Cancer Drugs Fund

Managed Access Agreement

Avelumab for treating metastatic merkel cell carcinoma

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Avelumab for treating metastatic Merkel cell carcinoma (ID1102)

Company name: Merck

Primary source of data collection: Ongoing clinical study (JAVELIN 200 Part B cohort)

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

NICE Agreement Manager	Linda Landells, Associate Director
NHS England Agreement Manager	Peter Clark, CDF Clinical Lead
Public Health England Agreement Manager	Martine Bomb, Head of Data Projects
Merck Agreement Manager	Ceilidh Stapelkamp, Head of HEOR, UK & ROI

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 avelumab for treating metastatic Merkel cell carcinoma [ID1102] (to be updated with TA number after final guidance has been published). A positive recommendation within the context of a managed access agreement has been decided by the appraisal committee for the chemotherapy-naïve population. This agreement sets out the proposal for reduction of uncertainty in Part B data with the maturing JAVELIN 200 trial.

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 of Part B cohort for JAVELIN 200 study is anticipated to conclude in May 2019. The process for

exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start. The company anticipates that data collection will end in May 2019, and the revised cost-effectiveness analysis will be available to submit to NICE in February 2020. These timelines align with the European Medicines Agency commitment to submit the study report for the primary analysis of Part B JAVELIN 200 cohort to the European Medicines Agency by January 30th 2020 (see section 5.1).

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 The population to be treated via the Cancer Drugs Fund during this managed access arrangement period are people with metastatic Merkel cell carcinoma who are chemotherapy-naïve. This is a subset of the population covered by the marketing authorisation.

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

- Confirmed histological or cytological diagnosis of Merkel cell carcinoma
- Patient has metastatic disease
- Patient is treatment naïve to any systemic anti-cancer therapy for Merkel cell carcinoma and in particular to any immune checkpoint blockade therapies
- Patient has an ECOG performance status of either 0 or 1. A patient with a performance status of 2 is not eligible for avelumab

- If a patient has brain metastases, then these have been treated and are stable
- Avelumab is to be used as monotherapy only
- Avelumab is to be continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment. Patients with radiological disease progression not associated with significant clinical deterioration (defined as no new or worsening symptoms **and** no change in performance status for greater than 2 weeks **and** no need for salvage therapy: all 3 conditions must apply) can continue treatment
- A formal medical review as to whether treatment with avelumab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
- Treatment breaks of up to 12 weeks beyond the expected cycle length of avelumab are allowed but solely to allow immune toxicities to settle
- Avelumab is to be otherwise used as set out in its Summary of Product Characteristics

3.3 Whilst precise numbers are difficult to forecast, Merck anticipates approximately 40 chemotherapy-naïve metastatic Merkel cell carcinoma patients may be treated in the Cancer Drugs Fund per annum. This estimate is based upon published incidence figures and an assumption about the proportion of patients with metastatic Merkel cell carcinoma who will be chemotherapy-naïve.

3.4 Merck anticipate that the mean time on treatment per treatment-naïve patient will be between 9-12 months (based on data from the JAVELIN 200 trial and economic modelling by both the company and the ERG).

4 Area(s) of clinical uncertainty

4.1 The Appraisal Committee have noted the following key sources of clinical uncertainty in the treatment-naïve cohort data:

- The absence of a randomised comparator arm in the JAVELIN trial
- A naïve comparison with observational data
- Small numbers of patients with short follow-up in the JAVELIN trial (specifically immaturity of survival (progression free and overall) estimates)

4.2 Merck acknowledge that the absence of a randomised comparator arm within the study is a source of uncertainty in the JAVELIN 200 trial. However, this cannot be addressed by data collection in the CDF. Merck have attempted to compensate for this uncertainty through the conduct and utilisation of high quality observational data to estimate the outcomes of patients who are treated with the standard of care (see Section 6.2). UK expert opinion confirms these studies provide generalisable estimates of outcomes with current standard of care. The underlying datasets cannot be improved upon because avelumab has changed/is changing the standard of care globally.

4.3 Merck acknowledge the additional uncertainties relating to the small numbers of patients and limited follow up in patients who are chemotherapy-naïve in the metastatic setting; recruitment is ongoing in Part B of the JAVELIN 200 trial. The Cancer Drugs Fund will allow patients with metastatic Merkel cell carcinoma who are chemotherapy-naïve access to avelumab whilst the JAVELIN 200 trial matures and reduces these uncertainties.

5 Source(s) of data collection

Clinical trial

5.1 The primary source of data during the managed access arrangement period is the maturing Part B cohort of the JAVELIN 200 trial. The table below provides the anticipated data cuts for Part B in the coming 2 years.

Table 1: Anticipated analyses of Part B of JAVELIN 200 trial

Cut-off date	Total patients enrolled	Maturity	Headline results	Patient level data available	Analyses complete (e.g. remodeling)
26 September 2017	N=74	N=50 with at least 13 weeks follow up	Mid December 2017	Late December 2017	March 2018
August 2018	N=112 (fully recruited)	N=112 with at least 6 months follow up	December 2018	December 2018	March 2019
May 2019 (primary analysis)	N=112 (fully recruited)	N=112 with at least 15 months follow up	September 2019	September 2019	February 2020

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 7.2

5.4 Public Health England will collect data, including the SACT dataset, alongside the primary source of data collection (JAVELIN 200 Part B trial).

6 Outcome data

Clinical trial

6.1 The JAVELIN 200 trial will collect and report data as per the study protocol and the EMA post-marketing requirement. After the final data cut (May 2019) highlighted in Table 1, individual patient level data will be used to update projections of survival and cost-effectiveness analyses to confirm the original projections in the treatment-naïve population.

Other data, including SACT

6.2 No additional data will be collected on the comparators.

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 overall survival and duration of therapy.

7 Data analysis plan

Clinical trial

7.1 Interim analyses (September 2017 and approximately August 2018) for the chemotherapy-naïve cohort in the JAVELIN 200 study will report on efficacy parameters for subjects with at least 13 weeks of follow-up including: best overall response, duration of response, progression free survival, overall survival, durable response rate, safety overview. No subgroup or biomarker data will be available in these interim analysis. Final analysis will following the analysis plan outlined in the trial protocol will be performed after the last subject enrolled has reached a minimum of 15 months follow-up including

efficacy parameters as noted above, in addition subgroup analyses will be performed and safety analyses. See Table 1 in Section 5.1.

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 the SACT dataset. 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 Merck in advance of the planned review of guidance. Completeness of SACT dataset reporting will be shared with NHS England and Merck on a quarterly basis.

8 Ownership of the data

8.1 For all clinical trial data listed above, Merck 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. Merck 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 at the end of the managed access period, which will be shared with Merck.

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 JAVELIN 200 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, alongside the primary data source will be planned by Public Health England. Merck will be given access to the report produced for NHS England for the review of the appraisal before the planned start of the review, or at least 28 days prior to publication (whichever is earlier), in order to prepare for media enquiries.

9.3 Publication of the analysis results of Blueteq's CDF system data collected alongside the primary data source will be planned by NHS England. Merck will be given access to the report produced for the review of the appraisal before the planned start of the review, or at least 28 days prior to publication (whichever is earlier), in order to prepare for media enquiries.

Commercial Access Agreement

Avelumab for treating metastatic merkel cell carcinoma

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.