A.5	Anti-PD-L1 immune checkpoint inhibitors – non-small cell lung cancer – EML
Draft recommendation	☐ Recommended ☒ Not recommended Justification: This Application refers to the inclusion of anti-PD1 and anti-PD-L1 immune-checkpoint inhibitors for • the treatment of metastatic non-small cell lung cancer (NSCLC) with PD-L1≥50% on tumour cells (pembrolizumab, atezolizumab, cemiplimab) • the consolidative treatment of locally-advanced, unresectable NSCLC post-chemo-radiotherapy with tumour expression of PD-L1≥1% (durvalumab). Anti-EGFR tyrosine kinase inhibitors are included in the WHO Model List for EGFR-mutated NSCLC, while for "wild type" NSCLC only all chemotherapeutics are listed. Their effect in terms of median overall survival is about 12 months. Nivolumab (with a square box indicating pembrolizumab as alternative) is included in the WHO Model List for the treatment of metastatic melanoma. No other treatments for melanoma are included. Immune checkpoint inhibitors have been previously considered for inclusion for NSCLC in 2019 and 2021. Listing was not recommended because, at current prices, these medicines are prohibitively expensive in many settings and treatment costs are also increased by the need for diagnostic testing for patient selection. Immune checkpoint inhibitor therapy has become part of the treatment of NSCLC patients without druggable mutations (wild-type or non-oncogene), based on favourable improvements in clinical outcomes. Overall, immune checkpoint inhibitors meet the minimum thresholds for overall survival benefit for possible inclusion on the WHO EMLs: medicines for solid tumours must have an ESMO Magnitude of Clinical Benefit Scale of 4 or 5 in the non-curative setting (at least 4–6 months indicating high or substantial benefit). The Application proposes their inclusion in the first-line treatment, the setting that tend to offer better value to improve health outcomes. (Jenei et al., Lancet Glob Health 2022; 10: e1860–66) Feasibility, the extent to which a new medicine can be successfully implemented within a given setting, and cost of treatment are critical. Without a strategic approach for managing the introduction of innovative cancer therapies into health-care systems, including agreements with the manufacturer, there is a concrete risk that listing immune checkpoint inhibitor for NSCLC can increase discrepancies in access, rather than decrease them. In conclusion, while concerns about the robustness of efficacy data are dispelled by the data included in the current Application compared to the previous ones, feasibility and cost effectiveness issues remain. Therefore, this Reviewer cannot support the inclusion of immune-checkpoint inhibitors at this time.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: In 2020, 2.2 million people received a diagnosis of lung cancer, corresponding to 11.4% of all cancers diagnosed; 1.8 million died for this disease, that is 18% of all cancer-related deaths. Lung cancer is a highly lethal malignancy, with an economic impact estimated at around US$ 8 billion in lost productivity in emerging countries. Moreover, in the absence of wide coverage of an effective screening programme in place globally, lung cancer diagnoses occur in advanced stages in more than 60% of cases, with highly world regional variability. Up to 90% of lung cancers are linked to the tobacco consumption. Over 80% of the lung cancers are classified as NSCLC. Targeted therapies have redefined the therapeutic landscape for patients with molecularly druggable NSCLC (e.g., epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, ROS1 rearrangements, BRAF mutations, HER2 mutations or amplifications, NTRK1-3 fusions). However, these therapies are ineffective in the majority of NSCLC people who have tumours lacking such genetic alterations.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The Application is mainly based on the clinical guidelines of the European Society of Medical Oncology (ESMO) for the treatment of advanced-metastatic lung cancer (Planchard et al., Ann Oncol Off J Eur Soc Med Oncol. 2018;29(Suppl 4):iv192-iv237 and Wu et al., Ann Oncol. 2019;30(2):171-210). Additional information derives from recent abstract presented to the 2021-2022 main international oncology meetings. Overall, anti-PD1 immune checkpoint inhibitors meet the minimum thresholds for overall survival benefit for possible inclusion on the WHO EMLs: medicines for solid tumours must have an ESMO Magnitude of Clinical Benefit Scale of 4 or 5 in the non-curative setting (at least 4–6 months indicating high or substantial benefit). Systematic reviews and meta-analysis showed an improvement of overall survival in people with NSCLC and PD-L1 expression ≥50% (moderate quality of evidence) compared to platinum-based chemotherapy. The median OS prolongation is about 13 and 7 months with pembrolizumab and atezolizumab respectively. Trials also suggest a potential impact on PFS and ORR and a better safety profile. Data on quality of life are of low quality suggesting a possible effect. No head-to-head comparisons were reported; thus it is not possible to conclude on the comparative effectiveness of these treatments (Ferrara et al., Cochrane database Syst Rev. 2021;4(4). doi:10.1002/14651858.CD013257.PUB3) Below, a summary of the main trials included in the Application. **First-line metastatic EGFR-/ALK- NSCLC with PD-L1≥50%** *Pembrolizumab* KEYNOTE-024: 305 participants randomised to 200 mg pembrolizumab every 3 weeks (up to 2 years) or 4-6 cycles of standard platinum-doublet chemotherapy. At a median follow-up of 5 years, median OS was 26.3 months (95% CI, 18.3 to 40.4) for pembrolizumab and 13.4 months (9.4-18.3) for chemotherapy (HR, 0.62; 95% CI, 0.48 to 0.81). 66% effective crossover rate. Both the ICI and chemotherapy were not associated with a clinically meaningful change of the QoL. (refs: Reck et al., N Engl J Med. 2016;375(19):1823-33; Reck et al., J Clin Oncol. 2019;37(7):537-46; Brahmer et al., Ann Oncol. 2020;31:S1181-S2; Brahmer et al., Lancet Oncol. 2017;18(12):1600-9). *Atezolizumab* IMpower110 Study: 572 participants randomised to atezolizumab 1200 mg intravenously or 4-6 cycles of platinum-based chemotherapy once every 3 weeks. At a median follow-up of about 1.3 years, the median OS for atezolizumab and chemotherapy in the population with high-PD-1 was 20.2 months vs. 13.1 months; (HR 0.59, 0.40 to 0.89). A more mature analysis with a median follow-up of about 2.5 years (post hoc), reported a median OS of 20.2 months with atezolizumab and 14.7 months with chemotherapy, consistently with the primary analysis. No substantial differences in QoL. (refs: Socinski et al., N Engl J Med. 2018;378(24):2288-301; Marinis et al., J Clin Oncol. 2020;38(15_suppl):9594)

