Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Daiichi-Sankyo**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Breast Cancer Now
   b. METUP UK

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 17 October 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Daiichi Sankyo UK Ltd.

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Executive summary	**Summary:** Daiichi Sankyo has carefully considered the committee's assessment of the evidence submitted for trastuzumab deruxtecan (T-DXd) as a treatment for unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-low breast cancer (BC) after chemotherapy and would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to comment on the Draft Guidance Consultation (DGC) document. The company is disappointed by the draft recommendation not to recommend T-DXd. The company is keen to find a solution in partnership with NICE and NHS England for access to patients with HER2-low u/mBC after chemotherapy however remain concerned that the removal of the end-of-life (EOL) weighting in the updated NICE Methods (2022) has had a direct impact on this appraisal and would therefore welcome flexibility in committee decision-making. There is a high unmet clinical need for novel, targeted treatments in patients with HER2-low u/mBC after chemotherapy. T-DXd is an innovative, step-change treatment that is the first and only targeted treatment to demonstrate significant and substantial health-related benefits compared with current standard of care and subsequently receive GB marketing authorisation in a HER2-low population. T-DXd was awarded the Innovation Passport designation by the MHRA Innovative Licensing and Access Pathway (ILAP) steering group in May 2022 (ILAP reference number ILAP/IP/22/08265/01). Therefore, the company requests that the committee reconsiders the negative draft recommendation to enable timely access to this clinically effective treatment option for patients with a recognised high unmet need. Notably, in this response, the company has provided all additional analyses requested by the committee in the DGC, additional relevant Real-Word Evidence (RWE) to support survival extrapolations, a revised base case that incorporates a number of the committee's preferred assumptions, and a [redacted] to resolve areas of clinical and economic uncertainty and facilitate a positive NICE recommendation. The company revised base case is £[redacted] per quality adjusted life year (QALY). **Key updates in this response to ensure appropriate committee decision-making**: • **Treatment of Physician Choice (TPC) modelling:** To address uncertainty in modelling TPC, the revised company base case now uses efficacy and costs from a *post hoc* analysis of DESTINY-Breast04 aligned to NHS clinical practice (the "DB-04 NHS cohort") rather than the Full Analysis Set (FAS). In this analysis, which was first presented at the TE stage, patients assigned to gemcitabine and second-line (2L) eribulin pre-randomisation are removed from both treatment arms. This aligns to the committee's recommendation that TPC should be modelled to reflect NHS clinical practice and should exclude gemcitabine and second-line eribulin. In this DGC response, the company has provided further details on justification for choice of survival distributions and use associated utility data in this dataset, as requested by the committee in the DGC (section 3.9). For more information, see Issue 1 in this DGC response. • **Overall Survival (OS) extrapolation:** In order to align with the recently published NICE RWE framework[1] and the drive from NICE to incorporate RWE in decision-making, the company has provided an updated analysis of the real-world Flatiron study using a subgroup of HER2-low mBC patients reflective of NHS clinical practice ("Flatiron NHS" cohort; N=[redacted]). This RWE is the most relevant evidence to inform long-term survival extrapolations for this appraisal given that HER2-low is a new disease classification, meaning there is a paucity of evidence in the literature on long-term outcomes with standard of care. These RWE validate the revised company base case choice of the

	log-logistic curve to extrapolate OS for the "DB-04 NHS" cohort. For more information, see Issue 2 in this DGC response. • **Progression-free (PF) and post-progression (PP) utilities:** The company has opted to derive PF and PP utility values using a linear mixed model (LMM) for the revised base case. The use of LMM for PF utilities aligns with the committee-preferred base case. The use of LMM for PP utilities is more appropriate than the EAG base case (to apply a decrement from Lloyd et al) as it offers greater face validity and uses data from the DESTINY-Breast04 trial. To align with efficacy data in the revised company base case, utility data are derived from the "DB-04 NHS cohort". Furthermore, to reach resolution, the company has updated the duration of the utility benefit from 12 months to a more conservative 6 months. For more information, see Issues 5 and 6 in this DGC response. • **Impact of updated NICE Methods -** Until recently this appraisal would have been assessed under the end-of-life (EOL) criteria, resulting in a willingness-to-pay threshold of £50,000 per quality adjusted life year (QALY) for decision-making. Under the new NICE framework, this appraisal exceeds the minimum criteria for the 1.2x QALY modifier and the company considers that this modifier underestimates the severity of the condition and therefore ICERs presented with a x1.2 weighting are conservative. The company believes that flexibility should be considered when applying the severity modifier for this appraisal to ensure that the severity of the condition is appropriately reflected for an appraisal which would have robustly met the previous EOL eligibility criteria. Furthermore, the new framework does not adequately recognise the high unmet need, innovation, clinical value, and clinical and patient demand for T-DXd in HER2-low u/mBC. As the first and only treatment licensed for HER2-low u/mBC specifically, T-DXd is a highly innovative therapy (as recognised by the Medicines and Healthcare product Regulatory Agency (MHRA) innovation passport) and offers clear and substantial clinical benefits over current standard of care. T-DXd is expected to result in patient benefits not captured in the QALY calculations and wider societal benefits in terms of work productivity and quality of life (QoL) benefit for carers and families of patients with HER2-low u/mBC. These benefits should be appropriately quantified and qualitatively valued in committee decision-making. For more information, see Issues 9 and 10 in this DGC response. • **Updated PAS price:** The company affirms its commitment to ensuring timely access to T-DXd for patients with HER2-low u/mBC by providing [redacted]. The updated PAS price is [redacted] per 100mg vial, equating to a discount of [redacted]% from the list price and representing an [redacted] from the current T-DXd PAS price. With the updated PAS, the revised company base case incremental cost-effectiveness ratio (ICER) following changes at DGC is £[redacted] (with 1.2x modifier) and £[redacted] (with 1.7x modifier). [redacted]. At the revised PAS price, T-DXd is a cost-effective use of NHS resources in an underserved population with a high unmet need. For more information, see cost-effectiveness results in Table 11 of this DGC response.
1: Modelling TPC	***The revised company base case excludes gemcitabine and second-line eribulin from the treatment of physician's choice (TPC) arm to reflect agents used in NHS practice and align with the committee's recommended approach for modelling TPC.*** In the company base case at ACM1, TPC was modelled using the distribution of TPC agents in the DESTINY-Breast04 full analysis set (FAS; Clarification question B37). The EAG preferred to *"remove all eribulin and gemcitabine costs and assume that TPC efficacy was the same as in the trial"*. The EAG base case used efficacy data from the DESTINY-

	Breast04 FAS but excluded eribulin and gemcitabine costs from the TPC arm to more closely reflect NHS clinical practice. Despite the EAG base case removing eribulin costs from both second- and third-line (2L/3L), which is not aligned to NHS practice as eribulin is reimbursed in the 3L and beyond setting, the committee preferred the EAG's base case. The committee did, however, note that "*TPC should be modelled to reflect NHS practice and should exclude second-line eribulin and gemcitabine*." The company recognises that the use of eribulin in the 2L setting (after 1 prior line of chemotherapy) and the use of gemcitabine as a single-agent chemotherapy do not align with their current recommended use in NHS clinical practice. However, as stated in technical engagement (TE) response issue 1, the company considers the EAG's approach to completely remove all eribulin costs from TPC to be wholly inappropriate as eribulin is recommended by NICE for treating advanced or mBC after 2 or more lines of chemotherapy (TA423).[2] This is reflected in clinical expert comments in the DGC ("*The clinical experts agreed that in the NHS, eribulin is used at third line and is the most clinically effective option in the TPC group*") and also in the final scope, where 3L eribulin is listed as a relevant comparator.[3] Therefore, 3L eribulin is relevant to the decision-problem and should be included in the modelled TPC costs and efficacy. To address the committee's request for TPC to "*reflect NHS clinical practice"* and *"exclude second-line eribulin and gemcitabine*" (page 10, DGC), the company has updated the model base case to use the efficacy, costs, and utilities for both T-DXd and TPC based on the *post hoc* subgroup analysis of DESTINY-Breast04 (11 Jan 2022 data cut-off i.e., the data cut-off used in the company submission) described in TE response issue 1. In this *post hoc* analysis (hereon referred to as the "DB-04 NHS cohort"), patients assigned to gemcitabine (2L or 3L) or eribulin 2L, prior to randomisation, were removed from both arms of DESTINY-Breast04 to align the cost-effectiveness analysis with NHS clinical practice. This analysis was previously presented by the company in response to Issue 1 at the TE stage. The committee requested further details on justification for its choice of survival distribution and associated utility data (DGC, section 3.9), which the company has provided in this response. As the choice of TPC agent was declared for each individual subject before randomisation (see Protocol v5.0 Section 5.1.1), it was possible to exclude corresponding patients from the T-DXd arm (i.e., it was possible to exclude patients in the T-DXd arm who would have been assigned 2L eribulin or gemcitabine [2L or 3L] had they been randomised to receive TPC). This approach preserves randomisation, and the observed and unobserved patient characteristics remained balanced between the two treatment arms after excluding these patients. In addition, since the number of prior lines of chemotherapy was a randomisation stratification factor in the trial, the 2:1 distribution of T-DXd to TPC is maintained in this analysis. This "DB-04 NHS cohort" comprises 247 patients in the T-DXd arm and 118 patients in the TPC arm (compared with 373 and 184 in the T-DXd and TPC arms, respectively, in the FAS cohort). The distribution of the remaining agents in the TPC arm (based on safety analysis set data) is as follows: eribulin 3L (n=[redacted]%), capecitabine (n=[redacted]%), nab-paclitaxel (n=[redacted]%), and paclitaxel (n=[redacted]%). Full baseline characteristics from the "DB-04 NHS cohort" are provided in **Table 16** of Appendix A. Overall, the baseline characteristics of the "DB-04 NHS cohort" are similar to the baseline characteristics of the FAS population (Table 15 of the company submission [CS]). [redacted]. In addition, the proportion of patients with ECOG PS 0 and 1, central nervous system metastases, renal impairment, and HER2 status were comparable between the FAS and the "DB-04 NHS cohort" for each treatment arm. The most notable difference between the FAS and "DB-04 NHS cohort" was related to the number of prior lines of therapy, where a higher proportion of patients in the "DB-04 NHS cohort" received ≥2 prior lines of chemotherapy than in the FAS ("DB-04 NHS cohort" vs. FAS: [redacted]% vs [redacted]% in the T-DXd arm; [redacted]% vs [redacted]% in the TPC arm). This was as expected given that eribulin 2L patients were removed from the "DB-04 NHS cohort".

	In addition to similar baseline characteristics, similar efficacy outcomes were also observed in the "DB-04 NHS cohort" compared to the FAS. In the "DB-04 NHS cohort", T-DXd (N=247) was associated with a [redacted]% lower risk of progression or death compared with TPC (N=118; progression-free survival [PFS] by blinded independent central review [BICR] HR: [redacted]; 95% CI [redacted], [redacted]; p<[redacted]), which is consistent with the outcome for the FAS population (HR: 0.50; 95% CI: 0.40, 0.63; p<0.0001). T-DXd was also associated with a [redacted]% lower risk of death compared with TPC in the "DB-04 NHS cohort" (OS HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]), which was consistent with the outcome for the FAS population (HR: 0.64; 95% CI: 0.49, 0.84; p=0.001).[4] In summary, in order to address the uncertainty regarding modelling of TPC and align the cost-effectiveness analysis with NHS clinical practice, the revised company base case uses the "DB-04 NHS cohort" for efficacy, costs, and utilities. The revised company base case ICER, at the new PAS price, is £[redacted]. Full results of the revised company base case at DGC are provided in Table 10. Additional detail on baseline characteristics and efficacy results in the "DB-04 NHS cohort" is provided in Appendix A, while rationale on curve selection for OS, PFS, and time-to-treatment discontinuation (TTD) in the "DB-04 NHS cohort" is summarised in Issues 2, 3 and 4, respectively. Utilities are summarised in Issues 5 and 6.
2: OS extrapolation ("DB-04 NHS cohort")	***Log-logistic is the most appropriate curve to extrapolate OS in the "DB-04 NHS cohort" based on statistical fit and clinically plausibility at 5 (and 10) years, as confirmed by clinical expert opinion and Flatiron RWE. Weibull and gamma curves produce highly pessimistic extrapolations.*** As requested by the committee in the DGC, the company has provided justification on the chosen parametric curve to extrapolate OS data for the "DB-04 NHS cohort". Similar to the approach in the FAS population, the company took a comprehensive approach to determine the most appropriate curve for OS extrapolation in the "DB-04 NHS cohort", in line with best practice guidance from NICE Decision Support Unit Technical Support Document 14[5] (as discussed in CS Section B.3.3.2). A log-cumulative hazard plot (LCHP) was produced to assess whether the proportional hazards (PH) assumption may hold (**Figure 9**). Given that the PH assumption does not hold, a full range of six standard independent parametric curves were evaluated for statistical fit, visual fit, and long-term plausibility (based on consultation with UK clinical experts and comparison with relevant RWE). For completeness, the gamma curve was also assessed based on a request from the committee in the DGC. The company considers that log-logistic is the most appropriate curve to extrapolate OS in the "DB-04 NHS cohort", as it provides good statistical fit and clinically plausible long-term estimates that align with clinical opinion and highly relevant RWE from the Flatiron database. The Weibull and gamma curves are not appropriate for extrapolating OS in the "DB-04 NHS cohort" due to the highly pessimistic long-term estimates that do not align with clinical opinion or RWE, in particular at five years where the greatest clinical experience lies. Notably, the chosen base case of log-logistic is not the most favourable extrapolation of those considered to be clinically plausible. The log-normal extrapolation produces the most favourable predicted incremental survival benefit between T-DXd and TPC (see **Table 2**) and is a plausible choice based on clinical opinion and RWE. Applying the log-normal extrapolation in the model results in an ICER of £[redacted], which is £[redacted] lower than the company revised base case (£[redacted]/QALY). Therefore, the company choice of log-logistic in the base case is considered conservative. A full evaluation of the parametric curves is provided below and a summary is provided in **Table 1**.

Table 1: Summary of independent OS curve selection ("DB-04 NHS cohort")

Curve	Statistical fit	Visual fit	Clinical expert opinion	Real-world evidence
TPC				
Exponential			✓	
Weibull	✓	✓		
Gompertz				
Log-logistic	✓	✓	✓	✓
Log-normal	✓	✓	✓	✓
Gen gamma	✓	✓		
Gamma	✓	✓		
T-DXd				
Exponential				
Weibull	✓	✓		
Gompertz	✓	✓		
Log-logistic	✓	✓		
Log-normal				
Gen gamma	✓	✓		
Gamma	✓	✓		

Abbreviations: OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
As there is limited long-term clinical experience with T-DXd in patients with HER-2 low, the clinical expert opinion and real-word evidence assessment of T-DXd OS have not been presented in this table.

Initial assessment of OS survival distributions in the "DB-04 NHS cohort" based on proportional hazards, statistical fit, and visual fit

The company took a robust approach to determining suitable curves for OS extrapolation in the "DB-04 NHS cohort":

- **Proportional hazards:** As with the FAS data, the LCHP in the "DB-04 NHS cohort" shows that the curves are not parallel over time; intersecting at around 6–7 months. This indicates no clear evidence that the PH assumption holds (**Figure 9, Appendix A**). As the log-cumulative hazard lines are relatively straight, the six standard parametric forms and the gamma curve are appropriate and were fitted independently to the mature patient-level survival data from the "DB-04 NHS cohort". Use of independent parametric curves, fitted to mature patient-level data, is likely to result in better fitting curves for each treatment arm than the use of dependently fitted models.

- **Statistical fit:** AIC and BIC scores for the extrapolated OS curves for the "DB-04 NHS cohort" are presented in **Table 7, Appendix A**. For the TPC arm, the log-logistic curve provides the overall best fit based on the goodness-of-fit statistics. The Weibull, log-normal, generalised gamma and gamma curves were within 5 AIC or BIC points of the best fitting curve, indicating reasonable statistical fits.[6] For the T-DXd arm, the Weibull and Gompertz parametric curves provide the best statistical fit. Log-logistic, generalised gamma and gamma were within 5 AIC or BIC points of the best fitting curve and could also be considered a good statistical fit.

- **Visual fit:** Visual assessment of the observed Kaplan-Meier (KM) data of the "DB-04 NHS cohort" versus predicted OS curves indicates that the log-logistic, Weibull, generalised gamma, gamma and log-normal are an acceptable visual fit to the KM data for TPC. The log-logistic, Weibull, generalised gamma, gamma and Gompertz are all an acceptable visual fit to the KM data for T-DXd (**Figure 10** and **Figure 11**, **Appendix A**).

Based on these initial assessments, the Weibull, log-logistic, log-normal, generalised gamma, and gamma curves could be considered potential options for the TPC arm, based on statistical fit. For the T-DXd arm, log-logistic, Weibull, generalised gamma, gamma and

Gompertz could be considered potential options. Therefore, the Weibull, log-logistic, generalised gamma and gamma provide a good fit across both trial arms.

Evaluation of long-term clinical plausibility

Table 2 presents a landmark analysis of the predicted OS for the "DB-04 NHS cohort". These values were compared with clinical expert opinion and RWE to determine the most clinically plausible curves.

Table 2: OS in the "DB-04 NHS cohort": Predictions by independently fitted distributions in T-DXd and TPC

Distribution	Median (months)*	1-Year OS	2-year OS	3-Year OS	5-Year OS	10-Year OS
TPC						
Observed KM data	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd						
Observed KM data	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Median time in months and predicted OS are estimated after OS has been adjusted to include general population mortality.
Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Validation of long-term clinical plausibility through UK clinical expert opinion:

Clinical expert advice received by the company and EAG stated that [redacted] of patients treated with TPC would remain alive at 5 years and a small proportion (company) or ≤1% (EAG) would be alive at 10 years. Furthermore, advice to the company is that clinicians are more confidently able to input on 5-year OS estimates than 10 years as there is a greater depth of clinical experience with patients at 5 years compared to 10 years in the HER2-low u/mBC population relevant to this appraisal.

In the TPC arm, given that the Weibull long-term OS estimates in the FAS population were considered pessimistic by the EAG's clinical advisors (5-year OS estimate of [redacted]%), it is clear that the Weibull, gamma and generalised gamma curves in the "DB-04 NHS cohort" are also overly pessimistic (5-year OS estimates of [redacted]%, [redacted]% and [redacted]%, respectively). Similarly, 10-year OS estimates were also too pessimistic ([redacted]%, [redacted]% and [redacted]%, respectively) given that clinical experts consulted by the company expect a small proportion of patients to be alive at 10 years. This rules out these curves for consideration in the base case to extrapolate TPC OS.

By comparison, the log-logistic and log-normal curves estimate 5-year OS of [redacted]% and [redacted]%, respectively, in the "DB-04 NHS cohort" TPC arm, which is within the range of the 5-year OS estimates considered plausible for the FAS by the EAG's clinical advisors, who:

"*considered that it is more reasonable that the 5-year survival probability is approximately [redacted]% as predicted by the log-logistic model rather than approximately [redacted]% as predicted by the Weibull model*" and considered "*an estimate of 5% survival at 5-years was reasonable under current care*" (page 119–120 of the final EAG report).[7] The values predicted by the log-logistic and log-normal curves are also within the range estimated by clinical experts consulted by the company, who stated that "[redacted]*% of patients treated with TPC would be alive at 5 years."* The 10-year OS estimates with the log-logistic and log-normal distributions ([redacted]% and [redacted]%) are also aligned with clinical expert opinion. The company is therefore confident that the log-logistic and log-normal curves are the most clinically plausible curves to extrapolate TPC OS in the "DB-04 NHS cohort". For the company's revised base case using the "DB-04 NHS cohort", the log-logistic curve was preferred over log-normal to extrapolate OS in the TPC arm based on overall statistical and visual fit, and clinical plausibility.

For T-DXd, in the "DB-04 NHS cohort", the Weibull and gamma curves estimate 5-year OS landmarks of [redacted]% and [redacted]%, respectively. This is broadly in the range that clinical experts expected for survival in the TPC arm. Furthermore, the Gompertz and generalised gamma curves estimate 5-year OS as [redacted]% and [redacted]%, respectively, which is even lower than the estimates from clinical experts for the TPC arm. Therefore, these curves are considered by the company to be implausibly pessimistic given the mature, marked, and statistically significant OS benefit observed for T-DXd vs. TPC in DESTINY-Breast04. By comparison, the log-logistic distribution generates a 5-year OS estimate for T-DXd of [redacted]%, which appears to be clinically plausible given that clinical experts estimate 5-year survival of 5–10% for TPC. Based on clinical expert opinion, the company is confident that Weibull, Gompertz, gamma, and generalised gamma curves can be ruled out as appropriate parametric curves to extrapolate OS in the base case for T-DXd in the "DB-04 NHS cohort", whereas log-logistic appears to be the most clinically plausible.

Validation of long-term clinical plausibility based on RWE:
There is a lack of published long-term outcomes data for standard of care in a HER2-low mBC population and clinical experts were not able to confidently estimate 10-year survival rates at the first ACM. The company therefore considers it important to validate the OS curves against relevant RWE to reduce uncertainty. In addition, in the recently published NICE RWE framework (2022), it is stated that RWE evidence could be used more routinely to fill evidence gaps and speed up access for patients. The updated NICE strategy 2021 to 2026 also states NICE's aim to use real-world data to resolve gaps in knowledge.[1] Given the uncertainty raised by the EAG and committee with regards to the extrapolations of OS in the cost-effectiveness analysis (CEA) and lack of published long-term survival estimates in HER2-low mBC, RWE in this appraisal is key to supplement and validate clinical expert opinion and support the committee's decision making. This was also highlighted by clinical experts during the discussion at ACM1.

At the TE stage, in order to validate the OS estimates for the FAS population, the company presented an analysis from Flatiron which was a large observational study that examined survival outcomes amongst a US real-world cohort of [redacted].[8] The Flatiron data presented at TE related to the [redacted], referred to as [redacted] in the statistical analysis plan (SAP), which reflects eligibility criteria aligned to the FDA label and [redacted].The analysis comprised of a total of [redacted] patients and included patients treated with some therapies that were not available in DESTINY-Breast04. The analyses validated the use of log-logistic as a clinically plausible curve for extrapolating OS in the TPC and T-DXd arm and demonstrated that the Weibull curve was too pessimistic.

	However, in the EAG's critique of the company's response to TE, they stated that the comparator arm of the Flatiron study included TPC components that are "*arguably more effective treatments than those observed in DESTINY-Breast04 or real practice*" and that the study "*does not represent the TPC arm of the decision problem at hand*".[7] In order to address the EAG's concerns and present RWE most relevant to the decision problem and DESTINY-Breast04, the company has conducted further analyses on a subgroup of patients in the Flatiron study selected based on their alignment to NHS clinical practice (hereon referred to as the "Flatiron NHS Cohort"). The "Flatiron NHS Cohort" was developed using the following process (as detailed in the SAP provided as a reference). Firstly, Flatiron Cohorts B (N=[redacted]) and C (N=[redacted]) were selected, which include HER2-low mBC patients meeting additional DESTINY-Breast04 trial eligibility criteria not applied to Cohort A (DB-04 Label Cohort). Patients in Cohorts B and C received one and two lines of prior chemotherapy in the metastatic setting, respectively. Next, further eligibility criteria were applied to patients in Cohort B and C to align index treatments to those used in NHS clinical practice: • "Chemo Cohort B": patients who [redacted]" (N=[redacted]). • "Chemo Cohort C": patients who [redacted] (N=[redacted]). In order to achieve a similar distribution of number of prior lines of chemotherapy as the TPC arm of "DB-04 NHS cohort" ([redacted] with 1 prior line of chemotherapy, [redacted] with 2 prior lines of chemotherapy), this subset was further sampled as follows: • [redacted] • [redacted]. This resulted in [redacted] and [redacted] of patients in the final "Flatiron NHS Cohort" having 1 and 2 prior lines of chemotherapy, respectively. The final "Flatiron NHS cohort" consists of [redacted] patients (**Figure 1**). See **Table 21** for the full attrition criteria of the "Flatiron NHS cohort".

Figure 1: Flow diagram to derive the "Flatiron NHS cohort"

Additional selection criteria were used – please refer to the SAP and Appendix B for more information on the derivation of the Flatiron NHS cohort
Abbreviations: HER2, human epidermal growth factor receptor 2; LOT, line of therapy; NHS, National Health Service; SAP, statistical analysis plan

The full baseline characteristics for the "Flatiron NHS Cohort" are presented in **Table 22, Appendix B**. An SAP of the analyses carried out using the Flatiron study is available as a reference as part of this company response.

The baseline characteristics from the "Flatiron NHS cohort" (**Table 22, Appendix B**) were broadly aligned to the baseline characteristics in the TPC arm of the "DB-04 NHS cohort" of the DESTINY-Breast04 trial (**Table 16, Appendix A**). The mean age at the time of index treatment date for the "Flatiron NHS cohort" is similar to the mean baseline age of patients in the TPC arm of the "DB-04 NHS cohort" (vs years). The proportion of patients with ECOG performance status 0 is % and % for the "Flatiron NHS cohort" and "DB-04 NHS cohort", respectively. As expected due to the . Overall, the "Flatiron NHS cohort" and "DB-04 NHS cohort" populations are broadly comparable.

In the "Flatiron NHS cohort", the maximum follow-up time from index treatment date was months and the mean follow-up was months. There were OS events (**Figure 20, Appendix B**). Median OS was months (95% CI:).[8] This is the median OS in the TPC arm of the DESTINY-Breast04 "DB-04 NHS cohort" (months [95% CI:]), as indicated by overlapping 95% CIs. The that the "Flatiron NHS cohort" is highly relevant to this appraisal.

Notably, **Figure 2** and the landmark analysis in **Table 3** show that the "Flatiron NHS cohort" validates the log-logistic curve as a clinically plausible curve for OS extrapolation for the TPC arm. In the "Flatiron NHS cohort", the 5-year survival rate was % (95% CI;) and the 10-year survival rate was % (95% CI;). By comparison, the log-logistic curve in the company model using the "DB-04 NHS cohort" predicted 5- and 10-year survival rates of % and % in the TPC arm and the log-normal curve predicted

5- and 10-year survival rates of [redacted]% and [redacted]%, respectively, whereas the Weibull curve predicted 5- and 10-year survival rates of [redacted]% and [redacted]%, and the gamma curve predicted 5- and 10-year survival rates of [redacted]% and [redacted]%. This reinforces that the Weibull- and gamma-predicted 5-year and 10-year survival estimates are highly pessimistic for the TPC arm of the "DB-04 NHS cohort", whereas the log-logistic and log-normal curves are clinically plausible (**Table 3**).

Figure 2: Comparison of OS extrapolations from the TPC arm of the "DB-04 NHS cohort" of DESTINY-Breast04 with the "Flatiron NHS cohort" real-world OS KM data

Abbreviations: KM, Kaplan-Meier; NHS, National Health Service; OS, overall survival; TPC; treatment of physician's choice.

Table 3: Comparison of modelled landmark estimates from the TPC arm of the "DB-04 NHS cohort" with RWE from the "Flatiron NHS cohort"

Distribution	Median (months)*	1-Year OS	1.5-Year OS	2-Year OS	3-Year OS	5-Year OS	10-Year OS
Flatiron NHS cohort							
Observed KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DB-04 NHS cohort TPC arm							
Observed KM data	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Log-logistic (company base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull (EAG base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*OS in the extrapolated curves is estimated after OS has been adjusted to include general population mortality
Abbreviations: DB04, DESTINY-Breast04; FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; RWE, real-world evidence; TPC, treatment of physician's choice.

In summary, RWE from the "Flatiron NHS cohort", which consists of patients reflective of the TPC arm of the "DB-04 NHS cohort" and of NHS clinical practice, demonstrates that the log-logistic curve is a clinically plausible curve for OS extrapolation. The "Flatiron NHS Cohort" data also align with input from UK clinical experts. Importantly, the 5-year survival ([redacted]) for current standard-of-care, where there is greater clinical experience than at later timepoints, is within the range expected by UK clinicians. Aligned with clinical feedback, the data also shows a small proportion of patients are expected to survive in the long-term, and further confirm that the Weibull and gamma curve are pessimistic.

	The Flatiron study is a robust analysis of long-term survival with non-targeted chemotherapy in patients with HER2-low u/mBC in a cohort of patients aligned to NHS clinical practice and therefore represents the most relevant RWE for this appraisal. Flatiron data have been used across a range of previous NICE appraisals in oncology, including breast cancer (see **Table 29** in **Appendix E** for details of previous NICE TAs that have used Flatiron data to validate their selected survival curves[9–14]). For example, in TA801 (pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent u/mBC), Flatiron data were used to validate the clinical plausibility of OS curves.[15] Given the relevance of the analysis, reliability of the data source, and NICE's guidance on RWE to inform decision-making, the company considers that the Flatiron study is critical to decision-making and is able to support NICE in their ambition to "*use real-world data to resolve issues of uncertainty and improve access to new innovations for patients*".[16] **Conclusion** Given the comprehensive approach to evaluating the most appropriate parametric curves to extrapolate OS, including validation from clinical experts and RWE, the company is confident that the log-logistic OS curve is the most appropriate and clinically plausible curve to inform the TPC and T-DXd base case. In particular, consistency in 5-year survival estimates for TPC between UK clinicians and Flatiron compellingly support the log-logistic as a robust selection for the revised company base case. It should be noted that, of the clinically plausible extrapolations, the log-logistic is not the most optimistic and therefore can be considered a conservative choice. In contrast, the company considers that the long-term OS estimates derived from the Weibull and gamma curves are highly pessimistic and not appropriate for decision-making, as confirmed by input from clinical experts and comparison with RWE.
3: PFS extrapolation ("DB-04 NHS cohort")	***Log-logistic is the most appropriate curve to extrapolate PFS in the TPC and T-DXd arms of the "DB-04 NHS cohort" based on statistical fit, visual fit, and clinically plausible PFS estimates.*** The committee "*concluded that the generalised gamma [PFS in the FAS population] capped at the point of crossing should be used in the model"* (Section 3.11, DGC). Given that the company's revised base case uses the "DB-04 NHS cohort" instead of the FAS, the company has presented further justification for the PFS curve selection in the "DB-04 NHS cohort". A comprehensive approach was taken including assessing the full range of six standard parametric curves for statistical fit, visual fit, and long-term plausibility based on consultation with UK clinical experts. The company consider that the log-logistic curve is the most appropriate to extrapolate PFS in the TPC and T-DXd arms based on the "DB-04 NHS cohort", as it provides good statistical and visual fit to the observed data and clinically plausible long-term estimates. Importantly, the T-DXd and TPC log-logistic curves do not intersect at any time point. This is important as the company considers the intersection of T-DXd and TPC PFS curves to be implausible based on the DESTINY-Breast04 clinical trial data and other relevant NICE BC appraisals. A full evaluation of the parametric curve fitted to the "DB-04 NHS cohort" is provided below. **Initial assessment of curve selection in the "DB-04 NHS cohort" based on proportional hazards, statistical fit, and visual fit:** The company took a robust approach to determining suitable curves for PFS extrapolation in the "DB-04 NHS cohort": • **Proportional hazards:** The LCHP plot in the "DB-04 NHS cohort" shows no clear evidence that the PH assumption holds (**Figure 13**, **Appendix A**). As the LCHP lines are relatively straight, the six standard independent parametric forms are appropriate. These parametric curves were therefore fitted to patient-level PFS data from the "DB-04 NHS cohort".

- **Statistical fit:** AIC and BIC scores for the extrapolated PFS curves for the "DB-04 NHS cohort" are presented in **Table 18**, **Appendix A**. For the TPC arm, the generalised gamma and log-normal curves provide the best statistical fit as they have the lowest AIC and BIC values, respectively. The log-logistic curve also provides a good statistical fit with the third lowest AIC and BIC. For the T-DXd arm, the generalised gamma and Weibull curves provide the best statistical fit as they have the lowest AIC and BIC values, respectively. The log-logistic curve also provides a good statistical fit, with the third lowest AIC and second lowest BIC.
- **Visual fit:** Visual assessment of the observed KM data of the "DB-04 NHS cohort" demonstrates that all curves provide a reasonable fit for both TPC and T-DXd (**Figure 14** and **Figure 15**, **Appendix A**).

Long-term clinical plausibility

Overall, the log-logistic curve provides long-term TPC and T-DXd PFS estimates that are similar to the observed proportions in the "DB-04 NHS cohort" of DESTINY-Breast04 (**Table 4**). The 1-year estimates of PFS using the log-logistic curve are [redacted]% and [redacted]% for the TPC and T-DXd arms, respectively, which are closely aligned to the 1-year observed PFS from the "DB-04 NHS cohort" ([redacted]% and [redacted]%). Similarly, the 2-year estimate of PFS using the log-logistic curve in the T-DXd arm is [redacted]%, compared with the 2-year observed PFS of [redacted]% (corresponding data not available for the TPC arm).

While the generalised gamma produces landmark PFS estimates similar to the log-logistic in the first 1–2 years, the T-DXd and TPC generalised gamma curves intersect, which the company considers to be clinically implausible. In the "DB-04 NHS cohort", the generalised gamma parametric PFS curves cross before 3 years (**Figure 4**), which is even earlier than the point at which the curves intersect in the FAS cohort (5 years). Given the maturity of the PFS data, the magnitude and statistical significance of the PFS benefit in the "DB-04 NHS cohort" (HR: [redacted]; 95% CI [redacted], [redacted]; p<[redacted]), and the difference in the mechanism of action between T-DXd and TPC, the company considers that it would be highly unlikely that the PFS curves for both treatment arms would cross or be equal in the long-term. It is even more unlikely that this would happen before 3 years given that mature PFS KM data demonstrate a clear separation of curves and PFS benefit over the entire duration of the follow-up period of 2.5 years (30 months; **Figure 12**; median follow-up of [redacted] months in the FAS population).

While the company notes that the T-DXd KM curve falls to zero at the end of the follow-up period, the tail of the curve should be interpreted with caution as the numbers at risk in the last three months of the follow-up period is very low (3 or fewer) meaning each censoring or PFS event can have a great impact on the appearance of the KM curve.

The implausibility of intersecting PFS curves in the medium to long-term is supported by similar previous NICE appraisals with mature and statistically significant PFS data, in which the committee accepted a sustained progression-free benefit, without crossing of PFS curves, for at least 5 years (TA819, TA862, TA786 and TA423):[2,17–19]

- In TA819 (sacituzumab govitecan [SG] for treating unresectable triple-negative advanced BC after 2 or more therapies), SG demonstrated a statistically significant PFS benefit versus TPC (HR: 0.433 in the ITT population; p<0.0001) based on the mature PFS data from ASCENT (median follow-up: 17.7 months).[17] The fitted parametric survival distributions chosen by the company, and accepted by the appraisal committee, demonstrated a difference in PFS between SG and TPC arms at 5 years (PFS distribution of 0.68% with SG and <0.1% with TPC), and no caps were imposed for the PFS curves for the duration of the model time horizon.[17]
- In TA862 (2L T-DXd in HER2-positive u/mBC),[18] T-DXd was compared with T-DM1, a targeted therapy. After a median follow-up of 16.2 months in the T-DXd arm and 15.3 months in the T-DM1 arm, T-DXd demonstrated a statistically significant benefit in PFS (HR: 0.28; p<0.001). Based on these data, the extrapolated PFS curves predicted an incremental PFS benefit, and the committee accepted a progression-

free treatment benefit associated with T-DXd compared to T-DM1 with no crossover of PFS curves. Given that T-DM1 is a targeted therapy with the same mechanism of action as T-DXd, whereas TPC is a non-targeted therapy with a different mechanism of action, it is not consistent to assume that T-DXd would have equal efficacy to TPC at 5 years when a sustained PFS benefit was accepted for T-DXd versus T-DM1.

- In TA786 (tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced BC after 2 or more anti-HER2 therapies), the CEA was not based on head-to-head data from the HER2CLIMB trial but instead was based on an indirect treatment comparison of tucatinib combination versus non-targeted chemotherapies. Despite this use of an indirect comparison, the committee still accepted an indefinite PFS benefit.[19]
- In TA423 (eribulin for treating locally advanced or mBC after chemotherapy), the committee accepted indefinite PFS curve separation despite a modest and non-statistically significant difference in PFS by independent review between eribulin and TPC in EMBRACE (HR: 0.865) and eribulin and capecitabine in Study 301 (HR: 1.079).[2]

The company therefore considers that crossing of PFS curves or imposing a cap on the TPC curve, and thereby assuming equal PFS between T-DXd and TPC arms at 3 years, is not clinically plausible based on the DESTINY-Breast04 clinical data and precedence in decision-making in previous TAs with comparable data packages. This confirms that the generalised gamma curve choice for PFS is inappropriate.

Therefore, based on the above, the log-logistic curve remains the most clinically plausible for informing the extrapolation of PFS in the TPC and T-DXd arm based on strong statistical and visual fit, and clinical plausibility. The company considers the committee's preferred approach (for the FAS population), using generalised gamma parametric curves and applying a cap to ensure that TPC does not exceed T-DXd when the curves cross is not clinically plausible given the statistically significant and sustained PFS benefit with T-DXd vs. TPC in DESTINY-Breast04.

Table 4: PFS in the "DB-04 NHS cohort": Predictions by independently fitted distributions in T-DXd and TPC

Distribution	Median (months)*	1-Year PFS	2-year PFS	3-Year PFS	5-year PFS
TPC					
Observed KM data	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd					
Observed KM data	[redacted]	[redacted]	[redacted]	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Median time in months and predicted PFS are estimated after PFS has been capped by OS (log-logistic).
Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

	Figure 3. Observed KM versus predicted PFS for TPC and T-DXd in the "DB-04 NHS cohort" using the log-logistic curves  Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival; TPC, treatment of physician's choice. **Figure 4. Observed KM versus predicted PFS for TPC and T-DXd in the "DB-04 NHS cohort" using the generalised gamma curve**  Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan
4: TTD extrapolation ("DB-04 NHS cohort")	***The generalised gamma curve is the most appropriate to extrapolate TTD in the TPC and T-DXd arm of the "DB-04 NHS cohort" as it provides good statistical and visual fit to the observed KM data.*** Given that efficacy in the company's revised base case is based on the "DB-04 NHS cohort" (as stated in Issue 1), the company has provided justification for the chosen parametric curves to extrapolate TTD data from the "DB-04 NHS cohort" provided in this section. Similar to the approach in the FAS population, the company took a comprehensive approach to determine the most appropriate curve for TTD extrapolation in the "DB-04 NHS cohort", in line with best practice guidance from NICE Decision Support Unit Technical Support Document 14[5] (as discussed in CS Section B.3.3.2). The full range of six standard

parametric curves were evaluated for statistical goodness of fit, visual fit, and long-term plausibility.

As with the FAS, whereby the company and EAG agreed that generalised gamma was the most appropriate curve, the company is confident that the generalised gamma curve is the most appropriate curve to extrapolate TTD in the "DB-04 NHS cohort", as it provides good statistical and visual fit and clinically plausible TTD estimates.

Initial assessment of curve selection in the "DB-04 NHS cohort" based on proportional hazards, statistical fit, and visual fit

The company took a robust approach to determining suitable curves for TTD extrapolation in the "DB-04 NHS cohort":

- **Proportional hazards:** As with the FAS population, a log-cumulative hazards plot in the "DB-04 NHS cohort" shows no clear evidence that the PH assumption holds (**Figure 17**, **Appendix A**). The six standard independent parametric forms were therefore fitted to patient-level data from the "DB-04 NHS cohort".
- **Statistical fit:** AIC and BIC scores for the extrapolated TTD curves for the "DB-04 NHS cohort" are presented in **Table 19**, **Appendix A**. Overall, the log-logistic curve is the best fitting curve with the lowest AIC and BIC scores across both treatment arms. The log-normal and generalised gamma curves closely follow as the next best-fitting curves in both arms.
- **Visual fit:** Visual assessment of the observed KM data of the "DB-04 NHS cohort" versus predicted PFS curves demonstrates that all curves provide a reasonable fit for both TPC and T-DXd (**Figure 31** and **Figure 32**, **Appendix A**).

Long-term clinical plausibility

As demonstrated in **Table 5**, all curves provide plausible long-term estimates for TTD in the "DB-04 NHS cohort" compared to the observed data due to the maturity and completeness of the TTD data. Notably, the generalised gamma curve provides a 1-year TTD estimate of [redacted]% and [redacted]% in the TPC and T-DXd arm, respectively. This is compared to the observed TTD at 1-year of [redacted]% and [redacted]% for TPC and T-DXd, respectively. By 5 years, all TTD estimates in the TPC arm of the "DB-04 NHS cohort" are between [redacted]% and [redacted]%. Similarly, at 5 years in the T-DXd arm, TTD estimates are all equal to or below [redacted]%. The curves therefore have a broadly similar fit to the observed KM data in the "DB-04 NHS cohort". Based on this, the company maintains the use of the generalised gamma curve for the extrapolation of TTD in the "DB-04 NHS cohort". This is also aligned with the company and EAG's preferred curve for extrapolating TTD in the FAS.

Table 5: TTD in the "DB-04 NHS cohort": Predictions by independently fitted distributions in T-DXd and TPC

Distribution	Median (months)	1-Year TTD	2-Year TTD	5-Year TTD
TPC				
Observed KM data	[redacted]	[redacted]	[redacted]	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd				
Observed KM data	[redacted]	[redacted]	[redacted]	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	

Median time in months and predicted TTD are estimated after TTD has been capped by PFS (log-logistic).
Abbreviations: KM, Kaplan-Meier; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TTD, time-to-treatment discontinuation

Exploring TTD based on KM data in the "DB-04 NHS cohort"

In response to the committee request (DGC, section 3.12), the company has explored the direct use of KM to estimate TTD in the model in the "DB-04 NHS cohort" as a scenario. In this scenario, the TTD KM data from the DESTINY-Breast04 "DB-04 NHS cohort" is used to determine the proportion of patients on treatment in each model cycle until the cohort size reduces beyond a point where it is robust due to the small number of patients (defined as 10 patients at-risk). After this, the generalised gamma parametric curve is used to estimate the proportion of patients on treatment for each cycle. For TPC, the number of patients at risk falls to below 10 at 14 months; for T-DXd, the number of patients at risk falls to 10 at 23 months (**Figure 16**). Using the KM to model TTD has a minimal impact on the ICER; the ICER increases from £[redacted] to £[redacted] (**Table 15**).

Given the minimal difference in ICER between the KM approach and the parametric approach, the company has continued to use parametric curves to model TTD in the revised company base case and maintains the choice of generalised gamma. This is because generalised gamma is a good statistical and visual fit to the "DB-04 NHS cohort" data.

5: Progression-free utilities

The company has accepted the committee's preferred approach to modelling progression-free (PF) utilities derived using a Linear Mixed Model (LMM)

In the DGC, the committee raised concerns regarding the company's approach to estimating PF utilities, as the utility values were considered too high and lacking face validity. Both the EAG and the committee preferred to use treatment-specific PF utilities estimated from a linear mixed model (LMM): *"The committee considered that the company's utility values were too high and lacked face validity. It considered that the EAG's estimates were lower and likely more plausible. It concluded that the EAG's estimates for progression-free utilities should be used in the modelling."*

To align with the committee's preferred assumptions and support timely decision making, the company has accepted the LMM approach. In addition, to align with efficacy data in the economic model, the revised company base case uses the health state utility values from the "DB-04 NHS cohort" of DESTINY-Breast04 (see Issue 1 for context and Issues 2–4 for summary of efficacy in this cohort). The revised company base case PF utilities, derived from the LMM for the "DB-04 NHS cohort", are as follows (see **Table 20, Appendix A** for LMM regression coefficients):

- T-DXd PF (LMM) in the "DB-04 NHS cohort": [redacted]
- TPC PF (LMM) in the "DB-04 NHS cohort": [redacted]

The PF utilities derived from the LMM in the "DB-04 NHS cohort" are similar to those in the FAS population. For completeness, the company also conducted a scenario analysis, where the PF and PD utilities derived from the LMM for the FAS population were applied. Please see issue 6 below for further details.

6: Post-progression utilities

The company has updated the economic model to use trial-based post-progression (PP) utility values derived from a LMM regression, consistent with the methodology used for PF utilities, and, in line with the EAG's preferred approach, has included a conservative PP utility benefit of 6 months for T-DXd.

Summary

At ACM1, the company estimated the PP utility values in the model using the Lloyd *et al.* (2006)[20] algorithm and assumed a PP utility benefit for T-DXd vs. TPC that was maintained for 12 months, after which all patients adopted the PP utility value for TPC. The EAG preferred to estimate PP utilities by applying the PP utility decrement from Lloyd *et al.* (0.243) to the LMM PF utility values from DESTINY-Breast04. In addition, the EAG considered that it is more appropriate for the T-DXd PP utility benefit to be maintained for 6 months instead of 12 months. The committee preferred the EAG's approach to estimate PP utilities but considered that there was uncertainty regarding whether it is appropriate to include a differential effect in PP utilities between the treatment arms.

The company has responded to this issue by (i) updating the base case to use the LMM to derive PP utility values directly from DESTINY-Breast04, and (ii) changing the duration of a PP utility benefit for T-DXd from 12 months to a more conservative 6 months. The company believes that the LMM values offer greater face validity than the values derived using the EAG's approach. The company also maintains that a 12-month treatment-specific PP utility benefit with T-DXd vs. TPC is plausible, but, to reach a resolution, has assumed a PP benefit of 6 months, consistent with what has been accepted by NICE in a recent NICE appraisal.[17]

More detail on the rationale for the revised company base case approach is detailed below, including a comparison of the PF and PP utility values derived by the EAG and revised company base case (**Table 6**). The revised company base case uses the "DB-04 NHS cohort" utility values (to align with efficacy in the revised base case, as discussed in Issues 1–4 and in response to a request from the committee). and the FAS PP utility values are explored in a scenario analysis.

Rationale for deriving PP utility values from the LMM

The company disagrees with the EAG's approach to apply the PP utility decrement from Lloyd *et al.*[20] to the trial PF utilities derived from LMM as this results in the PP utilities (T-DXd: [redacted], TPC: [redacted]; FAS) being implausibly low and inconsistent with what has been used in previous TAs for mBC after one or more lines of chemotherapy in the metastatic setting (range from 0.540–0.653; **Table 6**).[2,17–19,21] The company also considers it suboptimal to apply a decrement from one data set (Lloyd et al.) to another, unrelated data set (DESTINY-Breast04 trial data). Therefore, an alternative approach to modelling PP utilities is needed.

Table 6: PP utility values from previous relevant NICE TAs

NICE TA	Treatment arm	PP utility value
TA423[2]	Eribulin 3L	0.588*
	TPC 3L	0.588*
TA862[18]	T-DXd 2L	0.596
	T-DM1 2L	0.596
TA819[17]	SG 3L	0.653**
	TPC 3L	0.569**
TA704[21]	T-DXd 3L	0.588
	SoC 3L	0.588
TA786[19]	Tucatinib 3L	0.698**
	Eribulin/capecitabine/vinorelbine 3L	0.588**

*Derived mid-point value – the committee agreed that a PP utility value between 0.496 and 0.679 was appropriate ; **Values are for the period of time when a treatment-specific PP utility difference is assumed. Abbreviations: 2L, second-line; 3L, third-line; NICE, National Institute for Health and Care Excellence; PP, post-progression; SG, sacituzumab govitecan; SoC, standard of care; TA, technology appraisal; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

To support resolution and timely decision-making, the company proposes using LMM regression to model PP utility values, consistent with the LMM preferred by the EAG for PF utilities. As described in response to Issue 8 of TE, the LMM was constructed to obtain mean utility scores by progression status.[22] The trial-derived LMM PP utility values for the

FAS and "DB-04 NHS cohort" are summarised in **Table 7**. Given that the PP utility values for both arms for the "DB-04 NHS cohort" (TPC: [redacted], T-DXd: [redacted]) and the FAS (TPC: [redacted], T-DXd: [redacted]) are within the range previously accepted by NICE committees for similar mBC appraisals (0.596–0.698; Table 6),[2,17–19,21] and given that a consistent methodology is used for PF and PP utilities, the company considers that the LMM approach is more appropriate than the EAG's approach and offers greater face validity. The company has therefore used the LMM PP utility values from the "DB-04 NHS cohort" in the revised base case.

Table 7: Comparison of utility values in the EAG post-TE base case and company revised base case

Model version	Parameter	Utility source	Utility value		
			T-DXd	TPC	T-DXd and TPC difference
EAG post-TE base case*	PF	Trial LMM	[redacted]	[redacted]	[redacted]
	PP (initial 6 months)	Lloyd *et al.* decrement	[redacted]	[redacted]	[redacted]
	Decrement	–	0.243	0.243	0
	PP (long-term)	TPC arm	[redacted]	[redacted]	0
	Decrement		[redacted]	[redacted]	[redacted]
Company revised base case ("DB-04 NHS cohort")	PF	Trial LMM	[redacted]	[redacted]	[redacted]
	PP (initial 6 months)	Trial LMM + PP difference	[redacted]	[redacted]	[redacted]
	Decrement	–	[redacted]	[redacted]	0
	PP (long-term)	Trial LMM	[redacted]	[redacted]	0
	Decrement	–	[redacted]	[redacted]	[redacted]
Company revised scenario analysis (FAS)	PF	Trial LMM	[redacted]	[redacted]	Trial LMM
	PP (initial 6 months)	Trial LMM + PP difference	[redacted]	[redacted]	[redacted]
	Decrement	–	[redacted]	[redacted]	0
	PP (long-term)	Trial LMM	[redacted]	[redacted]	0
	Decrement		[redacted]	[redacted]	[redacted]

*Current committee preferred base case
Abbreviations: EAG, external assessment group; LMM, linear mixed model; PF, progression-free; PP, post-progression; T-DXd, trastuzumab deruxtecan; TE, technical engagement; TPC, treatment of physician's choice

Rationale for a 6-month PP benefit with T-DXd

The company and EAG agree that a PP utility benefit should be applied for a duration of time in the base case. However, the committee "*had concerns about the assumption of a differential benefit after progression depending on treatment arm*". In the revised base case, the company maintains a PP utility benefit, but has conservatively assumed that this would apply for 6 months rather than 12 months. This duration aligns with QoL data collection in DESTINY-Breast04 (data were collected 40 days following treatment discontinuation and then 3 months following the 40-day assessment) and was the duration accepted in the appraisal of SG in TNBC (TA819).[17]

The company has modelled this 6-month PP utility benefit associated with T-DXd by adding the incremental PF utility benefit of T-DXd vs. TPC ([redacted] - [redacted] = [redacted]; "DB-04 NHS cohort") to the PP utility value for TPC ([redacted]; "DB-04 NHS cohort"). The resulting PP utility value for T-DXd ([redacted]) was assumed to last for 6 months, after which the T-DXd PP utility value is equalised to the PP utility value in the TPC arm (i.e., [redacted]; **Table 7**). The company considers this to be a conservative approach considering that clinical experts expected a 6–12-month PP treatment benefit (ACM1 Part 1 discussion.

The company maintains that a PP utility benefit for T-DXd vs TPC is appropriate and should be included in the base case. The application of a 6-month PP utility benefit between T-DXd and TPC is in line with the EAG's comments in the DGC: *"[The EAG] assumed that the difference in post-progression utilities between arms would last for 6 months, after which everyone adopts the TPC utility"* and consistent with the clinical expert opinion: *"The clinical experts believed that the trial response rate suggested a treatment benefit, and that this*

reduced tumour size would lead to a reduced symptom burden that would continue into the post-progression state."

In addition to the clinical experts' comments above, the company believes a PP utility benefit is appropriate based on evidence from DESTINY-Breast04, in which T-DXd demonstrated clear and statistically significantly improved disease control rates (87.1% vs 65.8; p<0.0001) and objective response rates (52.3% vs 16.3%; p<0.0001) over TPC, which clinical experts agreed would lead to a lower tumour burden and in turn better QoL at progression. This was demonstrated in DESTINY-Breast04, where QoL was maintained on treatment with T-DXd across a range of generic (EQ-5D-5L) and cancer-specific (EORTC QLQ-30 and EORTC QLQ-BR45) PRO instruments, with longer time to definitive deterioration across almost all measures and scales compared with TPC.[23] Further, DESTINY-Breast04 demonstrated higher utility in the T-DXd arm at the point of progression which highlights that a PP utility benefit is plausible. Given that experts considered 6–12 months to be appropriate for the duration of the PP utility benefit, the company consider a 6-month utility benefit to be conservative.[24]

The company also notes that a differential effect in PP utilities between treatment arms has previously been accepted in prior NICE submissions for breast cancer, such as TA819 (SG for 3L unresectable triple-negative advanced BC)[17] and TA786 (tucatinib with trastuzumab and capecitabine for 3L HER2-positive advanced BC),[19] as presented in **Table 6.**

The company also notes that a PP utility benefit for T-DXd was not accepted by the NICE committee in previous appraisals for T-DXd (TA862 and TA704),[18,21] but the company maintains that a PP utility benefit is appropriate for the current appraisal. A comparison between this appraisal and TA704 (T-DXd for 3L HER2-positive u/mBC)[21] is inappropriate as the DESTINY-Breast01 trial was a single-arm trial where HRQoL data were not collected, making it difficult to assess the utility benefit with T-DXd in the absence of clinical trial data. In TA862 (T-DXd for 2L HER2-positive u/mBC),[18] T-DXd was compared against T-DM1, which has the same antibody (trastuzumab) and the same mechanism of action as T-DXd and is a targeted treatment; conversely this appraisal assesses T-DXd against non-targeted single-agent chemotherapies (TPC). A PP treatment-specific utility benefit is therefore appropriate to apply to this appraisal as it was accepted in TA819 and TA786, which also compared the interventions with non-targeted chemotherapies in u/mBC.[17,19]

Exploring uncertainty
In the DGC, the committee requested *"to see an analysis assuming no differential effect".* To address this, the company has presented a scenario analysis where no PP utility benefit is applied between T-DXd and TPC arms. Assuming no PP utility benefit is applied between T-DXd and TPC arms has a minimal impact on the ICER; the ICER increases from [redacted] to [redacted] (**Table 15**). However, the company maintains that a 6-month PP utility benefit with T-DXd should be considered for this appraisal and has applied it in the revised company base case for the reasons discussed above.

For completeness, the company has also conducted a scenario analysis where the PF and PP utilities derived from the LMM for the FAS population were applied, with a 6-month PP utility benefit (**Table 7**). Using the PF and PP utilities derived from the LMM for the FAS population has a minimal impact on the ICER; the ICER decreases from [redacted] to [redacted] (**Table 15)**.

Conclusion
The revised company base case has been updated to model PP utility values derived from the LMM using data from the "DB-04 NHS cohort". This revised company base case provides utility values with improved face validity compared to the EAG's preferred approach. The company remains confident that a difference in PP utilities between the treatment arms should be maintained, in line with recently accepted BC appraisals,[17,19] and has conservatively limited the PP utility benefit to 6 months in its revised base case, in line with the EAG's base case.

7: Comparison of T-DXd and SG	***The company considers that a cost-minimisation analysis (CMA) vs SG provides relevant evidence for the appraisal of the HER2-low/HR-negative subgroup and encourages pragmatism in committee decision-making to ensure access to effective treatment options in this small subgroup of patients with the highest unmet need.*** **Overview** The company acknowledges the challenges with committee decision-making regarding the comparison of T-DXd with SG given that there is no direct comparative evidence and that the company and EAG have agreed that an indirect treatment comparison (ITC) would be highly uncertain and biased. The company therefore maintains that a CMA provides relevant evidence for decision-making. Given the challenges, the company would welcome pragmatism in committee decision-making to ensure that the high unmet need in this population is recognised given the following: • The comparison of T-DXd with SG is in patients with HER2-low/HR-negative u/mBC, which is the population with the highest unmet need given the poor outcomes (median PFS in the DESTINY-Breast04 TPC arm for the HR-negative cohort: 2.9 months; median OS: 8.3 months). Clinical experts and patient groups have been unanimous that more targeted treatment options are needed for patients with HER2-low/HR-negative u/mBC. • DESTINY-Breast04 data show that T-DXd is significantly more effective than TPC in HER2-low/HR-negative u/mBC, highlighting that it should be made available to patients to offer them the possibility of better outcomes compared to current chemotherapy treatment. • The triple-negative u/mBC population represents only ~10% of all patients with HER2-low u/mBC.[25] SG is therefore only a relevant comparator in a small proportion of the full population under consideration in this appraisal. For completeness, the company has provided a summary of the issue below. In response to the committee request, and to support timely decision-making, the company has also provided the results from an ITC, despite being highly uncertain, potentially biased, and not robust for decision-making. **Appropriateness of an ITC** The company notes that the committee "*would like to see an indirect treatment comparison of trastuzumab deruxtecan and sacituzumab govitecan rather than a naive, unadjusted comparison*" and "*further analyses to show the clinical effectiveness of trastuzumab deruxtecan compared with sacituzumab govitecan for the hormone receptor-negative subgroup*" (Section 3.18 and Section 3.22 of DGC). While the company understands the rationale for this request, there is no comparative effectiveness evidence of T-DXd versus SG in patients with HER2-negative u/mBC, and a robust ITC is not feasible, as noted in Section 3.18 of the DGC: *"The company acknowledged that an unadjusted indirect treatment comparison between trastuzumab deruxtecan and sacituzumab govitecan may be biased. But it explained that using a matching-adjusted indirect comparison may lead to a much smaller sample, limiting the reliability of the estimates.*" As discussed at the TE stage of this appraisal (Issue 2), findings from two independent ITC feasibility assessments concluded that an ITC between T-DXd (DESTINY-Breast04) and SG (ASCENT) in HER2-low/HR-negative u/mBC would be highly uncertain and not sufficiently robust for decision-making due to the following reasons: • Differences in the study populations and study designs • Small sample sizes in the two HER2-low/HR-negative subgroups. • Limited reporting of baseline characteristics in the HER2-low/HR-negative subgroup of ASCENT.

- Differences in the population characteristics for which data were reported in both DESTINY-Breast04 and ASCENT.

The listed reasons limit the ability to adjust for differences and any adjustment would further reduce the sample sizes. The infeasibility of a robust treatment comparison was confirmed by the EAG on page 297 of the committee papers: "*The EAG agrees with the findings from the two feasibility assessments that there are differences in the population characteristics between DESTINY-Breast04 and ASCENT which may result in a biased ITC estimates without adjustments. The EAG also agrees that using a matching-adjusted indirect comparison (MAIC) may lead to small effective sample size"*.

Equivalent efficacy

While a naïve comparison highlights that median PFS and OS are longer with T-DXd than SG, the company acknowledges differences in trial eligibility criteria, meaning some patients in ASCENT are treated at a later line than in DESTINY-Breast04. Despite this, a naïve, unadjusted comparison of outcomes from DESTINY-Breast04 vs. ASCENT shows a similar treatment effect vs. TPC for PFS and OS for T-DXd and SG, as highlighted by similar HRs vs. TPC and considerably overlapping 95% CIs (**Table 8**). In the absence of more robust evidence, the company considers that the naïve comparison is sufficient to assume comparable treatment efficacy between T-DXd and SG.

Table 8: DESTINY-Breast04 and ASCENT PFS and OS outcomes

Study (population)	Comparison	Outcome	Median, months	Difference in median, months	HR (95% CI)
ASCENT (HER2-low/HR-negative)[30]	SG vs. TPC	PFS	SG: 6.2 TPC: 2.9	3.3	0.44 (0.27, 0.72)
		OS	SG: 14.0 TPC: 8.7	5.3	0.43 (0.28, 0.67)
DESTINY-Breast04 (HER2-low/HR-negative)[4]	T-DXd vs. TPC	PFS	T-DXd: 8.5 TPC: 2.9	5.6	0.46 (0.24, 0.89)
		OS	T-DXd: 18.2 TPC: 8.3	9.9	0.48 (0.24, 0.95)

Abbreviations: CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR-negative, hormone receptor negative; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

ITC of T-DXd vs. SG in patients with HER2-low/HR-negative u/mBC

Any method of ITC, whether network meta-analysis (NMA) or matching-adjusted indirect comparison (MAIC), would require the use of available data from the *post-hoc* HR-negative/HER2-low subgroups of the DESTINY-Breast04 (N=42) and ASCENT (N=63) trials. With small effective sample sizes, differing patient populations, and inconsistent or unavailable reporting of patient characteristics, it is not feasible to perform an NMA or MAIC to compare T-DXd with SG in the HER2-low/HR-negative population.

If an NMA were to be attempted between T-DXd and SG in the HER2-low/HR-negative population, the large differences identified between studies in the patient characteristics would impact the relative treatment effect estimates and introduce significant biases into the results. Furthermore, analysis of the feasibility of an NMA shows that there is violation of the key requirements of an NMA: connectivity (i.e., are the trials well connected through similar treatments), consistency (i.e., are the trials consistent in their results of similar treatments), and transitivity (i.e., are the investigated populations similar enough to be in a network).

A MAIC is also not possible for a comparison of T-DXd and TPC in HER2-low/HR-negative u/mBC. A MAIC would be based on a heavily reduced effective sample size, leading to extreme uncertainty in the validity of the results. Furthermore, without detailed published

reporting of patient characteristics from the small *post-hoc* HER2-low subgroup of ASCENT or from the original ASCENT publication itself, performing a MAIC would be extremely difficult and would result in confounded and uninformative results.

In conclusion, neither an NMA nor a MAIC are considered appropriate for comparing T-DXd with SG in the HER2-low/HR-negative u/mBC population. Recognising the committee would like to see an ITC of T-DXd and SG rather than a naïve, unadjusted comparison, the company has presented ITC results from a simple, unadjusted Bucher analysis in [redacted]

Table 9 below. While the results should be interpreted with caution, they confirm that [redacted]

Table 9: ITC – Bucher analysis results

Comparison	Outcome	Bucher HR (95% CI)
T-DXd vs SG (using ITT population of ASCENT)	PFS	[redacted]
	OS	[redacted]
T-DXd vs SG (using HER2-low subgroup of ASCENT)	PFS	[redacted]
	OS	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intent-to-treat; PFS, progression-free survival; OS, overall survival

Relevant comparator

While the company acknowledges that SG is a relevant comparator in a small subset (~10%)[25] of the HER2-low population relevant to this appraisal, SG has not been evaluated in a HER2-low population by regulatory agencies or NICE and has not shown to be cost-effective in a HER2-low/HR-negative u/mBC population. Given this, and because any ITC vs. SG would not be robust, the company would like to highlight that the comparison of T-DXd vs TPC is the most useful for decision-making in this appraisal as it is informed by head-to-head data from DESTINY-Breast04.

Cost-minimisation analysis: base case

In light of the challenges in generating robust comparative effectiveness estimates for T-DXd vs SG, any potential cost-effectiveness analysis of T-DXd compared to SG would result in unreliable and highly uncertain cost-effectiveness results. The company has pragmatically proposed a CMA of T-DXd vs SG to support committee decision-making in this small subset of HER2-low patients with a high unmet need and limited treatment options. The CMA assumes that T-DXd and SG have similar efficacy, as shown by the similar HRs versus TPC and overlapping 95% CIs between the DESTINY-Breast04 and ASCENT subgroups by naïve comparison and by the simple unadjusted Bucher ITC analysis. Consistent with results in the DESTINY-Breast04 FAS and HR-positive cohorts, T-DXd demonstrated a significant benefit in the HER2-low/HR-negative subgroup: PFS HR 0.46 (vs. 0.51 in the HR-positive cohort); OS HR 0.48 (vs. 0.64 in the HR-positive cohort).

The company notes that the trial-specific (DESTINY-Breast04 and ASCENT) Grade ≥3 treatment-emergent adverse events (TEAE) for T-DXd and SG were already incorporated into the company CMA base case at ACM1, as highlighted by the committee in the DGC: *"it*

	preferred to see a scenario in which the company applied grade 3 or above treatment-emergent adverse events." In this approach, TEAE rates from the SG arm in ASCENT are applied to the SG arm of the cost-minimisation model and the corresponding rates from DESTINY-Breast04 are applied to the T-DXd arm in the model. Therefore, in the company CMA base case, using the revised PAS price and updated administration costs (further information regarding administration costs is presented in Issue 8), T-DXd is associated with a total cost of £[redacted] and SG is associated with a total cost of £[redacted], meaning that T-DXd is associated with a savings of £[redacted] over a lifetime time horizon. **Cost-minimisation analysis: scenario** The company also notes the committee's request to conduct a scenario analysis in the CMA that incorporates the trial-specific time-on-treatment (ToT) values for T-DXd and SG from DESTINY-Breast04 and ASCENT, respectively. As discussed at TE (Issue 2), the company does not consider the use of SG ToT data from the full ASCENT population in the CMA to be appropriate. The ASCENT and DESTINY-Breast04 trial populations are different, and ToT is dependent on, and may impact, a wide range of clinical factors, including toxicity and efficacy. In the CMA, it is therefore inappropriate to use longer PFS and OS for SG from DESTINY-Breast04 while retaining shorter ToT for SG from the full ASCENT population. Despite this, in the absence of ToT data for the ASCENT HER2-low subgroup, and in an attempt to more robustly model a trial-specific ToT scenario, the company has included a scenario to estimate ToT in the SG HER2-low/HR-negative subgroup using PFS in the full ASCENT population and the ASCENT subgroup. In this scenario, the ratio of median PFS in the full ASCENT population vs the HER2-low population was calculated as 1.29 (4.8 vs 6.2 months, respectively). This ratio was then applied to the ASCENT full population mean ToT (6.12 months) to derive a ToT estimate of 7.9 months for the HER2-low subgroup. In this CMA scenario, T-DXd is associated with a total cost of £[redacted] and SG is associated with a total cost of £[redacted], resulting in T-DXd associated with a savings of £[redacted] over a lifetime time horizon.
8: Admin costs	***The company has updated the administration costs in the model in line with the DGC.*** In the revised company base case, Healthcare Resource Group (HRG) code SB11Z (deliver exclusively oral chemotherapy) was used to calculate the administration costs for capecitabine, and SB12Z (deliver simple parenteral chemotherapy) was used for T-DXd and all TPC agents delivered intravenously. The company applied the day-case cost for the first cycle of the model, and the outpatient cost was applied for all subsequent cycles. However, during the ACM, the Cancer Drugs Fund (CDF) clinical lead noted that the administration costs in the model should be updated to include the following total costs, which would be more appropriate for the administration of each treatment (Section 3.16 of DGC): • *£361.53 for all cycles of T-DXd (HRG code SB12Z: simple parenteral at first attendance of each cycle)* • *£245.23 per cycle for capecitabine (HRG code SB11Z: exclusively oral chemotherapy)* • *£361.53 for day 1 and £470.62 for day 8 per cycle for eribulin (HRG codes SB12Z: simple parenteral at first attendance of each cycle and SB15Z: subsequent elements of a chemotherapy cycle).* In response to this request, the company has updated the economic model to incorporate the administration costs proposed by the CDF Clinical Lead, as noted in the DGC. Moreover, the CDF clinical lead also recommended the inclusion of costs for outpatient consultation in addition to chemotherapy delivery: *"they suggested that there should be an additional medical oncology outpatient consultation at every 6 weeks for all treatments, at a cost of £217 per consultation."* However, this has not been included in the revised company

	base case, to avoid double-counting, as the company base case assumes more frequent outpatient visits (every 4 weeks) than what was recommended by the CDF clinical lead (every 6 weeks). In summary, the revised company base case model has been updated to incorporate the administration costs requested by the CDF clinical lead. This change had a minimal impact on the ICER (Table 11).
9: Severity Modifier	***A severity weight of 1.2 underestimates the severity of the disease for this end-of-life treatment.*** The DGC states: *"Both the company and EAG's estimates resulted in a severity weight of 1.2x. So, the committee concluded that the severity weight of 1.2 applied to the QALYs was appropriate."* The company remains concerned with the change in NICE methods for assessing the value of technologies for late-stage metastatic cancers and maintains that moving from the previous end-of-life (EOL) criteria to the severity modifier has considerable implications for this appraisal. This appraisal would have met the previous EOL criteria and therefore qualified for a willingness-to-pay threshold equivalent to £50,000 per QALY gained, whereas the severity weight of 1.2x effectively results in a significantly lower willingness-to-pay threshold equivalent to £36,000 per QALY gained. While this appraisal qualifies for the 1.2x severity modifier according to the current NICE framework, the company considers that this underestimates the severity of the condition in the population with HER2-low u/mBC. This is highlighted by comments from METUPUK, who voiced their concern regarding the use of severity modifier during the TE response stage of the appraisal: *"The severity modifier, with the discrete 1.2 and 1.7 categories does not provide the flexibility to capture the impact on this devastating disease. With a median survival of just 16.8 months, T-DXd increased survival by over 6 months, easily meeting the previous end of life funding of £50,000 per QALY gained".*[7] The company maintains that the 1.2x severity modifier underestimates the severity of the condition for this appraisal making it much more challenging to demonstrate cost-effectiveness. The company would welcome the committee applying flexibilities in decision-making given the high unmet need, innovation, and clinical value of T-DXd in HER2-low u/mBC, which could potentially benefit a large cohort of people in England improving population health.
10: Innovation and benefits not captured in the QALY calculations	***T-DXd is innovative and offers benefits not captured in the QALY calculations in the model.*** The DGC states: *"The committee acknowledged that there may be benefits with trastuzumab deruxtecan, but that these were captured in the modelling".* However, as previously discussed in the CS (Section B.3.13) and at the TE stage (Additional issue 1), the company maintains that T-DXd is an innovative therapy that offers benefits not captured in the QALY calculations in the model. **<u>Benefits not captured in the QALY</u>** • A recent study by Hernandez Alava and colleagues at SchARR (2023) identified that the impact of BC on patients' personal appearance, relationships, and sleep is not well captured by EQ-5D, and therefore, technologies that differ from standard of care treatment in these areas may be significantly misvalued in cost-effectiveness studies.[27] In addition, the relationship of patients with HER2-low u/mBC and their loved ones can be impacted by the disease as it may impact their ability to socialise, maintain usual life activities and cause considerable anxiety and fear for their loved ones.[9] Given that DESTINY-Breast04 showed that T-DXd demonstrated a statistically significant delay in time-to-definitive deterioration in the EORTC QLQ-C30 domains of body image, sexual function, and social functioning when compared

	with TPC,[24] the company considers that the QALY calculations in the model may underestimate the benefit of T-DXd in HER2-low u/mBC, both to patients and their loved ones. • [redacted] **<u>Innovation</u>** There is a high unmet need in patients with HER2-low u/mBC, as reflected by strong patient and clinician demand for effective treatments options such as T-DXd. DESTINY-Breast04 demonstrated that T-DXd was associated with a statistically significant improvement in median OS of over 6 months compared with TPC (23.4 months vs. 16.8 months, respectively, for T-DXd and TPC; FAS). These data led to T-DXd becoming the first and only targeted treatment to demonstrate significant survival benefit compared with current standard of care and subsequently receive marketing authorisation in a HER2-low population. T-DXd was awarded the Innovation Passport designation by the MHRA ILAP steering group in May 2022 (ILAP reference number ILAP/IP/22/08265/01). In the patient submission from METUPUK, it was noted that *"HER2-low u/mBC is a severe incurable and life-limiting disease"* and that the T-DXd results "*significantly outperform current standard of care*" and "*offers hope to patients with this severe end of life disease".*[9] As highlighted by the MHRA Innovation Passport and comments in the DGC: "*Because trastuzumab deruxtecan is the first HER-2 low targeted treatment option [for] metastatic or unresectable breast cancer, the clinical experts considered it to be a step-change in managing the condition."* T-DXd is therefore an innovative treatment with the potential to make a significant and substantial impact on health-related benefits, representing a step-change in the treatment paradigm for patients with HER2-low u/mBC. Given the above, the company does not agree that an ICER towards the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained) is appropriate for decision-making, and strongly considers that a higher threshold should be applied. This is in recognition of the challenges associated with evidence in a new indication and because the uncertainty raised by the committee in the DGC has been reduced through the further analyses presented in this response and the [redacted]. Further, T-DXd is an innovation in the treatment of u/mBC and there are additional benefits not captured within the QALY calculations. While difficult to quantify, these potential benefits of T-DXd should not be underestimated and should be qualitatively considered in committee decision-making.
11: Clarifications and factual inaccuracies in the DGC	***The company requests that NICE considers the following clarifications regarding the content reported in the DGC.*** ***<u>Positioning of T-DXd</u>*** The DGC states: *"The company positioned it after chemotherapy in the second and third-line settings, for both hormone-receptor positive and negative disease, which is narrower than the marketing authorisation."* The company would like to clarify that T-DXd is positioned as monotherapy for the treatment of adult patients with HER2-low u/mBC who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. This positioning is not narrower than the marketing authorisation as it reflects the EMA label, UK marketing authorisation, and DESTINY-Breast04 eligibility criteria. The DGC states: *"The clinical experts explained that trastuzumab deruxtecan is a first-line targeted treatment that may mean a person does not have to have chemotherapy."* This is a

	factually inaccurate statement as T-DXd is positioned for patients with HER2-low u/mBC who have received prior chemotherapy in the metastatic setting or developed disease recurrence within 6 months of completing adjuvant chemotherapy. T-DXd cannot be used prior to chemotherapy; it is positioned as an alternative to second- or later-line chemotherapy and may delay the need for subsequent chemotherapy. ***Reporting of the OS extrapolations*** Overall, an appropriate top-line summary of the company's approach to modelling OS and the EAG's evaluation has been given within the DGC. However, the company would like to highlight some points throughout the document which may have caused some ambiguity around the issue of OS and therefore impacted the committee's assessment of the suitability of log-logistic as the base case OS curve. The key RWE presented at the TE was not included in the DGC or discussed during Part 1 (open session) at ACM1. As detailed above, the Flatiron study is key in supplementing the clinical effectiveness data presented throughout this appraisal. It demonstrates real-world outcomes amongst a large patient cohort aligned to patients in the DESTINY-Breast04 trial receiving the current standard of care (SoC). It also strongly supports the company's selection of the log-logistic curve for extrapolating OS in the TPC and T-DXd arms. The company incorporated the Flatiron study at TE stage to help address the uncertainty highlighted by the EAG throughout previous post-submission stages. However, the study was not discussed during Part 1 (open session) at ACM1, and the DGC does not provide any details of the analyses from the Flatiron study that the company presented, or the importance of the OS outcomes observed across landmark timepoints. As a result, all the relevant evidence may not have been taken into account and therefore the summary of cost-effectiveness is not a reasonable interpretation of the evidence. Given the committee's uncertainty around the most plausible parametric curve for extrapolating OS, input from clinical experts can have a substantial impact on decision making. Clinical expert advice received by the company and EAG stated that [redacted] of patients treated with TPC would remain alive at 5 years and a small proportion (company) or 1–2% (EAG) would be alive at 10 years. Furthermore, advice to the company is that clinicians are more confidently able to input on 5-year OS estimates than 10 years as there is greater depth of clinical experience with patients at 5 years compared to 10 years in the HER2-low u/mBC population relevant to this appraisal. However, the DGC does not include this input from clinical experts and instead states: "*The clinical experts could not provide a view on which curves provided more plausible survival estimates, particularly for 10 years. This is because they see relatively few people with this condition still alive at this point, so there is limited available data.*" ***Reporting of the purpose of the company's cost-minimisation analysis*** The DGC states: *"The company compared sacituzumab govitecan with trastuzumab deruxtecan using a cost-minimisation analysis. This attempted to address the absence of sacituzumab govitecan from the trial TPC arm."* This statement does not accurately describe the company's purpose of conducting the CMA. The company would like to clarify that, as mentioned at the TE stage of this appraisal (Issue 2), given that it is not possible to conduct a robust ITC between T-DXd and SG for the HER2-low/HR-negative subgroup, the company used a naïve comparison to assume comparable relative efficacy between T-DXd and SG and consequently conducted a CMA as a pragmatic solution to explore the incremental cost of T-DXd vs. SG.

Key changes to the company base case from ACM1

The company has revised the base case to support appropriate and timely decision-making. The changes to the company base case are detailed in **Table 10**.

Table 10: Revised company base case, with reference to base case at ACM1

Economic input	Company's base case at ACM1	Change(s) made in response to DGC
Changes in response to key issues		
Modelling TPC	TPC (costs and efficacy) was modelled using the distribution of TPC agents in DESTINY-Breast04 FAS.	To address the committee's request for TPC to "*reflect NHS clinical practice"* and *"exclude second-line eribulin and gemcitabine*" (page 10, DGC), the company has updated the model base case to include efficacy, costs and utilities for both T-DXd and TPC based on the FAS population excluding patients treated with gemcitabine and 2L eribulin. This *post-hoc* analysis is referred to as the "DB-04 NHS cohort". This analysis was previously presented by the company as a scenario at the TE stage (referred to as the "truncated dataset" in the DGC). The committee requested further details on justification for its choice of survival distribution and associated utility data (DGC, section 3.9), which the company has provided in this response.
PF utilities	PF utility values were based on treatment-specific utilities for T-DXd and TPC derived from a GLMM using EQ-5D collected directly from DESTINY-Breast04.	The company has used a LMM to derive PF utilities based on the analysis of the "DB-04 NHS cohort"; this is consistent with the committee- and EAG-preferred approach.
PP utilities	PP utility values were estimated using the Lloyd *et al.* (2006)[20] algorithm. A 12-month PP utility benefit was included for T-DXd vs. TPC, after which all patients adopted the TPC PP utility value.	The company has used a LMM to derive PF and PP utilities based on the analysis of the "DB-04 NHS cohort". The company conservatively assume a PP utility benefit of 6 months (as in the EAG base case), after which patients adopt the TPC PP utility value.
Administration costs	The company applied administration costs using Healthcare Resource Group (HRG) code SB11Z (deliver exclusively oral chemotherapy) to calculate the administration costs for capecitabine, and SB12Z (deliver simple parenteral chemotherapy) for T-DXd and all TPC agents delivered intravenously. A day-case cost was used for the first cycle of the model, and the outpatient cost was applied for all subsequent cycles.	The company has amended administration costs to align with the costs suggested by the committee in the DGC.
Additional changes		
PAS price of T-DXd	The company applied a PAS discount of [redacted]% resulting in a fixed net price of £[redacted] for T-DXd.	The company has updated the PAS discount to [redacted]%, resulting in a fixed net price of £[redacted] for T-DXd. This is an additional [redacted] from the current PAS price.

Abbreviations: CDF, cancer drug fund; DGC, draft guidance consultation; ICER, incremental cost-effectiveness ratio; NHS – national health service; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

"DB-04 NHS cohort": Revised company base case results

Deterministic results for revised base case

The deterministic cost-effectiveness results for the revised company base case with the 1.2x severity modifier applied are presented in **Table 11**. For completeness, results are also presented with a 1.7x severity modifier, which is broadly commensurate with the previous NICE EOL criteria weighting that this indication would have robustly met prior to the change in NICE Methods in 2022. **Table 12** presents the net-health benefit (NHB) at the £30,000/QALY WTP threshold.

Table 11: Revised company base case (1.2x and 1.7x severity modifier; T-DXd PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (1.2x severity modifier)	ICER (£) (1.7x severity modifier)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 12: Net health benefit (1.2x severity modifier; T-DXd PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £30,000 WTP threshold
TPC	[redacted]	[redacted]	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; WTP, willingness-to-pay.

Sensitivity analyses for the revised base case

The mean probabilistic sensitivity analysis (PSA) results for the revised company base case, with 1.2 severity modifier and at the revised T-DXd PAS price, are presented in **Table 13**. The incremental cost-effectiveness plane is provided in **Figure 5** and **Figure 6** presents the cost-effectiveness acceptability curve for T-DXd vs. TPC.

Table 13: Probabilistic analysis results (revised company base case; 1.2x severity modifier applied; T-DXd PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 5: Cost-effectiveness plane (revised company base case; 1.2x severity modifier applied; T-DXd PAS price)

Abbreviations: CEP, cost-effectiveness plane; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 6: Cost-effective acceptability curve (1.2x severity modifier; T-DXd PAS price vs. TPC)*

*20% variation applied in the PSA, in the absence of SE or CIs.
Abbreviations: PAS, patient-access scheme; QALY, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Results of the one-way sensitivity analysis (OWSA) for the top 10 parameters that had the largest impact on the ICER, for the revised company base case (with 1.2x severity modifier and at the revised T-DXd PAS price) are presented in **Table 14** and **Figure 7**.

Table 14: One-way sensitivity analysis results (revised company base case; 1.2x severity modifier; T-DXd PAS price)

Parameter	ICER at lower bound	ICER at upper bound
Average weight (kg)	[redacted]	[redacted]
Relative dose intensity -Trastuzumab deruxtecan - 100	[redacted]	[redacted]
Utilities - Progression-free - Trastuzumab deruxtecan	[redacted]	[redacted]
Utilities - Progression-free - Physician's choice	[redacted]	[redacted]
Administration costs - Trastuzumab deruxtecan	[redacted]	[redacted]
Average body surface (m2)	[redacted]	[redacted]
Drug cost - Eribulin - 0.88mg vial	[redacted]	[redacted]
Relative dose intensity -Eribulin - 0.88	[redacted]	[redacted]
Health state cost - Progression-free - Total	[redacted]	[redacted]
Health state cost - Progressed - Total	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; T-DXd, trastuzumab deruxtecan.

Figure 7: One-way sensitivity analysis tornado diagram (revised company base case; 1.2x severity modifier; T-DXd PAS price)

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

Table 15: Scenario analysis (deterministic results; T-DXd [PAS price] vs. TPC; 1.2x and 1.7x severity modifier)

Parameter	Scenario number	Base case	Scenario	Incremental costs	Incremental QALYs	ICER (1.2x modifier)	ICER (1.7x modifier)
Base case							
Discount rate	1	Discount rates - Costs: 3.5%, outcomes: 3.5%	Discount rates - costs: 1.5%, outcomes: 1.5%				
OS extrapolations (applied to T-DXd and TPC)	2	Log-logistic	Log-normal				
	3		Gamma				
	4		Weibull				
PFS extrapolations (applied to T-DXd and TPC)	5	Log-logistic	Log-normal				
	6		Generalised gamma				
TTD extrapolations (applied to T-DXd and TPC)	7	Generalised gamma	Log-logistic				
	8		KM + extrapolated TTD using generalised gamma				
PP utility benefit	9	Sustained for 6 months	Sustained for 12 months				
	10		No treatment benefit applied				
Utility source for PF and PP	11	LMM ("DB-04 NHS cohort")	LMM (FAS)				

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PF, progression-free; PFS, progression-free survival; PP, post-progression; QALY, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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References

1. NICE. NICE Real-world evidence framework. (2022).
2. NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens | NICE [TA423]. https://www.nice.org.uk/guidance/ta423.
3. NICE. Final scope. Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]. https://www.nice.org.uk/guidance/indevelopment/gid-ta10813/documents (2023).
4. Modi, S. *et al.* Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *New England Journal of Medicine* **387**, 9–20 (2022).
5. NICE. NICE DSU Technical Support Document 14: Survival Analysis For Economic Evaluations Alongside Clinical Trials - Extrapolation With Patient-Level Data. https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD14-Survival-analysis.updated-March-2013.v2.pdf (2013).
6. Burnham, K. P., Anderson, D. R. & Huyvaert, K. P. AIC model selection and multimodel inference in behavioral ecology: some background, observations, and comparisons. *Behav Ecol Sociobiol* **65**, 23–35 (2011).
7. NICE. Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935] Committee Papers. (2023).
8. Daiichi Sankyo Inc. REAL-WORLD OVERALL SURVIVAL IN HER2 LOW METASTATIC BREAST CANCER PATIENTS PREVIOUSLY TREATED WITH CHEMOTHERAPY USING FLATIRON DATABASE. Data on File. (2023).
9. NICE. Dabrafenib plus trametinib for treating BRAF V600 mutation-positive advanced non-small-cell lung cancer | NICE [TA898]. https://www.nice.org.uk/guidance/ta898 (2023).
10. NICE. Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer | NICE [TA705]. https://www.nice.org.uk/guidance/ta705 (2021).
11. NICE. Pralsetinib for treating RET fusion-positive advanced non-small-cell lung cancer | NICE [TA812]. https://www.nice.org.uk/guidance/ta812 (2022).
12. NICE. Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer | NICE [TA760]. https://www.nice.org.uk/guidance/ta760 (2022).
13. NICE. Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer | NICE [TA781]. https://www.nice.org.uk/guidance/ta781 (2022).
14. NICE. Olaparib for adjuvant treatment of BRCA mutation-positive HER2-negative high-risk early breast cancer after chemotherapy | NICE [TA886]. https://www.nice.org.uk/guidance/ta886 (2023).
15. NICE. Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer | NICE [TA801]. https://www.nice.org.uk/guidance/ta801.

16. NICE. NICE strategy 2021 to 2026: Dynamic, Collaborative, Excellent. (2021).
17. NICE. Sacituzumab govitecan for treating unresectable triple-negative advanced breast cancer after 2 or more therapies | NICE [TA819]. https://www.nice.org.uk/guidance/ta819.
18. NICE. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 therapies | NICE [TA862]. https://www.nice.org.uk/guidance/indevelopment/gid-ta10804/documents (2023).
19. NICE. Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies | NICE [TA786]. https://www.nice.org.uk/guidance/ta786.
20. Lloyd, A., Nafees, B., Narewska, J., Dewilde, S. & Watkins, J. Health state utilities for metastatic breast cancer. *Br J Cancer* **95**, 683–690 (2006).
21. NICE. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies | NICE [TA704]. https://www.nice.org.uk/guidance/ta704.
22. Daiichi Sankyo, Inc. Technical engagement response form. Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]. Data on File. (2023).
23. Daiichi Sankyo Inc. Clinical Study Report for DS8201-A-U303. Data cut-off date: 11 Jan 2022. Data on File. (2022).
24. Daiichi Sankyo Inc. Trastuzumab deruxtecan for treating HER2-low unresectable or metastatic breast cancer after chemotherapy [ID3935]. Document B. Company evidence submission. (2023).
25. Dodson, A. *et al.* Breast cancer biomarkers in clinical testing: analysis of a UK national external quality assessment scheme for immunocytochemistry and in situ hybridisation database containing results from 199 300 patients. *J Pathol Clin Res* **4**, 262–273 (2018).
26. Alava, M. H., Pudney, S. E. & Wailoo, A. J. Does EQ-5D Tell the Whole Story? Statistical Methods for Comparing the Thematic Coverage of Clinical and Generic Outcome Measures, With Application to Breast Cancer. *Value in Health* **26**, 1398–1404 (2023).
27. Overview | Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy | Guidance | NICE. https://www.nice.org.uk/guidance/ta520 (2018).

Appendix A: "DB-04 NHS cohort" analyses

Overview

The "DB-04 NHS cohort" is a subgroup of the DESTINY-Breast04 FAS, in which patients assigned to gemcitabine (2L or 3L) or eribulin (2L), prior to randomisation, were removed from both the T-DXd and TPC arms of the analysis. It was introduced in response to EAG (TE stage) and committee (DGC) comments regarding the generalisability of the TPC arm of DESTINY-Bresat04. This appendix provides further information and analyses of the "DB-04 NHS cohort" in response to comments from the committee in the DGC.

As the choice of TPC agent was declared for each individual subject *before* randomisation (see Protocol v5.0 Section 5.1.1), it was possible to exclude corresponding patients from the T-DXd arm (i.e., it was possible to exclude patients in the T-DXd arm who would have been assigned 2L eribulin or gemcitabine (2L or 3L) had they been randomised to receive TPC). This approach preserves randomisation, as the observed and unobserved patient characteristics remained balanced between the two treatment arms after excluding these patients. In addition, since the number of prior lines of chemotherapy was a randomisation stratification factor in the trial, the 2:1 distribution of T-DXd to TPC is maintained in this analysis.

Baseline characteristics

Table 16 presents the baseline characteristics of the "DB-04 NHS cohort" of DESTINY-breast04.

Table 16: Patient baseline characteristics for the "DB-04 NHS cohort", a *post hoc* subgroup analysis of the DESTINY-Breast04 FAS

Characteristic	DB-04 NHS Cohort	
	T-DXd (N=247)	TPC (N=118)
Age (years)		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Age (years)		
<65	[redacted]	[redacted]
>=65	[redacted]	[redacted]
Weight (kg)		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Body mass index (kg/m2)		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Race		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]

Characteristic	DB-04 NHS Cohort	
	T-DXd (N=247)	TPC (N=118)
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
ECOG performance status		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Stratification factor HER2 status - IXRS		
HER2 IHC 1+	[redacted]	[redacted]
HER2 IHC 2+/ISH-	[redacted]	[redacted]
Stratification factor HR/CDK status - IXRS		
HR-positive with prior CDK4/6 inhibitor treatment	[redacted]	[redacted]
HR-positive without prior CDK4/6 inhibitor treatment	[redacted]	[redacted]
HR-negative	[redacted]	[redacted]
Stratification Factor Number of Prior Lines of Chemotherapy - IXRS		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
Hormone receptor status - Derived		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Number of prior lines of chemotherapy in the metastatic setting		
1	[redacted]	[redacted]
>=2	[redacted]	[redacted]
Prior CDK4/6		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Lines of endocrine therapy received in the metastatic setting		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
>=3	[redacted]	[redacted]
Best response to prior cancer systemic therapy		
Complete Response (CR)	[redacted]	[redacted]
Partial Response (PR)	[redacted]	[redacted]
Stable Disease (SD)	[redacted]	[redacted]
Progressive Disease (PD)	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
NA	[redacted]	[redacted]
History of CNS metastases		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Renal impairment at baseline		
Normal	[redacted]	[redacted]
Mild/Moderate	[redacted]	[redacted]

Characteristic	DB-04 NHS Cohort	
	T-DXd (N=247)	TPC (N=118)
Missing	[redacted]	[redacted]
Hepatic impairment at baseline		
Normal	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Baseline of visceral disease		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Lines of prior systemic therapy in any setting		
< 3	[redacted]	[redacted]
>=3	[redacted]	[redacted]
Lines of prior systemic therapy in a metastatic setting		
0-1	[redacted]	[redacted]
2	[redacted]	[redacted]
>=3	[redacted]	[redacted]

Abbreviations: BMI, body mass index; CDK, cyclic-dependent kinase; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HR-positive, hormone receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridisation; ITT, intent-to-treat; IXRS, interactive web/voice response system; PS, performance status; SD, standard deviation; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Sources: Daiichi Sankyo Inc., 2023 (Data on File)

Overall survival

Assessment of proportional hazards in the "DB-04 NHS cohort"

OS data are mature, with medians reached in both arms (**Figure 8)**. Extrapolation of outcomes was performed to inform cost-effectiveness estimates over a lifetime horizon.

Figure 8: OS KM from DESTINY-Breast04 in the "DB-04 NHS cohort" (T-DXd and TPC)

Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (Data on file)

Prior to the fitting of parametric models, a LCHP was produced to assess whether the proportional hazards (PH) assumption may hold. **Figure 9** presents the LCHP based on OS data from "DB-04 NHS cohort". As can be seen from the LCHP, the curves are not parallel over time, intersecting at around 6–7 months. This indicates that the ratio of the hazards between the two treatment arms is not constant and there is no clear evidence that the PH assumption holds. While the lines in the LCHP are not parallel, they are relatively straight, indicating that the standard parametric distributions are sufficient for extrapolating OS.

Figure 9: Log-cumulative hazard plot of OS from DESTINY-Breast04 in the "DB-04 NHS cohort" population

Abbreviations: LCHP, log-cumulative hazard plot; OS, overall survival.

Assessment of statistical fit and visual fit for fitted models

AIC and BIC scores for the extrapolated OS for "DB-04 NHS cohort" are presented in **Table 17**. Lower AIC and BIC scores indicate a better statistical fit to the observed data.

Table 17: Statistical fit (OS, independent models) in the "DB-04 NHS cohort"

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential				
Weibull				
Gompertz				
Log-logistic				
Log-normal				
Generalised gamma				
Gamma				

Bold indicates best statistical fit.

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; FAS, full analysis set; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 10: Observed KM versus predicted OS for TPC over a 3-year time horizon in the "DB-04 NHS cohort"

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician's choice.

Figure 11: Observed KM versus predicted OS for T-DXd over a 3-year time horizon in the "DB-04 NHS cohort"

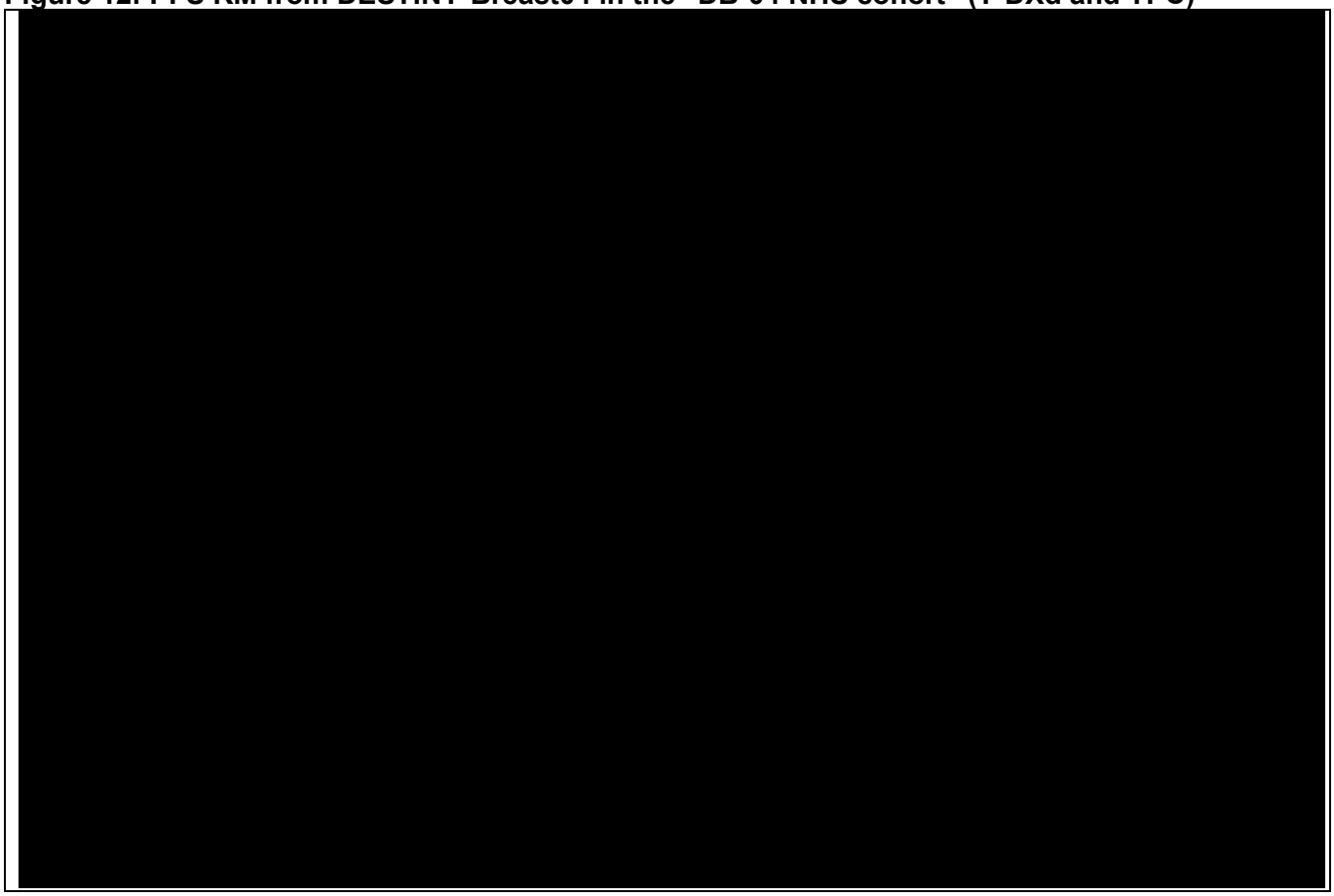
Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; T-DXd, trastuzumab deruxtecan.

PFS

Assessment of proportional hazards in the "DB-04 NHS cohort"

Figure 12 presents the observed KM data from the "DB-04 NHS cohort" of DESTINY-Breast04.

Figure 12: PFS KM from DESTINY-Breast04 in the "DB-04 NHS cohort" (T-DXd and TPC)



Abbreviations: BICR; blinded independent central review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival; TPC, treatment of physician's choice; T-DXd, trastuzumab deruxtecan.
Source: Daiichi Sankyo Inc., 2022 (Data on File).

As with OS data, a LCHP was produced for PFS (**Figure 13**). The LCHP shows that the curves are not consistently parallel over time, intersecting at ~2 months and beginning to converge towards the end. This suggests that there is no clear evidence of a constant hazard of progression and the PH assumption does not hold for the duration of the data.

Figure 13: DESTINY-Breast04: Log-cumulative hazard plot – PFS, "DB-04 NHS cohort"

Abbreviations: FAS, full analysis set; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Assessment of statistical fit and visual fit for fitted models in the "DB-04 NHS cohort"

AIC and BIC scores for the extrapolated PFS for DESTINY-Breast04 data are presented in **Table 18**.

Table 18: Statistical fit (PFS, independent models) in the "DB-04 NHS cohort"

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates best statistical fit
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; FAS, full analysis set; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Visual assessment of observed KM data versus predicted PFS curves is presented in **Figure 14** and **Figure 15**.

Figure 14: Observed KM versus predicted PFS (TPC) over a 3-year time horizon in the "DB-04 NHS cohort"

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival; TPC, treatment of physician's choice.

Figure 15: Observed KM versus predicted PFS (T-DXd) over a 3-year time horizon in the "DB-04 NHS cohort"

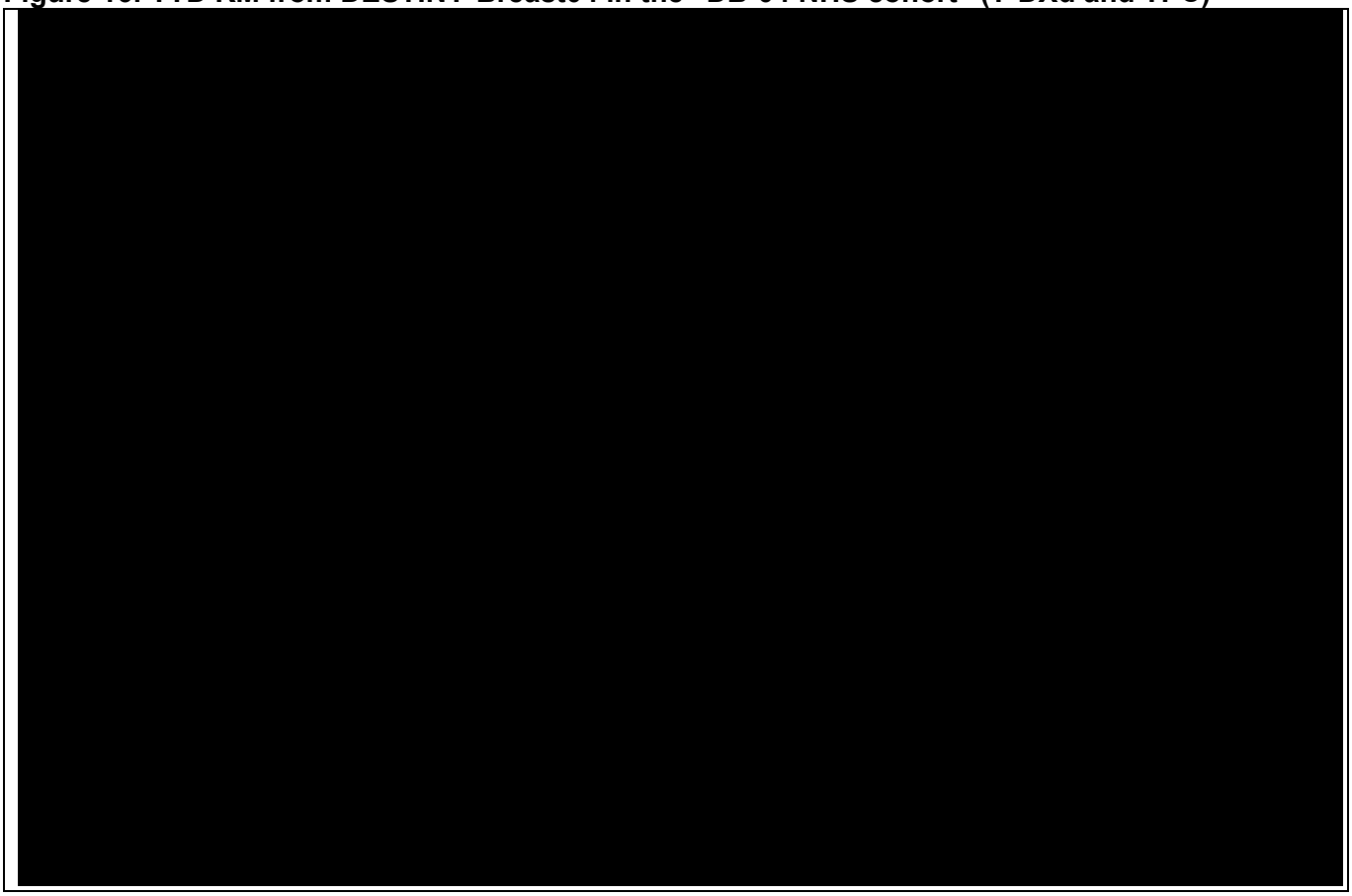
Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

Time-to-treatment discontinuation

Assessment of proportional hazards in the "DB-04 NHS cohort"

Figure 16 presents the observed KM data from the "DB-04 NHS cohort" of DESTINY-Breast04.

Figure 16: TTD KM from DESTINY-Breast04 in the "DB-04 NHS cohort" (T-DXd and TPC)



Abbreviations: BICR; blinded independent central review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival; TPC, treatment of physician's choice; T-DXd, trastuzumab deruxtecan.
Source: Daiichi Sankyo Inc., 2022 (Data on File).

The LCHP shows that the curves are relatively parallel over time, but, given that there remains no clear evidence or strong clinical rationale for the PH assumption to hold, independent curves were fitted to the DESTINY-Breast04 data to inform TTD for T-DXd and TPC (**Figure 17**).

Figure 17: DESTINY-Breast04; log-cumulative hazard plot (TTD, "DB-04 NHS cohort")

Abbreviations: FAS, full analysis set; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Assessment of the statistical goodness-of-fit scores and visual fit for fitted models

AIC and BIC scores for the extrapolated TTD for DESTINY-Breast04 data are presented in **Table 19**.

Table 19: Statistical scores (TTD, independent models) in the "DB-04 NHS cohort"

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates best statistical fit
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; FAS, full analysis set; T-DXd, trastuzumab deruxtecan; TTD, time-to-treatment discontinuation; TPC, treatment of physician's choice.

Visual assessment of observed KM data versus predicted TTD curves is presented in **Figure 18** and **Figure 19**.

Figure 18: Observed KM versus predicted TTD (TPC) over a 4-year time horizon in the "DB-04 NHS cohort"

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; TPC, treatment of physician's choice; TTD, time-to-treatment discontinuation

Figure 19: Observed KM versus predicted TTD (T-DXd) over a 4-year time horizon in the "DB-04 NHS cohort"

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; T-DXd, trastuzumab deruxtecan; TTD, time-to-treatment discontinuation

LMM based on progression status

The company provided a scenario analysis in the TE response to issue 8 in which PF utilities were derived through LMM analysis. The approach and methodology described in this TE response was repeated for the LMM in the "DB-04 NHS cohort". Results are provided in **Table 20**.

Table 20. Results of LMM based on progression status in the "DB-04 NHS cohort"

	Regression coefficients* (95% CI)
Intercept	[redacted]
p-value	[redacted]
Treatment arm (T-DXd vs TPC)	[redacted]
p-value	[redacted]
Progression status (progression vs progression-free)	[redacted]
p-value	[redacted]
AIC	[redacted]
BIC	[redacted]

* Unstructured covariance matrix was used to model the correlation within subject. Please see the company TE response to Issue 8 for more information on the methodology and approach to the LMM.

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, confidence intervals; DB-04, DESTINY-Breast04; LMM, linear mixed model; NHS, national health service; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

Appendix B: "Flatiron NHS cohort"

The Flatiron study is a large observational study that examined survival outcomes among a US real-world cohort of [redacted]. The "Flatiron NHS cohort" is a subgroup analysis of the "Flatiron Full Cohort" in which the eligibility criteria was broadly aligned to DESTINY-Breast04 and NHS clinical practice.

The "Flatiron Full Cohort" included [redacted]. The "Flatiron NHS Cohort" was created by first subsetting the "Flatiron Full Cohort" to [redacted]. Next, this subset of the "Flatiron Full Cohort" was further [redacted]

- [redacted].
- [redacted]
- This resulted in [redacted] in the "Flatiron NHS cohort" having 1 or 2 prior lines of chemotherapy, respectively.

Table 21 presents the attrition of the Chemo Cohort of the Flatiron study.

Table 21: Cohort attrition for "Flatiron NHS cohort" (Chemo Cohort) of the Flatiron study

Attrition Criteria	Patients (N)
Inclusion Criteria (Full Cohort)	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Exclusion Criteria (Full Cohort)	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Full Cohort	[redacted]
Inclusion Criteria (Flatiron NHS Cohort)	

Attrition Criteria	Patients (N)
[redacted]	[redacted]
[redacted]	[redacted]
Flatiron NHS Cohort	[redacted]

Abbreviations: DB-04, DESTINY-Breast04; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemical; ISH, in situ hybridization; LOT, line of therapy; mBC, metastatic breast cancer.
*Referred to as the Chemo Cohort in the statistical analysis plan and source materials.
Note: The Full Cohort includes [redacted]. The "Flatiron NHS Cohort" was created by first [redacted] In order to [redacted] as the "DB-04 NHS cohort" ([redacted]), this subset was further sampled as follows: [redacted].
[a] HER2-low test result defined as IHC 1+, or IHC 2+ and ISH- with maximum of 7 days between IHC and ISH tests.
[b] Patients who died within the 90-day window were not excluded from analysis.
[c] HER2-positive test result defined as IHC 3+, or IHC 2+ and ISH+ with maximum of 7 days between IHC and ISH tests. In the case of an absent IHC test result, ISH+ alone was considered a HER2+ test result.

Table 22 presents the baseline characteristics of patients included in the Chemo cohort of the Flatiron study.

Table 22: Patient demographic and clinical characteristics of the "Flatiron NHS cohort" (also referred to as the Chemo Cohort) of the Flatiron study (N=[redacted])

Characteristic	Timepoint			
	General[a]	mBC Diagnosis	Start of Qualifying Chemo	Index Treatment Date
Age (years)				
Category, n (%)				
18-39	[redacted]	[redacted]	[redacted]	[redacted]
40-54	[redacted]	[redacted]	[redacted]	[redacted]
55-64	[redacted]	[redacted]	[redacted]	[redacted]
65-74	[redacted]	[redacted]	[redacted]	[redacted]
≥75	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Gender[a], n (%)				
Female	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Race[a], n (%)				
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity[a], n (%)				
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	Timepoint			
	General[a]	mBC Diagnosis	Start of Qualifying Chemo	Index Treatment Date
Practice type[a], n (%)				
Academic	[redacted]	[redacted]	[redacted]	[redacted]
Community	[redacted]	[redacted]	[redacted]	[redacted]
Region[a,b], n (%)				
West	[redacted]	[redacted]	[redacted]	[redacted]
Midwest	[redacted]	[redacted]	[redacted]	[redacted]
South	[redacted]	[redacted]	[redacted]	[redacted]
Northeast	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)				
Category, n (%)				
Underweight (<18.5)	[redacted]	[redacted]	[redacted]	[redacted]
Normal (18.5 - <25)	[redacted]	[redacted]	[redacted]	[redacted]
Overweight (25 - <30)	[redacted]	[redacted]	[redacted]	[redacted]
Obese (≥30)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
De novo stage IV, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	Timepoint			
	General[a]	mBC Diagnosis	Start of Qualifying Chemo	Index Treatment Date
No	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
HR status, n (%)				
HR+	[redacted]	[redacted]	[redacted]	[redacted]
HR-	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Line number of index LOT, n (%)				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
≥6	[redacted]	[redacted]	[redacted]	[redacted]
Year of initial BC diagnosis[a], n (%)				
<2000	[redacted]	[redacted]	[redacted]	[redacted]
2000-2004	[redacted]	[redacted]	[redacted]	[redacted]
2005-2009	[redacted]	[redacted]	[redacted]	[redacted]
2010-2011	[redacted]	[redacted]	[redacted]	[redacted]
2012-2013	[redacted]	[redacted]	[redacted]	[redacted]
2014-2015	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	Timepoint			
	General[a]	mBC Diagnosis	Start of Qualifying Chemo	Index Treatment Date
2016-2017	[redacted]	[redacted]	[redacted]	[redacted]
2018-2019	[redacted]	[redacted]	[redacted]	[redacted]
≥2020	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Calendar year of timepoint, n (%)				
2011	[redacted]	[redacted]	[redacted]	[redacted]
2012	[redacted]	[redacted]	[redacted]	[redacted]
2013	[redacted]	[redacted]	[redacted]	[redacted]
2014	[redacted]	[redacted]	[redacted]	[redacted]
2015	[redacted]	[redacted]	[redacted]	[redacted]
2016	[redacted]	[redacted]	[redacted]	[redacted]
2017	[redacted]	[redacted]	[redacted]	[redacted]
2018	[redacted]	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]	[redacted]
2022	[redacted]	[redacted]	[redacted]	[redacted]
2023	[redacted]	[redacted]	[redacted]	[redacted]
Time from mBC diagnosis to timepoint (months)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Time from mBC diagnosis to start of 1L (months)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	Timepoint			
	General[a]	mBC Diagnosis	Start of Qualifying Chemo	Index Treatment Date
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up time from index treatment date (months)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
ET in metastatic setting prior to index LOT, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines containing ET in the metastatic setting				
Among patients with ≥1 prior line of ET				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Among all patients (including zeroes)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
CDK 4/6 inhibitor in metastatic setting prior to index LOT, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines containing CDK 4/6 inhibitor in the metastatic setting				
Among patients with ≥1 prior line of CDK 4/6 inhibitor				
N	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	Timepoint			
	General[a]	mBC Diagnosis	Start of Qualifying Chemo	Index Treatment Date
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Among all patients (including zeroes)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy in metastatic setting prior to index LOT, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines containing immunotherapy in the metastatic setting				
Among patients with ≥1 prior line of immunotherapy				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Among all patients (including zeroes)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Q1, Q3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines containing chemotherapy in metastatic setting, n (%)				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line; BMI, body mass index; CDK, cyclin-dependent kinase; DB-04, DESTINY-Breast04; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HR, hormone receptor; LOT, line of therapy; mBC, metastatic breast cancer; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation; US, United States.

Note 1: The “Flatiron NHS Cohort” was created by first subsetting the Full Cohort to patients whose index therapy was capecitabine, paclitaxel, docetaxel, or vinorelbine following 1 line of chemotherapy, or whose index therapy was capecitabine, paclitaxel, docetaxel, vinorelbine, or eribulin following 2 lines of chemotherapy (monotherapies only). In order to achieve a similar distribution of number of prior lines of chemotherapy as the “DB-04 NHS cohort” ([redacted]), this subset was further sampled as follows: All patients ([redacted]) with 2 prior lines of chemotherapy were selected; [redacted] patients were randomly selected from the group of patients with 1 prior line of chemotherapy

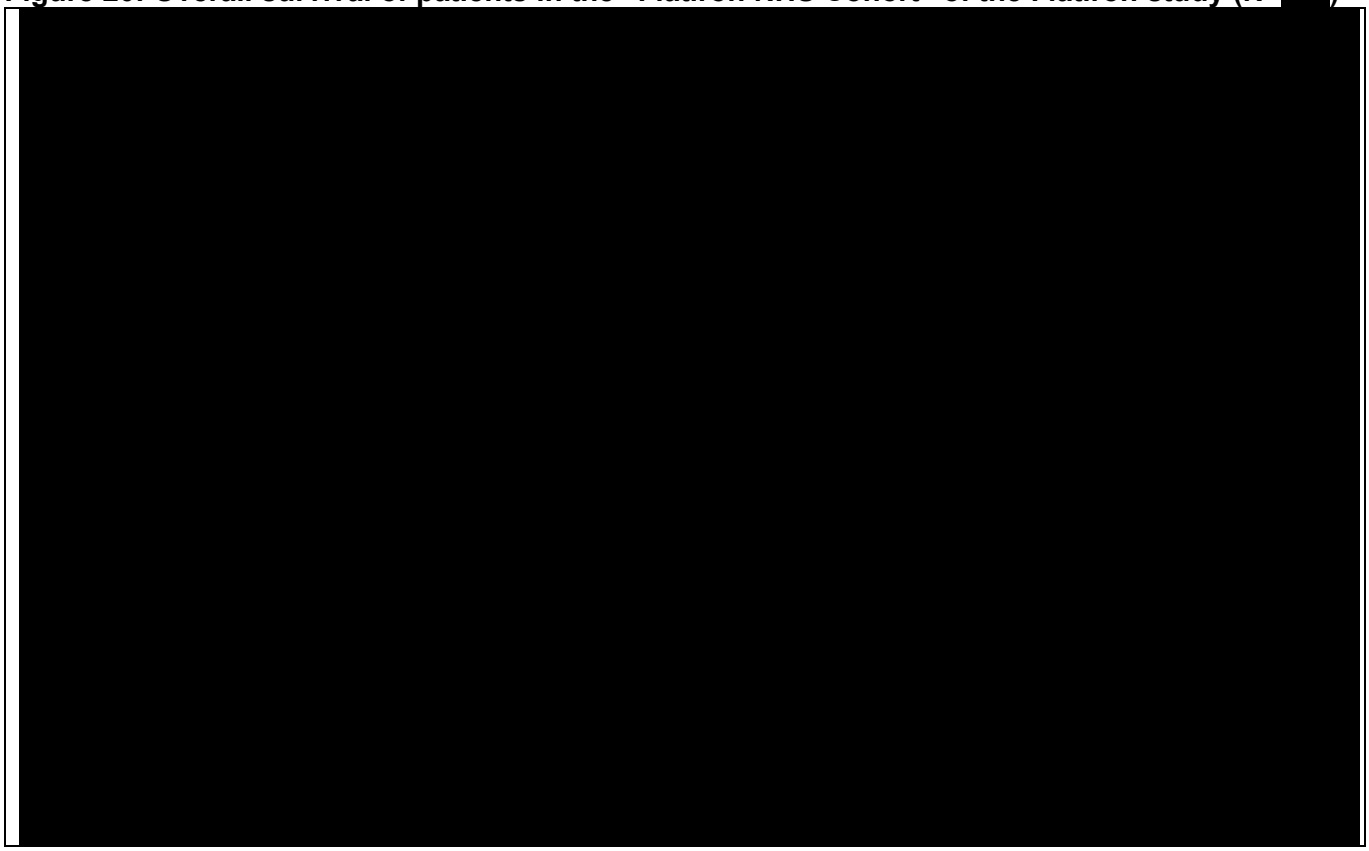
Note 2: In general, baseline characteristics were evaluated at mBC diagnosis date, at the start of the qualifying line of chemotherapy, and at the index treatment date. If a characteristic was not evaluated at a specific timepoint, '--' is displayed in the cell. Characteristics that are not anchored on a specific timepoint or are anchored on a different timepoint are superscripted with an 'a', and results are displayed in the column for ‘General'.

[a]Characteristic not evaluated at a specific timepoint, or characteristic evaluated at a different timepoint than those displayed (with timepoint indicated in the row label). Results are displayed in the column for ‘General’.

[b]Assigned based on mapping from state of residence to US Census Region. Residents of Puerto Rico were assigned to the South region.

Figure **20** presents the OS of patients in the “Flatiron NHS Cohort” of the Flatiron study.

Figure 20: Overall survival of patients in the “Flatiron NHS Cohort” of the Flatiron study (N=)



Appendix C: Responding to issues in the DGC related to extrapolation of OS, PFS and TTD in the FAS population

The company revised base case uses efficacy, safety, and utility data from the DESTINY-Breast04 "DB-04 NHS Cohort" (rather than the FAS) to reflect agents used in NHS practice and align with the committee's recommended approach for modelling TPC. This means that the FAS is no longer the key population for decision-making and is presented as a supporting scenario only.

Despite this, the company notes that the DGC includes discussion around the most relevant assumptions and inputs for OS, PFS, and TTD extrapolations in the FAS population. For completeness, the company has responded to these discussions below.

OS extrapolation (FAS)	***The company strongly considers that log-logistic is the most appropriate curve to extrapolate DESTINY-Breast04 FAS OS data in the TPC and T-DXd arms based on statistical fit, visual fit, clinical expert opinion, and comparison with Flatiron RWE.*** ***The company's revised base case includes OS data derived from the "DB-04 NHS cohort" of DESTINY-Breast04. For completeness, the company has also provided further discussion on the suitability of the log-logistic curve in the FAS population, in response to the committee's request in the DGC.*** **Background:** During the appraisal, the EAG raised concerns over the selected parametric survival distribution that has been fitted to the KM data from DESTINY-Breast04 to model OS. The company maintain that the log-logistic curve is most appropriate, as it provides good statistical fit to the observed data and clinically plausible long-term estimates. The EAG prefer the Weibull curve in their base case despite stating that it adopts a pessimistic assumption, as noted by clinical advice to the EAG, that approximately [redacted] of patients remain alive at 5 years in the TPC arm. The committee acknowledged that Weibull is likely to be too conservative whilst stating that log-logistic is optimistic and agreed with the EAG that the gamma curve should be explored. Based on the committee's request, the company has explored the gamma curve for extrapolation of OS in the FAS. Below is a comparison of the six standard parametric curves and the additional gamma curve in terms of statistical goodness of fit, visual fit, and long-term plausibility (assessed through consultation with UK clinical experts and comparison with relevant RWE from the Flatiron study). A summary of the curve selection process is provided in **Table 23** and in the bullet points below, while figures and tables for each step in the model selection process are provided below. **Log-logistic remains the most appropriate curve:** In summary, log-logistic is the only curve that is a good statistical and visual fit as well as providing OS estimates that are clinically plausible, as validated by UK clinical experts and RWE: • **Statistical fit.** The log-logistic curve provides the best overall fit to the FAS data for the TPC arm, while Weibull, gamma, and generalised gamma were within 5 points of log-logistic. For the T-DXd arm, log-logistic remained within 5 AIC and BIC points of the best-fitting curve (Gompertz) and was therefore a good statistical fit, along with Weibull, gamma, and generalised gamma.[6] • **Visual fit.** Log-logistic, gamma, generalised gamma and Weibull curves appear to be reasonable visual fits to the FAS TPC data, while Gompertz, log-logistic, generalised gamma, Weibull, and gamma were reasonable visual fits to the T-DXd data. • **Long-term plausibility.** Clinical expert advice sought by the EAG and company during the NICE TE stage was that [redacted]% of patients treated with

TPC would be alive at 5 years and a small proportion would be alive at 10 years. Based on this feedback, the Weibull, gamma and generalised gamma 5-year estimates ([redacted]%, [redacted]% and [redacted]%) and 10-year estimates ([redacted]% [redacted]% and [redacted]%) are too pessimistic and not clinically plausible to inform the FAS TPC OS extrapolation. By contrast, log-logistic produces plausible 5- and 10-year estimates of [redacted]% and [redacted]%, respectively. For T-DXd, clinical experts consulted as part of an advisory board by the company stated that some patients would be expected to be alive at 10 years and therefore considered the Weibull curve to be too pessimistic, with a 10-year OS estimate of [redacted]% compared with [redacted]% using the log-logistic curve. For 5-year estimates, the Weibull, gamma and generalised gamma curves estimate T-DXd OS rates of [redacted]%, [redacted]% and [redacted]% which are below or broadly in the range expected by clinical experts for the TPC arm ([redacted]%). By comparison, the log-logistic T-DXd OS extrapolation was more plausible, as the 5-year and 10-year estimates ([redacted]% and [redacted]%) are higher than clinical expert estimates for the TPC arm, which should be the case given that DESTINY-Breast04 shows that T-DXd significantly improves OS compared with TPC.

- **RWE from the "Flatiron NHS cohort" confirms that the log-logistic curve is appropriate to model OS in the TPC arm.** As stated in Issue 2, to address EAG concerns regarding the Flatiron analysis presented at TE, the company has provided new analyses of the Flatiron data using a population reflective of patients with HER2-low treated in UK clinical practice ("Flatiron NHS" cohort; N=[redacted]). This "Flatiron NHS" cohort demonstrates 5-year estimates of [redacted]%, which further highlights that Weibull ([redacted]%) and gamma ([redacted]%) 5-year estimates for TPC are too pessimistic while log-logistic ([redacted]%) is clinically plausible.

Based on the above, the company maintains that log-logistic is the most appropriate curve for OS extrapolation as it is a good statistical fit, visual fit, and is clinically plausible based on both clinical expert opinion and, critically, relevant RWE (**Table 23**). Further details on each model validation step are provided below **Table 23**.

Table 23: Summary of OS curve selection based on the DESTINY-Breast04 FAS

Curve	Statistical fit	Visual fit	Expert opinion	Real-world evidence
TPC				
Exponential			✓	✓
Weibull	✓	✓		
Gompertz				
Log-logistic	✓	✓	✓	✓
Log-normal				✓
Gen gamma	✓	✓		
Gamma	✓	✓		
T-DXd				
Exponential				
Weibull	✓	✓		
Gompertz	✓	✓		
Log-logistic	✓	✓		
Log-normal				
Gen gamma	✓	✓		
Gamma	✓	✓		

Abbreviations: OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
As there is limited long-term clinical experience with T-DXd in patients with HER-2 low, the clinical expert opinion and real-word evidence assessment of T-DXd OS have not been presented in this table.

Figures and tables related to selection of the OS curve in the FAS

Statistical fit

AIC and BIC scores for the extrapolated OS curves for the FAS population are presented in **Table 24**. The log-logistic curve remains the best statistical fit for the TPC arm. The Weibull and gamma and generalised gamma within 5 AIC or BIC points of the best fitting curve, indicating reasonable statistical fits.

For T-DXd, the Gompertz parametric curve provides the best statistical fit. The log-logistic, gamma, Weibull, and generalised gamma curves are within 5 AIC or BIC points of the best fitting curve and in both treatment arms and can also be considered a good statistical fit.

Table 24: Statistical goodness-of-fit scores (OS, independent models) in the FAS population

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	765.60	768.81	1389.90	1393.83
Weibull	751.16	757.59	1366.90	1374.74
Gompertz	756.20	762.63	**1366.87**	**1374.71**
Log-logistic	**751.10**	**757.53**	1371.38	1379.22
Log-normal	759.16	765.59	1390.55	1398.39
Generalised gamma	753.01	762.65	1367.59	1379.35
Gamma	751.12	757.55	1369.34	1377.18

Bold indicates best statistical fit.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; FAS, full analysis set; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Fitting of parametric models and visual fit against KM data

Visual assessment of observed KM data versus predicted OS curves (**Figure 21** and **Figure 22**) shows that the log-logistic, gamma, generalised gamma and Weibull curves are a good visual fit to the TPC arm OS KM data in the FAS. For the T-DXd arm, the Gompertz, log-logistic, gamma, generalised gamma and Weibull curves appear to be good visual fits.

Figure 21: Observed KM versus predicted OS for TPC over a 3-year time horizon in the FAS population

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician's choice.

Figure 22: Observed KM versus predicted OS for T-DXd over a 3-year time horizon in the FAS population

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; T-DXd, trastuzumab deruxtecan.

Long-term clinical plausibility: clinical expert validation

Table 25 presents a landmark analysis of the predicted OS, including the gamma distribution.

Clinical experts noted during the NICE TE stage that [redacted]% of patients treated with TPC would be alive at 5 years and the EAG's clinical advisors "*considered that it is more reasonable that the 5-year survival probability is approximately [redacted]% as predicted by the log-logistic model rather than approximately [redacted]% as predicted by the Weibull model*" and "*an estimate of 5% survival at 5-years was reasonable under current care*" (page 119–120 of the final EAG report). Furthermore, advice to the company is that clinicians are more confidently able to input on 5-year OS estimates than 10 years as there is a greater depth of clinical experience with patients at 5 years compared to 10 years in the HER2-low u/mBC population relevant to this appraisal. Based on this, the Weibull and gamma curves are pessimistic (5-year OS estimate of [redacted]% and [redacted]%) whereas log-logistic is clinically plausible ([redacted]%).

For T-DXd, the gamma and Weibull curves estimate 5-year OS rates of [redacted]% and [redacted]%, respectively. This is broadly in the [redacted]% range expected by clinical experts for the TPC arm. This is clinically implausible given that T-DXd is associated with a mature, statistically significant improvement in OS versus TPC. The generalised gamma estimates T-DXd 5-year survival to be lower than that expected with TPC. By comparison, the log-logistic curve generates a 5-year OS estimate of [redacted]%, which appears to be clinically plausible as the [redacted]% OS estimates for TPC should serve as a minimum estimated OS for T-DXd given the statistically significant benefit in OS for T-DXd vs. TPC in DESTINY-Breast04.

At 10 years, the gamma curve estimates OS to be [redacted]% in the TPC arm and [redacted]% in the T-DXd arm, which is very similar to assuming that there are no patients alive at 10 years. Clinical experts indicated that a small proportion of patients would still be expected to be alive at 10 years in the TPC and T-DXd arms and therefore considered the Weibull curve to be too pessimistic. Given the very similar OS estimates predicted by the gamma and Weibull curves, the gamma curve is also too pessimistic. The log-logistic curve estimates OS to be [redacted]% and [redacted]% for the TPC and T-DXd arm,

respectively, which supports the clinical expert input that some patients would be expected to be alive at 10 years.

Table 25: OS in the FAS population: Predictions by independently fitted distributions in T-DXd and TPC

Distribution	Median (months)*	1-year OS	3-year OS	5-year OS	10-year OS
TPC					
Observed KM data	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull (EAG base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic (company base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd					
Observed KM data	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull (EAG base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic (company base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Median time in months is estimated after OS has been capped by the general population mortality.
Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Clinical plausibility: Comparison with Flatiron RWE

Given the uncertainty raised by the EAG and committee with regards to the extrapolation of OS in the CEA, RWE is key to supplement clinical expert opinion and support the committee's decision making. The use of RWE is in line with the recently published NICE RWE framework (2022) and is particularly important to this appraisal to reduce uncertainty given that HER2-low is a new indication and there is therefore a paucity of published long-term comparator data in this population.

As stated in response to Issue 2 of this document, at the TE stage, the company presented an analysis from the [redacted] of Flatiron.[8] The analyses supported the use of log-logistic as a conservative and clinically plausible curve for extrapolating OS in the TPC arm of the FAS population and demonstrated that Weibull was a pessimistic curve. This Flatiron analysis was not discussed or presented in Part 1 (open session) of ACM1 as the EAG considered it to include TPC components that are "*arguably more effective treatments than those observed in DESTINY-BREAST04 or real practice*" and that the study "*does not represent the TPC arm of the decision problem at hand*".[7]

Therefore, to further address the EAG's concerns and more closely reflect standard of care in NHS practice, the company has conducted further analyses on subgroups of patients in the Flatiron study that more closely reflect the TPC arm of the decision

problem at hand (i.e., the “Flatiron NHS Cohort” discussed in detail in Issue 2 of this document).

The baseline characteristics from the “Flatiron NHS Cohort” (**Table 22, Appendix B**) are broadly aligned to the baseline characteristics of TPC patients in the DESTINY-Breast04 FAS population (Table 15 of the CS). For example, mean age at index date for the “Flatiron NHS cohort” is similar to the baseline age in the TPC arm of the DESTINY-Breast04 FAS ([redacted] years vs. [redacted] years). The “Flatiron NHS Cohort” included [redacted]% of patients with ECOG status 0 and [redacted]% with ECOG status 1, whereas the TPC arm of the FAS included [redacted]% of patients with ECOG status 0 and [redacted]% with ECOG status 1.

In the “Flatiron NHS Cohort”, the maximum follow-up time from index treatment date was [redacted] months and the mean follow-up was [redacted] months. There were [redacted] OS events (**Figure 20, Appendix B**). Median OS was [redacted] months (95% CI: [redacted]) and the 1- and 2-year survival rate was [redacted]% and [redacted]%, respectively.[8] The median OS in the TPC arm of the DESTINY-Breast04 FAS was [redacted] months (95% CI: [redacted]) and 1-year and 2-year survival rates were [redacted]% and [redacted]%, respectively.

As with the “DB-04 NHS cohort” in Issue 2, **Figure 23** shows that the “Flatiron NHS Cohort” validates the log-logistic curve as a clinically plausible curve for OS extrapolation for the TPC arm in the FAS population of DESTINY-Breast04. As per the landmark estimates in **Table 26**, in the “Flatiron NHS Cohort”, the 5-year survival rate was [redacted]% (95% CI; [redacted]) and the 10-year survival rate was [redacted]% (95% CI; [redacted]). This highlights that the Weibull curve is pessimistic as it predicts much lower 5- and 10-year survival rates of [redacted]% and [redacted]%, respectively. Similarly, the gamma curve is pessimistic as it predicted a 5-year and 10-year survival rate of [redacted]% and [redacted]%, respectively. In comparison, the log-logistic curve predicted 5-year and 10-year survival rates of [redacted]% and [redacted]% in the TPC arm, which is closer to the “Flatiron NHS cohort” and highlights that the log-logistic curve is more clinically plausible than Weibull or gamma.

Figure 23. Comparison of OS extrapolations from the TPC arm of DESTINY-Breast04 (FAS) with the “Flatiron NHS cohort”

Abbreviations: CI, confidence interval; FAS, full analysis set; mBC, metastatic breast cancer; OS, overall survival; RWE, real-world evidence; TPC, treatment of physician’s choice.

Table 26. Landmark OS estimates for the TPC arm (FAS)

Distribution	Median (months) *	1-Year OS	1.5-Year OS	2-Year OS	3-Year OS	5-Year OS	10-Year OS
Flatiron NHS Cohort (observed KM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DB-04 FAS (observed KM)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Log-logistic (company base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull (EAG base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Median time in months and predicted OS in the extrapolated curves are estimated after OS has been adjusted to include general population mortality
Abbreviations: DB04, DESTINY-Breast04; FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; RWE, real-world evidence; TPC, treatment of physician's choice.

In summary, RWE from the "Flatiron NHS Cohort", which consists of patients reflective of NHS clinical practice, further confirms that the log-logistic curve is a clinically plausible curve for OS extrapolation in the FAS. The Flatiron database is robust, as indicated by its use to validate OS curves for other oncology NICE appraisals (**Table 29, Appendix E**).[9–14] In this appraisal, the "Flatiron NHS cohort" represents the most relevant RWE for long-term survival with non-targeted chemotherapy in patients with HER2-low u/mBC in a cohort of patients aligned to NHS clinical practice. The Company therefore considers that the Flatiron study is critical to decision-making and is able to support NICE in their ambition to "*use real-world data to resolve issues of uncertainty and improve access to new innovations for patients*".[16]

Conclusion
Given the comprehensive approach to evaluating the most appropriate parametric curves to use within the company base case, the input from clinical experts, and the strong supporting RWE, the company maintains that the log-logistic curve is the most clinically plausible curve to inform the TPC and T-DXd base case extrapolations for OS in the FAS. By comparison, the long-term OS estimates derived from the Weibull and gamma curves, as highlighted by clinical experts and the Flatiron study, are highly pessimistic.

13: PFS extrapolation (FAS)

The log-logistic distribution remains the most appropriate model for PFS extrapolation in the FAS as the crossing of curves with generalised gamma is clinically implausible and inconsistent with previous similar TAs.

The company's revised base case includes PFS data derived from the "DB-04 NHS cohort" of DESTINY-Breast04. For completeness, the company has also provided further discussion on the suitability of the log-logistic curve in the FAS population, in response to the committee's request in the DGC.

The company base case at TE applied the log-logistic distribution to extrapolate PFS. The company maintains that this is the most appropriate model for extrapolation of PFS data for the FAS based on statistical fit, visual fit, clinical validation, and the implausibility of the T-DXd and TPC generalised gamma curves crossing at approximately 5 years. The EAG considered the log-logistic distribution to overestimate the tail of the T-DXd arm and preferred to extrapolate PFS using the generalised gamma distribution, despite the crossover of T-DXd and TPC curves at 5 years. The committee agreed with the EAG that it would be more appropriate to use generalised gamma, noting: *"The committee considered that the generalised gamma*

provided closer estimates to the observed trial data for the TPC arm. It concluded that the generalised gamma capped at the point of crossing should be used in the model."

The company disagrees with the EAG and committee's preference for the generalised gamma curve capped at the point of crossing based on clinical implausibility and precedence from previous similar TAs.

The generalised gamma curve is clinically implausible because the mature trial data from DESTINY-Breast04 demonstrate a statistically significant improvement in PFS by BICR in the T-DXd vs. TPC arm (median PFS: 9.9 months vs. 5.1 months; HR: 0.50; p<0.001; FAS),[23] and, as shown by the observed KM data (**Figure 24** and **Figure 25**), there is clear curve separation between T-DXd and TPC. Given the maturity of the data, magnitude and statistical significance of the PFS benefit, and the difference in mechanism of action between T-DXd and TPC, it is highly unlikely that the PFS curves for both treatments arms would cross or be equal (as in the generalised gamma curve).

Whilst the company notes that there is an observed decline at the end of the PFS KM curve for T-DXd, this is due to the very small number of patients at risk in the later timepoints of the study. As detailed in Figure 12 of the CS, only [redacted] patients are at risk at [redacted] months in the TPC arm, after which [redacted] patient has an event and then 3 patients are censored. Similarly, only [redacted] patients are at risk at [redacted] months in the T-DXd arm. Given the very few remaining patients at the later timepoints, each censoring or PFS event can have a great impact on the appearance of the KM curve. The tail of the observed KM plots for both T-DXd and TPC should therefore be interpreted with caution.

Figure 24. Observed KM versus predicted PFS for TPC and T-DXd in the FAS population using the log-logistic curves

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival; TPC, treatment of physician's choice.

	Figure 25. Observed KM versus predicted PFS for TPC and T-DXd in the FAS population using the generalised gamma curve with TPC capped by T-DXd at 5 years  Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan Based on the above, the company maintains that the log-logistic is the most appropriate model for extrapolation of PFS data based on strong statistical fit, good visual fit to the KM data, plausible long-term estimates, and the implausibility of the T-DXd and TPC generalised gamma curves crossing at 5 years. This conclusion is supported by the extrapolation approaches used for PFS in previous similar appraisals accepted by NICE.[17–19]
14: TTD extrapolation (FAS)	***The company maintains the use of the generalised gamma curve for the extrapolation of time-to-treatment discontinuation (TTD), aligned to the EAG's preferred curve.*** ***The company's revised base case includes TTD data derived from the "DB-04 NHS cohort" of DESTINY-Breast04. For completeness, the company has also provided a summary of TTD in the FAS population, including the use of KM data to estimate TTD, as requested by the committee in the DGC.*** As noted in the DGC (Section 3.12), the EAG "*suggested using the mature Kaplan-Meier data to directly estimate treatment stopping in the model and limit parametric extrapolations to the time-period beyond this.*" The company considered at TE (Issue 7) that this would provide limited additional value and would have minimal impact on the ICER. This is because all parametric curves used to estimate TTD are a good fit to the KM data due to the maturity of TTD in DESTINY-Breast04 (as shown in Figure 40 and 41 of the CS). In addition, parametric curves to model TTD allow for time-on-treatment to be included in sensitivity analyses, such as a probabilistic sensitivity analysis (PSA). To reduce uncertainty (Section 3.21 of DGC), the company explored the use of KM to estimate treatment stopping in the model, as requested by the EAG and committee. In this scenario, the TTD KM data from DESTINY-Breast04 FAS is used to determine the proportion of patients on treatment in each model cycle until the cohort size reduces beyond a point where it is robust (i.e., at 10 patients at-risk) due to the small number of patients. After this, the parametric curve is used to estimate the proportion of patients on treatment for each cycle. For TPC, the number of patients at risk falls to 10 at 15 months; for T-DXd, the number of patients at risk falls below 10 at 24 months (Figure 38, of the CS).

	Using the KM to model TTD in the FAS has a minimal impact on the ICER; the ICER marginally increases from £[redacted] to £[redacted] (**Table 28**). Given the minimal difference in ICER between the KM approach and the parametric approach, the company has continued to use parametric curves to model TTD in the FAS and maintains the choice of generalised gamma. This is because generalised gamma is a good statistical and visual fit. The generalised gamma is also the EAG's preferred choice.

Appendix D: FAS population: deterministic cost-effectiveness results

Deterministic results using the FAS population

The revised company base case is based on efficacy, safety, and utility data from the "DB-04 NHS Cohort" of DESTINY-Breast04, rather than the FAS. While the FAS cost-effectiveness results are no longer key to this appraisal, for completeness, the company has provided the deterministic results using the FAS population with the 1.2x and 1.7x severity modifier applied (**Table 27** and **Table 28**).

Table 27: Deterministic cost-effectiveness results using the FAS population (1.2x and 1.7x severity modifier; T-DXd PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (1.2x severity modifier)	ICER (£) (1.7x severity modifier)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 28: Scenario analysis (deterministic results – T-DXd [PAS price] vs. TPC, for 1.2x and 1.7x severity modifier)

Parameter	Scenario number	Base case	Scenario	Incremental costs	Incremental QALYs	ICER (1.2x modifier)	ICER (1.7x modifier)
Base case				[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	1	Discount rates - Costs: 3.5%, outcomes: 3.5%	Discount rates - costs: 1.5%, outcomes: 1.5%	[redacted]	[redacted]	[redacted]	[redacted]
OS extrapolations (applied to T-DXd and TPC)	2	Log-logistic	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
	3		Gamma	[redacted]	[redacted]	[redacted]	[redacted]
	4		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
PFS extrapolations (applied to T-DXd and TPC)	5	Log-logistic	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
	6		Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
TTD extrapolations (applied to T-DXd and TPC)	7	Generalised gamma	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
	8		KM + extrapolated TTD using generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
PP utility benefit	9	Sustained for 6 months	Sustained for 12 months	[redacted]	[redacted]	[redacted]	[redacted]
	10		No treatment benefit applied	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

Appendix E: Previous NICE TAs that have used the Flatiron database to validate the appropriateness of their selected survival curves.

Table 29 includes a non-exhaustive list of oncology TAs that have used the Flatiron database to validate the appropriateness of selected survival curves. This highlights the suitability of the Flatiron analyses presented in this DGC response.

Table 29. The list of previous NICE oncology technical appraisals that have used Flatiron database to validate the survival curves for their treatment and comparator arms.

NICE TAs	Indication
TA898[9]	Dabrafenib with trametinib for treating advanced BRAF V600 mutation positive non-small-cell lung cancer
TA705[10]	Atezolizumab monotherapy for untreated PD-L1 positive metastatic non-small-cell lung cancer
TA812[11]	Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer
TA760[12]	Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer
TA781[13]	Sotorasib for previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer
TA886[14]	Olaparib for adjuvant treatment of high risk HER2-negative, BRCA-positive early breast cancer after chemotherapy
TA520[27]	Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy

NICE National Institute for Health and Care Excellence

Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 17 October 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Breast Cancer Now

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Based on the appraisal stakeholder list (the company and comparators), Breast Cancer Now has not received funding towards our services from companies listed in the last 12 months. The last funding we received from the drug company Daiichi Sankyo was £45,000 towards our Living with Secondary Breast Cancer face-to-face service in December 2021. Breast Cancer Now does not accept any funding towards our policy and influencing work, which includes all of our work on access to medicines.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Breast Cancer Now welcomes the opportunity to respond to the Draft Guidance Document for trastuzumab deruxtecan (Enhertu) for treating HER2-low metastatic (also known as secondary) or unresectable breast cancer after chemotherapy.

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	We are pleased that a 2nd committee meeting has been scheduled in for 7 November as we urgently need a resolution and we urge the Committee to invite patient and clinical experts back to contribute to this important appraisal. We are incredibly disappointed that NICE has been provisionally unable to recommend this treatment for routine use on the NHS – trastuzumab deruxtecan could bring certain patients living with incurable secondary breast cancer the hope of more time to live and more time before their disease progresses. Recommending this treatment for use on the NHS would be a crucial moment to change practice and for the first time, provide an effective HER2-targeted treatment for patients whose breast cancer is HER2-low. We would reiterate our comments from our initial submission that a diagnosis of incurable secondary breast cancer can have a substantial impact physically and psychologically on both patients and their families. Patients can live with the constant fear and anxiety about when their treatment may stop working and running out of available treatment options. There remains a significant unmet need for effective treatment options following chemotherapy that can delay progression and extend life, giving people precious extra time with their loved ones and to do the things that matter most to them. There is clear evidence of the significant benefit this treatment could bring as highlighted in our original patient organisation submission and throughout the appraisal process. Trastuzumab deruxtecan is the first HER2-targeted therapy for this specific patient population, crucially providing an additional effective treatment line. We are pleased that NICE also "recognises potential of new targeted treatment for type of advanced breast cancer". As referenced later in our submission, there is huge anticipation regarding this treatment and the benefits it could bring patients and we hope the committee will consider the evidence from the many patients we have heard from since the consultation opened – of both the impact of breast cancer and the hope this treatment could bring them. We urge NICE and the drug company Daiichi Sankyo to find a solution to ensure this treatment can become routinely available – to provide hope to the 1000 people that are estimated to be eligible each year in England if approved. This should include NICE reviewing any additional flexibilities and the company exploring the further analyses requested, and considering scope to improve the cost-effectiveness of trastuzumab deruxtecan for use on the NHS.
2	• are the provisional recommendations sound and a suitable basis for guidance to the NHS? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We do not believe that a decision to not recommend this treatment is a sound and suitable basis for guidance to the NHS for the reasons set out below. We welcome the Committee's recognition that: - Metastatic (secondary) breast cancer can have a profound impact on a person's quality of life and that people with the condition would welcome new effective targeted treatment options - There is an unmet need for targeted treatments for HER2-low breast cancer - Trastuzumab deruxtecan is innovative

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	Post-progression utilities During the first committee meeting, the clinical experts highlighted that the trial responses rate suggested a treatment benefit and that the reduction in tumour size could lead to a reduction in symptom burden that would continue in the post-progression state and that ultimately people would likely be in a better position for subsequent lines of treatment after progression. We agree that given the evidence from the clinical trial in terms of the response rates, it should be expected that generally patients may be in a better position when starting their next line of treatment. Whilst we are unable to comment on the exact duration that this may take place for, we would suggest that is reasonable to expect utility benefit after progression. We would urge the Committee to consider whether a 6-month timeframe is a plausible timeframe that could be acceptable. We would suggest that NICE consults again with the clinical experts on the clinical plausibility of the utility benefit after progression. We are currently unclear as to why analyses have been requested when assuming no differential effect and we would be concerned if an approach is taken which suggests there is no utility benefit with this effective treatment after progression. Furthermore, we have participated in other appraisals where a difference in post progression utility has been recognised and considered. For example, we note that the NICE Committee has considered scenarios in which there was carry-over beneficial effect after progression in other breast cancer appraisals, for example, for sacituzumab govitecan [TA819] in 2022. It is important that there is consistency in approach, especially with the available evidence for trastuzumab deruxtecan. Currently we are unclear given the evidence for trastuzumab deruxtecan and the comments made by the clinical experts, what more would be needed for the committee to consider there could be a differential effect in post-progression utilities. *Severity modifier* Whilst we recognise that both the company and the EAG estimates resulted in a severity weight of 1.2 being applied to the QALYs according to the new NICE framework for methods, it is very difficult for the patient community to comprehend how incurable secondary breast cancer and also the positioning of where in the treatment pathway trastuzumab deruxtecan would fit (after prior chemotherapy) would not reach the upper band of severity and therefore the higher QALY weighting. We would welcome flexibility, to truly recognise the severity of secondary breast cancer and the value this treatment could bring this patient group. At the time of the methods review, whilst we along with others broadly welcomed the severity modifier for potentially being able to benefit a wider group of conditions, we did raise specific concerns about the implications for some medicines for incurable cancers with the removal of the end-of-life modifier and the way in which the severity modifier was being introduced. We're worried that we are now seeing these concerns impact this appraisal to the detriment of patients living with incurable secondary breast cancer. We understand that all NICE assessments evaluated using the new methods are being tracked and analysed to identify how the introduction of the severity modifier and other changes have been utilised. The outcome of this review is due to be presented to the NICE Board towards the end of 2023. We urge NICE to consider this appraisal when reviewing the impact of its new methods for evaluating health technologies. We must avoid the incredibly distressing prospect of patients being

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	denied access to potentially life-extending medicines that may have previously been approved on the NHS. *Other comments* We note that given the uncertainty that the committee considered key to this appraisal, the committee agreed that an acceptable ICER would be towards the middle of the range normally considered a cost-effective use of NHS resources. We hope that if the committee is provided with the additional analyses requested and if they feel the uncertainty is reduced, that the whole range will be considered to help ensure this treatment can be approved for routine use on the NHS. As per our earlier submission, we are also keen to reiterate the additional benefits this treatment could bring. For patients who are working when diagnosed, having a treatment that could control disease progression, may allow people increased time to spend in good quality of life compared to standard treatment. For those who wish to continue working, this could bring benefits not necessarily captured. One patient explains if this treatment was approved, it could give them the chance of extra time before disease progression and "it would also give me longer to work as a nurse, a career that I have always loved and means so much to me." A treatment which brings hope of people being able to lead a normal life for longer than current standard of care, could also provide significant benefit to loved ones which cannot be underestimated.
3	The patient community is very aware of the clinical benefits that can be associated with trastuzumab deruxtecan. Accessing this medicine, could provide reassurance to both patients and their loved ones that they are receiving the optimum treatment available. The possible psychological benefit of this should not be underestimated. We would be very concerned given the evidence about the benefits this treatment could bring, if NICE and the drug company could not collectively resolve the issues and ensure trastuzumab deruxtecan can be recommended for routine use on the NHS. We cannot be left in a situation where an important innovative and new effective treatment option for this new categorisation of secondary breast cancer patients is left just out of reach.
4	• has all of the relevant evidence been taken into account? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? Following the provisional decision, we have been contacted by a significant number of patients with HER2-low secondary breast cancer who are extremely concerned about this and for who now have the anxious wait to find out whether a treatment that could be an option for them, will be able to be made available on the NHS. Breast Cancer Now has received a number of statements from women and their families who are either: 1) currently being treated with trastuzumab deruxtecan in this indication through medical insurance and want others to have the same opportunity to benefit from this treatment or 2) have incurable secondary HER2-low breast cancer and need this drug to be available so they can access it when they need it. These statements from patients (documented below) highlight the value that patients attach to the delay in progression of their disease, and the hope of more time to live. We would like the Committee to take account of these statements in making its final decision as we feel that these people's personal experiences of the drug and the implications of not having access for whom this

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	could be a future treatment option form a significant base of important qualitative evidence for this appraisal. **Patients who have experience of trastuzumab deruxtecan in this indication:** • That any treatment that could extend survival is priceless. I had a 9 and 11 year old when diagnosed. That knowing other people in other comparable economic countries have access to drugs that we don't in the UK can be very distressing. The availability of drug options has a huge impact on mental health. Feeling that we are 'worth it' in monetary terms is vital. There are many young patients that in economic terms are still trying to contribute in terms of working and providing care to dependents (both children and elderly relatives). New targeted treatments such as Enhertu are vital to allow life to go on with MBC. I had a lot of problems with standard chemo prior to this. Capecitabine caused bowel obstruction and put me in hospital. I had recurrent allergic reactions to paclitaxel and ended up admitted with urinary sepsis twice. I am fortunate in that my private healthcare will provide access to Enhertu. My experience with enhertu (which we know is more targeted) has been better so far. After just one cycle of enhertu my tumour markers have dropped by more than 20%. I have not had this good a response to any other treatment in terms of markers and this has given both me and my oncologist some optimism where things have looked very bleak for the past 6 months. There are few options out there for HER2 'negative' patients beyond traditional chemotherapy and a large proportion of these patients we now know are HER2 low. The evidence from destiny04 is good and to reject the drug on cost effectiveness is very wrong especially when Europe, USA, Canada and Australia are allowing access. • Living with SBC is like living with a gun to your head, never knowing when the trigger will be pulled, not if but when. But still every single second of every day is cherished and appreciated and only access to drugs will continue to give me more time with my loved ones. In May I was in intensive care with progression, pneumonia and sepsis. I was told I wouldn't make the night… long story short I did. After regaining strength my amazing oncologist agreed to try more treatment. I was on 2-3 units of oxygen support. Enhertu was one of my last lines of treatment as HER2 low +2. Thankfully my private health approved this. Side effects are manageable and after my 3rd infusion I had a scan hoping for stability, to give me more time. Instead I got 'slight improvements' after only 3 Enhertu my lungs had slight improvements, one of my liver tumours had reduced by 5mm… I still can't quite believe it!!! I now go up-to 10 days without oxygen support. I get to take my teenagers out! I get to be here. The advantages of having this drug available on NHS is so important, I know of many, many ladies that are on their last treatment lines and will die if this drug is not available to them. In February 2018 I was given palbociclib and at the time my friend was not able to access it on NHS. My friend died in December that year, I still feel guilty that I am still here as palbociclib gave me another 5 years. Now history is repeating itself and it has to stop. Every human being should be treated equally, we should not be treated less favourably because we have an incurable cancer. We should be given the opportunity to access

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	drugs that can extend our lives. This drug is already approved for HER2 positive in this country and trials in HER2 low patients has shown to reduce risk of progression. It's a drug that received a standing ovation from the Global Medical community because of the results of the trials! Not giving HER2 low patients access to this drug is pulling the trigger of that gun at our heads! We are worth more than that and we are certainly worth the cost of this drug. • Living with this disease is to live with constant fear, uncertainty, pain or discomfort as well as all the psychological traumas it brings, from self esteem about changes in appearance, changed relationships, impact on families. But we need to balance that with every day life, as the world turns with all those normal daily things and find ways of enjoying things to look forward to. what helps enable that ability is having the hope that we have treatments available or can access future treatments that can help control or put this disease in remission - to give us some semblance of a future, to let us plan and take joy in our life I have been taking Enhertu as part of a clinical trial since March 2021. So almost three years. I was diagnosed with triple negative MBC in the January 2021. I had fast growing mets to lungs, liver and sternal nodes. Despite being classed as triple negative, I was HER2 low (+1) and lucky enough to be admitted to this trial … within six months my CT scans showed no evidence of disease. I have remained NED since then, so for two years now. I do suffer side effects as is the case with many cancer medications, and that can be very challenging. But I manage this carefully so that I can make the most of my life and my time with my family. Enhertu ultimately has enabled me to still be here for my family, to see my boys grow (they are 13 and 16). I fear without this drug it would have been a very different story, Knowing the historically poor prognosis for triple negative metastatic breast cancer. Drugs like enhertu are ground breaking and could make all the difference to many people that have some HER2 expression. There are so many women who may be traditionally classed as HER2 negative that actually do have some her2 expression …but can't benefit from traditional HER2 drugs. Enhertu opens up an amazing new treatment for many people that may not have many other options. Particularly so for triple negative. It is vital that NICE give all those other low HER2 people the same fighting chance. I recently lost a dear friend who was TN MBC and her2 low also… but this treatment option wasn't made available to her, despite it being accessible in other countries around the world. She could see I was benefitting from it, all the while knowing she couldn't access it. She was 47 years old. This is the real human cost of NICE decision. • I was diagnosed with breast cancer at age 26, initially it was treated with a combination of chemotherapy, surgery and radiotherapy. When I had chemotherapy I had the worst time of it and was frequently on deaths door with how badly I experienced the side effects of it, rapidly lost weight, unable to keep food down at all and chronic fatigue and migraine to name a few with terrible quality of life and frequently being admitted to my ward for days at a time. Post my main treatment I was on tamoxifen and zoladex, but a year later I had the recurrence and was diagnosed with stage 4 metastatic breast cancer, found in my hip bones, lower back, chest and lungs initially. I was put onto a variety of chemotherapy options which worked for a bit but then my markers started to climb up again and I was really feeling the effects of the treatment with maybe a couple of days each month where I

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	felt ok enough to do nice things. The markers continued to climb and it was evident that it had also spread to my liver. I have accessed Enhertu and have a single + for the HER2 receptors. The aim of this, or similar treatment was to slow down tumour growth and prevent further spread. The results so far have been absolutely incredible and even my consultant is baffled. In 3 months the number of tumours has reduced, there is signs of the bones healing as opposed to tumours in the bones, my lungs are looking clearer and of the tumours that were present in my liver they have reduced in size from 44mm to 18mm, 29mm to 16mm and 16mm to 13mm to quote the CT report. In terms of quality of life I am having more good days than bad days and able to do my job, spend time with my husband and family and maintain a relatively active lifestyle. The side effects are manageable and I haven't been admitted to hospital once. We are continuing on this treatment at the moment and remain hopeful that it continues on this trajectory and I am able to do so because of the quality of life that is there and the fact that my body seems to tolerate it well, compared to other chemotherapies. I think this drug is incredibly important as it is promising for patients in terms of possible response and tumour shrinkage, as well as it being of a better calibre of quality of life with what time the patient does have available to them • I am fortunate enough to be treated with Enhertu I'm HER2 low ER positive. I am 54 and I was diagnosed stage 4 de novo in 2020 with mets to my mediastinum. My organs and bones clear. I have had many lines of treatments, none of which have worked. Then my insurance company agreed to fund 6 months of Enhertu. After 1 infusion my skin mets visibly improved after 2 they were gone and after the 3rd infusion I now have a virtual complete metabolic response all the cancer in my neck nodes chest and arms has gone. I'm now on my 6th infusion. I really hope my experience adds weight to the fact that all her2 low women should be given a chance with this drug. **Patients who need this treatment to be an option for them on the NHS:** • I have a 2-year-old grandson and my hope is that I live long enough for him to remember his granny. A secondary breast cancer diagnosis is devastating and life changing. It's a roller coaster of emotions, good days, bad days and even worse days. Trastuzumab deruxtecan is a treatment that could give people like me more time to spend with my family and friends. The possibility of living longer and enjoying life. Any new treatment gives us hope for a future. Hope that one day this disease could be chronic and not terminal. Without hope things can seem bleak. • I was diagnosed with secondary breast cancer in 2022 which is hormone positive and HER2-low. I failed my first line of treatment within 6 months of my diagnosis so the option of Enhertu is very important to me. I am a nurse and have worked in the NHS for 30 years so I understand the need to make sure that treatment is clinically effective and cost effective. The evidence for Enhertu in HER2-low secondary breast cancer is irrefutable. It was given a standing ovation when the

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	trial results were presented to the breast oncology community and was heralded as a game changer. It is already being used for HER2-low secondary breast cancer in the US and Europe. We are supposed to have one of the best health systems in the world but we are failing patients with HER2-low secondary breast cancer unless they have private insurance or the ability to finance this themselves. This seems morally wrong and goes against the principles of the NHS. This is the only targeted therapy available for HER2-low secondary breast cancer patients and we are being denied it purely on a financial basis. If Enhertu was approved by NICE it could give me the chance of extra time before further progression and ultimately more time before I die. This would mean so much to me, my family and my friends. I would be given the extra time to see my son qualify as an acturist and my daughter to qualify as a detective in the police force. I may even live long enough to become a grandmother. It would also give me longer to work as a nurse, a career that I have always loved and means so much to me. As a patient with secondary breast cancer I often feel like a second class citizen when it comes to access to treatment lines and trials. You are made to feel that as this disease is incurable and life limiting that we, as a group are not worth investing in. This decision has compounded this feeling. • I can live with secondary breast cancer very well when the right treatments are available. My current treatment has kept me alive for over 4 years and I have been able to work, travel and still enjoy my life. Knowing that your treatment options are limited is terrifying and secondary cancer patients literally live from scan to scan. We know that when our treatment options run out, we will die. Our reality is harsh. I have not taken Enhertu yet but it is a treatment line applicable to me and my Oncologist will prescribe for me when I need it if/when it is approved in the future. There are multiple advantages to reversing this decision. Eligible cancer patients will have their lives extended, improving their wellbeing and that of their loved ones. Many cancer patients still work, either paid or voluntary and contribute positively to society and the economy. As we become more ill the impact on us and our families is devastating. We deserve more time. Time to create special memories for those we love, time for further advances in medicine and enhanced life extension. There is also the mental health impact of this provisional decision to consider. I have felt that I have had to literally beg for my life. That my life is not deemed important enough. Stress is known to have a negative impact on cancer outcomes and this decision has caused myself, my family, and countless others increased stress at what is an already incredibly difficult diagnosis to live with. • Life is an unknown, I have no idea how many months I have left with my 6 year old daughter. The treatment options are limited and the cancer is aggressive. I hope by some miracle what treatments are available will allow me a few more years but there is no telling. Having other treatment options are priceless, when I am looking at a diagnosis with such poor prospects every month, week, even day matters more than anything and so any treatment that can give me that I need. My daughter has to live with a mum who is dealing with facing death, leaving her child motherless and contending with numerous hospital investigations, treatments etc. I have had to give up work as I have weekly chemo. Financially we struggle because I can't work. As a family we fear for the future and what it will bring. Knowing there are more treatment options to try can help relieve it a bit, it gives hope which is vital in these circumstances.

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	I have my daughter and she is everything to me, and me to her. Any extra time brought for me to be in her life is priceless. Every day counts as we try to build lasting fun memories and I so desperately want her to remember me, and not just as a poorly cancer patient and a mum who as always ill, but a mum who could have fun too and enjoy our time together. Extra treatments like Enhertu can help give us this time and important memories- how can you put a price on that? Our treatment options are already massively limited, any thing that might help should be made available. Not enough money is spent on secondary breast cancer research as it is, I can't quite comprehend therefore that when you have a drug that can help with not only secondary but one where treatments are limited you don't authorise it. It hurts very deeply on a very personal level, it feels like you are saying our lives aren't worth it, they don't matter. • Living with low Her2 secondary breast cancer – it's a continuous loop of tests, scans, appointments and medications. I have spent a lot of time getting my "house in order" like wills, powers of attorney, advance treatment decisions, and in addition the "nice" legacy stuff like recordings for my kids, photo albums, letters etc. i was medically retired so financially am ok but do feel the loss of a profession and a "purpose" in life. Much of the time I feel ok, although there are niggly side effects, but when a line of treatment stops working I have been know to feel really unwell, with kidney function directly affected and talk of nephrostomies. It's an extreme roller coaster that I didn't want to ride on. It could extend progression free survival for low Her2 patients. The cost needs to be considered against what would otherwise be spent on that patient in terms of other treatment regimes and also wrap around care particularly when they deteriorate and/or have side effects. You cannot put a value on quality of life and hope. • I have HER2-low and am devastated. I worked in Clinical Trials for 10 years...after it was presented at ASCO I remember talking excitedly but desperately about when it might become available with my oncologist. But here we are. A significantly life prolonging treatment out of reach of those unable to afford fund it privately. It's close to mental torture knowing the data I have a three year old daughter who I desperately want to see settled in primary school. My tumour markers have shot up and I am being scanned on Friday. Potentially facing the next line of treatment with enhertu off the table is frightening. • We should absolutely have the same access to drugs that other countries have. I am 41 years old with MBC, I was diagnosed with this at 39 years old with no previous diagnosis. I have a wife and two children of 8 years old. I understand that my disease will never be cured but it absolutely is and should be treatable using all drugs available. When you live with this condition the only way that you manage to continue day in day out is hope. Hope that this current drug lasts for as long as possible and then that the next one works and that whilst I am doing this hard work day in day out that others are also doing all they can to find and approve other drugs that will give us longer. Approving a drug like this is not about another '2 years', it is about putting it next to other drugs that give us longer in the hope that we can we be here long enough to live our lives, long enough to love our families and raise our children so that they are not completely

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	damaged by losing a parent so early on. The treatment and care that goes into primary cancer is way above that the secondary patients get anyway but not allowing us access to drugs that work is incomprehensible. These treatments that are being developed are astonishing - I am able to work as a deputy headteacher in a really deprived area of the country - I know that I am making a difference to the community that I work in. This should also be taken into consideration - we are not a drain on society but an active part of society. I truly believe that this type of cancer can and should become a chronic condition such as diabetes due to all the new drugs being researched and developed. However, this is never going to be a possibility if the people who approve it then decide that we are just not worth the money. I don't believe for a second that if it was your wife, daughter or sister whose life needed saving that you wouldn't do all you could to help give her hope and give her life. We should not be seen as a number or a percentage but as real people who work hard, who love and are loved. • Secondary breast cancer HER2- low is an incurable, life- limiting disease. As a mother, wife and NHS physician its mental and physical hurdles are extraordinary. I know that I am unlikely to see my children grow up to reach adulthood and that 2024 has become the year I am likely to die as I have brain mets. My husband has become my carer and I cannot treat or heal patients any longer. I have lost virtually everything apart from my life and that too will be taken from me with such a life- limiting illness. In short, it's a death sentence. It never leaves me apart from when I sleep and even then I don't sleep well and wake up worrying again. I am HER2-low triple negative and I am already through 2 lines of chemo. With brain progression I know this is a systemic disease and that radiotherapy can be given but it is limited. The am therefore appalled that NICE has not recommended trastuzumab deruxtecan. No experience of using the drug but I am well aware of the side effects and would be happy to take the risk given the overall benefits as I have been able to share experiences with women who have accessed the drug privately in the U.K. and many have seen good benefit. I have seen crowd funders try to access this drug and it's awful they should have to do this while having the stress of stage 4 cancer to deal with. This drug not only has shown that it is a superior approach to untargeted chemotherapy but it is the only treatment that has been shown to have a confirmed objective response for women with HER2 low tumours in both hormone receptor positive breast cancer and hormone receptor negative. Destiny 04 also showed clearly that in ALL patients there was improved median overall survival. This was a median OS of 6 months compared to physicians choice but was consistent for all patients. It's also possible for it to extend life by more than that and there is the choice of another therapy. Everyone knows that patients are individuals not statistics and in some cases this drug has meant life extension for well over a year. I know this because of the feedback of other patients and this is not just in Her 2+ patients. Extra time spent with friends and family cannot be valued. It is priceless. The safety profile of this drug too was acceptable and therefore it is very important that HER2- low women can access the drug and not be discriminated against in terms of receptor efficacy as this has been shown to be effective for HER2-low breast cancers as a whole. Breast cancer can strike women in the prime of life when they are mothers to young children. Generational pain too has been caused by this disease not only the

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	personal pain and grief of dealing with an incurable illness. ENHERTU is also more effective at crossing the blood brain barrier and critically would offer more options for this hard to treat group which I also sadly belong to. There are fewer options for treating hormone receptor negative cancer too and it is more likely to enter the CNS so both hormone receptor positive patients and negative could benefit. NICE should make ENHERTU available on the NHS to HER2-low women. This was a landmark trial, especially Destiny 04. I am grateful to them for offering me hopefully more time with my family and NICE should not make a largely economic decision when, for all the reasons I have explained, it cannot be justified. • It's very hard to keep a positive outlook when the treatment options are so limited. I have gone through three lots of chemo that did nothing to help my cancer and suffered horrible side effects along the way. The treatments available seem very biased towards hormonal cancer. A huge boost for people in my position to know there is a targeted treatment for my type of cancer. Just now it is very much a cookie cutter approach whereby everyone is being given chemotherapy that primarily works for hormonal cancer. If occasionally it works for HER2 low then that's a bonus, we deserve a treatment that has better odds at being effective. This would have a huge positive impact on mental health also. The thought of a new innovative treatment line specifically for this type of cancer provides women like myself with Hope and this is exactly what we need. If this treatment was being rejected and there were others in the pipeline then not so bad but how many years and lives will be lost before something else becomes available???? This is here now and would benefit so many women. We just want the chance to spend more time with our families. • Living with HER2 low secondary breast means that everyday is spent knowing that my life has been cut short. All my dreams, hopes and plans for the future have been ripped away. I am a single mum and my daughter needs and depends on me. It breaks both of our hearts not knowing how long we have left together. My job is to protect her and take care of her for as long as I humanly can. My mum is beyond devastated that she will outlive me and feels utterly helpless that there isn't anything she can do to help.. My diagnosis not only impacts me but me but everyone close to me. Enhertu would be a dream for myself, my daughter and all of my loved ones. Those of us were Her2 low secondary breast cancer are already incredibly limited with our treatment options and lines due to massive underfunding and investment into our cancer. Myself and all the other women have and will continue to make valuable contributions to society and deserve to live as much as those who are fortunate enough to have health insurance or the finances to pay for it privately. Reversing this decision would show that women in England are valued,just like they are in all the other countries where it's used, and that we are not discriminated against because we can't afford it. I love my life, I love living on this planet and there is so much more I want and need to do. Every woman I know with my diagnosis is a mum, daughter, sister, aunt, grandmother, colleague, wife, partner, and friend. They are all incredible women full of passion and love for life and a deep determination to be here their families.

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	We are more than just a stat. We fight tirelessly for treatments which is shameful, especially this day and age. The NHS used to held in such high regard all over the world, but now you are publicly announcing to the entire world that women (who make up 52% of the population) aren't "cost effective" or worth investing in. You can give us that extra lifeline and time that each and everyone of us so fully deserve to have and I implore you do so. • I've been living with secondary breast cancer for nearly two years. I'm lucky enough to be on my first line of treatment. It's mental torture living with sbc. Every slight ache or pain I immediately think is progression. Lucky as I am to have a scan every four months to check for progression, this too is mental torture- the build up to the scan, the worrying waiting for the results, the fear when I see my oncologist as to what he is going to tell me - it's mentally the toughest experience I've ever had, all the while trying to maintain a normal life for my partner and my 18 year old daughter, not worry them and trying to wring every bit of life out of each day. This experience isn't going to stop - I will always need medication and much as I hate to admit it, I will get progressively worse. The thought that a line of treatment is being withheld from me, when there are fewer lines available for her2 low, is added stress and torture and makes me fear for the future - just why? I haven't asked for this dreadful disease, I need help to continue my life. I understand that this drug can add up to two more YEARS to my life. Please re consider your decision. I need to spend years with my daughter, to see her in to adulthood, surely my ability to do this can't come down to cost? • My oldest sister is in this situation currently [of Enhertu needing to be available on the NHS], and is a single mother trying to make the best life for her and her daughter. To be knocked down at the first hurdle to try and improve their lives is just inhumane. Having watched my oldest sister have to battle through some of the toughest times of her life has had a real impact on myself, our father and wider family.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the

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following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	METUPUK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Funding from Daiichi Sankyo £5000 educational grant towards metastatic breast cancer conference in Manchester on 13th June 2023 co-hosted with NHS Greater Manchester Alliance and the Mayor of Greater Manchester Daiichi Sankyo had no input in the agenda or selection of speakers. This was a one off payment and was not related to the product being appraised.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the NICE methods do not take into personal circumstances of patients. Many patients also work, care for young children, grandchildren or elderly parents. Many of patients who would be eligible for this drug are either themselves

Please return to: **NICE DOCS**

Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 17 October 2023. Please submit via NICE Docs.

	economically active or support an economically active person who might otherwise become inactive if they have to take on new caring tasks. Many are unpaid caregivers to elderly family members who would otherwise require additional support packages from health and social care services. In addition, the contribution of parents to the lives of their children should also be taken into account. Giving parents additional time with their children is important at a familial level, and also at a societal level. Many cancer patients spend additional time creating memories and taking photographs for family members to look back on, if their treatment regimen confers sufficient quality of life to enable this. One patient wrote, "Enhertu would mean… Time to help raise my kids so they can fly strong, not burden them too soon. Extra days with my loved ones. To dare to dream of years. Time to pay tax! Time to contribute to building a better world in my work. More time to increase my chances of the drug that makes this chronic not terminal."
2	The summaries of clinical evidence are reasonable interpretations of the evidence. To quote from the NICE draft guidance document trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy, trastuzumab deruxtecan "increases how long people live and how long they have before their cancer gets worse compared with chemotherapy treatments used for HER2-negative breast cancer," and "there is an unmet need for targeted treatments for HER2-negative and HER2-low breast cancer." It is difficult to comment meaningfully on the cost effectiveness, given the discounts offered are confidential. However, as a patient group we call on NICE and Daiichi Sankyo to work together with urgency to agree on a fair cost for this important drug. It is notable that trastuzumab deruxtecan (T-DXd) is the only treatment which has been shown in a phase 3 clinical trial to increase PFS and OS in patients with HER2-low MBC. Patients in the physician's choice arm in the DESTINY-Breast04 trial had 17.5 months median OS, and in the T-DXd arm had 23.9 months median OS. Prior to the NICE methods and process review of 31 Jan 2022, any treatment for a condition with a median OS of less than 24 months on standard of care, which increased OS by three months or more would have been eligible for an ICER of £50,000 per QALY gained under End of Life criteria. Implementing the absolute and proportional shortfall from the NICE methods and process review gives T-DXd for HER2-low MBC a severity modifier of 1.2, a figure which is not disputed by the company, the EAG and the NICE committee. A severity modifier of 1.2 gives a maximum ICER of £36,000 per QALY gained. However, because of uncertainties in the evidence submitted, the committee has recommended a figure below the maximum ICER of £36,000 per QALY gained. If implementation of the severity modifier results in patients not accessing an innovative drug, this is a concern and we would hope it would be scrutinised without delay. Patients with metastatic breast cancer support the aims of the NICE methods and process review, but want it to work for them too. We understand that there are

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	uncertainties in modelled data and that in some instances the physician's choice arm in the trial differs from standard NHS care. We hope that these can be resolved for the benefit of patients, noting that DESTINY-Breast04 was a multi-country trial which was designed using international standards, not NHS standards, and so some divergence is to be expected. The DESTINY-Breast04 study was first presented at a Plenary Session of the 2022 ASCO Annual Meeting. The results were met with standing ovation from the international oncology community, and the media coverage which followed has generated great excitement within the patient community. Patients are now expecting this drug to be approved and feel frightened and powerless that their chance of months of extra life are held in the balance of these negotiations. We urge the company and NICE to work together to ensure the right drug access is delivered for patients. The hope of bringing trastuzumab deruxtectan into the NHS is summarised by this patient who writes, "It would give me a sense of my own worth but also the worth of all humans - that we do not literally have a price on our heads. It would give me faith that the brilliant scientific breakthroughs that are being funded and worked for are worth it."
3	The provisional recommendations are not a sound and suitable basis for guidance to the NHS. There is an unmet need for an effective treatment for HER2-low metastatic breast cancer. Trastuzumab deruxtecan is the only drug shown to increase median OS and PFS in a phase 3 clinical trial for patients with HER2-low metastatic breast cancer. Trastuzumab deruxtecan offers benefits for patients with both hormone receptor-positive and hormone receptor negative HER2-low metastatic breast cancer. Treatment choices for HER2-low metastatic breast cancer after chemotherapy are limited to untargeted cytotoxic chemotherapy. Trastuzumab deruxtecan has been applauded by the international oncology community as a step-change drug and has been approved for the treatment of HER2-low metastatic breast cancer by the EMA, FDA, Health Canada and the Therapeutic Goods Administration (Australia) to name a few. Within the UK there are some patients accessing trastuzumab deruxtecan for HER2-low metastatic breast cancer outside of clinical trials. These are patients who are either self funding or who have a private health insurance scheme that has agreed to fund the regimen. We believe that all patients should be able to access the best evidence based international standard of care for their metastatic breast cancer subtype, regardless of ability to pay. This is stated in section 2 of the NHS constitution "Access to NHS services is based on clinical need, not an individual's ability to pay." We now call on NICE and Daiichi Sankyo to work hard to bring this drug to patients to fulfil section 6 of the NHS constitution, "The NHS is committed to providing best value for taxpayers' money."

NICE National Institute for Health and Care Excellence

Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935]

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	We remain optimistic that the above principles of the NHS are not mutally exclusive.
4	Our final comments will be from the patient community. “We live with our disease as well as contribute to society, we are working women with full time & part time careers, being caregivers to elderly parents, to our children, home makers & we should not have our lives & hope reduced to begging because we are not seen as a worthwhile investment due to cost. What is the point of a drug that is developed for our disease if we cannot access it. Other countries are accessing it, private patients are accessing it & yet our lives seem to be worthless.” “I think that's the thing with Enhertu for me...not recommending it would be the complete opposite of working towards the advancement of cancer care and treatment. I thought we wanted better outcomes for patients? Praying it's a pricetag game of chess.” “It would mean precious time with my family. Time to watch them create their own lives, time to make more memories, time for further advances in treatment options. Time for life. Please do not write us off.”
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is ‘commercial in confidence’ in turquoise and information that is ‘academic in confidence’ in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: ‘academic / commercial in confidence information removed’. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935]

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Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Comments on the draft guidance received through the NICE website

Respondent 1. [redacted]
This is a drug which is a breakthrough in treating women who have stage 4 breast cancer, a kind of cancer that seems to be affecting more and more women in their 30s, 40s and 50s, women who are mothers, active citizens and who have been given - on average - only 5 years to live after diagnosis. It's a drug which as you admit has been proven to have exceptionally positive affects - extending their lives by two years and giving quality of life in that time. It's a drug which has been licensed in the US and Europe. And yet one of the richest countries in the world, the UK, is unable to find the funds to provide this for its tax paying citizens. I urge you to reverse this decision at the earliest opportunity.

Represents an organisation – No

Tobacco links – No

Respondent 2. [redacted]
Her2- patients should absolutely be given the right and access to this drug which has proven to extend their lives. Who can put a price on extra months of anyone's life? These women are someone's daughter, wife, friend or mother. These women could be you. Give them the access to the meds that give them extra life.

Represents an organisation – No

Tobacco links – No

Respondent 3. [redacted]
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

At the moment there are very few treatments for patients with HER 2 low BC. As a result these patients are spending more time on chemotherapy that causes a number of side effects and often does not prolong life as much as hoped. Surely the cost effectiveness should take into account the anxiety and distress caused by the lack of treatments for this group of patients. Many patients know of T-DXd and it seems wrong that this treatment can improve our quality of life and hopefully give us more time to live and yet at the moment it is not accessible.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Do the recommendations stress the lack of treatments for patients with HER 2 low BC. At the moment there are very few options for patients with this type of BC. This group of patients suffer with increased anxiety and distress because of lack of treatment. Given the success of T-DXd in trials surely it needs to be available for use on on the NHS as soon as possible.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

So far there have been many new treatments for secondary breast cancer which have been developed over recent years. However there has been a real lack of progress in treatments for HER2 low. This is a large group of patients who are struggling with this diagnosis. The development of T-DXd has offered a real hope and has been offered to a number of patients. However this option is now not available for HER 2 low patients. Surely this is unfair to patients in this group who are now being denied a treatment which could give them extra hope and life.

Represents an organisation – No

Tobacco links – No

Respondent 4. [redacted]
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Committee concluded that there is a definite need for this treatment so I am devastated it is down to money. I feel my life is being given little value here.

The committee concluded that trastuzumab deruxtecan is innovative.

Little other treatment available for me that is effective. So I m devastated for all the ladies like myself who had high hopes for this treatment line to be available to ourselves. Do our lives matter that little because we are in the minority??

I could understand if there were other more cost effective treatments around the corner BUT THERE ARE NOT.

Devastated does not begin to describe how I am feeling on this decision. I dread to think of the devastating impact this has had on our our mental healths and how much this will cost the NHS to address?

An amazing innovative treatment had just been rejected…clearly financial…but need other reasons to reject it…I HOPE PEOPLE ON THE COMMITTEE ARE NOT IMPACTED BY THIS HORRIBLE DISEASE FURTHER DOWN THE LINE AND FIND THEIR LIVES LIKE MINE ARE NOT WORTH SAVING.

Represents an organisation – No

Tobacco links – No

Respondent 5. [redacted]
From reading the information provided (but I am no expert) I understand that this drug is effective and I would therefore ask that you reconsider your decision.

Represents an organisation – No

Tobacco links – No

Respondent 6. [redacted]
From the information provided this drug is effective in prolonging life. I would therefore ask that the decision not to recommend it is reversed.

Represents an organisation – No

Tobacco links – No

Respondent 7. [redacted]
Has all of the relevant evidence been taken into account?

I think that whilst the document may have considered various pieces of evidence, there might be certain elements that would benefit from further exploration, in particular the potential improvements and longer term benefits for patients such as my dear friend who under current criteria would not be eligible.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I don't think so. The document appears to focus on short-term costs, whilst overlooking the potential improved long term patient outcomes. It ignores the preciousness of life in favour of the perceived economic effects.

Are the recommendations sound and a suitable basis for guidance to the NHS?

In my opinion, the recommendations appear to focus on narrow criteria to the detriment of the potential value this drug could bring to patients, such as my friend.
A more in-depth analysis is needed which takes into account the long-term benefits to a wider set of potential recipients would provide a more accurate basis for NHS guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I believe that the current recommendations disproportionately affect patients such as my friend who has reached a point where she has limited treatment options. This implies that there is definitely not fair access to innovative treatments and that there is discrimination based on cost.

Represents an organisation – No

Tobacco links – No

Respondent 8. [redacted]
I disagree with your decision. My laypersons understanding of the trial outcomes were they were fantastic and it's available in Europe and the USA means it's passed their stringent testing. Please reconsider.

Represents an organisation – No

Tobacco links – No

Respondent 9. [redacted]
With a younger and younger population being affected with breast cancer (and so a proportion of those being HER-low), as a doctor who has also had cancer young, to deny people the chance to live another 23 months on average(potentially with young families in tow) is not just. I understand cost effectiveness that comes into play but these are patients who now are fully aware, there are treatments that can help them but won't be funded, and there are no other options with such outcome measures. I would be grateful if you would reconsider. Kind Regards Dr xxxxxx xxxxx

Represents an organisation – No

Tobacco links – No

Respondent 10. [redacted]
Has all of the relevant evidence been taken into account?

No, the document says there was a higher proportion of asian people in the study vs that what is found in the general NHS population. Does it take into account that asians have a higher risk of stage 4 diagnosis? And potentially this would mean they make up a higher percentage of stage 4 breast cancer patients in the UK regardless? I do not feel that is relevant to the document in this case

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Are the recommendations sound and a suitable basis for guidance to the NHS?

No - if there is statistical significance in preventing disease progression then why is this ruled against? Many metastatic breast cancer patients are of working age and would provide a benefit back to the economy potentially, so how significant would cost be on this scenario realistically?

Represents an organisation – No

Tobacco links – No

Respondent 11. [redacted]
The research proves that enhertu extends life in low Her cancer patients. So why are you denying patients this access? This should not be permitted. Please can this be reviewed.

Represents an organisation – No

Tobacco links – No

Respondent 12. [redacted]
1.1
Trastuzumab deruxtecan is not recommended, within its marketing authorisation, for treating HER2-low metastatic or unresectable breast cancer in adults after:chemotherapy in the metastatic setting or recurrence during adjuvant chemotherapy or within 6 months after finishing it.
I ask that this recommendation is reconsidered in light of effects on survival noted in trials

3.21
the committee agreed that an acceptable ICER would be towards the middle of the range normally considered a cost-effective use of NHS resources
I note the cost was considered to be in the middle of the range normally considered a cost-effective use of NHS resources

3.4
The committee concluded that there is an unmet need for targeted treatments for HER2-negative and HER2-low breast cancer. It concluded that the positioning of trastuzumab deruxtecan at the second and third-line settings is appropriate and likely reflects how it would be used in NHS clinical practice.
I agree with the committee that trastuzumab deruxtecan can treat Her2-low breast cancer at 2nd and 3rd line settings.

3.4
It concluded that the positioning of trastuzumab deruxtecan at the second and third-line settings is appropriate and likely reflects how it would be used in NHS clinical practice.
This is an important conclusion ie that it can treat HER2-low breast cancer

3.5
They acknowledged that the trial recruited people who were younger and fitter than most people in the NHS with this condition. But they considered that these people reflect who would likely have trastuzumab deruxtecan in NHS practice, because they are more likely to tolerate the side effects. The committee concluded that the DESTINY-Breast04 trial population was likely to be broadly representative of people in the NHS with HER2-low metastatic breast cancer who would have trastuzumab deruxtecan.
I note the trial included HER2-low patients

3.7
For everyone in the trial who had trastuzumab deruxtecan, regardless of hormone-receptor status, there were statistically significant improvements in progression-free survival
It is noted that everyone on the trial, regardless of hormone-receptor status, had improvements in progression-free survival

3.7
The committee concluded that, compared with TPC, trastuzumab deruxtecan delayed disease progression and improved overall survival in people with HER2-low metastatic or unresectable breast cancer.
I think it is important to note that trastuzumab deruxtecan delayed disease progression and improved overall survival in people with HER2-low metastatic breast cancer.

3.24

Because trastuzumab deruxtecan is the first HER-2 low targeted treatment option metastatic or unresectable breast cancer, the clinical experts considered it to be a step-change in managing the condition. The committee acknowledged that there may be benefits with trastuzumab deruxtecan, but that these were captured in the modelling. The committee concluded that trastuzumab deruxtecan is innovative.
I note these comments re this 'is the first HER-2 low targeted treatment option' and 'The committee concluded that trastuzumab deruxtecan is innovative'

3.25
trastuzumab deruxtecan could not be recommended for treating HER2-low metastatic or unresectable breast cancer in adults.
I ask that this recommendation is reconsidered in light of effects on survival noted in trials

Represents an organisation – No

Tobacco links – No

Respondent 13. [redacted]
My stepmum needs this drug. Please reverse this decision. I don't want her to die.

Represents an organisation – No

Tobacco links – No

Respondent 14. [redacted]
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I feel that this decision would unlawfully discriminate against women and particularly those who have HER2 negative metastatic breast cancer due to the increased incidence of this type of breast cancer in women as compared to men, plus a lack of treatment options for this cohort. I also think it is discriminating against this cohort as they will have followed NICE guidelines in regards to accepting first and second line treatment options, and because of this can then not access this drug.

I feel that this decision would unlawfully discriminate against women and particularly those who have HER2 negative metastatic breast cancer due to the increased incidence of this type of breast cancer in women as compared to men, plus a lack of treatment options for this cohort. I also think it is discriminating against this cohort as they will have followed NICE guidelines in regards to accepting first and second line treatment options, and because of this can then not access this drug.

Represents an organisation – No

Tobacco links – No

Respondent 15. [redacted]
Has all of the relevant evidence been taken into account?

Obviously much evidence has been taken into account, but some aspects have not been fully considered, especially the potential long-term benefits and quality of life impact for patients like my daughter, whose prognosis would not only improve physically, but psychologically, which is recognised as an important factor in cancer survival.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

respectfully disagree with the interpretation of the evidence. The document may have focused heavily on short-term costs, possibly overlooking the long-term savings and improved patient outcomes, which could lead to reduced hospitalisations and other medical and social expenses.

Are the recommendations sound and a suitable basis for guidance to the NHS?

In my opinion, the recommendations do not seem to consider fully the potential value this drug could have for patients like my daughter. I believe a more in-depth analysis , considering the wider and more long-term benefits, would provide a more accurate basis for NHS guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am concerned that the current recommendations might disproportionately affect those patients with very limited treatment options, especially those like my daughter who have been told there are no further treatments available. Surely all patients should have fair access to innovative treatments without discrimination based on cost alone.

Whilst recognising the work of Nice in compiling this document, I would strongly but respectfully disagree with its decision.The potential benefits of this drug for patients like my daughter, who have at present no alternative available treatment, should be given more weight. I would strongly urge a reconsideration, taking into account the massive potential impact on the lives of patients and their families, especially young families like my daughter's who will need so much support from other people. A longer life ,even in terms of months, for my daughter would give her and her family so much more opportunity to organise their lives and for my daughter to help her family achieve some of their aims.

Represents an organisation – No

Tobacco links – No

Respondent 16. [redacted]
As a breast cancer patient myself this is devastating news I am only 33 years of age have a 4 year old son and I am incurable. This treatment could give thousands of people more precious time ! Why spend time fundraising for vital research when it’s not going to be used ?

Represents an organisation – No

Tobacco links – No

Respondent 17. [redacted]
It is so concerning that this treatment that has been proven to extend lives has been declined on grounds of cost. How do you put a price on someone’s life? Please reconsider your decision.

Represents an organisation – No

Tobacco links – No

Respondent 18. [redacted]
This is so so vital. This is an absolute must.

Represents an organisation – No

Tobacco links – No

Respondent 19. [redacted]
Please reconsider this decision. This is a potential life extender to so many, and this decision deprives them of a much needed alternative option. Please reconsider.

Represents an organisation – No

Tobacco links – No

Respondent 20. [redacted]

Hi my names is xxx xxxxxxxxx and I'm 17, This will massively affect me and my brother because my mum will not be able to access this drug, therefore reducing the amount of precious time we have left with her. I am currently doing my A levels and it is really important to my mum that she can see me and my brother graduate, if she does not get this drug then there is only a 50% chance she will live long enough to see me graduate. Please can you pass this drug so I can get more time with her.

Represents an organisation – No

Tobacco links – No

Respondent 21. [redacted]

I'm so disappointed that this drug is no longer being offered to secondary cancer patients. They deserve so much better! They deserve the opportunity to have more moments with their families, their kids, their friends. Cancer is so pervasive and has touched my family three times - my grandma, my mum and me. Please reconsider the decision!

Represents an organisation – No

Tobacco links – No

Respondent 22. [redacted]

Has all of the relevant evidence been taken into account?

Having read the evidence, it appears that there remains uncertainties about the how effective the treatment is for people with HER2-low metatastic or reselectable breast cancer. This would indicate the need to continue evidence-gathering, not to deny treatment.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Having read the evidence, it appears that Trastuxumab deruxtecan can prolong life and reduce disease progression for all patients, including those with HER2 Low metatastic or unreselectable breast cancer. Given the uncertainties referenced in the trial and the devastating impact the draft recommendation will have on the people effected, the summaries do not seem reasonable. Further evidence is surely required with a more representative population, in 'real-world' scenarios.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No - there are around 1000 people who are being denied the chance of a longer life with this recommendation, which is based on partial data. This is the first treatment licenced for HER2-low breast cancer and as such further evidence should be collected by approving the treatment and using it in real-world situations.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

If the trial included an over-representation of people of South Asian heritage, does this mean that there was an under-representation of people from other ethnicities?

Represents an organisation – No

Tobacco links – No

Respondent 23. [redacted]

Has all of the relevant evidence been taken into account?

It feels like a thorough review of the evidence, from what I have read. There seems to be uncertainties around QALY calculations that might influence overall decision outcomes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summaries seem to weigh heavily in terms of cost Vs clinical effectiveness. Given the relative other costs of treatment, this is not the most cost inefficient treatment used by the healthcare provider. In addition, this being one of very few treatments for patients with this diagnosis seems not to have fully weighted in the effectiveness assessments.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I would support a reassessment with greater consideration of point raised in other questions.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Not from my understanding.

Represents an organisation – No

Tobacco links – No

Respondent 24. [redacted]
Has all of the relevant evidence been taken into account?

Yes it has. Thoroughly

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes they are clearly stated

Are the recommendations sound and a suitable basis for guidance to the NHS?

Very sound and suitable. Definitely.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Clear and informative information, showing cost effective benefits of this treatment to in need patients.

Represents an organisation – No

Tobacco links – No

Respondent 25. [redacted]
My friend needs this drug. She's only 41. I don't want her to die. Especially not because she was denied the drug she needed because it wasn't cost effective.

Represents an organisation – No

Tobacco links – No

Respondent 26. [redacted]
This appears to be a purely financial decision which makes women with Secondary Breast Cancer feel physically sick, worthless and hopeless about their futures and what the Government, NICE & NHS think of them. This decision again helps the UK fall behind Europe & USA with regards to treatment, it's embarrassingly callous and not forward thinking. Nicky Nicklau a famous Instagrammer/Campaigner for Secondary Breast Cancer has just died at age 35 after suffering with bone mets for 5 years. I feel we're not even reacting to women in their 30's dying from this any more? How can this be right? I implore you to not make this grave decision be about money & approve this drug please to be used in the NHS. Thank you - I hope. A Secondary Sister.

Represents an organisation – No

Tobacco links – No

Respondent 27. [redacted]
I don't understand why this fund won't be funded when the evidence has proven that the drug works works really well. It's effectively choosing the coat of drug over a human life and feels quite unfair. This is valuable extra time for patients to spend with loved ones / do more work on this earth cost etc.
I believe the trials have shown that enhertu gives 6-8months of extra time compared with conventional chemo and the median survival is 23 months longer.

Please reconsider.

Represents an organisation – No

Tobacco links – No

Respondent 28. [redacted]
It seems to be a very complex and technical piece of work, designed to confuse the layman. The commercial detail also seems very vague and needs comparison with other similar issues. And ultimately what price do you put on 2 years of someone's life?

Represents an organisation – No

Tobacco links – No

Respondent 29. [redacted]
Not acceptable at all! Taking away a possible 2 extra years of people's lives in a decision that hasn't been properly considered

Represents an organisation – No

Tobacco links – No

Respondent 30. [redacted]
This drug will add 23mths to my friends life. Enabling her spend precious time with her two sons and plan for their care beyond that.

Represents an organisation – No

Tobacco links – No

Respondent 31. [redacted]
I have no medical experience or expertise but if this could potentially be a life saving drug for many or even 1. It has to be approved, it's the least you can do.

Represents an organisation – No

Tobacco links – No

Respondent 32. [redacted]
Please review this decision. I am a patient who has finished treatment for primary breast cancer that is triple negative, but with her 2 Low. If my cancer were to come back Enhertu would be a lifeline for me to have more time with my family. I have best friends in the community who are living with MBC and so desperately were hoping that Enhertu would be an option for them. To have more time with their loved ones. Please please think again about this. This is so needed for a group of women with a type of breast cancer that has limited options. This would make all the difference. This is so needed. This is a devastating blow to our community that you have not approved it today for use on the NHS. This feels so cruel. So unjust. And I hope and pray that this decision can be turned over. And that you give people access to this drug and in doing so give them all anyone with MBC wants... More time.

Represents an organisation – No

Tobacco links – No

Respondent 33. [redacted]
Has all of the relevant evidence been taken into account?

I feel strongly that patient voice has not been adequately taken into account during this process. Living with metastatic breast cancer (MBC) is devastating for patients and their families and friends. Being diagnosed with MBC at the age of 38 has devastated my and my husband's lives. Gone are the dreams of adopting the much-wanted children we were so excited about caring for. My father, only a few years after losing his wife (my mum), is currently bearing witness to the decline and subsequent death of his daughter. I've never had to do anything so difficult in my life as to go to his house and tell him that I had been diagnosed with terminal cancer. He thought I was going round to tell him that we were going to be having a child. I don't feel he's ever recovered from this moment and neither have I, nor will I.

The whole point of cancer research is to develop and release new, innovative, tolerable treatments which can extend the lives of those unfortunate enough to be diagnosed with this horrific disease. To hear that trastuzumab deruxtecan is so well-regarded within the cancer community, and is already being used in similar-income territories such as Australia, Canada, the US and Europe, yet has been rejected here on the basis of cost is devastating.

I'm currently 'fortunate' enough to be HER2+, but if my cancer mutates to HER2-low, how will I explain to my dad and husband that my life has been deemed not worthy of extending? How do I tell them that the wonder drug they've read about in the newspapers that I may need in the future and that would help us to spend more precious time together as a family would be denied to me on cost grounds? How do I tell a 71-year-old man on a state pension having worked all his life that he's going to have to help me self-fund a drug which is readily available to other patients with a slightly different subtype? Also, thinking about the here and now, how do I look my HER2-low and triple negative friends in the eye when I, as a HER2+ positive patient would be eligible for this drug while they would not?

Are the recommendations sound and a suitable basis for guidance to the NHS?

As above, I feel that this recommendation has been made based far too heavily on the cost of this drug, rather than on its life-extending benefits for patients.

It's patently obvious to everyone that to continue their research and development work, drug companies need to make a profit on their innovations. My fear is that by making recommendations like these, in which excellent new drugs are developed and then rejected on cost grounds, may lead to drug companies switching their focus from metastatic breast cancer research and treatments, to focus on other diseases. This will create a huge unmet need in the metastatic breast cancer research field. After all, why should drug companies bother spending all that time and money developing a new drug if organisations such as NICE are just going to recommend that it not be used?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I feel that this recommendation is discriminatory towards women, who make up around 99% of the MBC population, with men making up just 1%. I also feel that to push patients towards having to self-fund trastuzumab deruxtecan would discriminate against patients who are unable to work or on a reduced income due to disability caused by their MBC, and patients who are currently unable to work due to being on maternity leave.

Also, given that Black women and women of Ashkenazi Jewish descent are disproportionately affected by triple negative MBC, I consider this recommendation to be discriminatory towards these groups too.

2.3
Is trastuzumab deruxtecan administered every three weeks? If so, £1,455 every three weeks does not seem excessive when taking into account the extra months/years of survival it likely confers. It cost is also comparable to other cancer treatments such as Phesgo which is currently widely used within the NHS.

2.4
It is not clear here what "commercial in confidence" means, does this mean you can't tell us the size of the discount? Could the NHS negotiate a larger discount if possible?

Represents an organisation – No

Tobacco links – No

Respondent 34. [redacted]
Has all of the relevant evidence been taken into account?

No. Reports from the Enhertu trials stated that 55% of breast cancer patients are classified, by biopsy, as 'Low HER2'. This means that this sub-group is the dominant group with respect to HER2 status. And yet your draft decision is to not approve this treatment for a subgroup that forms the majority of patients.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, for the reason as outlined in the first question. NHS guidance will not cover the majority group.

Represents an organisation – No

Tobacco links – No

Respondent 35. [redacted]
It is stated in the document 'people taking trastuzumab deruxtecan were more likely to have delayed disease progression and improved overall survival' How is this not relevant to NICE's view of the drug not being 'cost effective'. These are parents with dependents, young people (it is also stated the profile for the drug recipient will tend to be younger) with a future contribution to society. Not to allow these people this drug means picking up costs in other services. This is not a 'cost effective' decision.

Represents an organisation – No

Tobacco links – No

Respondent 36. [redacted]
The document explains the situation around HER2-low patients in relation to enhertu. But as a patient who this line of treatment could be a crucial option, I find that the basis of not confirming it's use for this group of patients screams financial.
I was lucky enough to receive palbociclib before it was passed by NICE as being an option on the NHS. Life expectancy at that time was expected to increase by approximately 10 months. Nice at that time thought this was not worthwhile. In the first 10 months of being on palbociclib, I got to see my nephew marry, see my daughter graduate and have many memorable holidays with my family. I have now been on palbociclib for over 6 years & my cancer remains stable to date. As

I got the drug on early access, the NHS do not have to fund this. I want to have drugs available that could extend my life further and enable me to enjoy precious time with my family. I strongly recommend that you rethink your decision. I understand that the NHS budget is extremely tight, but we must give patients the opportunity to live longer. It is callous to have this drug as a viable option, but snatch it away from certain patient groups.
It is obvious that the decision makers on this drug are not in the position as myself and many of my friends with metastatic breast cancer. Think about taking the emotional strain off patients and off the NHS by making this drug available to HER2 low patients.

Represents an organisation – No

Tobacco links – No

Respondent 37. [redacted]
It is disappointing to hear that the limited availability for treatment of metastatic breast cancer has the possibility of being further limited.
The evidence reported admits that there is prolongation of life in patients with the use of this medication.
Cost appears to be the issue on the current recommendation. I disagree with this and would strongly urge that the decision to not recommend this medication be overturned. You cannot put a price on a loved one that has already limited and low options for treatment. These patients are fighting enough please help them with their fight and do not limit their options further. More time is what patients need to help further aid both research and development and of course the utmost to prolong the time they have to spend it with their loved ones.

Please reconsider

Represents an organisation – No

Tobacco links – No

Respondent 38. [redacted]
This is a devastating conclusion for those whose lives would be altered, improved or made longer by this drug.
Please reconsider.

Represents an organisation – No

Tobacco links – No

Respondent 39. [redacted]
Has all of the relevant evidence been taken into account?

I am sure that all relevant evidence has been considered, however I believe that there could be aspects that were not fully explored, with respect to potential long-term benefits and quality of life improvements for patients like my friend.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The review might have focused heavily on the short-term costs, possibly overlooking the long-term savings from imprved patient outcomes which could result in reduced hospitalisations and other expenses.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I am not convinced that the committee have fully consider the potential value this drug could bring to patients, like my friend. A more in-depth analysis looking at the long-term benefits may be needed to provide guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am concerned that the current recommendations might disproportionately affect patients, especially those with limited treatment options. It's essential to ensure fair access to innovative treatments without discrimination based on cost alone.

I have read the document and appreciate the committee's effort in coming to its conclusion. However, I respectfully disagree with the decision.

The potential benefits of this drug, especially for patients like my friend Claire, should be weighed more heavily.

I therefore urge the committee to reconsider its decision, taking into account the long-term impact on patients' lives and the potential advancements in breast cancer treatment.

Represents an organisation – No

Tobacco links – No

Respondent 40. [redacted]
I understand you are not recommending the drug Enhertu for MBC in HER2-low patients. This is shocking. This is a life extending drug for these people. They want to live. Please give them a chance

Represents an organisation – No

Tobacco links – No

Respondent 41. [redacted]
It makes no sense for this amazing drug not to be given to the women who desperately need this as a mater of life or death. It is approved almost worldwide. My daughter is HER2-low and was reassured last year by her Oncologist that this is the way forward and that in no way could the UK refuse to grant this approval. Yet they have done so. Why? Cost yet again whilst billions are squandered by this government. How dare they treat valuable people like this. Mothers, daughters, wives, friends. This is a national disgrace and shame on our country.

Represents an organisation – No

Tobacco links – No

Respondent 42. [redacted]
I've been promised this by my consultant as my 4th line of treatment and NICE have the downright audacity to say NO to us SBC just trying to survive!!! Reverse your decision or have the wrath of us the SBC community to deal with, worried from Romford

Represents an organisation – No

Tobacco links – No

Respondent 43. [redacted]
It seems to me that we can spend billions on PPE fulfilment contracts that line the pockets of a minority. However, when it comes to lives of our wives, mothers, daughters and sisters, you're placing a literal, and shamefully low price, on the value of their lives. A price, which it seems could be even lower because the manufacturer's discount hasn't yet been applied due to this recommendation.

The medication has proven results and will improve the quality of life of women with this condition. The decision is inhumane and you risk being on the wrong side of history unless you change this morally reprehensible recommendation. Your sisters, daughters, wives and partners, mothers, and friends all deserve the opportunity to not have the rest of their lives unfairly snatched away from them and their loved ones.

Please don't be so cruel as to place so low a price on the lives of women. You can still make a decision that demonstrates moral courage and your own humanity.

The medication works and will improve the quality of life in those in need of it. Science supports the right thing to do. There is no scale, no standard that should override the benefits this medication brings.

You have set a price on the lives of every women, and as a husband, father and son it is heartbreaking. They all deserve more time.

Represents an organisation – No

Tobacco links – No

Respondent 44. [redacted]
We need this drug. It works and can extend our lives. It's cruel to know there is something that can help us have longer with our loved ones but not none able to have it

Represents an organisation – No

Tobacco links – No

Respondent 45. [redacted]
The costings seem quite arbitrary as does the decision to not approve this drug. Why deny it to the HER2 low people due to cost when it is approved for HER positive people despite the benefits being great for both groups. The hope and extra months of life this could give people is well worth the cost.

Represents an organisation – No

Tobacco links – No

Respondent 46. [redacted]
Please reconsider the decision not to make this available. It could save/extend lives. This must be an option.

Represents an organisation – No

Tobacco links – No

Respondent 47. [redacted]
Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, as this treatment is proven to prolong life for these patients, the clinical effectiveness would far outweigh any cost implications.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, this treatment has been recommended and is already available in several other countries. The recommendations do not consider the impact that this could have on patients' and their families' lives. Further justification is needed to explain why this treatment would not be recommended especially in light of its availability in other countries.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Represents an organisation – No

Tobacco links – No

Respondent 48. [redacted]
Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I believe that it is primarily women who could benefit from this treatment and that even though this treatment is available in other areas of the NHS, the fact that this won't be available for women suffering from breast cancer is discrimatory

I can't believe that NICE are denying the chance of hope and a longer life for people with this type of breast cancer. Having targeted, individualised, tolerable treatments that can extend and improve quality of life are vitally important to people with the condition, and it's imperative that the funding for this type of medication stretches to women who are in this heart breaking situation. Stage 4 breast cancer affects so many people and this ground breaking treatment was met with a standing ovation at the recent cancer treatment conference, so how on earth can NICE deny people who need this vital treatment the chance at a longer life? I stand against this decision and hope that it is overturned.

Represents an organisation – No

Tobacco links – No

Respondent 49. [redacted]
Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

N/a

I strongly believe that any individual suffering from a disease thst can be treated, even if it offers only months to their life, is worth providing. For those who are already facing life limiting illnesses a ray of hope is so important. I recommend that we give these people hope.

Represents an organisation – No

Tobacco links – No

Respondent 50. [redacted]
Has all of the relevant evidence been taken into account?

No, more needs to be done for secondary breast cancer

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, more needs to be done for secondary breast cancer

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, more needs to be done for secondary breast cancer

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No, more needs to be done for secondary breast cancer

Represents an organisation – No

Tobacco links – No

Respondent 51. [redacted]
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I don't think they are as they don't give sufficient weight to the benefit to affected individuals.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, because they are based on anaylis that doesn't give sufficient weight to the benefit to affected individuals.

1.2
Even when considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are above the range NICE considers an acceptable use of NHS resources
This assessment of cost-effectiveness is unreasonable given the huge benefit to each individual personally from trastuzumab deruxtecan increasing how long they live and how long they have before their cancer gets worse.

3.21
These points are noted, but given the positive evidence from trials described above in my view this treatment should be made available. There can always be reconsideration in the light of further evidence obtained from this wider use of the treatment.

3.21
could mean
As this is simply an inference, and given the huge benefit to any individual of an increase in life expectancy or time before their cancer gets worse, the treatment should be made widely available. Data from its wider use can then be analysed over time and the cost benefit can always be reassessed in the light of that better information.

3.21
Again, given the huge importance of this treatment to those with HER-2 low metastatic or unresectable breast cancer and the huge benefit to them of increasing their life expectancy and the time before their cancer gets worse this treatment should be made available whilst any further analysis is undertaken and the additional evidence derived from this can contribute to any further analysis.

3.2
These submissions bear out the unreasonablenss of not offering Trastuzumab deruxtecan to those with HER-low breast cancer.

3.7
Compared with TPC, people taking trastuzumab deruxtecan were more likely to have delayed disease progression and improved overall survival. For everyone in the trial who had trastuzumab deruxtecan, regardless of hormone-receptor status, there were statistically significant improvements in progression-free survival (hazard ratio 0.5 [95% confidence interval 0.4 to 0.6]) and overall survival (hazard ratio 0.6 [95% confidence interval 0.5 to 0.8]) compared with TPC.
This indicates the value and benefit of offering Trastuzumab deruxtecan as there were statistically significant improvements in progression-free survival and overall survival for all participants, regardless of hormone status.

3.17
I'm not equipped to comment on the detail of the weighting etc., but from a moral and ethical point of view the value of providing treatment which is evidenced as increasing life expectancy and how long people have before their cancer gets worse overrides the costs and Trastusumab deruxtecan should be made available where it's identified as a potential treatment for an individual.

Represents an organisation – No

Tobacco links – No

Respondent 52. [redacted]
I don’t support the decision to not recommend the decision to not use this drug on the NHS. I feel it is the wrong decision as cost is not a sufficient justification to not support this drug on the NHS.

Represents an organisation – No

Tobacco links – No

Respondent 53. [redacted]
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Your system is ridiculous for posting comments. All I ask is that you see this from a human perspective and not financial. Would your answer still be the same if it was your mum in this situation that could add years onto her life. If this decision stands, you all have blood on your hands and I don't know how you sleep at night!

Represents an organisation – No

Tobacco links – No

Respondent 54. [redacted]
This decision to deny a drug to so many people who would benefit from time on this earth has floored me. I am in remission from her2 positive breast cancer. Knowing the drug I was given wasn’t around before the 1990s terrifies me that so many women died of my type of cancer. This is real for me. I am so fortunate to have had the BEST treatment for my cancer type. These women who have a different type of her2 levels are not receiving ALL the possible drugs to give them more time on this planet. Why should they be treated any different to me. All lives are equal. This drug can give women more time to live. Full stop. MORE time on this planet to make memories, be with

their children, make a difference to the cancer community, to live! There should be no price on this. Please. Everyone should be given every drug to prolong their lives where applicable.

Represents an organisation – No

Tobacco links – No

Respondent 55. [redacted]

Has all of the relevant evidence been taken into account?

Clearly much work has been done but having experienced the journey of my sister-in-law , I would suggest that further evidence based research on anticipated individual response needs to be undertaken. My sister-in-law is an example of patients where there is additional need to understand and appreciate the full long-term benefits and improvements in quality of life that treatment can offer

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The interpretations are understandably focussed on the short term benefits of cost reduction From the perspective of a close family member as well as member of wider society I didn't feel that the full additional long term savings of improved patient outcome and the reduction in associated costs as a result had been fully considered

Are the recommendations sound and a suitable basis for guidance to the NHS?

I didn't feel that the recommendations are suitable basis for guidance for the NHS. There are significant and prolonged benefits that this drug could bring to patients who fall into the same medical category as my sister-in-law. Given the known postive outcomes of teh treatment, further exploration is important for both existing and future patients.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Given how important the treatment is to a category of patients such as my sister-in-law, it is critical that access to the drug is not based on ability to pay which by its very nature discriminatory. NICE must ensure that all have equal access to the advances in medicine

The documents and recommendations are clear however I don't believe that the potential benefits for both patient and wider society have been fully weighted given the impact on the lives of all those concerned. Extending the quality of life of the patient when they are still able to contribute must be foremost . I write as the brother in law who has known the patient and the family for over 55 years and seen extraordinary, exponential advances in Breast Cancer treatment over the last few years.

Represents an organisation – No

Tobacco links – No

Respondent 56. [redacted]

Secondary breast cancer is as important as any other cancer, it is crucial the colossal amount of young/old ladies with it get what they deserve and that is anything that prolongs/supports their harrowing journey with this awful disease. I follow a friend and her journey Jeannie Ambrose, she is absolutely inspirational but also goes through too much for one person to cope with. These ladies are so brave and to not approve a life prolonging drug to them is a disgrace!!!

I also would like to add the adverts for cancer research tell us they are learning and improving etc etc all the time, i myself have done many runs/ walks for cancer research as I have lost lots of family to cancer, along with thousands of others, we give so much and we deserve to be supported in every way possible no matter what the cost.

Represents an organisation – No

Tobacco links – No

Respondent 57. [redacted]
Has all of the relevant evidence been taken into account?

this needs to consider the NHS surveillance decision from January 2023 on CG81 which changes these steps to include CDK4/6 inhibitors for example

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Why are patients better served in Europe, or Switzerland, as its approved by the EMA and is use in those countries ?

https://www.ema.europa.eu/en/medicines/human/EPAR/enhertu#:~:text=Enhertu%20has%20been%20given%20%27conditional,provide%20additional%20evidence%20after%20authorisation.

Are the recommendations sound and a suitable basis for guidance to the NHS?

EMA and FDA approvals should be considered for HR+, HER2-low, why are NHS patients denied a drug which is used elsewhere successfully ?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

none

3.21
Because this uncertainty could mean that the true ICER is above what NICE normally considers a cost-effective use of NHS resources, the committee agreed that an acceptable ICER would be towards the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).Comment on section: Further analyses
Why are patients better served in Europe, or Switzerland, as its approved by the EMA and is use in those countries ?

https://www.ema.europa.eu/en/medicines/human/EPAR/enhertu#:~:text=Enhertu%20has%20been%20given%20%27conditional,provide%20additional%20evidence%20after%20authorisation.

3.21
modelling TPC
agreed, TPC should include CDK4/6 inhibitors, as per your surveillance not January 2023 on CG81, https://www.nice.org.uk/guidance/cg81/resources/2023-surveillance-of-early-and-locally-advanced-breast-cancer-diagnosis-and-management-nice-guideline-ng101-and-advanced-breast-cancer-diagnosis-and-treatment-nice-guideline-cg81-11321031709/chapter/Surveillance-decision?tab=evidence

3.3
For metastatic breast cancer regardless of hormone-receptor status, NICE recommends:
this needs to consider the NHS surveillance decision from January 2023 on CG81 which changes these steps to include CDK4/6 inhibitors for example

3.4
They highlighted the unmet need for people with hormone-receptor and HER2-negative breast cancer, given the limited treatment options available compared with HER2-positive breast cancer. The committee concluded that there is an unmet need for targeted treatments for HER2-negative and HER2-low breast cancer. It concluded that the positioning of trastuzumab deruxtecan at the second and third-line settings is appropriate and likely reflects how it would be used in NHS clinical practice.

as used by other countries, in Europe incl. Switzerland where it is in standard usage for treating HER2-low, and was approved for such use -
https://www.ema.europa.eu/en/medicines/human/EPAR/enhertu#:~:text=Enhertu%20has%20been%20given%20%27conditional,provide%20additional%20evidence%20after%20authorisation .

3.6
The committee acknowledged that the TPC arm broadly reflected NHS clinical practice but concluded that second-line eribulin and lack of sacituzumab govitecan meant that the TPC arm was not fully generalisable to standard care in NHS clinical practice.
CDK4/6 inhibitors should also be considered as part of the TPC arm

3.25
All the ICERs in the company and EAG analyses were higher than the range NICE considers to be a cost-effective use of NHS resources even with the severity modifier 1.2 weight applied. So, trastuzumab deruxtecan could not be recommended for treating HER2-low metastatic or unresectable breast cancer in adults.
Why are patients better served in Europe, or Switzerland, as its approved by the EMA and is use in those countries ?

https://www.ema.europa.eu/en/medicines/human/EPAR/enhertu#:~:text=Enhertu%20has%20been%20given%20%27conditional,provide%20additional%20evidence%20after%20authorisation.

Represents an organisation – No

Tobacco links – No

Respondent 58. [redacted]
Has all of the relevant evidence been taken into account?

In terms of the effect of quality of life of both the patient and dependents and loved ones, it seems to me that the benefits have not been properly taken account of and that the utility values of the company have been dismissed too readily.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The clinical trial evidence shows that trastuzumab deruxtecan increases how long people live and how long they have before their cancer gets worse and undue weight is placed on the degree of uncertainty around the ICER.

Are the recommendations sound and a suitable basis for guidance to the NHS?

A number of somewhat arbitrary evaluations appear to have been made in relation to utility and uncertainty given the overwhelming evidence of the positive effect of trastuzumab deruxtecan on delaying progression and the benefits that has for the patient and dependents.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

It does not seem to me that full account has been given to the effect on women particularly, or the role they play in the the emotional and physical well being of dependent families. The clear benefits of trastuzumab deruxtecan should be used to maximise both the longevity and quality of life of the patient and their crucial contribution to the well being of their families.

Represents an organisation – No

Tobacco links – No

Respondent 59. [redacted]
The committee acknowledges trastuzumab deruxtecan is the first HER-2 low targeted treatment option for metastatic or unresectable breast cancer and that it is a step-change in managing the condition. This should be given greater weight to the final recommendation than a higher than acceptable ICER. There are no other treatment options available. Many women with this disease type are below 50 years of age with young children.

Represents an organisation – No

Tobacco links – No

Respondent 60. [redacted]
Has all of the relevant evidence been taken into account?

I question this as don't understand how NICE can reject this based on such amazing results

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No I dont feel it is, this drug is already in place for HER2 positive. Being HER2 low is still HER2 positive and requires the same specific treatment

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Secondary breast cancer is defined by The Equality Act, my type of cancer HER2 low is being discriminated against by nit allowing this treatment which has shown amazing and positive results in trials

Represents an organisation – No

Tobacco links – No

Respondent 61. [redacted]
It was deeply upsetting and alarming to read the report on Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy and the decision to not recommend it for routine use on the NHS

and I hope that it can be reconsidered.

The report does not dispute the effectiveness infact it clearly states that it

"increases how long people live and how long they have before their cancer gets worse" and the decision is purely based on financials.

Is that what we have become as a nation and a people? Where the chance to live, the chance to spend precious time with families and loved ones, the chance to improve our health is not as important as some financial figures on a spreadsheet.

The NHS constitution clearly states:
"The NHS belongs to the people.
It is there to improve our health and wellbeing, supporting us to keep mentally and physically well, to get better when we are ill and, when we cannot fully recover, to stay as well as we can to the end of our lives."

The options for this particular patient group are extremely limited and for many this treatment might be their only option, you cannot take the opportunity to live away from them.

At a time when patients and their families are already experiencing the most stressful and upsetting times of their lives, by not having the opportunity to avail of treatment on the NHS, people will instead be faced with the struggle

to try to fund this treatment themselves. Adding financial strain, debt and distress onto the stresses and strains of illness - the priority should be on keeping well not fighting for treatment to live.

Choosing to decide whether a person lives or dies based on money is the very antithesis of what the NHS is. Please reverse the decision and reinstate healthcare as it is meant to be.

Represents an organisation – No

Tobacco links – No

Respondent 62. [redacted]
Has all of the relevant evidence been taken into account?

I feel that some evidence has been used to draw this conclusion, but there may be some areas that have not been fully looked into.
I feel that more time needs to be given to look into how use of this drug could have long term benefits and certainly quality of life benefits for my friend.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not believe that this is the case. There is discussion around short term costs but possibly not for the longer term.
There may well be long term savings around patients needing less hospitalisation and other medical interventions if outcomes were improved.This needs to be looked at further.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I respectfully do not feel that this is the case.
I do not believe that the potential benefits to people like my friend have been explored enough and more detailed exploration is needed.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I feel that women like my friend who has very few options of treatment now left to her would be disproportionately affected by these decisions.
In my mind it is important that all treatments should be offered without discrimination around cost alone.

I appreciate what the document is trying to say but I respectfully disagree with it's conclusions.
I feel that there would be enormous benefits for use of this drug with patients in the same situation as my friend who has HER2 low cancer cells.
They would be given the chance to survive for longer and do the things that matter most to them. It would improve their psychological health knowing that there is another treatment out there that can extend their lives for a little longer.
My friend is an amazingly brave woman who has taken time and all her energy to look into all the treatments appropriate to her. She deserves every opportunity to extend her life and gain some greater quality of life.
Pease reconsider this decision.

Represents an organisation – No

Tobacco links – No

Respondent 63. [redacted]
This drug extends and saves precious lives!

Represents an organisation – No

Tobacco links – No

Respondent 64. [redacted]
This drug is a lifeline for so many who are living and dying from secondary cancer. To deem people's lives not worth it due to cost is both saddening and incomprehensible. Please continue to recommend this drug for her2 low patients to give them hope and more time.

Represents an organisation – No

Tobacco links – No

Respondent 65. [redacted]
I got a de-novo diagnosis of triple negative breast cancer {TNBC) and also negative to immunotherapy. It is widely accepted that TNBC is more aggressive with poor prognosis. It is also accepted that it disproportionally effect young women, Afro-Caribbean and ethnic minority women. I would like you to take account of these facts as removing one of the few options, Trastuzumab deruxtecan, for me and these groups of women could amount to unfair practice and inequality.

I only found out by chance that I have low expression of HR2 and when my treatment options have run out (which are significantly less then other breast cancers and they will run out sooner) all I have to hope for is getting some extra life possibly with Trastuzumab deruxtecan. I am brave and I fight every day for extra life. Every extra day/week/month is so precious. Please don't take away the few options I have.

I wrote a poem when I was told about my poor prognosis and about the lack of treatment options which I have copied below. It is trying to show you that having an aggressive cancer with few options can make you helpless and hopeless. And to make things even worse, one the few you have are being taken away in the UK (even though 40 other countries think it is good to have).

One of the Few

There's a nasty rumour I have a tumour. Where?
It has it's nest in my left breast. It's comfortable there,
has all the power, likes to devour my flesh.
Boastful in the shower.

There's a nasty rumour it's left it's nest and travelling
through my nodes, has come to rest in my bones.
Spine, pelvis, ribs, sternum, clavicle.
Multi-flora, too numerous to count.

It's rare I'm told, bold, an invasive subset.
There's nothing for you. Phew, hey, I'm special
in a very bad way. It's not my lucky day.
For me it's the, 'face up to your demise' way.

A bomb has been dropped on my life.
An emotional explosion with a count down vibe.
A river of grief held back by a lump in my throat.
My death bed, non-stop, a loop in my head.

I envy your retirement years.
Mine robbed from my blood sweat and tears.
My jealous mind wants others to have cancers of the worst kind.
Well, I am a malignancy, an ugly mutation.

What can I do? Should I fight, grovel, plead for some life?

Should I rage against my ‘end of life care’ with it’s nasty snare?
Or, should I disguise the death in my eyes, drag my ravaged
bones to my bed, bury my head and wait?

I mustn't make such a fuss, everyone has to die I’m told.
And you’re getting old. Seize the moment.
Come to terms with your fate. Have a nice cup of tea or coffee.
Really, is that all there is for me? NO, help me! It can’t be, surely?

Represents an organisation – No

Tobacco links – No

Respondent 66. [redacted]
Has all of the relevant evidence been taken into account?

No

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. This drug could be a vital lifeline to so many and absolutely should be available on the NHS.

Represents an organisation – No

Tobacco links – No

Respondent 67. [redacted]
It seems unbelievable that NICE should remove this proven drug from the already vanishing small range of treatment options open to breast cancer sufferers with HER2 low cancer. Please reconsider this decision which will prematurely rob many breast cancer sufferers of all hope and prematurely end their lives.

Represents an organisation – No

Tobacco links – No

Respondent 68. [redacted]
Please reconsider your evaluation and recommendations of this drug. Patients with secondary breast cancer need more options, especially with the number of younger people being diagnosed. Please reconsider and make this drug an option for patients.

Represents an organisation – No

Tobacco links – No

Respondent 69. [redacted]
Please reconsider your recommendation for this drug.

Represents an organisation – No

Tobacco links – No

Respondent 70. [redacted]
Has all of the relevant evidence been taken into account?

It would appear so but then ignored.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I am not a medical professional so this is outside of my area of expertise.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I was unable to add comments so will incl some of my observations here.

Is the decision making consistent with other similar considerations (for treatment of any illness) across the NHS?

If not, the recommendations are deciding who lives and who dies. If the drug is effective in prolonging and improving life, when considered against other drugs of the same impact, with budgetary approval, then this would seem a deliberate deprivation of the right to life aimed solely at breast cancer patients with this pathology. I believe this could be the subject of legal challenge.

The rationale does not satisfy a due diligence test, NICE may as well shut shop and say it's not considering any new drugs anymore due to cost. Or it is demonstrating a particular bias and attack on breast cancer patients.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I believe you are discriminating against women, who suffer breast cancer. Will you also be refusing life saving treatments for men with prostate cancer?

Represents an organisation – No

Tobacco links – No

Respondent 71. [redacted]
My friend needs this drug to survive. Please don't let her die!

Represents an organisation – No

Tobacco links – No

Respondent 72. [redacted]
My younger sister was diagnosed in Dec 2021 with metastatic breast cancer. She was 39. She is mum to 3 daughters under 10 years old. My sister would be eligible for this treatment. This treatment could give my sister precious extra time with the family she adores. It could do the same for the thousands of others living with this horrendous disease. Please reconsider the decision not to approve. People's lives literally depend on it.

Represents an organisation – No

Tobacco links – No

Respondent 73. [redacted]
Every day counts when it comes to keeping my friend alive and this drug is crucial to help that happen. Please ensure this remains available so that her teenage daughter has a mum for as long as possible. Thank you.

Represents an organisation – No

Tobacco links – No

Respondent 74. [redacted]

This is heartbreaking. To acknowledge the potential life extending impact of enhertu, then say it's not cost effective in the next sentence. The research into this drug for this patient population received a standing ovation when presented at international conference - clinicians saw the hope that it would give. When living with stage 4 cancer, hope is everything. Today it has been crushed.

The extra months or years of life that enhertu could have bought people is the difference between whether young children remember their mothers or not. I live with stage 4 breast cancer & this could well be my reality. I desperately try to imprint my love onto my son in the hope that it isn't.

Everything has a cost. These decisions must be very difficult. But the BNF list price for enhertu is £1455. Not a huge sum.

I work as a nurse front line in the NHS & see areas of waste daily. Huge sums of money spent on new management 'initiatives' only for them to be discarded when the next shiny suited business manager appears.

I urge you with all my heart to reverse this decision.

Represents an organisation – No

Tobacco links – No

Respondent 75. [redacted]

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The cost seems to be the prevailing factor in decision making here. This drug is already being used for HER2 positive patients in the UK as well as for HER2 low patients elsewhere in the world due to its huge success. It doesn't seem the clinical effectiveness is being taken into account in a strong enough way given the decision outcome that has been reached.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I don't believe they are; they look to be solely based on cost given how successful the trial outcomes have been in HER2 low patients. This group of patients already have significantly reduced treatment options vs. Other breast cancer patients and the recommendations are removing a vital and hugely successful treatment option for them. There needs to be some flexibility from Daiichi Sankyo here given how many more MBC patients wpild be eligible for treatment with this drug. This drug is already being used elsewhere in the world for HER2 low MBC and this, plus the clinical trial outcomes and it's reception in the world of oncology given just how successful it has been. You are denying people a chance to live with this recommendation completely going against all six of the core values in the NHS constitution, particularly 'improving lives' and 'everyone counts'. This decision is in stark contrast to this.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

As far as I can see and understand, there is a clear discrimination between the treatment of HER2 positive Breast cancer who already have access to this drug, and HER2 low where this drug has shown a huge success in extending life, yet has not been recommended for use. This is a clear discrimination given there is proven success in treatment of HER2 low MBC through clinical trials, yet the recommendation from NICE does not reflect this. Yet, HER2 positive MBC patients already have access with similar clinical outcomes.

Represents an organisation – No

Tobacco links – No

Respondent 76. [redacted]

I do not understand how the decision about whether an individual has the option to live for longer can come down to cost effectiveness. Many many women, young women, are dying from cancer. Something that this drug could help to delay. To enable individuals to live for longer, experience more time with their loved ones, and think that perhaps they might be able to make it to 40, or even 50 years old. How can we take this away from them based on cost? It is horrifically unfair and unjust

Represents an organisation – No

Tobacco links – No

Respondent 77. [redacted]

I am disgusted that we are not supporting the use of this drug for the her 2 low metastatic breast cancer community. So many young women with families now have one less life line.

Represents an organisation – No

Tobacco links – No

Respondent 78. [redacted]

I'm completely confused how Enhertu has been declined for use with the nhs for her2 low patients. People are dying every day with secondary breast cancer and this is a lifeline that is so very needed. I was diagnosed at 32 with breast cancer and these treatment options are so important for hope for the future. We can't continue to keep pushing money into primary cancer cures and forgetting those who go on to develop secondary disease. This is an incredibly disappointing decision and the breast cancer community are completely shocked

Represents an organisation – No

Tobacco links – No

Respondent 79. [redacted]

I appreciate the intention of the document but disagree with the conclusion & decision. The potential benefits of an extended lifespan to breast cancer patients like my friend (& myself) have not been weighted heavily enough & I urge you to reconsider. The impact on patients & their loved ones for a few more months & the potential for drug trials or other treatments being released is significant

Represents an organisation – No

Tobacco links – No

Respondent 80. [redacted]

Has all of the relevant evidence been taken into account?

It is questionable if the widespread impact of Covid has affected trial studies during that period in question. The drug performance was good but would it have been shown to have been better in a post Covid environment? For my daughter who has survived beyond expectations a few extra months of life is both precious for her and the whole of her family and friends.Evidence of quality of life cannot be measured and in her case not been taken into account.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Whilst the clinical and cost effectiveness evidence is compelling. If the evidence itself is insufficient because insufficient weighting of quality of life and impact on the patients wider family then any negative conclusions are suspect. The wider impact of not recommending this drug for use in my daughter case, is likely to cause mental health problems, possible physical problems and increased hospitalization and burden on the health service. The cost effectiveness is likely to be higher than the interpretation in the current recommendation.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. Whilst the pressure on cost savings in the NHS is great, the recommendation does not fully take into account the impact on patients and their families. When treatment options for those such as my daughter are so limited this innovative drug could extend life until another new drug prolongs life. Other countries have provided this drug in cases like my daughter, why should the NHS be guided to provide a worse service.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

My daughter is disabled, has a disabled car sticker, she is disabled by cancer. By not recommending this drug, would you be open to question on grounds of unlawful discrimination?

Represents an organisation – No

Tobacco links – No

Respondent 81. [redacted]
This treatment is vital for women with Her low breast cancer. They have few options already for their disease and this treatment has shown to give an average life extension of over 23 months. I would urge you to reconsider this outcome and make this drug available to those women who deserve to be able to spend time with their families

Represents an organisation – No

Tobacco links – No

Respondent 82. [redacted]
Having had a friend recently die leaving behind a 7 month old baby, there should be no cap on medicine which can give patients more time with their loved ones. It is heartbreaking to think that only the rich deserve/can access that all important life extending drug. Please reconsider this decision.

Represents an organisation – No

Tobacco links – No

Respondent 83. [redacted]
I was diagnosed with HER2-low secondary breast cancer just after the 2022 ASCO conference where the Destiny-Breast04 trial results were presented. In a room full of the world's leading oncology experts and researchers, the findings- that in women with 'HER2-low' SBC, Enhertu SIGNIFICANTLY improved overall survival compared standard chemotherapy- were met with a standing ovation.

I'm pretty certain that I read at the time that this was the first standing ovation since Herceptin was presented (a drug which we know has now revolutionised treatment for HER2-positive breast cancer).

However, despite that standing ovation from the world class researchers and experts present at ASCO, you have provisionally 'not recommended' this treatment. A treatment that is already proving effective in those able to fund it privately or through insurance, and one that has given so much hope for the rest of us waiting for the NICE appraisal.

Knowing the data, it is utterly heartbreaking to think this treatment could now be off the table. Not revising this draft guidance would also be a serious impediment on the advancement of breast cancer treatments, care and outcomes.

Please, please, reconsider. And to the pharmaceutical companies, please make the proposed deal realistic. We want more time.

Represents an organisation – No

Tobacco links – No

Respondent 84. [redacted]
I just don't understand why you'd be against using a drug that's working?! It's abhorrent and another move to privatising the NHS. YOU
SHOULD BE ASHAMED.

Represents an organisation – No

Tobacco links – No

Respondent 85. [redacted]
Disagree with e the decision to take this option away for this drug during stage 4 where options are already limited for cancer patients

Represents an organisation – No

Tobacco links – No

Respondent 86. [redacted]
Women with secondary breast cancer deserve the opportunity of prolonged life.

Represents an organisation – No

Tobacco links – No

Respondent 87. [redacted]
We should be advocating for medical advances in treating stage 4 breast cancer and taking advantage of new medicines rather than prohibiting these. These medicines might give someone 10 years more with their family, and as a primary breast cancer survivor with a risk of reoccurrence it hugely upsets me both for potentially myself but mostly people affected by this disease who are losing their lives on a daily basis. It feels like a step backwards to not allow medicine for a low HER2+ cancer patient when it is proven that it may increase their lifespan.

Represents an organisation – No

Tobacco links – No

Respondent 88. [redacted]
This decision needs to be over turned, I am her2 low and a
Single mother of 3, any extra
Time I can get to
See
My children grow up is
Priceless, as it
Is
For everyone fighting this awful disease, stage 4 needs more support

Represents an organisation – No

Tobacco links – No

Respondent 89. [redacted]
Has all of the relevant evidence been taken into account?

While it is clear that a large amount of evidence has been considered, it's possible that some aspects haven't been fully considered, including the potential long-term benefits and quality of life for patients with HER2-low breast cancer, and I would like to see that revisited.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It's possible that the document has mainly focussed largely on short-term costs, while overlooking the long-term savings and improved patient outcomes

Are the recommendations sound and a suitable basis for guidance to the NHS?

I don't believe that they are. I believe that not enough consideration has been given to the quality of life of HER2-low patients, and I think that should be revisited before guidance is issued to the NHS

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

There doesn't appear to be any discrimination against the groups of people mentioned, but I do believe that there is discrimination between HER2-positive and HER2-low patients, and I believe that they should have equal rights in being given access to life-extending treatment

I disagree with the decision not to fund trastuzumab deruxtecan for people with HER2-low breast cancer. It is clear that there is an unmet need for targeted treatment for HER2-low, and that trastuzumab deruxtecan is a licenced treatment for HER2-low breast cancer. It may be true that HER2-postive patients may have their life extended for longer that HER2-low patients, but are HER2-low patients less worthy of life-extending medication? This seems to be the basis of NICE's funding decision, and a real blow to those patients who were given hope when they heard about this new treatment. I have a friend who is HER2-low, she is still capable of living a good life and does so, including doing voluntary work so no funding for her will also be a loss to all the people she currently provides help and support to

Represents an organisation – No

Tobacco links – No

Respondent 90. [redacted]
Has all of the relevant evidence been taken into account?

N/A

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

N/A

Are the recommendations sound and a suitable basis for guidance to the NHS?

N/A

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Everyone deserves the chance to live

People deserve more time with their families and it shouldn’t be down to the expense of how much a it costs!!

Represents an organisation – No

Tobacco links – No

Respondent 91. [redacted]
I was diagnosed with stage 3 primary breast cancer in 2021, 5yrs to the day after losing my husband to cancer. I am a lone parent to two children who were just 2&4 when they lost their dad. I am high risk for reoccurrence secondary breast cancer and it frightens me beyond anything that these valuable treatment lines are not being approved for use due to cost effectiveness. The fear of leaving my young children without a mother or father haunts me everyday. Please, please reconsider approving this treatment line as one that may give me valuable extension to my life for both myself and my children and many others like myself.

Represents an organisation – No

Tobacco links – No

Respondent 92. [redacted]
This decision puts us at odds with and behind the US and Europe. Most cancer drugs buy a couple of months progression free- this one is a median of 6 months! The decision is wrong!

Represents an organisation – No

Tobacco links – No

Respondent 93. [redacted]
You cannot put a price on up to two additional years spent with family and loved ones! There are very few treatment lines open to these specific patients and this line is proven to work.

Represents an organisation – No

Tobacco links – No

Respondent 94. [redacted]
Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations are based on cost to the NHS not on improving quality of life or prolonging life. Improving quality of life significantly reduces cost demands on theNHS as people are able to live independently.

Represents an organisation – No

Tobacco links – No

Respondent 95. [redacted]
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I argue that it is possible we are being discriminated against as disabled people.

I am appalled at this decision to not fund this drug for low-HER2 metastatic breast cancer patients. I, along with many of my friends, belong to this category of patient. We are members of society, contributing as tax payers, parents, carers and community
member in many capacities. We are mostly young - well below retirement age. To deny us the chance to live longer in this way, by providing us with treatment that has such good outcomes in clinical trials, is tantamount to neglect - it is the writing off of the lives of thousands of women as well as the men who also suffer from this disease. It is shocking to be told that we are undeserving of this chance to live, and that there is indeed a price on our lives.
I urge you to reverse this decision.

Represents an organisation – No

Tobacco links – No

Respondent 96. [redacted]
This is beyond disappointing. Watching someone I love go through the emotional distress of secondary cancer, seeing the hope of this proven drug then that being taken away… no words. A cost decision based on list price not an NHS negotiated price makes no sense.
If it's proven to prolong life this surely should be pushed?

Represents an organisation – No

Tobacco links – No

Respondent 97. [redacted]
Life is an unknown, I have no idea how many months I have left with my 6 year old daughter. The treatment options are limited and the cancer is aggressive. I hope by some miracle what treatments are available will allow me a few more years but there is no telling. Having other treatment options are priceless, when I am looking at a diagnosis with such poor prospects every month, week, even day matters more than anything and so any treatment that can give me that I need. My daughter has to live with a mum who is dealing with facing death, leaving her child motherless and contending with numerous hospital investigations, treatments etc. I have had to give up work as I have weekly chemo. Financially we struggle because I can't work. As a family we fear for the future and what it will bring. Knowing there are more treatment options to try can help relieve it a bit, it gives hope which is vital in these circumstances

I have my daughter and she is everything to me, and me to her. Any extra time brought for me to be in her life is priceless. Every day counts as we try to build lasting fun memories and I so desperately want her to remember me, and not just as a poorly cancer patient and a mum who as always ill, but a mum who could have fun too and enjoy our time together. Extra treatments like Enhertu can help give us this time and important memories- how can you put a price on that?

Our treatment options are already massively limited, any thing that might help should be made available. Not enough money is spent on secondary breast cancer research as it is, I can't quite comprehend therefore that when you have a drug that can help with not only secondary but one where treatments are limited you don't authorise it.

It hurts very deeply on a very personal level, it feels like you are saying our lives aren't worth it, they don't matter.

Represents an organisation – No

Tobacco links – No

Respondent 98. [redacted]
Has all of the relevant evidence been taken into account?

The evidence on QALY gains from this treatment is too narrowly defined to capture the real-world gains that making the treatment available would secure for patients. The very fact of denying this treatment will itself adversely impact the QALYs of the group in question.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The committee acknowledges considerable uncertainty in the calculations on which it has based its recommendation. Given that it seems premature to rule out a treatment that could benefit a group of patients who are badly in need of support.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. They are based on too many uncertainties and on too narrow an appraisal of potential benefits to be a sound basis for a decision that is so important for many people.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

There is a lack of age profile modelling to ensure that there is no indirect discrimination on grounds of age. It seems likely that the recommendation will in fact have a disproportionate impact on older cohorts.

The committee seems to have reached a firm decision based on cost-effectiveness of the treatment but acknowledges that there is considerable uncertainty in the modelling. Given the recognition of benefits in the treatment is seems premature to firmly recommend against recommending it.

Moreover in assessing QALYs insufficient attention has been paid to the proportional gain in quality of life for those with breast cancer for whom other treatments such as chemotherapy are running out. The gain in quality of life from delaying progression for this group is proportionally higher and this should be factored in.

Lastly, the committee failed to identify any equality issues. However there is no modelling presented of the age profile of those affected by the decision and thus no assurance that there is not indirect age discrimination as a result of this recommendation.

Represents an organisation – No

Tobacco links – No

Respondent 99. [redacted]
Has all of the relevant evidence been taken into account?

Has all available evidence been considered from global/EU studies. I note that the European Medicines Agency has authorised Enhertu for HER-Low patients. As HER-Low is a relatively new designation should there not be longer term studies of the impact of Enhertu on HER-Low patients which could be achieved by NICE approving the drug.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summaries appear to have focused primarily on short-term costs and have not factored in the health benefits, economic productivity and positive societal inputs that women living longer with successful treatment of HER2-Low cancer can provide.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I believe the recommendations are not sound. My wife xxxxxxxxxxxxxx has been successfully treated for secondary breast cancer for over 8 years at Weston Park Hospital. xxxxxx has recently been told her cancer is HER2-Low and the results of Enhertu on HER2-Low patients has proved to be effective. To deny people such as xxxxxx who have managed to maintain a high quality of life for so long an effective treatment appears to me to be cruel and unnecessary. Women with HER2-Low metastatic breast cancer should be afforded additional months of progression free life that Enhertu can provide.

Represents an organisation – No

Tobacco links – No

Respondent 100. [redacted]
As a person who has secondary breast cancer, I feel strongly that every possible line of treatment should be available. We already have very little funding directed into research which could extend lives. Therefore to refuse the use of a proven successful drug line Enthertu is in human. Please look again. Give us in the SBC world hope that we are listened to.

Represents an organisation – No

Tobacco links – No

Respondent 101. [redacted]
I urge you to reconsider the decision taken not to approve the use of this medication for her2lite breast cancer patients. In doing so you are taking away their opportunity to spend precious time with their loved ones and to contribute to society. Putting a price on anyone's life is abhorrent and in this case doubly so as there are so many young women, many of whom are mothers who suffer from this dreadful disease

Represents an organisation – No

Tobacco links – No

Respondent 102. [redacted]
Has all of the relevant evidence been taken into account?

No. Your committee papers state that 'There is an unmet need for effective targeted therapies in HER2-low u/mBC given that current treatment after prior chemotherapy is limited to non-targeted chemotherapies which are associated with limited efficacy'. Enhertu is a treatment that can increase life expectancy by around 2 years and has been hailed by experts such as Professor Peter Schmid of Barts. The success of this drug and the lives of those which could be dramatically extended appears not to have been taken into account.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. DestinyBreast trial, that looked at Enhertu in HER2-low patients, showed impressive results. In the committee papers Emma Beddowes states 'Statistically significant increases in progression free survival' these fact seems to have been completely ignored by the draft recommendation. The papers state that there would be no increased cost to administering the drug as settings are already trained and using this drug on other patients. The argument that it is not cost effective does not seem reasonable when the drug is already approved, paid for and used by the NHS for HER2+ metastatic breast cancer patients.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. Enhertu has already been approved for use in the NHS for HER2+ Metastatic Breast Cancer patients. Trastuzumab deruxtecan (Enhertu®) is now approved to treat secondary HER2-low breast cancer in more than 30 countries including the US and the EU (AstraZenica.com). Many of these countries have comparable healthcare systems. The recommendations do not appear sound.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes. Cancer patient are covered by the disability act. I feel that you are discriminating against HER2-low patients by not approving Enhertu while it is already approved for HER2+ patients (which your Public Committee slides state HER2+ is more common). In my opinion that is discrimination by disability, discrimination against those for having HER2-low cancer type.

Has all of the relevant evidence been taken into account?
No. Your committee papers state that 'There is an unmet need for effective targeted therapies in HER2-low u/mBC given that current treatment after prior chemotherapy is limited to non-targeted chemotherapies which are associated with limited efficacy'. Enhertu is a treatment that can increase life expectancy by 2 years and has been hailed by experts such as Professor Peter Schmid of Barts, and Oncologist Emma Beddowes you consulted on your Committee. The success of this drug and the lives of those which could be dramatically extended appears not to have been taken into account.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. DestinyBreast trial, that looked at Enhertu in HER2-low patients, showed impressive results. In the committee papers Emma Beddowes states 'Statistically significant increases in progression free survival' these fact seems to have been completely ignored by the draft recommendation. The papers state that there would be no increased cost to administering the drug as settings are already trained and using this drug on other patients. The argument that it is not cost effective does not seem reasonable when the drug is already approved, paid for and used by the NHS for HER2+ metastatic breast cancer patients

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. Enhertu has already been approved for use in the NHS for HER2+ Metastatic Breast Cancer patients. Trastuzumab deruxtecan (Enhertu®) is now approved to treat secondary HER2-low breast cancer in more than 30 countries including the US and the EU (AstraZenica.com). Many of these countries have comparable healthcare systems. The recommendations do not appear sound.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes. Cancer patient are covered by the disability act. I feel that you are discriminating against HER2-low patients by not approving Enhertu while it is already approved for HER2+ patients (which your Public Committee slides state HER2+ is more common). How can this be refused on cost when you approved it for use with HER2+? That is discrimination by disability, discrimination against those for having HER2-low cancer type.

3.2
The socioeconomic impact of access to healthcare has a trickle down effect. Many cancer patients still work, either paid or voluntary and have a lot to offer to society and the economy. As we become more ill the impact on us and our families is devastating. We deserve more time. Time to create special memories for those we love, time on these treatments for monitoring and teaching for those patients to come. This decision based on cost is grossly short sighted.

3.23
Cancer patient are covered by the disability act. I feel that you are discriminating against HER2-low patients by not approving Enhertu while it is already approved for HER2+ patients (which your Public Committee slides state HER2+ is more common). In my opinion that is discrimination by disability, discrimination against those for having HER2-low cancer type.

Represents an organisation – No

Tobacco links – No

Respondent 103. [redacted]
I strongly urge the committee to reconsider the availability of trastuzumab deruxtecan for HER2-Low cancer patients. The clear benefits of extending the lives of these patients should be taken into account.

Represents an organisation – No

Tobacco links – No

Respondent 104. [redacted]
Please can this recommendation be reviewed and the drug approved. As a breast cancer patient reading this document it appears cost is the reason. Please don't put a price on someone's life. These drugs are being developed and yet not being made available on nhs. Nhs should be supporting these new drugs and moving forward in treatment plans. This group of people by having this drug would then no longer need to be accessing other expensive treatments which may not be as successful. By accessing this drug their treatment and outcome could

change and in the long run reduce other costs that the nhs would incur. As a country we are slipping behind other countries in breast cancer treatments. Please, these patients need these ground breaking drugs. Thank you

Represents an organisation – No

Tobacco links – No

Respondent 105. [redacted]
Has all of the relevant evidence been taken into account?

I would like the long-term benefits to my friend to be reconsidered, on top of the evidence already explored

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I respectfully disagree with the interpretation of the evidence. Any benefits to patients could reduce hospital stays and medication in the future

Are the recommendations sound and a suitable basis for guidance to the NHS?

I don't believe the recommendations consider the benefits to my friend of having valuable extra time with her loved ones. I believe a more in-depth look at the long-term benefits is required.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I believe they have a negative impact on people like my friend who has very limited treatment options left. It seems unfair to discriminate on a cost basis with such an innovative treatment

Sadly I have to strongly disagree with this decision. This drug has potential benefits to people like my childhood friend Claire, a loving wife and mother of two, who would do anything to have her life extended by a few months. I therefore strongly urge you to reconsider this decision

Represents an organisation – No

Tobacco links – No

Respondent 106. [redacted]
Patients across the UK with metastatic breast cancer would welcome access to the availability of the impressive Enhertu for HER2 metastatic BC.
Enhertu is approved on the NHS for a different type of BC and to divide and deny patient groups with HER2-low, is completely devastating. Please reconsider. There are few options available for patients after chemo and this is the first drug to improve outcomes. Access is imperative - women are suffering and NICE can help to extend lives.

Represents an organisation – No

Tobacco links – No

Respondent 107. [redacted]
I wish to disagree with the consultation documents conclusion not to make this breast cancer drug available on the NHS. The report clearly indicates that the drug has significant benefits to patients which is why it has been cleared for use in both the EU and the USA. I strongly hope that the final decision of NICE will be to make it similarly available in the UK through the NHS.

Represents an organisation – No

Tobacco links – No

Respondent 108. [redacted]

Has all of the relevant evidence been taken into account?

I am concerned that the approval of TD for treatment of HER2 low in the US and EU has not been taken into account . In particular, where the committee departs from the modelling proposed by the company what view did the approval authorities in the US and EU take ? Was it the same or more favourable to the company's account ? If NIHCE has departed from the views of those agencies why is that the case ?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summaries seem to give excessive weight to immediate costs of the treatment and too little to the potential beneficial effects and savings of HER2 low patients having better health outcomes whilst in receipt of treatment and to undervalue the potential social and psychological benefits to a group of patients with limited treatment options especially in light of the compelling evidence of the devastating effects of secondary breast cancer set out in the responses from patient groups . It also does not seem to take into account - (the modelling is however technical and opaque and makes it difficult to see exactly what has been taken into account)the potential benefits to the NHS such as reduced need for access to NHS services and reduced need for hospitalisation whilst well in receipt of this treatment.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I am concerned that the recommendations do not explain why the treatment is considered not to be cost effective for HER2 low patients but according to your guidance appears to be approved for some HER2 positive patients . This is unclear. I am concerned it reflects the binary approach to HER2 - and HER 2 + patients when the proper comparator appears to be with HER2 low patients as a distinct group rather than as a subgroup . Otherwise the points made to the other questions all apply.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

As a barrister specialising in , inter alia, equality and human rights I am concerned that the committee has focused too narrowly on the protected characteristics under the Equality Act 2010 . It has not apparently considered the application of Article 14 European Convention on Human Rights on the prohibition of discrimination. Article 2 (right to life) , Art 8 (right to family and private life) and clearly engaged and thus decisions made by a public authority such as NIHCE must not violate Article 14 under Section 6 Human Rights Axct 1998 . Article 14 prohibits difference in treatment on the grounds not only of the domestically recognised protected characteristics but also on the grounds of "other status" . That can include particular health status. The European Court of Human Rights states that a status may be based on an identifiable characteristic .In this case that would be as an HER2 patient with metastatic breast cancer. The question then is whether they are being treated differently from those with a relevantly similar status . As it is now recognised that there are significant potential benefits for patients with this status as well as for patients in the HER2 positive group that test is met.The NIHCA guidance refers to some HER2 positive patients receiving this treatment on the NHS.There must then be objective and reasonable justification shown by NIHCE for treating these two groups of patients differently. I cannot see this in your guidance document at present. The driving issue appears to be cost including arising from the fact that the size of the group of patients who are HER2 low appears to be signficantly higher. As health status is a " suspect ground" akin to that of disability however defined in ECHR caselaw the justification must be clear and compelling and it does not seem to me to be so for the difference in treatment in the guidance as presently drafted why one group should have access to this treatment but not another.

I disagree with the conclusions in the draft guidance . Whilst the draft recognises that trastuzumab deruxtecan may well have significant benefits for this " sub-group" of HER 2 negative patients it appears to me to not consider the position from the wrong perspective by adopting a historical binary approach to HER 2 negative and positive. Rather than approaching HER2 low group of patients as a group on their own especially in light of the limited treatments available for this group as explained in the Breast Cancer Now submission . The document is extremely technical but it is not at all clear to me also as to what analysis there was of the potential benefits to those HER2 low patients who had survived more than 5 years after diagnosis of metastatic breast cancer and who had good responses to earlier

treatments . I also consider that little weight appears to have been given to the fact that significant increases in survival times with good quality of life for patients in this group has not been considered in context of how that may then lead to the opportunity to have new treatments that develop in the period of survival. Whilst I recognise that NIHCE has its own criteria as to approval of treatments and in particular to cost I was surprised that i could not see in the guidance any consideration by the committee as to why this treatment for HER2 low patients has been approved in the US and EU . Was this solely a question of cost ?

Represents an organisation – No

Tobacco links – No

Respondent 109. [redacted]
This is a devastating and completely unacceptable decision. This is clearly an exceptional treatment which has superb results, and to deprive young women of more time with their families is totally unacceptable.
Nice must reconsider this decision

Represents an organisation – No

Tobacco links – No

Respondent 110. [redacted]
As treatment options for people with HER2-low disease are very limited, this is extremely disappointing decision with significant and unacceptable consequences.

Represents an organisation – No

Tobacco links – No

Respondent 111. [redacted]
Has all of the relevant evidence been taken into account?

Evidence in the benefit of this drug for extending life of metastatic BC patients hasn't been taken into account sufficiently. Can NICE out a value on an additional two years of life for a patient? If a patient has dependent children can NICE not factor in the value of adding additional years of life to a parent? Metastatic patients are disappointed with this decision and their views have not been taken into full consideration.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. The clinical cost needs to be measured against social benefits of an additional line of treatment for metastatic patients. Life for these patients needs to be valued much more highly than NICE currently values it. If the evidence of extending life for patients is there NICE must take this into account and not dismiss patients' lives as not worth the cost of this treatment.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. The evidence of clinical benefit must be factored in and benefit to NHS not simply in the basis of cost.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The decision not to fund this is wrong and discriminatory for metastatic breast cancer patients who are covered by the disabilities legislation and NICE must take into account their human right to life and access to treatment

Represents an organisation – No

Tobacco links – No

Respondent 112. [redacted]
Negotiations with the drug company should be fast tracked, as women are dying now for lack of this treatment. It is shameful that a wealthy country like the UK is now behind Europe, the USA, Canada and Australia in terms of access to this drug for HER2 low MBC. My oncologist keeps telling me to hold on, that new treatments are coming through, but there is always this pricing game while we suffer and die. This is a devastating decision for women with HER2 low disease. To have one treatment recognised as effective for a new MBC subtype but declined feels cruel. To allow Enhertu to be given to women with HER2+ disease but not HER2 low disease feels cruel too. The NHS can negotiate a better price. Please do this quickly to extend lives.

Represents an organisation – No

Tobacco links – No

Respondent 113. [redacted]
Has all of the relevant evidence been taken into account?

Has the committee heard from people that will be impacted? There are so few options for people with this type of disease should the one realistic hope of more time be taken away because of finances?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I'm afraid not considering the few options offered at present to sufferers.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No the NHS is surely about saving lives with every bit of new research taken on board. Not condemning people a realistic chance of survival because of money.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Definite discrimination by a committee made up mainly of men in response to a matter affecting almost exclusively women.

Represents an organisation – No

Tobacco links – No

Respondent 114. [redacted]

2.4
Hopefully NICE will continue to negotiate a fair price as they have done with many other drugs such as Trodelvy.

3.25
As a patient with HER2 low metastatic breast cancer I am disappointed in this conclusion. I implore you to renegotiate with the company and to reconsider your decision.

Represents an organisation – No

Tobacco links – No

Respondent 115. [redacted]
This decision will have a devastating effect on many women and their families. Use of the drug will give women more time.

Represents an organisation – No

Tobacco links – No

Respondent 116. [redacted]

Trastuzumab deruxtecan is the first licensed treatment for HER2-low metastatic or unresectable breast cancer, and it specifically targets HER2.'

Presently, no other treatment is available - there is no argument therefore that this treatment should be rejected on grounds of cost - no cheaper alternative is yet available.

3.1

The committee acknowledged that HER2-low is a subgroup of the previously classified HER2-negative group.'

This is a newly defined subgroup with only one treatment available. As a currently unique treatment, it can be expected for its initial costs to be higher than other well-established treatments. The cost is therefore secondary to the unique benefits provided.

Represents an organisation – No

Tobacco links – No

Respondent 117. [redacted]

I am shocked and dismayed that women are being denied this medication that is available in other countries such as the US. I have heard individual cases of women aged as young as 35, with 2 children, who might benefit from it. In a case like this an additional 22 months of life is immeasurable in benefit. The Uk is one of the richest countries in the world. We should be at the forefront of using such medication, improving quality and length of life and contributing to the body of evidence on it. This decision by NICE will further confirm us as one of the poorest countries for cancer treatment. I urge the panel to reconsider.

Represents an organisation – No

Tobacco links – No

Respondent 118. [redacted]

Has all of the relevant evidence been taken into account?

I believe that not all aspects have been fully explored, especially for life expectancy and quality of life such as my friend

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I respectfully disagree, focus appears to be on the short term savings, not on the long term savings from costs of hospitalization, medical interventions and as well as emotional and physiological effects

Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not feel that the recommendations take into account the long term effects and potential benefits for people such as my friend. I believe a more in depth analysis should be considered to provide a more accurate basis for NHS guidance

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Whilst I acknowledge that careful consideration should be taken into account , this potential guidance will affect my friend, and those with limited treatment lines dispositionally and therefore discriminate her on cost alone.

I respectfully disagree with the documents decision, the benefits of this drug , especially for people whose life expectancy is shortened due to breast cancer and options running out.
I urge a reconsideration especially in respect to long term benefits and advances in breast cancer treatment.

Having a friend who would benefit from this drug advancement and now seeing that this potential life extending drug may not be available is a health inequality and potential death sentence sooner rather than later.

By having the availability of this drug, whilst expensive would outway the cost of the treatment and care she would need without it. Notwithstanding the emotional and psychological impact this would mean on her and her family and friends and a potential premature death without it.

Represents an organisation – No

Tobacco links – No

Respondent 119. [redacted]
Has all of the relevant evidence been taken into account?

All the relevant evidence has not been taken into account as the personal experiences of patients on ENHERTU (Trastuzumab Deruxtecan)have not been taken into consideration. Although of course I have no personal experience of using this drug as it is not currently available on the NHS, I am well aware of the side effects I and many women I am sure who would be happy to take the safety risks given the overall benefits. I note that breast cancer also affects 1% of men.The side effects are well known and there is already a robust system set uo for monitoring the drug's safety in the UK. I have however been able to share experiences with women who have accessed the drug privately in the U.K. Many have seen positive benefit. On the other hand I have seen crowd funders by NHS patients to try to access this drug and it's awful UK patients should have to do this while having the stress of stage 4 cancer to deal with. This evidence has not been taken into account.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Trastuzumab Deruxtecan has been shown to be a superior approach to physician's choice chemotherapy but it is the only treatment that has been shown to have a confirmed objective response for women with HER2 low tumours in both hormone receptor positive breast cancer and hormone receptor negative.

The European Union have approved this drug for metastatic HER2-low breast cancer so they obviously have concluded its cost effective. Many EU countries they have a publicly available healthcare system which enables use of the drug and although there may be some exceptions to this in terms of particular countries, in general I believe this to be true. We in the U.K. simply feel once again that we are unable to benefit from the cutting edge of the drugs on offer for this incurable, life-limiting disease.

DESTINY-Breast04 Trial Investigators showed clearly that in HER2-low patients there was improved progression-free and median overall survival https://www.nejm.org/doi/full/10.1056/NEJMoa2203690. This paper showed a median OS of 6 months compared to physicians choice but was consistent for all patients. It's also possible for Trastuzumab Deruxtecan to extend life by more than this based on the range of life expectancy in the NEJM paper and from what I have heard from many HER-low women and men. There is also the choice of another line therapy. It is well known that some people respond to treatments, while others do not but they then can respond to another drug. I know this also in my experience as an NHS physician having treated hundreds of patients over the years, albeit not in Oncology but the principle is the same.

Trastuzumab Deruxtecan is also more effective at crossing the blood brain barrier and critically would offer more options for this hard to treat group which I also sadly belong to. There are much fewer options for treating hormone receptor negative cancer too and it is more likely to enter the CNS so both hormone receptor positive patients and negative could benefit.

As patients we are individuals not statistics. In some cases this drug has meant life extension for well over a year(s). I know this because of reading and reviewing the landmark work in the NEJM papers on Trastuzumab Deruxtecan and most especially the work of the DESTINY-Breast04 Trial Investigators

https://www.nejm.org/doi/full/10.1056/NEJMoa2203690. There are also the voices NICE should take into account of metastatic HER2-low patients. Extra time spent with friends and family,progression free, cannot be valued. It is priceless.

The safety profile of this drug too was acceptable and therefore it is very important that HER2- low women can access the drug and not be discriminated against in terms of receptor efficacy as this has been shown to be effective for HER2-low breast cancers as a whole.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Breast cancer can strike women (and men) in the prime of life when they are mothers/fathers to young children. Secondary breast cancer, in particular, causes generational pain as there is both personal and family pain and grief of dealing with an incurable illness. NICE should have recommended making Trastuzumab Deruxtecan available on the NHS to patients with HER2-low metastatic breast cancer. This was, I strongly believe, the wrong decision.

As a mother, wife and NHS physician I have personal experience of the reality of HER2-low metastatic breast cancer and this experience is similar, I am sure, to so many women and men of the same type of cancer, be they ER+ or Triple negative HER2-low. The mental and physical hurdles are extraordinary. I know that I am unlikely to see my children grow up to reach adulthood and that 2024 has become the year I am likely to die as I have brain mets. My husband has become my carer and I cannot treat or heal patients any longer. I have lost virtually everything apart from my life and that too will be taken from me with such a life- limiting illness. In short, it's a death sentence. I am therefore appalled that NICE has not recommended trastuzumab deruxtecan

I am grateful in particular to the DESTINY-Breast04 Trial Investigators who worked so hard. Their evidence based published work https://www.nejm.org/doi/full/10.1056/NEJMoa2203690 offered HER2-low women more time with their family in progression free and overall survival. NICE should not make a largely economic decision when, for all the reasons I have explained above, it cannot be justified.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

NICE should be doing its absolute best in 2023 to reduce the appalling figure of 11,499 lives lost in the UK to breast cancer between 2017-2019. Although breast cancer cases have fallen, this study notes, overall there is no doubt women who die from it lose a significant number of years (25 on average) because it affects younger people disproportionately (Cancer Research UK) https://www.nature.com/articles/s41416-023-02422-8. This decision therefore discriminates against younger women in particular who lose more life and are often mothers to families resulting in generational pain and other consequences as I have explained above

In females in the UK, breast cancer is the 2nd most common cause of cancer death (15% of all female cancer deaths). In males in the UK, it is not among the 20 most common causes of cancer death (less than 1% of all male cancer deaths).

99% of breast cancer deaths in the UK are in females, and 1% are in males (2017-2019).

Breast cancer mortality rates (European age-standardised rates in the UK are significantly higher in females than in males (2017-2019). (All stats from Cancer Research UK https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/mortality#heading-Zero)

There should also not be discrimination based on grounds of receptor positivity when Trastuzumab Deruxtecan has been shown particularly by the DESTINY-Breast04 Trial Investigators to be of benefit in unresectable HER2-low patients. They showed that there was improved progression-free and median overall survival https://www.nejm.org/doi/full/10.1056/NEJMoa2203690. This paper showed a median OS of 6 months compared to physicians choice but was consistent for all patients.

1.1

Breast cancer can strike women (and men) in the prime of life when they are mothers/fathers to young children. Secondary breast cancer, in particular, causes generational pain as there is both personal and family pain and grief of dealing with an incurable illness. NICE should have recommended making ENHERTU available on the NHS to patients with HER2-low metastatic breast cancer. This was the wrong decision.

As a mother, wife and NHS physician I have personal experience of the reality of HER2-low metastatic breast cancer and this experience is similar, I am sure, to so many women and men of the same type of cancer, be they ER+ or Triple negative HER2-low. The mental and physical hurdles are extraordinary. I know that I am unlikely to see my children grow up to reach adulthood and that 2024 has become the year I am likely to die as I have brain mets. My husband has become my carer and I cannot treat or heal patients any longer. I have lost virtually everything apart from my life and that too will be taken from me with such a life- limiting illness. In short, it's a death sentence. I am therefore appalled that NICE has not recommended trastuzumab deruxtecan

I am grateful in particular to the DESTINY-Breast04 Trial Investigators who worked so hard. Their evidence based published work https://www.nejm.org/doi/full/10.1056/NEJMoa2203690 offered HER2-low women more time with their family in progression free and overall survival. NICE should not make a largely economic decision when, for all the reasons I have explained above, it cannot be justified.

3.20
The committee considered that none of the analyses reflected their preferred assumptions.
I have made individual comments above in these conclusions.

I have no personal experience of using this trastuzumab deruxtecan as it is sadly not currently available on the NHS for HER2-low metastatic breast cancer patients. I note that breast cancer also affects 1% of men, I have been able to share my experiences mainly with women therefore who have accessed the drug privately in the U.K. Many have seen positive benefit. On the other hand I have seen crowd funders by NHS patients to try to access this Trastuzumab Deruxtecan and it's awful UK patients should have to do this while having the stress of stage 4 cancer to deal with. This evidence has not been taken into account

3.21
See text

3.21
Because this uncertainty could mean that the true ICER is above what NICE normally considers a cost-effective use of NHS resources, the committee agreed that an acceptable ICER would be towards the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).
I must repeat that NICE should be doing its absolute best in 2023 to reduce the appalling figure of 11,499 lives lost in the UK to breast cancer between 2017-2019 by providing as broad a range of appropriate treatment as possible. It is well known that patients can respond in different ways to different lines of therapy.

Although breast cancer cases have fallen, this study notes, overall there is no doubt women who die from it lose a significant number of years (25 on average) because it affects younger people disproportionately (Cancer Research UK) https://www.nature.com/articles/s41416-023-02422-8. This decision therefore discriminates against younger women in particular who lose more life and are often mothers to families resulting in generational pain and other consequences as I have explained above
In females in the UK, breast cancer is the 2nd most common cause of cancer death (15% of all female cancer deaths). In males in the UK, it is not among the 20 most common causes of cancer death (less than 1% of all male cancer deaths).

99% of breast cancer deaths in the UK are in females, and 1% are in males (2017-2019).

Trastuzumab deruxtecanhas been shown particularly by the DESTINY-Breast04 Trial Investigators to be of benefit in HER2-low patients. They showed that there was improved progression-free and median overall survival https://www.nejm.org/doi/full/10.1056/NEJMoa2203690. This paper showed a median OS of 6 months compared to physicians choice but was consistent for all patients.

3.22

See text selection

3.22
The committee considered that it would like to see the following analyses and further evidence to help with its decision making about the cost effectiveness of trastuzumab deruxtecan compared with TPC
These analyses can be done I'm sure and I am not saying they aren't appropriate, but it should not delay trastuzumab deruxtecan being recommended on the NHS for all the reasons I have stated before.

HER2-low metastatic breast cancer patients face an incurable, life- limiting death sentence. Time is not on our side. As I am sure the commitee are aware especially in triple negative HER2-low metastatic breast cancer the median life expectancy is 3 years and once there is CNS involvement it can he as short as just a few months. More lines of therapy are desperately needed and this needs to be considered to in this hard to treat disease: not more delay.

As a mother, wife and NHS physician its mental and physical hurdles are extraordinary. I know that I am unlikely to see my children grow up to reach adulthood and that 2024 has become the year I am likely to die as I have brain mets. My husband has become my carer and I cannot treat or heal patients any longer. I have lost virtually everything apart from my life and that too will be taken from me with such a life- limiting illness.

3.1
The safety profile of this drug was acceptable and therefore it is very important that HER2- low women can access the drug and not be discriminated against in terms of receptor efficacy as this has been shown to be effective for HER2-low breast cancers as a whole. It is an extra line of therapy which is specifically directed at HER2-low breast cancers enabling benefit.

3.2
The evaluation committee should take into account the views of all HER2-low metastatic breast cancer patients. Extra time spent with friends and family,progression free with improved overall survival cannot be valued. It is priceless. I am grateful in particular to the DESTINY-Breast04 Trial Investigators who worked so hard. Their evidence based published work https://www.nejm.org/doi/full/10.1056/NEJMoa2203690

3.3
DESTINY-Breast04 Trial Investigators showed clearly that in HER2-low patients there was improved progression-free and median overall survival https://www.nejm.org/doi/full/10.1056/NEJMoa2203690. This paper showed a median OS of 6 months compared to physicians choice of chemotherapy and was consistent. The side effects are well known of Trastuzumab deruxtecan and there is already a robust system set up for monitoring the drug's safety in the UK.

3.4
It's also possible for Trastuzumab deruxtecan to extend life by more than this based on the range of life expectancy in the NEJM paper and from what I have heard from many HER-low women and men. There is also the choice of another line therapy. It is well known that some people respond to treatments, while others do not but they then can respond to another drug. I know this also in my experience as an NHS physician having treated hundreds of patients over the years, albeit not in Oncology but the principle is the same.

Trastuzumab deruxtecan is also more effective at crossing the blood brain barrier than physicians choice of chemotherapy and critically would offer more options for this hard to treat group with NHS involvement which I also sadly belong to. There are much fewer options for treating hormone receptor negative cancer too and it is more likely to enter the CNS so both hormone receptor positive patients and negative could benefit.

As patients we are individuals not statistics. In some cases this drug has meant life extension for well over a year(s). I know this because of reading and reviewing the landmark work in the NEJM papers on ENHERTU and most especially the work of the DESTINY-Breast04 Trial Investigators https://www.nejm.org/doi/full/10.1056/NEJMoa2203690.

3.5
I disagree with the statement of the EAG that the trial population was unlikely to be representative of the people in NHS clinical practice who would have trastuzumab deruxtecan. I would argue that this is speculative. These are not grounds to fail to recommend approval of Trastuzumab deruxtecan on the NHS.

I note that the final comment in this sections concludes " The committee concluded that the DESTINY-Breast04 trial population was likely to be broadly representative of people in the NHS with HER2-low metastatic breast cancer who would have trastuzumab deruxtecan."

3.6
The statement that "second-line eribulin and lack of sacituzumab govitecan meant that the TPC arm was not fully generalisable to standard care in NHS clinical practice " is true but I have heard that Iboth eribulin and sacituzumab govitecan are not always tolerated by triple negative HER2-low metastatic breast cancer patients patients and in any case trastuzumab deruxtecan offers an extra line of therapy.

This is a very hard to treat group of patients with very limited options, especially with CNS disease. We also know that trastuzumab deruxtecan crosses the blood brain barrier and in triple negative breast cancer in particular there is an up to 50% chance of disease in the brain which can be rapidly fatal. Trastuzumab deruxtecan offers an extra line of therapy to sacituzumab govitecan especially as it may be more specific to HER2-low patients in their reponse.

3.7
I agree with the conclusion of the committee

"The committee concluded that, compared with TPC, trastuzumab deruxtecan delayed disease progression and improved overall survival in people with HER2-low metastatic or unresectable breast cancer."

3.9
"[The EAG] questioned whether this analysis was generalisable to the NHS, in which people will likely have trastuzumab deruxtecan at second line".

I think this should be flexible based on patients and physicians choice. There should not be a natural assumption that it can only be used as second line therapy in the NHS. Patients are aware of the side effects of trastuzumab deruxtecan and may opt for it third line. The point is NICE should not be denying them the choice here in the UK on the NHS.

The European Union have approved this drug for HER2-low breast cancer so they obviously have concluded its cost effective. Many EU countries they have a publicly available healthcare system which enables use of the drug and although there may be some exceptions to this in terms of particular countries, in general I believe this to be true. We in the U.K. simply feel once again that we are unable to benefit from the cutting edge of the drugs on offer for this incurable, life-limiting disease.

3.10
" [The EAG] acknowledged that estimates using the Weibull distribution may be conservative."

"The clinical experts could not provide a view on which curves provided more plausible survival estimates, particularly for 10 years. This is because they see relatively few people with this condition still alive at this point, so there is limited available data. "

My comment would be why not give patients more of a chance to live 10 years? This just feels like we as a group of metastatic HER2-low patients are being "written off" as if we don't really matter and prolonging our quality and quantity of life is just too expensive to be justified.

In the DESTINY-Breast04 Trial Investigators showed trastuzumab deruxtecan to be a superior approach to physician's choice chemotherapy. It is the only treatment that has been shown to have a confirmed objective response for women with HER2 low tumours in both hormone receptor positive breast cancer and hormone receptor negative.

3.11
Why deny an extra line of treatment to NHS HER2-low metastatic breast cancer patients when it is admitted that "the clinical experts could not provide a view on which curves provided more plausible estimates. "

3.12

"The committee considered that there is uncertainty about the most appropriate way to model time-to-treatment stopping."

Where there is uncertainty the benefit should be given in favour of the patient especially as the European Union have approved trastuzumab deruxtecan and have not found the necessity to "[use] the mature Kaplan-Meier data to directly estimate treatment stopping in the model and limit parametric extrapolations to the time-period beyond this. "

This sounds like kicking the crucial ball of trastuzumab deruxtecan into the long grass and will lead to delay in approving it to HER2-low metastatic breast cancer patients who need it on the NHS.

3.13
"The clinical experts could not provide a view on the plausibility of the utility values."

I note the uncertainty of the clinical experts here with concern

3.14
The clinical experts believed that the trial response rate suggested a treatment benefit, and that this reduced tumour size would lead to a reduced symptom burden that would continue into the post-progression state. They considered that people would likely be in a better position for subsequent lines of treatment after progression. The committee considered that there was
I agree

3.14
The committee considered that there was uncertainty about the assumption of a differential effect in post-progression utilities. It would like to see an analysis assuming no differential effect.
I disagree with the committee.

The European Union have approved this drug for metastatic HER2-low breast cancer so they obviously have concluded it was cost effective. Many EU countries they have a publicly available healthcare system which enables use of the drug and while there may be some exceptions to this in terms of particular countries, in general I believe this to be true. We in the U.K. simply feel once again that we are unable to benefit from the cutting edge of the drugs on offer for this incurable, life-limiting disease.

3.15
The Cancer Drugs Fund clinical lead agreed with the company's estimate of 75% given the size of the HER2-low population. The committee concluded that 75% vial wastage should be assumed in the model.
I agree with the he Cancer Drugs Fund clinical lead and the committee

3.17
Both the company and EAG's estimates resulted in a severity weight of 1.2. So, the committee concluded that the severity weight of 1.2 applied to the QALYs was appropriate.
As a mother, wife and NHS physician I have personal experience of the reality of HER2-low metastatic breast cancer and this experience is similar, I am sure, for so many women and men of the same type of cancer, be they ER+ or Triple negative HER2-low. The mental and physical hurdles are extraordinary.

I know that I am unlikely to see my children grow up to reach adulthood and that 2024 has become the year I am likely to die as I have brain mets. My husband has become my carer and I cannot treat or heal patients any longer. I have lost virtually everything apart from my life and that too will be taken from me with such a severe life- limiting illness. In short, it's a death sentence.

3.18
it would like to see an indirect treatment comparison of trastuzumab deruxtecan and sacituzumab govitecan
It is still very important that HER2- low women can access the drug as trastuzumab deruxtecan also gives us more choice as another line of therapy in HER2-low metastatic breast cancer patients. It has been shown to also been shown to be the only effective specific treatment for HER2-low metastatic breast cancers as a whole.

3.19
NICE should be doing its absolute best in 2023 to reduce the appalling figure of 11,499 lives lost in the UK to breast cancer between 2017-2019 by recommending as broad a range of appropriate treatment as possible. It is well known that patients can respond in different ways to different lines of therapy.

3.19
it preferred to see a scenario in which the company applied grade 3 or above treatment-emergent adverse events. it will be interesting to see this but I and many women would prefer to see the commitee recommending trastuzumab deruxtecan, despite the side effects which were described by the Destiny Breast 04 investigators as "acceptable" . I knowfrom personal experience)albeit in a different field of medicine that many patients have different thresholds for side effect tolerability. I can therefore speak from experience and personally that I would much rather that trastuzumab deruxtecan was recommended as it gives us a broader range of options compared with the death sentence of HER2-low metastatic breast cancer, especially triple negative which I have. It is necessary for the committee to put themselves in our shoes.

3.23
I must disagree with the committee as equality is about equal access in its widest sense and this has not have been considered.

This drug not only has shown that it is a superior approach to untargeted chemotherapy but it is the only treatment that has been shown to have a confirmed objective response for women with HER2 low tumours in both hormone receptor positive breast cancer and hormone receptor negative.

The other inequality issue is that in the UK some patients with HER2-low metastatic breast cancer women have been able to access it on trials and keep going on it AND it is available privately only for HER2-low metastatic breast cancer who can afford insurance or pay for it themselves. It is completely out of reach for many patients. Why should patients who get private treatment or trial patients have the advantage of extended life and overall survival ? Therefore the committee should have identified inequality of access.

3.24
I agree

3.25
I strongly disagree with this decision. The committee should have recommended making trastuzumab deruxtecan available on the NHS to patients with HER2-low metastatic breast cancer although I take on board some of the assumptions around the analyses.

I do hope that Daiichi Sankyo, evaluation committee and the external assessment group can work together to resolve the issues for all HER2-low metastatic breast cancer patients in the UK so that we can benefit as a whole from Trastuzumab deruxtecan.

I hope that you can work on this quickly and not delay the approval of Trastuzumab deruxtecan. I am grateful in particular to the DESTINY-Breast04 Trial Investigators who worked so hard. Their evidence based published work https://www.nejm.org/doi/full/10.1056/NEJMoa2203690 offered HER2-low women more time with their family in progression free and overall survival.

Unfortunately I fear that many women with HER2-low metastatic breast cancer simply believe that the commitee has made a largely economic decision and that our voices are not being listened to.

Destiny 04 showed that in ALL patients there was improved median overall survival. This was a median OS of 6 months compared to physicians choice but was consistent for all patients. It's also possible for it to extend life by more than that and there is the choice of another therapy.

Everyone knows that patients are individuals not statistics and in some cases Trastuzumab deruxtecan has in some patients meant life extension for well over a year and this is not just in Her 2+ patients.

Extra time spent with friends and family cannot be valued. It is priceless.

Represents an organisation – No

Tobacco links – No

Respondent 120. [redacted]
Has all of the relevant evidence been taken into account?

I am not qualified to answer this question.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I am not qualified to answer this question.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are not. The analysis concludes that it is a viable and innovative treatment that is proven to lengthen the lives of patients, giving them more time with their loved ones, in some cases twice the amount of time as current standard of care provides. To make this about the cost of the treatment is in my opinion inhumane. I was 34 when I was diagnosed with breast cancer, while breastfeeding my 9-month-old daughter. There isn't anything I wouldn't do in order to have more time with her. To deny women like me this opportunity on the basis of cost when a treatment already exists is rank cruelty. Please reconsider.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am not qualified to answer this question.

Represents an organisation – No

Tobacco links – No

Respondent 121. [redacted]
Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Not sure

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Please reconsider your decision to overturn this drug for metastatic breast cancer. It is a lifeline for patients who have very few treatment options left.

Represents an organisation – No

Tobacco links – No

Respondent 122. [redacted]
Please do not refuse to offer this treatment to people. It will give patients many months of life with their loved ones.

Represents an organisation – No

Tobacco links – No

Respondent 123. [redacted]
Has all of the relevant evidence been taken into account?

Yes

Please allow the NHS to use/find this drug so it's available to as many people as possible. Any drug that allows for additional time for patients shouldn't ever be taken away.

Represents an organisation – No

Tobacco links – No

Respondent 124. [redacted]
Has all of the relevant evidence been taken into account?

All the relevant evidence has not been taken into account as the personal experiences of patients on ENHERTU (Trastuzumab Deruxtecan)have not been taken into consideration. Although of course I have no personal experience of using this drug as it is not currently available on the NHS, I am well aware of the side effects I and many women I am sure who would be happy to take the safety risks given the overall benefits. I note that breast cancer also affects 1% of men.The side effects are well known and there is already a robust system set uo for monitoring the drug's safety in the UK. I have however been able to share experiences with women who have accessed the drug privately in the U.K. Many have seen positive benefit. On the other hand I have seen crowd funders by NHS patients to try to access this drug and it's awful UK patients should have to do this while having the stress of stage 4 cancer to deal with. This evidence has not been taken into account.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

ENHERTU has not only been shown to be a superior approach to physician's choice chemotherapy but it is the only treatment that has been shown to have a confirmed objective response for women with HER2 low tumours in both hormone receptor positive breast cancer and hormone receptor negative.

The European Union have approved this drug for HER2-low breast cancer so they obviously have concluded its cost effective. Many EU countries they have a publicly available healthcare system which enables use of the drug and although there may be some exceptions to this in terms of particular countries, in general I believe this to be true. We in the U.K. simply feel once again that we are unable to benefit from the cutting edge of the drugs on offer for this incurable, life-limiting disease.

DESTINY-Breast04 Trial Investigators showed clearly that in HER2-low patients there was improved progression-free and median overall survival https://www.nejm.org/doi/full/10.1056/NEJMoa2203690. This paper showed a median OS of 6 months compared to physicians choice but was consistent for all patients. It's also possible for ENHERTU to extend life by more than this based on the range of life expectancy in the NEJM paper and from what I have heard from many HER-low women and men. There is also the choice of another line therapy. It is well known that some people respond to treatments, while others do not but they then can respond to another drug. I know this also in my experience as an NHS physician having treated hundreds of patients over the years, albeit not in Oncology but the principle is the same.

ENHERTU is also more effective at crossing the blood brain barrier and critically would offer more options for this hard to treat group which I also sadly belong to. There are much fewer options for treating hormone receptor negative cancer too and it is more likely to enter the CNS so both hormone receptor positive patients and negative could benefit.

As patients we are individuals not statistics. In some cases this drug has meant life extension for well over a year(s). I know this because of reading and reviewing the landmark work in the NEJM papers on ENHERTU and most especially the work of the DESTINY-Breast04 Trial Investigators https://www.nejm.org/doi/full/10.1056/NEJMoa2203690.

There are also the voices NICE should take into account of HER2-low patients. Extra time spent with friends and family,progression free, cannot be valued. It is priceless.

The safety profile of this drug too was acceptable and therefore it is very important that HER2- low women can access the drug and not be discriminated against in terms of receptor efficacy as this has been shown to be effective for HER2-low breast cancers as a whole.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Breast cancer can strike women (and men) in the prime of life when they are mothers/fathers to young children. Secondary breast cancer, in particular, causes generational pain as there is both personal and family pain and grief of dealing with an incurable illness. NICE should have recommended making ENHERTU available on the NHS to patients with HER2-low metastatic breast cancer. This was the wrong decision.

As a mother, wife and NHS physician I have personal experience of the reality of HER2-low metastatic breast cancer and this experience is similar, I am sure, to so many women and men of the same type of cancer, be they ER+ or Triple negative HER2-low. The mental and physical hurdles are extraordinary. I know that I am unlikely to see my children grow up to reach adulthood and that 2024 has become the year I am likely to die as I have brain mets. My husband has become my carer and I cannot treat or heal patients any longer. I have lost virtually everything apart from my life and that too will be taken from me with such a life- limiting illness. In short, it's a death sentence. I am therefore appalled that NICE has not recommended trastuzumab deruxtecan

I am grateful in particular to the DESTINY-Breast04 Trial Investigators who worked so hard. Their evidence based published work https://www.nejm.org/doi/full/10.1056/NEJMoa2203690 offered HER2-low women more time with their family in progression free and overall survival. NICE should not make a largely economic decision when, for all the reasons I have explained above, it cannot be justified.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

NICE should be doing its absolute best in 2023 to reduce the appalling figure of 11,499 lives lost in the UK to breast cancer between 2017-2019. Although breast cancer cases have fallen, this study notes, overall there is no doubt women who die from it lose a significant number of years (25 on average) because it affects younger people disproportionately (Cancer Research UK) https://www.nature.com/articles/s41416-023-02422-8. This decision therefore discriminates against younger women in particular who lose more life and are often mothers to families resulting in generational pain and other consequences as I have explained above

In females in the UK, breast cancer is the 2nd most common cause of cancer death (15% of all female cancer deaths). In males in the UK, it is not among the 20 most common causes of cancer death (less than 1% of all male cancer deaths).

99% of breast cancer deaths in the UK are in females, and 1% are in males (2017-2019).

Breast cancer mortality rates (European age-standardised rates in the UK are significantly higher in females than in males (2017-2019). (All stats from Cancer Research UK https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/mortality#heading-Zero)

There should also not be discrimination based on grounds of receptor positivity when ENHERTU has been shown particularly by the DESTINY-Breast04 Trial Investigators to be of benefit in HER2-low patients. They showed that there was improved progression-free and median overall survival https://www.nejm.org/doi/full/10.1056/NEJMoa2203690. This paper showed a median OS of 6 months compared to physicians choice but was consistent for all patients.

Represents an organisation – No

Tobacco links – No

Respondent 125. [redacted]
Has all of the relevant evidence been taken into account?

I acknowledge that the document has taken into account several items of evidence, but I believe there may be certain facets that warrant more comprehensive exploration, particularly in terms of the potential long-term advantages and enhancements in quality of life for patients such as my mother.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I respectfully hold a differing view on the interpretation of the evidence. The document may have placed significant emphasis on short-term costs, potentially at the expense of recognising the long-term savings and improved patient outcomes, such as for my mum which could lead to her living longer, reduced hospitalisations and other medical expenses.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I think the recommendations don't seem to fully consider the potential value this drug could bring my ill Mum. I believe a more in-depth analysis, considering the long-term benefits, like mentioned above - increasing her life expectancy should be assessed.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I recognise the importance of a thorough review, but I have concerns that the present recommendations may unduly impact patients, particularly those with limited treatment alternatives like my mum. It's crucial to guarantee equitable access to innovative treatments, with cost considerations not leading to discrimination.

This matters to me because my Mother has secondary breast cancer and has Breast Cancer HER2-low. She is currently on her final treatment Eribulin and this could be the only next possible treatment option for her to extend her life.

Represents an organisation – No

Tobacco links – No

Respondent 126. [redacted]
Has all of the relevant evidence been taken into account?

"Trastuzumab deruxtecan (ENHERTU) is the first licensed treatment for HER2-low metastatic or unresectable breast cancer, and it specifically targets HER2."

I can speak from personal experience. I have been one of the lucky ones who has been able to get hold of ENHERTU on my private insurance despite living in the UK. I note that the FDA has approved it and also in Europe. Infact, it is totally wrong that the NHS hasn't considered to effect this could have. I am Her2 low and after ENHERTU was added to my regime, I went into remission having had both extensive liver and bone disease. This has meant more time to bring up my very young family who are aged 4 and 8. I am their main carer as a single mother. This is the ONLY treatment for HER2 low cancers I am aware of and for me, although it has quite difficult side effects I am delighted with my results.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"Trastuzumab deruxtecan (ENHERTU) is the first licensed treatment for HER2-low metastatic or unresectable breast cancer, and it specifically targets HER2."

No as they put a price on human life and how long we are " allowed" to survive. I am not a statistic and individually

my young family depend on me for everything. This treatment should be available to all patients in my position. We should be recognised as having HER2low cancer and ENHERTUas the only treatment currently on offer in this area. All women who need it should be able to have access to it on the NHS. I have personally seen a dramatic improvement in a short space of time (months!) how is it possible to say that its not cost effective

Are the recommendations sound and a suitable basis for guidance to the NHS?

"HER2-low is a newly classified subgroup of breast cancer previously considered HER2-negative. People with HER2-low metastatic or unresectable breast cancer have cancer cells with low amounts of HER2. "

Absolutely right and its the only treatment we have as part of the classification of being Her2 low

"Even when considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are above the range NICE considers an acceptable use of NHS resources. So, trastuzumab deruxtecan is not recommended."

Absolutely wrong. My understanding is that it improves my survival and I have evidence of it. I want to spend as long as I can bringing up my young family. NICE is making a decision based on money and thats wrong when so many of us are suffering.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

yes
Gender discrimination- most of breast cancer affects women so you are denying women a chance of extended time with their families and this is a disease which has directly affected me as a mother in untold ways. Nobody can imagine what its like to live every day with metastatic breast cancer. It's HELL.

Also there should be no discrimination based on the type of cancer receptors you have. This drug helps HER2 low women so they should ALL get it and this should be no different from HER2 positive women which means you are discriminating as its been shown to be effective in HER2 low and HER 2 positive so there should not be a difference based on cancer type.

Represents an organisation – No

Tobacco links – No

Respondent 127. [redacted]
This is a heartbreaking decision on a drug that has the potential to give thousands of women more time, including my mother. Women all over the country have been told this could be an extra life line for them and to have this taken away now is cruel. Secondary breast cancer needs more drugs, more options, and it needs it now. Please reconsider this decision.

Represents an organisation – No

Tobacco links – No

Respondent 128. [redacted]
This treatment needs to be allowed in the NHS it is not fair disregarding secondary cancer patients…
My friend is battling secondary breast cancer by not being able to have this treatment on the NHS you are limiting the time she has with her beautiful girls! Please take action and allow this treatment on the NHS 🙏👌

Represents an organisation – No

Tobacco links – No

Respondent 129. [redacted]
My daughter was diagnosed with breast cancer at 29. (HER2-)She has 2 young children. Her cancer is now secondary and she will be depending on ENHURTU as she has recently been tested and is HER2- low. Please don't take this chance of more time with her precious children away.

Represents an organisation – No

Tobacco links – No

Respondent 130. [redacted]
24.3 months extra life. TNBC is so underfunded and underrepresented and finally we have a breakthrough and you won't approve it. This decision could put scientists off bothering to try new research for us TNBC ladies. We need and deserve more.

Represents an organisation – No

Tobacco links – No

Respondent 131. [redacted]
Has all of the relevant evidence been taken into account?

No. I am not convinced that a trial of how effective the drug will be for HER2 low patients has been carried out for long enough. I also question whether we know how many people have HER2 low metastatic cancer as I don't believe this is routinely tested for. I also don't think we know how many people even have metastatic cancer. All of this evidence needs to be gathered before an acceptable decision can be made. All of this evidence would be relevant when deciding whether to approve the drug. How can you decide whether it's an "acceptable use of NHS resources" when you don't know how many people it might help to live longer and you don't know how much longer it might allow the unknown number to live for. All of these items are discoverable if the effort was applied to investigate.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

See answer to first question.

Are the recommendations sound and a suitable basis for guidance to the NHS?

See answer to first question.

Represents an organisation – No

Tobacco links – No

Respondent 132. [redacted]
I disagree with this decision as the treatment clearly works and to reject it is to take peoples lives before they need to be taken.

Represents an organisation – No

Tobacco links – No

Respondent 133. [redacted]
I am commenting to request reconsideration of the use of Enhertu to include all of those patients which trial data has demonstrated measurable benefits. That includes those with low HER2 expression. Unlike Lord Sumption in 2021, I do not consider the lives of those with stage 4 cancer (in this context secondary breast cancer) less valuable and I hope such thinking has not unconsciously biased the consideration of this drug and its application.

Represents an organisation – No

Tobacco links – No

Respondent 134. [redacted]
It is disappointing and distressing to hear this decision. If the research shows there is an increased life expectancy from taking this drug , then it should at least be an option for patients who have no other treatment path available

Represents an organisation – No

Tobacco links – No

Respondent 135. [redacted]
this drug should be allowed if it gives people a chance to live why are you not allowing it

Represents an organisation – No

Tobacco links – No

Respondent 136. [redacted]
I strongly disagree with this decision. NICE found (in their own words): " The committee concluded that, compared with TPC, trastuzumab deruxtecan delayed disease progression and improved overall survival in people with HER2-low metastatic or unresectable breast cancer." How can this treatment then be denied to patients whose only other option is imminent death, knowing that this treatment could provide valuable and good quality extra time. The estimated amount of time that it provides should not be used alone in the crass calculation of "cost effectiveness" used to make this decision. PLEASE RECONSIDER this decision using the broader context of the impact of this treatment.

Represents an organisation – No

Tobacco links – No

Respondent 137. [redacted]
This drug as you know, has been shown to work for patients with low HER2, a group of patients who don't have many other lifelines. It is really important they are able to access this option. Self funding for most people wouldn't be an option. Please reconsider this decision.

Represents an organisation – No

Tobacco links – No

Respondent 138. [redacted]
I would like to comment strongly that the decision not to recommend Enhertu for routine NHS use is wrong. It works, it extends precious life. Lives of women who deserve treatment that is effective at giving them more time with their families. Please reverse this decision. On behalf of friends, family and all of those who might need the treatment in the future, please reverse this decision.

Represents an organisation – No

Tobacco links – No

Respondent 139. [redacted]
Due to lack of treatments for TNBC this treatment is a lifeline for the TNBC community. Think of a single mum with two kids and this is her only treatment. This must be available to a evidence based NHS a treatment plan.

Represents an organisation – No

Tobacco links – No

Respondent 140. [redacted]

Has all of the relevant evidence been taken into account?

No, there is insignificant coverage for the case for the approving the drug.

Also their is no patient experience documented. This implies it has not been taken. Therefore how can this be demonstrated as being in the patient interest if it has not captured the patient voice.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Clinical is a detailed argument for the case against. There is clear challenge to the 75% wastage claim. However, there is not a rebuttal or a counter argument by the company to accusations that their statistics were unfounded. So this is just conjector from an unnamed source which weakens a valid argument.

Are the recommendations sound and a suitable basis for guidance to the NHS?

NHS values follow patient choice as a key factor. There is no patient or public preconsultation engagement work demonstrated in these documents. This would imply none was taken. There are nameless stakeholders but also implying that this is the first time the recommendation is shared with the public. If a proposal has no public involvement in a recommendation it is not suitable for NHS guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

None in this instance. There are other factors though thatake this case at risk.for judicial review if not addressed before the next stage.

You have not identified your stakeholders. This is important for clarity and integrity.

1.2
For a recommendation you have only factored the comments for not having this as a recommended drug. This implies bias by not stating any acknowledgement for the case for, even by stating that there are not any.

3.14
Evidence by Healthwatch suffolk as part of a 2022 travel survey demonstrated for the east of England, 50% of participants would travel regionally and 25% would travel nationally for a procedure or treatment. If using centres of excellence to centralise the process wouldn't that allow a reduction of estimates of wastage.

Represents an organisation – No

Tobacco links – No

Respondent 141. [redacted]

I was diagnosed with primary breast cancer at 29 and with secondary breast cancer at 39. I am now 41 years old and facing the prospect of not living until I'm 50. I have a husband, three stepchildren and a thriving career. I write books and share podcasts that aim to raise awareness and support people living with breast cancer. This is a drug that could extend lives like mine and those of other patients, be it for a year or ten. It is VITAL you approve this drug for use in people like me. Whether I live or die should not be put down to cost effectiveness. More and more young women are dying from this disease every single day. PLEASE reverse this decision.

Represents an organisation – No

Tobacco links – No

Respondent 142. [redacted]
How can you make the decision not to extend lives because it isn't cost effective? This treatment is impossible to put a value on for the people who's lives it could extend.

Represents an organisation – No

Tobacco links – No

Respondent 143. [redacted]
To whom it concerns,
I urge you to reconsider yesterday's decision not to recommend Enhertu for routine use on the NHS, in metastatic or unresectable HER2 low breast cancer patients.

Having reviewed the evidence from the Destiny-Breast04 Trial, you are aware that it improves overall survival and progression free survival in these patients.
You are also aware that it is the first licensed treatment option for this type of breast cancer.

Treatment options are limited for this group of patients.
Current treatments are generic and outdated, with multiple side effects.

You seem to have based your decision solely on cost effectiveness.
I understand the NHS is under pressure, but what happens to these patients?
How will they get treatment?
Will they be forced to seek treatment privately?
Will they need to beg/borrow/steal to afford it?
What happened to free healthcare at the point of access?

Money Vs human life?
How has it come to this?

Please overturn your decision it could give many people more precious time with their families.

I am a 39 yr old GP with metastatic breast cancer. I have a 6 year old.
I implore you to reconsider.

Yours Sincerely,
xxxxxx xxxxxxxx

Represents an organisation – No

Tobacco links – No

Respondent 144. [redacted]
Has all of the relevant evidence been taken into account?

I am not a professional but I personally do not feel it has. HER2-Low breast cancer is a small segment of the beast cancer population and is in need of a more effective treatment option. Enhertu is that, is has proven results and has been approved by the similar income nations. Enhertu is the first drug shown to improve outcomes in HER2-low metastatic breast cancer. Results from the pivotal DESTINY-Breast04 trial showed Enhertu reduced the risk of disease progression or death by 50% and the risk of death by 36% in a group of patients with previously treated HER2-Low metastatic breast cancer.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

When discussing cost effectiveness, surely a 50% reduction of progression and a 36% reduction in death is a viable reason for the financial spend. With limited treatments an many of TMBC patients being younger women with family, these sort of stats could be a much needed lifeline when the available treatments are limited.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I personally feel that a second opinion from cancer and oncology experts is needed.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

There is a danger that the UK could fall behind other EU and global countries in the treatment of TNBC for cancer outcomes and survival rates. As a husband to an amazing woman who is battling TNBC and a father to an 8 year old that needs his mum to be alive for as long as possible, Enhertu was a much needed lifeline that we were hoping would be available when all else fails. How can a drug that receives a standing ovation by industry peers at a global breast cancer conference in 2022 for its novel action and ability to extend life be refused funding by NICE?

Represents an organisation – No

Tobacco links – No

Respondent 145. [redacted]
Has all of the relevant evidence been taken into account?

I believe the document has considered various evidence, but I think there might be aspects that haven't been fully explored, especially regarding the potential long-term benefits and quality of life improvements for patients like my friend.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I respectfully disagree with the interpretation of the evidence. The document might have focused heavily on short-term costs, possibly overlooking the long-term savings and improved patient outcomes, which could result in reduced hospitalizations and other medical expenses.

Are the recommendations sound and a suitable basis for guidance to the NHS?

In my opinion, the recommendations don't seem to fully consider the potential value this drug could bring to patients, including my friend. I believe a more in-depth analysis, considering the long-term benefits, would provide a more accurate basis for NHS guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

While I acknowledge the need for careful consideration, I am concerned that the current recommendations might disproportionately affect patients, especially those with limited treatment options like my friend. It's essential to ensure fair access to innovative treatments without discrimination based on cost alone.
No

I appreciate the document's effort, but I respectfully disagree with the decision. The potential benefits of this drug, especially for patients like my friend, should be weighed more heavily. I urge a reconsideration, taking into account the long-term impact on patients' lives and the potential advancements in breast cancer treatment.

Represents an organisation – No

Tobacco links – No

Respondent 146. [redacted]
The evaluation committee is meeting to consider this decision and will take on board comments from steakholders! A chance at LIFE or DEATH should be top of this list, surely those steakholders pay the highest price literally! Some cancer meds already approved work longer for some people than others, for aome people they dont work at all. We deserve the chance to extend our lives even if that's for months or years. Why bother with innovation, research and trials otherwise. Such a backwards decision and very upsetting to hear!

Represents an organisation – No

Tobacco links – No

Respondent 147. [redacted]
Has all of the relevant evidence been taken into account?

The treatment is proven to work and provides another effective line of treatment for the second and third lines where other options are limited. The evidence suggests that cancer patients would welcome other options and that this treatment could be used at different stages.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Obviously were this treatment to be adopted then costs would be driven down as the manufacturers would offer a better discount.
There appeared to be no real comparisons of side effects between the different lines of treatment. This means that this newer treatment may be dismissed purely on the grounds of apparent cost whereas the costs of managing side effects of older treatments may make this new treatment financially more viable.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations highlight cost-effectiveness (or lack thereof) as opposed to other factors. The treatment is proven to work and provides another effective line of treatment for the second and third lines where other options are limited.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

On their own admission, the trial as compared to control groups may not be wholly representative - (557 v 184). Also, the treatments in the control group were not wholly comparable
The trial group was younger and fitter and had a higher proportion of Asian participants. This may on these three counts not be representative.

Represents an organisation – No

Tobacco links – No

Respondent 148. [redacted]
Has all of the relevant evidence been taken into account?

I think the document has considered some evidence but not explored all the aspects such as the long term benefits that this drug would provide for my friend.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I think the document has focused too heavily on short term costs. If it were to look at the long term benefits, such as improved patient outcomes and less hospitalizations, there would surely be a reduction in medical expenses.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I don't think the recommendations go far enough in considering the value this drug could bring to patients like my friend. There needs to be a much more in depth analysis to consider the long term benefits to the NHS.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

My friend has no options left and I fear if this option isn't offered to her because of cost, this in itself is discrimination. Her life matters just as much as anyone else and cost should not be a factor. Shouldn't she have the right to a longer life if there is a drug available that would provide her that?

I understand the efforts of the document but have to disagree with the decision. My friend would potentially benefit immensely from the use of this drug to prolong her life. It would improve her quality of life and quite possibly with the advancements in breast cancer drugs, mean that she has another line of defense against this awful disease. Her life matters to me, her family and her many friends around the world. Please reconsider your decision to allow this drug to be made available to those patients with HER2-low. Thank you for your consideration.

Represents an organisation – No

Tobacco links – No

Respondent 149. [redacted]
Dear Decision makers,

The evidence is unequivocal, Enhertu Improves Survival for Metastatic “HER2-Low” Breast Cancer. Enhertu is approved in more than 40 countries including the US, the EU, and China for patients with unresectable metastatic HER2-low breast. I therefore implore you to reconsider your decision regarding the cost-effectiveness of Enhertu. Other countries have a model, we can re-use their approach.

Lives hang in the balance, and the consequences of denying access to these medications are dire. By prioritising short-term financial gain over human lives, we undermine the very essence of our moral duty to support vulnerable people in the UK.

Imagine your own relative battling cancer. The fear, uncertainty, and anguish would be overwhelming. Now, envision being told that life-saving cancer drugs are too costly and inaccessible. The desperation and helplessness would consume you.

Denying these drugs not only condemns individuals to unnecessary suffering and premature death, but it also sends a chilling message to UK society about our priorities.

Investing in life-extending cancer drugs a strategic investment in the future well-being of our communities. By providing access to these medications we reduce the strain on the NHS, and promote a healthier, more resilient society.

Reconsider your decision. Follow the economic case adopted by other countries. Ensure that every cancer patient in the UK, has access to the treatments they desperately need. The value of a human life should not be determined by profit margins but by our shared humanity.

Yours Faithfully,

xxxx xxxxxxx

Represents an organisation – No

Tobacco links – No

Respondent 150. [redacted]

Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are no! It is absolutely shocking to take this lifeline drug away from all the women that need it, just because it is not cost effective.

I think that it is absolutely disgusting and inhuman in this day and age to say all the good things this drug can do for women but then say it is not cost effective. Women with mestatic breast cancer live with a noose around their neck daily, and any drug that can prolong their life is worth giving it a try!

Represents an organisation – No

Tobacco links – No

Respondent 151. [redacted]

Having read through the document, the draft decision by NICE not to approve Trastuzumab detuxtecan (Enhertu) for treating HER2-low metastatic or unresectable breast cancer after chemotherapy is based on perceived gaps in evidence from Daiichi Sankyo regarding their modelling assumptions and evidence base. The opportunity for DS to address this is reassuring because it appears that the bullet point list that articulates the further supporting evidence that NICE requires can be provided promptly by DS in the timescales given.

I am a secondary breast cancer patient who, in the future, could potentially benefit from this drug but I know many people within the breast cancer community who require this drug now to extend their lives, meaning they have extra time with their loved ones.

Further scrutiny and evidence provided by DS on overall survival rates will inform what I sincerely hope, is approval of this drug.

Represents an organisation – No

Tobacco links – No

Respondent 152. [redacted]

I feel it is extremely important and necessary to allow this drug to be available on the NHS. As a very close friend of someone who lost their beautiful mum suddenly to secondary breast cancer, having just a little bit more time would have been everything. She had just become a first time grandmother and had next to no time to spend quality time with her new granddaughter. I really hope that this is something that can change in the near future and give others the chance to live have have more time.

Represents an organisation – No

Tobacco links – No

Respondent 153. [redacted]

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes. This particular cancer effects Asian women disproportionately.

NICE recommends the NHS Funds assisted conception treatment for single women who are not clinically infertile but "socially infertile." At my ICB, this can cost £22k for a single woman to have a child.

Based on an average female weight of 72.1kg (https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2021/part-4-trends#:~:text=In%202021%2C%20the%20mean%20weights,to%2072.1kg%20among%20women) and recommended dose of 5.4mg/kg for this cancer type, this equates to a max of £5664 per cycle per patient (not

including commercial in confidence discount which would likely make this lower in reality). Therefore, even if the NHS could fund 4-6 cycles for each eligible patient, this would really give them more time to make memories, given the significant results obtained on survival time.

Represents an organisation – No

Tobacco links – No

Respondent 154. [redacted]
Has all of the relevant evidence been taken into account?

The review does seem to have taken account of the evidence which points to a benefit for patients, including delayed progression and additional months of life, but suggests that the cost of the treatment outweighs these benefits. But for the individuals involved these extra months are precious and as people react differently to treatments, some may get much longer additional time.
One of my very close friends has been told she could benefit from this new treatment option. In her mid 50s, she has had secondary breast cancer for over 8 years and still has a good quality of life. So the extra time which this new treatment could bring is not for someone who is already very sick, but someone who has the potential to live longer and live well. And there are probably other women in her situation. By allowing this treatment the company and the NHS could maybe learn and monitor the progress that many more can benefit in future.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The interpretation of the evidence is more focused on short term costs of the treatment rather than long term savings and improved patient outcomes which in turn could reduce hospitalisations and other medical expenses.
Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendation not to fund this drug means that the NHS will not see the same advances in breast cancer treatment as other developed countries. This is clearly detrimental to patients and to public confidence. More weight could be given to the potential benefits for patients and the learning opportunities of the new treatment for clinicians.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

There is clearly a gender dimension to the decision and access to this innovative treatment could take more account of the benefits to this group of women who have limited alternative treatment options.

These are comments on the overall document. As I read it, the provisional decision recognises that there are benefits, including delaying disease progression and improved overall survival in HER2 low breast cancer patients, but cost is a key issue. All public health systems are under pressure, but I understand that many if not most EU countries and the USA are funding this treatment because of the clear evidence of benefits. If the NHS cannot fund this treatment not only will individual women with advanced breast cancer lose out, but we will not make advances in cancer treatment and risk lagging behind similar countries. I am aware of the enormous pressures on the NHS and the difficulty of these decisions, but ask the Committee to look again at the potential benefits and the company to look at ways of making sure this treatment is made available for the benefit of all.

Represents an organisation – No

Tobacco links – No

Respondent 155. [redacted]
I am living with stage 4 triple negative metastatic breast cancer!
I have outlived my prognosis that's to newly approved drugs and now a clinical trial.
It's been 2years of living and seeing my daughter grow.

Recently I've had to come off one of the clinical trial drugs and that has prompt us to search for new options. ENHERTU was that option.

To give me time.

This decision robs my daughter and many other children loved ones from precious time with us.

It's heartbreaking that we are not valued enough.

Our lives don't matter.

Why???

Represents an organisation – No

Tobacco links – No

Respondent 156. [redacted]
I think it's disgraceful that this treatment has not been passed.
My daughter has secondary breast cancer, as a her mother I feel a treatment that has had such good results should be given to anyone who needs it.
My daughter has three young children does she not deserve the best chance of being able to see her children grow up.
I believe this is has more to do with cost than concern for the thousands of woman who could benefit from this treatment and that is absolutely disgraceful.
I hope for the sake of my daughter and all the thousands of other woman out there this decision is reversed very soon!

Represents an organisation – No

Tobacco links – No

Respondent 157. [redacted]
Has all of the relevant evidence been taken into account?

No, with respect more value needs to put on people lives rather than the cost of the drug. There are many people within the clinical community who were astonished by this drug and what it could do for people and this hasn't been considered. This drug could have a significant impact on people with secondary cancers lives and needs to be approved.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, with respect more value needs to put on people lives rather than the cost of the drug. This drug could have a significant impact on people with secondary cancers lives and needs to be approved.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. The NHS needs to be an organisation that looks after everyone equally, regardless of the condition, value cannot be put on people's lives. Approving the drug could drastically improve people's lives.

Represents an organisation – No

Tobacco links – No

Respondent 158. [redacted]
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No - cost should not be the reason someone doesn't live as long as possible. Given the results and the quality of life that can be extended for a significant period this is the wrong decision.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No - see below comment

I am 38 years old and was diagnosed with breast cancer at the end of 36. Instances of breast cancer are being diagnosed more frequently in younger women who all have families, lives and are worth fighting for. Please reverse the decision not to fund this treatment because it provides further treatment options for many women for whom there are far too few. Cost should not be the reason why someone's life is not extended to make wonderful memories with their loved ones.
Please support the cancer community to give us hope.

Represents an organisation – No

Tobacco links – No

Respondent 159. [redacted]
It is distressing to see that this drug that could give more time and quality of life is being denied to the many secondary cancer patients in the UK.
Secondary patients are again being given a lesser deal than other cancer patients.
How can cost effectiveness be the driver in decisions about life.

Represents an organisation – No

Tobacco links – No

Respondent 160. [redacted]
Has all of the relevant evidence been taken into account?

Reading the report, it seems that this guidance has ignored the most important stakeholders which are the patients living with this condition. The report highlights the significant impact that this disease has on patients (3.2), however the conclusion to not recommend this treatment appears entirely focused on cost. There is a hugely significant burden that having this disease has on patients and families. Living with an incurable cancer is something that destroys lives, careers, relationships. These patients seem to have been given some hope with the effectiveness of this drug only to have this taken away. The evidence shows the effectiveness of this treatment and I am shocked that the draft guidance has not recommended it. I urge you to reconsider.

Represents an organisation – No

Tobacco links – No

Respondent 161. [redacted]
This is disgraceful. One of the very few treatment lines for a patients which has proven positive results with very few side effects is being removed due to cost. My 41yr old sister received Enhertu and it extended her life by 2years plus whilst allowing her to have a good quality of life due to very limited side effects. Please allow others to access this treatment on the NHS to give them a prolonged quality of life. We cannot put a price on that!

Represents an organisation – No

Tobacco links – No

Respondent 162. [redacted]
Has all of the relevant evidence been taken into account?

Yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

N/A

I think it's shocking and terrible that this drug should not be available to all patients in the UK as it is elsewhere. Anything that works for these patients should be accessed and made available no matter where you live.

Represents an organisation – No

Tobacco links – No

Respondent 163. [redacted]
Please reverse this decision. Giving metastatic low her2 bc patients access to this drug is proven to give an average extension of life of 2 years, this time, for women who this could help, is priceless and hugely significant. Please don't do this, the US and Europe have both approved the use of this drug, why would the UK do differently? It's just not right, and it's awfully sad. This can, and should be reconsidered and reversed.

Represents an organisation – No

Tobacco links – No

Respondent 164. [redacted]
Has all of the relevant evidence been taken into account?

I believe they have but there may be further evidence to consider, particular the efficacy of using this drug for low HER2 patients.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

This document seems to focus considerably on the short term costs while over-looking possible long term benefits. Improved patient outcomes, for those in receipt of the drug, might reduce the financial cost for hospitalisation and other medical expenses. Hence long term the costing would be more efficient

Are the recommendations sound and a suitable basis for guidance to the NHS?

I don't believe these recommendations fully take into account the potential benefit for patients such as my friend, Clare, who is HEP2 low. I feel that patients such as Clare should be part of a longer term study which would provide more depth to the study and, therefore, provide a more accurate base for the NHS guidance

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Although this study has given careful consideration to a certain cohort, there are patients with limited treatment options for whom this drug would be of great benefit. The current study and recommendations may adversely affect their chances of receiving this treatment. We need to ensure that there is fair access to innovative treatments such as this and not discriminate on the basis of coast alone.

Represents an organisation – No

Tobacco links – No

Respondent 165. [redacted]
These recommendations endorse the feelings of multiple metastatic breast cancer patients who report feeling overlooked and failed on so many levels. The reported outcomes of 23 extra months of life this drug could provide is

a vital lifeline which must not be taken away and whilst I am not a scientist or researcher, the disparity between those who can afford provide treatment and those who sadly cannot afford this luxury cannot be widened further by this heartbreakingly cruel decision

Represents an organisation – No

Tobacco links – No

Respondent 166. [redacted]
I am adding another voice to those concerned about the draft decision regarding making trastuzumab deruxtecan available to HER2 low secondary breast cancer patients on the NHS. It has been demonstrated that this drug has been effective in prolonging the lives of those living with this type of secondary cancer by nearly 2 years. That amount of additional time with their loved ones is precious and as such it should be heavily weighted in any decision making regarding the availability of this drug.

Represents an organisation – No

Tobacco links – No

Respondent 167. [redacted]
Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No.
The document clearly identify the need for such a treatment to be made available in the NHS "HER2-low subgroup is much larger than the HER2-positive subgroup, for which trastuzumab deruxtecan is recommended with managed access". NICE cannot ignore impacting positively so many cancer patients lives. There is enough evidence of clinical effectiveness, and enough evidence of the need and of the demand for introducing new cancer treatments to us, TNBC patients.
Holding onto the price of such a game changing treatment is penalising everyone, and put people's life at risk.
I am a mum of à 4 years old daughter with spécial needs, and since she was born I have been dealing with TNBC. 1 more year with her means the world to me. And I hope I will be able to have my life extended as luch as possible, by accessing new treatment options as long as possible.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No they're not sound as they purely concentrate on a value for money criteria, and disregard the effectiveness of such a new treatment for TNBC people with fewer treatment options and a shorter prognosis.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Help single mothers live longer for their child. At least target these. You'll save 2 lives, not just one.

Represents an organisation – No

Tobacco links – No

Respondent 168. [redacted]
I appreciate the cost of drugs that come new to the market and the difficulty of balancing drug availability and cost. But the recommendation not to make this drug available in the U.K. seems ill-conceived given that the evidence base in the document indicates significant benefits to users over what, for them, could be a considerable addition to

their lifespan. The validity of these benefits against cost have already been recognised by other countries. I firmly believe that such benefits should be available to sufferers in the U.K.

Represents an organisation – No

Tobacco links – No

Respondent 169. [redacted]
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No - how much value do you put on additional years of human life? Those years also allow the opportunitynfor further drugs to be developed and come online. Anything that gives as much extra time as this drug seems to should be approved for all.
No

Are the recommendations sound and a suitable basis for guidance to the NHS?

No - the NHS should not make judgements about life extending treatment on the basis of cost. It should so everything it can to extend the lives of those living with incurable cancer.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

This recommendation absolutely discriminates on the basis of disability. Those with certain cancers or who have had certain treatments already are discriminated against and not given the opportunity for this treatment.

Represents an organisation – No

Tobacco links – No

Respondent 170. [redacted]
As a Secondary Breast Cancer patient, let me ask you one thing. What if I were your 35 year old daughter/wife/niece, would you still have the same decision down to cost?
Let's not be stupid, you have the evidence that this drug works for this group of patients. So back to the first question, what if I were your 35 year old daughter/wife/niece?

Represents an organisation – No

Tobacco links – No

Respondent 171. [redacted]
Has all of the relevant evidence been taken into account?

Patients with low HER2 are being discriminated against. This drug is readily available for metastatic HER2 positive patients, for whom treatments are varied. Triple Negative / low HER2 breast cancer patients have limited treatment options and therefore NICE are discriminating against this sub-group.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Removing this treatment option from a sub set of stage 4 breast cancer patients IS discriminatory. HER2 levels can fluctuate as the disease progresses therefore some HER2 positive patients may have access to this drug but if tested at a later date their levels may become so low they are not included as "positive" any longer. However, these patients will have had access to the drug whereas a patient, suffering with the same disease but with low HER2

levels will not. All patients with HER2 levels should be granted access to the same drugs irrespective of whether they are low or positive.

Represents an organisation – No

Tobacco links – No

Respondent 172. [redacted]
Has all of the relevant evidence been taken into account?

Enhurtu has been deemed successful enough to be approved for use in the EU, America, Canada and Australia. Why are British women being denied it?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Thé improvement in quality of life, and length, have been proved in clinical trials. There are too few treatments available for her2 low secondary breast cancer and this would greatly improve our chances to live longer. NICE approval of Palbocyclib in 2018 has enhanced both quality and length of life for us and Enhurtu would increase that for many. More treatment options are urgently needed for secondary breast cancer, too many women in their 30s and 40s are dying too soon from this disease, often leaving young children behind.

Represents an organisation – No

Tobacco links – No

Respondent 173. [redacted]
Has all of the relevant evidence been taken into account?

While I acknowledge the document's inclusion of diverse evidence, I am of the opinion that there are other aspects yet to be thoroughly investigated, particularly in terms of the significant advantages and enhancements in the quality of life for affected patients.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I disagree with the interpretation of the evidence presented. It appears that the document may have placed undue emphasis on short-term costs, potentially neglecting the substantial long-term savings and the potential for enhanced patient outcomes. These factors could, in fact, lead to a reduction in hospitalisations and associated medical expenses.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I contend that the current recommendations fail to encompass the potential value this drug could offer to patients. I believe that a more rigorous analysis, one that thoroughly examines the long-term benefits, would undoubtedly yield a more precise foundation for guiding the NHS's decisions.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I have concerns regarding the current recommendations, which could potentially place an undue burden on patients, particularly those with limited treatment alternatives. It is of utmost importance to guarantee equitable access to ground breaking treatments, free from any form of discrimination solely driven by cost considerations.

It is imperative to prioritise the substantial advantages of this drug. I'd suggest a thorough re-evaluation, with a strong focus on the long-term implications it holds for patients' well-being and the significant benefits it could bring to the realm of breast cancer treatment.

Represents an organisation – No

Tobacco links – No

Respondent 174. [redacted]
I would like to disagree with the decision NICE has made to not allow the use of the drug Trastuzumab deruxtecan. How can this decision be made when lives could be lengthened or saved by its use? It is shameful. If this were your sister or mother would the same decision be made?

Represents an organisation – No

Tobacco links – No

Respondent 175. [redacted]

Given the vast number of women who are affected by breast cancer each year, it's extremely disappointing to see this drug be refused because of the cost increase vs other drugs which perform nowhere near as well.

Millions of pounds is spent on finding a 'cure' for cancer and yet we're happy to discard a drug that is proven to work because it's too expensive.

As someone with a family history - I may need this drug in the future and I hope to god the correct decision is made.

Represents an organisation – No

Tobacco links – No

Respondent 176. [redacted]
This is a ridiculous decision, a drug that will give these patients a good 2 years of quality life with their loved ones is declined. Most of these patients are young mothers, my 35 year old friend with 2 young children has metastatic breast cancer and though this does not affect her think how many people this does. This needs to be overturned now.

Represents an organisation – No

Tobacco links – No

Respondent 177. [redacted]
Please reverse this! My good friend and inspiration Alice will benefit so much from this drug and have a chance to spend more time with her loved children, please!

Represents an organisation – No

Tobacco links – No

Respondent 178. [redacted]
Has all of the relevant evidence been taken into account?

I am not experienced in breast cancer research, I'm a teacher and psychotherapist who works with children, young people and families. My own mother's secondary breast cancer (2004) was discovered too late for anything other than end of life care and no time to research drugs that may have helped her to live longer than the 5 months we had.
I respect and trust the knowledge of charities such as "Breast Cancer Now" and feel that if they are urging for a way to be found, allowing Trastuzumab Deruxtecan for HR2 patients then I totally support them.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It feels that if every other country in the EU and the USA can fund it, then it is essential that NICE and Daiichi Sankyo work together to explore and find a solution.
I am a psychotherapist who works with children, young people and families and witness the long term financial costs to families and therefore society, when a parent is terminally ill. The knowledge that life extending medication is available but just out of reach can be very damaging to families mental health which in turn can lead to further costs to the NHS, through the extra support needed.
I would urge every effort to find a way to resolve this.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I would like to disagree with the decision to deny certain patients with secondary breast cancer the opportunity to use trastuzumab deruxtecan, giving them extra time for more quality and length of life. I believe more analysis of the long term implications of the impact on patients and and their families is imperative for a balanced and durable decision for guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am concerned that the current recommendations will affect patients who have limited treatment options.

Represents an organisation – No

Tobacco links – No

Respondent 179. [redacted]
Please reconsider this treatment as a life-extending and life-saving alternative to chemotherapy.

Represents an organisation – No

Tobacco links – No

Respondent 180. [redacted]
I oppose your decision to deny HER2low patients this drug.
This decision is inhumane as you are knowingly depriving people with HER2low extra time with children/families.
This drug is available in US and Europe. It's a financial decision to deny this treatment to some in the UK.
The draft document admits its more effective than what what is currently on offer!

You currently give this drug to HER2 plus so why discriminate against HER2 low.

Please please give everyone the opportunity to benefit from this significantly effective drug.

Represents an organisation – No

Tobacco links – No

Respondent 181. [redacted]
Has all of the relevant evidence been taken into account?

There are some gaps in the evidence and there has not been much evidence from patients. To make a decision on these grounds is to cause a disadvantage to the many patients who could derive a huge benefit from it.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

For any drug that could extend life in the way that this one reputably can, there can be no question of cost benefit- there can be no price on a life.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations are based on a limited evidence base and yet deprive patients of the chance of receiving this treatment.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Most of the patients who would benefit from this drug are female and classed as disabled, which means that they already have barriers to inclusivity.

Represents an organisation – No

Tobacco links – No

Respondent 182. [redacted]
I was diagnosed with MBC (Her2+) de novo in 2020 at 39 with a 10 month old (my first child). After my first line treatment failed in March 22, my private insurance allowed me to skip TDM1 in favour of having Enhertu as a second line, based on trial evidence from the US.
I am on round 24 of Enhertu and it has been a wonder drug for me. It's allowed me to continue working, go on a 100km trek for CoppaFeel in the Sahara (raising £10,000 for charity in the process), see my 3 year old daughter learn to ride a bike, spend Christmas with my family in the US and go on some lovely holidays all over the world. I'm hopeful it will allow me to meet my new niece/nephew this December and see my daughter start primary school next September. These are the same hopes and dreams so many of my friends in the breast cancer community share-this drug would undoubtedly give many of them extra years with loved ones, extra years contributing to society and just enjoying the gift of life. You acknowledge the drug works and it IS working in the US and EU for Her2 low patients. Acknowledging this yet refusing access due to cost is an absolute kick in the gut to these people. Please reconsider this position.

Represents an organisation – No

Tobacco links – No

Respondent 183. [redacted]
If patients can get an additional 22 months relief, this means that their families can do.

Your responsibility is surely to take a generous, and pragmatic view on this?

The generosity is to the patients and their families, and pragmatic? Lengthen the time when potentially more expensive auoport ensues.

If patients can get an additional 22 months relief, this means that their families can do.

Your responsibility is surely to take a generous, and pragmatic view on this?

The generosity is to the patients and their families, and pragmatic? Lengthen the time when potentially more expensive auoport ensues.

Represents an organisation – No

Tobacco links – No

Respondent 184. [redacted]
As a women in remission who had triple positive breast cancer. I am extremely grateful for the medication and targeted treatments out there. Not making this an option for patients , leaves patients without families . Please

rethink this we patients are human.
What's the point in making the drugs if patients cannot have them.
Please reconsider this decision.

Represents an organisation – No

Tobacco links – No

Respondent 185. [redacted]
If this drug is more effective than chemotherapy and extends patients life, as it has been shown to do in the document, it should be prescribed. Cost is not a valid reason to deny patients a longer life

Represents an organisation – No

Tobacco links – No

Respondent 186. [redacted]
How is this ok that a value has been put on my life and thousands of other women and men when the data suggests that this is a ground breaking treatment. I know people who have had access to this drug via trials and private medical with HER2 low and they are still on this 12-18 months later with fantastic results. This needs to be reviewed with a matter of urgency , we can't afford to loose more treatment lines due to costs! We need more time and options.

Represents an organisation – No

Tobacco links – No

Respondent 187. [redacted]
Please reverse this decision and allow all HER2 low patients access. This drug will benefit lots of secondary breast cancer patients and has been proven in the trials. This decision cannot come down to cost and should be based on the success of the trial alone. Thank you.

Represents an organisation – No

Tobacco links – No

Respondent 188. [redacted]
This would change my friends life who has been suffering with Secondary Breast Cancer for too long now.

Represents an organisation – No

Tobacco links – No

Respondent 189. [redacted]
decision to not fund this drug is incredibly upsetting, especially when your own review highlights that the drug increases the length of life someone can expect to live. You also recognise that living with this type of cancer has a profound effect on an individual physically, emotionally and psychologically. This news has come as a deep blow to all of us effected by this illness and those suffering from it should not have to suffer.

Represents an organisation – No

Tobacco links – No

Respondent 190. [redacted]
I am writing to you to ask you to reverse this decision. Enhertu is a targeted drug which could give thousands of patients extra time. Not insignificant extra time either, a median of 2 years. That progression free time on a drug in

the secondary breast cancer world is incredible. The US and EU are giving people this drug, they are giving them hope and the opportunity at living better and longer lives. People with this dreadful disease have already been punished once, why are you taking away this source of hope from them now? This is my sisters final treatment option. She has two children. Without this treatment she will die. With this treatment she will have the opportunity to live on, maybe two years, maybe if we are lucky longer. In two years other drugs may come on to the market which could help her. Don't her children (who are 11 and 5) deserve more? Doesn't she at the young age of 42 deserve more? Just imagine for a moment that this decision decided if your mother/daughter/sister/auntie/friend lived or died. Would finances matter then? The thousands of women who are eligible for this drug should not be left to DIE.

Represents an organisation – No

Tobacco links – No

Respondent 191. [redacted]
Please, please rethink what you are suggesting. This is a lifeline for people who often have no other. Extending life where there is no other option. Look at it from their point of view. Have some humanity and give these people hope where there isn't a great deal left. Take this away and you may as well take away their heartbeat.

Represents an organisation – No

Tobacco links – No

Respondent 192. [redacted]
Has all of the relevant evidence been taken into account?

The data set needs to be increased in size and broadened in terms of patient types such as HER2-Low. The potential for extending and improving quality of life must be given more weight.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Short term costs should not outweigh the potential to improve patient outcomes. Delaying progression, extending life, improving quality of life, reducing time in hospital, reducing alternative drug bills, should be more heavily weighted.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The reccommendations do not go far enough. It's important to continually widen your data set, including a larger cohort of HER2-Low patients, to provide more accurate guidelines.
No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

There are limited treatment options available to my friend who is currently on Eribulin. I believe she is being discriminated against by not being offered this drug when data suggests it could delay progression, extending both the length and quality of her life.

Represents an organisation – No

Tobacco links – No

Respondent 193. [redacted]
I find this decision hugely challenging and depressing. This consultation acknowledges what a step change this drug could be for these patients. We know that Breast Cancer is the single biggest killer of women under 50. Breast cancer cases are rising, the numbers of young women with breast cancer are rising. The prognosis for secondary

breast cancer patients is poor and has remained so for too long. It isn't just about losing the women themselves, which is in itself terrible but these women are often mothers - the ongoing impact on their children and families is horrendous. I find it beggars belief that as a society we can develop a breakthrough drug such as this but we cannot organise ourselves in a way to be able to deliver it cost-effectively to those who need it. It is shameful. Please work with Daiichi Sankyo to address this and deliver this breakthrough to the thousands of women and families who need it.

Represents an organisation – No

Tobacco links – No

Respondent 194. [redacted]
This needs to be overturned. Women need this drug desperately. Imagine if this was your wife, mum, daughter.

Represents an organisation – No

Tobacco links – No

Respondent 195. [redacted]
Please reconsider your decision on Enhertu when it may give so many families that bit of extra time with their loved ones.

Represents an organisation – No

Tobacco links – No

Respondent 196. [redacted]
“Clinical trial evidence shows that trastuzumab deruxtecan increases how long people live and how long they have before their cancer gets worse compared with chemotherapy treatments used for HER2-negative breast cancer.”
Refusing to fund this is condemning people to an early death - please reconsider

Represents an organisation – No

Tobacco links – No

Respondent 197. [redacted]
3.21
Because this uncertainty could mean that the true ICER is above what NICE normally considers a cost-effective use of NHS resources, the committee agreed that an acceptable ICER would be towards the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).
Given the multiple references to "uncertainty" this sounds like you are keen to err on the side of caution when it comes to how much money is spent rather than erring on the side of patients whose lives less easily boil down to a numerical value.

3.5
This was because they were younger and there was a higher proportion of people with Asian ethnicity than would be expected in NHS practice.
This is ignoring the fact that more patients with metastatic breast cancer are being diagnosed younger. Further, they are more likely than older patients to present with aggressive subtypes, meaning that they are more likely to run out of active lines of treatment, and sooner.
Further, due to cultural factors and systemic racism, Asian patients are normally less likely to be represented in clinical trials, meaning there is no way of knowing whether they might be more likely to have HER2-low breast cancer.

