A.1	Anti PD-1 and PDL-1 checkpoint inhibitors as a therapeutic group for the treatment of non-oncogene addicted locally advanced and metastatic NSCLC
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments:
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Patients with stage IV NSCLC. The 5 years relative survival rates with chemotherapy are <10%. Immunotherapy has altered the treatment approach for patients with NSCLC without oncogenic driver mutations and PD-L1 >50%. In this group pf patient's single agent checkpoint inhibitors have prolonged both PFS and OS compared to chemotherapy. PDL-1 + ve tumors account for 20-25% of all NSCLC. KEYNOTE-024. Phase III trial with >50% PD-L1 staining (n=305). Median F/U 11.2 months. PFS 10.3 months vs 6 months; HR 0.50,95% CI 0.37-0.68. ORR: 45% vs 28% Median duration of response NR with pembrolizumab vs 6.3 months with chemotherapy.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: A recent publication: Association between first line immune checkpoint inhibition and survival for Medicare insured patients with advanced NSCLC (1). Patient number = 19,529, age >65, first line immunotherapy, immunotherapy + chemotherapy and chemotherapy. Median OS 11.4 months for immunotherapy (15 months shorter than KEYNOTE-024) and 12.9 months (10 months shorter than survival outcome with chemoimmunotherapy) in patients receiving chemoimmunotherapy. However, this maybe related to poor selection patients with low PDL-1 which may not provide substantial benefit, poor performance status and more ill. Patient selection for immunotherapy extremely important

<table>
<tr><td>Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?</td><td>☒ Yes
☐ No
☐ Not applicable

Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).

<table><tr><th>N = 305</th><th>Pembrolizumab</th><th>Chemotherapy</th></tr><tr><td>Overall survival (median)</td><td>26.3 m (95% CI, 18.3 – 40.4)</td><td>13.4 m (95% CI, 9.4 – 18.3)</td></tr><tr><td>5-year OS</td><td>31.9% (95% CI, 24.5 – 39.5)</td><td>16.3 (95% CI, 10.6 – 23.0)</td></tr><tr><td>PFS at 3 y
PFS at 5 y</td><td>22.8% (95% CI, 16.3 – 29.9)
12.8% (95% CI, 7.4– 19.8)</td><td>4.1% (95% CI, 1.3 – 9.4)
0</td></tr></table>>66% cross over rate in the trial.

A recent meta-analysis shows similar performance of different PD-1 antibodies.

Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?

NO</td></tr>
<tr><td>Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?</td><td>☒ Yes
☐ No
☐ Not applicable
Comments:</td></tr>
<tr><td>Are there any adverse effects of concern, or that may require special monitoring?</td><td>☒ Yes
☐ No
☐ Not applicable
Comments:

Treatment related grade 3-5 adverse event 31.2% with pembrolizumab vs. 53% in patients who received chemotherapy. 2 treatment related death in pembrolizumab and 3 in chemotherapy arm. Discontinuation rate 13.6% pembrolizumab and 10.7% chemotherapy</td></tr>
<tr><td>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</td><td>With Pembrolizumab as monotherapy 5 years overall survival rate is approximately 30% in patients with advanced. NSCLC

Patients treated with pembrolizumab had improved 5-year overall survival rates compared with patients treated with platinum-based chemotherapy (31.9% v 16.3%).

Pembrolizumab continues to provide long-term improved patient outcomes over chemotherapy for patients with metastatic NSCLC with PD-L1 >50% in the first-line treatment setting.

Evidence for other checkpoint inhibitors is not as robust yet.

However, a recent meta-analysis suggests similar performances for other checkpoint inhibitors including, nivolumab + ipilimumab, atezolizumab (which have regulatory</td></tr>
</table>

	approval for metastatic NSCLC) could be considered as possible alternatives.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Pembrolizumab monotherapy in patients with >50% PD-L1 expression has MCBS score of 5 and significant median OS gain of 16 months. There was a greater than 50% cross-over in trial. Nivolumab in first line does not meet the EML criteria for survival gain (median OS gain 3.2 months (squamous), median OS gain 2.8 months (non-squamous). Nivolumab in combination with ipilimumab is effective Atezolizumab in first line: Has shown efficacy. Overall quality of evidence is high and long-term data is available.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: The companion diagnostic test to determine PDL-1 expression for pembrolizumab PD-L1 IHC 22C3. For Nivolumab: PD-L! IHC. 28-8 For atezolizumab: SP142 assay Need monitoring of thyroid function tests, cortisol levels
Are you aware of 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:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: pembrolizumab and nivolumab have been approved for treatment of melanoma and listed on the EML. .

Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Pembrolizumab first line for PDL-1 >50% is considered cost effective by NICE and CADTH. Cost effectiveness in other countries not proven using the price list available. In low middle income countries, the cost-effectiveness is not proven using the list price available in countries, but rather at discounted prices negotiated with health system payers. Weight based dosing maybe preferred (2mg/kg) over fixed dosing due to lower cost without loss of benefit. Budget impact will be very high in LMICs. Individual negotiations at the country level will have to be done by the governments concerned. Not all checkpoint inhibitors are approved and available in low middle income countries. The current price for atezolizumab for 12 cycles on a patient access program (buy1 get 1 free) is approximately ($12,905) while 6 cycles of chemotherapy are <$2000.
Any additional comments	1 The observed differences in trial results between drugs may be related trial design and patient's selection 2. It is not possible to rule out possibility of inherent differences between drugs within the class. 3. Price competition is minimal where all medicines are available in high income countries. 4. Since meta-analysis shows that checkpoint inhibitors show more or less similar efficacy, so possible alternatives for selection can be considered.
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	Based on available data Checkpoint inhibitors have changed the landscape of NSCLC without a driver mutation especially in patients with PDL-1>50%. The application is for inclusion of PD-1/PD-L1 immune checkpoint inhibitors (pembrolizumab, nivolumab and atezolizumab) as first line treatment for metastatic NSCLC with PD-L1 expression >50%. The strongest evidence is available for **pembrolizumab**. Unfortunately, the financial implications of approving these extremely expensive medicines will decimate the entire health care budget of LMICs. We should review the application once biosimilars are available and the cost of treatment becomes more sustainable for the governments and patients. NOT APPROVED 1. Median duration of treatment suggested is until disease progression. 2. Approval applied for locally advanced/metastatic disease for which treatment is palliative. 3. Severe financial implications as lung cancer is the second most common cancer in the world. 4. Most LMICs are unable to negotiate with MNC to bring the cost of treatment at a sustainable level.
References (if required)	1. Association between first line checkpoint inhibition and survival for Medicare-Insured patients with advanced Non-Small Cell Lung Cancer. Kiel et al, JAMA Network Open, May 21, 2021.