	NO
Biliary tract cancer (1 trial)					
Durvalumab-based treatment	P1	4	NR	MODERATE	NO
Oesophageal Squamous Cell Carcinoma (2 trials)					
Pembrolizumab-based treatment regimens	P1	4	PD-L1 CPS ≥ 10	LOW	NO
Nivolumab-based treatment regimens	P1	4	PD-L1 ≥ 1%	LOW	NO
Ipilimumab/nivolumab	P1	4	PD-L1 ≥ 1%	LOW	NO
ERBB2-negative gastric and gastro-oesophageal adenocarcinoma (3 trials)					
Pembrolizumab-based treatment				VERY LOW	NO
Nivolumab-based treatment				LOW	NO
Colorectal carcinoma (1 trial)					
Pembrolizumab monotherapy	P1	4	dMMR/MSI-H	LOW	YES
Triple-negative breast cancer (1 trial)					
Pembrolizumab-based treatment				LOW	NO
Cervical cancer					
Pembrolizumab-based treatment	P1	4	PD-L1 CPS ≥1	HIGH-MODERATE	YES
Endometrial carcinoma					
Dostarlimab-based treatment	P1	4	dMMR/MSI-H	LOW	NO

Does adequate evidence exist for the safety/harms associated with the proposed medicine?

☒ Yes ☒ No
☐ Not applicable

Immunotherapy-related adverse events are different from those resulting from chemotherapy and other cancer treatments. It is crucial to establish thorough screening protocols and vigilance for early detection and effective management of these events. ICIs lead to the downregulation of checkpoints that essentially block the body's immune response, leading to autoimmune phenomena. The most common immune-related adverse events (irAE) are cutaneous irAE, colitis, pneumonitis, hepatitis and endocrinopathies like thyroiditis or adrenal insufficiency. However, a variety of organ systems may be affected. The occurrence of immune-related adverse events is unpredictable but may occur with the first dose and has also been documented up to a year after treatment has been discontinued. In instances of suspected or likely irAE, further autoimmune and organ-specific diagnostics should be considered on a case-by-case basis.

Twenty per cent of people receiving an immune checkpoint inhibitor experience severe or life-threatening adverse events related to treatment. The most common serious adverse events are hypertension, anemia, nausea, and fatigue[7].

WHO CC supports the same indications based on safety outcomes (adverse events). The Experts favor

first-line monotherapy over the combination of immune checkpoint inhibitors with chemotherapy to reduce treatment-limiting toxicities[2]. Across indications, additional benefits from significant reductions of higher-grade adverse events were only noted for ICI monotherapy. The combination of immune checkpoint inhibitors (RR 3.49, 95% CI 2.12 to 5.77) probably increased toxicity compared to chemotherapy; and probably increased toxicity (RR 3.83, 95% CI 2.59 to 5.68) compared to monotherapy with anti-PD1 monoclonal antibodies. Grade 3-4 AEs may be less frequent with single-agent ICI compared to platinum-based chemotherapy (RR: 0.41, 95% CI 0.33 to 0.50, IU = 62%, 5 RCTs, 3346 participants, low certainty evidence)[3]. Compared to traditional chemotherapy, ICIs have a low risk of emetogenicity. Simultaneous administration with corticosteroids should be avoided. Infusion reactions caused by ICIs are rare, ranging from 0.2 to 5.8%. Management of infusion-related reactions should be according to severity and follow established standard operating procedures.	
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? The beneficial effects of ICIs may be lost if patients do not meet certain PD-L1 expression thresholds or MSI status requirements. These limitations still restrict the transferability of findings to broader cancer populations. Due to the selective nature of participant inclusion in efficacy studies, the generalisability of the data is limited and applies only to patients with good overall performance status and relatively few comorbidities. Patients with a history of autoimmune disease and infectious diseases such as HIV, hepatitis B, C, or tuberculosis were excluded from studies. Most ICIs approved for prioritised indications were supported only by single studies, (no comparisons of different ICI regimens). Thus, considering the limitations of head-to-head comparisons, application does not provide information on the interchangeability of different regulatory-approved ICI-containing treatment regimens.	☐ Yes ☒ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? The Cancer Experts noted that this advice for immune checkpoint inhibitors reflects on-label use as per the European Medicines Agency (EMA). (CC) PD-L1 expression can be used as a biomarker to predict the response to PD-1 and PD-L1 inhibitors. Among the most established PD-L1 expression scoring methods are the Tumour Proportion Score (TPS), Combined Positive Score (CPS), Tumour Cell Score (TC), and Immune Cell Score (IC). While for tumours with high PD-L1 expression levels, the exact threshold for positivity may be less critical, for tumours with lower PD-L1 expression levels, precise thresholds are of higher relevance because the difference between PD-L1 positive and negative, or even positivity at different cut-offs may impact the likelihood of outcome improvements. The WHO Cancer Experts raised concerns over feasibility in LICs related to the need for companion diagnostic tests to identify patients with ≥50% PD-L1 expression and rule out patients with tumors that harbor a targetable alteration, such as an EGFR mutation or ALK rearrangements. This may pose a problem in LMIC, even if in MIC searching for molecular alterations is more often available, and the cost associated with tests is a small fraction of the cost associated with treatment. All proposed ICIs are administered intravenously and may be given in an outpatient treatment setting, depending on the regimen, including regimens with chemotherapy. None of the drugs require co-medications, but, corticosteroids or immunosuppressants should be avoided before starting ICIs due to their potential interference with the drug's pharmacodynamic activity and efficacy. However, for prevention of infusion reactions, as premedication, is permitted. No primary preventative antiemetic medication is required. The administration of ICIs via peripheral venous access is generally considered safe, due to mechanism of action and in absence of cytotoxic medication. Nevertheless, extravasation should be avoided. In case of lower-grade reactions (grade 1-2 reaction), and continuation of the infusion is considered, the infusion rate should be decreased and patients closely monitored. Subsequent treatment doses should be given under close monitoring, and the need for premedication with antipyretics and antihistamines should be evaluated. In the case of grade 3-4 infusions-related reactions, aside from the appropriate emergency measures, including the administration of corticosteroids, treatment with the ICI should permanently be discontinued.	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? The WHO Cancer Committee Experts noted that even narrowing the indications and selection of immune checkpoint inhibitors to those that offer the greatest cost-benefit profile, immune checkpoint	☒ Yes ☐ No ☐ Not applicable

