

A.1 (item number)	Anti-PD1 immune checkpoint inhibitors – NSCLC (application title)
Does the application adequately address the issue of the public health need for the medicine?	<p>g Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: <i>Lung cancer is the most diagnosed and the first cause of death for cancer worldwide, estimating 2 million new cases and 1.7 related deaths in 2018, according to Global Cancer Observatory 2018 [IARC 2020].</i></p> <p><i>In additional to its clinical impact, lung cancer is associated with an economic burden estimated around \$8 billion productivity lost in the BRICS countries [Miguel 2017].</i></p>
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.	<p><i>The applicant requested the addition in the EML of the following anti-PD immune checkpoint inhibitors ICI) for locally advanced and metastatic NSCLC: pembrolizumab, nivolumab, atezolizumab and durvalumab.</i></p> <p><i>The following indications were recommended:</i></p> <ul style="list-style-type: none"> <i>• Frontline (pembrolizumab, atezolizumab) in metastatic NSCLC expressing high levels of PD-L1.</i> <i>• Frontline (pembrolizumab) in combination with cytotoxic chemotherapy in metastatic squamous and nonsquamous NSCLC irrespective of tumour PD-L1 expression.</i> <i>• As frontline consolidation (durvalumab) for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on $\geq 1\%$ of tumour cells and whose disease has not progressed following platinum based chemoradiation therapy.</i> <i>• After chemotherapy failure, as second line regimen, in PD-L1 positive (pembrolizumab) or non-PD-L1 selected patients (nivolumab, atezolizumab) in NSCLC. Both the indications are intended for squamous and nonsquamous histology NSCLC.</i>
Have all important studies and all relevant evidence been included in the application?	<p><input type="checkbox"/> Yes</p> <p>g No</p> <p><input type="checkbox"/> Not applicable</p> <p>If no, please provide brief comments on any relevant studies or evidence that have not been included:</p> <p><i>A recent Cochrane review that assessed single or combined immune checkpoint inhibitors compared to first-line platinum-based chemotherapy with or without bevacizumab for people with advanced NSCLC was not included in the application [Ferrara 2021].</i></p>

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<p>Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>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).</p> <p><i>The applicant presented individual evidence from RCTs for each of the proposed therapeutic scenario. Overall, all RCTs found some benefit of anti-PD1 ICI on OS for locally advanced or metastatic NSCLC.</i></p> <p>Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?</p> <p><i>No subgroups analysis was provided for low-resource settings.</i></p>
<p>Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p>
<p>Are there any adverse effects of concern, or that may require special monitoring?</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p>
<p>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</p>	<p><i>Because of the suggested benefit from RCTs in clinically relevant endpoints, such as overall survival, favouring all assessed anti-PD1 immune checkpoint inhibitors for each specific indication, the overall benefit to risk ratio is favourable.</i></p>
<p>Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)</p>	<p><i>The overall quality of evidence is low to moderate, with some concerns around risk of bias and imprecision for some relevant endpoints, especially safety endpoints.</i></p>
<p>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)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments: <i>Most of indications for anti-PD1 ICI would require a PD-L1 testing for identifying eligible patients. This may be also of concern in low resource settings.</i></p>
<p>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)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p>

<p>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)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: not found.</p>
<p>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</p>	<p><i>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.</i></p> <p><i>The applicant did not present a cost projection in different settings but provided results from different cost-effectiveness analysis published in the literature that covers some of the therapies inclusion proposals.</i></p> <p>A Frontline treatment with pembrolizumab as monotherapy in PD-L1-high, EGFR/ALK wild type NSCLC</p> <p><i>CEA alongside a clinical trial (US third-party, public healthcare payer) [Huang 2017]</i></p> <ul style="list-style-type: none"> • 5-year time horizon: ICER = \$US99,998/LY or \$US122,024/QALY • 10-year time horizon: ICER = \$US83,065/LY or \$US103,101/QALY <p>Use of immune-checkpoint inhibitor pembrolizumab in combination with cytotoxic chemotherapy in first line for unselected NSCLC patients without actionable oncogenic driver.</p> <ul style="list-style-type: none"> • NICE technology appraisal guidance [(TA600) 11 September 2019] concluded that “The long-term OS benefit with pembrolizumab combination therapy was uncertain because of the very short duration of the interim data from KEYNOTE-407”. The committee decided that “the ICER was not within the range usually considered a cost-effective use of resources” and that the further OS data is required to reduce cost-effectiveness uncertainty [NICE 2019]. <p>Use of frontline consolidation durvalumab for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum based chemoradiation therapy.</p> <p><i>Modelling study (US third-party, public healthcare payer)</i></p> <ul style="list-style-type: none"> • Durvalumab consolidation therapy was cost-effective compared with no consolidation therapy at a \$100,000 per quality-adjusted life-year willingness-to-pay threshold, with an estimated incremental cost-effectiveness ratio of \$67,421 per quality adjusted life-year [Criss 2019]. <p><i>Markov model from 3-year follow up of a clinical trial (Swiss health care payers)</i></p> <ul style="list-style-type: none"> • In the unselected/PD-L1-positive patients, durvalumab showed an incremental effectiveness of 0.76/1.18 quality-adjusted life-year (QALY) and incremental costs of Swiss Francs (CHF) 67,239/78,177, resulting in incremental cost-effectiveness ratios of CHF 88,703/66,131 per QALY gained, respectively [Panje 2020]. <p>Use of immune-checkpoint inhibitors in second line for NSCLC without actionable oncogenic driver after the failure of platinum- containing first line standard chemotherapy.</p> <p><i>Partitioned-survival model using results from a clinical trial (US third-party, public</i></p>

	<p>healthcare payer)</p> <ul style="list-style-type: none"> The incremental cost per QALY gained with pembrolizumab vs docetaxel is \$168,619/QALY (patients with PD-L1 > 50% in the second second-line) [Huang 2017].
Any additional comments	--
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.	<p>As per studies presented by the applicants and other studies identified in the literature during this expert review, the available evidence has shown a benefit of anti PD-1 ICI in overall survival for locally advanced or metastatic NSCLC when compared with platinum-based or other therapeutical schemes.</p> <p>However, concerns regarding access should be highlighted and cost-effectiveness may not be positive even for developed countries. Agreements with the manufacturer to allow incorporation into health care systems or medical insurance are needed to guarantee the affordability of anti-PD1 ICI.</p> <p>Considering these facts, the recommendation is favourable for adding these medicines to the list, but under concerns related to its cost and cost-effectiveness.</p>
References (if required)	<p>Criss SD, Mooradian MJ, Sheehan DF, et al. Cost-effectiveness and Budgetary Consequence Analysis of Durvalumab Consolidation Therapy vs No Consolidation Therapy After Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer in the Context of the US Health Care System. <i>JAMA Oncol.</i> 2019 Mar 1;5(3):358-365. doi: 10.1001/jamaoncol.2018.5449.</p> <p>Ferrara R, Imbimbo M, Malouf R, et al. Single or combined immune checkpoint inhibitors compared to first-line platinum-based chemotherapy with or without bevacizumab for people with advanced non-small cell lung cancer. <i>Cochrane Database Syst Rev.</i> 2021 Apr 30;4(4):CD013257. doi: 10.1002/14651858.CD013257.pub3.</p> <p>Huang M, Lou Y, Pellissier J, et al. Cost Effectiveness of Pembrolizumab vs. Standard-of-Care Chemotherapy as First-Line Treatment for Metastatic NSCLC that Expresses High Levels of PD-L1 in the United States. <i>Pharmacoeconomics.</i> 2017;35(8):831-44.</p> <p>International Agency for Research on Cancer (IARC). <i>Global Cancer Observatory.</i> 2020.</p> <p>Miguel LS, Lopes FV, Pinheiro B, et al. Cost Effectiveness of Pembrolizumab for Advanced Melanoma Treatment in Portugal. <i>Value Health.</i> 2017;20(8):1065-73.</p> <p>National Institute for Health and Care Excellence (NICE). <i>Technology appraisal guidance [TA600].</i> https://www.nice.org.uk/guidance/ta600/chapter/1-RecommendationsPembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer. 2019.</p> <p>Panje CM, Lupatsch JE, Barbier M, et al. A cost-effectiveness analysis of consolidation immunotherapy with durvalumab in stage III NSCLC responding to definitive radiochemotherapy in Switzerland. <i>Ann Oncol.</i> 2020 Apr;31(4):501-506. doi: 10.1016/j.annonc.2020.01.007.</p>