



Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

# Australian Public Assessment Report for Keytruda

Active ingredient: Pembrolizumab

Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd

June 2023

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## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
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## About AusPARs

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- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

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# Contents

<b>List of abbreviations</b> _____	<b>4</b>
<b>Product submission</b> _____	<b>6</b>
Submission details _____	6
Product background _____	7
Current treatment options -----	10
Regulatory status _____	11
Product Information _____	17
<b>Registration timeline</b> _____	<b>17</b>
<b>Submission overview and risk/benefit assessment</b> ____	<b>17</b>
Quality _____	18
Nonclinical _____	18
Clinical _____	18
Summary of clinical studies-----	18
Pharmacology -----	18
Efficacy-----	19
Safety-----	32
Risk management plan _____	36
Risk-benefit analysis _____	36
Delegate’s considerations -----	36
Indications-----	38
Proposed action-----	38
Advisory Committee considerations -----	39
<b>Outcome</b> _____	<b>42</b>
Specific conditions of registration applying to these goods _____	45
<b>Attachment 1. Product Information</b> _____	<b>46</b>

## List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
BICR	Blinded independent central review
$C_{avg}$	Average plasma concentration
CD	Cluster of differentiation
cHL	Classical Hodgkin lymphoma
CI	Confidence interval
$C_{max}$	Maximum plasma concentration
CMI	Consumer Medicines Information
$C_{min}$	Minimum plasma concentration
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLP	Data lock point
DOR	Duration of response
FDA	Food and Drug Administration (United States of America)
GvHD	Graft versus host disease
HL	Hodgkin lymphoma
IWG	International Working Group
ORR	Objective response rate
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression free survival
PI	Product Information
PR	Partial response
PSUR	Periodic safety update report

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<b>Abbreviation</b>	<b>Meaning</b>
RMP	Risk management plan
SCT	Stem cell transplant
TGA	Therapeutic Goods Administration
ULN	Upper limit of normal

# Product submission

## Submission details

<i>Type of submission:</i>	Extension of indications
<i>Product name:</i>	Keytruda
<i>Active ingredient:</i>	Pembrolizumab
<i>Decision:</i>	Approved
<i>Date of decision:</i>	20 October 2021
<i>Date of entry onto ARTG:</i>	21 October 2021
<i>ARTG numbers:</i>	226597 and 263932
<i>, <a href="#">Black Triangle Scheme</a> for the current submission:</i>	No
<i>Sponsor's name and address:</i>	Merck Sharp & Dohme (Australia) Pty Ltd Level 1, Building A 26 Talavera Rd Macquarie Park, NSW, 2113
<i>Dose forms:</i>	Powder for injection and concentrated solution for injection
<i>Strengths:</i>	50 mg (powder for injection) and 100 mg/4 mL (concentrated solution for injection)
<i>Containers:</i>	Vials
<i>Pack sizes:</i>	Powder for injection: single vial pack Concentrated solution for injection: single vial pack
<i>Approved therapeutic use for the current submission:</i>	<p><b><i>Classical Hodgkin Lymphoma (cHL)</i></b></p> <p><i>Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of adult and paediatric patients with relapsed or refractory classical Hodgkin Lymphoma (cHL):</i></p> <ul style="list-style-type: none"> <li><i>following autologous stem cell transplant (ASCT) or</i></li> <li><i>following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.</i></li> </ul> <p><i>The approval of this indication in paediatric patients is on the basis of objective response rate from patients aged 11 years and older from single arm trial data and extrapolation from adult</i></p>

*data (see Section 5.1 Pharmacodynamic properties, Clinical Trials).*

*Route of administration:* Intravenous infusion

*Dosage:*

***Classical Hodgkin Lymphoma (cHL)***

Treatment must be initiated and supervised by specialised healthcare professionals experienced in the treatment of cancer.

Keytruda is administered as an intravenous infusion over 30 minutes.

The recommended dose of Keytruda in adults is either:

- 200 mg every 3 weeks or
- 400 mg every 6 weeks

The recommended dose of Keytruda in paediatric patients is 2 mg/kg (up to a maximum of 200 mg) every 3 weeks (see Section 4.2 Dose and method of administration, Paediatric patients of the Product Information).

Patients should be treated with Keytruda until disease progression or unacceptable toxicity.

For further information regarding dosage and dose modifications, refer to the Product Information.

*Pregnancy category:*

D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

## Product background

This AusPAR describes the submission by Merck Sharp & Dohme (Australia) Pty Ltd (the sponsor) to register Keytruda (pembrolizumab) 50 mg powder for injection vial and

100 mg/4 mL concentrated injection vial strength, for the following proposed extension of indications:<sup>1</sup>

*Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of adult and paediatric patients with relapsed or refractory classical Hodgkin Lymphoma (cHL).*

Pembrolizumab is a highly selective humanised monoclonal antibody that binds to human programmed cell death 1 (PD-1) and blocks the interaction between the PD-1 pathway receptor and its ligands, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2) on antigen presenting tumours cells. The PD-1 pathway is a negative regulator of the adaptive immune response. Ligand binding to PD-1 on the surface of T cells mediates immune inhibition.

Hodgkin lymphoma (HL) is a lymphoid malignancy. It has a bimodal age distribution with peak incidence at 15 to 35 years and again after 50 years of age. The incidence is much lower in the younger paediatric age group. It can be classified into classical Hodgkin lymphoma (cHL) (95% of cases) or nodular lymphocyte predominant Hodgkin lymphoma. Hodgkin lymphoma is generally considered a highly curable disease.<sup>2</sup>

Diagnosis is made by histology from a lymph node biopsy or surgically resected tissue, and the characteristic picture is that of disease-defining Reed-Sternberg cells associated with other Hodgkin cells surrounded by a heterogenous inflammatory infiltrate. There are four subtypes. Expression of cluster of differentiation (CD) markers assists in differentiation of classical Hodgkin lymphoma from nodular lymphocyte predominant Hodgkin lymphoma and non-Hodgkin lymphoma subtypes. Typically CD15, CD30 CD20, CD79a and CD3 are sufficient. Classical Hodgkin lymphoma cells are typically CD15 and CD30 positive and CD45 negative.

The staging of classical Hodgkin lymphoma is based on the Lugano classification (shown in Table 1, below) that captures the extent of nodal involvement and other disease features.<sup>3,4,5</sup> In general classical Hodgkin lymphoma is considered early stage (Stages I and II) or late stage (Stages III or IV). Early and late stages can further be considered as either favourable or unfavourable.

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<sup>1</sup> This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

<sup>2</sup> Eichenauer DA, Aleman BMP, Andre M et al Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up; *Annals of Oncology* 2018 29(4):iv19-iv29

<sup>3</sup> Lugano classification of staging lymphomas derived from Ann Arbor staging with Cotswold modifications.

<sup>4</sup> Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989; 7:1630.

<sup>5</sup> Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; 32:3059



**Table 1: Lugano classification for staging of lymphomas (derived from Ann Arbor staging with Cotswolds modifications)**

<b>Stage I</b>	Involvement of a single lymph node region (for example, cervical, axillary, inguinal, mediastinal) or lymphoid structure such as the spleen, thymus, or Waldeyer's ring.
<b>Stage II</b>	Involvement of 2 or more lymph node regions or lymph node structures on the same side of the diaphragm. Hilar nodes should be considered to be 'lateralised' and when involved on both sides, constitute stage II disease. For the purpose of defining the number of anatomic regions, all nodal disease within the mediastinum is considered to be a single lymph node region, and hilar involvement constitutes an additional site of involvement. The number of anatomic regions should be indicated by a subscript (for example, II-3).
<b>Stage III</b>	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm. This may be subdivided stage III-1 or III-2: stage III-1 is used for patients with involvement of the spleen or splenic hilar, celiac, or portal nodes; and stage III-2 is used for patients with involvement of the para-aortic, iliac, inguinal, or mesenteric nodes.
<b>Stage IV</b>	Diffuse or disseminated involvement of 1 or more extra-nodal organs or tissue beyond that designated 'E', with or without associated lymph node involvement.

All cases are subclassified to indicate the absence (A) or presence (B) of the systemic symptoms of significant unexplained fever, night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

The designation 'E' refers to extranodal contiguous extension (ie, proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. More extensive extranodal disease is designated stage IV.

Bulky disease: A single nodal mass, in contrast to multiple smaller nodes, of 10 cm or  $\geq \frac{1}{3}$  of the transthoracic diameter at any level of thoracic vertebrae as determined by CT; record the longest measurement by CT scan. The term 'X' (used in the Ann Arbor staging system) is no longer necessary.

The subscript 'RS' is used to designate the stage at the time of relapse.

For advanced disease the International Prognostic Index score is used as an evaluation tool, and includes patient age, gender, disease stage, and measurements of serum albumin, haemoglobin, white blood cell count, and absolute lymphocyte count.<sup>6</sup> Other prognostic factors include tumour grade, inflammatory infiltrate (high grade associated with a higher relapse rate) and the presence of Epstein-Barr virus (considered unfavourable).

The Deauville Five Point Scale (Deauville 5PS);<sup>7</sup> is a diagnostic score of the fluorodeoxyglucose avidity of a Hodgkin lymphoma tumour mass on fluorodeoxyglucose positron emission tomography and computed tomography scan used in the initial staging and assessment of treatment response in Hodgkin lymphoma and certain types of non-Hodgkin lymphoma based on the visual interpretation of the uptake of fluorodeoxyglucose for each lesion and can be used for follow-up.

Primary refractory disease refers to patients who do not attain complete remission after initial therapy.<sup>8</sup> The incidence varies with the stage of disease at diagnosis and the treatment regimen used. Durable responses and remission may be achieved in about half of these patients with second-line chemotherapy that incorporates drugs not used in the initial treatment, followed by

<sup>6</sup> Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med*. 1998 Nov 19;339(21):1506-14.

<sup>7</sup> Barrington SF, Qian W, Somer EJ et-al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. *Eur J Nucl Med Mol Imaging*. 2010;37 (10): 1824-33.

<sup>8</sup> Brice P. Managing relapsed and refractory Hodgkin lymphoma. *Br J Haematol* 2008; 141:3.

high dose chemotherapy and autologous haematopoietic cell rescue. Patients with a second relapse or progressive, resistant disease are candidates for high dose chemotherapy and autologous haematopoietic cell transplantation.

## Current treatment options

Patients with classical Hodgkin lymphoma who relapse after prior treatment with chemotherapy are generally treated with either conventional chemotherapy combined with radiation therapy or high dose chemotherapy and autologous haematopoietic cell transplantation with or without radiation therapy, depending on prognostic factors. For classical Hodgkin lymphoma, relapses typically occur within the first three years following initial treatment. Post haematopoietic stem cell transplantation high risk patients with relapsed or refractory classical Hodgkin lymphoma may receive brentuximab vedotin maintenance.<sup>9</sup>

In response to questions the sponsor provided the following account of current therapies for relapsed or refractory classical Hodgkin lymphoma:

‘While salvage chemotherapy followed by autologous stem cell transplant remains the standard in most patients with relapsed or refractory classical Hodgkin lymphoma, the concept of chemo-free approach incorporating brentuximab vedotin and checkpoint inhibitors has been adopted in patients unable to tolerate conventional chemotherapy. This includes patients who are determined to not be candidates for intensive chemotherapy either due to their advanced age, presence of comorbidities, or poor performance status. Monotherapy with brentuximab vedotin or pembrolizumab provides a viable option to achieve a response in these patients.

The second group consists of patients nonresponsive to prior salvage regimen/s and are therefore considered chemo-refractory. The outcome remains dismal in these patients and any further chemotherapy adds to the toxicity. These patients are best suited for a chemo-free approach incorporating novel agents.

