Cancer Drugs Fund

Managed Access Agreement

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies (ID2697)

Company name: Daiichi Sankyo UK Ltd.

Primary source of data collection: DESTINY-Breast02 (NCT03523585; ongoing Phase III clinical trial)

Secondary source of data collection: DESTINY-Breast01 (NCT03248492; ongoing Phase II clinical trial); Systemic Anti-Cancer Therapy (SACT) dataset during managed access agreement; NHS England and NHS Improvement's Blueteq data

NICE Agreement Manager	Brad Groves, Associate Director, Managed Access
NHS England and NHS Improvement Agreement Manager	Prof Peter Clark, CDF Clinical Lead
Public Health England Agreement Manager	Katherine Henson, Partnership Analytical Lead
Daiichi Sankyo Agreement Manager	Farhan Mughal, Director, Market Access and HEOR

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 trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies (ID2697) (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	Q4 2023

IA, interim analysis

2.3 Daiichi Sankyo anticipate 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 Q4 2023. The delay between data availability and evidence submission (>2 months) is due to the evidence submission being based on a different trial and model to the original NICE submission. Daiichi Sankyo will therefore need to analyse trial data (DESTINY-Breast02), develop networks for comparative efficacy, develop an economic model, and develop the submission dossier.

2.4 Daiichi Sankyo 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 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 trastuzumab deruxtecan in the Cancer Drugs Fund include:

- Application for trastuzumab deruxtecan for the treatment of unresectable locally advanced or metastatic breast cancer is being made by, and the first cycle of trastuzumab deruxtecan will be prescribed by, a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- patient has unresectable locally advanced or metastatic breast cancer
- patient has histologically documented breast cancer which is HER2 3+ by immunohistochemistry and/or has a HER2 amplification ratio of ≥2.0 by in situ hybridization
- patient has previously been treated with trastuzumab emtansine and is now either resistant or refractory to trastuzumab emtansine or had to discontinue trastuzumab emtansine due to intolerance
- the patient has received two or more anti-HER2 therapies which must have included trastuzumab and trastuzumab emtansine
- prior to consideration of treatment with trastuzumab deruxtecan the patient has a baseline left ventricular ejection fraction (LVEF) of at least 50%
- patient has an ECOG performance status of 0 or 1
- patient does not have untreated or symptomatic brain metastases

- patient has had no prior treatment with trastuzumab deruxtecan unless it has been received as part of the Daiichi Sankyo early access scheme and the patient meets all the other criteria set out here
- trastuzumab deruxtecan will be used as monotherapy and commencing at a dose of 5.4 mg/Kg administered every 3 weeks
- trastuzumab deruxtecan will be given until disease progression or unacceptable toxicity or patient choice to stop treatment.
    - Note: trastuzumab deruxtecan is not to be used beyond first disease progression outside the CNS.
    - Note: it is advised that trastuzumab deruxtecan is not (at least initially) discontinued if disease progression is within the CNS alone.
- When a treatment break of more than 6 weeks beyond the expected 3-weekly cycle length is needed, a treatment break approval form is required to restart treatment, including as appropriate if the patient had an extended break on account of Covid-19
- trastuzumab deruxtecan will be otherwise used as set out in its Summary of Product Characteristics (SmPC)

3.2 The company has an approved named patient program (NPP) for compassionate use in the UK which started in March 2021. However, stock of trastuzumab deruxtecan will not be available in the UK until the start of April 2021. While no patients have received access via the NPP to date, any early access patients enrolled in the NPP can be included as part of the SACT data collection agreement.

