A.22 PD-1 / PD-L1 immune checkpoint inhibitors – EML 12 cancer entities

Reviewer summary

☒ Supportive for a number of the drug proposed

☐ Not supportive of the proposal

Justification (based on considerations of the dimensions described below):

Supported:

- Pembrolizumab monotherapy for
  - 1) colorectal cancer (deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H))
  - 2) non-small cell lung cancer (PD-L1 ≥50%)
- Pembrolizumab + chemotherapy for cervical cancer (CPS ≥1)
- Atezolizumab monotherapy for non-small cell lung cancer (PD-L1 ≥50%)
- Cemiplimab monotherapy for non-small cell lung cancer (PD-L1 ≥50%)

Not supported:

Durvalumab + chemotherapy for biliary tract cancer.
- Gain in overall survival below WHO threshold (3.6 months).

Durvalumab + chemotherapy for endometrial cancer (dMMR/MSI-H).
- Lack of mature overall survival data.
- ESMO-MCBS = 3.

Pembrolizumab + chemotherapy for gastric or gastro-esophageal junction adenocarcinoma.
- Gain in overall survival below WHO threshold (3.2 months).
- Possible increase in adverse events.

Nivolumab + chemotherapy for gastric or gastro-esophageal junction adenocarcinoma.
- Moderate gain in overall survival (4.8 months) offset by no difference in health-related quality of life and possible increase in adverse events.

Pembrolizumab + chemotherapy for head and neck squamous cell carcinoma.
- Moderate gain in overall survival (6 months) offset by poor performance status of patients outside of clinical trials. In these patients, adding pembrolizumab to chemotherapy is likely to be associated with a less pronounced gain in overall survival.

Camrelizumab for nasopharyngeal carcinoma.
- Lack of mature overall survival data.

Durvalumab monotherapy for hepatocellular carcinoma.
- Gain in overall survival below WHO threshold (2.3 months).
- Gains in overall survival varied across immune checkpoint inhibitors for this indication. This heterogeneity was interpreted as a limiting factor.

Atezolizumab + bevacizumab for hepatocellular carcinoma.
- Lack of mature overall survival data.
- Gains in overall survival varied across immune checkpoint inhibitors for this indication. This heterogeneity was interpreted as a limiting factor.

Durvalumab combined with tremelimumab for hepatocellular carcinoma.
- Gain in overall survival below WHO threshold (3.9 months).
- Gains in overall survival varied across immune checkpoint inhibitors for this indication. This heterogeneity was interpreted as a limiting factor.

Nivolumab combined with ipilimumab for malignant melanoma.
- Concerns over cost and adverse events associated with two immune checkpoint inhibitors and the additional burden of procuring and administering multiple medicines. Despite the benefit, adding another immune checkpoint inhibitor to be used in combination with nivolumab would present a further challenge in several settings, confounding the priorities that should remain the large-scale adoption of one PD-1 or PD-L1 immune checkpoint inhibitor.

Pembrolizumab + chemotherapy for non-small cell lung cancer (irrespective of PD-L1 expression).

	• Decision to support monotherapy over combination therapy based on strong biological rationale that patients with increased PD-L1 expression are likely to benefit more and the potential to avoid cytotoxic effects from chemotherapy. Nivolumab combined with ipilimumab and chemotherapy for non-small cell lung cancer (irrespective of PD-L1 expression). • Decision to support monotherapy over combination therapy based on strong biological rationale that patients with increased PD-L1 expression are likely to benefit more and the potential to avoid cytotoxic effects from chemotherapy. Cemiplimab + chemotherapy for non-small cell lung cancer (irrespective of PD-L1 expression). • Decision to support monotherapy over combination therapy based on strong biological rationale that patients with increased PD-L1 expression are likely to benefit more and the potential to avoid cytotoxic effects from chemotherapy. Durvalumab combined with tremelimumab for non-small cell lung cancer (irrespective of PD-L1 expression). • Decision to support monotherapy over combination therapy based on strong biological rationale that patients with increased PD-L1 expression are likely to benefit more and the potential to avoid cytotoxic effects from chemotherapy. Pembrolizumab + chemotherapy for esophageal squamous cell carcinoma. • Noted that pembrolizumab + chemotherapy was one of five immune checkpoint inhibitor-based treatments being proposed for this indication. • Less cost-effective compared to toripalimab and tislelizumab. • Against this backdrop, moderate gain in overall survival offset by cost, uncertainty in response durability, unclear role of PD-L1 expression as a predictive biomarker, potential for increased harms associated with poorer prognosis at baseline and lack of long-term data across the immune checkpoint inhibitors. Nivolumab combined with ipilimumab and chemotherapy for esophageal squamous cell carcinoma. • Noted that nivolumab combined with ipilimumab and chemotherapy was one of five immune checkpoint inhibitor-based treatments being proposed for this indication. • Less cost-effective compared to toripalimab and tislelizumab. • Against this backdrop, moderate gain in overall survival offset by cost, uncertainty in response durability, unclear role of PD-L1 expression as a predictive biomarker, potential for increased harms associated with poorer prognosis at baseline and lack of long-term data across the immune checkpoint inhibitors. Nivolumab + chemotherapy for esophageal squamous cell carcinoma. • Noted that nivolumab + chemotherapy was one of five immune checkpoint inhibitor-based treatments being proposed for this indication. • Less cost-effective compared to toripalimab and tislelizumab. • Against this backdrop, moderate gain in overall survival offset by cost, uncertainty in response durability, unclear role of PD-L1 expression as a predictive biomarker, potential for increased harms associated with poorer prognosis at baseline and lack of long-term data across the immune checkpoint inhibitors. Pembrolizumab + TKI (lenvatinib or axitinib) for renal cell carcinoma. • Heterogeneity in the results from randomized trials decreased confidence in the pooled estimate of benefit. • Concerns over cost-effectiveness outside of high-income countries. Nivolumab combined with ipilimumab for renal cell carcinoma. • Large gain in overall survival (13 months) offset by prohibitively high price of two immune checkpoint inhibitors. • Concerns over costs associated with two immune checkpoint inhibitors and additional burden of procuring and administering multiple medicines. Despite the benefit, the addition of another immune checkpoint inhibitor to be used in combination with nivolumab would present a further challenge in several settings, confounding the priorities that should remain the large-scale adoption of PD-1 or PD-L1 immune checkpoint inhibitors. Pembrolizumab + chemotherapy for triple-negative breast cancer. • Heterogeneity in the results from randomized trials. • Concerns over cost-effectiveness outside of high-income countries.

	• Feasibility concerns due to diagnostic requirements. Nivolumab combined with ipilimumab for colorectal cancer (dMMR/MSI-H). • Concerns over the cost associated with two immune checkpoint inhibitors and the additional burden of procuring and administering multiple medicines. Adding another immune checkpoint inhibitor to be used in combination with nivolumab would present a further challenge in several settings, confounding the priorities that should remain the large-scale adoption of one PD-1 or PD-L1 immune checkpoint inhibitor.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) • *Biliary tract cancer* **Not to be included** durvalumab combined with chemotherapy for the first-line treatment of biliary tract cancer, irrespective of PD-L1 expression. Small median OS benefit? (3.6 months more, 95% CI 1.1 more to 6.4 more) and does not meet the WHO EML Expert Committee recommended threshold for benefit of at least 4-6 months OS%/ gain for inclusion in the EML list. • *Cervical cancer* **Support** PD-1 antibody pembrolizumab combined with chemotherapyon the EML as a combination treatment for cervical cancer ≥1% PD-L1 expression (CPS ≥1) based on long-term (median follow-up of 39.1 months) and large gains in median overall survival (11 months more, 95% CI 5.8 more to 17.2 more). The subgroup analysis comparing OS in patients with or without concomitant bevacizumab found no difference (hazard ratio (HR) 0.63, 95% CI 0.47 to 0.87 and HR 0.74, 95% CI 0.53 to 1.04, respectively). No addition of bevacizumab. The global distribution of cervical cancer and the disproportionate burden in sub-Saharan Africa, where HIV prevalence is also high. Real-world evidence showed no difference in PD-L1 expression between squamous cervical carcinomas of Mozambican women living with and without HIV. In these areas, the cancer is often diagnosed at an advanced stage, leaving most patients without curative treatment options. As a result, management typically relies on palliative care through chemotherapy and/or radiotherapy, though many patients either develop resistance or experience recurrence. Women without and with HIV could benefit from pembrolizumab. Data demonstrate the safety of immune checkpoint inhibitor use in people living with HIV, where there is viral suppression through antiretroviral therapy. Therapeutic effects in this immunocompromised population could be confirmed via randomized trials in HIV endemic settings. • *Colorectal cancer* **Support** inclusion of pembrolizumab on the EML as monotherapy for dMMR/MSI-H colorectal cancer based on long-term and large gains in median overall survival. Higher and longer than can be obtained with chemotherapy. Appearance of a plateau. Update (5 year follow up) *André et al Ann Oncol 2025*Pembrolizumab monotherapy may result in a slight increase in health-related quality of life and a moderate decrease in adverse events compared to chemotherapy. There may be a problem in having access to proper IHC and next-generation sequencing to identify tumors with high MSI in countries with more resources. Additionally, there is evidence supporting the use of nivolumab combined with ipilimumab. Here, hurdles may be the price and access to two immune checkpoint inhibitors when compared to one PD-1 checkpoint inhibitor or chemotherapy, and the additional burden of procuring and administering multiple medicines. Furthermore, the	☒ Yes ☐ No ☐ Not applicable

added value of ipilimumab to nivolumab might be limited. Therefore, **this combination is not supported**

- *Endometrial cancer:* **Not supported** Dostarlimab combined with chemotherapy resulted in extremely large and long-term gains in overall survival (66.7 months more, 95% CI: 18.4 more to 153.3 more), and quality of life (QoL) improved slightly. Overall survival data for pembrolizumab combined with chemotherapy were promising but immature.
Concerns regarding the lack of access to established backbone chemotherapy in their settings. Paclitaxel plus carboplatin, as standard first-line chemotherapy for endometrial cancer, offers meaningful gains in overall survival and should be prioritized for addition to the WHO EML before considering immune checkpoint inhibitors for this indication.

- *Gastric or gastro-esophageal junction adenocarcinoma* **No support** for the inclusion of pembrolizumab combined with chemotherapy and nivolumab combined with chemotherapy for the 1st-line treatment of erythroblastic oncogene B (ErbB) 2-negative gastric/gastro-esophageal junction adenocarcinoma with ≥1% PD-L1 expression and ErbB2-negative, gastric/gastro-esophageal junction adenocarcinoma with ≥5% PD-L1 expression, respectively. Limited gains in median OS (3.17 months more for pembrolizumab-based treatment and 4.76 months more for nivolumab-based treatment), trivial to no difference in health-related quality of life, and possible increases in adverse events (CTCAE ≥ 3).

- *Head and neck squamous cell carcinoma* **No support** for the inclusion of pembrolizumab combined with chemotherapy for the 1st-line treatment of head and neck squamous cell carcinoma. The magnitude of benefit, of OS gain was moderate (6 months more).

- *Hepatocellular carcinoma* **No support** for the inclusion of atezolizumab combined with bevacizumab, durvalumab monotherapy, and durvalumab combined with tremelimumab for the 1st-line treatment of hepatocellular carcinoma, irrespective of PD-L1 expression.
The largest effect on OS was observed in the randomized trial addressing atezolizumab combined with bevacizumab, which also had the shortest follow-up (median OS 6.9 months longer based on a median follow-up of 15.6 months). The magnitude of effect was below the EML threshold of 4-6-month overall survival gain after long-term follow-up of patients randomized to durvalumab monotherapy (median overall survival 2.25 months more based on a median follow-up of 47.9 months) and durvalumab combined with tremelimumab (median overall survival 3.9 months more based on a median follow-up of 48.2 months).
The duration of follow-up and gains in OS varied across immune checkpoint inhibitors. This heterogeneity was interpreted as a factor limiting the generalizability of a benefit.

- **Malignant melanoma** *No support* for the inclusion of nivolumab combined with ipilimumab for the 1st-line treatment of malignant melanoma irrespective of PD-L1 expression or BRAF V600-mutation.
The Cancer Experts concluded that nivolumab combined with ipilimumab, compared to monotherapy (ipilimumab or nivolumab), provided long-lasting and substantial benefits in overall survival (OS) in patients with malignant melanoma, regardless of PD-L1 expression (median 12.8 months more OS, based on a median follow-up of 34.6 months). There is an increased price and adverse events with combination therapy vs monotherapy with nivolumab or pembrolizumab. Only a minority of settings have the resources to recognize and address treatment-related adverse events promptly. Nivolumab and pembrolizumab (as a therapeutic alternative to nivolumab) have been listed on the Model List for malignant melanoma as monotherapies since 2019. The adoption of immune checkpoint inhibitors is still in its infancy in many countries. Despite being beneficial, the addition of another immune checkpoint inhibitor to be used in combination with nivolumab would present a further challenge in several

settings, potentially confounding the priorities of large-scale adoption of nivolumab or pembrolizumab.
Given the dominant role of pembrolizumab in the therapeutic landscape for malignant melanoma and other cancers, it can be considered to list nivolumab as a therapeutic alternative to pembrolizumab instead, reversing the current listing in the EML.
Application addressing pembrolizumab and nivolumab for the treatment of malignant melanoma in children, relevant for inclusion in the EMLc in the future.