Finally, there also exists a considerable proportion of patients who have primary refractory disease and are not deemed suitable for autologous stem cell transplant with the currently approved conventional salvage regimes. The results of conventional therapies have shown poor outcomes in primary refractory patients, and there is no standard of care.’

Nivolumab;<sup>10</sup> as monotherapy, is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin. This indication was granted prior to the provisional registration coming into effect in Australia and is based primarily on objective response rate (60% and 68%) from two single-arm studies.

## Project Orbis

This evaluation was facilitated through [Project Orbis](#), an initiative of the United States Food and Drug Administration (FDA) Oncology Center of Excellence. Under this project, the FDA, Health Canada, Swissmedic (Switzerland), and the TGA collaboratively reviewed the submission. This

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<sup>9</sup> Hoppe RT, Advani RH, Ai WZ, et al. Hodgkin Lymphoma, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2020;18(6):755-781.

<sup>10</sup> Opdivo nivolumab concentrated solution for IV infusion vial (ARTG R 231868) was first registered in Australia on 11 January 2016.

evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

## Regulatory status

Keytruda (pembrolizumab) received initial registration on the [Australian Register of Therapeutic Goods \(ARTG\)](#) on 1 May 2015 for the treatment of unresectable or metastatic melanoma.<sup>11</sup> Since that time, Keytruda has been approved for a wide range of different malignancies. At the time that this extension of indication submission was considered Keytruda was approved for the indications in Table 2.

**Table 2: Keytruda indications as of 19 October 2021**

Indication	
Melanoma	<p><i>Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of unresectable or metastatic melanoma in adults.</i></p> <p><i>Keytruda (pembrolizumab) is indicated as monotherapy for the adjuvant treatment of patients with melanoma with lymph node involvement who have undergone complete resection.</i></p>
Non-small cell lung cancer (NSCLC)	<p><i>Keytruda (pembrolizumab), in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumour aberrations.</i></p> <p><i>Keytruda (pembrolizumab), in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.</i></p> <p><i>Keytruda (pembrolizumab) is indicated as monotherapy for the first-line treatment of patients with NSCLC expressing PD-L1 [tumour proportion score (TPS) <math>\geq 1\%</math>] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and is</i></p> <ul style="list-style-type: none"> <li>• Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or</li> <li>• metastatic.</li> </ul> <p><i>Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of patients with advanced NSCLC whose tumours express PD-L1 with a <math>\geq 1\%</math> TPS as determined by a validated test and who have received platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received prior therapy for these aberrations prior to receiving Keytruda .</i></p>

<sup>11</sup> An AusPAR describing the submission for initial registration of Keytruda (pembrolizumab) can be found at: [AusPAR for Keytruda \(nivolumab\) Merck Sharp & Dohme \(Australia\) Pty Ltd - PM-2014-01928-1-4](#)

<b>Indication</b>	
Head and Neck Squamous Cell Cancer (HNSCC)	<p><i>Keytruda (pembrolizumab), as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of patients with metastatic or unresectable recurrent HNSCC, and whose tumours express PD-L1 [Combined Positive Score (CPS) <math>\geq 1</math>] as determined by a validated test.</i></p> <p><i>Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of patients with metastatic or unresectable recurrent HNSCC with disease progression on or after platinum containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) <math>\geq 1</math>] as determined by a validated test.</i></p>
Classical Hodgkin Lymphoma (cHL)	<p><i>Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin Lymphoma (cHL):</i></p> <ol style="list-style-type: none"> <li><i>1. following autologous stem cell transplant (ASCT) or</i></li> <li><i>2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.</i></li> </ol> <p><i>The approval of this indication is on the basis of objective response rate (ORR). See Section 5.1 Pharmacodynamic Properties, Clinical Trials).</i></p>
Primary mediastinal B-Cell Lymphoma (PMBCL)	<p><i>Keytruda (pembrolizumab) is indicated for the treatment of adult and paediatric patients with refractory primary mediastinal B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy. The approval of this indication is on the basis of objective response rate (ORR) and duration of response from non-randomised studies. See Section 5.1 Pharmacodynamic Properties, Clinical Trials.</i></p>

<b>Indication</b>	
Urothelial carcinoma	<p><i>Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin containing therapy and whose tumours express PD-L1 [Combined Positive Score (CPS) <math>\geq 10</math>] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication is approved based on overall response rate and duration of response in a single-arm study. Improvements in overall survival, progression-free survival, or health-related quality of life have not been established.</i></p> <p><i>Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy.</i></p> <p><i>Keytruda (pembrolizumab) is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy. This indication was approved via the provisional approval pathway based on complete response rate and duration of response. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.</i></p>

<b>Indication</b>	
<p>Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer</p>	<p><b>Colorectal (previously untreated)</b></p> <p><i>Keytruda (pembrolizumab) is indicated for the first-line treatment of patients with unresectable or metastatic colorectal cancer (CRC) that is MSI-H or dMMR as determined by a validated test.</i></p> <p><b>Colorectal (previously treated)</b></p> <p><i>Keytruda (pembrolizumab) is indicated in adult and paediatric patients for the treatment of unresectable or metastatic CRC that is MSI-H or dMMR as determined by a validated test, and that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication was approved via the provisional approval pathway, based on objective response rate and response duration in a single-arm trial. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials.</i></p> <p><b>Non-colorectal</b></p> <p><i>Keytruda (pembrolizumab) is indicated in adult and paediatric patients for the treatment of unresectable or metastatic solid tumours that are MSI-H or dMMR as determined by a validated test, that have progressed following prior treatment and when there are no satisfactory alternative treatment options. This indication was approved via the provisional approval pathway, based on the pooling of data on objective response rate and response duration across multiple different tissue types in a single-arm trial. Sample sizes for individual tissue types were too small to provide data on clinical utility of the MSI-H/dMMR tests for each of the tissue types, individually. The assumption that MSI-H/dMMR-status is predictive of the treatment effect of Keytruda for every tissue type has not been verified. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials. The safety and effectiveness of Keytruda in paediatric patients with MSI-H/dMMR central nervous system cancers have not been established.</i></p>
<p>Endometrial carcinoma</p>	<p><i>Keytruda (pembrolizumab), in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR as determined by a validated test, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This indication was approved via the <b>provisional approval</b> pathway, based on objective response rate and duration of response in a single-arm trial. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.</i></p>
<p>Renal Cell Carcinoma (RCC)</p>	<p><i>Keytruda (pembrolizumab), in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).</i></p>

<b>Indication</b>	
Cutaneous Squamous Cell Carcinoma	<i>Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of adult patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation. This indication was approved via the provisional approval pathway based on objective response rate and duration of response from a single-arm study. Improvements in overall survival, progression-free survival, or health-related quality of life have not been established. Full registration for this indication depends on submission of further clinical data to confirm the clinical benefit of the medicine.</i>
Oesophageal Cancer	<i>Keytruda (pembrolizumab), in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced or metastatic carcinoma of the oesophagus or HER2 negative gastroesophageal junction adenocarcinoma (tumour centre 1 to 5 centimetres above the gastroesophageal junction) that is not amenable to surgical resection or definitive chemoradiation.</i>
Tumour Mutational Burden-High (TMB-H) cancer	<i>Keytruda (pembrolizumab) is indicated for the treatment of adult and paediatric patients with unresectable or metastatic tumour mutational burden-high (TMB-H) [<math>\geq 10</math> mutations/megabase (mut/Mb)] solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. This indication was approved via the provisional approval pathway, based on the pooling of data on objective response rate and response duration across multiple different tissue types in a single-arm trial. The assumption that TMB-H status is predictive of the treatment effect of Keytruda for every tissue type has not been verified. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.</i>

At the time the TGA considered this submission, a similar submission for the proposed extension of indications had been approved in the United States of America, European Union, Canada, Switzerland and New Zealand.

The following table summarises these submissions and provides the indications where approved.

**Table 3: International regulatory status**

<b>Region</b>	<b>Submission date</b>	<b>Status</b>	<b>Approved indications</b>
United States of America	30 April 2020	Approved on 14 October 2020	<i>Keytruda is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL). Keytruda is indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.</i>
European Union	13 May 2020	Approved on 9 March 2021	<i>Keytruda as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.</i>
Canada	15 May 2020	Approved on 5 February 2021	<i>Keytruda as monotherapy is indicated for the treatment of adult and pediatric patients with refractory or relapsed classical Hodgkin Lymphoma (cHL) who have failed autologous stem cell transplant (ASCT), or who are not candidates for multi-agent salvage chemotherapy and ASCT. An improvement in overall survival has not yet been established</i>
Switzerland	1 July 2020	Approved on 26 March 2021	<i>Pembrolizumab as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) or following at least one prior therapy when ASCT is not a treatment option.</i>
New Zealand	1 July 2020	Approved on 12 November 2020	<i>Keytruda is indicated for the treatment of adult and paediatric patients with relapsed or refractory classical Hodgkin Lymphoma (cHL).</i>



## Product Information

The [Product Information \(PI\)](#) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and [Consumer Medicines Information \(CMI\)](#), please refer to the TGA [PI/CMI search facility](#).

## Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the [standard prescription medicines registration process](#).

**Table 4: Timeline for Submission PM-2020-02312-1-6**

Description	Date
Submission dossier accepted and first round evaluation commenced	30 June 2020
Evaluation completed	17 May 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 July 2021
Sponsor's pre-Advisory Committee response	14 July 2021
Advisory Committee meeting	5 and 6 August 2021
Registration decision (Outcome)	20 October 2021
Completion of administrative activities and registration on the ARTG	21 October 2021
Number of working days from submission dossier acceptance to registration decision*	253

\*Statutory timeframe for standard submissions is 255 working days

## Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- [EMA/CHMP/27994/2008/Rev 1](#) Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials
- [EMA/CHMP/703715/2012](#) Rev.2 Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man Condition specific guidance

## Quality

Quality evaluation is not required for this submission as there are no proposed changes to the quality of the currently approved product in Australia. The quality of the currently approved product is suitable for the proposed changes in this submission. A full quality evaluation was conducted at the time this product received initial registration.<sup>11</sup>**Error! Bookmark not defined.**

## Nonclinical

No new nonclinical data or further nonclinical evaluation were required for this submission. The TGA considers that previously submitted and evaluated data satisfactorily address nonclinical aspects of safety/efficacy relating to this submission.

## Clinical

### Summary of clinical studies

The clinical dossier mainly consisted of:

- KEYNOTE 204 trial - A Phase III, randomised open-label, clinical trial to compare pembrolizumab with brentuximab vedotin in subjects with relapsed or refractory classical Hodgkin lymphoma
- KEYNOTE 087 trial - A Phase II clinical trial of pembrolizumab in subjects with relapsed or refractory classical Hodgkin lymphoma
- KEYNOTE 051 trial - A Phase I/II trial of pembrolizumab in children with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumour or lymphoma

## Pharmacology

### *Population pharmacokinetic data*

The predicted maximum, average and minimum plasma concentration ( $C_{max}$ ,  $C_{avg}$  and  $C_{min}$ ) for pembrolizumab dosed at 2 mg/kg once every three weeks based on data from patients aged 2 to 6 years (n = 22), 6 to 12 years (n = 35), 12 to 18 years (n = 93) and 18 years and older patients (n = 200) were similar. The existing population pharmacokinetics model was updated with additional data from children with solid tumours and classical Hodgkin lymphoma in the KEYNOTE 051 trial and adult data in relapsed or refractory classical Hodgkin lymphoma from the KEYNOTE 204 trial. The evaluation concluded the observed clinical data and the updated population pharmacokinetic model were consistent with previous findings and supported the proposed dosing in children of 2 mg/kg once every three weeks.

### *Pharmacodynamics*

Evaluation of the immunogenicity data from 125 children from the KEYNOTE 051 trial found two patients (1.6%) had non-treatment emergent pembrolizumab antibodies, and no patients had treatment-emergent antidrug antibodies. This was consistent with immunogenicity rates in adults (2.1%).