3.3 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:

1. Immaturity of the progression-free and overall survival data
2. Generalisability of data from the DESTINY-Breast01 study to UK clinical practice
3. Relative effectiveness of trastuzumab deruxtecan compared with capecitabine, vinorelbine, and eribulin

4.2 The committee concluded that further data collection within the Cancer Drugs Fund could resolve these uncertainties. 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)	○ DESTINY-Breast02
Secondary sources	○ DESTINY-Breast01 ○ Systemic Anti-Cancer Therapy (SACT) dataset

	○ NHS England and NHS Improvement's Blueteq data

Description of sources

5.1 Primary data source: DESTINY-Breast02 is an ongoing Phase III active-controlled randomised controlled trial of trastuzumab deruxtecan versus treatment of investigator's choice (trastuzumab + capecitabine or lapatinib + capecitabine) in HER2+, unresectable and/or metastatic breast cancer patients previously treated with trastuzumab emtansine. This trial will form the basis of the full marketing authorisation application for trastuzumab deruxtecan in this indication.

5.2 Secondary data source: DESTINY-Breast01 is an ongoing Phase II study, evaluating trastuzumab deruxtecan in adult patients with pathologically documented HER2+ unresectable or metastatic breast cancer who had received previous treatment with trastuzumab emtansine.

5.3 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 (PHE) for the Cancer Drugs Fund evaluation purposes. The lawfulness of this processing is covered under article 6(1)e of the United Kingdom General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). PHE, through the National Cancer Registration and Analysis Service, does have permission to process confidential patient information (without prior patient consent) afforded through Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

5.4 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.

5.5 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 Outcome data to be collected from DESTINY-Breast02 and DESTINY-Breast01 during the data collection arrangement

DESTINY-Breast02

- Progression-free survival (primary efficacy endpoint)
- Overall survival
- Objective response rate
- Duration of response
- Health economics and outcomes research (HEOR) endpoints:
  - European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30
  - EORTC QLQ-BR45
  - EuroQol-5 dimensions-5 levels of severity (EQ-5D-5L)
  - Hospitalisation-related endpoints
- Safety endpoints
- Pharmacokinetic endpoints

Results from DESTINY-Breast02 will provide comparative efficacy, safety, and HEOR endpoints for trastuzumab deruxtecan versus the treatment of investigator's choice (trastuzumab + capecitabine or lapatinib + capecitabine) in HER2+, unresectable and/or metastatic breast cancer patients previously treated with trastuzumab emtansine. Comparison of trastuzumab deruxtecan versus capecitabine

(a comparator listed in the final scope for this appraisal) will be possible via a network meta-analysis.

DESTINY-Breast01

- Objective response rate (primary efficacy endpoint)
- Progression-free survival
- Overall survival
- Duration of response
- Safety endpoints
- Pharmacokinetic endpoints

Whilst preliminary median overall survival was reached in the June 2020 data-cut of DESTINY-Breast01, additional analyses will provide more mature data to evaluate key efficacy (overall survival and progression-free survival) and safety endpoints for trastuzumab deruxtecan in adult patients with pathologically documented HER2+ unresectable or metastatic breast cancer who had received previous treatment with trastuzumab emtansine.

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

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

- Number of applications to start treatment
- Number of prior anti-HER2 therapies
- Previous use of pertuzumab plus trastuzumab-containing regimens and trastuzumab-containing regimens

7 Data analysis plan

Clinical trials

7.1 Details of analysis in DESTINY-Breast02 and DESTINY-Breast01

DESTINY-Breast02

The target sample size will be approximately [redacted] subjects, randomised in a 2:1 ratio into two treatment groups (trastuzumab deruxtecan versus investigator's choice [trastuzumab+capecitabine or lapatinib+capecitabine]). The primary analysis for progression-free survival (primary efficacy endpoint) will be performed when approximately [redacted] blinded independent central review-assessed progression-free survival events are observed. The end of the study hypothesis-testing period is defined as the date when approximately [redacted] overall survival events have been observed. Therefore, treatment through follow-up is projected to be continued for approximately [redacted] after the last subject is enrolled. The anticipated duration of the study is approximately [redacted]. Due to DESTINY-Breast02 having non-UK comparators (trastuzumab + capecitabine or lapatinib + capecitabine), Daiichi Sankyo intend to conduct a network meta-analysis to ensure comparative effectiveness estimates can be derived vs. NICE scoped comparator(s).

Subgroup analyses for progression-free survival, overall survival, objective response rate, duration of response, and clinical benefit ratio will be performed for the

intention-to-treat analysis set. Subgroup analyses are considered exploratory because of smaller sample sizes. Subgroup analyses will include:

- Hormone receptor status
- Lines of prior systemic therapy not including hormone therapy
- Prior treatment with pertuzumab
- Lines of prior pertuzumab treatment
- Lines of prior trastuzumab emtansine treatment
- Renal impairment at baseline
- Hepatic impairment at baseline
- History of visceral disease
- Best response to trastuzumab emtansine therapy
- Clinically inactive central nervous system metastases
- Age
- Race
- Region
- Country
- Eastern Cooperative Oncology Group performance status

Final analyses will be produced in line with protocol [redacted]. All decisions regarding final analysis, as defined in the statistical analysis plan document, will be made prior to database lock and unblinding of study data.

DESTINY-Breast01

The estimated study completion date of DESTINY-Breast01 is by [redacted]; one final data-cut is expected. As of the 8 June 2020 data-cut, 184 patients received trastuzumab deruxtecan at the recommended dose of 5.4 mg/kg.

The following subgroups will be examined for the objective response rate (primary endpoint) and duration of response (secondary endpoint). Subgroup analyses are considered exploratory and include:

- Hormone receptor status
- Lines of prior systemic therapy not including hormone therapy
- Prior pertuzumab
- Prior pertuzumab in first- or second-line in advanced/metastatic breast cancer
- Renal impairment at baseline
- Hepatic impairment at baseline
- Best response to trastuzumab emtansine therapy
- Clinically inactive brain metastases
- Age
- Race
- Region
- Ethnicity
- Eastern Cooperative Oncology Group performance status

Final analyses will be produced in line with protocol [redacted]. All decisions regarding final analysis, as defined in the statistical analysis plan document, will be made prior to database lock and unblinding of study data.

7.2 Trial updates for DESTINY-Breast02 and DESTINY-Breast01 that will become available during the data collection period

DESTINY-Breast02

There is no planned interim analysis of the primary endpoint (progression-free survival). Overall survival will be tested only if the test of the primary efficacy endpoint progression-free survival is statistically significant. Group sequential testing

with two overall survival interim analyses is planned (one at the time of primary analysis for progression-free survival based on blinded independent central review, and the second when approximately [redacted] overall survival events have been observed ([redacted] information fraction). The final overall survival analysis will occur after approximately [redacted] have been documented. See Table 1.

Table 1: DESINY-Breast02 – Efficacy stopping boundaries and estimated analysis times

Endpoint		PFS				OS			
				Boundary				Boundary	
PFS	OS	PFS events	IF	2-sided p-value	HR	OS events	IF	2-sided p-value	HR
[redacted]									

DESTINY-Breast01

The estimated study completion date is by the [redacted]. Public disclosure is anticipated [redacted].

7.3 Dates for database locks and data availability for DESTINY-Breast02 and DESTINY-Breast01

DESTINY-Breast02

Top line results (TLR) from the final PFS analysis and 1st interim OS analysis are anticipated to be available in [redacted]. The 2nd interim analysis for OS is anticipated to be available in [redacted]. DESTINY-Breast02 is expected to complete, with final OS results, in [redacted]. It is anticipated that data from the 2nd interim analysis, in combination with the other sources of data collection, will be sufficient to resolve the key uncertainties identified by the NICE appraisal committee.

Table 2: DESTINY-Breast02 – Planned database locks and anticipated data availability dates

Endpoint			DBL	Data availability Top Line Results (TLR)	Clinical Study Report (CSR)
PFS	OS	Estimated maturity of OS			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IA, interim analysis

DESTINY-Breast01

The estimated study completion date is [redacted].

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, Daiichi Sankyo 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. The lawfulness of this processing is covered under article 6(1)e of the United Kingdom General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). PHE, through the National Cancer Registration and Analysis Service, does have permission to process confidential patient information (without prior patient consent) afforded through Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

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 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.

9.3 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 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 Daiichi Sankyo, 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.