Cancer Drugs Fund

Managed Access Agreement

Pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable [TA522]

Company name: Merck Sharp & Dohme Ltd. (MSD)

Primary source of data collection: KEYNOTE-361

Secondary source of data collection: Public Health England routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set

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1 Purpose of data collection arrangement

1.1 The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable [TA522]. A positive recommendation within the context of a managed access agreement has been decided by the appraisal committee.

2 Commencement and period of agreement

2.1 This data collection arrangement shall take effect on publication of the managed access agreement. The data collection period for KEYNOTE-361 is anticipated to conclude November 2019 (analysis for the study is event driven). Full details relating to the study design, endpoints, and analysis plan can be found in Section 5. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

2.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in the addendum to NICE's methods and processes when appraising cancer technologies.

3 Patient eligibility

The patient eligibility for this Data Collection Arrangement has been updated in July 2018. In July 2018 the European Medicines Agency restricted the use of pembrolizumab for untreated urothelial carcinoma. It should now only be used in adults with high levels of PD-L1. For more information, see the summary of product characteristics for pembrolizumab.

People who started treatment under the previous patient eligibility criteria may continue without change to the funding arrangements in place for them.

3.1 The patient population to be treated during the managed access arrangement period is as follows: Adults with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

3.2 Key patient eligibility criteria, as per KEYNOTE-052 and KEYNOTE-361, for the use of pembrolizumab in the Cancer Drugs Fund include:

- Patient has histologically or cytologically documented transitional cell carcinoma of the urothelial tract
- Patient has disease that is either locally advanced (ie T4b any N or any T N2-3 disease) or metastatic (any T any N M1 disease)
- Patient has not received previous chemotherapy for inoperable locally advanced or metastatic urothelial cancer
- The patient has EITHER not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy for localised urothelial cancer OR, if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy for localised urothelial

cancer, has relapsed more than 12 months since completing the platinum-based chemotherapy*

* Patients meeting this criterion are eligible to be considered as treatment naïve for locally advanced/ metastatic disease but must satisfy all other criteria

- Patient has an ECOG performance status (PS) of 0-2.

  Note: treatment of patients with performance status 2 with pembrolizumab should only proceed with caution as there is limited safety data on PS 2 patients with urothelial carcinoma treated with pembrolizumab

- Patient is ineligible for platinum-based chemotherapy for one of the following reasons:
  - impaired renal function (EDTA-assessed glomerular filtration rate >30 and <60 mls/min)
  - hearing loss of 25 dB as assessed by formal audiometry
  - NCI CTCAE grade 2 or worse peripheral neuropathy
- Tumour expresses PD-L1 with a combined positive score of 10 or more. CPS is defined as ≥10% of tumour cells and mononuclear inflammatory cells within tumour nests and adjacent supporting stroma expressing PD-L1 at any intensity. The CPS is thus the addition of the numbers of positive tumour and mononuclear inflammatory cells and then this sum is divided by the number of all tumour cells, the result being expressed as a percentage (the maximum of which is set at 100%)
- Patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless it was received as part of the pembrolizumab compassionate access scheme for this indication and the patient meets all other criteria listed here
- Patient has no symptomatically active brain metastases or leptomeningeal metastases

- Pembrolizumab is being given as monotherapy and will commence at a fixed dose of 200 mg per infusion
- A formal medical review as to whether treatment with pembrolizumab should continue or not will be scheduled to occur at least by the end of the third cycle of treatment
- Patient will be treated until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment, whichever is the sooner
- The patient will receive a maximum treatment duration with pembrolizumab of 2 years
- Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle
- Pembrolizumab will otherwise be used as set out in its Summary of Product Characteristics (SPC).

3.3 MSD is not aware of any data that could contribute to the data collection arrangement described within this document for patients who started pembrolizumab before it was recommended by NICE.

3.4 It was originally estimated a maximum of 635 patients would to receive treatment per annum. Following the updated marketing authorisation a maximum of 185 patients with high PD-L1 expression are estimated to receive treatment per annum.

3.5 The expected mean duration of treatment, based on the KEYNOTE-052 trial, is 5.27 months or 8.20 cycles. The maximum treatment duration would be 2 years. The company's mean estimate of overall survival is aligned to the company's submission and is 36 months for the high PD-L1 positive population.

4 Area(s) of clinical uncertainty

4.1 The evidence base is limited and does not allow for comparison between pembrolizumab and carboplatin plus gemcitabine directly. In the absence of head-to-head data the prediction model methodology (simulated treatment

comparison) and resulting indirect treatment comparison (ITC), allow for estimates of comparative efficacy that are more valid than those that could be obtained from a naïve comparison. This was due to the study design on KEYNOTE-052, a phase II, single arm non-comparative clinical trial. This method of population adjusted indirect comparison is subject to weakness and clinical uncertainty. Clinical areas of uncertainty include:

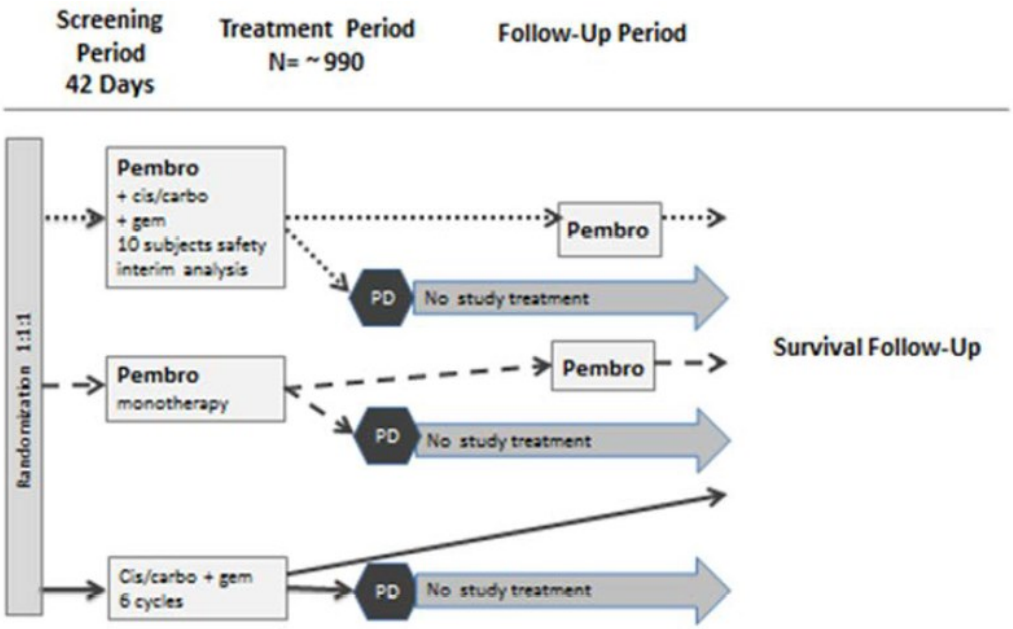
- Magnitude of overall survival (OS) and progression-free-survival (PFS) benefit of pembrolizumab as compared with the UK standard of care for metastatic/ advanced urothelial cancer patients who are cisplatin ineligible (e.g. hazard ratio, duration of effect).

5 Source(s) of data collection

KEYNOTE-361 (NCT02853305)

5.1 The primary source of data collection during the managed access agreement period will be KEYNOTE-361. This is an ongoing phase III randomised control trial designed to determine the efficacy and safety of pembrolizumab versus chemotherapy in patients with advanced or metastatic urothelial carcinoma. This study will report PFS and OS as the primary objectives. In addition, safety and tolerability will be assessed, and EuroQoL EQ-5D among all subjects will be reported. Randomisation was stratified by PD-L1 expression (CPS ≥10% or CPS <10%), and the high PD-L1 status population (CPS ≥10%) comprises approximately a third of the full trial population. Full details are summarised in the figure and table below.

