Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Pembrolizumab

Proprietary Product Name: Keytruda

Sponsor: Merck Sharp and Dohme (Australia) Pty Ltd

November 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
1L	First line
2L	Second line
3L	Third line
ADA	Anti-drug antibody
AE	Adverse event
AEOSI	Adverse event of special interest
ALT	Alanine aminotransferase
APaT	All patients as treated
AST	Aspartate aminotransferase
BICR	Blinded independent central review
CI	Confidence interval
CPS	Combined positive score
CR	Complete response
CSR	Clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group-Performance Status
eCRF	Electronic case report form
EOC	Executive Oversight Committee
EORTC QLQ-C30	Electronic European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
ePRO	Electronically collected patient-reported outcome

Abbreviation	Meaning
EQ-5D	European Quality of Life 5 Dimensions
ERC	Ethics Review Committee
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FWER	Family-wise type 1 error rate
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
IA	Interim analysis
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival

Abbreviation	Meaning
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death 1- ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PRO	Patient-reported outcomes
PT	Preferred term
PTT	Partial thromboplastin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QALY	Quality-adjusted life-year
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RPSFT	Rank Preserving Structural Failure Time
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class (MedDRA)
TPS	Tumour progression score
ULN	Upper limit of normal
US	United States

I. Introduction to product submission

Submission details

Type of submission:	Extensions of Indications
Decision:	Approved
Date of decision:	9 January 2018
Date of entry onto ARTG:	11 January 2018
ARTG numbers:	226597 and 263932
Active ingredient:	Pembrolizumab
Product name:	Keytruda
Sponsor's name and address:	Merck Sharp & Dohme (Australia) Pty Limited 26 Talavera Road Macquarie Park, NSW 2113
Dose form:	Powder for injection; and concentrated solution for injection
Strengths:	50 mg and 100 mg/4 mL
Container:	Single use vial
Pack size:	1 vial
Approved therapeutic use:	*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. This indication is approved based on overall response rate and duration of response. 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.*
Route of administration:	Intravenous (IV)
Dosage:	Keytruda is administered as an intravenous infusion over 30 minutes every 3 weeks. The recommended dose of Keytruda is 200 mg for urothelial carcinoma. Patients with urothelial carcinoma without disease progression can be treated for up to 24 months or 35 cycles [see Clinical Trials].

Product background

This AusPAR describes the application by the sponsor to extend the currently registered indications for Keytruda to include urothelial carcinoma (UC).

The proposed indications as taken from the draft PI are:

> *Keytruda (pembrolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing therapy.*
>
> *Keytruda (pembrolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have received platinum containing chemotherapy.*

The following dosage regimen is proposed:

> *200 mg administered intravenously over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.*

Two presentations of pembrolizumab are currently registered:

- A vial containing 50 mg powder for injection. The powder is reconstituted with sterile water for injection (2.3 mL) and then added to normal saline or 5% dextrose prior to intravenous (IV) infusion.
- A vial containing a concentrated solution of 100 mg in 4 mL. This solution is added to normal saline or 5% dextrose prior to IV infusion.

No new formulation or presentation has been proposed for the new indications.

Urothelial carcinoma

The sponsor states:

> '*Urothelial carcinoma, also known as transitional cell carcinoma or urothelial bladder cancer, refers to carcinomas that arise from the urothelial endothelium that lines the renal pelvis, ureter, bladder and urethra, with more than 90% of urothelial carcinomas originating in the bladder. About 80 to 90% of all bladder cancers start from the urothelial cells that line the bladder wall. This is sometimes called transitional cell carcinoma. Urothelial carcinoma can be papillary or flat…, and it can also occur in the ureters and kidneys.*'

This differs from squamous cell carcinoma (1 to 2% of all cases) and adenocarcinoma (1% of all cases) of the bladder, which is not the cancer type for which registration is being sought in this application.

Risk factors include smoking, exposure to environmental carcinogens as well as inherited predisposition syndromes due to mismatch repair gene defects (Lynch syndrome) or Phosphatase and tensin homolog (PTEN) [1] mutations (Cowden syndrome).

Staging of UC of the renal pelvis/ureter is similar to that for bladder cancer and is based upon the recently revised Tumour Node Metastasis classification by the American Journal of Cancer Classification;[2] (staging sections using search terms urothelial bladder cancer, urethral carcinoma and renal pelvis or ureteric carcinoma. The stages which are captured

[1] PTEN acts as a tumor suppressor gene through the action of its phosphatase protein product. This phosphatase is involved in the regulation of the cell cycle, preventing cells from growing and dividing too rapidly. It is one target of cancer drugs.
[2] McKiernan JM, Hansel DE, Bochner BH, et al. Renal Pelvis and Ureter. In: AJCC Cancer Staging Manual, 8th, Amin MB. (Ed), Springer, New York 2017. p.749.

within clinical trial inclusion criteria in both pivotal trials presented here include those, which are inoperable, locally advanced, and/or with distant metastases. Those with Stage IV disease include patients with locally invasive tumours spreading into surrounding tissues, and/or local nodal spread and/or distant metastases.

No contextualisation of the proposed usage in Australia was provided in the application. A separate report (Report title '04FZLR'), 'Systematic literature review and meta-analysis' was included in the submission comparing historical outcomes from 18 clinical trials in patients who were treated with first line therapy, but were not considered eligible for cisplatin-based therapies. Specific Australian statistics for the incidence of UC as opposed to bladder cancer are not available. The Australian Institute of Health and Welfare (AIHW) statistics from 2006-2010 state that bladder cancer accounted for 2% of all cancers, making it the tenth most common cancer in Australia. These statistics indicate that more than 2400 Australians are diagnosed with bladder cancer each year, most of whom are 60 years of age or older. Men are three to four times more likely than women to be diagnosed with bladder cancer. Bladder cancer was noted to be the eighth most common cancer and the thirteenth most common cause of cancer death in men and the seventeenth most common cancer and cause of cancer death in women.[3] Extrapolating from these figures, approximately 2100 cases of UC of the bladder are diagnosed each year in Australia. Statistics for the incidence of UC of the upper urinary tract in Australia could not be found.

Anatomical location and histological grading have historically been the key determinants guiding treatment plans for patients with urothelial cancer. Low grade urothelial cancer of the bladder has a different prognosis and treatment options compared with high-grade muscle invasive disease. Patients presenting with muscle invasive have a high risk of relapse and together with those with locally advanced or metastatic disease are recommended to receive chemotherapy with surgery or chemotherapy plus radiation as options for local control. Given the much higher frequency of bladder cancer, most studies have enrolled patients with tumours arising in the bladder rather than upper genitourinary tract UCs.

First-line, good performance status and able to tolerate chemotherapy

Cisplatin-based combination therapy either in the form of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or gemcitabine plus cisplatin (GC) is the most commonly used regimens, for those able to tolerate chemotherapy. Initial response rates to combination chemotherapy are high in previously untreated patients but long term survival is rare. In a head-to-head study comparing GC with MVAC in patients with locally advanced inoperable or metastatic UC of the bladder, median progression free survival (PFS) was 7.7 months and 8.3 months, overall survival for was 14.0 months and 15.2 months (MVAC), and 5-year progression-free survival rates were 13% and 15.3%, respectively[4]). Six year continuous disease free survival rates were reported as 3.7% in another study using MVAC[5] Significant prognostic factors favouring overall survival included better baseline performance status, the absence versus presence of metastatic disease, low/normal alkaline phosphatase level, number of disease sites ≤3) and the

[3] Cheluvappa R, Smith DP, Cerimagic S, Patel MI. A comprehensive evaluation of bladder cancer epidemiology and outcomes in Australia.Int Urol Nephrol. 2014 Jul; 46(7):1351-60. Epub 2014 Feb 1.
[4] Sternberg CN1, Yagoda A, Scher HI, Watson RC, Geller N, Herr HW, Morse MJ, Sogani PC, Vaughan ED, Bander N, et al.Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer. 1989 Dec 15; 64(12):2448-58.
[5] Saxman SB, Propert KJ, Einhorn LH, Crawford ED, Tannock I, Raghavan D, Loehrer PJ Sr, Trump D. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol. 1997 Jul;15(7):2564-9.

absence of visceral metastases.[6] The toxicities of chemotherapy are significant with a reported treatment-related death rate for MVAC of 3%, and high rates of ≥ Grade 3 neutropenia (58%) and associated sepsis (25%)[4]; additional toxicities include nephropathy and neuropathy. It was noted that patients with poor performance status were unlikely to experience long term disease free survival with MVAC chemotherapy.[5]

First line, not able to tolerate cisplatin chemotherapy

Given the advanced age at which many patients are diagnosed and comorbidities that may include impaired renal function, many will not be able to tolerate chemotherapy, and in particular, cisplatin. A consensus working group[7] defined those who were considered less likely to tolerate cisplatin as having the following features:

1. World Health Organization (WHO)/Eastern Cooperative Oncology Group[8] performance status (ECOG-PS) ≥ 2 or a Karnofsky Performance Status of 60 to 70 percent or less;
2. Creatinine clearance less than 60 mL/min;
3. Hearing loss (measured at audiometry) of 25 dB at two contiguous frequencies;
4. Grade 2 or greater peripheral neuropathy (that is, sensory alteration or paraesthesia, including tingling but not interfering with activities of daily living);
5. New York Heart Association (NYHA) Class III or greater heart failure.[9]

This is the patient group for whom the sponsor is seeking registration of pembrolizumab for use first line as monotherapy. Currently, for such patients, options include carboplatin-based combination regimens or a non-platinum-based regimen such as paclitaxel and gemcitabine. The following results were obtained in a randomised Phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients

[6] von der Maase H, Lehmann J, Gravis G, Joensuu H, Geertsen PF, Gough J, Chen G, Kania M. A phase II trial of pemetrexed plus gemcitabine in locally advanced and/or metastatic transitional cell carcinoma of the urothelium. Ann Oncol. 2006 Oct; 17(10):1533-8. Epub 2006 Jul 27.