inhibitors are not affordable and indeed acceptable to several countries and health systems, especially those in LMICs and LICs, due to high cost, need for companion diagnostics and the risk of diverting resources at the expense of other essential medicines. For pembrolizumab prices per mg vary between approximately 12 USD (Australia) to 62 USD (US). For nivolumab, 11 (France) to 34 (US). Prices are stable over time (2018 on). Doses range form 200 to 500mg per cycle, which amounts to 2400 USD to 31000 USD depending on country, indication, dose. There is substantial evidence that much lower doses of both nivolumab and pembrolizumab provide maximal binding to their receptors, and that such binding is maintained for considerably longer than the registered dosing intervals of 2 or 4 weeks for nivolumab and 3 or 6 weeks for pembrolizumab. This could cut treatment costs while maintaining effectiveness. Additionally, vial sharing is a practical approach to cutting costs and improving access. Vial sharing allows precise doses to be administered without wastage, particularly in weight-based regimens, but proper techniques must be used to protect from contamination risks. Contributors of price: selective indications, role of diagnostics for treatment (biomarkers), like PD-L1 expression, MSI-H/dMMR (microsatellite instability), and TMB (tumor mutational burden), limited number of head-to-head studies. Some countries have conducted CE studies (Canada, Ireland, Norway) and price reductions are necessary to achieve CE thresholds – from 21 to 81 %, depending on indication, for pembrolizumab. For nivolumab, a 36-95% price reduction.	
Is the medicine available and accessible across countries? Based on the analysis of pembrolizumab and nivolumab, biosimilar entry is anticipated in the next 3 to 5 years (2028-2013 for pembrolizumab and to 2033 for nivolumab, in US, UK, Europe, China and Japan). It is anticipated that upon biosimilar entry, the cost of pembrolizumab will decrease up to 60%, while nivolumab may see a more moderate reduction. Despite these anticipated price reduction predictions, achieving prices that meet specific cost-effectiveness criteria will likely require additional strategies beyond the introduction of biosimilars. Patent barriers are still in place and will require strategies (i.e., biosimilars, procurement mechanisms, and tired licensing strategies) for expansion of access. Other ICIs vary in patent protection periods; cemiplimab may have full patent protection until 2025 and avelumab until 2036. The anticipated entry window of biosimilars between 2028 and 2033 could encounter delays due to actions (development of new formulations, alternative methods of use, combinations of APIs, and the pursuit of patent litigation) by the innovator to extend their exclusivity period. Evergreening is under way for subcutaneous formulations.	☐ Yes ☒ No ☐ Not applicable
Does the medicine have wide regulatory approval? ICIs have received regulatory approval in several countries. Findings of the WHO CC are based on EMA regulations. Regulatory approval in some indications only exists for treatment combinations rather than as single agents.	☒ Yes, for the proposed indication ☒ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable

Additional References

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