Cancer Drugs Fund

Managed Access Agreement

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 therapies [ID3909]

Cancer Drugs Fund – Data Collection Arrangement

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 therapies [ID3909]

Company name: Daiichi Sankyo UK Ltd.

Primary source of data collection: DESTINY-Breast03 (NCT03529110; ongoing, randomised, Phase III clinical trial)

Secondary source of data collection: Systemic Anti-Cancer Therapy (SACT) dataset during managed access agreement; NHS England & Improvement's Blueteq data

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NHSE Agreement Manager	Prof Peter Clark, CDF Clinical Lead
NHS Digital Agreement Manager	Martine Bomb, Head of Data Projects
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 1 or more anti-HER2 therapies [ID3909] (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 a guidance update are:

End of data collection (primary source)	[redacted]
Data available for development of company submission	[redacted]
Anticipated company submission to NICE for a guidance update	Q4 2024

2.3 Daiichi Sankyo anticipates that 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 2024. The delay between data availability and evidence submission (>2 months) is due to the time required for Daiichi Sankyo to analyse trial data, update the economic model, and develop the submission dossier based on the final DESTINY-Breast03 data cut.

2.4 Daiichi Sankyo acknowledges its responsibility to adhere as closely as possible to the timelines presented in this document.

2.5 NICE will, as far as is practicable, schedule the guidance update into the technology appraisal work programme to align with the estimated dates for the end of data collection.

2.6 The NICE guidance update will follow the process and methods applicable to guidance updates that are in place at the time the invitation to participate of the guidance update is issued. These may be different from the process and methods applicable to guidance updates when entered into the managed access agreement.

2.7 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 guidance update follows the standard timelines.

2.8 The company is responsible for paying all associated charges for a guidance update. Further information is available on the NICE website.

2.9 The company must inform NICE and NHS England (NHSE) in writing of any anticipated changes to the estimated dates for data collection at the earliest opportunity.

2.10 Any changes to the terms or duration of any part of the data collection arrangement must be approved by NICE and NHSE.

2.11 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 guidance update 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).

2.12 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 NHSE, 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 NHS Digital to provide data over the extended period.

2.13 Daiichi Sankyo acknowledges its responsibility to provide an evidence submission for this technology to NICE under all circumstances following a period of managed access.

2.14 In the event that Daiichi Sankyo does not make a submission to NICE for the purpose of updating the guidance, NICE and NHSE will require the company agree to submit the clinical evidence collected during the managed access period, and to participate in an engagement meeting convened by NICE with attendance from NHSE, patient and professional group stakeholders, with the company presenting the clinical evidence collected during the managed access period and an explanation of the decision to proceed with withdrawal of the guidance.

2.15 NICE and NHSE 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 (T-DXd) in the Cancer Drugs Fund include:

- 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.
- The patient has unresectable locally advanced or metastatic breast cancer.
- The 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 hybridisation.
- Whether this patient received a HER2-targeted neoadjuvant regimen and if so its nature:
    - the patient was not treated with a HER2-targeted **neoadjuvant** regimen, or

  - the patient was treated with a HER2-targeted neoadjuvant regimen which contained both pertuzumab and trastuzumab, or
  - the patient was treated with a HER2-targeted neoadjuvant regimen which contained trastuzumab as the sole HER2-targeted agent.

- Whether the patient received a HER2-targeted **adjuvant** regimen and if so its nature:
  - the patient was not treated with a HER2-targeted adjuvant regimen, or
  - the patient was treated with a HER2-targeted adjuvant regimen which contained both pertuzumab and trastuzumab, or
  - the patient was treated with a HER2-targeted adjuvant regimen which contained trastuzumab as the sole HER2-targeted agent, or
  - the patient was treated with a HER2-targeted adjuvant regimen which contained trastuzumab emtansine.
- Whether the patient has received a HER2-targeted regimen for locally advanced/metastatic disease which included **both** pertuzumab and trastuzumab:
  - the patient was not treated with a HER2-targeted regimen for locally advanced/metastatic disease which included both pertuzumab and trastuzumab, or

  - the patient was treated with a HER2-targeted regimen for locally advanced/metastatic disease which contained both pertuzumab and trastuzumab.

- the patient has received a HER2-containing regimen for locally advanced/metastatic disease which included trastuzumab as the sole HER2-targeted agent.
  - the patient was not treated with a HER2-targeted regimen for locally advanced/metastatic disease which included trastuzumab as the sole HER2-targeted agent, or
  - the patient was treated with a HER2-targeted regimen for locally advanced/metastatic disease which contained trastuzumab as the sole HER2-targeted agent.
- The patient has been treated with a prior regimen which contained at least trastuzumab and a taxane for advanced/metastatic breast cancer or developed disease recurrence during or within 6 months of completing either an adjuvant or neoadjuvant treatment regimen which contained at least trastuzumab and a taxane or adjuvant treatment with trastuzumab emtansine:
  - the patient was treated with a prior regimen for advanced/metastatic breast cancer which contained at least trastuzumab and a taxane, or
  - the patient has not yet been treated for advanced/metastatic breast cancer and has relapsed during or within 6 months of completing adjuvant or neoadjuvant therapy containing at least trastuzumab and a taxane, or

  - the patient has not yet been treated for advanced/metastatic breast cancer and has relapsed during or within 6 months of completing adjuvant therapy with trastuzumab emtansine.

- The patient has received one or more anti-HER2 therapies which must have included trastuzumab. Clinician to record how many anti-HER2 therapies this patient has received in all clinical settings (neoadjuvant, adjuvant and locally advanced/metastatic indications; e.g. a treatment pathway of neoadjuvant pertuzumab plus trastuzumab regimen followed by adjuvant trastuzumab and then a 1st relapse treated with a pertuzumab plus trastuzumab regimen counts as 3 separate anti-HER2 therapies).

- The patient has **NOT** been previously treated with trastuzumab emtansine for advanced/metastatic breast cancer.

- Prior to consideration of treatment with trastuzumab deruxtecan the patient has a baseline left ventricular ejection fraction (LVEF) of at least 50%.

- The patient has an ECOG performance status of 0 or 1.

- The patient does not have untreated or symptomatic brain metastases.

- The patient has had no prior treatment with trastuzumab deruxtecan.

- Trastuzumab deruxtecan will be used as monotherapy and will commence 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.

- The clinician is aware that cases of interstitial lung disease/pneumonitis have been reported with trastuzumab deruxtecan and fatal outcomes have been observed. The clinician also confirms that an appropriate imaging schedule is being used to detect early interstitial lung disease and that they will ensure that all patients are aware of the need to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms. In addition, the clinician confirms that if a diagnosis is made of interstitial lung disease/pneumonitis, management will include dose interruptions and modifications of trastuzumab deruxtecan as described in sections 4.2 and 4.4 of the drug's Summary of Product Characteristics (SmPC).

- When a treatment break of more than 6 weeks beyond the expected 3-weekly cycle length is needed, the clinician will confirm that they will complete a treatment break approval form 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 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	Year 1: 585 Year 2: 878 Year 3: 1,024

4 Patient safety

4.1 The company and NHSE have the responsibility to monitor the safety profile of the technology and must provide an overview of any new or updated safety concerns to NICE. If any new safety concerns are confirmed, NICE and NHSE will take steps, as appropriate, to mitigate the risk including but not limited to updating the eligibility criteria or recommending that the managed access agreement be suspended.

5 Area(s) of clinical uncertainty

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

1. Immature data from DESTINY-Breast03 including overall survival and progression-free survival
2. Time on treatment within the NHS

5.2 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 Draft Guidance.