## Efficacy

### KEYNOTE 204 trial

The KEYNOTE 204 trial is an ongoing multi-centre, randomised, open-label, investigator-blind, active controlled study that compared pembrolizumab given as 200 mg once every three weeks intravenously with brentuximab vedotin 1.8 mg/kg intravenously in relapsed or refractory classical Hodgkin lymphoma patients. The comparator of brentuximab vedotin was justified based on the standard of care at the time of the trial. Data are presented from the second pre-specified second interim analysis of the study. The median exposure was 10.02 months in the pembrolizumab arm and 4.81 months in the brentuximab vedotin arm.

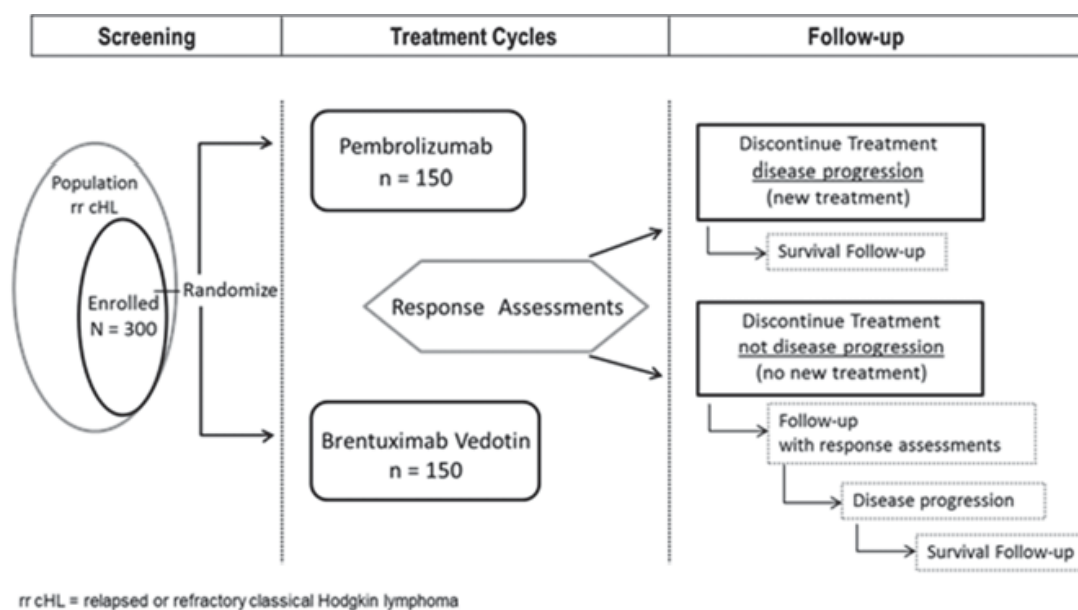
### Study design

The first patient first visit was on 29 June 2016 and the last patient's last visit was 16 January 2020. The data cut-off date for this second interim analysis was 16 January 2020. The clinical study report is dated 10 April 2020.

The study was conducted over a total of 123 sites across 20 countries.

A summary of the study schema and patient flow is in Figure 1 below.

**Figure 1: KEYNOTE 204 trial Summary schema and patient flow**



During screening 338 patients were screened and 304 patients were randomised.

There were two treatment arms: pembrolizumab 200 mg intravenously once every three weeks (n = 151) or brentuximab vendotin 1.8 mg/kg intravenously once every three weeks (n = 153). The treatment continued for up to 35 cycles or until documented disease progression.

The patient flow at the second interim analysis (16 January 2020) was as follows:

- Received treatment: 148/151 (98%) pembrolizumab; 152/153 (99%) brentuximab vedotin
- Completed treatment: 25/151 (16.6%) pembrolizumab; 3/153 (2%) brentuximab vedotin
- Continuing treatment: 13/151 (8.6%) pembrolizumab; 3/153 (2%) brentuximab vedotin

- Discontinued treatment: 110/151 (72.8%) pembrolizumab; 146/152 (96%) brentuximab vedotin
- Discontinued due to adverse events: 20/151 (13.2%) pembrolizumab; 29/153 (19%) brentuximab vedotin
- Discontinued due to progressive disease: 58/151 (38.4%) pembrolizumab; 75/153 (49%) brentuximab vedotin
- Discontinued due to bone marrow transplant: 16/151 (10.6%) pembrolizumab; 17/153 (11.1%) brentuximab vedotin

### ***Key inclusion criteria***

The key inclusion criteria were:

- Age 18 years or older with relapsed or refractory classical Hodgkin lymphoma
- No minimum prior therapies; prior brentuximab vedotin therapy allowed not required (if prior brentuximab vedotin therapy or brentuximab vedotin containing regimen had achieved complete response or partial response)
- The inclusion criteria related to prior transplant and transplant eligibility changed through the conduct of the study
- Relapsed (disease progression after most recent therapy) or refractory (failure to achieve complete response (CR) or partial response (PR) to most recent therapy) classical Hodgkin lymphoma
- ECOG performance status 0 or 1 (fully active (0), or restricted in physically strenuous activity but ambulatory and able to carry out light work (1))
- Four or more weeks since last therapy
- With laboratory results fulfilling the following criteria:
  - Absolute neutrophil count  $\geq 1000/\mu\text{L}$ ,
  - platelets  $\geq 75,000/\mu\text{L}$ ,
  - haemoglobin  $> 8 \text{ g/dL}$ ,
  - creatinine  $\leq 1.5 \times$  upper limit of normal (ULN) or  $\geq 60 \text{ mL/min}$ ;
  - total bilirubin  $\leq 1.5 \text{ ULN}$ ,
  - aspartate transaminase and alanine transaminase  $\leq 2.5 \times \text{ULN}$  ( $\leq 5 \times \text{ULN}$  with liver involvement).

### ***Key exclusion criteria***

Key exclusion criteria included:

- Diagnosis of immunosuppression or receiving more than 10 mg prednisolone or equivalent or any immunosuppressant within seven days prior to first dose of trial treatment
- Monoclonal antibody within four weeks of first study treatment or not recovered ( $\leq$  Grade 1 at Baseline) from adverse events due to agents given more than four weeks prior

- Chemotherapy, targeted small molecule therapy, or radiational therapy including investigational agents within four weeks of study Day 1 or not recovered ( $\leq$  Grade 1 at Baseline) from adverse events due to prior agents
- Allogenic stem cell transplant less than 5 years ago
- Active central nervous system metastases or carcinomatous meningitis but could have previously treated radiologically stable, clinically stable brain metastases not requiring steroid for at least 14 days
- Active autoimmune disease requiring systemic treatment in past two years
- Known additional malignancy that was progressive or needing active treatment in previous three years
- Prior (non-infectious) pneumonitis requiring steroids
- Eligible for allogenic or autologous stem cell transplant (note this exclusion criterion changed throughout the study, see *Protocol amendments and deviations*, below)
- Administration of live vaccines, anti-PD-1, anti-PD-L1, anti PD-L2 agents, anti-CD137 antibodies, or OX-40, or medicine specifically targeting T-cell co-stimulation or checkpoint pathways.

## Endpoints

### Primary

The primary end-points are dual primary efficacy endpoints of progression free survival (PFS) assessed by blinded independent central review (BICR) to the Internal Working Group (IWG) classification for response in clinical trials response;<sup>12</sup> including clinical and imaging data following autologous stem cell transplant or allogenic stem cell transplant, and overall survival. Overall survival was to be formally analysed at the third interim analysis.

### Secondary

The secondary endpoints are progression-free survival excluding clinical and imaging with censoring for stem cell transplant, objective response rate and complete remission rate (assessed by BICR) censoring for stem cell transplant and PFS (assessed by the investigator).

### Exploratory

Exploratory endpoints include second progression-free survival, as assessed by the investigator (time from randomisation to first of subsequent disease progression after initiation of new anti-cancer therapy or death from any cause). Patients alive without a second progression would be censored at the last time known to be alive and without second disease progression. Other endpoints include duration of response (DOR), and quality of life assessments (EORTC QLQ-C30 and EuroQoL EQ-5D)

### Safety

Adverse events monitored once every three weeks from the first dose of study treatment.

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<sup>12</sup> Cheson B, Pfistner B, Juweid ME et al Revised Response Criteria for Malignant Lymphoma *J Clin Oncol* 2007;25(5):579-586

## Statistics

The study was randomised in a 1:1 ratio.

*Primary endpoint (progression free survival or overall survival)*

*Progression free survival per the Independent Review Committee without censoring for stem cell transplant:* 194 progression free survival events gave 85% power, hazard ratio (HR) = 0.622 (pembrolizumab versus brentuximab vedotin) with  $\alpha = 0.0120$  (assumes progression free survival follows exponential distribution with median 5.6 months in control arm).

*Key secondary overall survival:* 146 overall survival events gave a HR = 0.6 (pembrolizumab versus brentuximab vedotin) with 80% power,  $\alpha = 0.0125$  (assumes overall survival follows exponential distribution with median 22.4 months in control arm).

*Key secondary objective response rate:* only if progression free survival hypothesis rejected, 90% power (1-sided  $\alpha = 0.006$ ) to detect 18% to 20% improvement on experimental arm assuming true objective response rate ranges from 60 to 70%.

Both key secondary endpoints assume one interim analysis for progression free survival, two interim analyses for overall survival, an enrollment period of 12 months and a cumulative drop-out of 5% at the end of 3 years. Both also assumed median progression free survival of 5.6 months and overall survival of 22.4 months (from published study with brentuximab vedotin and prior stem cell transplant).

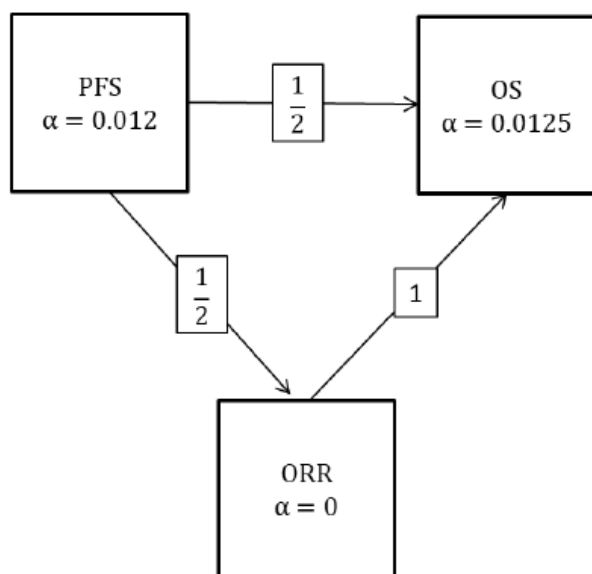
*Interim analyses*

Four interim analyses were planned. The second interim analysis was presented to support the submission.

*Multiplicity*

The overall control of type 1 error was to 0.25 (1 sided) with testing of progression free survival, overall survival and objective response rate hypotheses. The multiplicity strategy is shown in Figure 2.

**Figure 2: KEYNOTE 204 trial Strategy to control for multiplicity**



Abbreviations: PFS = progression free survival, OS = overall survival, ORR = objective response rate

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## **Protocol amendments and deviations**

### *Major amendments*

*Initial protocol:* Enrolment of patients who failed autologous stem cell transplant or had received one or more multi-agent chemotherapy regimen.

*Amendment 2:* Allowed prior treatment with brentuximab vedotin or brentuximab vedotin-containing regimens provided subject responded (achieved a complete response or partial response) to prior brentuximab vedotin or brentuximab vedotin-containing regimens. Based on results from Cohorts 1 and 2 in the KEYNOTE 087 trial. Allowed enrolment of subjects who have relapsed or refractory classical Hodgkin lymphoma and have received at least one prior chemotherapy regimen regardless of transplant eligibility. Additional follow-up included to allow for collection of events of clinical interest data post allogeneic stem cell transplant was included per FDA request.

*Amendment 3:* Addition of exclusion of subjects eligible for allogeneic or autologous stem cell transplant.

*Amendment 4:* Due to the larger than expected number of participants who received an autologous or allogeneic stem cell transplant in the context of the study, the sponsor changed the exploratory endpoint of progression free survival based on IWG per BICR incorporating imaging data post-stem cell transplant to the primary endpoint. To conduct the progression-free analysis within a reasonable timeframe, the power of progression-free analysis was reduced to 85% and an interim for progression-free analysis was added.

*Amendment 5:* To clarify that both clinical and imaging data following autologous or allogeneic-stem cell transplant will be collected and included in the evaluation of the primary progression-free survival endpoint. For subjects who receive consolidative therapy following autologous or allogeneic stem cell transplant and have not yet progressed, data after the initiation of post-stem cell transplant consolidative therapy will not be collected; these subjects will be censored at the date of their last assessment prior to initiation of the post-transplant consolidative therapy in the primary progression free survival analysis. Progression or death after two or more consecutive missed disease assessments will not be considered as events in the primary progression free survival analysis.

### *Important Protocol Deviations*

Twenty-four (24) subjects had one or more protocol deviations, of which there were three in the pembrolizumab arm (two patients that did not have relapsed or refractory classical Hodgkin lymphoma) and one in the brentuximab vedotin arm were considered clinically important. Major protocol deviation leading to discontinuation in 1% in each arm.

### *Baseline characteristics*

A summary of the baseline characteristics of patients is in Table 5.

**Table 5: KEYNOTE 204 trial: Patient baseline characteristics**

		<b>Pembrolizumab (n = 151)</b>	<b>Brentuximab vedotin (n = 153)</b>
Age	Median (range)	36 (18-84)	35 (18-83)
Age group	< 65 years	124 (82.1%)	131(85.6%)
	≥ 65 years	27(17.9%)	22 (14.4%)
Sex	Male	84 (55.6%)	90 (58.8%)
	Female	67 (44.4%)	63 (41.2%)
Race	White	119 (78.8%)	115 (75.2%)
	Asian	13 (8.6%)	13 (8.5%)
Location	North America	27 (17.9%)	30 (19.6%)
	EU	49 (32.5%)	46 (30.1%)
	Rest of World	66 (43.7%)	70 (45.8%)
ECOG status	0	86 (57%)	100 (65.4%)
	1	64 (42.4%)	179 (34.6%)
	2	1 (0.7%)	0
Disease subtype	cHL Mixed Cellularity	23 (15.2%)	17 (11.1%)
	cHL nodular sclerosis	119 (78.8%)	128 (83.0%)
	cHL Lymphocyte Depleted	3 (2.0%)	3(2.0%)
	cHL Lymphocyte Rich	1 (0.7%)	1 (0.7%)
	Missing	5 (3.3%)	5 (3.3%)
Stratification	Prior auto-SCT	56 (37.1%)	56 (36.6%)
	No prior auto-SCT	95 (62.9%)	97 (63.4%)
	Disease after frontline therapy		
	Primary refractory disease	61 (40.4%)	62 (40.5%)
	Relapsed < 12 months	42 (27.8%)	42 (27.5%)
	Relapsed ≥ 12 months	48 (13.8%)	49 (32.0%)
Response to first therapy before study treatment	Refractory	47 (31.1%)	40 (26.1%)
	Relapse	97 (64.2%)	102 (66.7%)
	Other	7 ( 4.6%)	11 (7.2%)
Response to last therapy before study treatment	Refractory	65 (43.0%)	64 (41.8%)
	Untreated Relapse	50 (33.1%)	61 (39.9%)
	Other	36 (23.8%)	28 (18.8%)
Prior therapy	Median lines of therapy	2	3
	Prior regimen , medians	2	3

Most (94%) of the pembrolizumab arm and 87% of the brentuximab vedotin arm expressed PDL1 ≥ 1%. Most had no baseline bone marrow involvement (around 94%), had no baseline B symptoms (around 74%), had no bulky disease (around 80%), had no prior radiation (61%) and no prior use of brentuximab vedotin (95%).



## Efficacy results

The KEYNOTE 204 trial efficacy results are shown in Table 6.

**Table 6: KEYNOTE 204 trial Efficacy results**

<b>Overall relapsed /refractory classical Hodgkin lymphoma – KEYNOTE 204 trial efficacy (N=304)</b>	
PFS (BICR, IWG response criteria) [Cheson, 2007]	
Median PFS, months (95% CI)*	HR: 0.65 (95% CI: 0.48, 0.88; p=0.00271) Pembrolizumab arm: 13.2 (10.9, 19.4) Brentuximab arm: 8.3 (5.7, 8.8)
PFS-secondary, (BICR, IWG response criteria)[Cheson 2007] (no alfa spent at 1A2)	
Median PFS, months (95% CI)*	HR 0.62 (95% CI: 0.46, 0.85) Pembrolizumab arm: 12.6 (8.7, 19.2) Brentuximab arm: 8.2 (5.6, 8.6)
ORR, CR + PR, CRR and DOR efficacy response (BICR, IWG response criteria)	
Participants with response (CR + PR)	Pembrolizumab arm: 37 (24.5%) and 62 (41.1%) Brentuximab arm: 37 (24.2%) and 46 (30.1%)
ORR % (95% CI)	Pembrolizumab arm: 65.6% (57.4, 73.1) Brentuximab arm: 54.2% (46.0, 62.3) % Difference: 11.3 (95% CI: 0.2, 22.1; p=0.023, p threshold 0.006)
CRR (95% CI)	Pembrolizumab arm: 24.5% (17.9%, 32.2%) Brentuximab arm: 24.3% (17.6%, 31.8%)
DOR, median (range)*	Pembrolizumab arm: 20.7 months (0+, 33.2+ months) Brentuximab arm: 13.8 months (0+, 33.9+ months)

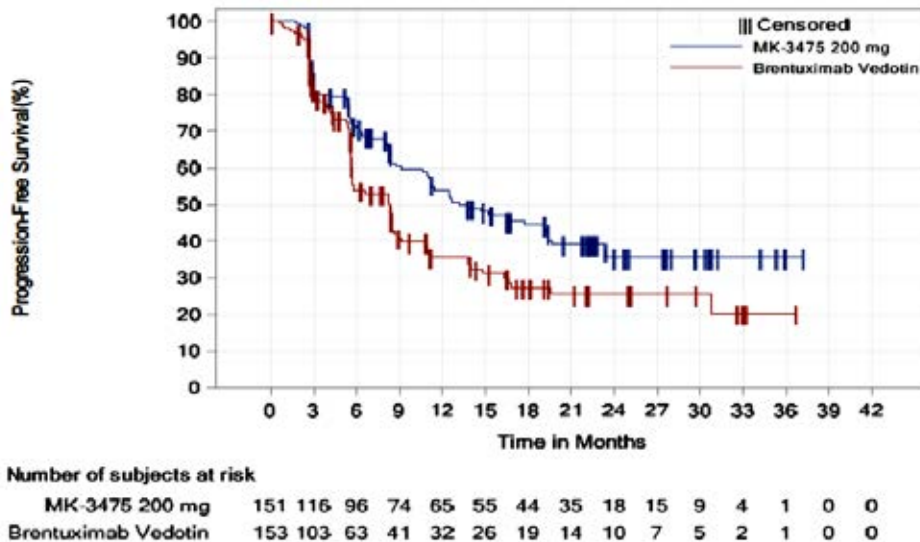
\* estimate from product-limit (Kaplan-Meier) method for censored data

Abbreviations: CI = confidence interval; PFS = progression free survival, ORR = objection response rate; CR = complete response; CRR = complete response rate; HR = hazard reduction; PFS = progression-free survival; PR = partial response, DOR = duration of response.

Criteria according to: Cheson B, Pfistner B, Juweid ME et al. Revised Response Criteria for Malignant Lymphoma J Clin Oncol 2007;25(5):579-586

Figure 3 shows the Kaplan-Meier curves for pembrolizumab and Figure 4 is a Forest plot depiction of progression-free survival by subgroups.

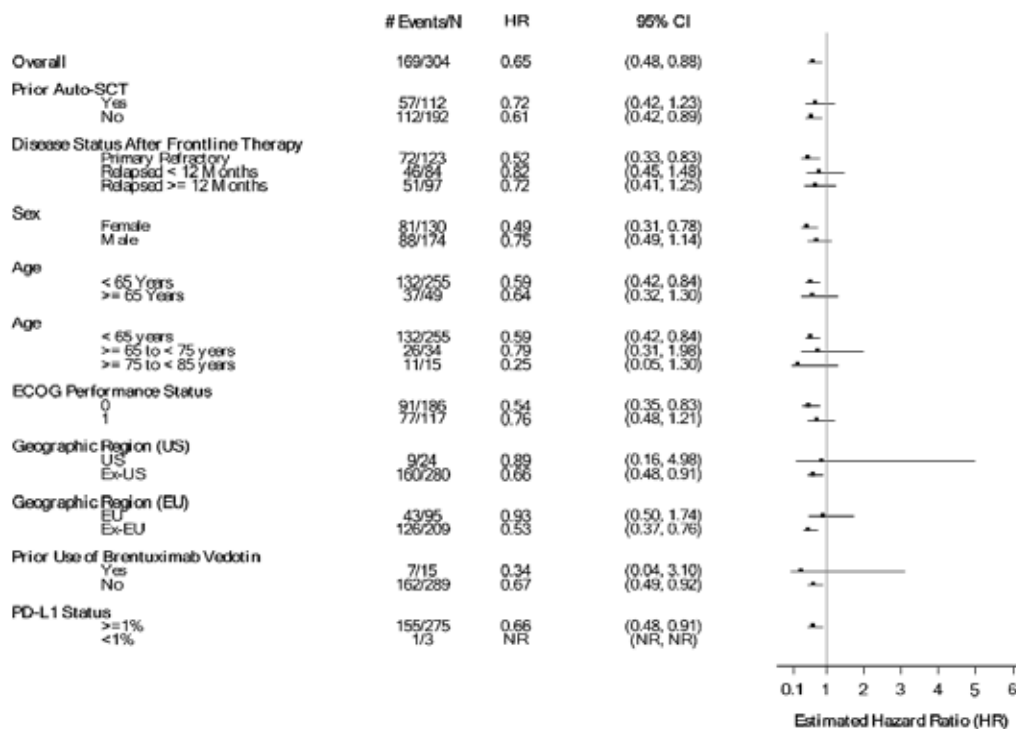
**Figure 3: KEYNOTE 204 trial Kaplan-Meier estimates of progression free survival**



Abbreviation: MK-3475 = pembrolizumab.

Blinded independent central review as per Cheson B, Pfistner B, Juweid ME et al Revised Response Criteria for Malignant Lymphoma *J Clin Oncol* 2007;25(5):579-586.

**Figure 4: KEYNOTE 204 trial Forest plot of progression-free survival by subgroups factors**



Abbreviations: HR = hazard ratio; NR = not reached.

Notes: Hazard ratio and 95% CI are based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy). Database Cut-off Date: 16 January 2020.

Progression-free survival by blinded independent central review as per Cheson B, Pfistner B, Juweid ME et al Revised Response Criteria for Malignant Lymphoma *J Clin Oncol* 2007;25(5):579-586

Overall survival data are immature and overall survival was not formally tested. The first formal analysis is expected at 91 events.

The response rates by BICR by prior lines of therapy were calculated. Of the 27 patients with one prior line of therapy 15% achieved a complete response, 52% achieved a partial response and 22% had stable disease. Of the 124 patients who have two or more prior lines of therapy 27% achieved a complete response, 39% a partial response, and 19% had stable disease. The groups by lines of therapy 41% and 40%, respectively, comprised primary refractory disease.