[7] Galsky MD1, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, Dreicer R, Vogelzang N, Sternberg CN, Bajorin DF, Bellmunt J. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol. 2011 Jun 10; 29(17):2432-8. Epub 2011 May 9.

[8]

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

[9]

NYHA grading		MET*
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction).	>7
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF).	5
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).	2-3
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).	1.6

MET (metabolic equivalent) is defined as the resting VO_2 for a 40-year-old 70kg man. MET = 3.5mL O_2/min/kg body weight.

Reproduced from: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated October 2011.

with advanced urothelial cancer who were deemed unable to tolerate cisplatin based chemotherapy [10]:

- best objective response rates (ORRs) were 41.2% (36.1% confirmed response) for patients receiving GC versus 30.3% (21.0% confirmed response) for patients receiving M-CAVI (P = .08);
- median overall survival (OS) was 9.3 months in the GC arm and 8.1 months in the M-CAVI arm (p = 0.64);
- no difference in PFS (p = 0.78) between the two arms;
- severe acute toxicity (death, Grade 4 thrombocytopenia with bleeding, Grade 3 or 4 renal toxicity, neutropenic fever, or mucositis) was observed in 9.3% of patients receiving GC and 21.2% of patients receiving M-CAVI.

In 54 patients with ECOG-PS 0-2, receiving 2 weekly gemcitabine and paclitaxel as first line therapy for advanced UC, the overall response rate was 37% (with 9.2% complete response (CR) and 28% partial response (PR)) with a median progression-free survival of 5.8 months and overall survival of 13.2 months.[11]

Second line following progression on cisplatin

There is no established standard of care for patients whose disease progresses after cisplatin chemotherapy. For those with ECOG-PS of 0 or 1, vinflunine monotherapy has shown a very modest 1.5 month improvement in progression-free survival but no overall survival benefit. This is approved in Australia and the PI contains the following precaution, *'Vinflunine has a narrow safety threshold. If vinflunine is used in patients with poor performance status or patients likely to progress quickly to poor performance status, close observation is required since toxicity may be excessive.'* Dose reductions are required for those with ECOG-PS 1.

Combination gemcitabine/paclitaxel or a taxane alone may also be used as second line palliative treatment. Sternberg et al (2001)[12] report response rates of 60% (95% confidence interval [CI], 45, 75%) including a complete response in 28% and partial response in 33% of patients treated with the combination following progression after MVAC given either in the neoadjuvant or metastatic setting. Response rates were higher in those treated following neoadjuvant chemotherapy compared with after metastatic disease progression (80% versus 27%); the median duration of survival after failing neoadjuvant or adjuvant M-VAC was 12 months (range, 2– 43) compared with 8 months (range, 2–28) for patients who had been treated after failure of prior therapy for metastatic disease. For all patients, the median duration of response was 6.4 months (range, 2–43.3 months), and the median survival was 14.4 months (range, 2–43).

Several immunotherapy agents are in development and two are FDA approved for the second line treatment of UC following progression on cisplatin. On 18 May, 2016, the FDA granted atezolizumab a Programmed cell death 1- ligand 1(PD-L1) inhibitor, accelerated approval for the treatment of patients with UC with either disease progression during or after chemotherapy or relapsing within 12 months of neoadjuvant or adjuvant platinum

[10] De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30(2):191-9
[11] Calabrò F, Lorusso V, Rosati G, Manzione L, Frassineti L, Sava T, Di Paula ED, Alonso S, Sternberg CN. Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. Cancer. 2009 Jun 15; 115(12):2652-9.
[12] Sternberg CN, Calabrò F. Pizzocaro G. Marini L. Schnetzer S. Sella A. Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. Cancer 92(12): 2993-2998

containing therapy. On 2 February 2017, nivolumab was granted accelerated approval for the treatment of patients with platinum refractory UC as follows: locally advanced or metastatic UC who have disease progression during or following platinum containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum containing chemotherapy. Durvalumab received breakthrough designation status from the FDA in February 2016 for the treatment of patients with PD-L1 positive inoperable or metastatic urothelial bladder cancer whose tumour has progressed during or after one standard platinum based regimen. Pembrolizumab has received breakthrough designation therapy status for the treatment of previously treated patients with UC but not for treatment as a first line therapy.

Thus, there is significant unmet need at the time of writing this report, particularly for novel agents with a better toxicity profile but this is an area of intense clinical investigation and rapidly changing treatment algorithms.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 16 April 2015.

Pembrolizumab has had a *regular* FDA approval in the post platinum setting and *accelerated* approval in the first line, cisplatin ineligible setting (see Tables 1 and 2 below). These tables also summarise the European Medicines Agency (EMA) approvals.

Table 1: First line, cisplatin ineligible

	FDA	EMA
Approval date	May 2017	August 2017.
Indication	*For the treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and duration of response.* *This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.*	*For the treatment of locally advanced or metastatic UC in adults who are not eligible for cisplatin-containing chemotherapy.*

Table 2: Second line, post platinum-based therapy

	FDA	EMA
Approval date	May 2017	August 2017

	FDA	EMA
Indication	*For the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy.*	*For the treatment of locally advanced or metastatic UC in adults who have received prior chemotherapy.*

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, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Description	Date
Submission dossier accepted and first round evaluation commenced	28 February 2017
First round evaluation completed	31 July 2017
Sponsor provides responses on questions raised in first round evaluation	31 August 2017
Second round evaluation completed	29 September 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	25 October 2017
Sponsor's pre-Advisory Committee response	3 November 2017
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	9 January 2018
Completion of administrative activities and registration on ARTG	11 January 2018
Number of working days from submission dossier acceptance to registration decision*	182

*Statutory timeframe for standard applications is 255 TGA working days

III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor indicates that after the Study KEYNOTE-012 Cohort C demonstrated that more than half of pembrolizumab treated patients (64%) experienced tumour shrinkage with very limited toxicity and this indicated that an initial trial with pembrolizumab was reasonable and worthwhile for cisplatin ineligible patients. In light of the relatively limited benefit from cytotoxic chemotherapy in subjects with advanced/unresectable (inoperable) or metastatic UC who cannot receive cisplatin and the promising results with pembrolizumab and other anti-PD-1 pathway agents, pembrolizumab was evaluated as monotherapy in this population with that of Study KEYNOTE-052.

The sponsor states that, '*Promising efficacy results from KEYNOTE-012 Cohort C provided provided the impetus to initiate the pembrolizumab clinical development program in UC. The clinical development program in UC includes KEYNOTE-012 (Cohort C), KEYNOTE-052, KEYNOTE-045, KEYNOTE-057, and KEYNOTE-361*.'

Guidance

The following guidelines and references were considered relevant to this application:

- EMA Guideline on Points to consider on application with one pivotal study
- EMA Guideline on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety
- EMA Guideline on the evaluation of anticancer medicinal products in man.
- FDA Guidance for Industry Adaptive design clinical trials for drugs and biologics
- Uptodate.com for: urothelial bladder cancer; renal pelvis/ureteric UC; and urethral carcinoma, accessed on 31 March 2017.
- Bellmunt, J et al Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum containing regimens. *J Clin Oncol.* 2010 Apr 10; 28(11):1850-5.
- Calabro, F Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated UC. Cancer. 2009; 115(12):2652.

Contents of the clinical dossier

The sponsor provided no background information on the current clinical algorithm and approved products for the treatment of UC in Australia to support this application. The information about any potential differences in the datasets lodged with the different regulatory authorities was not stated and clarification has been sought.

Scope of the clinical dossier

The sponsor has submitted an application to register two indications to treat UC supported by two different pivotal Studies KEYNOTE-045 and KEYNOTE-052. These have not been integrated and essentially constitute two separate applications, each with its own separate summary as these were lodged separately with the FDA and EMA. Additional efficacy data were provided after commencement of the first round evaluation. The following data were submitted:

- Pivotal studies, one for each indication, each with a separate Clinical Overview, Summary of Efficacy and Summary of Safety
- 1 document titled 'TGA KN52 Update.pdf' (provided after commencement of evaluation)
- 1 supportive Phase Ib study
- 4 reports containing PK tables and figures, and a modelling, simulation report including data from urothelial cancer studies
  - Report 04JQ34 Modeling and simulation report – Extension of population PK analysis of pembrolizumab to patients with UC (Protocols 001, 002, 006, 012 Cohort C, 045, 052)
  - Report 04JR0J PK tables and figure for pembrolizumab Study KN052 and comparison of PK across indications, dated 9 November, 2016.
  - Report 04JT5G PK tables and figure for pembrolizumab Study KN045 and comparison of PK across indications, dated 11 November 2016.
  - Report 04JQV8 PK Tables and Figures for Pembrolizumab Study KN012 Cohort C Urothelial Carcinoma (UC) and comparison of PK across indications, dated11 November 2016
- 2 modelling and simulation reports for QTc
  - Report 03TLCF modelling and simulation report, Exposure-QTc analysis of MK-3475, dated February 2014
  - Report 03WKGP modelling and simulation report, Exposure-QTc analysis of MK-3475 – P001 Part F dated April 2014
- Report pertaining to immunogenicity
  - Report 04L4FS Integrated pembrolizumab Immunogenicity analysis, dated 11 January 2017
- Clinical studies providing pivotal efficacy and safety data:
  - First line not eligible for cisplatin
    - Study KEYNOTE-052 A Phase II Clinical Trial of Pembrolizumab (MK-3475) in Subjects with Advanced/Unresectable or Metastatic Urothelial Cancer
  - Recurrent or Progressive Metastatic Urothelial cancer:

- § Study KEYNOTE-045 A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer

· Supportive study:

– Study PN012V02 A Phase Ib Multi-Cohort Study of MK-3475 in Subjects with Advanced Tumors

The approach adopted by the sponsor for demonstration of the proposed first line strategy is has elements of a hybrid submission that is a combination of data with reliance upon a systematic literature review and meta-analysis undertaken by the sponsor to provide comparative or historical data. The literature search strategy for the systematic review and meta-analysis was not presented to the TGA prior to submission. This document, Report 04FZLR, has not been formally evaluated.