6 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	• DESTINY-Breast03
Secondary sources	• Systemic Anti-Cancer Therapy (SACT) dataset • NHSE's Blueteq data

Description of sources

6.1 DESTINY-Breast03 is a phase 3, multicentre, open-label randomised trial to compare the efficacy and safety of trastuzumab deruxtecan (T-DXd) with trastuzumab emtansine (T-DM1) in patients with HER2+ unresectable or metastatic breast cancer, previously treated with trastuzumab and a taxane. This trial is the basis of the full marketing authorisation application for T-DXd in this indication.

6.2 NHSE's Blueteq database captures the Cancer Drugs Fund population. NHSE shares Blueteq data with NHS Digital 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). NHS Digital, through the National Disease Registration Service, does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHSE.

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

6.4 NHS Digital will collect data, including via the SACT dataset, alongside the primary source of data collection.

7 Outcome data

Clinical trial

7.1 Outcome data to be collected from DESTINY-Breast03 during the data collection arrangement:

- Overall Survival (OS)
- Progression-free survival (PFS) by blinded independent central review (BICR; primary efficacy endpoint)
- PFS by investigator assessment (IA)
- Response rates by BICR
- Response rates by IA
- Clinical benefit rate by BICR
- Duration of response by BICR
- Time to response
- Patient-reported outcomes and hospitalisation:
    - EQ-5D-5L
    - EORTC QLQ-C30
    - EORTC QLQ-BR45
    - Hospitalisation-related endpoints
- Safety (adverse events)

7.2 Whilst a statistically significant hazard ratio for PFS (BICR) was demonstrated in the May 2021 data-cut of DESTINY-Breast03 (interim analysis of PFS [IA1], used in the current submission), further follow-up will provide more mature data to evaluate key efficacy endpoints which the committee have identified as uncertain (OS, PFS, and time to treatment discontinuation) in adult patients with HER2+ unresectable or metastatic breast cancer who had received previous treatment with trastuzumab and a taxane.

Other data, including SACT

7.3 NHS Digital 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

7.4 NHSE'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

8 Data analysis plan

Clinical trials

DESTINY-Breast03

8.1 DESTINY-Breast03 is a phase 3, multicentre, open-label randomised trial to compare the efficacy and safety of T-DXd with T-DM1 in patients with HER2+ unresectable or metastatic breast cancer previously treated with trastuzumab and a taxane.

8.2 As of the interim analysis of PFS (21 May 2021; IA1), 524 patients were enrolled, of whom 261 were randomised to T-DXd 5.4 mg/kg and 263 patients to T-DM1 3.6mg/kg. The analysis was conducted after ≥234 PFS events.

8.3 The primary endpoint is PFS by BICR. The key secondary endpoint is OS. Other endpoints include PFS by IA, objective response rate (BICR and IA), duration of response (BICR), adverse events, and HRQoL.

8.4 Further follow-up data are expected to resolve the uncertainties highlighted by the NICE committee.

8.5 Data collection is driven by the number of events and is defined in the DESTINY-Breast03 protocol (Version 6.0, September 2020):

1. **Interim PFS by BICR analysis | conducted at [redacted] PFS events (May 2021 data cut-off):** the observed two-sided p-value threshold was p=0.000204 to conclude superiority of T-DXd over T-DM1 for the primary endpoint.
    - *A statistically significant reduction in risk was demonstrated for the primary endpoint.*

- *Because PFS was statistically significant, an OS analysis was conducted. The OS analysis did not demonstrate statistical significance, as the reduction in risk did not cross the pre-specified significance boundary of p<0.000265.*

2. **Final PFS analysis | conducted at [redacted] PFS events:** the observed two-sided p-value threshold is [redacted] to conclude superiority of T-DXd over T-DM1 for the primary endpoint.
   - **If PFS not statistically significant:** OS analysis not conducted.
   - **If PFS statistically significant and OS not significant at first interim analysis:** second interim OS analysis conducted. Efficacy boundaries were scaled, such that for exactly [redacted] OS events, the two-sided significance boundaries would be [redacted].
3. **Final OS analysis:**
   - **Conducted at [redacted] OS events if any PFS analysis significant and OS not significant at either previous OS analysis:** the overall two-sided significance level for OS at final analysis is [redacted], based on an expected [redacted] events.

8.6 Both IA2 and the final OS analysis are anticipated to become available during the data collection period. However, if statistical significance for OS is demonstrated at IA2, the trial and data collection period will stop earlier than the date at which [redacted] OS events occur (planned final OS analysis; [redacted] information fraction, estimated [redacted] from start of trial). See Table 1 for stopping boundaries.

Table 1 DESTINY-Breast03 efficacy stopping boundaries

Endpoint		PFS				OS			
PFS	OS	Events	IF	Boundary		Events	IF	Boundary	
				p-value	HR			p-value	HR

*Not defined in original protocol; conducted in order to provide additional follow-up if IA2 is statistically significant.
**Conducted if IA2 is not statistically significant. If IA2 demonstrates statistically significant OS, FA2 is not required to be conducted as per protocol.
Abbreviations: FA, final analysis; HR, hazard ratio; IA, interim analysis; IF, information fraction; OS, overall survival; PFS, progression-free survival.

8.7 Daiichi Sankyo anticipates that the final analysis of PFS (IA2) will demonstrate statistical significance for OS. If OS is statistically significant at IA2 then there is no protocol requirement for further OS analysis. However, Daiichi Sankyo will be able to provide one further analysis of OS at [redacted] information fraction.

8.8 The estimated study completion ([redacted] information fraction) is [redacted]. Top-line results (TLR) are anticipated to be available [redacted] and Clinical Study Report (CSR) [redacted].

Table 2 DESTINY-Breast03 Planned database locks and anticipated data availability dates

Analysis	Endpoint					DBL	TLR	CSR
	PFS		OS					
	Analysis	Events	Analysis	Events	Maturity (IF)			

*Not defined in original protocol; conducted in order to provide additional follow-up if IA2 is statistically significant.
**Conducted if IA2 is not statistically significant. If IA2 demonstrates statistically significant OS, FA2 is not required to be conducted as per protocol.

Other data

8.9 At the end of the data collection period NHS Digital will provide a final report for NHSE which provide analyses based on NHSE'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 guidance update. 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.

9 Ownership of the data

9.1 For all clinical trial data listed above, Daiichi Sankyo will be the owner.

9.2 This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Disease Registration Service, which is part of NHS Digital. The company will not have access to the NHS Digital patient data, but will receive de-personalised summary data, with appropriate governance controls in place.

9.3 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 NHS Digital, have been established with NHS Trusts and NHSE.

9.4 Blueteq's Cancer Drugs Fund system data is owned by NHSE. NHSE is responsible for implementing Blueteq data collection and generally for

the analysis of these data. NHSE, however, shares Blueteq data with NHS Digital 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 (UK 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). NHS Digital, through the National Disease Registration Service, does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care. The lawfulness of NHS Digital's processing is covered under article 6(1)(c) of the UK GDPR – processing is necessary for compliance with a legal obligation to which the controller is subject (the NDRS Directions).

10 Publication

10.1 The details/authorship of any proposed publications arising from these studies will be planned with the publication of the final study results.

10.2 NHS Digital will produce a final report which includes analysis of data collected through SACT and from NHSE's Blueteq system. This report will be provided to NHSE and the company at the end of the managed access period. The final report will form part of NHSE's submission to the guidance update, and will therefore be publicly available at the conclusion of the guidance update.

10.3 NHS Digital will produce interim reports, which will be shared with NHSE, 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 update.

10.4 Publications of any data from the NHS Digital reports is not permitted until after the date of publication of the NICE committee papers (on the NICE website) following the first NICE guidance update committee meeting.

10.5 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.

11 Data protection

11.1 The terms of clause 7 (data protection) of the managed access agreement, that apply between NHSE 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

12 Equality considerations

12.1 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.