- *Non-small cell lung cancer (NSCLC)* **Support the inclusion of pembrolizumab, atezolizumab, and cemiplimab as monotherapy for oncogenic-driver wild-type NSCLC ≥50% PD-L1 expression, which reflects EMA-approved on-label use.**

No support for inclusion of tislelizumab combined with chemotherapy for oncogenic-driver wild-type non-small cell lung cancer ≥50% PD-L1 expression.
No support for inclusion of cemiplimab combined with chemotherapy, durvalumab combined with tremelimumab combined with chemotherapy, nivolumab combined with ipilimumab combined with chemotherapy, pembrolizumab combined with chemotherapy, and sugemalimab combined with chemotherapy for the 1st-line treatment of oncogenic-driver wild-type NSCLC irrespective of PD-L1 expression.
Meaningful gains in OS with immune checkpoint inhibitors in treating NSCLC in the 1st-line setting. Cemiplimab monotherapy increased median OS by 8 months (95% CI 4.1 more to 12.6 more; median follow-up of 35 months), pembrolizumab monotherapy increased median OS by 6.3 months (95% CI 3.9 more to 9.2 more; median follow-up of 61 months) and atezolizumab monotherapy increased median OS by 3.7 months (95% CI 1.1 fewer to 11.8 more; median follow-up of 35.6 months). The gain in median OS with atezolizumab monotherapy might be underestimated, given that a proportion of trial participants received immune checkpoint inhibitors in the subsequent treatment line. Furthermore, atezolizumab is one of the few immunotherapies tested in a phase 3 international trial including patients with advanced NSCLC who were ineligible for platinum-based chemotherapy due to poor performance status, advanced age, or comorbidities. While OS is poor irrespective of therapy (atezolizumab, vinorelbine, or gemcitabine), atezolizumab was associated with less severe toxicities.
The tislelizumab combined with chemotherapy for NSCLC ≥50% PD-L1 expression with no EGFR or anaplastic lymphoma kinase (ALK) positive mutations in the first-line setting, received an ESMO-MBS non-curative score of 4, partly based on an improved quality of life. The evidence and regulatory approval for tislelizumab monotherapy for NSCLC ≥50% PD-L1 expression. is lacking; therefore, no support for the inclusion of this combination therapy.
The decision to support the inclusion of monotherapy over combination therapy is based on the strong biological rationale that patients with increased PD-L1 expression are likely to benefit more and the potential to avoid cytotoxic effects from chemotherapy. Pembrolizumab monotherapy probably results in a large reduction in adverse events (risk ratio 0.49, 95% CI 0.37 to 0.66) and may result in a meaningful improvement in health-related quality of life. The addition of chemotherapy may compromise such improvements in safety and health-related quality of life. Indirect evidence shows that tislelizumab as monotherapy is associated with OS benefits when used as second- or third-line treatment in NSCLC. In this setting, tislelizumab OS benefit was considered relevant compared to docetaxel (median 17.2 versus 11.9 months).
There may be some 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. The scenario is more variable in middle-income countries, where searching for molecular alterations is more often available, and the price associated with tests is a small fraction of the price associated with treatment.
Immune checkpoint inhibitors for NSCLC are likely not cost-effective in most settings, especially in low-resource settings, and risk diverting resources at the expense of other essential medicines. However, supporting the inclusion of immune checkpoint inhibitor monotherapy in patients with ≥50% PD-L1 expression over combination therapy in all patients, irrespective of PD-L1 expression, can guide countries in prioritizing these

