Cancer Drugs Fund

Managed Access Agreement

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [ID1652]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Olaparib with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer (ID1652)

Company name: AstraZeneca UK

Primary source of data collection: Ongoing PAOLA-1 study

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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Public Health England Agreement Manager	Katherine Henson, Analytical lead
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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 olaparib with bevacizumab for maintenance treatment of homologous recombination deficiency (HRD) positive (+) advanced ovarian, fallopian tube or primary peritoneal cancer [ID1652] (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.

2 Commencement and period of agreement

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

2.2 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	December 2022

2.3 AstraZeneca UK anticipates the results from the additional data collected during the Cancer Drugs Fund period will be incorporated into an evidence submission and the updated economic model by December 2022. PAOLA-1 is an externally sponsored study (ESR) and was conducted by the Association de Recherche sue les Cancers Gynécologiques (ARCAGY) group on behalf of the European Network for Gynaecological Oncological Trial (ENGOT) and the Gynaecologic Cancer InterGroup (GCIG). Data collection and cleaning will be performed by the ARCAGY group; the timelines indicated represent the best estimates available to AstraZeneca at the time this agreement was generated.

2.4 AstraZeneca UK acknowledges its 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 Cancer Drugs Fund 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 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 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 olaparib in its tablet formulation in combination with bevacizumab in the Cancer Drugs Fund include:

- application for maintenance olaparib in combination with bevacizumab to be made by, and the first cycle of systemic ant-cancer therapy with olaparib and bevacizumab to be prescribed by, a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.

- patient has a proven histological diagnosis of predominantly high grade serous or high grade endometrioid or high grade clear cell ovarian, fallopian tube or primary peritoneal carcinoma.

- patient's cancer has documented evidence of a positive status for homologous recombination deficiency (HRD) defined by the presence of either deleterious/suspected deleterious BRCA 1 and/or BRCA 2 mutation(s) or genomic instability as defined by a score of ≥42 by the Myriad HRD test.

- patient has recently diagnosed FIGO stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma.

- confirmation as to whether the patient did or did not receive an upfront or interval attempt at optimal cytoreductive surgery and, if applicable, the outcome of the surgery.

- patient has just completed 1st line platinum-based chemotherapy and has received a minimum of 4 cycles of platinum-based treatment.

- confirmation as to whether the patient did or did not receive bevacizumab as part of 1st line platinum-based chemotherapy

- patient is in response to the recently completed 1st line platinum-based chemotherapy and has achieved a partial or complete response to treatment and has no evidence of progressive disease on the post-treatment scan or a rising CA125 level.

- patient is currently less than 9 weeks from the date of the last infusion of the last cycle of 1st line chemotherapy.

- patient has not previously received any PARP inhibitor.

- confirmation that olaparib will be used in combination with bevacizumab.

- confirmation that olaparib is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment or for a maximum total treatment duration of 2 calendar years, whichever is the sooner.

- confirmation that the maintenance dose of bevacizumab is 15mg/Kg and that maintenance bevacizumab will be given until whichever is the sooner of: disease progression or unacceptable toxicity or patient choice to stop treatment or for a maximum total bevacizumab treatment duration of 15 calendar months (as measured from the start of bevacizumab-containing treatment, whether this was with chemotherapy or as maintenance therapy).

- patient has an ECOG performance status (PS) of either 0 or 1.

- confirmation that a first formal medical review as to whether maintenance treatment with olaparib in combination with bevacizumab should continue or not will be scheduled to occur at least by the start of the third cycle of treatment.

- confirmation that when a treatment break of more than 6 weeks beyond the expected 4-weekly cycle length is needed, a treatment break approval form to restart treatment, including as appropriate if the patient had an extended break on account of Covid-19 will be completed.

- confirmation that olaparib in its tablet formulation is to be otherwise used as set out in its Summary of Product Characteristics.

- confirmation that bevacizumab is to be otherwise used as set out in its Summary of Product Characteristics.

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

As estimated by the company	[redacted]
As estimated by NICE Resource Impact Assessment team	[redacted]

4 Area(s) of clinical uncertainty

4.1 The appraisal committee identified the following key areas of uncertainty during the course of the appraisal process:

- Immaturity of the progression-free survival (PFS) and overall survival (OS) data,

- Generalisability of data from the PAOLA-1 study.

4.2 The committee concluded that further data collection within the Cancer Drugs Fund could resolve the long-term PFS and OS uncertainties. Committee were aware that the issues regarding the generalisability of the trial would not be resolved by the Cancer Drugs Fund. For further details of the committee's discussion see section 3 of the Final Appraisal Document.

5 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	○ Ongoing PAOLA-1 study
Secondary sources	○ Systemic Anti-Cancer Therapy (SACT) dataset ○ NHS England and NHS Improvement's Blueteq data

Description of sources

5.1 PAOLA-1 is a multi-centre, randomised, double-blind, placebo-controlled, phase III externally sponsored study (ESR) that assessed the efficacy and safety of olaparib added to bevacizumab, versus placebo added to bevacizumab, in 806 women with newly-diagnosed advanced (FIGO Stage III or IV) ovarian cancer who were in complete or partial response following first-line platinum-taxane chemotherapy with bevacizumab. The subgroup relevant to this appraisal are people with HRD+ disease. This was a prespecified subgroup comprising 47.5% of the olaparib plus bevacizumab arm and 49.1% of the placebo plus bevacizumab arm.

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

Clinical trial

6.1 The following outcome data will be collected during the data collection arrangement:

- PFS and OS data from the PAOLA-1 study.

  In accordance with the study protocol, a final summary of OS for the full analysis set (including the HRD-positive subgroup relevant to this data collection arrangement) will be performed when the OS data are approximately 60% mature, or three years after the main PFS analyses (i.e. [redacted]), whichever occurs first. This will provide up to 3 years of additional follow-up data, relative to the evidence presented in the NICE appraisal ID1652 (22 March 2019 data cut-off) and should resolve the clinical uncertainty regarding the longer-term survival benefit of olaparib added to bevacizumab maintenance (versus bevacizumab maintenance alone) in the patient population covered by this managed access agreement.

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
- Baseline patient characteristics, including gender, age and performance status
- Treatment duration

- Overall survival[1]

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

- Number of applications to start treatment
- Predominant histology
- HRD status (either positive for BRCA 1 and/or 2, or HRD positive)
- FIGO stage of disease (III or IV)
- whether the person received an upfront or interval attempt at optimal cytoreductive surgery and, if applicable, the outcome of the surgery (no visible disease or visible residual disease)
- Whether the person received bevacizumab as part of the first-line platinum-based chemotherapy
- Response status (complete or partial) before start of maintenance therapy

7 Data analysis plan

Clinical trials

7.1 In accordance with the study protocol, a final summary of OS for the full analysis set (including the HRD-positive subgroup relevant to this data collection arrangement) will be performed when the OS data are approximately 60% mature, or three years after the main PFS analyses (i.e. [redacted]), whichever occurs first. This will provide up to 3 years of additional

[1]The number of events observed through SACT are anticipated to be low for this outcome. The SACT Operational Group will determine whether meaningful analyses can be produced prior to development of the Public Health England final report.

follow-up data, relative to the evidence presented in the NICE appraisal ID1652 (22 March 2019 data cut-off).

7.2 The data cut-off for the final analysis of OS is anticipated to occur by [redacted]. As noted elsewhere, PAOLA-1 is an ESR; it is anticipated that these data will be available to AstraZeneca UK for development of submission materials by [redacted].

Other data

7.3 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 PAOLA-1 was conducted by ARCAGY Research on behalf of the European Network for Gynaecological Oncological Trial [ENGOT] and the Gynaecologic Cancer InterGroup [GCIG]. AstraZeneca are entitled to provide the data being collected from the PAOLA-1 study to NICE as part of existing arrangements with ENGOT and GCIG.

8.2 The data collection is being managed by the ARCAGY group under the PAOLA-1 clinical trial protocol.

8.3 AstraZeneca UK will be responsible for ensuring they have permission to share the clinical study report, including non-patient identifiable data and analysis as part of their submission for the guidance review.

8.4 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.

8.5 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.

8.6 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 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 managed access

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.

9.2 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.

9.3 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.

9.4 The contribution of all relevant individuals must be acknowledged in any publications regarding the data collection or analyses generated from the data collection arrangement. Authors will need to contact the NICE Managed Access Team for the full list of relevant individuals.

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 AstraZeneca UK, 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?

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.