A sensitivity analysis of the impact of protocol amendments 2, 3 and 4 was requested, and is presented below. In the KEYNOTE 204 trial, 160 patients were randomised before amendment 2, 101 were randomised under amendment 2 and 43 patients randomised under amendment 3 and all were randomised prior to amendment 4. A total of 8, 36 and 11 patients received pembrolizumab as second line before amendment 2, under amendment 2 and under amendment 3, respectively. Of these 55 patients, the reasons for not receiving autologous stem cell transplant before enrolling in the KEYNOTE 204 trial were chemorefractory to primary therapy (38.2%), age (20%), comorbidity (3.6%) and other clinical decisions (38.3%). The progression free survival results for each subgroup are presented separately, and cumulatively, below.

**Table 7: KEYNOTE 204 Progression free survival by randomisation during operation of protocol amendment (intent to treat population)**

Separate			Cumulative		
	N <sup>†</sup>	HR <sup>‡</sup> (95% CI) <sup>‡</sup>		N <sup>†</sup>	HR <sup>‡</sup> (95% CI) <sup>‡</sup>
Prior to Amendment 2	160	0.65 (0.43, 0.99)	Prior to Amendment 2	160	0.65 (0.43, 0.99)
Amendment 2	101	0.68 (0.39, 1.18)	Up to and Including Amendment 2	261	0.68 (0.49, 0.95)
Amendment 3	43	0.46 (0.18, 1.15)	Up to and Including Amendment 3*	304	0.65 (0.48, 0.88)

All analyses are based on the PFS primary definition per Amendment 5  
<sup>†</sup> Number of subjects randomized under the respective amendment(s); enrollment was completed prior to Amendment 4  
<sup>‡</sup> Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and disease status after frontline therapy (primary refractory, relapsed less than 12 months after completion of frontline therapy, relapsed 12 months or more after completion of frontline therapy)  
 \*same as the PFS primary analysis in the KEYNOTE-204 CSR [Ref. 5.3.5.1: P204V01MK3475: Table 11-1].  
 Database Cutoff Date: 16JAN2020

Abbreviation: CI = confidence interval; HR = hazard ratio; PFS = progression-free survival.

Progression free survival by blinded independent central review as per Cheson B, Pfistner B, Juweid ME et al Revised Response Criteria for Malignant Lymphoma *J Clin Oncol* 2007;25(5):579-586

### **KEYNOTE 087 trial**

The KEYNOTE 087 trial is an ongoing Phase II, single arm, multi-cohort study of pembrolizumab 200 mg once every three weeks in relapsed or refractory classical Hodgkin lymphoma patients who:

- failed to achieve a response or progressed after autologous stem cell transplant and relapsed after treatment with, or failed to respond to treatment with brentuximab vedotin (brentuximab vedotin) post-autologous stem cell transplant (Cohort 1);

- were unable to achieve a complete response or partial response to salvage chemotherapy and did not receive autologous stem cell transplant but relapsed after treatment with, or failed to respond to treatment with brentuximab vedotin (Cohort 2);
- failed to achieve a response to, or progressed after, autologous stem cell transplant, and had not received brentuximab vedotin after autologous stem cell transplant and did or did not, receive brentuximab vedotin as part of primary treatment or salvage treatment (Cohort 3).

Patients had received a median of four prior lines of therapy, 61% had received an autologous stem cell transplant, 38% were transplant ineligible, 17% had no prior brentuximab vedotin use and 36% had prior radiation therapy.

This study supported the initial registration of the indication for relapsed or refractory classical Hodgkin lymphoma, together with the KEYNOTE 013 trial.<sup>13</sup>

Updated KEYNOTE 087 trial efficacy results (database cut-off date: 21 March 2019) are shown below in Table 8.

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<sup>13</sup> The Keynote 013 trial (Study 3475-013): A Phase Ib multi-cohort trial of MK-3475 (Pembrolizumab) in subjects with haematologic malignancies. ClinicalTrials.gov Identifier: NCT01953692

**Table 8: KEYNOTE 087 trial; Updated efficacy results**

	<b>Cohort 1</b>	<b>Cohort 2</b>	<b>Cohort 3</b>	<b>Total</b>
ORR by BICR, n (%; 95% CI)	n = 69	n = 81	n = 60	N = 210
Based on IWG criteria	54 (78.3, 66.7 to 87.3)	52 (64.2, 52.8 to 74.6)	43 (71.7, 58.6-82.5)	149 (71.0, 64.3 to 77.0)
Based on Lugano criteria	58 (84.1, 73.3 to 91.8)	55 (67.9, 56.6 to 77.8)	41 (68.3, 55.0 to 79.7)	154 (73.3, 66.8 to 79.2)
<b>CRR by BICR, n (%)</b>	<b>n = 69</b>	<b>n = 81</b>	<b>n = 60</b>	<b>N=210</b>
Based on IWG criteria	18 (26.1)	21 (25.9)	19 (31.7)	58 (27.6)
Based on Lugano criteria	25 (36.2)	23 (28.4)	21 (35.0)	69 (32.9)
<b>DOR, months</b>	<b>n = 54</b>	<b>n = 52</b>	<b>n = 43</b>	<b>N = 149</b>
Median (range); <sup>c</sup>	25.0 (0.0+, 36.1+)	11.1 (0.0+, 35.9+)	16.8 (0.0+, 39.1+)	16.6 (0.0+, 39.1+)
<b>PFS by BICR</b>	<b>n = 43</b>	<b>n = 54</b>	<b>n = 36</b>	<b>N=133</b>
Median (95% CI), months	16.4 (11.3, 27.6)	11.1 (7.3,13.5)	19.4 (8.4, 22.1)	13.6 (11.1, 16.7)
Rate at 12 months; <sup>d</sup> %	61.3	43.0	53.9	52.3
Rate at 24 months; <sup>d</sup> %	41.6	21.9	34.0	32.2
<b>OS</b>	<b>n = 69</b>	<b>n = 81</b>	<b>n = 60</b>	<b>N = 210</b>
Median, months	Not reached	Not reached	Not reached	Not reached

Abbreviations: BICR = blinded independent central review; CI = confidence interval; PFS = progression free survival, ORR = objection response rate; CR = complete response; CRR = complete response rate; HR = hazard reduction; PFS = progression-free survival; PR = partial response, DOR = duration of response.

<sup>a</sup> For Lugano criteria, see Table 1, above.

<sup>b</sup> International Working Group (IWG) criteria as per: Cheson B, Pfistner B, Juweid ME et al Revised Response Criteria for Malignant Lymphoma *J Clin Oncol* 2007;25(5):579-586

<sup>c</sup> "+" indicates there was no progressive disease at the time of the last disease assessment.

<sup>d</sup> By Kaplan-Meier estimation.

The objective response rate is consistent with the initial study results (objective response rate 69%). The median duration of response was 11.1 months in the initial data set. Progression free survival and overall survival at 12 months or more was not available at the time of initial approval of the relapsed or refractory classical Hodgkin lymphoma indication.

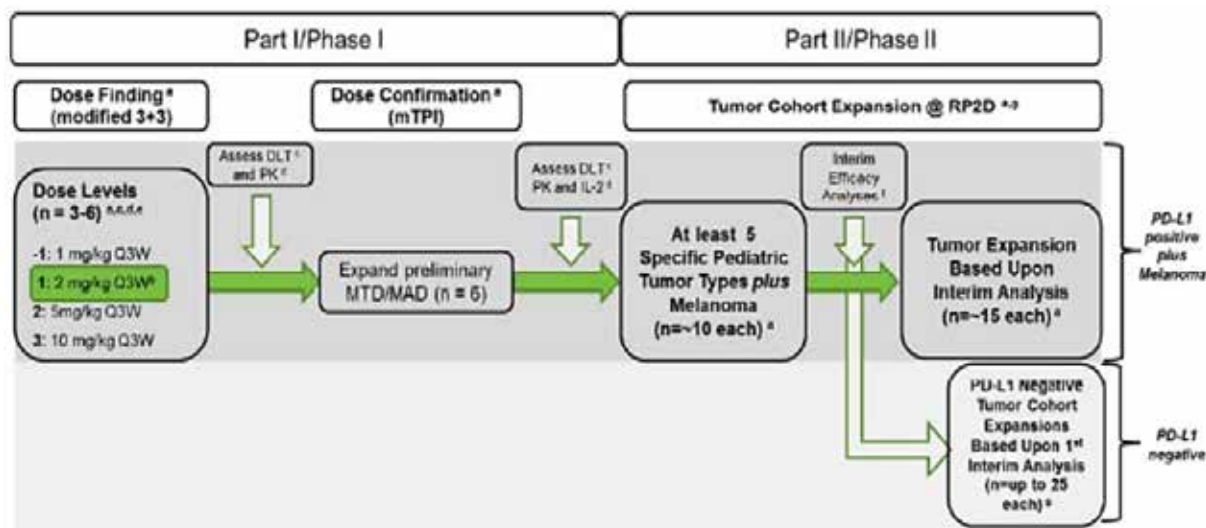
### **KEYNOTE 051 trial**

KEYNOTE 051 trial is an ongoing, two part, Phase I/II, non-randomised, open-label, single-arm multi-centre, multi-national study pharmacology and safety study of pembrolizumab 2 mg/kg once every three weeks in paediatric patients with advanced melanoma, or a PD-1 positive advanced, relapsed or refractory solid tumour or lymphoma. Part I was dose confirming (pembrolizumab 2 mg/kg intravenously once every three weeks) and is complete. It established

2 mg/kg once every three weeks as the recommended Phase II dose for pembrolizumab for paediatric patients. Part II is ongoing and is a tumour cohort expansion. It includes patients with advanced melanoma, PD-L1 advanced, relapsed or refractory solid tumours or other lymphoma, relapsed or refractory classical Hodgkin lymphoma, or advanced, relapsed or refractory high microsatellite instability (MSI-H) solid tumours.

The study design of KEYNOTE 051 trial is summarised in Figure 4.

**Figure 5 KEYNOTE 051 trial study schematic**



Abbreviations: mTPI = modified Toxicity Probability Interval; MTD = maximum tolerated dose; MAD = maximum administered dose; RP2D = recommended Phase II dose; Q3W = once every three weeks; DLT = dose limiting toxicity

Note:

<sup>a</sup> Paediatric subjects with melanoma or PD-L1 positive advanced relapsed or refractory solid tumour or lymphoma between the ages of 6 months and less than 18 years

<sup>b</sup> The starting dose level will be 2 mg/kg Q3W (Dose level 1)

<sup>c</sup> De-escalation decisions will be informed by DLT according to modified 3+3 and mTPI approaches

<sup>d</sup> Escalation decisions will be informed by assessment of pharmacokinetics (PK) and/or pharmacodynamics (PD)

<sup>e</sup> Escalation to additional dose levels may occur based upon PK/PD modelling

<sup>f</sup> Interim analysis as defined.

<sup>g</sup> PD-L1 negative subjects may be enrolled following the first interim analysis. Enrolment will only remain open for the PD-L1 negative cohort while enrolment to the PD-L1 positive cohort is open.

The dedicated classical Hodgkin lymphoma cohort is an expansion cohort of the study (n = 7) for which accrual is ongoing. It is including paediatric patients aged 3 to 17 years, with relapsed or refractory classical Hodgkin lymphoma, defined as refractory to front-line therapy; high-risk and relapsed from front-line therapy; or relapsed or refractory to second line therapy (relapsed: disease progression after most recent therapy, refractory: failure to achieve complete response or partial response). Other inclusion criteria included a requirement for lymph node biopsy tissue, measurable disease (> 15 mm in long axis or > 10 mm in short axis), a Lansky Play Scale or Karnofsky score  $\geq$  50 score and demonstrated adequate organ function.