medicines for the indications in which the benefits would be the largest. Consider prioritization, supporting the inclusion of pembrolizumab monotherapy as the class representative for this indication on the WHO EML and highlighting that atezolizumab monotherapy and cemiplimab monotherapy may be used as therapeutic alternatives. • *Esophageal squamous cell cancer* **No support** for the inclusion of pembrolizumab combined with chemotherapy for 1st-line treatment of esophageal squamous cell carcinoma ≥10% PD-L1 expression, nor nivolumab combined with chemotherapy and nivolumab combined with ipilimumab combined with chemotherapy for the first-line treatment of esophageal squamous cell carcinoma ≥1% PD-L1 expression. Pembrolizumab combined with chemotherapy, nivolumab combined with chemotherapy, and nivolumab combined with ipilimumab combined with chemotherapy are three of five immune checkpoint inhibitor treatments considered for the front-line treatment of esophageal squamous cell cancer. Against the backdrop of this comprehensive evaluation of immune checkpoint inhibitors, pembrolizumab, nivolumab, and nivolumab combined with ipilimumab are likely the least cost-effective options when compared to tislelizumab and toripalimab, which are covered in separate applications. Evidence from a network meta-analysis addressing the comparative effectiveness of immune checkpoint inhibitors for esophageal squamous cell cancer, which found consistent magnitudes of relative effects on OS survival between the medicines. The absolute effects calculated in the current application were also comparable. The median increases in OS were 6.6, 6.3, and 5.6 months for pembrolizumab combined with chemotherapy, nivolumab combined with chemotherapy, and nivolumab combined with ipilimumab combined with chemotherapy, respectively. The gains in OS from pembrolizumab combined with chemotherapy, nivolumab combined with chemotherapy and nivolumab combined with ipilimumab combined with chemotherapy to be moderate in size, but that these benefits were offset by the price, uncertainty in response durability, unclear role of PD-L1 expression as a predictive biomarker, potential for increased harms associated with poorer prognosis at baseline, and lack of long-term data across the immune checkpoint inhibitors. • *Renal cell carcinoma* **No Support** There is heterogeneity in results addressing immune checkpoint inhibitors for renal cell carcinoma and concerns over cost-effectiveness outside of HICs. The inclusion of nivolumab combined with ipilimumab and pembrolizumab-based treatments (pembrolizumab combined with axitinib and pembrolizumab combined with lenvatinib) for 1st-line treatment of renal cell carcinoma irrespective of PD-L1 expression is not supported. The same is the case for not including nivolumab combined with cabozantinib, as well as avelumab combined with axitinib, for which additional evidence was presented during the in-person meeting. The increase in median OS for patients randomized to nivolumab combined with ipilimumab versus sunitinib is large (13 months more, 95% CI 6.5 more to 20.8 more). Still, it is questionable whether the benefit is justified given the increased price associated with treatment based on two immunotherapy drugs when the price of one immunotherapy drug is already prohibitively high in most settings. When compared to sunitinib, the the pooled estimate from the meta-analysis of two randomized trials – one evaluating pembrolizumab combined with lenvatinib and the other pembrolizumab combined with axitinib – demonstrated a meaningful benefit (HR for death 0.83, 95% CI 0.72 to 0.94). However, heterogeneity in the results of the individual trials, which decreased their certainty of the magnitude of the pooled estimate. The Cancer Experts flagged additional uncertainty regarding the optimal positioning of immune checkpoint inhibitors and TKIs (e.g., in sequence or in combination). Additional evidence from trials addressing nivolumab combined with cabozantinib and avelumab combined with axitinib – both of which randomized patients to sunitinib in the control arm. Based on ESMO-MCBS scorecards, nivolumab combined with cabozantinib and avelumab combined with axitinib resulted in limited benefit (non-curative scores of 1 and 3, respectively).	

Nivolumab combined with ipilimumab may reduce adverse events compared to sunitinib; however, adding a TKI to pembrolizumab probably increases adverse events slightly. Thus, immunotherapy alone may be better tolerated than TKIs, but not when used with a TKI. The price of sunitinib is lower than that of other TKIs included as immunotherapy partners, and if used with immunotherapy instead of lenvatinib, axitinib, or cabozantinib, it has the potential to reduce the price of immunotherapy combined with TKI combination treatments. • *Triple-negative breast cancer* **No support** for the inclusion of pembrolizumab combined with chemotherapy for the 1st-line treatment of advanced triple-negative breast cancer, CPS ≥10, because of heterogeneity in results and concerns over cost-effectiveness outside of HICs and feasibility due to diagnostic requirements. The median OS benefit with pembrolizumab-based treatment is moderate (6 months more, 95% CI 0.8 to 13.2 months more). A phase 3 trial of chemotherapy with or without atezolizumab for early relapsing unresectable locally advanced or metastatic triple-negative breast cancer found no OS benefit with atezolizumab-based treatment.	
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable For the indications suggested to be approved
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) IHC, geneotyping And knowledge regarding side effects of immune checkpoint inhibitors	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? See Cherny et al, Ann Oncol 2025	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes) See also Chernu et al, Ann Oncol 2025	☒ Yes ☐ No ☐ Not applicable Although not always not all
Does the medicine have wide regulatory approval?	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable