A.34	Tislelizumab – Hodgkin Lymphoma
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Suggested as a treatment option for treatment of Relapsed or Refractory classical Hodgkin Lymphoma (R/R cHL) after at least one second-line chemotherapy
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.	This new anti-PD1 monoclonal antibody that is registered as later line treatment for R/R cHL in China. It is administered intravenously every 3 weeks until disease progression or unacceptable toxicity, and is suitable for patients who have relapsed after an autologous stem cell transplant (SCT) or who are medically unsuitable for a SCT. It is not a current alternative to the front-line chemotherapy drugs for cHL already included on the EML. The drugs currently listed on the AML for Hodgkin Lymphoma comprise highly effective regimens delivering high rates of cure for patients for patients with early stage disease and favourable prognosis advanced stage disease.
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:
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ 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). The application includes data from a Phase 1A/B trial and an open label, single arm Phase 2 trial, the latter in patients with R/R cHL and with the primary endpoint of response rate. In the Phase 2 study, reported in 2020, 70 pts were enrolled and all were evaluable, achieving an overall response rate of 82% (including 63% complete response rate). After a short median follow up of 9.6 months, the 6 month estimated duration of response was 84% and 9 mth PFS point estimate was 75%. These are very short durations of follow up and this limits assessment of the importance of the responses. While comparative response rates for other PD-1 monoclonal antibodies are included in the application, these analyses are difficult to meaningfully interpret as they require cross-trial comparisons in different population mixes of R/R cHL, and are restricted to surrogate endpoints. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? No.

Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Data from pooled analyses of safety across multiple trials in various diseases are provided. They seem to indicate a pattern of toxicity similar to other PD-1 inhibitors, but without randomized comparisons it is difficult to reach any firm conclusion. The incidence of AEs of all grades was 71.0% among the 821 patients treated with tislelizumab, with fatigue, rash, hypothyroidism, increased alanine aminotransferase, and increased aspartate aminotransferase occurring in >10% of patients. The incidence of grade 3 or higher adverse reactions was 18.4%. These important toxicities included pulmonary inflammation, liver function abnormalities, severe skin reaction and anemia.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: As for other PD-1 inhibitors there is a risk of severe autoimmune reactions and monitoring for such is necessary.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The benefit:risk ratio is favorable for patients with heavily previously treated R/R cHL. No estimation of comparative benefits or harms is possible in the absence of randomized trials against either other PD-1 inhibitors or other alternative therapies.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Formally, in the absence of multiple randomized trials, the quality of evidence is low.
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: There is a need for careful monitoring for autoimmune complications and the need to have availability of expensive anti-inflammatory biologicals if the autoimmune complications are not responsive to steroids and drug withdrawal.
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: Currently, only has approval in one country - China.

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:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	This is a very high cost medicine (approximately ¥106,900 per annum) that has registration only in China. As such, there are major issues relating to access and cost.
Any additional comments	This application appears premature given how early this drug is in clinical development. Further data on comparative effectiveness and safety are required.
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.	Recommend against including on the EML given major uncertainty about effectiveness and the presence of major barriers related to registration and very high cost.
References (if required)	