Patients were excluded if they had a diagnosed immunodeficiency or were receiving immunosuppressive therapy, recent treatment (within 2 weeks) with radiotherapy, and/or systemic anticancer agents, and had recovered from related toxicities of these treatments

(Grade 1 or less for systemic anticancer treatments). Patients with known active central nervous system metastases were excluded, as were patients who had undergone any solid organ transplant or allogeneic haematopoietic stem cell transplant within the past 5 years.

In the data set, three patients, all aged 11 years or older, received pembrolizumab as their second-line therapy, and 86% had received two or more lines of therapy.

Of the 161 participants, 22 had relapsed or refractory classical Hodgkin lymphoma, of which 15 were enrolled in the PD-L1 positive solid tumours and other lymphoma cohort. All had at least one post-baseline assessment of measurable tumour size in target lesions, and all had a reduction in tumour size post-baseline. Prior therapies included radiation therapy for 10 patients.

For the relapsed or refractory classical Hodgkin lymphoma cohort the study reported objective response rate per investigator. The results from the 10 January 2020 data cut-off are summarised in Table 9.

**Table 9: KEYNOTE 051 trial summary of baseline characteristics and efficacy results**

Parameter		n (N = 22)
<b>Baseline Characteristics</b>		
Age	Median (range)	15 (11 to 17)
	14 - 17 years	16 (82%)
	11-13 years	4 (18%)
Country	Australia	3 (14 %)
Race	White	15 (68%)
	Mixed race	16 (27%)
	Asian	1 (4.6%)
Tumour PD-L1 status	Positive	19 (86%)
	Unknown	3 (14%)
Prior lines of therapy	Median (range)	2 (1 to 5)
	1	3 (14%)
	2	10 (45%)
	3	2 (9%)
	4 or 5	7 (32%)
<b>Efficacy Results</b>		
Treatment	Median duration (days)	344
	Median number of doses	17
ORR per INV <sup>a</sup>	ORR	13 (59%; 95% CI, 36 to 79)
	CR	3 (RECIST 1.1/IWG)
	PR	10 (9 RECIST 1.1/1 IWG)

Parameter		n (N = 22)
	Stable Disease	5 (2 RECIST 1.1/ 3 IWG)
	Progressive Disease	4 (3 RECIST 1.1/1 IWG)
ORR per INV according to Cohort	Initial Phase I study period (n = 15)	67%
	cHL expansion cohort (n=7)	43%
DOR per INV	DOR ≥ 6 months	10 (77%)
	DOR ≥ 12 months	6 (46%)
	Range of DOR	0+ to 28.7 months
	Number censored	6 (46%)

Abbreviations: cHL = chronic Hodgkin lymphoma; CI = confidence interval; PFS = progression free survival, ORR = objection response rate; CR = complete response; CRR = complete response rate; HR = hazard reduction; INV = investigator; PFS = progression-free survival; PR = partial response, DOR = duration of response.

International Working Group (IWG) (2007) criteria as per: Cheson B, Pfistner B, Juweid ME et al Revised Response Criteria for Malignant Lymphoma *J Clin Oncol* 2007;25(5):579-586

RECIST version 1.1 criteria: Response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1).

<sup>a</sup> confirmed RECIST 1.1 criteria (n=15) or 2007 IWG criteria (n=7)

Of the 22 relapsed or refractory classical Hodgkin lymphoma patients, 16 were treated for six months or more, and nine for 12 months or more. Subsequent therapy was received by 14 out of 22 patients. Seven patients received haematopoietic stem cell transplantation (allogenic or autologous) after discontinuing pembrolizumab.

The limitations of the objective response rate data included small patient numbers, a paucity of patients with only one prior line of therapy, the lack of Independent Review Committee assessment of the outcome measure, and the heterogenous response were noted.

## Safety

### Exposure and data sets

The sponsor summarised safety data from the KEYNOTE 204 trial (n = 148 patients exposed to pembrolizumab); pooled safety data from the KEYNOTE 204 trial, the KEYNOTE 087 trial (studies described under efficacy, above) and the KEYNOTE 013 trial (n = 389 patients with classical Hodgkin lymphoma);<sup>13</sup> and noted safety from the reference pembrolizumab data sets for monotherapy (n = 2799). The reference data set reflects exposure to Keytruda as a single agent in 2799 patients in three randomised, open-label, active-controlled trials (the KEYNOTE 002, KEYNOTE 006, and KEYNOTE 010 trials), which enrolled 912 patients with melanoma and 682 patients with non-small cell lung cancer (NSCLC), and one single-arm trial (the KEYNOTE 001 trial), which enrolled 655 patients with melanoma and 550 patients with NSCLC.

Patients were predominantly White, less than 65 years of age (younger than the reference data set), with the nodular sclerosing subtype of classical Hodgkin lymphoma, and were balanced for gender, race and ECOG performance status across the data sets. In the KEYNOTE 204 trial the median duration of exposure was 10 months in the pembrolizumab arm and 4.8 months in the brentuximab vedotin arm.



## Safety summary

**Table 10: Summary of safety findings**

	KEYNOTE 204 trial (n = 310)		Pembrolizumab (classical Hodgkin lymphoma pool); <sup>a</sup> (N = 389)	Reference safety data set for pembrolizumab; <sup>b</sup> (N = 2799)
	pembrolizumab (N = 148)	brentuximab vedotin (N = 152)		
<b>Treatment-emergent adverse events (TEAE)</b>				
Any adverse event (AE)	145 (98.0%)	143 (94.1%)	381 (97.9%)	2727 (97.4%)
<b>Most common adverse events &gt;15% in either arm of KEYNOTE 204 trial</b>				
Upper respiratory tract infections	41%	24%		
Musculoskeletal pain	32%	29%		
Diarrhoea	22%	17%		
Pyrexia	20%	13%		
Fatigue	20%	22%		
Cough	20%	14%		
Rash	20%	19%		
Hypothyroidism	19%	3%		
Pruritis	18%	12%		
Nausea	14%	24%		
Vomiting	14%	20%		
Peripheral neuropathy	11%	43%		
Any AE of CTCAE Grade 3 to 5	65 (43.9%)	66 (43.4%)	147 (37.8%)	1273 (45.5%)
<b>Most common ≥ Grade 3 adverse events KEYNOTE 204 trial (≥ 2% either treatment arm)</b>				
Peripheral neuropathy	0.7%	7%		
Pneumonitis	5%	3%		
Diarrhoea	2.7%	1.3%		
Any ADR	74.3%	77.0%	73.3%	73.7%
Any CTCAE Grade 3 - 5 ADR	19.6%	25.0%	15.9%	13.8%
<b>Serious adverse events (SAE)</b>				
Any SAE	44 (29.7%)	32 (21.1%)	104 (26.7%)	1042 (37.2%)
<b>Most common serious adverse events by System Organ Class</b>				
Infections	12%	8%		
Respiratory/thoracic	7%	4%		
<b>Serious drug-related adverse events</b>				
Any drug-related SAE	16.2%	10.5%	11.8%	10.1%

	KEYNOTE 204 trial (n = 310)		Pembrolizumab (classical Hodgkin lymphoma pool); <sup>a</sup> (N = 389)	Reference safety data set for pembrolizumab; <sup>b</sup> (N = 2799)
	pembrolizumab (N = 148)	brentuximab vedotin (N = 152)		
<b>Deaths</b>				
Fatal ADRs	0.7%	0%	0.3%	0.4%
<b>Discontinuations</b>				
Due to AE	13.5%	17.8%	10.5%	11.9%
Due to ADR	12.8%	16.4%	9.3%	5.2%
Due to SAE	9.5%	5.3%	6.2%	9.0%
Due to drug-related SAE	8.8%	3.9%	5.1%	3.6%
<b>Drug dosing interruption</b>				
Due to AE	29.7%	33.6%		
Due to ADR	18.9%	28.9%		

Abbreviations: ADR = adverse drug reaction; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event; TEAE = treatment emergent adverse event.

<sup>a</sup> Pooled safety data from the KEYNOTE 204 trial, the KEYNOTE 087 trial and the KEYNOTE 013 trial (total n = 389 patients with classical Hodgkin lymphoma).

<sup>b</sup> The reference data set reflects exposure to Keytruda as a single agent in 2799 patients in three randomised, open-label, active-controlled trials (the KEYNOTE 002, KEYNOTE 006, and KEYNOTE 010 trials), which enrolled 912 patients with melanoma and 682 patients with non-small cell lung cancer (NSCLC), and one single-arm trial (the KEYNOTE 001 trial), which enrolled 655 patients with melanoma and 550 patients with NSCLC.

The most frequently reported adverse events that led to interruption of study drug were pneumonia (3.4%) and upper respiratory tract infection (3.4%) in the pembrolizumab arm and neuropathy peripheral (5.9%) and infusion-related reactions (4.6%) in the brentuximab vedotin arm.

In the reference population data set classical Hodgkin lymphoma safety data set there were numerically higher incidences of pneumonitis and thyroid events compared with solid tumour data set. It is noted the duration of exposure may differ between indications.

Based on the TGA's clinical assessment the most frequent serious adverse events in the pembrolizumab arm were pneumonitis (7%), pneumonia (5%), and pyrexia (2.7%), respiratory tract infection, site unspecified (2%), myocarditis (1.4%), febrile neutropenia (1.4%), sepsis (1.4%) and acute kidney injury (1.4%). In the brentuximab vedotin arm the most frequent serious adverse events were pneumonia (3.9%), infusion-related reactions (2.0%), peripheral neuropathy (2.0%), pneumonitis (1.3%) and thrombosis.

No new immune-related adverse drug reactions were identified in the KEYNOTE 204 trial. Higher frequencies of hypothyroidism and pneumonitis were observed than were expected from the reference safety data set. The sponsor noted the study included a more heavily pre-treated population who had been exposed to radiation and chemotherapy such as bleomycin.

Laboratory abnormalities were consistent with those previously found for pembrolizumab.

## **KEYNOTE 087 trial**

The sponsor provided summary safety information from 210 patients who received pembrolizumab in the KEYNOTE 087 trial. This study formed the basis of registration of pembrolizumab for relapsed or refractory classical Hodgkin lymphoma.

Around 65% of patients experienced Grade 1 or 2 events, 26.2% experience Grade 3 events, 5.2% experienced Grade 4 events and 12.4% experience Grade 5 events. The most common events were pyrexia (30%), cough (26.2%), fatigue (22.9%), and diarrhoea and upper respiratory tract infection (20.5% each). The most common Grade 3 or 4 treatment-related adverse events were neutropenia (five patients), and diarrhoea and pericarditis (two patients each). Deaths from adverse events included acute graft-versus-host disease (GvHD), post-procedural infection, and septic shock (one patient each). None of the events was considered related to study drug.

Serious adverse events (up to 90 days post last dose of pembrolizumab) were reported in 22.9%: most commonly pneumonia (2.9%), pneumonitis and pyrexia (1.9% each), and acute GvHD (1.4%). Four cases of pneumonitis and two cases of pericarditis were considered drug-related.

Adverse events of special interest (33.8%) included hypothyroidism (15.7%), infusion-related reactions (5.2%), pneumonitis (4.8%). Events included one participant with Grade 3 necrotising myocarditis and Grade 4 myocarditis.

Of the 32 patients (15.2%) underwent allogeneic stem cell transplant after stopping pembrolizumab. Of these 23 experienced a post-allogeneic stem cell transplant adverse event: most commonly acute GvHD (n = 11, including one hyperacute), chronic GvHD (n = 2) or both (n = 5). Eight patients had more than one GvHD event. There were four deaths post allogeneic stem cell transplant, one each from acute GvHD, hyperacute GvHD, pneumonia and sepsis.

## **KEYNOTE 051 trial**

Pembrolizumab safety in the paediatric relapsed or refractory classical Hodgkin lymphoma was in part described from the 22 patients with classical Hodgkin lymphoma and from patients with other tumours (n = 139) from the KEYNOTE 051 trial. Grade 3 or higher adverse events occurred in 47% of patients, serious adverse events occurred in 39%, and 6.2% had adverse event-related treatment discontinuation.

In the total paediatric cohort of 161 patients, 96.3% had one or more adverse event, with the most common pyrexia (32.9%), vomiting (29.8%), headache (25.5%), abdominal pain (22.4%), anaemia (21.1%), cough (20.5%), constipation (19.9%), fatigue (19.3%), nausea (19.3%), and diarrhoea (18.3%).

Thirty patients (18.6%) from the total paediatric cohort had one or more adverse event of special interest. Grade 3 to 5 events (n = 4) included colitis, myositis, pruritus (all Grade 3) and pneumonitis (Grade 5). At the data cut-off, 17 had not resolved and 12 involved endocrinopathies requiring long-term hormone replacement therapy.

The most frequent laboratory abnormalities in the total paediatric cohort were elevations of alkaline phosphatase  $\geq 1.5 \times$  the upper limit of normal (ULN; 14.4%), alanine transferase or aspartate aminotransferase  $\geq 3 \times$  ULN (12.5%).

Two classical Hodgkin lymphoma patients underwent allogeneic stem cell transplant after discontinuing pembrolizumab. One developed Grade 2 chronic GvHD and the other acute GvHD.

## Risk management plan

The Risk Management Section did not require a revised risk management plan for this submission because pembrolizumab already has been approved by the TGA for other indications related to the current indication including relapsed or refractory classical Hodgkin lymphoma in adults, and in paediatric patients has approval in primary mediastinal large B-cell lymphoma (PMBCL) and high microsatellite instability (MSI-H) cancer. The agreed risk management activities in place for these indications are sufficient for the current indication.

The sponsor is required to comply with product vigilance and risk minimisation requirements.

The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in [risk management plans for medicines and biologicals](#) and [the TGA's risk management approach](#). Information on the [Australia specific annex \(ASA\)](#) can be found on the TGA website.

## Risk-benefit analysis

### Delegate's considerations

#### *Adult population*

The original indication for relapsed or refractory classical Hodgkin lymphoma was based on the findings of the KEYNOTE 087 trial. The objective response rate at the time of initial approval of this indication was 69% with 22% CR and 27% partial remissions in a heavily pre-treated population.

In this submission, in the KEYNOTE 204 trial, the comparator for pembrolizumab is brentuximab vedotin. This monoclonal antibody is a targeted therapy option in the treatment algorithm for relapsed or refractory classical Hodgkin lymphoma that was broadly available for use at the time the study commenced. It is registered has a similar indication to the current pembrolizumab indication, following on from autologous stem cell transplantation and was an available therapy in the countries in which the study was conducted.

The KEYNOTE 204 trial builds on the body of evidence supporting pembrolizumab in relapsed or refractory classical Hodgkin lymphoma. In this study pembrolizumab provided benefits for progression free survival over brentuximab vedotin with a hazard ratio of 0.65 (95% confidence intervals (CI): 0.48, 0.88) in favour of pembrolizumab. Similar results were seen with censoring for stem cell transplantation following pembrolizumab treatment. Demonstrable alteration of the slopes of the Kaplan-Meier curves for brentuximab vedotin and pembrolizumab occur at about 6 months. Around 7 months greater duration of response was seen with pembrolizumab, although it is recognised that this is an exploratory endpoint.

Although the objective response rate was 11.3% greater in the pembrolizumab arm, because of the alpha spending rules, statistical significance was not reached in this interim analysis.

The data for overall survival are immature and the analysis exploratory at this time.

The progression free survival hazard ratio point estimates all favour pembrolizumab over brentuximab, although for patients based in the USA or EU, and those patients with early relapse, the outcomes were less compelling.

Classical Hodgkin lymphoma is typically highly expressive of programmed death-ligand 1 (PD-L1) and in the KEYNOTE 204 trial 94% of the pembrolizumab group, and 90.5% of the overall trial population expressed were PD-L1 positive at 1% expression or more. Too few patients expressed PD-L1 less than 1% to allow meaningful conclusions.

There are limited data in the use of pembrolizumab in adults who have had only one prior line of therapy (18% of the intent to treat population). The TGA's clinical analysis of outcomes for this population show for complete response and partial response for those with one and two or more prior lines of therapy were comparable.

Supportive findings are provided from updated efficacy results from the single-arm KEYNOTE 087 trial, from a more heavily pre-treated population with relapsed or refractory classical Hodgkin lymphoma. In this setting the objective response rate was 71% and the median duration of response was 16.6 months. progression-free survival was 52.3% at 12 months, and 32.2% at 24 months.

The safety data set in adults is adequate for a safety assessment for this population. Around 30% of patients experienced a serious adverse event. Pneumonitis was a serious adverse event and a cause of treatment related discontinuation. Of the adverse events of special interest, which comprise immune-mediated or presumed immune-mediated events, hypothyroidism, pneumonitis and infusion reactions were the most commonly seen. The safety profile of pembrolizumab bears similarities to the safety profile elucidated previously in this indication and across the spectrum of conditions for which pembrolizumab has registered indications in Australia.

In the KEYNOTE 204 trial, 14% of the pembrolizumab arm and 12% of the brentuximab vedotin arm underwent stem cell transplant as their most immediate next treatment, and 28% and 29% of each arm subsequently underwent stem cell transplant at any point.

There is a recognised risk of graft versus host disease (GvHD) in patients who undergo allogeneic stem cell transplant after PD-L1 immunotherapy. Although prescribers need to consider this risk in planning therapeutic strategies for their patients this risk is not of itself considered sufficient to preclude pembrolizumab use in relapsed or refractory classical Hodgkin lymphoma.

The safety data overall reflect the known risks of pembrolizumab, and the risks are considered acceptable in the context of the proposed use.

### ***Paediatric population***

Data from the KEYNOTE 051 trial and an updated population pharmacokinetic model supported the weight-based pembrolizumab dosing of 2 mg/kg once every three weeks in children.

The use of pembrolizumab in the paediatric relapsed or refractory classical Hodgkin lymphoma group is supported by the findings of the classical Hodgkin lymphoma patients from the KEYNOTE 051 trial. Only a small number of relapsed or refractory classical Hodgkin lymphoma patients were included in the study, consistent with the relative rarity of relapsed or refractory classical Hodgkin lymphoma in the paediatric age group. In this single-arm data set the objective response rate was 59%, and the duration of response was 77% at 6 months or longer and 46% at 12 months and ranged from 0 to 28.7 months. Extrapolation of the findings of adult studies to support the paediatric data is necessary to support the indication and is reasonable based on this similarity of classical Hodgkin lymphoma in young adults and adolescents in particular.

There is limited safety information in children with relapsed or refractory classical Hodgkin lymphoma. Additional safety data in children is extrapolated from the solid tumour cohorts in

the KEYNOTE 051 trial. While over 160 patients received pembrolizumab this still represents small numbers. Safety data may be further extrapolated from the primary mediastinal B-cell lymphoma (PMBCL). The long term sequelae of pembrolizumab exposure is not well characterised, in particular for patients who develop immune-mediated adverse effects.

For paediatric patients with relapsed or refractory classical Hodgkin lymphoma the sponsor is seeking approval for use as second line therapy. The data in paediatric patients are limited and only three patients received pembrolizumab as first line. These data alone are considered insufficient clinical trial evidence to support a first line therapeutic indication. Given the limited data and the established efficacy of second line chemotherapy regimens, the proposal is to limit the indication to patients with primary refractory disease, and those with relapsed disease after at least two prior lines of therapy. The KEYNOTE 051 trial is ongoing and accrual of patients with relapsed disease may inform future refinements to the population.

## **Indications**

The sponsor proposes to amend the wording of the indication of relapsed or refractory classical Hodgkin lymphoma in adults to incorporate the requirement for prior autologous stem cell transplant and established ineligibility for autologous stem cell transplant.

Protocol changes altered the eligibility criteria through the study in relation to prior autologous stem cell transplant. Patients randomised through the period of these protocol changes had similar outcomes to those for the overall study. Outcomes by subgroup did not demonstrate a clear benefit of prior autologous stem cell transplant over the remainder of the patient population.

The proposed indication is less restrictive than its predecessor indication; previously patients were required to have relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant or for pembrolizumab to be third line therapy only when autologous stem cell transplant or multi-agent chemotherapy were not options. The proposed indication is line agnostic but does not preclude the option of autologous stem cell transplant or other lines of therapy, and this approach may offer an option for patients with chemo-insensitive disease.

The approach to the paediatric indication appears reasonable given the very limited data from the first line setting. The indication is not proposed to require a failed autologous stem cell transplant although that remains an option.

The comment of the Advisory Committee on Medicines (ACM) is sought on the wording of the indications for adults and children.

## **Proposed action**

While a decision was yet to be made, at this stage the Delegate was inclined to approve the registration of the product.

Advice is sought from the ACM on the wording of the indication.

If registration was approved the Delegate would propose the following additional conditions of registration:

- Submit the final results characterising the risk of immune-mediated or potentially immune-mediated toxicities, serious adverse events and long-term safety in paediatric patients with lymphoma enrolled in the KEYNOTE 051 trial. All patients with Hodgkin lymphoma should be followed for safety for a minimum of 6 months on pembrolizumab.

- Submit the final clinical study report for all paediatric patients who received pembrolizumab for Hodgkin lymphoma in the KEYNOTE-051 trial.

## Advisory Committee considerations

The [Advisory Committee on Medicines \(ACM\)](#) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

### Specific advice to the Delegate

- 1. Based on the findings of the KEYNOTE 087 trial, pembrolizumab was indicated after autologous stem cell transplant or as third line therapy for patients ineligible for autologous stem cell transplant or multi-agent chemotherapy.**

#### ***Does the evidence support the proposed broader indication in adults?***

The ACM were of the view that the adult indication should align with the study population within the KEYNOTE 087 trial and the majority of the KEYNOTE 204 trial, as the evidence demonstrates efficacy within this population. Based on this, the ACM were supportive of using the wording used in the European Medicines Agency's (EMA) indication as follows:

*'[pembrolizumab is indicated for use in patients] with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option'.<sup>14</sup>*

- 2. The sponsor proposes to limit the use of pembrolizumab to second line treatment for refractory and relapsed chronic Hodgkin lymphoma in paediatric patients.**

#### ***Does the ACM agree with this approach?***

The ACM were of the view that adequate data has not been provided to support an indication for relapsed or refractory classical Hodgkin lymphoma in paediatric patients.

The ACM expressed concern regarding the immaturity of the data provided in support of this proposed paediatric indication and agreed that neither safety nor efficacy have been appropriately demonstrated for this population. The ACM agreed that there is a high level of uncertainty from the limited preliminary data arising from the non-controlled study.

The ACM agreed that the safety data is premature regarding the long-term safety of Keytruda in paediatric patients. Paediatric safety data was provided within the KEYNOTE 051 trial for multiple tumours (n = 161), and the ACM noted that 12 paediatric patients (7.5%) had endocrinopathies requiring long-term hormone replacement (predominantly hypothyroidism). The ACM were of the view that additional safety data would be required to better understand the long-term safety profile within this population.

The ACM agreed that while some efficacy within the trial had been demonstrated, with 13 out of 22 patients experiencing complete or partial remission, this data was very early and included limited follow up. The ACM were of the view that it is too early to understand how this translates outside of the clinical trial setting.

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<sup>14</sup> The European Public Access Report (EPAR) pertaining to the submission related to this indication (Assessment report: EMA/97222/2021; Procedure No. EMEA/H/C/003820/II/0090) is available online at: [Keytruda: INN-pembrolizumab \(europa.eu\)](#)

The ACM noted that the paediatric data provided is derived from an ongoing trial that continues to recruit participants in Canada, the USA, and Australia.