KEYNOTE-361 study design



PD=progressive disease; pembro=pembrolizumab; cis=cisplatin; carbo=carboplatin; gem=gemcitabine

Summary of KEYNOTE-361 trial characteristics

Population	Male and female subjects with advanced/unresectable (inoperable) or metastatic urothelial carcinoma of the renal pelvis, ureter [upper urinary tract], bladder, or urethra at least 18 years old
Study design	~990 Phase III, global, multi-centre, randomised (1:1:1), three-arm, unblinded open-label clinical trial
Study arms	Randomised 1:1:1 ratio Pembrolizumab (MK-3475) Pembrolizumab with chemotherapy (cisplatin or carboplatin with gemcitabine) Chemotherapy (cisplatin or carboplatin with gemcitabine)
Cross over	The protocol does not allow subjects to cross over to pembrolizumab if they have progression on chemotherapy
Primary endpoint	Progression-free survival (PFS) for combo vs chemo only in the all-subject population using BICR and RECIST 1.1 to determine disease progression, and overall survival (OS) for combo vs chemo only in the all-subject population and OS for pembrolizumab only vs chemo only in the PD-L1 CPS ≥10% and all-subject population.
Selected secondary end-points	Objective response rates (ORR), disease control rate (DCR), and duration of response (DOR) using BICR and RECIST 1.1 to determine disease progression, for both the PD-L1 CPS ≥10% population and the all-subject population. The proportion of subjects who are progression-free at specific time points will also be assessed
Stratification	Treatment allocation/randomization will be stratified according to the following factors: Chemotherapy drug: Investigator choice cisplatin or carboplatin PD-L1 expression (CPS ≥10% or CPS <10%)
Key inclusion criteria	Have a histologically or cytologically confirmed diagnosis of advanced/unresectable (inoperable) or metastatic urothelial carcinoma of the renal pelvis, ureter [upper urinary tract], bladder, or urethra. Both transitional cell and mixed transitional/non-transitional cell histologies are allowed, but transitional cell carcinoma must be the predominant histology Have measurable disease based on RECIST 1.1 as determined by the local site investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions Have received no prior systemic chemotherapy for advanced or metastatic urothelial carcinoma, with the following exceptions: a. Neoadjuvant platinum-based chemotherapy with recurrence >12 months from completion of therapy is permitted. b. Adjuvant platinum-based chemotherapy following radical cystectomy with recurrence >12 months from completion of therapy is permitted

Other data

5.2 NHS England's Blueteq database captures the CDF population. NHS England shares Blueteq data with Public Health England for the CDF evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and Public Health England.

5.3 Public Health England identifies, collects, collates, quality-assures and analyses large population-level datasets for specific diseases and conditions, including cancer. These datasets include the Systemic Anti-cancer Therapy (SACT) dataset, which is a mandated dataset as part of the Health and Social Care Information Standards. Public Health England will use the routinely-captured data collected during the period of the data collection arrangement to provide analyses as defined in sections 6.3 and 7.3

5.4 Public Health England will collect data, including via the SACT dataset, alongside the primary source of data collection.

KEYNOTE-052 (NCT02335424).

5.5 Additional follow up will be available from the KEYNOTE-052 clinical trial as per the company's evidence submission to NICE. A final study report is expected April 2019.

6 Outcome data

KEYNOTE-361 clinical trial

6.1 As specified above, the endpoints OS and PFS will be collected in KEYNOTE-361. The primary objective relates to the OS hypotheses for pembrolizumab monotherapy versus chemotherapy only. Secondary objectives of KEYNOTE-361 include an estimate of PFS at milestone time-points (6 months, 12 months, 18 months, and 24 months) in PD-L1 positive tumours (PD-L1 CPS ≥10% using RECIST 1.1 as assessed by BICR in the following treatment groups: a) Pembro only/ b) Combo/ c) Chemo only.

6.2 These data will allow for comparative estimates of relevant endpoints (OS and PFS for people with high levels of PD-L1) versus chemotherapy alone,

which was not possible from KEYNOTE-052. The design of KEYNOTE-361 means that randomisation will not be broken when considering the cisplatin ineligible and high PD-L1 population, as patients were identified and randomised after cisplatin ineligibility and PD-L1 status were confirmed. Therefore, within the relevant treatment arm effect modifiers and confounding factors should be balanced.

6.3 Subgroup analyses will be required and are described in Section 7.1.

Other data, including SACT

6.4 Data will be collected via Public Health England's routine population-wide datasets, including the SACT dataset. This collection will support data collected in the clinical trial. During the managed access agreement period, Public Health England will collect data to provide information on overall survival and duration of therapy.

7 Data analysis plan

KEYNOTE-361 Clinical trials

7.1 The interim PFS/OS analysis is event-driven. The first interim analysis will be carried out if 1) all subjects are enrolled; and 2) approximately 347 PFS events have been observed in the combo' and chemo only arms in all subjects (152 in combo and 195 in chemo only).

7.2 The second interim analysis will be carried out if approximately 357 OS events have been observed among the combo and chemo only treatment arms in all subjects (158 and 199 in combo' and chemo only arm respectively). The information fraction of OS events observed is around 0.85. This is projected to occur around 28 months after the trial starts.

7.3 Once available MSD will provide the relevant outcome data; there will also be a commitment to collect and provide follow-up survival data after trial completion.

7.4 As of the 20th March 2018 a total of [redacted] patients have been randomised across [redacted] sites within KEYNOTE-361. Within England specifically, [redacted]

are actively recruiting, and have thus far enrolled [redacted] patients. Across the global trial, there are approximately [redacted] patients outstanding with a target enrollment of 990 patients. The overall monthly recruitment rate is [redacted] patients (December 2017 to February 2018), which would suggest that recruitment will be complete by [redacted]. After taking into account overall patient numbers in the NHS and the remaining number of patients left to recruit worldwide, it is anticipated that admitting pembrolizumab to the Cancer Drugs Fund in this indication is unlikely to adversely affect patient accrual to KEYNOTE-361 in England.

Other data

7.5 At the end of the data collection period Public Health England will provide a final report for NHS England based on routinely collected population-wide data, including that collected via SACT. The report will present depersonalised summary data, including the total number of patients starting treatment, overall survival and treatment duration. The necessary controls will be put in place to ensure that patient confidentiality is not put at risk. The report will be shared with MSD in advance of the planned review of guidance. Completeness of SACT dataset reporting will be shared with NHS England and MSD on a quarterly basis.

7.6 At a minimum, an annual report will be provided by any other organisation collecting the data, and should be submitted to NHS England to check whether the data collection is on track, and to establish whether any additional action is needed.

8 Ownership of the data

8.1 For all clinical trial data listed above, MSD will be the owner.

8.2 The data analysed by Public Health England is derived from patient-level information collected by the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of Public Health England. Access to the data was facilitated by the Public

Health England Office for Data Release. MSD will not have access to the Public Health England patient data, but will receive de-personalised summary data, with appropriate controls in place to cover this. Public Health England will provide a report to NHS England and the MSD at the end of the managed access period.

8.3 The SACT dataset is a mandated dataset as part of the Health and Social Care Information Standards. All necessary governance arrangements through SACT, and other datasets brought together by Public Health England, have been established with NHS Trusts and NHS England.

8.4 Blueteq's CDF system data is owned by NHS England. NHS England is responsible for implementing Blueteq data collection and generally for analysis of these data. NHS England, however, shares Blueteq data with Public Health England for CDF evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and Public Health England.

9 Publication

9.1 The details/authorship of any proposed publications arising from these studies will be planned with the publication of the final study results.

9.2 Publication of the analysis results of data collected by Public Health England, including through SACT and the data from Blueteq's CDF system, will be planned and implemented by Public Health England.

Commercial Access Agreement

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The contents of this document have been redacted as they are confidential

- A glossary of terms relating to managed access agreements in the Cancer Drugs Fund is available here.