Cancer Drugs Fund

Managed Access Agreement

Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [ID1547]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Avelumab with axitinib for untreated advanced renal cell carcinoma (ID1547)

Company name: Merck[1], Pfizer[2] (Merck and Pfizer are in an alliance for the co-promotion of avelumab)

Primary source of data collection: Ongoing clinical Trial (JAVELIN Renal 101 study)

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

NICE Agreement Manager	Brad Groves, Associate Director, Managed Access
NHS England and NHS Improvement Agreement Manager	Peter Clark, CDF Clinical Lead
Public Health England Agreement Manager	Rebecca Smittenaar, Analytical Lead
Merck Agreement Manager	Amerah Amin, Market Access and Pricing Director, UK & ROI
Pfizer Agreement Manager	Susan Donaldson, Head of Health & Value

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 with axitinib for

[1] Merck Serono Limited as the manufacturer and marketing authorisation holder of avelumab (BAVENCIO®)

[2] Pfizer UK Limited as the sponsor of the JAVELIN Renal 101 trial.

untreated advanced or metastatic renal cell carcinoma (ID 1547) (to be updated with TA number after final guidance has been published). A positive recommendation within the context of a managed access agreement (MAA) has been decided by the appraisal committee. This agreement sets out the proposal for reduction of uncertainty with the maturing JAVELIN Renal 101 trial.

2 Commencement and period of agreement

2.1 This data collection arrangement shall take effect on publication of the managed access agreement.

2.2 The data collection period for JAVELIN Renal 101 is anticipated to conclude in [redacted]. Estimated dates for data collection, reporting and submission for CDF guidance review are:

End of data collection (primary source)	[redacted]
Data available for development of company submission	[redacted]
Anticipated company submission to NICE for Cancer Drugs Fund review	March 2024

2.3 Merck anticipate the results from the additional data collected during the Cancer Drugs Fund period will be incorporated into an evidence submission and if appropriate, the updated economic model, by March 2024.

2.4 Merck acknowledge their responsibility to adhere as closely as possible to the timelines presented in the document.

2.5 NICE will, as far as is practicable, schedule a Cancer Drugs Fund review into the technology appraisal work programme to align with the estimated dates for the end of data collection. The review will use the process and methods in place at the time the invitation to participate in the guidance review is issued, which will be no earlier than 4 weeks prior to the anticipated company submission date. For further details of the expected timelines for the Cancer Drugs Fund guidance review see 6.27 of the technology appraisal process guide.

2.6 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the end of data collection and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the Cancer Drugs Fund guidance review timelines described in NICE's guide to the processes of technology appraisal.

2.7 The company is responsible for paying all associated charges for a review. Further information is available on the NICE website.

2.8 The company must inform NICE and NHS England and NHS Improvement of any anticipated changes to the estimated dates for data collection at the earliest opportunity.

2.9 Any changes to the terms or duration of any part of the data collection arrangement must be approved by NICE and NHS England and NHS Improvement.

2.10 If data collection is anticipated to conclude earlier than the estimated dates for data collection, for example due to earlier than anticipated reporting of an ongoing clinical trial, the company should note:

- Where capacity allows, NICE will explore options to reschedule the Cancer Drugs Fund guidance review date to align with the earlier reporting timelines.
- It may be necessary to amend the content of the final SACT or real-world data report (for example if planned outputs will no longer provide meaningful data).

2.11 If data collection is anticipated to conclude later than the estimated dates for data collection, the company should note:

- The company must submit a written request to NICE and NHS England and NHS Improvement, with details of the extension requested, including an explanation of the factors contributing to the request.
- It may be necessary for the company to take action to mitigate the impact of any delay, and reduce any risks of further delays.
- In the event of an extension, it may not be possible to amend the date of the final SACT or real-world data report, although NICE will explore options with Public Health England to provide data over the extended period.

2.12 NICE and NHS England and NHS Improvement may consider the data collection agreement no longer valid, and withdraw the technology from the Cancer Drugs Fund for the following, non-exhaustive, grounds:

- The primary sources of data are delayed, without reasonable justification.
- The primary sources of data will not report outcome data for an interim review.
- The primary sources are unlikely to report outcome data that could resolve the uncertainties identified by the technology appraisal committee.
- Amendments are made to the marketing authorisation.

3 Patient eligibility

3.1 Key patient eligibility criteria for the use of avelumab and axitinib in the Cancer Drugs Fund include:

- Application is made for the first cycle of systemic anti-cancer therapy by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- Prescribing clinician is fully aware of the management of and the treatment modifications that may be required for immune-related adverse reactions due to checkpoint inhibitor treatments including pneumonitis, colitis, nephritis, endocrinopathies and hepatitis
- Patient has unresectable locally advanced or metastatic renal cell adenocarcinoma (RCC)
- Risk status is assessed using the international metastatic RCC database consortium (IMDC) system
- Patient is either completely treatment naïve for systemic therapy for RCC or if the patient has received prior systemic therapy in the context of adjuvant/neoadjuvant therapy, then such treatment was completed ≥12 months previously
- Patient has an ECOG performance status of 0 or 1
- Patient has no symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control
- Patient is to be treated until loss of clinical benefit or excessive toxicity or patient choice, whichever is the sooner. If either avelumab or axitinib has to be permanently discontinued on account of toxicity, treatment with the other drug can be continued as monotherapy as long as there is no evidence of progressive disease.

- Avelumab and axitinib will otherwise be prescribed and administered as outlined in the avelumab summary of product characteristics and in the axitinib summary of product characteristics (SPC)

- A formal medical review to assess the tolerability of treatment with avelumab and axitinib will be scheduled to occur at least by the start of the 3rd 4-weekly cycle of treatment and thereafter on a regular basis

- Treatment breaks of up to 12 weeks beyond the expected 4-weekly cycle length are allowed but solely to allow any toxicities to settle

- That if the disease progresses on the avelumab and axitinib combination and further systemic therapy is appropriate, the next line of treatment will be chosen from those options which are routinely commissioned to be used after VEGF- or VEGFR-targeting and immune-modulating therapies.

3.2 An Early Access to Medicines Scheme (EAMS) for avelumab and axitinib in advanced RCC has been operational since August 2019

3.3 As of 26th May 2020 [redacted] in England and Wales have received avelumab and axitinib for the treatment of advanced RCC. These early access patients will be included as part of the SACT data collection agreement.

3.4 The estimated patient numbers per year for this technology within the Cancer Drugs Fund are:

As estimated by the company	Year 1: 197 Year 2: 565 Year 3: 1,081

As estimated by NICE Resource Impact Assessment team	Year 1: 398 Year 2: 637 Year 3: 637

4 Area(s) of clinical uncertainty

4.1 The appraisal committee identified the following key areas of clinical uncertainty:

1. the immaturity of the overall survival data and the companies' approach to modelling overall survival over the long term
2. the lack of data on whether the treatment is effective for non-clear-cell disease and
3. the companies' methods for adjusting both the costs and benefits of subsequent treatments to reflect NHS practice.

4.2 The committee concluded that further data collection within the Cancer Drugs Fund could resolve uncertainty relating to the immaturity of the overall survival data and lack of data on whether the treatment is effective for non-clear-cell disease. Please refer to the Final Appraisal Document for a full description of the clinical uncertainty.

5 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	○ Ongoing JAVELIN Renal 101 study
Secondary sources	○ Systemic Anti-Cancer Therapy (SACT) dataset ○ NHS England and NHS Improvement's Blueteq data

Description of sources

5.1 JAVELIN Renal 101 is an ongoing Phase 3, multinational, multicentre, open-label, parallel two-arm, randomised (1:1) study, designed to assess the efficacy, safety and tolerability of avelumab plus axitinib (also referred to as the 'combination arm' or 'combination treatment') versus sunitinib for the first-line treatment of aRCC (including metastatic disease) [clinicaltrials.gov: NCT02684006]. JAVELIN Renal 101 aims to demonstrate that avelumab plus axitinib is superior to sunitinib monotherapy in prolonging PFS or OS in the first-line treatment of patients with aRCC.

Table 1 JAVELIN Renal 101 clinical trial

JAVELIN Renal 101 – total population, n = 886 patient with previously untreated aRCC across all risk groups)
Description: Multicentre, open-label, randomised phase III study, with avelumab 10 mg/kg* intravenous infusion Q2w combined with axitinib 5 mg twice daily (BD)
Primary endpoint: Co-primary endpoints of BICR-assessed PFS in patients with PD-L1 positive tumours and OS in patients with PD-L1 positive tumours. A gatekeeping procedure was used to allow further testing of PFS and OS in patients irrespective of PD-L1 expression. According to the statistical analysis plan, if PFS and/or OS was statistically significant in the PD-L1-positive group, PFS and/or OS in the entire study population was to be analysed for statistical significance.
Secondary endpoints: BICR-assessed PFS, in in the overall population, irrespective of PD-L1 expression; OS in patient unselected for PD-L1 expression; Objective response (OR), Disease control (DC); Time to response (TTR); Duration of response (DOR); PFS on next-line therapy (PFS2); Safety; Patient Reported Outcomes (PRO)
*dose has since been changed to 800mg flat dose (refer to EMA EPAR documentation)

5.2 NHS England and NHS Improvement's Blueteq database captures the Cancer Drugs Fund population. NHS England and NHS Improvement

shares Blueteq data with Public Health England for the Cancer Drugs Fund evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and NHS Improvement and Public Health England.

5.3 The Systemic Anti-Cancer Therapy (SACT) dataset, is a mandated dataset as part of the Health and Social Care Information Standards. Public Health England is responsible for the collection, collation, quality-assurance and analysis of this dataset.

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

6 Outcome data

JAVELIN Renal 101 clinical trial

6.1 The key outcome to be collected is long-term overall survival. This data shall become available from the ongoing JAVELIN Renal 101 trial and will be provided to NICE when the guidance is reviewed. The JAVELIN Renal 101 trial will collect and report data as per the study protocol. After the final data cut ([redacted]) individual patient level data will be used to update projections of survival and cost-effectiveness analyses to confirm the original projections.

Other data, including SACT

6.2 Public Health England will collect the following outcomes through SACT unless it is determined by the SACT Operational Group that no meaningful data will be captured during the period of data collection:

- Number of patients starting treatment
- Treatment duration
- Overall survival

- Baseline characteristics: age and gender

6.3 NHS England and NHS Improvement's Blueteq system will collect the following outcomes:

- Number of applications to start treatment
- Baseline patient characteristics: performance status, IMDC risk status, histology.
- Previous adjuvant therapies if administered (in clinical trials).

7 Data analysis plan

Clinical trials

7.1 The primary source of data during the managed access arrangement period is the maturing JAVELIN Renal 101 trial, which collects data on aRCC patients regardless of IMDC risk group. Final analysis will follow the analysis plan outlines in the trial protocol and will be performed after the last subject enrolled has reached a minimum of 66 months follow-up. The table below provides the anticipated data cuts in the coming 4 years.

Table 2 Anticipated analyses of JAVELIN Renal 101 trial

Cut-off date	Total patients enrolled	Maturity	Headline results	Patient level data available	Analyses complete (e.g. remodeling)
[redacted])	N = 886 (fully recruited)	N = 886 with at least 28 months follow up	Publication plan TBD	[redacted]	N/A

[redacted] (primary analysis)	N = 886 (fully recruited)	N = 886 with at least 66 months follow up (based on 368 deaths in the PD-L1+ population)	[redacted]	[redacted]	[redacted]

7.2 As shown above in Table 2, the data cutoff data for interim analysis 3 (IA3) is expected in [redacted].

7.3 At the end of the data collection period, the updated data from the ongoing JAVELIN Renal 101 trial will be used to update survival extrapolations and other parameters within the cost-effectiveness model.

Other data

7.4 At the end of the data collection period Public Health England will provide a final report for NHS England and NHS Improvement which provide analyses based on NHS England and NHS Improvement's Blueteq data and routinely collected population-wide data, including that collected via SACT. The necessary controls will be put in place to ensure that patient confidentiality is not put at risk. The report will be shared with the company in advance of the planned review of guidance. Where SACT is a secondary source of data, availability of the final SACT report will be aligned to the availability of data from the primary source. The end of SACT data collection will be 8 months prior to the availability of the final SACT report to allow for NHS trusts to upload SACT data, data cleaning, and report production.

8 Ownership of the data

8.1 For all clinical trial data listed above, Merck and Pfizer 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 is facilitated by the Public Health England Office for Data Release. The company will not have access to the Public Health England patient data, but will receive de-personalised summary data, with appropriate governance controls in place.

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 and NHS Improvement.

8.4 Blueteq's Cancer Drugs Fund system data is owned by NHS England and NHS Improvement. NHS England and NHS Improvement is responsible for implementing Blueteq data collection and generally for the analysis of these data. NHS England and NHS Improvement, however, shares Blueteq data with Public Health England for Cancer Drugs Fund evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and NHS Improvement 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 Public Health England will produce a final report which includes analysis of data collected through SACT and from NHS England and NHS Improvement's Blueteq system. This report will be provided to NHS England and NHS Improvement and the company at the end of the data collection period. The final report will form part of NHS England and NHS Improvement's submission to the Cancer Drugs Fund guidance review, and will therefore be publicly available at the conclusion of guidance review.

9.3 Public Health England will produce interim reports, which will be shared with NHS England and NHS Improvement, NICE and the company at regular intervals during the data collection period. These reports will be used to determine whether real-world data collection is proceeding as anticipated and will not form part of the guidance review.

9.4 Publications of any data from the Public Health England reports is not permitted until after the date of publication of the NICE committee papers (on the NICE website) following the first NICE guidance review committee meeting.

9.5 The contribution of all relevant individuals must be acknowledged in any publications regarding the Managed Access. Authors will need to contact the NICE Managed Access Team for a full list of group members.

10 Data protection

10.1 The terms of clause 7 (data protection) of the managed access agreement, that apply between NHS England and NHS Improvement and Merck, 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

Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [ID1547]

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.