	Cemiplimab EMPOWER-lung 1: 563 participants randomised to cemiplimab or 4-6 cycles of platinum-based doublet chemotherapy. At a median follow up of 10.8 months, median OS was not reached with cemiplimab (17.9- not evaluable) vs 14.2 months (11.2 – 17.5) with chemotherapy (HR: 0.57, 0.42 to 0.77). No substantial differences in QoL. (ref: Sezer et al., Lancet 2021;397(10274):592-604; Gumus et al., Cancer 2023;129(1):118-129) **First-line for locally-advanced, unresectable EGFR-/ALK- NSCLC post-chemo-radiotherapy with tumour expression of PD-L1≥1%** Durvalumab PACIFIC: 713 participants (irrespective of PD-L1 level) randomised 2:1 to receive 10 mg/kg durvalumab or placebo via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. At a median follow-up of 34.2 months, the median OS was 47.5 months with durvalumab versus 29.1 months with placebo (stratified HR 0.68, 0.53-0.87). The exploratory analysis based on the PD-L1 expression showed that patients seemed to derive the greatest benefit when PD-L1 was ≥1%. No substantial differences in QoL. Data interpretation is affected by post progression treatment/re-treatment and by the choice of population (concomitant chemotherapy).
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: According to the Cochrane Review published in 2021, immune checkpoint inhibitors were associated with reduced grade 3 to 5 adverse events compared to platinum-based chemotherapy (RR: 0.41, 95% CI 0.33 to 0.50, 5 RCTs, 3346 participants, low certainty evidence). No difference in toxic deaths (grade 5 adverse events) was found. Immune-mediated adverse events, e.g., pneumonitis, hepatitis, colitis, endocrinopathies, are common with immune checkpoint inhibitors. The most common adverse events with pembrolizumab are diarrhea, fatigue, pyrexia, and pruritus, generally of low to modest grade. The most common adverse events with atezolizumab and cemiplimab are anaemia, neutropenia, thrombocytopenia, hepatic laboratory abnormalities, rash, and hypothyroidism. The most common adverse events with durvalumab are thyroid disorders, dermatitis, and rash, and diarrhea.

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Immune-mediated adverse reactions may be severe and fatal in some circumstances. Identification, evaluation, and management of cutaneous, gastrointestinal, lung, endocrine, musculoskeletal, renal, hematologic, cardiovascular toxicities are desirable and influence the decision of treatment suspension.
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)	☒ Yes ☐ No ☐ Not applicable Comments: The selection of people with NSCLC that may benefit from the treatment with immune checkpoint inhibitors is of utmost importance. Firstly, there is the need to exclude the presence of druggable mutations, through an appropriate testing for EGFR, ALK and ROS1 status. Secondly, there is the need to assess the PD-L1 tumour expression using a validated test. Therefore, access to appropriate infrastructure, valid companion diagnostics, quality assurance programs and training should be ensured to adequately administer immune checkpoint inhibitor. These issues apply to other target therapies for cancer, but they are likely to have a bigger impact in this setting.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: It is reasonable to expect that treatment with anti-PD1 immune checkpoint inhibitors will be relatively costly, and despite its benefits in OS, the threshold for cost-effectiveness may be exceeded in different settings and countries. The analyses included in the Application reported that immune checkpoint inhibitors are not cost effective in several setting. Duration
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: Pembrolizumab, atezolizumab, cemiplimab, durvalumab are licensed in several countries for the treatment of NSCLC and other malignancies. Primary patents will expire not earlier than 2028 (Pembrolizumab), 2029 (Atezolizumab), 2035 (Cemiplimab), 2030 and 2034 (Durvalumab). A variety of secondary patents also exists.

Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: