Cancer Drugs Fund

Managed Access Agreement

Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence [ID1266]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Pembrolizumab for the adjuvant treatment of resected melanoma with high risk of recurrence (ID1266)

Company name: Merck, Sharp and Dohme

Primary source of data collection: KEYNOTE-054

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 the adjuvant treatment of resected melanoma with high risk of recurrence [ID1266]. 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 estimated availability of data for distant metastases free survival (DMFS) is [redacted] and for overall survival (OS) is [redacted] (analysis for the study is event driven). The results of the analysis are anticipated to be available within [redacted] months of the above dates. It is therefore expected that the data collection period will conclude by December 2021. 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

3.1 Pembrolizumab has been recommended for use in the Cancer Drugs Fund for adjuvant treatment of melanoma with lymph node involvement in adults who have had complete resection.

3.2 Key patient eligibility criteria for the use of pembrolizumab in the Cancer Drugs Fund include:

- Patient has melanoma which has been staged as stage III disease (according to the AJCC 8th edition) that has been completely resected either via sentinel lymph node biopsy ('sentinel lymphadenectomy') or when indicated via completion lymph node dissection
- Clinician has discussed with the patient the benefits and toxicities of adjuvant pembrolizumab in stage III disease in relation to the risk of disease relapse if a routine surveillance policy is followed
- Patient has an ECOG performance status of either 0 or 1
- Pembrolizumab will be continued for a maximum of 12 months (or a maximum of 18 cycles if given 3-weekly) from the start of treatment in the absence of disease recurrence, unacceptable toxicity or withdrawal of patient consent

- 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 first 9 weeks of treatment

- Treatment breaks of up to 12 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow any immune toxicities to settle

- Pembrolizumab is to be otherwise used as set out in its Summary of Product Characteristics

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 The annual estimate of the number of patients expected to be eligible for treatment with adjuvant therapy is around [redacted] in England. NHS England anticipates that approximately 75% of patients eligible for treatment with adjuvant therapy will choose to use a PD-L1 inhibitor.

3.5 Pembrolizumab as adjuvant treatment is administered until disease recurrence or unacceptable toxicity, or completion of one year of treatment. The median number of cycles on pembrolizumab therapy in KEYNOTE-054 is 18 per patient treated with pembrolizumab 200mg every three weeks. The estimated mean overall survival for a patient with stage III melanoma following lymph node resection from the cost-effectiveness model is 9.8 years, following treatment with pembrolizumab.

4 Area(s) of clinical uncertainty

4.1 The appraisal committee concluded the key areas of uncertainty relate to the distant metastases free survival (DMFS) and overall survival (OS) benefit of pembrolizumab compared to routine surveillance, in the population under consideration. It also concluded there is uncertainty regarding the use of subsequent treatments in the metastatic setting and the role of rechallenge with pembrolizumab.

5 Source(s) of data collection

KEYNOTE-054

5.1 The primary source of data collection during the managed access agreement period will be KEYNOTE-054. KEYNOTE-054 (NCT02362594) is an international, double blind, placebo-controlled phase III study of the EORTC Melanoma Group, evaluating adjuvant therapy with pembrolizumab (KEYTRUDA) versus placebo after complete resection of stage IIIA (>1mm lymph node metastasis), IIIB and IIIC melanoma (classified using the AJCC 7th edition). The primary endpoint was recurrence-free survival (RFS) which has been met and reported.[1] RFS is defined as the time from randomisation until date of first recurrence (local, regional or distant metastasis) or death from any cause. KEYNOTE-054 will continue to the next endpoint, distant metastases free survival (DMFS), followed by overall survival (OS), which are event driven endpoints. DMFS is defined as the time from randomisation to distant metastases or death from any cause. Part 2 of the KEYNOTE-054 study involves crossover or re-challenge with pembrolizumab treatment, following disease recurrence after adjuvant treatment. To be eligible for pembrolizumab re-challenge, patients must have completed the full year of adjuvant treatment and experienced disease recurrence >6 months later. Patients eligible for rechallenge or cross-over could receive treatment with pembrolizumab until progression/recurrence or up to two years.

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.

[1] Eggermont AM, Chiarion-Sileni V, Grob J-J, Dummer R, Wolchok JD, Schmidt H, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. New England Journal of Medicine. 2016;375(19):1845-55.

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.

5.5 Data will be collected via Blueteq on the performance status of patients and the proportions of patients with Stage IIIA, Stage IIIB, Stage IIIC and Stage IIID (according to the AJCC 8th edition) disease who receive pembrolizumab in the Cancer Drugs Fund.

6 Outcome data

Clinical trial

6.1 As specified above, the endpoints DMFS and OS continue to be collected in KEYNOTE-054. KEYNOTE-054 will continue to the next endpoint, DMFS, followed by OS. Data is also being collected in part two of the study. This data should resolve the clinical uncertainty, as identified by the NICE Appraisal Committee, regarding the improvement in DMFS and OS in the patient population covered by this managed access arrangement.

Other data, including SACT

6.2 These data will allow for relevant outcomes to be reported for pembrolizumab and routine surveillance, the current relevant comparator for this patient population.

6.3 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

time to next treatment and the distribution of subsequent therapies given. Notification of applications via Blueteq will be made available by NHS England for use of adjuvant pembrolizumab, and for any subsequent stage IV therapies. Data collection will continue unless it is determined by the SACT Operational Group that no meaningful data will be captured during the period of data collection.

7 Data analysis plan

Clinical trials

7.1 The details and timeframe of the data analyses are as follows:

KEYNOTE-054: The point at which to conduct final analysis of DMFS and OS are protocol driven, namely when [redacted] (distant metastases or deaths) events and [redacted] deaths have occurred. This study is an event driven study; therefore accrual rates of events and deaths are variable. However, based on current projections of reaching the required number of events/deaths to initiate the final analysis of DMFS and OS, the proposed time lines for this study are as follows:

- Analysis of DMFS is expected to take place in [redacted].
- Analysis of OS is expected in [redacted].

Subgroup analyses will be provided for both DMFS and OS for a PD-L1 population. An analysis of data from part two of the study is expected [redacted]. The results of the analysis are anticipated to be available within [redacted] months of the above dates.

Other data

7.2 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, time to next treatment and distribution of subsequent therapies given. 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.

7.3 Completeness of SACT dataset reporting will be shared with NHS England and MSD at regular intervals during the data collection period. Public Health England will provide summary results for time to next treatment and distribution of subsequent therapies given to NHS England and MSD on an annual basis, to check the continuing validity of the period of the data collection arrangement.

7.4 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. It should be noted that KEYNOTE-054 is a study of the EORTC Melanoma Group but for the purposes of this agreement, MSD will serve as the data 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.

10 Data protection

10.1 The terms of clause 7 (data protection) of the managed access agreement, as apply between NHS England and MSD, shall also apply between the parties to this data collection arrangement in relation to the performance of their obligations under this data collection arrangement

11 Equality considerations

11.1 Do you think there are any equality issues raised in data collection?

☐ Yes ☒ No

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.