Two integrated summaries were submitted:

· Integrated summary of efficacy

· Integrated summary of safety

The clinical dossier contains two studies in support of the proposed 2 indications, multiple PK reports and separate supporting documents pertaining to each pivotal clinical study report and proposed indication. Additional data were provided based on responses to the FDA's questions regarding Study KEYNOTE-052 and provided to the TGA after commencement of the first round evaluation.

Paediatric data

No paediatric data are provided which is acceptable.

Good clinical practice

The sponsor states that these studies were conducted in substantial conformance with Good Clinical Practice requirements and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Pharmacokinetics

Studies providing pharmacokinetic data

No new pharmacokinetic (PK) or pharmacodynamics (PD) studies were provided, but the dossier included a number of reports including in some just tables and figures as well as a population pharmacokinetic analyses, modelling and simulation in urothelial cancer patients.

Evaluator's conclusions on pharmacokinetics

The data for the first line usage are too immature to characterise the PK adequately as there are insufficient patients contributing data due to both early discontinuations and the immaturity (short duration of exposure and follow up) of this study. On what was presented, these appeared to have different clearance and exposure compared with other solid tumours and in comparison with the previously treated UC patients. Comparisons of observed PK parameters based on the same dosing strategy of 200 mg every 3 weeks

(Q3W) would provide more relevant comparisons once more mature data for this study are available.

The model does not adequately account for the differences between the populations in terms of ECOG, that is, no data were presented on the effect of the poorer ECOG on key parameters and those with ECOG-PS 2 were not accommodated by the existing fields in the model and presumably censored.[13]

No data were presented on the clearance as determined by body weight in this generally lighter population. The data on the effect of increasing age of these patients on clearance and volume of distribution was difficult to interpret.

It is noted that in a previous evaluation, that the sponsor has been requested to provide key information about the development of the base model. While the sponsor has presented this model as established for use in this report, this has yet to be confirmed by a TGA evaluation. Thus, there is a caveat, that acceptance of the validity of this model is required.

Second round evaluator comment: This response has been provided to the TGA and the model is considered acceptable.

Overall, this model does not provide any insights into the PK for this population, nor is it possible given the very wide inter-individual variability observed in the PK parameters including clearance and exposure, for each of the individual UC populations, to have confidence in the ability of the model to provide accurate predictions at an individual level. Its utility is very uncertain. Fittingly, no changes are proposed to the PI based on this report. Note is made that the Pharmacokinetics section does not incorporate a discussion of the 200 mg Q3W flat regimen and this should be addressed, given the number of indications for which this dosing strategy is proposed and the 2 mg/kg Q3W appears to have been largely superseded. (PI Comments)

Pharmacodynamics

Studies providing pharmacodynamic data

No new studies were provided but two reports on the effect of pembrolizumab exposure on QTc were included.[14] Data populations were from Study KN001 (melanoma and non-small cell lung cancer (NSCLC)) and the dose regimens studied included patients receiving 2mg/kg Q3W and 10 mg/kg Q3W. As such, this spans the likely exposure seen for the patients receiving the proposed dosage for this application of 200 mg Q3W but does not directly inform regarding this usage.

No PI changes are proposed based on these simulation and modelling reports and given neither indicated a clinically relevant change in QTc at the highest exposure and dose level, these documents were reviewed but have not been evaluated in detail. Note is made of the sponsor's proposed shift to the 200 mg Q3W dose regimen for all future clinical studies.

[13] The ECOG-PS (Eastern Cooperative Oncology Group Performance Status) provides a score from 0 to 5 (0 denoting perfect health, 5 denoting death) quantifying general wellbeing and ability to perform activities of daily living.

[14] QTc=Corrected QT interval.
In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarisation and repolarisation of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

Evaluator's conclusions on pharmacodynamics

Given there is no known mechanism for pembrolizumab to affect cardiac repolarisation and the small degree of change observed at even very much higher doses and with exposures exceeding those likely to result from the 200 mg Q3W regimen, these conclusions seem reasonable.

Dosage selection for the pivotal studies

The dosage proposed is 200 mg Q3W, which is being used in the clinical development program for pembrolizumab. Initial studies investigated differing regimens: 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W.

The flat dosing schedule is approved for the treatment of NSCLC (previously untreated).

Efficacy

Studies providing efficacy data

The following studies provided efficacy data:

- Study KEYNOTE-045 Phase III randomised, open label, active controlled study in patients with recurrent or progressive urothelial cancer following cisplatin-based therapy (200 mg Q3W)
- Study KEYNOTE-052 Phase II non randomised, open label trial in patients who have received no prior systemic therapy and who are ineligible for cisplatin (200 mg Q3W)
- Study PN012v02 Phase Ib multi-cohort study of MK-3475 in subjects with advanced tumours (10 mg/kg Q2W)

Evaluator's conclusions on efficacy

Indication 1: for the treatment of patients with locally advanced or metastatic UC who have received platinum containing chemotherapy

Study KEYNOTE 045 demonstrates a statistically significant and clinically meaningful improvement in overall survival in the study population of patients with locally advanced or metastatic urothelial cancer who have received platinum containing chemotherapy. Progression free survival was not improved but secondary and exploratory endpoints (ORR, time to progression (TTP) data) support the positive conclusion based on OS.

It should be noted that only 6 subjects with performance status ECOG-PS 2 were included in this study and those with ECOG-PS > 2 were excluded and clinical efficacy has not been demonstrated in these groups.

Indication 2: for the treatment of patients who have received no prior systemic therapy for UC who are not eligible for platinum containing chemotherapy

In this open label, single arm study with very short median durations of follow-up and exposure, establishing whether there has been a clinically meaningful benefit of therapy is more difficult. The sponsor provided an update of ORR and duration of treatment in response to questions from the FDA, with a reported rate of ORR of 106/370 (28.6%). However, the use of the term 'confirmed' ORR is still somewhat unclear and requires the response to the evaluator's clinical questions as it is not clear if this refers to RECIST 1.1 confirmation (minimum of 2 scans) or that is was confirmed on other RECIST 1.1 criteria by central radiological review. Based on the updated data, 55 of these 106 patients treated to date (described in the updated data) had a response duration exceeding 6 months. This

appears to be the strongest data in support of a clinically meaningful response as these patients would have had at least 2 scans in this time period and have had central radiological review and therefore appear to establish the basis for a claim of efficacy. This clinical evaluator accepts that this information indicates that the response rate meeting the criteria as defined in the Statistical analysis plan (SAP) at least 14.9% and may be revised with the sponsor's clarification. The reported ORR of 28.6% is marginally below the figure of 30% the sponsor had prespecified as being of clinical importance.

However, response duration in excess of 6 months is notable for this population but caution has to be exercised in interpreting these results as there was no comparator arm and UC is a chemo sensitive disease. Updated data would allow an assessment of the extent of and the durability of any observed response, with the latter the hallmark of benefit from immunotherapy. Updated data are also required as this rate may change as more patients reach the time point where a RECIST 1.1 confirmed response can be determined.

Safety

Studies providing safety data

A single randomised Phase III trial was provided in support of the indication for previously treated patients, and a Phase II open label, single arm study in support of the indication for patients who have received no prior systemic therapy. In the evaluation of the safety data, the randomised study data are provided as the pivotal safety dataset with supportive evidence at the same dose level from the Phase II study. The Phase Ib study population received a different dose regimen, and will be evaluated for safety signals only. The sponsor has not provided an integrated safety summary of the first and second line populations and thus, these datasets will all be considered separately.

Pivotal studies that assessed safety as the sole primary outcome

None provided.

Patient exposure

Study KEYNOTE-045

This was a Phase III randomised, open label, active-controlled study in patients with recurrent or progressive urothelial cancer following cisplatin-based therapy.

The durations of exposure (median months on therapy) for the APaT population were 3.45 months for the pembrolizumab arm compared with 1.54 months in the control arm (paclitaxel: 1.45 months; docetaxel: 1.43 months; vinflunine: 2.10 months). For a summary of these data please see Table 3 below.

Of the 266 subjects in the pembrolizumab arm, 95 (35.7%) received treatment for ≥ 6 months and 43 (16.2%) received treatment for ≥ 12 months. Of 255 subjects in the control arm, 29 (11.4%) received treatment for ≥ 6 months and 3 (1.2%) received treatment for ≥ 12 months.

Table 3: Study KEYNOTE-045 Summary of drug exposure all patients as treated

	Control	Pembrolizumab
	N=255	N=266
Time on Therapy (months)		
Mean	2.74	5.60
Median	1.54	3.45
SD	2.71	5.37
Range	0.03 to 14.19	0.03 to 20.04
Number of Administrations		
Mean	4.74	8.81
Median	3.00	6.00
SD	3.71	7.61
Range	1.00 to 20.00	1.00 to 30.00
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine. Database Cutoff Date: 07SEP2016		

Table 4: Study KEYNOTE-045 Duration of exposure all patients

Duration of Exposure	Control		Pembrolizumab	
	n	(%)	n	(%)
> 0 m	255	100.0	266	100.0
≥ 1 m	184	72.2	213	80.1
≥ 3 m	83	32.5	139	52.3
≥ 6 m	29	11.4	95	35.7
≥ 12 m	3	1.2	43	16.2
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date +1. Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine. Database Cutoff Date: 07SEP2016				

While only a relatively small proportion are still receiving pembrolizumab treatment at 12 months, this is greater than the control arm and will provide some information about the longer term safety profile in this population.

Study KEYNOTE-052

This was a Phase II non-randomised, open label trial in patients who have received no prior systemic therapy and who are ineligible for cisplatin chemotherapy (200 mg Q3W).

Study KN052 is an ongoing study. The last subject was enrolled on 21 June 2016. At the time of data cutoff, the median duration of follow-up was 2.79 months (range 0.03-15.84 months).

Table 5: Study KEYNOTE-052 Clinical trial exposure All subjects population

Duration of Exposure	Pembrolizumab	
	n	(%)
> 0 m	370	100.0
≥ 1 m	297	80.3
≥ 3 m	157	42.4
≥ 6 m	72	19.5
≥ 12 m	9	2.4
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date +1. Database Cutoff Date: 01SEP2016		

The median duration of follow-up indicates the immaturity of these data and this, together with the open label, single arm study design limits the ability of this study to detect new safety signals or to confirm the safety profile with longer exposure for this usage. There is reliance upon the investigator's assessment given the specialist expertise of these oncologists in treating this malignancy to determine likelihood of any AEs being treatment-related.