The ACM were of the view that this early data set may be better suited to the provisional registration process.

**3. If the ACM disagrees with the sponsor's approach for the adult or the paediatric indication, is there alternative wording that it recommends?**

The ACM is of the view that the paediatric population should not be included within the indication and as such the ACM recommends the following amendment to the currently approved indication for pembrolizumab for classical Hodgkin lymphoma:

*Keytruda as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.*

## Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

*Keytruda as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.*

The ACM agreed that Keytruda had an overall negative benefit-risk profile for full registration of the indication for the paediatric population as the evidence submitted did not satisfactorily establish the efficacy and safety of the product.

## Post-ACM considerations

The Delegate considered that in order to follow the ACM advice, the sponsor would need to agree to withdraw the submission and submit a request for [provisional determination](#).<sup>15</sup> If eligible, it would need reassessment of the submission and a reconsideration of the decision. As this was an unexpected outcome of the request for advice, the Delegate offered the sponsor an opportunity to respond to the ACM minutes.

The sponsor indicated it has no intention of withdrawing the submission, and pointed out several aspects of its submission:

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<sup>15</sup> **Provisional determination** is a formal process whereby the sponsor must submit an application for determination and have this application approved before the sponsor can lodge a submission for provisional registration. The process allows the TGA to make a decision regarding whether the medicine is eligible for registration via the provisional approval pathway.

The **provisional approval pathway** allows for provisional registration of medicines on the basis of preliminary clinical data. However, the TGA always require comprehensive non-clinical data on safety, quality and compliance with Good Manufacturing Practice. These requirements are the same as in the standard registration process for prescription medicines. For further information, see the [Provisional registration process](#).

If and when a provisional determination is in place, a submission to approve an application for a new or expanded indication is processed through the provisional registration pathway (section 23AA of the Act).

A sponsor however cannot seek and the TGA is unable to accept a submission for provisional registration unless the provisional determination is in place at the time when the sponsor lodges the section 23 submission for registration. This means that a sponsor cannot lodge a determination application in parallel to or after the pre-submission planning form (PPF).



- in accordance with the protocol in which a minimum of 20 patients and a maximum of 25 patients were proposed for the cohort of paediatric patients with relapsed or refractory classical Hodgkin lymphoma.
- the extrapolation from adult studies was conducted in accordance with the TGA-adopted EU guidelines.<sup>16,17</sup>

The Delegate has recognised there are merits to the sponsor's objections, and has considered that while there are limitations to the evidence based on small patients numbers and that the submission does rely on extrapolation of adult data based on the similarity of the disease process of relapsed or refractory classical Hodgkin lymphoma in young adults and paediatric aged patients.

Taking the sponsor's response into consideration and the intent of the ACM advice, the Delegate has proposed to the sponsor that including a description of the limitations of the current evidence into the wording of the indication, in a way that would deliver a similar message about the limitations of the data to prescribers. Such a limitation could potentially be removed if more data were provided at a later time. The Delegate proposed the following indication that has been accepted by the sponsor:

*Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of adult and paediatric patients with relapsed or refractory classical Hodgkin Lymphoma (cHL):*

1. *following autologous stem cell transplant (ASCT)*
2. *following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.*

*The approval of this indication in paediatric patients is on the basis of objective response rate from patients aged 11 years and older from single arm trial data, and extrapolation from adult data (see Section 5.1 Pharmacodynamic Properties, Clinical Trials).*

A number of changes were requested of the presentation of the information in the Product Information (PI) that aligns the presentation of the data for the adult population more closely with the USA and EU prescribing information for Keytruda, and also includes a statement about the paediatric data including the results for the clinical trials section.

An acceptable PI has been negotiated.

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<sup>16</sup> International Council for Harmonisation (ICH) topic E11 - [Note for guidance on clinical investigation of medicinal products in the paediatric population](#) (CPMP/ICH/2711/99). TGA-adopted; effective date: 19 April 2001.

<sup>17</sup> EMA: [Reflection paper on the use of extrapolation in the development of medicines for paediatrics](#) (EMA/189724/2018). TGA-adopted; effective date: 15 July 2019.

## Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Keytruda (pembrolizumab) 50 mg powder for injection vial and 100 mg/4 mL concentrated solution for injection vial indicated for the following extension of indications:

### **Classical Hodgkin Lymphoma (cHL)**

*Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of adult and paediatric patients with relapsed or refractory classical Hodgkin Lymphoma (cHL):*

1. *following autologous stem cell transplant (ASCT) or*
2. *following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.*

*The approval of this indication in paediatric patients is on the basis of objective response rate from patients aged 11 years and older from single arm trial data and extrapolation from adult data (see Section 5.1 Pharmacodynamic properties, Clinical Trials).*

As such, the full indications at this time were:

### **Melanoma**

*Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of unresectable or metastatic melanoma in adults.*

*Keytruda (pembrolizumab) is indicated as monotherapy for the adjuvant treatment of patients with melanoma with lymph node involvement who have undergone complete resection.*

### **Non-small cell lung cancer (NSCLC)**

*Keytruda (pembrolizumab), in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumour aberrations.*

*Keytruda (pembrolizumab), in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.*

*Keytruda (pembrolizumab) is indicated as monotherapy for the first-line treatment of patients with NSCLC expressing PD-L1 [tumour proportion score (TPS)  $\geq 1\%$ ] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and is*

- *stage III where patients are not candidates for surgical resection or definitive chemoradiation, or*
- *metastatic.*

*Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of patients with advanced NSCLC whose tumours express PD-L1 with a  $\geq 1\%$  TPS as determined by a validated test and who have received platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received prior therapy for these aberrations prior to receiving Keytruda .*

### **Head and Neck Squamous Cell Cancer (HNSCC)**

*Keytruda (pembrolizumab), as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of patients with*

*metastatic or unresectable recurrent HNSCC, and whose tumours express PD-L1 [Combined Positive Score (CPS)  $\geq 1$ ] as determined by a validated test.*

*Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of patients with metastatic or unresectable recurrent HNSCC with disease progression on or after platinum containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS)  $\geq 1$ ] as determined by a validated test.*

### **Classical Hodgkin Lymphoma (cHL)**

*Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of adult and paediatric patients with relapsed or refractory classical Hodgkin Lymphoma (cHL):*

- 1. following autologous stem cell transplant (ASCT) or*
- 2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.*

*The approval of this indication in paediatric patients is on the basis of objective response rate from patients aged 11 years and older from single arm trial data and extrapolation from adult data (see Section 5.1 Pharmacodynamic properties, Clinical Trials).*

### **Primary mediastinal B-Cell Lymphoma (PMBCL)**

*Keytruda (pembrolizumab) is indicated for the treatment of adult and paediatric patients with refractory primary mediastinal B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy. The approval of this indication is on the basis of objective response rate (ORR) and duration of response from non-randomised studies. See Section 5.1 Pharmacodynamic properties, Clinical Trials.*

### **Urothelial carcinoma**

*Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin containing therapy and whose tumours express PD-L1 [Combined Positive Score (CPS)  $\geq 10$ ] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication is approved based on overall response rate and duration of response in a single-arm study. Improvements in overall survival, progression-free survival, or health-related quality of life have not been established.*

*Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy.*

*Keytruda (pembrolizumab) is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy. This indication was approved via the **provisional approval** pathway based on complete response rate and duration of response. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.*

**Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer Colorectal (previously untreated)**

*Keytruda (pembrolizumab) is indicated for the first-line treatment of patients with unresectable or metastatic colorectal cancer (CRC) that is MSI-H or dMMR as determined by a validated test.*

#### *Colorectal (previously treated)*

*Keytruda (pembrolizumab) is indicated in adult and paediatric patients for the treatment of unresectable or metastatic CRC that is MSI-H or dMMR as determined by a validated test, and that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication was approved via the **provisional approval** pathway, based on objective response rate and response duration in a single-arm trial. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials.*

#### *Non-colorectal*

*Keytruda (pembrolizumab) is indicated in adult and paediatric patients for the treatment of unresectable or metastatic solid tumours that are MSI-H or dMMR as determined by a validated test, that have progressed following prior treatment and when there are no satisfactory alternative treatment options. This indication was approved via the **provisional approval** pathway, based on the pooling of data on objective response rate and response duration across multiple different tissue types in a single-arm trial. Sample sizes for individual tissue types were too small to provide data on clinical utility of the MSI-H/dMMR tests for each of the tissue types, individually. The assumption that MSI-H/dMMR status is predictive of the treatment effect of Keytruda for every tissue type has not been verified. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials.*

*The safety and effectiveness of Keytruda in paediatric patients with MSI-H/dMMR central nervous system cancers have not been established.*

#### **Endometrial carcinoma**

*Keytruda (pembrolizumab), in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR as determined by a validated test, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This indication was approved via the **provisional approval** pathway, based on objective response rate and duration of response in a single-arm trial. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.*

#### **Renal Cell Carcinoma (RCC)**

*Keytruda (pembrolizumab), in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).*

#### **Cutaneous Squamous Cell Carcinoma**

*Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of adult patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation. This indication was approved via the provisional approval pathway based on objective response rate and duration of response from a single-arm study. Improvements in overall survival, progression-free survival, or health-related quality of life have not been established. Full registration for this indication depends on submission of further clinical data to confirm the clinical benefit of the medicine.*

#### **Oesophageal Cancer**

*Keytruda (pembrolizumab), in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced or metastatic carcinoma of the oesophagus or HER2 negative gastroesophageal junction adenocarcinoma (tumour centre 1 to 5 centimetres above the gastroesophageal junction) that is not amenable to surgical resection or definitive chemoradiation.*

#### **Tumour Mutational Burden-High (TMB-H) cancer**

*Keytruda (pembrolizumab) is indicated for the treatment of adult and paediatric patients with unresectable or metastatic tumour mutational burden-high (TMB-H) [ $\geq 10$  mutations/megabase (mut/Mb)] solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. This indication was approved via the **provisional approval** pathway, based on the pooling of data on objective response rate and response duration across multiple different tissue types in a single-arm trial. The assumption that TMB-H status is predictive of the treatment effect of Keytruda for every tissue type has not been verified. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.*

The above extension of indications are inclusive of the previous approved indications.

## **Specific conditions of registration applying to these goods**

- This approval does not impose any requirement for the submission of Periodic Safety Update reports. You should note that it is a requirement that all existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.

You are reminded that sections 29A and 29AA of the Therapeutic Goods Act 1989 provide for penalties where there has been failure to inform the Secretary in writing, as soon as a person has become aware, of:

- (a) information that contradicts information already given by the person under this Act;
  - (b) information that indicates that the use of the goods in accordance with the recommendations for their use may have an unintended harmful effect;
  - (c) information that indicates that the goods, when used in accordance with the recommendations for their use, may not be as effective as the application for registration or listing of the goods or information already given by the person under this Act suggests;
  - (d) information that indicates that the quality, safety or efficacy of the goods is unacceptable.
- Additional conditions of registration:
    - a. Submit the final results characterising the risk of immune-mediated or potentially immune-mediated toxicities, serious adverse events and long-term safety in paediatric patients with lymphoma enrolled in KN-051 [KEYNOTE 051 trial]. All patients with Hodgkin lymphoma should be followed for safety for a minimum of 6 months on pembrolizumab.
    - b. Submit the final clinical study report for all paediatric patients who received pembrolizumab for Hodgkin Lymphoma in Keynote-051.
  - For all injectable products the Product Information must be included with the product as a package insert.

## Attachment 1. Product Information

The PI for Keytruda approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA [PI/CMI search facility](#).

## **Therapeutic Goods Administration**

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Reference/Publication #