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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- 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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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUA	American Urological Association
BCG	Bacillus Calmette-Guérin
CI	Confidence interval
CIS	Carcinoma in-situ
CMI	Consumer Medicines Information
CPS	Combined Positive Score
CTU	Computer tomography uroscopy
DLP	Data lock point
EAU	European Association of Urology
ECOG (PS)	Eastern Cooperative Oncology Group (performance status)
EMA	European Medicines Agency (European Union)
EU	European Union
FDA	Food and Drug Administration (United States of America)
IBCG	International Bladder Cancer Group
NCCN	National Comprehensive Cancer Network
NMIBC	Non-muscle invasive bladder cancer
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PI	Product Information
PSUR	Periodic safety update report
RMP	Risk management plan
SUO	Society of Urologic Oncology
TGA	Therapeutic Goods Administration
TNM	Tumour, Nodes, Metastasis (staging system)
TURBT	Transurethral resection of bladder tumour
US(A)	United States (of America)

Product submission

Submission details

Type of submission:	Extension of indications
Product name:	Keytruda
Active ingredient:	Pembrolizumab
Decision:	Approved
Date of decision:	12 July 2021
Date of entry onto ARTG:	14 July 2021
ARTG numbers:	226597, 263932
, *Black Triangle Scheme*	Yes
for the current submission:	As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
Sponsor's name and address:	Merck Sharp & Dohme (Australia) Pty Ltd 26 Talavera Road Macquarie Park, NSW 2113
Dose forms:	Powder for injection and concentrated injection
Strengths:	50 mg (powder for injection) 100 mg/4 mL (concentrated injection)
Container:	Vial
Pack size:	One single use vial
Approved therapeutic use for the current submission:	*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.*
Route of administration:	Intravenous infusion
Dosage:	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).

For the treatment of high-risk BCG-unresponsive non-muscle invasive bladder cancer, Keytruda should be administered until persistent or recurrent high-risk non-muscle invasive bladder cancer, disease progression, unacceptable toxicity, or up to 24 months.

No dose reductions of Keytruda are recommended. Withhold or discontinue Keytruda to manage adverse reactions as described in Table 1 (Recommended Dose Modifications) of the Product Information; see also, Section 4.4 Special warnings and precautions for use of the Product Information.

For use in combination, see the Product Information for the concomitant therapies. When administering Keytruda as part of a combination with intravenous chemotherapy, Keytruda should be administered first. Patients should be treated with Keytruda until disease progression or unacceptable toxicity.

For further information regarding dosage, 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 provisionally register Keytruda (pembrolizumab (rch)) 50 mg powder for injection (vial); and Keytruda (pembrolizumab (rch)) 100 mg/4 mL concentrated injection (vial), for the following proposed extension of indications:[1]

> *For the treatment of patients with Bacillus Calmette-Geurin (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.*

Bladder cancer (urothelial carcinoma)

Urothelial carcinoma is a malignancy arising in the urothelium (transitional cell epithelium) which lines the luminal surface (or innermost layer) of the bladder and urinary tract. Malignancies arising from these urothelial cells account for over 90% of all bladder cancer cases.[2] Other forms of bladder cancer include squamous cell carcinoma making up 5% of cases, and adenocarcinomas comprising of about 2% of cases.[3]

Cancer of the bladder is estimated to be the tenth most common cancer globally.[2] The incidence of bladder cancer increases with age, and the average age at diagnosis is 75 years.[4] Australian Institute of Health and Welfare (AIHW) data reported that in 2018, there were 2,968 new cases of bladder cancer diagnosed in Australia (2,250 males and 717 females) with almost 77% of cases occurred in male subjects.[4]

Smoking tobacco and exposure to tobacco smoke is the greatest known factor to urinary bladder cancer and accounts for 50-65% of cases, and may explain the greater incidence in men.[2,5] After smoking, past exposure to occupational or environmental toxins are the next greatest contributor, however the proportion can difficult to ascertain as bladder cancer develops decades after exposure, even if the exposure may have only lasted several years.[2]

Non-muscle invasive bladder cancer is usually first suspected due to haematuria (blood in urine) that is usually painless, which may or may not be accompanied by vague urinary-type symptomology. Diagnosis is then confirmed via cystoscopy, or following further investigations and imaging including telescopic endoscopy of the bladder, transabdominal ultrasound, and/or computer tomography urography (CTU).[2]

[1] 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.

[2] Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of Bladder Cancer. *Med Sci* (Basel). 2020;8(1):15.

[3] Dahm P, Gschwend JE. Malignant non-urothelial neoplasms of the urinary bladder: A review. *European Urology*. 2003;44(6):672-681.

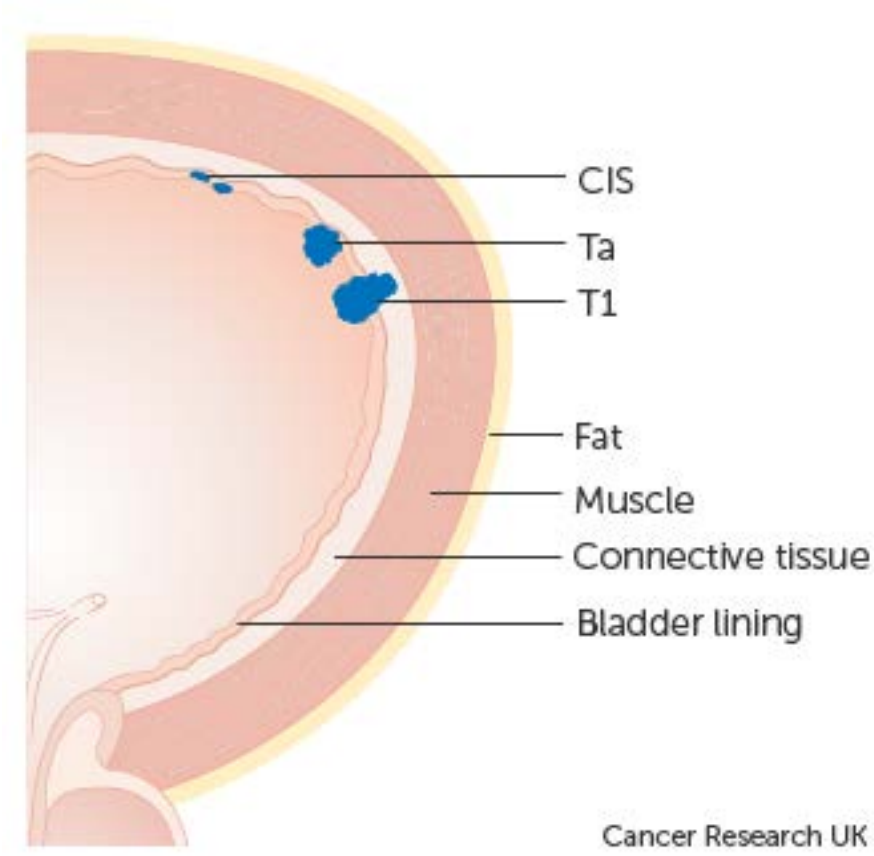
[4] Data sourced from Australian Institute of Health and Welfare (AIHW) Cancer Data in Australia 2022 web report and supplementary data tables. More information about incidence rates for the most common cancers diagnosed can be found on the NCCI website available online at: https://ncci.canceraustralia.gov.au/diagnosis/cancer-incidence/cancer-incidence

[5] Zeegers MP, Tan FE, Dorant E, van Den Brandt PA (2000). The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies. *Cancer*. 89 (3): 630–9.

Bladder cancer is commonly staged according to the Tumour, Node, Metastasis (TNM) staging system.[6,7] Descriptions and staging of non-muscle invasive bladder cancer is based upon the T (tumour) stages and includes urothelial carcinoma of the Ta stage (non-invasive papillary carcinoma), Tis stage (carcinoma in-situ) and T1 stage (where the tumour has spread to the subepithelial connective tissue beneath the urothelium. A pictorial representation of the stages involved is given in Figure 1, with a text summary given in Table 1 (below).

Higher stages of bladder tumours (T2, T3 and T4 disease; not depicted in Figure 1) are considered to be muscle-invasive bladder cancer, as by definition these stages describe cancer cells have spread into or through the muscle layer of the bladder wall.

Figure 1: TNM staging and anatomy of non-muscle invasive bladder cancer



Tumour (T) staging is based on extent of invasion into the bladder wall. Non-muscle invasive bladder cancer includes Ta, Tis (carcinoma-in-situ) and T1 disease whereby there is no evidence of cancer cells invading into or beyond the muscle layer of the bladder.

CIS (carcinoma-in-situ) are small lesions in the innermost layer of the urothelium, high grade; may be referred to as a 'flat tumour'.

Ta tumours (or non-invasive papillary carcinoma) are restricted to the urothelium.

T1 tumours describe tumours have started to grow into the lamina propria, the (subepithelial) connective tissue lying underneath the urothelium.

Diagram adapted from: Cancer Research UK uploader, CC BY-SA 4.0, via Wikimedia Commons.

[6] The **Tumour, Nodes and Metastasis** (**TNM**) staging system describes the amount and spread of cancer in a patient's body. T describes the size of the tumour and any spread of cancer into nearby tissue; N describes spread of cancer from its original location to nearby lymph nodes; and M describes metastasis (spread of cancer to other parts of the body).

[7] American Joint Committee on Cancer (AJCC). AJCC Cancer Staging Manual. 8th edition. New York: *Springer;* 2017.

Table 1: AJCC (2017) TNM (Tumour, Nodes, Metastasis) classification of bladder cancer

Stage	Definition
T: Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N: Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M: Distal metastasis	
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastases

Information from American Joint Committee on Cancer (AJCC). AJCC Cancer Staging Manual. 8th edition. New York: Springer; 2017.

Papillary tumours that protrude into the bladder lumen but do not extend beyond the bladder lining are Ta. Tis refers to urothelial carcinoma-in situ, a flat tumour only found on or near the surface of the bladder. T1 tumours reach the layer of connective tissue, a layer called the lamina propria, that separates the lining of the bladder from the muscle beneath, but does not extend into the muscle layer.

Approximately 75 to 80% of subjects newly diagnosed with urothelial carcinoma of the bladder present with non-muscle invasive bladder cancer.[8,9] Of these patients, approximately 45% present with Ta, 24% with T1, and 10% with Tis (carcinoma-in-situ) staged tumours.[9] The remainder present with muscle-invasive disease of T2 or higher stages.

Histological grade is an important prognostic factor for urothelial carcinoma of the bladder.[10,11] Papillary tumours can be classified as either high grade (cancer cells with a greater propensity to grow and spread) or low grade (fewer or less irregular cancer cells with a lower propensity to grow and spread), but carcinoma in-situ (Tis) is always considered a high grade lesion.[11]

Other adverse prognostic factors for disease progression include high stage, large tumour size, multifocal lesions, high number of recurrences, the presence of lymphovascular invasion in the lamina propria, and certain histological variants.[8]

Based on prognostic factors, non-muscle invasive bladder cancer is classified as low-, intermediate-, or high-risk for disease recurrence/progression.[12,13,14] As defined by the International Bladder Cancer Group (IBCG), high-risk disease includes T1 tumours, any high-grade papillary tumour, and carcinoma in-situ.[14]

Current treatment options

Initial treatment of bladder cancer involves cystoscopy and transurethral resection of bladder tumour (TURBT).[15] This may be followed a single dose of intravesical chemotherapy (usually gemcitabine or mitomycin) within 24 hours following the TURBT procedure. Complete removal of carcinoma in-situ via TURBT is often not feasible because the disease is often diffuse and difficult to visualise.

[8] Kamat AM, Hahn NM, Efstathiou JA et al. Bladder cancer. *Lancet*. 2016; 388 (10061): 2796-2810.
[9] Nielsen ME, Smith AB, Meyer AM et al. Trends in Stage-Specific Incidence Rates for Urothelial Carcinoma of the Bladder in the United States: 1988 to 2006. *Cancer*. 2014; 120: 86-95.
[10] National Comprehensive Cancer Network (NCCN): NCCN Clinical Practice Guidelines in Oncology – Bladder Cancer. Version 5.2020. May 12, 2020.
Available online at: https://www.nccn.org/professionals/physician_gls/default.aspx
[11] Comperat EM, Burger M, Gontero P et al. Grading of Urothelial Carcinoma and the New 'World Health Organisation Classification of Tumours of the Urinary System and male Genital Organs 2016'.
Eur Urol Focus. 2019; 5 (3): 457-466.
[12] Chang SS, Boorjian SA, Chou R et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Joint Guideline (2016).
Available online at: https://www.auanet.org/guidelines/bladder-cancer-non-muscle-invasive-guideline
[13] Babjuk M, Burger M, Compérat E et al. European Association of Urology (EAU) Guidelines on Non-Muscle-Invasive Bladder Cancer. 2020. Available online at: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/
[14] Kamat AM, Sylvester RJ, Böhle A et al. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. *J Clin Oncol.* 2016 Jun 1;34(16):1935-44.
[15] Understand Surgery: TURBT from Understanding Bladder Cancer A guide for people with cancer, their families and friends (2022). https://www.cancercouncil.com.au/bladder-cancer/non-muscle-invasive-treatment/surgery/

Recommended treatment for high-risk non-muscle invasive bladder cancer patients is an induction course of intravesical Bacillus Calmette–Guérin (BCG) once a week for 6 weeks.[16] Follow-up cystoscopy and urine cytology is generally performed 3 months after TURBT. In patients with negative cystoscopy and cytology a maintenance regimen of intravesical BCG lasting 1 to 3 years is recommended. In those with persistent or recurrent disease after a single induction course of BCG, a second induction course may be appropriate.

BCG therapy failure can be classified in to refractory, relapsing, intolerant or unresponsive, and is discussed in Table 2 (shown below).[14]

Table 2: Kamat et al. (2016) Classification of BCG failures

Classification	Description
Refractory	Persistent high-grade disease at 6 months despite adequate BCG* treatment. This category also includes any stage or grade progression by 3 months after the first BCG cycle (that is, high-grade T1 at 3 months after initial Ta, T1, high-grade disease, or CIS).
Relapsing	Recurrence of high-grade disease after achieving a disease-free state at 6 months after adequate BCG.* Although this category has previously been subdivided based on time to recurrence after stopping BCG (that is, early (less than 12 months), intermediate (1 to 2 years), or late (more than 24 months)), for the purpose of being included in the BCG-unresponsive category, patients should be within 6 months of the last BCG exposure (for example, patients receiving maintenance therapy).
Intolerant	Disease persistence as a result of inability to receive adequate BCG* because of toxicity. With current attention to abrogation of BCG adverse effects, we expect this category to represent a small portion of the BCG-treated population.
Unresponsive[1]	BCG refractory and BCG relapsing disease. The term BCG unresponsive, which essentially includes BCG refractory and BCG relapsing (within 6 months of last BCG exposure), is meant to denote a subgroup of patients at highest risk of recurrence and progression for whom additional BCG therapy is not a feasible option. These patients can be considered for single-arm studies.†

Abbreviations: BCG = Bacillus Calmette-Guérin; CIS = carcinoma in situ.

1: Classification derived from: Lerner SP, Dinney C, Kamat AM, et al. Short communication: Clarification of bladder cancer disease states following treatment of patients with intravesical BCG. *Bladder Cancer*. 2015;1:29–30.
* For clinical trials, adequate BCG therapy is when a patient has received at least five of six induction instillations and at least one maintenance (two of three instillations) in a 6-month period.
† Because there are often delays in referral to and enrolment in trials, we recommend that study designs account for a window from tumour recurrence, and patients can be within 6 to 9 months of the last BCG exposure, thereby allowing a 3-month lead time for referral.

Table adapted from Kamat AM, Sylvester RJ, Böhle A et al. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. *J Clin Oncol.* 2016 Jun 1;34(16):1935-44.

[16] **Bacillus Calmette–Guérin (BCG) vaccine** was originally developed as a vaccine to prevent tuberculosis (TB) infection and is still used for this purpose. Since the late 1970's the BCG vaccine, used differently to vaccination against TB, has been proven and used as an active immunotherapy in the treatment of nonmuscle-invasive bladder cancer. The exact mechanism is not fully characterised.

BCG unresponsive classifications includes BCG refractory and BCG relapsing (disease progression within 6 months of last BCG therapy), denoting a group of patients at the highest risk of recurrence and progression to invasive disease. The definition used in the key clinical study for this submission, the Keynote-057 trial, is discussed below under *Inclusion and exclusion criteria*.

In patients with high-risk non-muscle invasive bladder cancer, which is unresponsive to BCG, the recommended treatment is radical cystectomy which is curative. Radical cystectomy has associated 90-day mortality rates up to approximately 7% (possibly higher in the elderly), and substantial post-operative and long-term morbidity. For subjects with high-risk non-muscle invasive bladder cancer who are unfit or unwilling to undergo cystectomy:

- A 2016 American Urological Association (AUA) and the Society of Urologic Oncology (SUO) consensus guideline;[12] recommends enrolment in a clinical trial, or the use of intravesical chemotherapy when clinical trials are unavailable;
- The National Comprehensive Cancer Network (NCCN) 2020 guidelines;[10] recommend a change of intravesical agent (for example chemotherapy) or the use of pembrolizumab;
- The 2020 European Association of Urology (EAU) guidance;[17] recommends enrolment in a clinical trial, or other investigational bladder-preservation strategies such as cytotoxic intravesical therapies, device-assisted instillation, intravesical or systemic immunotherapy or gene therapy. The guideline states:

  > *'At the present time, treatments other than radical cystectomy must, however, be considered oncologically inferior in patients BCG-unresponsive disease.'*

In Australia, thiotepa is registered for intravesical administration for the treatment of *'superficial papillary carcinoma of the urinary bladder'* but its use is not recommended in current clinical practice guidelines.[10,12,13] Gemcitabine and mitomycin, recommended for intravesical use in some guidelines;[10] are not registered for such use in Australia. Intravesical valrubicin, which is approved for BCG-refractory carcinoma in-situ in patients unsuitable for cystectomy in the USA, but was not registered in Australia at the time of this submission.

Despite the lack of an accepted standard treatment, the Cancer Institute of NSW eviQ website includes a treatment protocol for the use of intravesical gemcitabine post-TURBT in non-muscle invasive bladder cancer patients who have progressed or relapsed after BCG therapy.[18]

Pembrolizumab

Programmed cell death protein 1 (PD-1) is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 pathway is an immune control checkpoint that may be engaged by tumour cells to inhibit active T-cell immune surveillance. Keytruda (pembrolizumab) is a high affinity antibody against PD-1, which exerts ligand blockade of the PD-1 pathway, including programmed death-ligands 1 and 2 (PD-L1 and PD-L2) on antigen presenting or tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, Keytruda reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates anti-tumour immunity.

[17] Babjuk M, Burger M, Compérat E et al. European Association of Urology (EAU) Guidelines on Non-Muscle-Invasive Bladder Cancer. 2020.
Available online at: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/
[18] Cancer Institute of NSW. eviQ. Bladder Intravesical gemcitabine. 2019.
https://www.eviq.org.au/medical-oncology/urogenital/bladder-and-urothelial/1758-bladder-intravesical-gemcitabine#

The PD-1/PD-L1 inhibitors pembrolizumab (Keytruda), nivolumab, durvalumab, and atezolizumab are registered for advanced urothelial carcinoma (see *Regulatory status*, below). At the time of this submission, no PD-1/PD-L1 inhibitors are registered in Australia for the treatment of non-muscle invasive bladder cancer.

Regulatory status

Keytruda (pembrolizumab) was initially registered on the Australian Register of Therapeutic Goods (ARTG) for the treatment of advanced melanoma on 16 April 2016.[19]

Since initial registration many subsequent submissions to extend the indications of Keytruda (pembrolizumab) have been approved for the treatment of range of solid tumour and haematological malignancies.

Most closely related to this submission, Keytruda (pembrolizumab) was approved in January 2018 for use in more severe presentations of bladder cancer, namely locally advanced or metastatic urothelial carcinoma in patients who are ineligible for cisplatin-containing therapy, or as monotherapy in patients who have previously received platinum-containing chemotherapy.[20] The indications for use in advanced urothelial carcinoma that were approved at the time this submission was considered were as follows:

> ***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) ≥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.*

At the time the TGA made a regulatory decision for this submission (July 2021), the approved indications for Keytruda (pembrolizumab) for use in Australia were as follows:

> ***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.*

[19] AusPAR for initial registration of Keytruda (pembrolizumab) Merck Sharp & Dohme (Australia) Pty Ltd, submission PM-2014-01928-1-4. Published online 18 October 2016.
Available online at: https://www.tga.gov.au/resources/auspar/auspar-pembrolizumab-rch

[20] Submission PM-2016-04328-1-4, an extension of indications for Keytruda (pembrolizumab) for the treatment of locally advanced or metastatic urothelial carcinoma: Further information is available online via the AusPAR for Keytruda (pembrolizumab) submission PM-2016-04328-1-4. Published online: 18 December 2018.

Non-small cell lung cancer (NSCLC)

Keytruda (pembrolizumab), in combination with pemetrexed and platinum chemotherapy, 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, 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) ≥ 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 ≥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 carcinoma (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 (CPD) ≥ 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) ≥ 1) as determined by a validated test.

Classical Hodgkin Lymphoma (cHL)

Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of adult 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 is on the basis of objective response rate (ORR). 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) ≥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.

Microsatellite instability-high 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, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer 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 single-arm trials. 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, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours 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 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, 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).

International regulatory status

At the time the TGA considered this submission, similar submissions had been approved in the United States of America (USA) on 8 January 2020 and in Canada on 14 December 2020.

Of note, the submission to the US Food and Drug Administration (FDA) was the subject of a meeting of the US Oncologic Drugs Advisory Committee on 17 December 2019 that recommended its approval. The minutes from this meeting are publicly available.[21]

Numerous other indications have been approved in both the USA and the European Union (EU), however during this submission, the sponsor has said it has no plans for a similar submission in the EU as the current one as discussed in this AusPAR.

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

Table 3: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	8 July 2019	Approved on 8 January 2020	*Keytruda 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 tumors who are ineligible for or have elected not to undergo cystectomy.* The US FDA granted Priority Review Designation for this indication.(a)
Canada	3 March 2020	Approved on 14 December 2020	*Keytruda 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 tumors who are ineligible for or have elected not to undergo cystectomy.* Issued with Notice of Compliance with conditions.(b)

[21] US FDA: Final Summary Minutes of the Oncologic Drugs Advisory Committee (ODAC) Meeting Dec 17, 2019; Food and Drug Administration, USA.
Available online at: https://www.fda.gov/media/134583/download

Region	Submission date	Status	Approved indications
New Zealand	30 September 2020	Approved on 22 April 2021	*Keytruda 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.*

(a) A Priority Review designation means the US FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review). A Priority Review designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.

(b) A Notice of Compliance with conditions (NOC/c) is authorisation from Health Canada to market a drug (in a Notice of Compliance (NOC)), with the condition that the sponsor undertake additional studies to verify the clinical benefit. It is intended to provide earlier market access to potentially life-saving drugs. Conditions associated with market authorisation allow Health Canada to monitor the drug through enhanced post-market surveillance.

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

This submission was evaluated under the provisional registration process. Pembrolizumab was granted provisional determination on 11 February 2020 for the following indication:

> *'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.'*

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

Table 4: Timeline for Submission PM-2020-01294-1-4

Description	Date
Determination (Provisional)	11 February 2020
Submission dossier accepted and first round evaluation commenced	30 April 2020
First round evaluation completed	30 September 2020
Sponsor provides responses on questions raised in first round evaluation	30 November 2020
Second round evaluation completed	15 January 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	28 February 2021

Description	Date
Sponsor's pre-Advisory Committee response	12 March 2021
Advisory Committee meeting	8-9 April 2021
Registration decision (Outcome)	12 July 2021
Completion of administrative activities and registration on the ARTG	14 July 2021
Number of working days from submission dossier acceptance to registration decision*	248

*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.

Guidance and definitions

The following guideline was referred to by the Delegate as being relevant to this submission:

- European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. EMA/CHMP/205/95/Rev.4; (2012); TGA-adopted, effective date: 1 April 2014

The US Food and Drug Administration (FDA) has issued specific guidance for industry on the development of drugs for BCG-unresponsive non-muscle invasive bladder cancer. This guidance is as follows:

- Food and Drug Administration (FDA): Bacillus Calmette-Guérin-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment. Guidance for Industry. (2018).

This FDA guidance has not been formally adopted by the TGA, but has informed the definition of BCG-unresponsive non-muscle invasive bladder cancer used in the clinical study plan for the Keynote-057 trial and this submission, and has been referred to in the evaluation of Keytruda by the TGA.

In this guidance, BCG-unresponsive disease is defined as being at least one of the following:

Table 5: US FDA (2018); Guidance for Industry, definition of BCG-unresponsive non-muscle invasive bladder cancer

For the purposes of this guidance, BCG-unresponsive disease is defined as being at least one of the following:

- Persistent or recurrent CIS [carcinoma in-situ] alone or with recurrent Ta/T1 (noninvasive papillary disease/tumor invades the subepithelial connective tissue) disease within 12 months of completion of adequate BCG therapy
- Recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy.
- T1 high-grade disease at the first evaluation following an induction BCG course (Steinberg et al. 2016).*

In this context, adequate BCG therapy is defined as at least one of the following:

- At least five of six doses of an initial induction course plus at least two of three doses of maintenance therapy
- At least five of six doses of an initial induction course plus at least two of six doses of a second induction course.

Extract from Food and Drug Administration (FDA): Bacillus Calmette-Guérin-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment. Guidance for Industry. (2018).

* Steinberg RL, Thomas LJ, Mott SL, O'Donnell MA. Bacillus Calmette-Guérin (BCG) Treatment Failures with Non-Muscle Invasive Bladder Cancer: A Data-Driven Definition for BCG Unresponsive Disease. Bladder Cancer. 2016 Apr 27;2(2):215-224.

Quality

A quality evaluation was not required for this submission as there are no proposed changes to the quality of the currently approved product in Australia. A full quality evaluation was conducted at the time this product received initial registration.[22]

The following is a summary of the quality characteristics of this product:

Keytruda (pembrolizumab) is a selective humanised monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Pembrolizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

One vial contains 100 mg of pembrolizumab in 4 mL of solution. The excipients are as follows: histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80, and water for injections.

Keytruda 100 mg/4 mL concentrated injection is a sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution. It should not be given as a direct infusion or injection.

Keytruda (pembrolizumab) 100 mg/4 mL concentrated injection has a shelf-life of 24 months. The product should protected from light and be stored in a refrigerator (at 2°C to 8°C). Do not freeze. Do not shake.

See the Product Information for information on preparation and administration.

Prior to preparation for administration equilibrate the vial of Keytruda to room temperature. Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Keytruda is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.

If not used immediately, diluted solutions of Keytruda may be stored at room temperature for a cumulative time of up to 6 hours. Diluted solutions of Keytruda may also be stored under refrigeration at 2°C to 8°C; however, the total time from dilution of Keytruda to completion of infusion should not exceed 96 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use. Translucent to white proteinaceous particles may be seen in the

[22] AusPAR for Keytruda (pembrolizumab) Merck Sharp & Dohme (Australia) Pty Ltd , submission PM-2014-01928-1-4. Published online October 2016. Available online at: https://www.tga.gov.au/resources/auspar/auspar-pembrolizumab-rch

diluted solution, and are not of concern, as particles will be removed by the filter during administration. Do not freeze the infusion solution.

This product is for single use in one patient only, The product does not contain preservative. A diluted product should be used immediately. Discard any residue.

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 main clinical data supporting the proposed indication included a full study report for the Keynote-057 trial;[23,24] and an integrated summary of safety data.

No paediatric data were included in the submission. Urothelial carcinoma of the bladder is very rare in children.[25] The sponsor had received a waiver from the US FDA for the conduct of paediatric studies on the grounds that *'necessary studies are impossible or highly impracticable'*.

The study report for the single clinical trial in the submission included an assurance that the study *'…was conducted in conformance with the ethical principles originating from the Declaration of Helsinki, GCP* [Good Clinical Practice] *requirements, and applicable country and/or local statutes and regulations …'*.

Efficacy

The Keynote-057 trial

Study MK-3475-057 (otherwise referred to as the Keynote-057 trial);[23,24] is an ongoing, multicentre, multinational, Phase II, open-label study in adult patients with high risk non-muscle-invasive bladder cancer unresponsive to BCG and ineligible for/or unwilling to undergo radical cystectomy. The study commenced in 2016 and is still ongoing.

Inclusion and exclusion criteria

Key inclusion criteria were:

- Adults; with

[23] Keynote-057: A Phase II clinical trial to study the efficacy and safety of pembrolizumab (MK-3475) and pembrolizumab in combination with other investigational agents in subjects with high risk non-muscle-invasive bladder cancer (NMIBC) unresponsive to Bacillus Calmette-Guerin (BCG) therapy. ClinicalTrials.gov Identifier: NCT02625961; EudraCT number: 2014-004026-17.
[24] Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study [published correction appears in Lancet Oncol. 2021 Aug;22(8):e347]. *Lancet Oncol.* 2021;22(7):919-930.
[25] Oda MH, dos Santos DV, Farias AK, et al. Bladder Urothelial Carcinoma in a Child: Case Report and Review of Literature. *Front. Pediatr.* 2019; 7:385.

- histologically confirmed high risk non-muscle-invasive bladder cancer (transition cell carcinoma/transition cell-dominant tumour);
- Ta/T1 tumours;[26] must have had complete transurethral resection of bladder tumour (TURBT) (absence of resectable disease after ≥ 2 cystoscopy/TURBT procedures and most recent (≤ 8 weeks prior to first treatment dose) or residual carcinoma in-situ not amenable to complete TURBT).[27]
- Adequate BCG therapy of 7 instillations (5 x induction instillations then ≥ 2 BCG maintenance instillations or second induction of 2 instillations starting ≤ 9 months from diagnosis), *or*
- BCG unresponsive high risk non-muscle-invasive bladder cancer (persistent high risk non-muscle-invasive bladder cancer 6 months after BCG initiation despite adequate BCG therapy; or high grade T1 disease after the first evaluation after adequate BCG induction; or stage/grade progression ≥ 3 months (± 4 weeks) despite adequate induction BCG therapy; or recurrence of high risk non-muscle-invasive bladder cancer < 9 months from last BCG treatment despite adequate treatment).
- Ineligible for radical cystectomy because of cardiovascular disease, chronic obstructive pulmonary disease; ECOG PS > 2;[28] prior abdominal and pelvic surgery (procedure unsafe); *or* unwilling to undergo radical cystectomy
- Tissue for biomarker analysis from 2 most recent cystoscopy/TURBT procedures (≤ 8 weeks from initial treatment)
- ECOG ≤ 2 (limited to <5% had ECOG 2).[28]

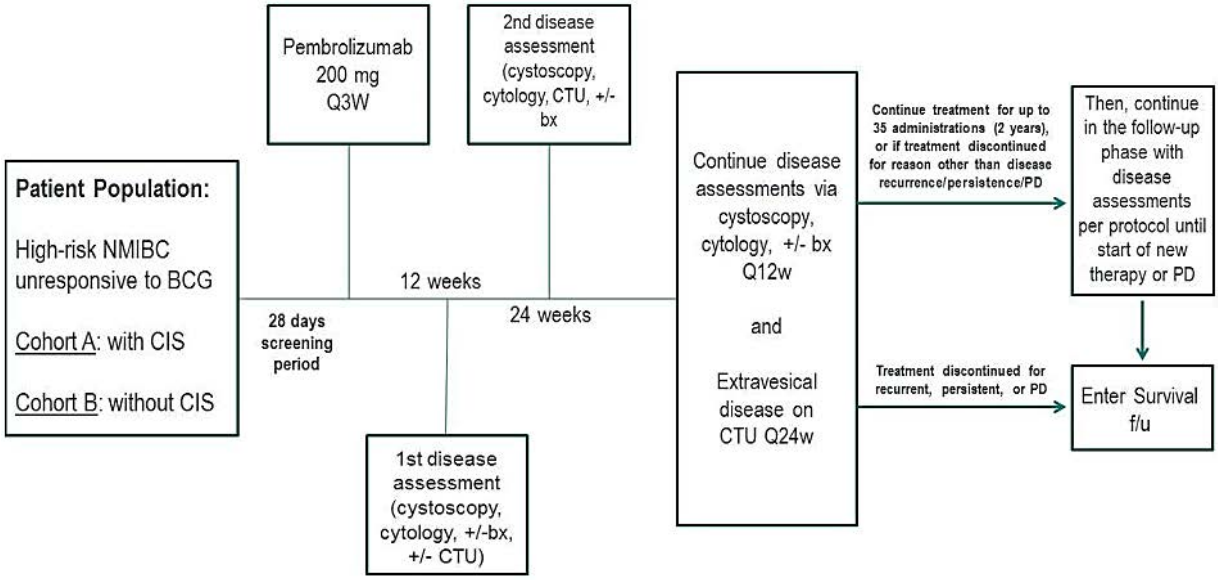
Exclusion criteria were numerous and included T2, T3, or T4 disease;[26] concurrent extra-vesical (that is urethra, ureter or renal pelvis) non-muscle invasive transitional cell carcinoma of the urothelium; any intravesical chemotherapy or immunotherapy from the time of the most recent cystoscopy/TURBT to the start of trial treatment; prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks of Cycle 1, Day 1 or who has not recovered (that is, ≤ Grade 1 or at Baseline) from adverse events due to a previously administered agent (Grade ≤ 2 neuropathy or alopecia may qualify); prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent, or with an agent directed to another co-inhibitory T-cell receptor (for example, CTLA-4, OX-40, or CD137).

[26] **TNM staging**: **Ta** = non-invasive papillary carcinoma; **Tis** = carcinoma in situ: 'flat tumour'; **T1** = tumour invading subepithelial connective tissue; **T2** = tumour invading muscle wall; **T3** = tumour invading perivesical tissue; **T4** = tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, or/and abdominal wall. See *Table 1* for further information.

[27] This requirement was amended twice in two different protocol amendments. The requirement to have two procedures was removed in 2016. In 2018 patients with high-grade Ta or any T1 with TURBT resection of all visible tumour ≤ 12 weeks from the first trial treatment dose were allowed. A restaging TURBT was recommended for T1 to ensure the absence of muscle invasion.

[28] **ECOG** (**Eastern Cooperative Oncology Group**) performance score:
0 = asymptomatic;
1 = symptoms but completely ambulatory;
2 = symptoms, in bed < 50% of the time can self-care but can't work;
3 = symptoms, in bed/chair > 50% of day, limited self-care;
4 = bedbound, completely disabled, no self-care, confined to bed/chair;
5 = dead.

Figure 2: Keynote-057 trial; Study schematic and overview



Abbreviations: bx = biopsy; CIS = carcinoma in situ; CTU = computerised tomography uroscopy; f/u = follow up; NMIBC = non-muscle-invasive bladder cancer; PD = progressive disease; Q12w = every 12 weeks; Q24w = every 24 weeks.

Note: Patients population also includes patients who refused or are ineligible for cystectomy. Cohort A comprises of patients with carcinoma in situ +/- papillary disease. Cohort B comprises of patients with papillary disease without carcinoma in situ.

Evaluations continue with cystoscopy, cytology +/- biopsy every 12 weeks for 2 years, then every 24 weeks for 3 years. For extravesical disease, computerised tomography uroscopy every 24 weeks for 2 years then every 48 weeks for 3 years.

For the cohorts in the Keynote-057 trial:

- Cohort A included subjects with carcinoma in situ at Baseline (carcinoma in situ only; Ta + carcinoma in situ; or T1 + carcinoma in situ);[26]
- Cohort B included subjects without carcinoma in situ at Baseline (high-grade Ta or any grade T1 tumour).[26]

Cohort A is relevant for the indication that is sought. Cohort B was not part of this submission, and is not discussed further in this AusPAR.

Baseline characteristics

The study population (specifically, the Cohort A population) was predominantly male (83.3%) with a median age of 73.0 years. 38.2% had PD-L1 positive disease (PD-L1 CPS ≥ 10);[29] 63.7% had carcinoma in situ only, 24.5% had carcinoma in situ with high grade papillary tumours, and 11.8% had CIS with T1 disease. Baseline high-risk non-muscle-invasive bladder cancer disease status was 27% persistent and 73% recurrent. All patients had prior intravesical BCG therapy, with a median of 12.0 prior installations, and none had prior antineoplastic agents.

Most patients (95.1%) refused cystectomy and 2.9% were considered ineligible for the procedure.

[29] **Combined Positive Score** (**CPS**) is used to classify tumours as PD-L1 positive or PD-L1 negative. CPS is the sum of the number of cells PD-L1–stained by immunohistochemistry assay (tumour cells, lymphocytes, macrophages), divided by the total number of viable tumour cells, and multiplied by 100. PD-L1 positive = CPS ≥ 10%.

Statistics

The null hypothesis for Cohort A was that a complete response for pembrolizumab would be ≤ 20%.

Assuming a complete response rate of 35%, a sample size of 130 would give about 97% power, at a 5% (two-sided) alpha level, to reject the null hypothesis with the lower bound of the 95% confidence intervals (CI) > 20%.

A US FDA/American Urology Association (AUA) workshop;[30] suggested that a complete response rate of 40% to 50% at 6 months, with a lower bound of the 95% confidence interval (CI) above 20%, could be clinically meaningful in BCG refractory non-muscle-invasive bladder cancer disease, based on previous data obtained with intravesical valrubicin (complete response was approximately 20%), and a meta-analysis of four trials of intravesical chemotherapy, two with valrubicin, and one each with docetaxel and nab-paclitaxel, that showed a pooled complete response rate of 21% (95% CI: 0.15 to 0.27).

Treatments

All patients received at least one dose of study treatment. Patients were dosed at 200 mg intravenously infused over 30 minutes on Day 1 of a 21 day cycle until one of the following:

- persistent high-risk disease was detected at the 12-week disease assessment;
- high risk recurrence at any time point (including in the upper urinary tract);
- disease progression (by grade or stage) at any time point;
- completed 24 months of treatment with pembrolizumab;
- completed at least 18 months of treatment with pembrolizumab and remained without evidence of disease (negative cystoscopy, negative cytology and negative cross-sectional imaging of abdomen and pelvis) at 2 or more consecutive evaluation visits.

Doses could be withheld in the event of toxicity, but dose reductions were not permitted. Antineoplastic chemotherapy or biological therapy (single dose of intravesical chemotherapy post-TURBT permitted), immunotherapy, other investigational agents, radiotherapy, live vaccines and glucocorticoids were not permitted.

Efficacy endpoints

Cystoscopy and urine cytology was performed every 12 weeks for the first 2 years then every 24 weeks for a total of 5 years. Cystoscopy could be performed using white light cystoscopy or fluorescence-guided cystoscopy (photodynamic diagnosis or blue light cystoscopy) but the same method had to be used for an individual patient throughout the trial.

Extra-vesical disease was assessed using computed tomography urography (CTU) of the abdomen and pelvis at screening, every 24 weeks for the first 2 years, and then annually.

Response criteria are shown in Table 6 as follows below.

[30] Jarow JP, Lerner SP, Kluetz PG et al: Clinical trial design for the development of new therapies for nonmuscle-invasive bladder cancer: report of a Food and Drug Administration and American Urological Association Public Workshop. *Urology* 2014; 83:262.

Table 6: Response categories and criteria/descriptions

Response category	Criteria or description of response
Complete response (CR)	absence of non-muscle-invasive bladder cancer disease, or progressive urothelial carcinoma
Persistent disease	pathologically confirmed carcinoma in situ ± papillary tumour (high grade Ta/T1)
Recurrent disease	pathologically confirmed papillary tumour (high grade Ta/T1) no carcinoma in situ
Non-muscle-invasive bladder cancer disease stage progression	pathologically confirmed increase in stage from baseline carcinoma in situ ± high grade Ta to T1 disease
Progression to T2	pathologically confirmed progression to muscle invasive bladder cancer.
Extravesical disease	lesions suspicious for locally advanced or metastatic bladder cancer present on imaging
Not evaluable	Patient/tumour not evaluable

TNM staging: Ta = non-invasive papillary carcinoma; Tis = carcinoma in situ: 'flat tumour'; T1 = tumour invading subepithelial connective tissue; T2 = tumour invading muscle wall; T3 = tumour invading perivesical tissue; T4 = tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, or/and abdominal wall.

Primary endpoint

The complete response rate is the proportion of subjects who had absence of high risk non-muscle invasive bladder cancer disease (carcinoma in situ, high grade Ta or T1), or progressive urothelial carcinoma.

Key secondary endpoints

Key secondary endpoints are as follows:

- complete response rate (as discussed under *Primary endpoint*) for the absence of any disease;
- duration of response (high-risk non-muscle invasive bladder cancer): the time from complete response to recurrence of high risk non-muscle invasive bladder cancer or worse; and
- duration of response (any disease): the time from complete response to recurrence of any disease.

Other secondary endpoints

Other secondary endpoints include:

- duration of response rate for specific time periods (these include at response at 6 months, 12 months, and so on);
- progression-free survival until:
  - worsening of grade, stage, or death; and
  - muscle invasive or metastatic disease or death; and

- Overall survival.

Results

Primary endpoint (complete response)

The final analysis was to be conducted 9 months after full enrolment. The protocol stated that no early stopping of the trial (for strong efficacy) was planned. After discussions with the US FDA and external experts the final analysis was to be conducted 15 months after full enrolment.

The study commenced in March 2016 and by 1 April 2018 (enrolment cut-off) 102 subjects had enrolled in Cohort A and had at least one dose of pembrolizumab.

The sponsor initially presented data for the primary endpoint at three cut-off points in the study. These were 20 February 2019, 24 May 2019, and 24 September 2019.

The 20 February 2019 and 24 May 2019 results were based on all the 102 patients enrolled in Cohort A. The 24 September 2019 results were based on only 96 of the 102 patients (5 were not considered BCG unresponsive, as defined in the FDA guideline (see *Guidance and definitions*) one did not have carcinoma-in-situ at Baseline).

Table 7: Keynote-057 trial; results for the primary efficacy endpoint (achieving complete response) at all data cut-off points

Cut-off date	**N**	**Median** (range) **follow up** (in months)	**Complete responses** (n)	**Complete response rate**	**95% CI**
20 February 2019	102	21.1 (4.6 to 33.4)	42	41.2%	31.5 to 51.4
24 May 2019	102	24.1 (4.6 to 36.5)	42	41.2%	31.5 to 51.4
24 September 2019	96	28.0 (4.6 to 40.5)	39	40.6%	30.7 to 51.1

Abbreviations: CI = confidence interval(s); N = total number of patients in study; n = number of patients with specified response.

As part of a response to TGA questions, the sponsor supplied data based on the 24 September 2019 data cut-off date where the complete response over time, which was not a defined endpoint per protocol, was as follows:

- Month 6: 30.2% (95% CI: 21.3 to 40.4);
- Month 12: 18.8% (95% CI: 11.5 to 28.0);
- Month 18: 15.6% (95%CI: 9.0 to 24.5).

Persistent of high-risk disease was the most common reason (41.7%) for not achieving a complete response. At Week 12, 9 patients progressed from carcinoma-in-situ to T1 disease, and none had muscle invasive disease.

Subgroup analysis was generally consistent with the primary analysis. The complete response rate in PD-L1 positive subjects was 28.6% (95% CI: 14.6 to 46.3), compared with 48.2% (95% CI: 34.7 to 62.0) in PD-L1 negative subjects.

Secondary endpoints

Complete response (absence of any disease)

Complete response (absence of disease) results at the 20 February 2019 and 24 May 2019 data cut-off dates, were identical to the primary endpoint. No updated data were provided at the 24 September 2019 data cut-off.

Duration of response (for high risk non-muscle invasive bladder cancer)

Table 8: Keynote-057 trial; duration of complete responses (for high risk non-muscle invasive bladder cancer) at all data cut-off points

Cut-off date	N	Complete responses (n)	Median duration of response (months)	Range
20 February 2019	102	42	13.5	0.0+ to 26.8+
24 May 2019	102	42	16.2	0.0+ to 26.8+
24 September 2019	96	39	16.2	0.0+ to 30.4+

Note '+' signifies ongoing response

The estimated proportion of subjects who would have a duration of response of at least 12 months was 56.8%. Complete response were ongoing for 17 of the 39 complete responses (43.6%) at the time of data cut-off. The duration of response for any disease results were identical to those for the primary endpoint (median duration of response = 13.5 months; range 0.0+ to 26.8+, with + indicating ongoing response).

Other secondary endpoints

Table 9: Keynote-057 trial; progression-free survival (worsening of grade or stage, for high risk non-muscle invasive bladder cancer) at specified data cut-off points

Cut-off date	N	PFS events (%)	Median PFS	KM estimate PFS at 6 months (95% CI)	KM estimate PFS at 12 months (95% CI)
Progression Free Survival (worsening of grade or stage)					
20 February 2019	102	12 (11.8%)	Not reached	86.1% (75.1 to 92.4)	83.4% (71.0 to 90.8)
24 May 2019	102	13 (12.7%)	Not reached	86.2% (75.3 to 92.5)	83.6% (71.4 to 90.9)
Progression Free Survival (muscle invasive disease, metastases or death)					
20 February 2019	102	3 (2.9%)	Not reached	96.6% (85.7 to 99.2)	96.6% (85.7 to 99.2)
24 May 2019	102	5 (4.9%)	Not reached	96.7% (86.3 to 99.2)	96.7% (86.3 to 99.2)

Abbreviations: CI = confidence interval(s); KM = Kaplan-Meier; PFS = progression-free survival.

Overall survival was not a key secondary endpoint and by the May 2020 the median overall survival was not reached and the 12 month overall survival was 95.7% (95% CI: 90.6%, 98.0%).

Subsequent treatments after pembrolizumab (24 September 2019 cut-off): 37.5% underwent cystectomy and 28.1% had further intravesical therapy, mostly with cytotoxic agents.

May 2020 data update (full analysis set)

In response to TGA questions the sponsor provided an update of the data from a data cut-off on 25 May 2020. At that time:

- 139 patients were enrolled in Cohort A. Baseline characteristics for the cohort are summarised:
  - As of the cut-off date all participants in Cohort A had the opportunity to complete 12-month efficacy evaluations (that is, they were 15 months from the study start). Median duration of follow-up was 32.0 months (range 2.9 to 48.5). Of the 139 subjects enrolled in Cohort A, 9 had completed a full course of pembrolizumab, 4 were still receiving treatment and the remainder (126) had discontinued.
  - Baseline characteristics for the 139 subjects in Cohort A were similar to those presented for the first 102 subjects. 83.5% were male, with a median age of 73.0 years. All subjects had good performance status (ECOG 0 or 1).[28]
  - 36.7% of subjects had PD-L1 positive disease (PD-L1 CPS ≥ 10).[29] 67.6% of subjects had carcinoma in situ only, 22.3% had CIS together with high grade Ta tumours and 10.1%

had carcinoma in situ together with T1 disease. Only 4.3% of subjects were considered ineligible for cystectomy whereas 92.8% had refused the procedure. All subjects had received prior intravesical BCG therapy, with a median of 12.0 prior installations.

- For the primary efficacy endpoint, the complete response rate (absence of high risk non-muscle invasive bladder cancer) was 36.7% (95% CI: 28.7 to 45.3).
- The complete response rate for the absence of any disease was identical to the primary endpoint result 36.7% (95% CI: 28.7 to 45.3).[31]
- The median duration of response (for absence of high-risk disease) was 13.5 months (range 0.0+ to 36.2 months). The estimated proportion of subjects who would have a duration of response of at least at 12 months was 57.2%. In 19 of the 51 complete responses (37.3%), complete response was ongoing.
- The median progression-free survival to worsening of stage, grade or death and to muscle invasive or metastatic disease or death was 27.0 months (95% CI: 25.1, not available) and 39.9 months (95% CI: 25.4, 39.9), respectively.

A sensitivity analysis conducted for the 134 patients who met the FDA Guidance for Industry criteria for BCG-unresponsive high-risk non-muscle invasive bladder cancer) (see *Guidance and definitions*) showed:

- a complete response of 36.6% (95% CI: 28.4 to 45.3);
- a median duration of response of 16.2 months (range 0.0 (and ongoing) to 36.2 months) and an estimated proportion with a duration of response of at least 12 months of 57.7%.

Of the total cohort 25.9% (70.6% of complete responders; Kaplan-Meier estimate 77.1%) had a complete response at 6 months or more, and 18% (49% of complete responders, Kaplan-Meier estimate 57.2%) had a complete response at 12 months or more after the initial response.

Of the 32 patients who had a complete response but were no longer responding 43.8% underwent cystectomy (most as their next treatment) and 40.6% received subsequent therapy or underwent another procedure (for example, TURBT). Of the 88 patients who never had a complete response, 45.5% underwent cystectomy after discontinuation (72.5% as the next treatment) and 53.4% received subsequent therapy or another procedure. The median time to the subsequent therapy or procedure treatment was similar in the responders or not responders. The median time to cystectomy from last dose of pembrolizumab for those who had a complete response and were no longer responding was 4.2 months (range: 1.4 to 28.3) compared with those who never had a complete response (3.1 months (range: 1.4 to 26.9)).

Safety

Exposure

The sponsor presented safety data from the Keynote-057 trial, and a comparison with other pembrolizumab safety data sets including pooled bladder cancer studies; the Keynote-045 and Keynote-052 trials in advanced bladder cancer; a reference safety data set from studies;[32] and a

[31] Persistent disease occurred in 43.2%, recurrent disease in 7.2% and non-muscle-invasive bladder cancer disease stage progression in 8.6%, progression to T2 0.7%, extravesical disease 0.7%

[32] The 'reference safety dataset' which included 2799 pembrolizumab-treated subjects, consisting of 1567 subjects with advanced melanoma from the Keynote-001, -002, and -006 trials, and 1232 subjects with non-small cell lung cancer (NSCLC) from the Keynote-001 and -010 trials. According to the sponsor this dataset represents the *established* safety profile for pembrolizumab;

running cumulative safety data set;[33] comprising 7,599 patients from completed and ongoing studies were presented separately.

In the whole of Keynote-057 trial, at the May 2019 cut-off 148 patients received pembrolizumab for a median of 4.3 months.

At the May 2020 update, data from a total of 254 patients of whom 139 patients were from Cohort A. At the data cut-off, 118 patients were continuing in the trial, but pembrolizumab had been discontinued in 126 (90.6%) and 9 had completed the study course. Persistent disease (38.8%) and progressive disease (30.9%) were the most common causes of study treatment discontinuation.

Adverse events

Results for Cohort A of the Keynote-057 trial are presented below in Table 10.

Table 10: Keynote-057 trial; summary of safety findings

Safety findings	n (%)
Cohort A (number of subjects):	139
Number (proportion) of subjects with:	
with one or more adverse events	134 (96.4%)
with no adverse events	5 (3.6%)
with drug-related adverse events	99 (71.2%)
with Grade 3 to 5 adverse events	43 (30.9%)
with Grade 3 to 5 drug-related adverse events	19 (13.7%)
with serious adverse events	35 (25.2%)
with drug-related serious adverse events	1 1 (7.9%)
who died	6 (4.3%)
who died due to a drug-related adverse events	0 (0%)
discontinued drug due to adverse events	14 (10.1%)
discontinued drug due to drug-related adverse events	11 (7.9%)
discontinued drug due to serious adverse events	6 (4.3%)
discontinued drug drug-related serious adverse events	4 (2.9%)

[33] A 'cumulative running safety dataset' (7598 pembrolizumab-treated subjects) which included data from all monotherapy studies that had been presented to a regulatory authority. This dataset included data from the urothelial carcinoma studies, the reference safety dataset and data from multiple other trials in various indications.

The most common adverse events (occurring in at least 15% patients) were pruritus (24.5%), fatigue (26.6%), diarrhoea (23.7%), haematuria (22.3%), cough (15.8%and nausea (15.1%). Grade 3 to 5 events were most commonly (that is, in more than 2%) pneumonia, hyperglycaemia and hyponatraemia. Five participants (3.6%) in Cohort A experienced Grade 4 events, including pneumonia, pyelonephritis, sepsis, septic shock, hyperkalaemia, hyperglycaemia, hyperuricemia, hyponatremia, and type 1 diabetes mellitus. Drug-related adverse events were most commonly pruritus (14.4%), fatigue (12.9%), diarrhoea (12.2%), and hypothyroidism (7.2%).

Adverse events leading to discontinuation included autoimmune nephritis and pneumonitis resulted in discontinuation of pembrolizumab in more than one patient.

Adverse events resulting in pembrolizumab interruption occurring in more than one patient resulting in interruption of pembrolizumab were blood creatinine increased, diarrhoea, arthralgia, hyponatremia, pruritus, rash maculopapular, urinary tract infection, hyperglycaemia, and oedema peripheral. Adverse events considered by the investigator to be drug-related in more than one patient were diarrhoea, arthralgia, hyponatremia, pruritus, and rash maculopapular.

The six deaths included events of acute kidney injury and septic shock; aspiration pneumonitis; congestive cardiomyopathy; acute respiratory failure; congestive cardiac failure; respiratory failure in a patient with resolving immune-related hepatitis; pancreatic carcinoma in a patient with immune-related type 1 diabetes mellitus. The causes of death were considered unrelated although concomitant adverse events may have been drug-related.

Serious adverse events reported as occurring in more than one patient were pneumonia, pulmonary embolism, septic shock, urinary tract infection, congestive cardiac failure and cellulitis.

Adverse events of special interest (that is, immune-mediated events and infusion-related reactions associated with pembrolizumab) occurred in 29 patients (20.9%). Those occurring in more than one patient were hypothyroidism (7.9%), hyperthyroidism, pneumonitis, colitis, autoimmune nephritis, and hypophysitis. Grade 3 to 5 adverse events of special interest occurred in 6 patients (4.3%); these included type 1 diabetes mellitus (Grade 4), rash maculopapular (Grade 3), pruritus (Grade 3), hypophysitis (Grade 3), adrenal insufficiency (Grade 3), and hepatitis (Grade 3). Hypophysitis, pruritus, and rash maculopapular were considered drug-related by the investigator.

No latent systemic adverse events from previous BCG treatment were found in the Keynote-057 trial.

Although not evaluated for this submission, a similar pattern of safety events was seen in the Cohort B population (subjects without carcinoma in situ at Baseline (high-grade Ta or any grade T1)).

Comparison with historical datasets

The submission included comparisons with historical safety data obtained in previous studies of pembrolizumab monotherapy in other indications (see *Exposure* for descriptions of these data set populations). The overall adverse event profile of pembrolizumab in the Keynote-057 trial appeared to be comparable with that observed in these previous studies.

The overall incidence of any adverse event in the Keynote-057 trial was 96.6% and was comparable in the two cohorts (Cohort A, 97.1% versus Cohort B, 95.7%). Diarrhoea and fatigue were the most common individual adverse event terms reported. The incidence of Grade 3 to 5 adverse events was 31.1% (at the 24 May 2019 data cut-off).

For the comparative datasets, the overall incidence of any adverse event was consistent across the four datasets presented (96.1% to 97.4%). The incidence of common individual adverse event terms was reasonably comparable across the four datasets with the exception of haematuria and urinary tract infection, which were more common in the bladder cancer studies. This is likely to be due to the disease and the need for cystoscopy, catheterisation and so on. The only other common adverse events which had a notably higher incidence in the Keynote-057 trial was nasopharyngitis (10.1% versus 3.8% to 6.5%).

The incidence of Grade 3 to 5 adverse events was lower in the Keynote-057 trial (30.4% at the 20 February 2019 cut-off) than in the comparative safety datasets (45.5% to 58.3%).

The overall incidence of drug-related adverse events was consistent across the four datasets presented (64.2% to 73.7%, and 69.6% for Keynote-057 trial). The pattern of individual adverse event terms was also fairly consistent across datasets.

The incidence of fatal adverse events was lower in the Keynote-057 trial (2.0%) compared with the other three datasets (3.9% to 5.3%). This was also true for drug-related fatal adverse events (0.0% in the Keynote-057 trial versus 0.4% to 0.8% for the various comparative datasets). There were no notable differences between the datasets in the patterns of fatal adverse events.

The incidence of serious adverse events in the Keynote-057 trial (26.4% as of the 20 February 2019 cut-off) was lower than that observed in the other datasets (37.2% to 44.3%). Apart from a higher incidence of haematuria and urinary tract infection in the bladder cancer studies there were no notable differences in the incidence of individual events.

The incidence of adverse events leading to discontinuation was comparable across the four datasets (10.8% to 12.8%) and was 10.8% for the Keynote-057 trial (overall) and 10.1% for the Cohort A population. There were no notable differences between the datasets in the types of adverse events leading to discontinuation. The only individual adverse event that led to discontinuation in ≥ 1% of subjects in any of the datasets was pneumonitis. The incidence of pneumonitis leading to discontinuation was comparable across datasets (1.2% to 1.4%).

For renal and urinary adverse events, the overall incidence of such adverse events was 37.8% in the Keynote-057 trial, with the most commonly reported events being haematuria (18.9%), dysuria (painful urination; 8.1%) and pollakiuria (increased urinary frequency; 4.1%). There was one report of nephritis. Across the comparative datasets, renal and urinary adverse events were reported more commonly in the advanced urothelial carcinoma datasets (37.8% and 32.5%) from the Keynote-045 and Keynote-052 trials than in the other two datasets (9.7% and 11.9%), which is attributable to the disease under study. The incidence figures for renal failure, renal impairment and nephritis were comparable across the four datasets.

Risk management plan

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 11 (shown below). Note that the TGA may request an updated risk management plan (RMP) at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.[34]

At the time that this submission was evaluated the most recently evaluated EU-RMP was version 25 (dated 12 July 2019; data lock point (DLP) 24 August 2018) and Australia-specific annex

[34] 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.

(ASA) version 20 (dated 24 February 2020). In support of the extended indications, the sponsor has submitted EU-RMP version 27 (dated 11 October 2019; DLP 24 August 2018) and ASA version 21 (dated 27 March 2020). EU-RMP version 27 has been approved by the European Medicines Agency (EMA) but does not include information regarding non-muscle invasive bladder cancer as the sponsor has no plans to submit the currently proposed indication. The accompanying ASA (version 21) includes the information relevant to non-muscle invasive bladder cancer.

Table 11: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Immune-related adverse reactions (including immune related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies)	ü	ü[1]	ü	ü[3]
Important potential risks	*For haematologic malignancies*: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab	ü	ü[1]	ü	ü
	Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)	ü	ü[1, 2]	ü	ü
Missing information	Long term safety	ü	ü[1]	–	–

1: Clinical trial;

2: Cumulative review of cases

3: Patient education.

The summary of safety concerns is the same as the safety summary evaluated previously as part of submission PM-2019-02633-1-4.[35] The proposed extension of indications is not expected to change the summary of safety concerns from an RMP perspective. The above summary of safety concerns is acceptable.

Routine and additional pharmacovigilance activities have been proposed as shown in Table 11 above. The sponsor has provided a clinical study plan as required for the provisional registration. The TGA will consider the adequacy of this plan.

The sponsor has proposed to discontinue the Healthcare Professional (HCP) education brochure in Australia. At the second round of RMP evaluation, the TGA has agreed to this change through a

[35] Submission PM-2019-02633-1-4 was a related submission to extend the indications of Keytruda (pembrolizumab) to include the treatment of renal cell carcinoma. The following extension of indications were registered on the ARTG for Keytruda (pembrolizumab) on 12 June 2020:
Renal Cell Carcinoma: Keytruda (pembrolizumab), in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

different submission than the submission currently under consideration [and discussed in this AusPAR]. The RMP evaluation considers the routine risk minimisation measures (that is, the Product Information) are acceptable, from an RMP perspective, to inform the HCPs about the adverse events associated with Keytruda. The patient education materials (a patient brochure and Patient Alert Card) continue to be implemented. The risk minimisation plan is acceptable.

The sponsor has committed to the following:

- To update the table in the ASA (Summary of the RMP in Australia) to correctly show the pharmacovigilance activities that are implemented for 'GVHD [graft versus host disease] after pembrolizumab administration in patients with a history of allogeneic SCT [stem cell transplantation]' and 'Long-term safety', when the ASA is next updated.
- To update the Consumers Medicines Information (CMI) to the new format as soon as practicable and revise the statement regarding provisional approval as per TGA recommended formatting, to include the term 'Provisional approval' in bolt text formatting, during this update.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> The Keytruda EU-Risk Management Plan (RMP) (version 27, dated 11 October 2019, data lock point 24 August 2018), with Australian Specific Annex (version 21, dated 27 March 2020), included with submission PM-2020-01294-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
>
> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

As Keytruda is being considered for a provisional registration, it should be included in the Black Triangle Scheme. Keytruda is currently included in the Black Triangle Scheme and should continue to be included for the entire period of provisional registration as a condition of registration. The following wording is recommended for the condition of registration:

> Keytruda (pembrolizumab) is to be included in the Black Triangle Scheme. The PI, CMI and additional risk minimisation materials for Keytruda must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.

As Keytruda is being considered for a provisional registration, the following wording regarding confirmatory trial data is recommended for the condition of registration:

> Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.
>
> Specifically the sponsor must conduct studies as described in the clinical study plan in version 21 (dated 27 March 2020) of the Australia-Specific Annex.

Risk-benefit analysis

Delegate's considerations

For patients with high-risk non-muscle invasive bladder cancer who are unresponsive to intravesical BCG;[16] the only currently accepted treatment is radical cystectomy, which is curative. This procedure has its own associated with significant morbidity and mortality that increases with increasing age. Non-surgical options are limited.

Keynote-057 trial

In this submission, the sponsor is seeking provisional registration for pembrolizumab for use in BCG-refractory non-muscle invasive bladder cancer based on the Keynote-057 trial, a single Phase II non-comparative trial study.[23,24]

The design of Cohort A part of the study was consistent with the recommendations of the European Medicines Agency's (EMA's) guideline on the evaluation of anticancer medicinal products, as they relate to Phase II studies;[36] and with the recommendations of a US Food and Drug Administration (FDA) guideline;[37] which specifically relates to BCG-unresponsive non-muscle invasive bladder cancer (see also *Guidance and definitions* for further information on this guideline). The use of the *complete response* endpoint is in concordance with the 2016 recommendations of the International Bladder Cancer Group (IBCG) on clinical trial designs for BCG-non-responsive non-muscle invasive bladder cancer.[38]

At the various data cut-off points from this study, the best complete response is the complete response (absence of high-risk disease) as reported in 40.6% of subjects (95% confidence intervals (CI): 30.7, 51.1) after 12 weeks of therapy. At the May 2020 data cut-off, the complete response rate (absence of high risk non-muscle invasive bladder cancer) was 36.7% (95% CI: 28.7, 45.3). At each data cut-off point the complete response rate compared favourably with historical data in subjects treated with intravesical chemotherapy, where a response rate of approximately 20% was observed, but these are non-randomised, cross-trial comparisons and should be approached with caution. On the basis of the lower bound of the 95% confidence interval of greater than 20%, the complete response results for the primary and key secondary endpoints of the Keynote-057 trial continue to satisfy the success criterion set out for the study. A sensitivity analysis of complete response based on the US FDA BCG-unresponsiveness criteria showed similar results.[21,37] Improvement over expectations from historical data is also seen for progression-free survival. PD-L1 status does not appear to be a predictor of response and appears consistent with the all-comer treatment approach for most of the approved indications for PD-L1 inhibitors in the treatment of more advanced urothelial cancer.

Responses diminish with time, with approximately half the patients with a complete response sustaining that response over more than one year in the data currently available. For many patients pembrolizumab may be a temporising measure prior to the consideration of the need for radical cystectomy.

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[36] European Medicines Agency (EMA): Guideline on the evaluation of anticancer medicinal products in man. EMA/CHMP/205/95/Rev.4; (2012); effective date: 1 April 2014

[37] United States Food and Drug Administration (US FDA): BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment Guidance for Industry; (2018). FDA, USA. Available online at: https://www.fda.gov/media/101468/download

[38] Kamat AM, Sylvester RJ, Böhle A et al. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. *J Clin Oncol.* 2016; 34 (16): 1935-44.

It is yet unknown whether a trial of pembrolizumab in this setting may in any way complicate a radical cystectomy should the patient undergo this surgical treatment option, particularly for patients on longer durations of therapy whose disease eventually progresses after some period of complete response.

Additional uncertainty arises from the single-arm, and open-label study design of the Keynote-057 trial. As there are no controls, historical controls have been referred to; however, nuanced differences in baseline characteristics and standard of care treatments can challenge and limit the robustness of this type of cross-study comparison.

The safety profile of pembrolizumab in this setting is consistent with that seen for aggregate of pembrolizumab safety data and the comparison of the total pembrolizumab data with the non-muscle invasive bladder cancer patient data set, explained under *Comparison with historical datasets* (see above) shows some events are less frequent in Keynote-057 trial. Less advanced disease and lower exposure to the toxicity of other therapies possible contributes to this observation. Nevertheless, problematic immune mediated events were also seen among non-muscle invasive bladder cancer patients.

Flat dosing of 200 mg given intravenously once every 3 weeks was used in the study. This dose was evaluated in previous submissions, and has been accepted on the basis of exposure-response relationships, supported by data showing full target saturations in the systemic circulation and tumour at 200 mg once every 3 weeks.

This submission represents a shift towards systemic therapy for a local disease, albeit one at high risk of progression to systemic disease and for which curative treatment is radical cystectomy. The Phase II single-arm study data from the Keynote-057 trial provide early data in support of pembrolizumab as a potential treatment option for patients not unwilling or unable to undergo radical cystectomy. The data are not yet fully mature but the durability of complete response and the impact on surgical difficulty and patient outcomes if radical cystectomy follows pembrolizumab are important areas of uncertainty potentially requiring considerable discussion between the treating physician and the patient.

If (subject to the advice of the Advisory Committee on Medicines (see *Advisory Committee considerations*, below)) this submission is approved, the patient selection, initiation of treatment and ongoing management of patients on pembrolizumab should remain the remit of specialised healthcare professionals experienced in the treatment of cancer, as is currently stated in the Keytruda PI.

Clinical study plan

An acceptable clinical study plan to provide comprehensive clinical data on the safety and efficacy of the medicine is a requirement for provisional registration. At this point in the decision making process, a clinical study plan has not yet been agreed with the TGA.

The sponsor has proposed the Keynote-676 trial;[39,40] a Phase III, multicentre, randomised, open-label, comparator controlled, parallel group study comparing pembrolizumab and intravesical BCG with BCG alone, in patients with high-risk non-muscle invasive bladder cancer that is persistent or recurrent following adequate BCG induction. Limited detail of this study has been

[39] Keynote-676 trial: A Phase III, randomised, comparator-controlled clinical trial to study the efficacy and safety of pembrolizumab (mk-3475) in combination with Bacillus Calmette-Guerin (BCG) in participants with high-risk non-muscle invasive bladder cancer that is either persistent or recurrent following BCG induction or that is naïve to BCG treatment.
ClinicalTrials.gov Identifier: NCT03711032. EudraCT number: 2018-001967-22.
[40] Kamat AM, Shore N, Hahn N, et al. KEYNOTE-676: Phase III study of BCG and pembrolizumab for persistent/recurrent high-risk NMIBC. *Future Oncol.* 2020;16(10):507-516.

provided in the submission so additional information about the study is sought from the sponsor (see *Questions for the sponsor*, below).

Proposed action

While at this point in the submission evaluation a decision was yet to be made, the Delegate was inclined, at the time, to approve the registration of the product.

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

1. The Keytruda EU-Risk Management Plan (RMP) (version 27, dated 11 October 2019, data lock point 24 August 2018), with Australian Specific Annex (version 21, dated 27 March 2020), included with submission PM-2020-01294-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

   An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

2. Keytruda (pembrolizumab) is to be included in the Black Triangle Scheme. The PI, CMI and additional risk minimisation materials for Keytruda must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.

There will be a condition of registration to submit confirmatory trial data (see *Clinical study plan*) as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence. The wording will be finalised following the review of the response to questions for the sponsor below and the receipt of the advice of the Advisory Committee on Medicines.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. The sponsor has identified the Keynote-676 trial as the confirmatory trial to support the conversion to full registration; a brief summary of the study was provided in response to earlier TGA questions.

a. Please provide details of the study design, estimated enrolment, and progress of recruitment.

The following are details of the study design, estimated enrolment and progress of recruitment:

Keynote-676 is a Phase III, randomised, comparator-controlled clinical trial to study the efficacy and safety of pembrolizumab in combination with Bacillus Calmette Guerin (BCG) in participants with high-risk non-muscle invasive bladder cancer (NMIBC) that is either persistent or recurrent following BCG induction or that is naïve to BCG treatment. The trial has 2 cohorts (that is, Cohort A (BCG Post-Induction) and Cohort B (BCG Naïve)) that operate in parallel and are independent of each other, with their own respective objectives and endpoints, inclusion and exclusion criteria, and timing for interim and final analyses. In addition, because the cohorts are independent, each cohort is assigned full alpha with no passing of alpha between the 2 cohorts.

Cohort A (BCG Post-Induction): For Cohort A, participants with high-risk NMIBC that have persistent or recurrent disease after receiving adequate BCG induction are randomised in a 1:1 ratio to receive BCG + pembrolizumab (Arm A-1) or BCG alone (Arm A-2); see Figure 3, below. Participants with persistent T1 disease after induction BCG are not eligible. Prior to enrolment, participants will have undergone recent cystoscopic procedure(s) to remove all resectable

disease (Ta and T1 components) and assure the absence of muscle invasive disease. Participants will undergo disease assessments with cystoscopy, urine cytology and biopsies/computed tomography urography (CTU) (as applicable) every 12 weeks for the first 2 years, then every 24 weeks for a total duration of 5 years.

Transurethral resection of bladder tumour (TURBT)/biopsies are required on study to confirm disease persistence/ recurrence or progression in the setting of suspicious or positive cystoscopy and/or urine cytology.

Pembrolizumab will be administered every 3 weeks for a total of 35 doses of treatment (approximately 2 years) and treatment with BCG will continue for a total of 147 weeks (approximately 3 years). Treatment will be discontinued if the participant experiences unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, the investigator's decision to withdraw the participant, the participant withdraws consent, pregnancy of the participant, or administrative reasons.

In addition, participants with pathology-confirmed high-grade Ta, T1, CIS or disease progression to T2 or worse at any time will be discontinued from the trial treatment. Participants with pathology-confirmed low-grade Ta persistence or recurrence at any time during the study will be permitted to undergo a TURBT to fully resect the low-grade Ta and are permitted to remain on trial treatment. The development of high-grade disease involving the upper tract will constitute recurrence of high-risk disease necessitating discontinuation from the study treatment.

As of March 2021, 183 participants have been randomised in Cohort A (planned total is 550). Recruitment is projected to be complete by the fourth quarter of 2025.

Cohort B (BCG Naïve): For Cohort B, participants with high-risk non-muscle invasive bladder cancer that have not been treated with BCG in the past 2 years for their non-muscle invasive bladder cancer will be randomised in a 1:1:1 ratio to receive pembrolizumab + BCG (reduced maintenance; Arm B-1), pembrolizumab + BCG (full maintenance; Arm B-2) or BCG alone (full maintenance; Arm B-3); see Figure 3, below.

Cohort B features 2 experimental arms, including an arm with reduced BCG maintenance, as reducing reliance on BCG in this disease setting would provide a significant benefit to patients. Prior to enrolment, participants will have undergone recent cystoscopic procedure(s) (within 12 weeks) to remove all resectable disease (Ta and T1 components) and assure the absence of muscle invasive disease.

Participants will undergo disease assessments with cystoscopy, urine cytology and biopsies (as applicable) every 12 weeks for the first 2 years, then every 24 weeks for a total duration of 5 years.

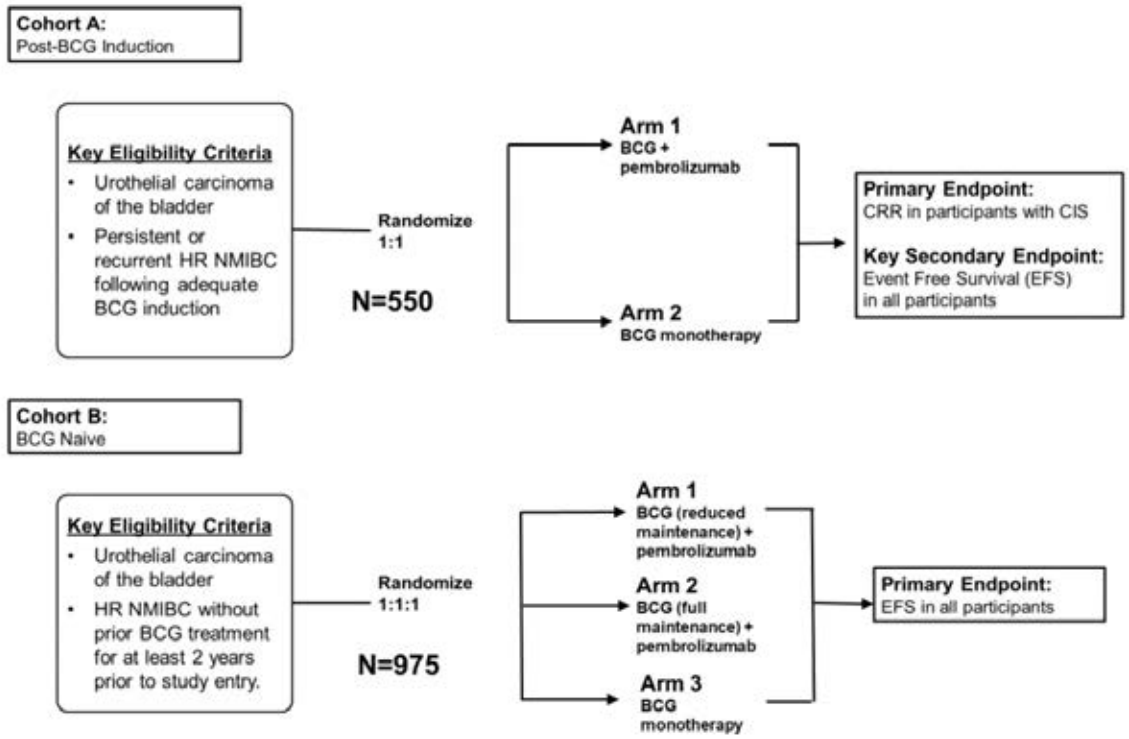
TURBT/biopsies are required on study to confirm disease persistence/recurrence or progression in the setting of suspicious or positive cystoscopy and/or urine cytology. CTU assessments will occur every 72 weeks, or more frequently as clinically indicated.

Pembrolizumab will be administered every 6 weeks in Arm B-1 and Arm B-2 for a total of 9 doses of treatment (approximate duration of one year). Participants in the pembrolizumab +BCG (reduced maintenance; Arm B-1) will receive up to 2 courses of BCG. Participants in the pembrolizumab + BCG (full maintenance; Arm B-2) and the BCG monotherapy arm (Arm B-3) will receive up to 5 courses of BCG. Treatment will be discontinued if the participant experiences unacceptable AE(s), intercurrent illness that prevents further administration of treatment, the investigator's decision to withdraw the participant, the participant withdraws consent, pregnancy of the participant, or administrative reasons.

In addition, participants with pathology-confirmed T1or disease progression to T2 or worse at any time, or high-grade Ta or CIS at the 24-week assessment or thereafter will be discontinued from the study intervention. Participants with pathology confirmed low-grade Ta persistence or recurrence at any time during the study will be permitted to undergo a TURBT to fully resect the low-grade Ta and are permitted to remain on trial treatment. The development of high-grade disease involving the upper tract will constitute recurrence of high-risk disease necessitating discontinuation from the study treatment. Participants in Cohort B are not eligible to be enrolled in Cohort A after discontinuing study intervention in Cohort B.

Cohort B began enrolment in March 2021 and is projected to be complete by June 2023.

Figure 3: Keynote-676 trial; Study design



Abbreviations: BCG = Bacillus Calmette-Guerin; CIS = carcinoma in situ; EFS=event-free survival; CRR = complete response rate; HR = high risk; NMIBC = nonmuscle-invasive bladder cancer.

Cohort A is based on participants with urothelial carcinoma with previous BCG treatment, The key eligibility criteria are urothelial carcinoma of the bladder; and persistent or recurrent high risk non-muscle invasive bladder cancer following adequate BCG induction.

Recruitment of 550 participants is planned. Patients with be randomised in a 1:1 ratio to Arm 1 (participants given BCG treatment plus pembrolizumab) or Arm 2 (participants given BCG alone as monotherapy). The primary endpoint is the complete response rate in participants with carcinoma in situ. The key secondary endpoint is event free survival in all participants.

Cohort B is based on participants with urothelial carcinoma with who are BCG naïve (that is, with no previous BCG treatment), The key eligibility criteria are urothelial carcinoma of the bladder; and high risk non-muscle invasive bladder cancer without prior BCG treatment for at least 2 years prior to study entry.

Recruitment of 975 participants is planned. Patients with be randomised in a 1:1:1 ratio to Arm 1 (participants given BCG treatment in the form of reduced BCG maintenance, plus pembrolizumab); or Arm 2 (participants given BCG treatment in the form of full BCG maintenance, plus pembrolizumab); or Arm 3 (participants given BCG alone as monotherapy). The primary endpoint is event free survival in all participants.

b. Does the sponsor still expect the study will be completed by the second quarter of 2026?

Based on current projections, the sponsor expects that data readouts from both cohorts will be available by June 2026.

c. There are two cohorts each with more than one study arm.

Will results from all cohorts form the confirmatory data? If not, which cohorts will be included?

When the sponsor initially proposed the Keynote-676 trial as the confirmatory trial for the Keynote-057 trial, the Keynote-676 trial only included patients who had persistent or recurrent high-risk non-muscle invasive bladder cancer post-BCG induction (Cohort A). Since the Keynote-676 trial now includes two separate cohorts, the sponsor proposes to allow data from either cohort to fulfil the requirements for confirmatory data. There is a significant unmet need for approved nonsurgical therapies for patients with BCG-unresponsive NMIBC. Thus, a Phase III study evaluating pembrolizumab monotherapy in the BCG-unresponsive NMIBC setting would be challenging due to the lack of available medical therapies that can be used as a comparator. Radical cystectomy (RC) has historically been the only standard of care in this disease setting but would not be a suitable comparator. Additionally, placebo controlled clinical trials are unethical because BCG-unresponsive high-risk NMIBC is associated with high risk of progression and mortality if left untreated. For the reasons mentioned above, the US FDA has published guidance stating that single arm trials utilising complete response rate as a primary endpoint supported by duration of response (DOR) may be appropriate for regular approval, or it may require a confirmatory trial post-approval. With regard to the confirmatory trial, since a randomised trial in the BCG-unresponsive population is not feasible, the FDA has proposed randomised trials versus BCG in the BCG- naïve or post BCG-induction NMIBC setting.[37]

As described, the Keynote-676 trial will enable confirmation of pembrolizumab monotherapy efficacy demonstrated in the Keynote-057 trial by combining it with standard-of-care BCG therapy in earlier stages of high-risk NMIBC, that is, in patients with persistent or recurrent disease following BCG induction (Cohort A) or BCG-naïve disease (Cohort B). The sponsor proposes that results from either cohort could serve as confirmatory for the Keynote-057 trial, given that both cohorts are randomised with a robust sample size and statistical analysis plan, as well as the similarity in patient population (high-risk NMIBC).

d. Other than the Keynote-676 trial, are other studies planned for inclusion in the clinical study plan?

At this time, no other studies are planned for inclusion in the clinical study plan.

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

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***Please advise on the strength of the evidence of benefits over harms of pembrolizumab in Bacillus Calmette-Geurin (BCG)-unresponsive, high-risk non-muscle invasive bladder cancer (NMIBC) in the setting of provisional registration.***

The ACM discussed that the Keynote-057 trial provided single-arm data for the use of pembrolizumab in BCG-unresponsive, high-risk non-muscle invasive bladder cancer, with study advice given by the US FDA.

The Keynote-057 trial showed a 41.5% complete response rate, with a median duration of response of 16.2 months in patients with BCG failure or recurred after BCG, and the ACM considered that there was a clinically meaningful but durable response rate of 21%.

The ACM advised that the magnitude of benefit of pembrolizumab for the proposed indication is moderate and considered this adequate to support provisional registration.

The ACM was of the view that the toxicity observed in Keynote-057 trial is within the bounds of use of pembrolizumab.

Additionally, the ACM commented on the importance of ongoing testing and bladder investigations throughout treatment, further stating that if no improvement is noted at the 3-month treatment mark the ongoing treatment with pembrolizumab should be reassessed.

2. ***An adequate plan to submit comprehensive clinical data on the safety and efficacy of the medicine is an important aspect of the provisional registration of a prescription medicine. Please comment on the adequacy of the clinical study plan to provide meaningful confirmatory data, noting additional detail is expected in the pre-ACM response.***

The ACM noted the Keynote-676 trial, including response, is a combination study with an uncertain control arm and noted that surgery was at times inevitable.

The ACM agreed that there needs to be a cystectomy free survival outcome as per US FDA advice, as the fifth secondary outcome.

The ACM advised that Cohort A needs further information on the surgical plan pre randomisation, to determine if they are not fit or to inform their refusal. If the patient is fit for cystectomy, the ACM questioned the risk management and ethical equipoise for delaying surgery.

The ACM expressed concern that, given the use of single agent pembrolizumab for this indication, how study crossover will be managed, as only the study endpoints of complete response and event-free survival will be interpretable (that is, short term gain). The ACM questioned how this is to be balanced against a systemic treatment with its own toxicity and the need to show a change in the natural history of the disease.

Conclusion

The ACM considered this product, including the proposed clinical study plan to have an overall positive benefit-risk profile for the provisional indication:

> *For the treatment of patients with Bacillus Calmette-Geurin (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.*

Outcome

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

> *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.*

As such, the full indications for Keytruda (pembrolizumab) at the time of approval of this submission 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 nabpaclitaxel, 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) ≥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 ≥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 5fluorouracil (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) ≥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 platinumcontaining chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

Classical Hodgkin Lymphoma (cHL)

Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of adult 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 is on the basis of objective response rate (ORR). 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 cisplatincontaining therapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥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).

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

Specific conditions of registration applying to these goods

The following specific conditions of registration apply to these goods:

- For all injectable products the Product Information must be included with the product as a package insert.
- Keytruda (pembrolizumab) is to be included in the Black Triangle Scheme. The PI, CMI and additional risk minimisation materials for Keytruda must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.
- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

Specifically the sponsor must conduct studies as described in the clinical study plan in version 21 (dated 27 March 2020) of the Australian-Specific Annex. The following study reports should be submitted to the TGA:

- The final analysis of study Keynote 057 in patients with high risk non-muscle invasive bladder cancer (NMIBC) unresponsive to Bacillus Calmette-Guerin (BCG) therapy
- Keynote 676, a study of pembrolizumab in combination Bacillus CalmetteGuerin (BCG) with in patients with high-risk non-muscle invasive bladder cancer that is either persistent or recurrent following BCG induction or that is naïve to BCG treatment.

Further guidance for sponsors is available on the TGA website.

- The Keytruda EU-Risk Management Plan (RMP) (version 27, dated 11 October 2019, data lock point 24 August 2018), with Australian Specific Annex (version 21, dated 27 March 2020), included with submission PM-2020-01294-1-4; and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

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.

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Reference/Publication #