Study PN012v02

This was a Phase Ib multi-cohort study of MK-3475 in subjects with advanced tumours (10 mg/kg Q2W).

All 33 patients received at least one dose of study treatment. Table 6 summarises the duration of exposure in Cohort C.

Table 6: Study PN012 Cohort C Duration of exposure

	Urinary Tract Cancer (MK3475 10mg/kg Q2W) n=33
Study Days On-Therapy (days)	
Mean	155.33
Median	71.00
SD	209.41
Range	1.00 to 708.00
Number of Administrations	
Mean	11.27
Median	6.00
SD	14.14
Range	1.00 to 51.00
Cohort C: Urinary Tract Cancer; (Database Cutoff Date: 01SEP2015).	

Source: [P012V02: analysis-adsl] [P012V02: tabulations-explus]

The pattern for the duration of exposure is similar to Study KEYNOTE-045, with 18.2% still receiving treatment after 12 months but half ceasing treatment within 3 months.

Events of clinical interest

These were defined as overdose, drug-induced liver injury (DILI) laboratory parameters, and selected adverse event (AE) terms of potential immune aetiology called adverse events of special interest occurring within 90 days after the last dose or 30 days if a new anticancer treatment was initiated.

Study KEYNOTE-045

Overview of AEs of special interest

Adverse events of special interest (AESI) are immune mediated events and infusion related reactions considered to be identified risks (adverse drug reactions) or potential risks for pembrolizumab. A prespecified list of preferred terms (PTs) was developed for assessing AEOSIs. These PTs are considered to be clinically equivalent to the immune mediated events and infusion related reactions. The prespecified list allowed the sponsor to consistently evaluate each AEOSI across the clinical program. All prespecified AE terms were included in the assessment of frequency and nature of AEOSIs for pembrolizumab, regardless of causality as reported by Investigators.

45 (16.9%) subjects in the pembrolizumab arm had 1 or more AEOSIs. In general, the frequency and severity of each AEOSI observed during the trial were similar to the previously described characterisation of the safety profile of pembrolizumab.

No indication specific AEOSI was identified (new immune mediated event causally associated with pembrolizumab).

Events of special interest that were reported in 45 patients in the pembrolizumab arm included 29 cases of thyroid disease (17 hypothyroid, 10 hyperthyroid, 2 thyroiditis), 11 pneumonitis, 6 colitis, 2 each of nephritis, infusion reaction and severe skin reaction. All other events were in single patients. These events reflect known toxicity of the drug.

Study KEYNOTE-052

To date, there have been 63 (17.0%) patients with 1 or more AEOSIs:

- 38 (10.3%) of subjects experienced Grade 1 and 2 AEOSIs
- 25 (6.8%) experienced Grade 3 or higher AEOSIs
- 1 patient died from myositis

While the frequencies and severity of each of the AEOSIs observed during the trial were generally similar to the previously described characterisation of the safety profile of pembrolizumab, one patient had an AEOSI of severe myositis with a fatal outcome. This may change with increased duration of exposure, as this trial is ongoing.

Study PN012v02

Not reported in the company study report (CSR).

Safety in special populations

In Study KEYNOTE-045, the majority of subjects were over 65 years of age and there was no major increase in adverse events in over 65 age subjects as compared with younger subjects although serious drug related AEs were more common (12.3 versus 6.8%) in the older group. Insufficient data were available to comment on safety in those with a poorer ECOG status (≥ 2).

In Study KEYNOTE-052, the data are too immature to make a definitive statement regarding whether the treatment tolerability is similar between this and other cancers for the different age groups (that is in comparison with the reference safety dataset) and there is no comparator arm to demonstrate whether it is better tolerated than alternative treatment options, such as chemotherapy or best supportive care.

Postmarketing data

At the time of the second round clinical evaluation report, this indication has only been registered in the US A and the Committee for Medicinal Products for Human Use (CHMP) of the EMA has made a recommendation for approval of the two proposed indications. There is no post-marketing information available yet for the proposed usage.

Evaluator's conclusions on safety

Study KEYNOTE-045

The overall safety profile of pembrolizumab as demonstrated in the current study was clearly superior to the control regimen of cytotoxic therapy (whichever of the 3 available control drugs was chosen). Pembrolizumab toxicities were as expected from those established in previous studies. Renal impairment, including acute kidney injury was increased in the pembrolizumab arm in this study. Pruritus, fatigue, nausea, rash and pyrexia were the common AEs attributed to the drug. Overall treatment discontinuation due to AE occurred in 8.3%, with 5.6% due to treatment-related AEs in the reference safety dataset. Pneumonitis (1.9%) was the most common AE leading to treatment discontinuation. The safety of pembrolizumab, while superior to cytotoxic options in the setting of post-platinum urothelial cancer, appears broadly similar to that reported for other monoclonal antibodies targeting PD-1. There was no signal of cardiac toxicity in this study.

Study KEYNOTE-052

Most of the adverse events observed in this open label, single arm study in patients with UC of whom 10 percent had received adjuvant or neoadjuvant cisplatin based chemotherapy, who had not received prior systemic therapy in the metastatic or inoperable setting and who were not eligible to receive cisplatin, appear consistent with those reported for pembrolizumab. Early safety signals from the comparison with the previously treated population and particularly compared with the reference safety dataset include a higher rate of events in this population including constipation, urinary tract infection, anaemia, peripheral oedema, haematuria, blood creatinine increased, abdominal pain and weight decreased. When the incidence data are included for severe events occurring at ≥ 1% frequency and restricted to those considered related to treatment, additional severe events appear to be increased: fatigue and muscular weakness. While these are most likely to be attributable to the underlying disease, it does raise concerns about the tolerability and safety profile of pembrolizumab in those with significant comorbidities and in particular, pre-existing renal impairment. In the absence of a comparator arm and given this trial is very immature with only a very short median duration of treatment and follow-up, no comments can be made about the comparative rates of these events at this time with any other population.

A signal that requires further investigation was severe neutropenia, for which there is no clear explanation at this time. One patient developed myocarditis and the PI needs to be updated to include this serious adverse event. The severity of events observed in this trial, which includes a fatal event of myositis require updates to be made to the PI.

No comparator arm was included in this study design, which limits the characterisation of the safety profile for this population. However, it might be reasonable to infer that treatment with pembrolizumab will be better tolerated than the chemotherapy options available to this population, but as no quality of life data were presented, it cannot be stated that it is better tolerated.

Study PN012v02

Limited data are available from this small cohort of patients with advanced and often heavily pre-treated 'urinary tract cancers'. Safety signals included myositis and rhabdomyolysis, with the latter needing to be included in the PI.

First round benefit-risk assessment

There are multiple clinical questions regarding the PK, efficacy, safety and immunogenicity data provided in support of the proposed usage, and to update the PI. Responses to these are required to provide clarification and to address uncertainties where possible. Responses to these may lead to a change in the assessments below.

First round assessment of benefits and risks

Indication 1: Locally advanced or metastatic urothelial cancer following platinum chemotherapy

The proposed indication is for an area of need as the current options (cytotoxic drug regimens) yield a modest rate of response and poor overall survival and carry high risks of serious toxicity.

Potential benefits

1. Improved median OS of almost 3 months compared with cytotoxic therapy; statistically significant and clinically meaningful, across whole study population.
2. Higher overall confirmed response rate, with apparently greater depth of response.

3. Early data suggested a prolonged duration of response in some individuals but extent unclear.
4. Better safety profile with fewer serious drug-related AEs compared with chemotherapy.
5. Tendency of survival curve to plateau, suggesting that a relatively small subset of patients may have long term benefit, which is rarely seen with cytotoxic therapy. This requires confirmation with longer-term data from this study.
6. Treatment population broadly reflective of that encountered in clinical practice in terms of age, with a majority of patients over 65 years.

Risks

1. Higher rate of discontinuations, adverse events and shorter median duration of treatment than currently reported for other cancer types in the PI. However, this was better than the chemotherapy arm.
2. Pembrolizumab is associated with specific toxicities, seen again in this population.
3. Pembrolizumab is associated with a non-significantly shorter interval of progression-free survival and an excess of early progression and early mortality in the first three months approximately, compared with the control arm of cytotoxic chemotherapy.
4. Worse initial PFS and OS (that is earlier progression and mortality) in a substantial subset of the whole population, including the PD-L1 positive and strongly positive subpopulations, in the pembrolizumab arm followed later by an improvement as indicated by crossing and lying above the control arm on the Kaplan-Meier plots.

Uncertainties

1. Although sufficient to establish an overall survival advantage, follow-up is relatively short and the number of long term survivors is unclear.
2. Progression-free survival was not improved. The reasons for the discordance between OS and PFS are not fully clear but an excess of early progression occurs in the pembrolizumab group compared with cytotoxic recipients.
3. The study was effectively restricted to subjects of ECOG-PS 0 or 1 due to stringent inclusion criteria for ECOG-PS 2 (resulting in only 6 patients with ECOG-PS 2 being recruited, of whom only 2 received pembrolizumab), and ECOG-PS>2 were excluded. Generalisability of results (efficacy and toxicity) to patients of ECOG-PS ≥ 2 is not established.
4. The importance and clinical utility of PD-L1 expression is not clear:
    a. Expression levels appear much lower in UC than in other cancer types.
    b. In this population, higher levels of expression were associated with a poorer OS in both the treatment and control arms, compared with the overall study population. Reasons for this are not clear.
    c. PD-1 blockade appeared to improve OS, but did not abrogate this observed apparent poor prognostic signal in those with a PD-L1 CPS≥ 10%;
    d. PD-L1 positivity has an association with improved OS with pembrolizumab but some PD-L1 negative cancers also respond.
    e. There is a lack of detailed data presented on the PD-L1 negative group.
    f. PD-L1 was introduced as an endpoint well after the study commenced, was not a stratification factor and therefore confounding factors cannot be excluded to explain the differing outcomes within each PD-L1 subgroup.

5. There is a lack of detailed analysis of the patients progressing, or dying, in the early months after commencement of pembrolizumab. Allowing that small numbers may result in large confidence intervals, it would nonetheless be potentially highly informative to have detailed analysis of subjects progressing or dying in the first 3 months, with Forest Plot analysis of sub-groups. In the absence of such data there is an impression that early progression and mortality in the pembrolizumab arm may be particularly concentrated on those subjects with rapidly progressing disease and/or large tumour volumes, and they possibly an identifiable sub-group who are disadvantaged by the use of pembrolizumab rather than chemotherapy, notwithstanding the benefit to the overall group.

Indication 2: Locally advanced or metastatic urothelial cancer in patients not eligible for cisplatin

Potential benefits

1. Somewhat uncertain but there appears to be efficacy demonstrated via an overall response rate that lasted ≥ 6 months in 55/307 patients.

Risks

1. No comparator arm to inform safety and efficacy accurately in this frail population.
2. Higher rate of discontinuation than other populations receiving pembrolizumab, including the previously treated UC population in Study KN045 (PI needs updating).
3. Higher incidence than currently indicated in the PI of constipation, urinary tract infection, anaemia, peripheral oedema, haematuria, blood creatinine increased, abdominal pain and weight decreased. When the incidence data are included for severe events occurring at ≥ 1% frequency and restricted to those considered related to treatment, additional severe events appear to be increased: fatigue and muscular weakness fatigue, renal injury, increase in blood creatinine, anaemia, musculoskeletal pain.
4. Some new toxicities including myocarditis and more severe toxicities than currently described in the PI including a death from myositis, requiring inclusion in the PI. The remainder of the treatment related toxicities were in general consistent with the known profile of pembrolizumab.
5. An unexplained high rate of severe neutropaenia.

Uncertainties

1. No comparator arm to determine if superior to existing treatment options – safety would appear likely to be improved, but this population is frail compared with those in Study KEYNOTE-045 (discontinuation rate due to AEs of 22% compared with 8.3%) and extrapolation is not possible.
2. With the submission of very early data for registration, there are short median durations of follow-up and exposure in this ongoing trial. Durations of responses not established (hallmark of benefit of immunotherapy).
3. This study relies on ORR, with secondary endpoint of duration of response.
4. Open label, single arm study with risk of bias.
5. Apparent use different meanings for the term 'confirmed' when describing endpoints, which requires clarification for all endpoints.
6. Overall response rate yet to be clarified.
7. The importance of PD-L1 expression is uncertain and requires prospective validation in a randomised controlled trial. Apparent enrichment of response in this study

population likely to be confounded by inclusion of population used to determine biomarker cut-off in analyses, and exclusion of patients with early relapse before 2 scans in setting this cut-off. Study KEYNOTE-045 indicated worse prognosis in those with higher expression. PD-L1 CPS ≥ 10% cut-off appears to have poor predictive value as response rates seen in those deemed negative and with lower expression.

8. Note is made that PD-L1 expression is not included as selection criteria in future studies planned for urothelial cancer.
9. Planned to undertake randomised controlled trial versus chemotherapy (platinum and non-platinum) as confirmatory study for recent US accelerated approval for this usage. Final CSR not anticipated before 2021.

First round assessment of benefit-risk balance

Indication 1: Locally advanced or metastatic urothelial cancer following prior platinum therapy

The overall balance of risks and benefits favours pembrolizumab. The establishment of an overall survival benefit is the most fundamental basis for this favourable assessment and it is supported by improvement in secondary/exploratory endpoints such as ORR and quality of life data and by lesser toxicity. Some patients appear to be disadvantaged and have a shorter median progression-free survival and as yet there is no reliable way of identifying such individuals.

Indication 2: Locally advanced or metastatic urothelial cancer in patients not eligible for cisplatin

The proposed indication is for an area of need as the current options (cytotoxic drug regimens) are limited due to comorbidities and yield a modest rate of response and poor overall survival and carry high risks of serious toxicity. No benefit-risk equation can be presented at this stage until a response to the clinical questions is provided.

First Round Recommendation Regarding Authorisation

Indication 1: Locally advanced or metastatic urothelial cancer following prior platinum therapy

Subject to the PI changes being made, the clinical evaluator recommends approval of pembrolizumab for this indication. The evaluator notes that the study population did not include poor performance status subjects (no ECOG > 2 and only six with ECOG = 2) and it is difficult in the absence of data to recommend approval for use in patients beyond ECOG-PS 0 or1 on the basis of Study KEYNOTE 045.

Indication 2: Locally advanced or metastatic urothelial cancer in patients not eligible for cisplatin.

No recommendation can be made at this time.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Locally advanced or metastatic urothelial cancer following platinum chemotherapy.

The proposed indication is for an area of need as the current options (cytotoxic drug regimens) yield a modest rate of response and poor overall survival and carry high risks of serious toxicity.

Potential benefits

1. Improved median OS of almost 3 months compared with cytotoxic therapy; statistically significant and clinically meaningful, across whole study population.
2. Higher overall confirmed response rate, with greater depth and duration of response (median duration of response yet to be reached with pembrolizumab compared with 4.4 months in the chemotherapy arm, at updated data cut-off).
3. Better safety profile with fewer serious drug-related AEs compared with chemotherapy.
4. Tendency of survival curve to plateau, suggesting that a relatively small subset of patients may have long term benefit, which is rarely seen with cytotoxic therapy. This requires confirmation with longer term data from this study.
5. Treatment population broadly reflective of that encountered in clinical practice in terms of age, with a majority of patients over 65 years.

Risks

1. Higher rate of discontinuations, adverse events and shorter median duration of treatment than currently reported for other cancer types in the PI. However, this was better than the chemotherapy arm. This is not currently adequately presented in the PI.
2. Increased risk of renal toxicity: 7.5% versus 4.7%; this is not currently included in the PI and is a new safety signal (also noted in FDA label for NSCLC treated with pembrolizumab + chemotherapy).
3. Pembrolizumab is associated with specific toxicities, seen again in this population.
4. Pembrolizumab is associated with a non-significantly shorter interval of progression-free survival and an excess of early progression and early mortality in the first three months approximately, compared with the control arm of cytotoxic chemotherapy. A subgroup analysis in the sponsor's response to the first round evaluation suggested that compared with the whole study population, a greater proportion of the following subgroups experienced early disease progression or death: >65 years, Asian patients and never smokers, with no predictive value for PD-L1 Combined Positive Score (CPS) status in identifying those at increased risk. Patients of 'White' race appeared to have a lower proportion with early death or progression. These analyses cannot be used to select or counsel patients as responses were observed across all subgroups.
5. Worse initial PFS and OS (that is earlier progression and mortality) in a substantial subset of the whole population, including the PD-L1 positive and strongly positive subpopulations, in the pembrolizumab arm followed later by an improvement as indicated by crossing and lying above the control arm on the Kaplan-Meier plots.

Uncertainties

1. Although sufficient to establish an OS advantage, follow-up is relatively short and the number of long term survivors is unclear.

2. PFS was not improved. The reasons for the discordance between OS and PFS are not fully clear but an excess of early progression occurs in the pembrolizumab group compared with cytotoxic recipients.
3. The study was effectively restricted to subjects of ECOG 0 or1 performance status due to stringent inclusion criteria for ECOG-PS 2 (resulting in only 6 patients with ECOG-PS 2 being recruited, of whom only 2 received pembrolizumab), and ECOG-PS > 2 were excluded. Generalisability of results (efficacy and toxicity) to patients of ECOG-PS ≥ 2 is not established. The inclusion criteria have been clearly stated in the Clinical Trials section of the PI.
4. PD-L1 CPS expression appears to lack clinical utility in UC and it is appropriate no information is included in the PI:
5. Expression levels appear much lower in UC than in some other cancer types;
    a. In this population, higher levels of expression were associated with a poorer OS in both the treatment and control arms, compared with the overall study population. Reasons for this are not clear.
    b. PD-1 blockade appeared to improve OS but did not abrogate this observed apparent poor prognostic signal in those with a PD-L1 CPS ≥ 10%;
    c. Increasing strength of PD-L1 positivity has an association with improved ORR and OS with pembrolizumab, but some PD-L1 negative cancers also respond;
    d. PD-L1 was introduced as an endpoint well after the study commenced was not a stratification factor and therefore confounding factors cannot be excluded to explain the differing outcomes within each PD-L1 subgroup.
6. There is an impression that early progression and mortality in the pembrolizumab arm may be particularly concentrated on those subjects with rapidly progressing disease and/or large tumour volumes and they are possibly an identifiable sub-group who are disadvantaged by the use of pembrolizumab rather than chemotherapy, notwithstanding the benefit to the overall group. The sponsor has included a statement to this effect in the PI.
7. Higher disease control rate/clinical benefit rate (CR+ PR+ stable disease (SD)) was observed overall in the chemotherapy arm, due to higher rates of stable disease, but no data on the duration of these stable disease responses were provided; the CR and PR were shorter in the chemotherapy arm. This may suggest some role for synergy with chemotherapy and immunotherapy in this population, perhaps for those presenting with rapidly progressive disease or heavy disease burden.

Locally advanced or metastatic urothelial cancer in patients not eligible for cisplatin.

Potential benefits

1. With a median duration of follow-up of 8 months, the overall response rate was 28% including 7% with complete responses.
2. The median duration of response has yet to be reached and 79% of those responding have had at least 6 months of response.

Potential risks

1. No comparator arm to inform safety and efficacy accurately in this frail population.
2. Early data mean only limited safety data are available to inform regarding rates and severity of AEs, discontinuations and treatment interruptions.

3. Higher rate of adverse events affecting >10% population compared with KN045 study patients, discontinuation due to adverse events (not just those deemed treatment-related) than other populations receiving pembrolizumab, including the previously treated UC population in Study KN045 (PI needs to include information specifically pertaining to this group).
4. Higher incidence than currently indicated in the PI of constipation, urinary tract infection, anaemia, peripheral oedema, haematuria, blood creatinine increased, abdominal pain and weight decreased. When the incidence data are included for severe events occurring at ≥ 1% frequency and restricted to those considered related to treatment, additional severe events appear to be increased: fatigue and muscular weakness fatigue, renal injury, increase in blood creatinine, anaemia and musculoskeletal pain.
5. An unexplained high rate of severe neutropaenia.
6. Some new toxicities, including myocarditis, and more severe toxicities than currently described in the PI including a death from myositis, requiring inclusion as a fatal event in the PI. The remainder of the treatment related toxicities were in general consistent with the known profile of pembrolizumab.

Uncertainties

1. No comparator arm to determine if superior to existing treatment options. Safety would appear likely to be improved but this population is frail compared with those in Study KEYNOTE-045 (discontinuation rate due to treatment emergent AEs (TEAEs) of 11.1% compared with 8.3%) and extrapolation is not possible.
2. With the submission of very early data for registration, there are short median durations of follow-up and exposure in this ongoing trial. Durations of responses not established (hallmark of benefit of immunotherapy).
3. This study relies on ORR, with secondary endpoint of duration of response.
4. Open label, single arm study with risk of bias.
5. Overall response rate yet to be clarified for entire population.
6. The importance of PD-L1 expression is uncertain and requires prospective validation in a randomised controlled trial. Some apparent enrichment of response in this study population but this lacks predictive value as responses were still observed in those deemed negative for PD-L1 expression.
7. Note is made that PD-L1 expression is not included as selection criteria in future studies planned for urothelial cancer.
8. Planned to undertake randomised controlled trial versus chemotherapy (platinum and non-platinum) as confirmatory study for recent US accelerated approval for this usage. Final CSR not anticipated before 2021.

Outstanding issues

Product information

The PI does not currently present any data on the Study KN052 population and confines adverse events to those treatment related discontinuations, whereas treatment discontinuation in a frail population due to any event informs of benefit-risk and likelihood of completion.

Several changes to the PI have been recommended to improve clarity and information specific to the rapidly expanding range of very different cancers for which pembrolizumab

is approved. This is a significant outstanding issue precluding recommendation of an approval of the PI at this time.

Neutropaenia in Study KN052

7 (8%) subjects from Study KN052 had a Grade 3 or 4 neutrophil decreased laboratory result that worsened from baseline among subjects with baseline and post-baseline results, and 10 (10%) had a 'clinically meaningful worsened from baseline' change defined as shift from less than Grade 3 to Grade 3-5, or from Grade 1 or 2 to more than Grade 3. A total of 12 (3.2%) subjects in Study KN052 had Grade 4 neutrophil decreased that worsened from the baseline laboratory result.

The absence of a comparator arm means the causality cannot be assessed or excluded although it is noted that a chemotherapy comparator would confound the issues through its own toxicity profile. No clear explanation can be proposed and this should be listed as an important potential risk. The clinical evaluator does not consider the frailty of the population in terms of renal function, hearing, cardiac function and the ECOG-PS 2 of 40% participants have a direct effect on neutrophil count and are not in themselves plausible explanations for the observed significant and serious decline in neutrophil count observed in at least 10% of patients.

Ninety percent of this population had newly diagnosed and previously untreated metastatic disease (10% had received systemic therapy in the neoadjuvant setting) and therefore would be unlikely to have bone marrow infiltration to account for this finding. Furthermore, this would be manifest initially as thrombocytopenia and this was not increased in this population. A decline in haemoglobin (Hb) in this population would not be a sensitive indicator of bone marrow infiltration due to the multiple other potential causes.

The evaluator concluded that this remains an outstanding issue requiring consideration for inclusion in the Risk Management Plan (RMP) list of 'Important potential risks'.

Renal toxicity in Study KN045

This is not currently included in the PI but represents a real risk for those patients who may already have undergone a nephrectomy for their urothelial cancer.[15]

Second round recommendation regarding authorisation

Subject to changes being made to the PI to the satisfaction of the TGA, the evaluator recommends the following modified indications for authorisation:

> *Keytruda (pembrolizumab) is indicated for the treatment of patients with locally advanced or metastatic UC whose disease has progressed during or following platinum containing chemotherapy.*

Given the early nature of the efficacy data and use of a surrogate endpoint with relatively limited follow-up duration, this needs to be presented clearly to indicate the basis on which any decision to approve may be based, for those patients ineligible for cisplatin.

> *Keytruda (pembrolizumab) is indicated for the treatment of patients with locally advanced or metastatic UC who are not eligible for treatment with cisplatin-containing chemotherapy. This approval is based on overall response rate and duration of response, and no improvement in progression-free survival, overall survival or quality of life have been demonstrated.*

[15] Immune-mediated nephritis is now addressed in the PI.

VI. Pharmacovigilance findings

Risk management plan[16]

Updated Keytruda RMP documents were submitted by the sponsor on 14 November 2017 (Keytruda Core-RMP version 15.0, Australian Specific Annex (ASA) version 9.0 and for reference only EU-RMP version 5.3). These are generally acceptable and include the changes recommended by RMP section.

No evaluation has been conducted but the significant changes are listed below (changes to ASA).

There are no outstanding RMP issues.

The suggested wording for the RMP condition for registration is detailed below.

Proposed wording for conditions of registration

Updated suggested wording for RMP condition of registration:

The Keytruda Core-RMP version 15.0 (dated 13 September 2017; data lock point 31 March 2017) with Australian Specific Annex version 9.0 (dated 3 November 2017), and any future updates, must be implemented.

Changes to the Keytruda ASA v9.0 include:

New important identified immune mediated risks

- Encephalitis
- Sarcoidosis
- Myasthenic syndrome

New important potential risk:

- Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transfer (SCT)

Included missing information (previously removed):

- Long term safety

ASA Section 1: updated international regulatory status.

ASA Section 3: updated risk minimisation table (changes recommended during evaluation).

[16] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended approval of both indications.

The pivotal studies were:

- First line cisplatin ineligible
  - Study KEYNOTE-052 (Phase II single-arm, ORR)
- Second line, post platinum
  - Study KEYNOTE-045 (Phase III randomised, open-label versus investigators' choice of vinflunine or taxane; OS, PFS)

Efficacy

Study KEYNOTE-052 first line, cisplatin ineligible

Design

- Phase II, non-randomised, open label trial
- 77 centres: US, EU, Canada, Singapore, Taiwan, Malaysia, Australia.
- Commenced: April 2015; follow-up is ongoing.
- CSR dated 2 December 2016, with a data cut-off date of 1 September 2016.
- Update with data cut-off 9 March 2017

A final study report is due second quarter of 2019 when all responders in Study KN052 have had at least two years of follow-up. Abstracts have been published but a complete published paper could not be identified in PubMed.

Table 7: Study design

Patients	N = 370 18+ years Cisplatin ineligible (one or more of) ECOG-PS 2 Creatinine clearance: 30-60 mL/min Hearing loss; Common Terminology Criteria for Adverse Events (CTCAE) (CTCAE) Grade 2+

	Peripheral neuropathy; CTCAE Grade 2+ Heart failure: NYHA Class III No previous systemic therapy (neoadjuvant or adjuvant > 2 years ago allowed) Measurable disease on RECIST 1.1 ECOG-PS: 0, 1, 2 *Exclusions* Active CNS metastases Immunodeficiency Systemic steroids within 7 days of first dose of trial medicine Autoimmune disease (Type 1 diabetes, resolved childhood asthma could be exceptions) Active cardiac disease Creatinine clearance < 30 mL/min
Intervention	Pembrolizumab 200 mg Q3W until RECIST defined progression, unacceptable toxicity or 2 years of pembro treatment. Patients with radiographic disease progression and a clinically stable status could continue to receive the therapy at the discretion of the investigator.
Comparator	Nil, single arm study
Endpoint	ORR by independent review; RECIST 1.1

PD-L1 status was not a stratification factor. Provision of tissue for biomarker analysis was a requirement for eligibility and the PD-L1 status was defined based on a CPS, including the PD-L1 expression on both tumour and infiltrating immune cells. This scoring system was selected based on the results from earlier Study KN012, in which two different scoring systems were used; one based on tumour cell staining alone and the other based on staining in both tumour cells and inflammatory cells. In both UC studies (that is, KN052, KN045), two PD-L1 CPS cut-offs were evaluated: PD-L1 CPS ≥ 1% determined exclusively using Study KN012 data and the CPS ≥ 10% defined based on the first 100 subjects in Study KN052 which served as the training data set.

PD-L1 was assessed at a central laboratory using the commercially available PD-L1 IHC 22C3 pharmDx assay.

Baseline characteristics

N = 370

Table 8: Study baseline characteristics

Age, Median (range)	**74 years (34, 94)**
Men	77%
PD-L1 status < 1% 1-10% 10+%	 21% 47% 30%

Age, Median (range)	74 years (34, 94)
Not reported	2%
ECOG-PS	
0 normal	22%
1 symptoms, but ambulatory	36%
2 ambulatory, unable to work	42%
3 limited self-care	<1%
Primary site	
Upper tract	19%
Lower tract	81%
Stage	
M0	13%
M1	87%
Met location	
Lymph node (LN) only	14%
Visceral	85%
Liver metastases	
No	79%
Yes	21%
Prior neo-adj/adj platinum based chemotherapy	
No	90%
Yes	10%
Chemotherapy naïve	
No	18%
Yes	82%
Reason for cisplatin ineligibility	
ECOG-PS 2	32%
Renal dysfunction	49%
ECOG-PS 2 and renal dysfunction	10%
Other (HF, hearing, neuropathy)	9%

Results

Data cut-off 9 March 2017: median follow-up: 9.5 months; range (0.1, 22.7).

N = 370.

Table 9: Study results

	n	%
CR	27	7.3
PR	81	21.9
Objective response: CR + PR	108	29.2
Stable disease (SD)	67	18.1
Disease control: CR + PR + SD	175	47.3
Progressive disease	155	41.9
Not evaluable	9	2.4
No assessment	31	8.4

Not evaluable: baseline imaging not evaluable. No assessment: No post-baseline imaging

ORR was higher in the subgroup with PD-L1 CPS > 10% (38%) but responses also occurred in the subgroup with CPS < 10% (21%) and CPS < 1% (17%).

Median (Md) (duration of response (DoR)): not reached, range: 1.4+, 19.6+ months (77/108 (82%) of those with a response had a response for 6+ months)

Md (PFS) = 2.1 months; 95% CI (2.1, 3.0)

Md OS) = 10.9 months; 95% CI (9.7, nr)

KEYNOTE 045 (KN045) post-platinum

Design

- 120 sites, 29 countries: the largest numbers of centres were in Japan (20) and the U.S. (19) with most of the remainder in European countries. There were 3 Australian centres
- Recruitment: Nov-2014 to Nov-2015
- Treatment assignment was not blinded (open label)
- Published as: Bellmunt J et al. NEJM (16-Mar-2017); 376:1015-26.
- Data cut-off September 2016; the same as for the CSR in the submitted dossier

Table 10: Study design

Patients	Pembrolizumab: n = 270, Investigators' choice of chemotherapy: n = 272 18+ years Urothelial carcinoma of renal pelvis, ureter, bladder Progression of advanced disease on platinum-based chemotherapy Recurrence after 12 months of platinum-based neo-adjuvant or adjuvant chemotherapy for muscle-invasive disease ECOG-PS 0 or 1 (ECOG-PS 2 allowed with caveats; very few recruited, see baseline

	characteristics, below) *Exclusions* Immunodeficiency Systemic steroids within 7 days of first dose of trial medicine Autoimmune disease (Type 1 diabetes, resolved childhood asthma could be exceptions) Active cardiac disease Creatinine clearance < 30 ml/min Active brain metastases Inadequate organ function >2 prior lines of systemic chemotherapy The inclusion and exclusion criteria are standard for a randomised clinical trial involving traditional cytotoxic agents and an anti PD-1 monoclonal antibody.
Intervention	Pembrolizumab 200 mg Q#W until RESIST-defined progression, unacceptable toxicity or 2 years of pembro treatment Patients with radiographic disease progression and a clinically stable status could continue to receive the therapy at the discretion of the investigator.
Comparator	Investigator's choice: Docetaxel n=84 Paclitaxel n=84 Vinflunine n=87
Endpoint	Co-primary OS PFS

Randomisation was stratified according to ECOG-PS score (0 or 1 versus 2), presence of liver metastases (yes versus no), haemoglobin concentration (< 10 g/dL versus ≥ 10 g/dl), and time since the last dose of chemotherapy (< 3 months versus ≥ 3 months).

PD-L1 status was not a stratification factor (see Study KN052 for measurement of PD-L1 status, above).

Patients in the pembrolizumab group who had a complete response could discontinue treatment if they had received pembrolizumab for at least 24 weeks and for at least two doses beyond the time of initial complete response.

There was no planned cross-over.

Tumour imaging was scheduled for Week 9, followed by every 6 weeks during the first year and every 12 weeks thereafter. Response to treatment was assessed according to RECIST by means of blinded, independent, central radiologic (BICR) review.

Baseline characteristics

Table 11 details baseline characteristics.

Table 11: Study baseline characteristics

	Pembrolizumab N = 270	Chemotherapy N = 272
Median age (range)	67 (29-88)	65 (26-84)
Men	74%	74%
ECOG-PS		
0	44%	39%
1	53%	58%
2	1%	2%
Current/former smoker	61%	69%
Pure transitional cell features	69%	73%
PD-L1, 10+%	29%	34%
Primary in bladder or urethra	86%	86%
Visceral metastases	89%	86%
LN only	11%	14%
Liver metastases	34%	35%
Hb < 10 g/dL	16%	17%
Previous therapy		
< 3 months ago	38%	38%
Prior platinum therapy		
Cisplatin	73%	78%
Carboplatin	26%	21%
Other (such as oxaliplatin)	1%	1%
Setting of prior therapy		
Neoadjuvant	7%	8%
Adjuvant	4%	11%
First line	68%	58%
Second line	20%	22%
Third line	0%	<1%
Cystectomy	77%	81%

Flow of patients

Disposition of participants in trial are detailed in Table 12 below.

Table 12: Disposition of participants

	Pembrolizumab N = 270	Chemotherapy N = 272
Discontinued	60%	75%
Adverse events	6%	5%
Deaths	51%	58%
Loss to FU / withdrawal / etc	4%	12%
Ongoing in trial	40%	25%

Disposition for study medication is shown below in Table 13.

Table 13: Disposition for study medication

Started	Pembrolizumab N = 266	Chemotherapy N = 255
Discontinued	82%	99%
Adverse events	11%	16%
Clinical progression	9%	9%
Progressive disease	55%	51%
Doctor / patient withdrawal / etc	4%	22%
Complete response	3%	<1%
Ongoing treatment	18%	1%

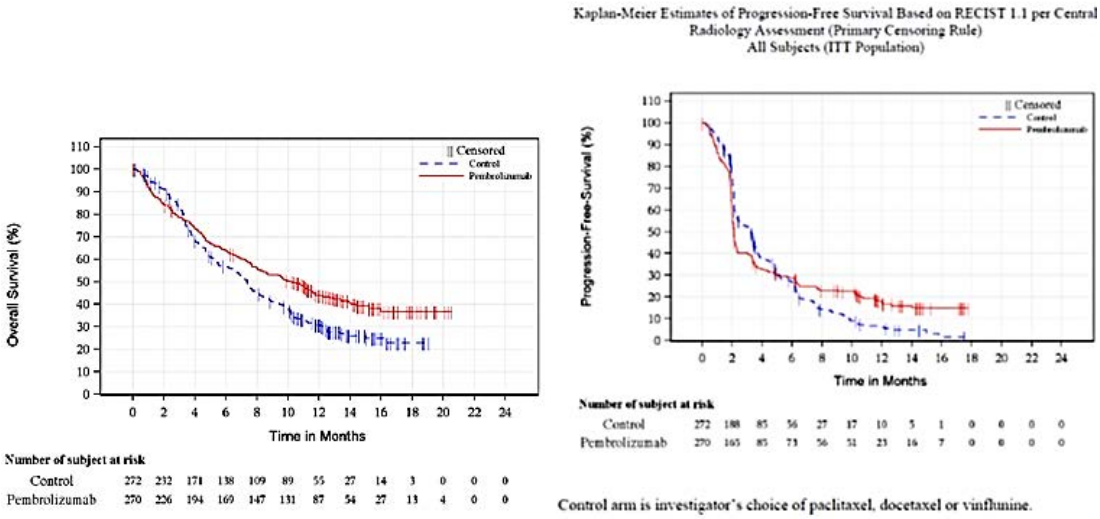
The median duration of follow-up was 14.1 months (range, 9.9 to 22.1). In the as-treated population, the median duration of study treatment was 3.5 months (range, < 0.1 to 20.0) in the pembrolizumab group and 1.5 months (range, < 0.1 to 14.2) in the chemotherapy group.

68 patients (25.2%) in the pembrolizumab group and 91 (33.5%) in the chemotherapy group received subsequent therapy, including 2 patients (0.7%) and 35 patients (12.9%), respectively, who received subsequent immunotherapy.

Results

Results for OS and PFS are plotted below.

Figure 1: Kaplan-Meier plots of OS and PFS



Overall survival rate, deaths and progression free survival (PFS) are tabulated below in Tables 14 and 15.

Table 14: Overall survival rate and deaths

	Pembrolizumab N = 270	Chemotherapy N = 272
Deaths	155 (57%)	179 (66%)
Death rate per 100 person-months	6.6%	9.3%
Survival rate at 6 months	64%	57%
Survival rate at 12 months	44%	31%

Table 15: OS and PFS

	Pembrolizumab N = 270	Chemotherapy N = 272
Md(OS)	10.3 months	7.4 months
HR(OS)	0.73 (0.59, 0.91); p = 0.002	
Md(PFS)	2.1 months	3.3 months
HR(PFS)	0.98 (0.81, 1.19)	

Md (OS) = 7.4 months in the control arm is consistent with historical data for single agent, second line treatment.

ORR and ORR by PD-L1 status are plotted below in Tables 16 and 17.

Table 16: ORR

	Pembrolizumab N = 270	Chemotherapy N = 272
ORR	21.1%	11.4%
Md(DOR), months (range)	NR (1.6+, 15.6+)	4.3 (1.4+, 15.4+)
DOR, 12+ months	68%	35%

Table 17: ORR by PD-L1 status

	Pembrolizumab	Chemotherapy
ITT	21.1%	11.4%
CPS>10%	20.3%	6.7%
CPS>1%	22.7%	8.3%
CPS<10%	19.4%	13.6%
CPS<1%	17.9%	13.6%

Results stratified by PD-L1 expression (with cut-points at 1% and 10%) did not show important differences in efficacy.

Safety

There were no major differences in the frequency and type of safety events for patients in the urothelial dataset (Studies KN045 and KN052) versus the Reference Safety Dataset (all indications for pembrolizumab).

The safety profile did not seem to be significantly influenced by previous platinum treatment or cisplatin ineligibility.

One fatal case of myositis was reported in Study KN052. This is the first reported with pembrolizumab (rare cases have been reported with other immunotherapies).

Data from Study KN045 in pembrolizumab versus chemotherapy groups showed that AEs leading to discontinuation of treatment were 6% versus 11%, respectively.

Risk management plan

See *Pharmacovigilance findings* above.

Risk-benefit analysis

Delegate's considerations

Cisplatin ineligible (Study KN052)

- After a median follow-up of 9.5 months, the ORR was 29%. This seems similar to the ORR of about 30% with carboplatin containing chemotherapy.[17]
- Median DoR with pembrolizumab was not reached; 82% of patients, who responded, had a DoR of at least 6 months. Median duration of response with carboplatin containing chemotherapy is about 6 months.
- Median OS was about 11 months; median OS with carboplatin containing chemotherapy is about 9 months.
- Responses occurred in all PD-L1 subgroups; responses were numerically higher in CPS > 10% subgroup.
- New therapies are needed for chemotherapy-ineligible patients; however these patients are not the patients enrolled in Study KN052. Instead, many of the patients in Study KN052 would have been eligible for carboplatin or single agent chemotherapy. The EMA has added the following statement to the Summary of Product Characteristics (SmPC): '*The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination or mono-chemotherapy. In the absence of comparative data, pembrolizumab should be used with caution in this population after careful consideration of the potential risk-benefit on an individual basis.*'
- There remains a lack of data on frail patients (for example, ECOG-PS 2+) who are ineligible for cisplatin or any chemotherapy.
- The safety profile was as expected.

Post platinum (Study KN045)

- There was a statistically significant gain in overall survival of about 3 months versus chemotherapy: 10 months versus 7 months; Hazard Ratio (HR) = 0.73 (0.59, 0.91).
- The safety profile was as expected; different AEs and lower frequency than with chemotherapy.
- The currently available data do not provide a basis to specify a PD-L1 CPS threshold for treatment.
- In the first 2 months, there was an excess of deaths in the pembro versus the chemo arm (43 versus 24). The Kaplan-Meier curves crossed-over at about 3 to 4 months. The EMA noted (in the EPAR) that patients with liver metastases and recurrence within 3 months of first line platinum chemotherapy had a higher risk of early death. The EMA have added a warning to the SmPC: '*Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In urothelial cancer, a higher number of deaths within 2 months were observed in pembrolizumab compared to chemotherapy*.'

[17] De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30(2):191-9

Note to indications

The cisplatin ineligible indication is based on a single arm study. There is no direct comparison of pembrolizumab to chemotherapy suitable for cisplatin ineligible patients (such as carboplatin). The indications should therefore include the following note: This indication is approved based on tumour response rate and duration of response in a single arm study. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Post-marketing requirements

The sponsor should report the results of the following studies (as a new application) as a condition of registration:

1. The two years of follow-up in Study KEYNOTE-052 entitled '*A Phase II clinical trial of pembrolizumab (MK-3475) in subjects with advanced/unresectable or metastatic urothelial cancer*'. Trial completion September 2018 and Final report submission: March 2019. This will provide data on the DoR at 2 years.
2. Study KEYNOTE-361 '*A Phase III randomised, controlled clinical trial of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy in subjects with advanced or metastatic UC*'. Trial completion: May 2021 and Final Report Submission: November 2021.

Summary of issues

Cisplatin ineligible 1L

Advanced or metastatic urothelial cancer is highly lethal.

The toxicities of cisplatin based chemotherapy are significant: treatment related deaths can occur and there are high rates of neutropaenia and associated sepsis; additional toxicities include nephropathy and neuropathy.

Patients ineligible for cisplatin are typically older patients with significant comorbidities such as renal impairment. There is significant unmet clinical need in this patient population.

Study KN052 (single-arm study, cisplatin ineligible, 1L) reported an ORR of 29%. These responses were durable: at least 6 months in 82% of patients who had a response.

Post-platinum, 2L

Study KN045 (randomised) reported an improvement in median OS of about 3 months (10 months versus 7 months) over investigator choice of chemotherapy (vinflunine, docetaxel, and paclitaxel). There was an excess of deaths in the pembrolizumab arm in the first 2 months, probably because of the delayed action of pembrolizumab versus chemotherapy, which could be important in patients who require rapid reduction of high tumour burden. This risk will be mitigated by statements in the PI.

Safety

No new safety concerns were identified for pembrolizumab in the setting of metastatic urothelial cancer (1L or 2L).

Proposed action

The Delegate had no reason to say, at this time, that the two proposed extensions of indications for Keytruda should not be approved.

Response from sponsor

Keytruda is registered in Australia, and is currently approved for a number of different indications, including melanoma, non-small cell lung carcinoma, head and neck squamous cell carcinoma, and classic Hodgkin lymphoma. This submission seeks to add two new indications:

> *Keytruda (pembrolizumab) is indicated for the treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing therapy. This indication is approved based on overall response rate and duration of response. Improvements in overall survival, progression-free survival, or health-related quality of life have not been established.*
>
> *Keytruda (pembrolizumab) is indicated for the treatment of patients with locally advanced or metastatic UC who have received platinum containing chemotherapy.*

These two indications are supported by two studies KEYNOTE-052 and KEYNOTE-045 (respectively).

Clinical data supporting this application

Study KEYNOTE-045

Study design

Study KEYNOTE-045 is a Phase III randomised, open label trial of pembrolizumab versus paclitaxel, docetaxel or vinflunine in subjects with progression or recurrence of UC following a first line platinum containing regimen for metastatic or inoperable locally advanced disease (that is, second line). The study randomised 542 patients to be treated with pembrolizumab 200 mg intravenous (IV) on Day 1 of each 3 week cycle (Q3W) (n = 270) OR either paclitaxel 175 mg/ m^2 IV, docetaxel 75 mg/ m^2 IV, or vinflunine 320 mg/m^2 IV Q3W (n = 272).

The primary outcome measures for this trial include OS and PFS as per RECIST version 1.1. Key secondary outcomes of this trial include ORR, PFS and ORR per modified RECIST 1.1.

Results summary

Efficacy findings from the total study population (n = 542) showed a clinically meaningful improvement in OS for subjects on pembrolizumab versus the control arm. As of the data cut-off date from the second interim analysis (7 September 2016), the median OS was 10.3 months (95% confidence interval (CI): 8.0, 11.8) for pembrolizumab compared with 7.4 months (95% CI: 6.1, 8.3) for the control arm (hazard ratio (HR) 0.73, p = 0.00224).

There was no statistically significant improvement in PFS for subjects in pembrolizumab versus the control arm. The median PFS was 2.1 months in the pembrolizumab arm and 3.3 months in the control arm. The PFS rate was 28.8% and 16.8% at 6 and 12 months, respectively, in the pembrolizumab arm and 26.8% and 6.2% in the control arm, suggesting that there is a stable and prolonged tail of the pembrolizumab Kaplan-Meier curve.

The median duration of response in subjects in the pembrolizumab arm was not reached as of the data cut-off date and 4.3 months in the control arm. Approximately twice as many subjects with response remained in response ≥ 6 months (pembrolizumab: 78%; control 40%) and ≥ 12 months (pembrolizumab: 68%; control 35%).

In subjects with UC who have progressed following platinum-based chemotherapy, pembrolizumab 200 mg Q3W treatment resulted in a statistically significant and clinically meaningful improvement in OS and ORR compared with chemotherapy agents paclitaxel, docetaxel, or vinflunine. The safety profile of pembrolizumab is remarkably more favourable than these chemotherapies, and is consistent with the established safety profile characterized from previous studies.

Study KEYNOTE-052

Study design

Study KEYNOTE-052 is a Phase II global, single-arm, multi-site, non-randomised, open-label trial, of pembrolizumab in patients with advanced, unresectable or metastatic UC who have not received prior systemic chemotherapy (that is, first line) and are ineligible for cisplatin based therapy. The study enrolled 370 subjects to be treated with pembrolizumab 200 mg IV on Day 1 of each 3 week cycle for up to 24 months and assessed for up to 3 years.

The primary endpoints are to evaluate the anti-tumour activity of pembrolizumab by ORR per RECIST 1.1 by blinded, independent, central radiology review in all subjects with results stratified by PD-L1 status.

Secondary Endpoints included DoR, PFS and OS at 6 and 12 months in all subjects, PD-L1 positive subjects and PD-L1 strongly positive subjects. Other secondary endpoints include evaluating the safety and tolerability of pembrolizumab as a 1L therapy for UC.

Results summary

The results of Study KEYNOTE-052 demonstrate compelling antitumor activity across the full spectrum of the cisplatin ineligible population. Treatment resulted in a clinically meaningful ORR of 29% (95% CI: 24%, 34%) as of the data cut-off date of 19 December 2016.

Responses were accompanied by unprecedented durability: DoR was not reached and the lower bound of the 95% CI of the median DoR was 11.1 months (95% CI 11.1, NR), which exceeds the upper bound of the 95% CI for chemotherapy, suggesting that the pembrolizumab response duration exceeds that which would be expected with chemotherapy. The ORR effect was observed consistently across population subgroups including among the elderly, the frail, and those with serious comorbid medical conditions. Complete responses were observed across age groups, including among the elderly subjects. Because Study KEYNOTE-052 included chemotherapy unfit subjects who would not have been candidates for a randomised clinical trial versus chemotherapy, this study is the largest conducted to date to the sponsor's knowledge among cisplatin ineligible patients with UC.

Conclusion

In conclusion, the sponsor agrees with the Delegate that the data that has been generated for Keytruda supports the proposed UC indications.

Advisory Committee Considerations[18]

The Delegate did not refer this application to the Advisory Committee on Prescription Medicines (ACM) for advice.

[18] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Keytruda pembrolizumab (rch) 50 mg powder for injection vial (AUST R 226597) and Keytruda pembrolizumab (rch) 100 mg/4 mL concentrated injection vial (AUST R 263932) in the Australian Register as follows:

- the amendment to the dosing regimen for the non-small cell lung carcinoma (NSCLC) indication for Keytruda containing pembrolizumab (rch)
- the registration of Keytruda containing pembrolizumab (rch) for the new indications:

  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. This indication is approved based on overall response rate and duration of response. 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.

Specific conditions of registration applying to these goods

1. The Keytruda pembrolizumab (rch) Core Risk Management Plan (RMP), version 15.0, dated 13 September 2017 (data lock point 31 March 2017) with Australian Specific Annex version 9.0, dated 3 November 2017, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. The sponsor should provide the results of the following studies (as a new application):

- The two years of follow-up in Study KEYNOTE-052 entitled 'A Phase II clinical trial of pembrolizumab (MK-3475) in subjects with advanced/unresectable or metastatic urothelial cancer'. Trial completion 09/2018 and Final report submission: 03/2019. This will provide data on the duration-of-response at 2 years.
- Study KEYNOTE-361 'A Phase III randomised, controlled clinical trial of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy in subjects with advanced or metastatic urothelial carcinoma'. Trial completion: 05/2021 and Final Report Submission: 11/2021

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 website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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