3.17
The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS)

It is hugely disappointing that, given the severity of the condition, the decision by NICE to reject the use of trastuzumab deruxtecan for HER2-low patients. The increased survival of patients, their improved quality of life, and their ability to contribute to society (and if you're concerned with money - the economy) far outweighs the monetary cost that the NHS would face.

3.24
Because trastuzumab deruxtecan is the first HER-2 low targeted treatment option metastatic or unresectable breast cancer, the clinical experts considered it to be a step-change in managing the condition. The committee acknowledged that there may be benefits with trastuzumab deruxtecan, but that these were captured in the modelling. The committee concluded that trastuzumab deruxtecan is innovative.
This goes beyond the committee assembled for this decision. This is something that physicians and scientists internationally agree should become standard of care for HER2-low patients.

3.25
All the ICERs in the company and EAG analyses were higher than the range NICE considers to be a cost-effective use of NHS resources even with the severity modifier 1.2 weight applied. So, trastuzumab deruxtecan could not be recommended for treating HER2-low metastatic or unresectable breast cancer in adults.
This is not just disappointing, but devastating for a group of patients running out of options in a fight for their lives. More so given that the drug is already approved for HER2-positive patients.
Many are being left largely only with the option of standard chemotherapies which are a blunt and toxic tool that offer marginal benefits from one to the next.
Since the rest of the report acknowledges the obvious benefits, the increased life span and quality of life, this decision boils down to the lives of these patients not being valuable enough or worth it.

Represents an organisation – No

Tobacco links – No

Respondent 198. [redacted]
Has all of the relevant evidence been taken into account?

Insufficient time and effort has been spent evaluating the effectiveness of the drug on HER2 Low patients. The evidence fails to explore the potential long term benefits and impact in terms of quality of life for HER2 Low patients such as my sister. In the EU and US this treatment is being provided for HER2 Low patients.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The evidence does not appear to fully appreciate the financial benefits of providing this treatment - possible savings resulting from lower hospitalisations and reduced medical expenses.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I believe the recommendations do not consider the potential benefits to HER2 Low patients like my sister. I think more consideration should be given to the reasons why other countries have approved usage and review effectiveness in terms of quality of life and extension of life for those patients.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

People registered as disabled are being disproportionately affected. I believe recommendations have been made to avoid expenditure on this group.

Represents an organisation – No

Tobacco links – No

Respondent 199. [redacted]

Has all of the relevant evidence been taken into account?

This treatment has already gone through trials and been approved . It's been shown to work . Don't play lottery with womans lives we are worth it and deserve it to get the best chance to live . Dont put a price on a woman's life

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It's gone through trials it's proved to work . Do t take a lifeline away from us due to cost . We need every option available to us just to live

Are the recommendations sound and a suitable basis for guidance to the NHS?

It's proven to work . Let us have this option . Our lives are precious

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Do no discriminate let all women try this drug just to survive

Represents an organisation – No

Tobacco links – No

Respondent 200. [redacted]

Has all of the relevant evidence been taken into account?

Yes.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. This drug has the ability to save many lives and is already available in other countries. There should be no reason to not make it available in the UK.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. The benefits of this drug far outweigh the costs.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The drug can offer up to 22 months more health and life. The results of studies into its effectiveness are brilliant, and it's already available in the US and Europe. These factors should influence decisions about its availability.

Represents an organisation – No

Tobacco links – No

Respondent 201. [redacted]

I would like to begin by expressing my gratitude for the opportunity to provide feedback on the decision regarding the drug Enhertu (trastuzumab deruxtecan). As a male breast cancer survivor, I understand the tremendous anxiety and stress that a breast cancer diagnosis can bring into one's life. Although I did not personally use this drug, I can empathize with the challenges faced by individuals dealing with this condition.

One concern that has resonated deeply within the breast cancer community is the apprehension and dismay

expressed by existing users of Enhertu. Many of them are deeply worried about the possibility that new patients, who may urgently require this drug at a critical juncture in their treatment journey, could be deprived of its potential benefits. This collective sentiment of outrage and concern within the patient community underscores the importance of a thorough and transparent evaluation process.

While I appreciate the efforts made by NICE in assessing the relevant evidence, it is crucial to acknowledge that this decision profoundly impacts the lives of individuals currently battling breast cancer. The prospect of depriving patients of a potentially effective treatment option during a pivotal moment in their treatment journey is understandably distressing.

In light of the emotional and physical challenges faced by breast cancer patients, it is my earnest request that NICE not only continues to evaluate the evidence diligently but also remains open to reassessment as new data emerges. The dynamic nature of medical research means that there is always room for the consideration of updated evidence that could influence the decision.

I wish to emphasize that the breast cancer community, both existing users and those who may benefit from Enhertu in the future, is united in its desire for the best possible outcomes. Ensuring that all relevant evidence is considered and that timely access to effective treatments is maintained is of utmost importance.

In conclusion, I would like to express my sincere hope that NICE remains attentive to the concerns and worries of the breast cancer community. Your commitment to transparency and evidence-based decision-making is vital for patients who are navigating the challenges of this diagnosis. Let us work together to ensure that the decision-making process prioritizes the well-being of those who rely on treatments like Enhertu.
Thank you for your attention to this matter.

Sincerely,

xxxxx xxxxxxxx

Represents an organisation – No

Tobacco links – No

Respondent 202. [redacted]
I can't belive that NICE has denied this drugs use on the NHS given its great outcomes in the trial for metastatic low her2+ people. How can money be the determined factor to deny this potential life extending drug, how much is days, months, years worth!!!

Represents an organisation – No

Tobacco links – No

Respondent 203. [redacted]
Has all of the relevant evidence been taken into account?

Without the full data about how many people are living with metastatic breast cancer the base line can not be accurately drawn. Now with new classification of her2 low again this is an unknown number of how many could be helped. This is not acknowledged

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, there are a number of us living well with metastatic breast cancer. We are running out of treatment options which is why we often lose our lives. Having targeted therapies increases quality of life compared to chemo drugs so all targeted therapy options should be explored. Use a chemo to knock it to sleep and use this to keep it asleep!

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, clinicians need flexibility to treat individuals

3.4
It would be good to retain the flexibility of having Trastuzumab deruxtecan as different treatment line options as it will allow those who were previously classed as HER2 negative and now HER2-Low to access the treatment lines. This new breakthrough classification would certainly help them going forward.
Those who are also hormone negative have been treated as triple negative so have had no options of repeated chemo. This targeted treatment could help give the bodies a 'break' and extend life.

Represents an organisation – No

Tobacco links – No

Respondent 204. [redacted]
I believe that the decision is purely financial based and yet how can you put a price on life!
All lives matter and should be treated equally and globally.
The favourable trials show this is medically advanced, and a far more favourable treatment compared to more older and outdated treatments you compare this with.

As a lady living with metastatic breast cancer, which has also spread to my brain, in the her2- low subgroup, I am grateful for the opportunity to receive this in Europe where my husband works.
It is very highly regarded.
Let the UK step in line with all other countries offering this.
DO NOT appear backward in making decisions and be forward thinking!!!!
Give the best to the patients, ALL patients who should have access to this.

Our desire is to return to the UK now, and yet this decision impedes us because Enhertu is not available to me.
I want to be near our daughters, family and friends right now, chemo is hard with no community support.
I do not want to die overseas.
I am scared and want to come home and yet what choice do I have....

This innovative new treatment, with proven favourable outcomes needs to be changed to be allowed for all.
Please reconsider renegotiating a deal with the Pharma company.
One day a decision like this could be for you or a loved one.
Thank you

Represents an organisation – No

Tobacco links – No

Respondent 205. [redacted]
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not believe so. See comment that the women that could benefit from this drug are contributing to the economy as they are younger and still working. By denying this drug these women will decline in health sooner, need to stop work and claim benefits.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

This is discriminating against a group of people with low HER 2 status. These people are metastatic and legally classed as disabled. By not offering the drug to this group you are discriminating against them

The denial of Trastuzumab deruxtecan for a number of women is hugely devastating to the metastatic breast cancer community.
As someone living with metastatic triple negative breast cancer diagnosed in the last year this was a potential life extending drug. We know we will not be cured but just want longer time.
The number of women that could be impacted by this drug is unknown. My original breast cancer was biopsied 2 years ago, before the HER 2 low classification and I was just given a negative score. So this reclassification of low status could pick up 1000s of women, the number would be unknown.
The benefits of this drug have been proven and it is giving people in the US and Europe longer. For Triple negative it is giving 18 months compared to 8 months on standard chemotherapy. Incidentally standard chemotherapy often doesnt work for Triple Negative whereas Trastuzumab deruxtecan has been proven to.
In regards to the economic decision surrounding this drug. The majority of women with triple negative that this drug could help are under 40. These women have careers and still work throughout treatment thus contributing to the economy. By not offering this drug these lives are shortened, and will decline sooner and these women will then need to claim support to provide for their families. The heartbreaking impact is that as these women are younger, they have young children who just want more time with their mums.
I urge a reconsideration with all the facts present. This is having a wide reaching positive impact in the US triple negative groups I am part of.

Represents an organisation – No

Tobacco links – No

Respondent 206. [redacted]
Has all of the relevant evidence been taken into account?

Evidence should also be considered from the USA and Europe where Enhertu is already licenced and used as standard. There is also a lot of evidence that can be gleaned in real world setting, as opposed to a trial, from patients who have accessed Enhertu in the UK privately or under compassionate grounds

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The clinical effectiveness does not appear to be in question. It clearly is effective.

As Enhertu is already licenced for HER+ MBC clearly cost has not been an issue there or if it was it was able to be resolved, so it is not unreasonable for the company and NICE to come to an agreement to make this drug available to thousands more patients so that Her 2 low patients are not discriminated against.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, the recommendation as it currently stands discriminates against a sub set of stage 4 breast cancer patients where it has proven to be effective. Furthermore HER2 levels can fluctuate as the disease progresses meaning some HER2 + patients would have access but if tested later their levels could have changed and would no longer be considered positive, but low, but would still have had the drug, whereas those with the same disease but low HER2 will not. All patients with HER2 levels should be granted access to the same drugs regardless of whether they are low or positive.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The evidence demonstrates that Enhertu is effective in those with TNBC for whom treatment options are limited compared to other forms of breast cancer. TNBC is more common in women under 40 and black women (Macmillan Cancer, Cancer Research), therefore by denying Enhertu to those with low HER2 (who would currently be classed as triple negative for treatment purposes) you are discriminating on the grounds of age and race.

Represents an organisation – No

Tobacco links – No

Respondent 207. [redacted]
The fact that this drug has been proven to extend life for this group of patients by an average of 2 years should make this a priority. 2 years for a woman to see her children grow up that little bit more, 2 years to make memories. Surely this is worth investment from our government?!

Represents an organisation – No

Tobacco links – No

Respondent 208. [redacted]
Has all of the relevant evidence been taken into account?

No,I believe the clinical trial efficacy and the fact this drug is used successfully in other Western countries with similar demographics and levels of this cancer has been grossly ignored

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No cost effectiveness is not. There are far more costly and less clinically effective drugs available on the NHS

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, I feel as this is a cancer affecting mostly women this isn't being given the same attention as one affecting men

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

See above

These women impacted by this decision gave families and children. The knock on cost of losing a mother prematurely, psychologically and health wise will be far more costly to the nhs than this drug

Represents an organisation – No

Tobacco links – No

Respondent 209. [redacted]
The preciousness of life for our people this relates too can’t be overstated, and the opportunity to enhance and prolong life here is clear! Please, please reconsider this decision, for the love of life and people, for the mothers and daughters and sisters and aunts and wives and lovers and friends!

Represents an organisation – No

Tobacco links – No

Respondent 210. [redacted]
You might not see this- I'm one of the invisible women with mbc who aren't worth investing in, or giving hope to. Apparently life has a monetary value after all. If only people who make these decisions could spend a bit of time living in the shoes of someone with mbc. By the way- I'm only 41, a Veterinarian, extremely fit and healthy before diagnosis, who has always cared and given my best to others.....cheers

Represents an organisation – No

Tobacco links – No

Respondent 211. [redacted]
Please can this decision be overturned as there are so many people and young mothers in the community that will need this drug to have more precious time with their babies and loved ones. It's already being used and working well in America and Europe. Why can't we have the same access? Please, please can this decision be overturned.

Represents an organisation – No

Tobacco links – No

Respondent 212. [redacted]
Please reconsider this decision, which will give people the chance to have a longer life, when they have a terminal cancer diagnosis

Represents an organisation – No

Tobacco links – No

Respondent 213. [redacted]
The findings in Section 3.2 which clearly emphasise the benefits of Enhertu on quality of life seem to carry little weight in the final decision of this guidance. Why?

Represents an organisation – No

Tobacco links – No

Respondent 214. [redacted]
It is extraordinary to think that an 'innovative' drug that can provide an alternative to chemotherapy and can offer significant improvements in progression free survival has been dismissed ostensibly due to cost. Please do reconsider this position in order to vastly improve the lives of so many women who are already struggling to get support for an illness that really should be treatable and allow those diagnosed to live for much longer.

Represents an organisation – No

Tobacco links – No

Respondent 215. [redacted]
'Only' around 1000 patients in the UK are likely to need Enhurtu and some of that number may be lucky enough to NOT need it. But for those unfortunates whose condition deteriorates, Enhurtu represents 'hope'. Not just for them but their family and friends too.
Knowing that if they lived in one of the many other civilized countries that have already approved this drug they would have access to Enhurtu is heartbreaking. Their chances of survival in the UK have been greatly reduced.
The decision to NOT allow its use for these cases in the UK has removed 'hope'. Not just for the individuals concerned but their children, parents, friends. I urge NICE to reconsider their decision and to approve the use of Enhurtu for this small group of patients who may desperately need it now or in the future. Give them back 'hope'.

Represents an organisation – No

Tobacco links – No

Respondent 216. [redacted]
The news that Enhertu has been stopped by NICE for use in the treatment of Metastatic Breast Cancer has come as a blow to the MBC community. This drug has given hope to so many women, and has actually prolonged the life of some. If it has treated someone for 2 years, and they remained stable, then what would cause it to be pulled? Why take away what is a potential lifeline for women with HER2 low MBC, women like me. I'm heartbroken to hear that this has gone as an option for treatment, an option that could potentially extend my life, and would like to know the

reason for this decision. Please also consider looking at more evidence that shows the drug has worked, talk to people who have actually benefitted,and please be aware of the impact this decision may have

Represents an organisation – No

Tobacco links – No

Respondent 217. [redacted]
Has all of the relevant evidence been taken into account?

This treatment Enhertu has been shown to be effective at prolonging the lives of patients living with secondary breast cancer (SBC) in The USA and The EU. The evidence for longer patient outcomes has been proven with clinical trials - it is a game changer as it provides a novel treatment for SBC. The evidence is clear, however this decision seems to be driven by cost and not by evidence.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

To the thousands of women living with Secondary Breast Cancer (and their families) you are asking them to weigh the cost effectiveness of a treatment that has been shown to prolong lives by 2 years on average. Therefore it is not a reasonable interpretation of the evidence.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations are not sound or suitable, the guidelines should INCLUDE Inhertu as a treatment option for women living with secondary breast cancer. Excluding this drug is an insult to all the public investments in cancer R & D, and an insult to all the millions of pounds of fundraising efforts to help bring these kinds of drugs to trial in the first place.

Represents an organisation – No

Tobacco links – No

Respondent 218. [redacted]
Has all of the relevant evidence been taken into account?

The document could better explore future and long term consequences for patients struggling with the condition and how they may benefit from it's use

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It would be interesting to consider whether the long term savings would outweyany short term costs. Short term costs of hospital visits, support services etc must surely be very high and likely more than the cost of funding

Are the recommendations sound and a suitable basis for guidance to the NHS?

Again, perhaps a thorough evaluation of the long term and future benefits and savings might potentially provide a more accurate basis for NHS guidance

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Whilst not necessarily being discriminated on the grounds listed above it would be relevant to consider any considerations given to patients who are at the final stages of treatment so that they are given a fair chance and do not lose out on the basis of cost

As a close friend of someone who has been battling secondary breast cancer and know in the category of low Her2 I am saddened by the decision laid out by the document. As she is now on the final treatment stages, funding of the drug would not only allow us to spend more precious time with her but also give hope to the many cancer patients bravely battling this cruel illness.

Represents an organisation – No

Tobacco links – No

Respondent 219. [redacted]
This is an extremely cruel and heartless decision considering this drug could give many women up to 22 mths or more extra time with their children and families. I am Her2 low and was banking on this drug down the line. I am devastated at your selfish decision. This drug would have changed the outcomes for Her2 negative cancer sufferers. All we have are outdated broad based chemotherapeutic that give people very little time. You need to reconsider your recommendations.

Represents an organisation – No

Tobacco links – No

Respondent 220. [redacted]
Has all of the relevant evidence been taken into account?

Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. Surely human life is more important than money.

As a HER2 low metastatic breast cancer patient I am appaled by this conclusion. How can you put a price on our lives?

We deserve the chance to live longer, like everyone else. You are depriving us of the ONLY drug available for HER2 low breast cancer patients. The trials have had great success, and to put money over our lives is disgusting. Like everyone else in the cancer community, please review this recommendation. I like others will be looking to this drug to help save and extend my life. It will be my only option.

Everyone has the right to the best treatment available to achieve the best outcome. Try and put yourself in our position. Is money more important than human life?

Represents an organisation – No

Tobacco links – No

Respondent 221. [redacted]
I oppose your decision to deny HER2low patients this drug.
This decision is inhumane as you are knowingly depriving people with HER2low extra time with children/families.
This drug is available in US and Europe. It's a financial decision to deny this treatment to some in the UK.
The draft document admits its more effective than what what is currently on offer!

You currently give this drug to HER2 plus so why discriminate against HER2 low.

Please please give everyone the opportunity to benefit from this significantly effective drug.

Represents an organisation – No

Tobacco links – No

Respondent 222. [redacted]
Reverse the decision NHS. Where is the parity with this being available in Europe and the US.

Secondary breast cancer patients deserve more.

This is a potential lifeline for so many being denied. I could need this in the future to enable me to stay alive. I am a recently diagnosed, young straight to secondary patient.

Represents an organisation – No

Tobacco links – No

Respondent 223. [redacted]
Has all of the relevant evidence been taken into account?

While I can see that many aspects of the suitability have been taken in to account, the human side needs greater weighting. The benefits for patients like Claire Molyneux cannot be under-emphasised: her quality of life, extending her life and giving her hope.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I have to respectfully disagree with the interpretation of the evidence. While the document may have looked at the short-term costings it has perhaps not thought about longer-term investment, like reducing hospital care in future, other medical expenses and improved outcomes for patients.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I strongly believe that more in-depth research and analysis needs to be carried out in order for the considerable long-term benefits this drug could bring to patients like my friend, Claire. 'Hope' cannot be underestimated. more research would provide a more accurate basis for NHS guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Having limited treatment options as Claire does, she and others in her position should be allowed fair access to new and innovative treatments without cost being the discriminatory factor.

While I appreciate the efforts of this document, I very much disagree with the decision to not fund this drug.. The potential benefits of it, especially for patients like my lovely friend, Claire,, should be given greater weighting. I would urge a reconsideration, taking into account the long-term impact on patients' lives and the potential advancements in breast cancer treatment. Even a few months more in this world could lead to further drugs or treatments being found and would be more than worth it for Claire, someone I have known as a friend for over 20 years. This matters to me because if I were Claire, I would also want that extra chance to be with family and friends, and most importantly, some hope.

Represents an organisation – No

Tobacco links – No

Respondent 224. [redacted]
Has all of the relevant evidence been taken into account?

There is not much weight given to patients perspective. Whilst existing evidence has been considered there is acknowledged gaps in the evidence, which therefore disadvantage patients who could benefit from this treatment because a decision has been made against use without better information.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

They are based on multiple assumptions and therefore seem unsatisfactory to refuse life extending treatment BASED on COST to patients. What price more time for patients?

Are the recommendations sound and a suitable basis for guidance to the NHS?

See above, the recommendations are based on assumptions and limited evidence base and effectively decline treatment options to patients

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

By the nature of secondary breast cancer the patients affected are predominately female and are classed as having a disability. The recommendations solely affect this group in an adverse way, who already have barriers to inclusivity.

The document outlines some reservations/shortfalls in evidence base which have contributed to its decision not to approve for low Her2 patients. However surely it would be better, given the recognition that this is acknowledged as an innovative treatment for a subset of breast cancers that have limited treatment options, to approve its use and therefore be part of continuous assessment of efficacy

Represents an organisation – No

Tobacco links – No

Respondent 225. [redacted]
I have metastatic breast cancer which has spread to bones and liver. I am currently on third line treatment Troveldy which is the first treatment which has worked for me albeit a subtle response. My only remaining treatment after this is enhurtu. Please please reconsider your decision.
It could potentially give me precious time with my children. I'm not ready to die yet.
I have been living with MBC for just one year. It's been a living hell which I would wish on no one.
Not enough is done for secondary breast cancer.
I am the 31. The darker side of pink.
My life is in your hands.

Represents an organisation – No

Tobacco links – No

Respondent 226. [redacted]
Making this drug available to women will extend their healthy living circumstances. Women's health is historically sub-standard because it is based on men. It's time to redress this imbalance and approving this drug is a small step in the right direction.

It will help to ensure women live healthy life's for longer, rather than living in illhealth (evidence shows women live longer in ill health than men and the gap in terms of life expectancy is reducing between these genders).

Represents an organisation – No

Tobacco links – No

Respondent 227. [redacted]
Will the decision for this drug not to be approved as a treatment option for HER2 positive cancer patients through the NHS please be re considered. There is limited options available for these patents, and having this as another line of treatment could give many people extra time with their loved ones and further their life expectancy.

Represents an organisation – No

Tobacco links – No

Respondent 228. [redacted]
This draft consultation is heartbreaking. It appears that Trastuzumab deruxtecan (Enhertu) has not been approved by NICE for treating HER2-low secondary breast cancer as it is not considered cost-effective or an acceptable use of NHS resources.

This is despite evidence of the drug being effective and providing patients with significant extra (progression free) life.

As a cancer patient I have been kept in the loop by my oncologist of the positive results from those patients taking Enhertu. Indeed, I fully expected this to be one of my (limited) treatment options in the future.

More treatment options are urgently needed. Based on the improvement in the quality and length of life this drug has been shown to provide in clinical trials, it should be made available to the secondary breast cancer community in the UK.

Represents an organisation – No

Tobacco links – No

Respondent 229. [redacted]
This is a massive blow for cancer patients in the UK. Without access to this drug, they are not being given a chance at life. Please reconsider!!!

Represents an organisation – No

Tobacco links – No

Respondent 230. [redacted]
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

As a patient living with secondary breast cancer I was disappointed to hear of NICE recent decision to not approve Enhertu as a treatment line for HER2 low and would like to express how important I feel it is for patients like myself to be offered it as an option in their treatment plan.
Knowing that once targeted therapy options have been exhausted life expectancy becomes extremely limited and quality of life is severely impacted which makes an urgent need of access to new drugs with potential to extend life. As the results to the trials of Enhertu were met with enthusiasm and hope (something secondary breast cancer patients have relatively little of) surely the UK needs to move forward and and embrace this drug as a much needed option. It seems the UK as a wealthy country is falling woefully behind US and European countries with its cancer death rates and an urgent update of secondary breast cancer treatment lines is needed with the inclusion of Enhertu for eligible patients.
The physical and mental impact of being diagnosed with this degree is immense. Time is precious and the knowledge that a drug with potential is being denied to us and being deemed as not cost effective is devastating.

Represents an organisation – No

Tobacco links – No

Respondent 231. [redacted]
This is a potentially lifeline drug for so, so many cancer sufferers and I believe the decision not to offer this should be reconsidered as soon as possible.

Represents an organisation – No

Tobacco links – No

Respondent 232. [redacted]
Having read this document I do not think that NICE has good enough reason to decide not to provide this drug to patients in the uk. I would urge you reconsider and approve this drug for use in the uk.

Represents an organisation – No

Tobacco links – No

Respondent 233. [redacted]
Has all of the relevant evidence been taken into account?

I believe the document has considered evidence carefully. However, there is more "human" evidence, as opposed to entirely scientific evidence, such as improving the quality of life for potential recipients which might enable them to be well enough to work and enjoy quality time with their loved ones for a significantly longer period of time than they would without it.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

With respect, perhaps more could have been done to consider longer term financial benefits. If more women stay well for longer, there are surely cost benefits because they may need to use NHS resources, such as contact with doctors and nurse and hospital stays, less.

Are the recommendations sound and a suitable basis for guidance to the NHS?

A focus on longer term financial benefits, as mentioned above, would be beneficial. Also, having stage 4 cancer is hugely stressful; the psychological harm of the withdrawal of the hope that this drug could bring to women with HER-2 low breast cancer is surely an important consideration.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

A study, published in BMJ Open in January 2023, found that Black women from Caribbean and African backgrounds are more likely to be diagnosed with certain types of cancer at later stages (3 or 4), when treatment is less likely to be successful. If trastuzumab deruxtecan is not made available to women with metastatic HER2-low breast cancer which is difficult to treat, existing inequalities could be exacerbated.

Breast Cancer Now estimates that an estimated one thousand women could benefit from trastuzumab deruxteca. Allowing women access to this potentially life-extending drug would surely cost little in the scale of NHS spending. But the benefits could be huge, not just for the women themselves, but for their families. Cancer robs so many young children of their mothers.

Cancer experts in the US, where the Food and Drug Administration approved trastuzumab deruxtecan for the treatment of HER2-low breast cancers in August 2022, are seeing the significant benefits of treating their HER2-low patients with trastuzumab deruxtecan. For example, breast cancer expert Dr Jane Meisel of Emory University's Winship Cancer Institute (who was not involved in the DESTINY-Breast04 trial), says the newly designated HER2-low form of metastatic breast cancer "traditionally [has been] quite difficult to treat". Also in 2022, she told journalists at the annual meeting of the American Society of Clinical Oncology (ASCO) that the findings of the DESTINY-Breast04 trial were "a huge win for our patients".

Dr Alexandra Zimmer from the Women's Malignancies Branch in the US' National Cancer Institute's Centre for Cancer Research, who also was not involved with the study, also agrees that the findings of the study are important and will provide a new treatment option for patients with metastatic HER2-low breast cancer.

Dr Shanu Modi led the DESTINY trial. She says trastuzumab deruxteca "is the first HER2-targeted therapy shown to provide clinically meaningful improvement in progression-free and overall survival compared with standard chemotherapy in people with HER2-low metastatic breast cancer."

It would be a tragedy for women in the UK not to have the hope of this drug, which could benefit them and their loved ones hugely.

Making this drug, which it is widely recognised could keep women well for longer, available to stage 4 HER2-low breast cancer patients, may enable many women to work and contribute to the economy. Many of us who are unfortunate enough to have stage 4 breast cancer will not live long enough to claim our state pensions. These pensions will die with us because those we love and leave behind will also not be able to claim them. I would respectfully point out that this is a cost saving to the state. Surely the cost of trastuzumab deruxtecan is a small price to pay in comparison to the state not paying pensions for those of us who have no hope or expectation of getting the state pensions we are entitled to?

This matters to me because I have friends who can potentially benefit from getting trastuzumab deruxtecan. As a mother of two children, who has a different form of stage 4 breast cancer, I know the worry of not being able to access a potential life-extending treatment.

Represents an organisation – No

Tobacco links – No

Respondent 234. [redacted]
Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

Not acceptable

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

N/A

My name is Sophie and I am living with secondary her2 low breast cancer. I am a single mum to a 16 year old daughter who I love more than anything. I love my life and I desperately want to live as long as possible so that I can raise and support her. By denying those of us another line of treatment you are robbing not only ourselves, but our children and loved ones precious extra time with us. It is approved for use in the US and EU so this callous decision makes absolutely no sense and is completely baffling. We are not disposable, our lives are worth as much as everyone else's and we should not be victims to cruel cost cutting. Why are we so behind in treating SBC here? Please reverse this horrendous decision and bring the UK level with the US and EU.

Represents an organisation – No

Tobacco links – No

Respondent 235. [redacted]
Has all of the relevant evidence been taken into account?

No, it has not because the drug has been found to extend the lives of those with HER-low breast cancer and the only reason it is not being recommended is because of cost. This could be a lifeline for many people and it is heart breaking that cost is more important that people's lives.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No again money should never be more important than people's lives.
You could argue the cost effectiveness of all of recommending this drug vs having to use other less effective drugs to treat this condition. It could be less cost effective to use other drugs in place of this one.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Arguably no because whilst the only reason it appears this drug is not bring recommended is because of the cost to the NHS but the NHS will still have to keep treating these patients with other methods so not recommending this drug does not eliminate the cost of treatment for these patients.
Money should not be more important than extending people's lives.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

N/A
Coat should not be a reason to not recommend a ground-breaking drug that was well received during trials and has shown to improve lives.

Represents an organisation – No

Tobacco links – No

Respondent 236. [redacted]
I urge you to please reconsider this decision not to recommend Enhurtu (Trastuzumab deruxtecan) for routine use on the NHS in HER2 negative metastatic breast cancer patients.

The Destiny Breast 04 Trial proved that this drug resulted in significantly longer progression free survival and overall survival than chemotherapy. Treatment options are limited for this group of patients and current treatments are outdated with many side effects.

Looking through the documents you seem to have based your decision solely on cost-effectiveness. I realise the NHS has limited resources but what about these patients, how is it fair that there is a drug available that can extend their life but they are denied access to it? Will they be forced to seek treatment privately? For many people this is not an option and this is a devastating blow.

This drug is already approved for use with a different sub set of breast cancer patients and so the NHS has considered it worthwhile for them but not for HER2 low patients. This is extremely unjust. How can a price be put on these patients lives?

Represents an organisation – No

Tobacco links – No

Respondent 237. [redacted]
Has all of the relevant evidence been taken into account?

The document has considered various evidence. However, it's failure is in it failing to recognise the benefits and quality of life improvements for all patients

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I disagree with the interpretation of the evidence. The documents has focused on short term costs, potentially over looking both long term savings and improved patient outcomes such as reduced hospitalisation.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations don't fully consider the potential value this drug could bring to patients, and an in depth analysis considering the full be benefits would provide a more accurate basis for NHS guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am concerned that as they stand the recommendations will disproportionately affect patients with limited treatment options. It is essential to ensure fair access to all innovative treatments without cost base discrimination

I appreciate the document's effort, but disagree with the outcome. The potential benefits of the drug should be more carefully considered. Consideration needs to be given to both the impact on the lives of patients and their families, as well as the advancements in breast cancer treatment.
My much loved cousin is HER2 low, and every potential extra moment we could have is precious to all of us.

Represents an organisation – No

Tobacco links – No

Respondent 238. [redacted]
If trastuzumab deruxtecan has proven to be effective, and there are no cheaper alternatives of equal efficacy, then we have a moral obligation to provide it for those who have no alternative. Where cheaper alternatives exist, we should use those, but we should not deny effective medication to those for whom this is the sole option.

Represents an organisation – No

Tobacco links – No

Respondent 239. [redacted]
I urge you to reconsider the decision not to recommend Enhertu for women in the subtype HER2-low. They and their families also deserve the chance of more time together.

Represents an organisation – No

Tobacco links – No

Respondent 240. [redacted]
Has all of the relevant evidence been taken into account?

As mentioned in my main comment, I believe that the evidence considered is not wide enough and the research is, in some dimensions, limited especially with the long term implications and the beneficial implications of patients who MAY need recourse to this drug as a future option gaining psychological, wellbeing and theraputic benefits even if they do not yet use the drug.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Once again, while the interpretations are OK as far as they go, there are limited weighting given to the longer term and less easy to interpret and value effects at the expense of prioritising the easy to interpret and value things (i.e. the cost [very easy] and the short term benefits [relatively easy])

Are the recommendations sound and a suitable basis for guidance to the NHS?

I believe that the NHS needs and deserves a much broader and holistic interpretation of th costs and benefits of such a drug. NHS practice looks across a wider set of implications and a longer term horizon than I believe has been fully represented by this advice.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I think that there is a risk that the lack of full consideration for patients who have been under longer term treatment and have limited remaining options could well leave the decision exposed to challenges for unlawful discrimination in at least one of the protected categories.

It seems to me that the full benefits that should have been taken into account for this drug - especially in the cases where it is in use as the only possible next possibility when other drugs become ineffective - is not fully valued. In such cases the inherent value is higher. Long term impacts in these cases are important as is the psychological effect of being able to know that there is access to 'the next drug' which in itself will create beneficial outcomes for patients even if they do not need recourse to the drug - the effects of knowing it WILL be available are important and not properly valued.

Represents an organisation – No

Tobacco links – No

Respondent 241. [redacted]
Metastatic breast cancer patients shouldn't be made to feel worthless, you cannot put a price on someone's life. This decision has to be reversed so that we can have more time.

Represents an organisation – No

Tobacco links – No

Respondent 242. [redacted]
Has all of the relevant evidence been taken into account?

I have invasive lobular breast cancer diagnosed as ER pos, her 2 neg in 2013. In 2021 it became metastatic & over time has become HR neg, her 2 low. I was not originally given chemotherapy as it is less sensitive for many ILC cases. I have apparently swapped from HR pos to her 2 low and the targeted treatments have not been long lasting (in part as not based on lobular breast cancer science) & I am now on capecitabine. I may well need this new drug at some stage in the future. You cannot deny me this.
I am effectively well & am making an ongoing contribution to the economy of GB, my community, my academic & industry, community, family..... Your science is failing to take into account the available decisions based on science and other factors accepted by organisations such as the FDA, EU Commission which showing benefit for HER 2 low metastatic people.
https://www.nejm.org/doi/full/10.1056/NEJMoa2203690
https://www.cancer.gov/news-events/cancer-currents-blog/2022/enhertu-her2-low-breast-cancer
https://www.europeanpharmaceuticalreview.com/news/178941/enhertu-approved-in-eu-for-her2-low-breast-cancer/

Your studies that you are relying on are not taking my case into account, someone who could live many years with treatment options available. I do not agree that the UK should go against the EU/US trend of accepting this drug.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. The reason for not accepting this drug based on cost effectiveness is not acceptable. Your decision has huge implications for my life, a life well lived & a life that could continue on with suitable options. You are doing this clearly because the NHS and funding channels are under-resourced. When you ask people to pay their fair share of taxation & grow the economy, the UK would be able to afford this drug. However, you make the calculations, my life is worth far less than your £1400 /cycle. However, I wholeheartedly disagree. I have a contract with this country to look after my best interests & this decision or calculation is failing to do this.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Absolutely not. You cannot put a price on what my life is worth & suggest that £1400 /cycle is not worth spending for me. I was not afforded early diagnosis for my breast cancer as I have invasive lobular breast cancer & it generally fails to show up on mammograms/ ultrasounds as was the case for me over many years. I therefore was diagnosed with 7 cm of ILC, with no imaging used by the government showing this. This has led to a metastatic ILC diagnosis & the NHS MUST have the ability to enable me to have the options available to extend my life. My doctors want the option to use this drug at some stage, as has been shown in the scientific literature and by the FDA, EU commission..... This country cannot lag behind because it does not choose to resource the NHS appropriately.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

You are discriminating against me based on my gender as a female by denying access to this drug. Naturally more women will be diagnosed with breast cancer than men. Therefore there are a large number of women who would benefit from this drug. This country does not keep records even of how many people live with metastatic breast cancer.
A 2023 recent article in the Lancet stated that: "of the 2.3 million women who die prematurely from cancer each year, 1.5 million deaths could be averted through primary prevention or early detection strategies, while a further 800,000 deaths could be averted if all women everywhere could access optimal cancer care."

I was not afforded early diagnosis as I have invasive lobular breast cancer. The NICE guidelines & NHS have failed to afford those with ILC early diagnosis. I therefore have gone on to develop metastatic ILC and it would be discriminatory to fail to provide me with optimal cancer care based on your decision to not enable me to access this drug when & if I require this in the future.

Please do not discriminate against me as you are doing here based on my being a female with breast cancer.

Reference: The lancet: Ginsburg (2023) Women, power, and cancer: a Lancet Commission DOI: https://doi.org/10.1016/S0140-6736(23)01701-4

Represents an organisation – No

Tobacco links – No

Respondent 243. [redacted]
I urge you to reconsider. Treatment for HER breast cancer is not equal for patients. Some of the research has been described as breathtaking in terms of the impact it has had. In the mist simple terms 23 months could be the difference between a child remembering their parent and not.

Represents an organisation – No

Tobacco links – No

Respondent 244. [redacted]
Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I understand the cost implication but do not agree it outweighs the benefit of the drug, available in many other countries.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations are clear but not suitable guidance as the drug can prolong life.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No.

Represents an organisation – No

Tobacco links – No

Respondent 245. [redacted]
I am 45 years and have been 'living' with metastatic breast cancer for over a year now, thanks to targeted treatment that is approved and available. I along with all the other women and men living with this disease, live in hope of successful treatment which affords us time, time to see our children grow, time to allow our children to have their Mum, our husbands to have a wife and our parents to have their child. TIME TO LIVE AND BE ALIVE for potentially new treatments. To put a price tag on my life and countless others by refusing funding for a drug, the trail results of which were applauded is incomprehensibly cruel.

Represents an organisation – No

Tobacco links – No

Respondent 246. [redacted]
As a mother of 3 teenage children and a secondary breast cancer patient at the age of 47 which was mis diagnosed by the doctors that should follow the NICE guidelines this drug could give me a median of 23.4 more months to live with my girls is that not worth it the NHS let me down now this drug could give me longer the 24 months 2 years could let me see my youngest go to her school prom my oldest finish her college course she has just started and middle daughter qualify in her apprenticeship all these things I will not see should this decision stay it's a disgrace I've worked for the NHS for over 20 years as a paramedic and it's a disgrace that this decision affects me and my family after given most of my life to the NHS being failed by the NHS and now denied this drug it's a disgrace and one that thousands of us secondary cancer patients need I'm just in absolute disgrace for this decision

Represents an organisation – No

Tobacco links – No

Respondent 247. [redacted]
Has all of the relevant evidence been taken into account?

I believe the document has considered various evidence, but I think there might be aspects that haven't been fully explored, especially regarding the potential long-term benefits and quality of life improvements for patients like my Mum.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I respectfully disagree with the interpretation of the evidence. The document might have focused heavily on short-term costs, possibly overlooking the long-term savings and improved patient outcomes, which could result in reduced hospitalizations and other medical expenses.

Are the recommendations sound and a suitable basis for guidance to the NHS?

In my opinion, the recommendations don't seem to fully consider the potential value this drug could bring to patients, including my Mum. I believe a more in-depth analysis, considering the long-term benefits, would provide a more accurate basis for NHS guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

While I acknowledge the need for careful consideration, I am concerned that the current recommendations might disproportionately affect patients, especially those with limited treatment options like my Mum. It's essential to ensure fair access to innovative treatments without discrimination based on cost alone.

Please keep my Mum alive a few more months.

Funding trastuzumab deruxtecan is crucial for patients with HER2-low metastatic or unresectable breast cancer based on compelling clinical evidence. The pivotal DESTINY-Breast04 trial, involving 557 participants across seven UK centers, demonstrated trastuzumab deruxtecan's superiority over 'treatment of physician choice' (TPC). Notably, trastuzumab deruxtecan significantly delayed disease progression and improved overall survival compared to TPC, showcasing its remarkable effectiveness. Although concerns were raised about the trial population's representativeness, clinical experts affirmed that the trial included individuals who would likely receive trastuzumab deruxtecan in real-world NHS practice. To ensure accurate modeling, the economic model employed a partitioned survival structure, allowing a comprehensive assessment of treatment outcomes. Recognizing the necessity of reflecting NHS clinical practice, an analysis excluding second-line eribulin and gemcitabine in the TPC arm was endorsed by experts and the committee alike. Considering these aspects, funding trastuzumab deruxtecan is not just an investment in innovative treatment; it's a lifeline for patients, offering hope and tangible progress in the battle against HER2-low breast cancer.

Represents an organisation – No

Tobacco links – No

Respondent 248. [redacted]

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I feel I am being discriminated against as a woman. This treatment has been given the go ahead for other types of cancer but breast cancer which is predominantly female, we have been told we are not worth the cost.

Cannot express how devastating this news is to so many of us in the stage 4 cancer world. I have a stage 4 triple negative diagnosis as well as a husband and an 8 year old son. My prognosis is 18 months to 2 years. It just isn't enough time with my little boy. It's so hard to hear there is a medicine which has such incredible 'proven' results and we are saying we can't use it due to funding. I will fight for this with everything I can. It saddens me so much that our priorities are such a mess. We can spend billions sending rockets to space but can't save the lives we already have.

Represents an organisation – No

Tobacco links – No

Respondent 249. [redacted]
This is a disgusting decision. It received a standing ovation. Playing with peoples lives who just want to be able to extend their lives to spend with loved ones. This needs u-turning asap to help all of us in the secondary breast cancer community.

Represents an organisation – No

Tobacco links – No

Respondent 250. [redacted]
Has all of the relevant evidence been taken into account?

Has evidence from Europe and the US been looked at regarding its use in practice as this may help with some of the queries brought up in the draft consultation

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

There seems to be some disagreement between the company and the committee regarding the interpretation of results and cost effectiveness. Is this being reviewed further? Is the company being asked to provide further information, data or evaluation?

Are the recommendations sound and a suitable basis for guidance to the NHS?

From my personal point of view as a patient they are not sound or suitable. When I have spoken to health care professionals working in breast cancer in the NHS they have been shocked at the decision not to recommend Trastuzumab deruxtecan for HER2-low

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Under the Equality Act 2010 having a cancer diagnosis is a disability so it could be said that this decision is going against this as an effective treatment is being denied.
As most people this decision affects will be female this could be seen as discrimination on the grounds of gender. It is already accepted that females have received a lower level of health care to their male counterparts in the past.

I am disappointed that this drug has not been recommended for use on the NHS in this draft guidance. I am one of the people who could benefit from this drug, gaining a longer time until further progression and a longer time before I die. I understand that cost has to be taken into account when NICE assess new treatments to be used in the NHS. However the trial that this evidence came from received a standing ovation from the oncology medical community when it was presented. It has been hailed as "a game changer" and could benefit so many people.
The drug is already been used for HER2-low in Europe and the US. It is also available in the UK for people who can pay for it privately or through private insurance, which seems very unfair.
A new subtype of HER2-low receptor breast cancer has been identified with a medication that can make such a difference to people with this but we are being denied it. Secondary breast cancer already feels like the poor relation to primary breast cancer despite 1 in 3 people who are diagnosed with primary breast cancer developing secondary breast cancer. As one of these people it makes me feel like I am not worth those extra months/years that Trastuzumab deruxtecan can give me.
I very much hope that a frank conversation is going to be had with Daiichi Sankyo regarding the cost of this product.

3.2
As a patient with metastatic breast cancer I would totally agree that any targeted therapy that can extend my time to progression and extend my life is extremely important to myself, my family and my friends

3.7
Compelling evidence that seems hard to ignore.

3.10
Whilst I don't understand much about the methods used to extrapolate overall survival data it does seem unfair to use a system that uses 10 year survival as its endpoint when real life data shows that life expectancy once you have a metastatic breast cancer diagnosis is much less than this

3.17
Having this treatment available would mean that people would live well for longer resulting in a better quality of life. The importance of this to the person and their family is difficult to show by statistics alone. For a lot of people it may also mean that they could also have a longer, more productive work life which has benefits to the wider community and economy.

3.25
As already mentioned in 3.24 this has been acknowledged as a step change in treatment for a sub type of breast cancer that currently has no targeted therapy. The results from the DESTINY04 trial are not in question either. I really hope that a conversation can be had with Daiichi Sankyo to make this innovative treatment cost effective to the NHS.

Represents an organisation – No

Tobacco links – No

Respondent 251. [redacted]
This is a shocking decision putting a price on my life . The drug is already approved for HER2+ . In trials Enhertu is the first drug shown to improve outcomes in HER2-low breast cancer .The DESTINY-Breast04 trial showed Enhertu reduced the risk of disease progression or death by 50% and the risk of death by 36% in a group of patients with previously treated HER2-low metastatic breast cancer . The results of the trial received a standing ovation at a global breast cancer conference in 2022.
This drug is another line of treatment for me . It would give me more time to see my 2 year old grandson grow up and front more time with my family . Am I not worth this , is my life of no importance? I am living well with this devastating disease despite the impact of treatment. In England alone around 1000 patients could benefit from this drug . Do we not matter . This new drug for HER2-low has given us all hope for the future , hope that we would have more time . We need this hope . This decision is devastating, metastatic breast cancer is the biggest killer of women aged 25 to 64 in the Uk . How can denying us this drug help change this shocking statistic? Please review this decision and approve Enhertu for HER2-low metastatic breast cancer.

Represents an organisation – No

Tobacco links – No

Respondent 252. [redacted]
Has all of the relevant evidence been taken into account?

As a non medic, I trust that the document has considered all relevant evidence. However, I don't feel this can be considered without addressing the issue of the potential long term benefits and quality of life for people like my friend.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I disagree with the interpretation of the evidence. How have improved patient outcomes and possible long term savings been taken into account - due to possible reduced hospitalisations and associated costs.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I don't think so. The value of this drug is more than it's financial cost; the recommendations need to take into account the value it could bring to my friend and others, considering the long term benefits. This will also affect those around them.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I think there is possibly discrimination based on unfair access to these innovative treatments purely based on cost. Surely my friend's life is as valuable as the next one? Not unlawful discrimination based on the list above but discriminating nonetheless.

Having read the recommendations in the report, I'm afraid I have to disagree with the decision. The benefits of this drug for those affected by HER2-low should be weighed more heavily.

My dear friend of 40 years has HER2-low breast cancer. She has battled with breast cancer and now secondary for 7+ years, has two children in their 20s . I feel she should be given every opportunity to extend her life to the full, this should not be based on cost.

I therefore urge a reconsideration of the decision, taking into account the impact the drug could have on my friend's, and those other affected, life. Surely these advancements should be made available to everyone if the outcome is as predicted.

Represents an organisation – No

Tobacco links – No

Respondent 253. [redacted]

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Lives lengthened and improved through the proven benefits of this drug remain productive and benefit all of society. Mothers remain present for their children and contribute to society. Others remain in the places of work contributing to the economy. It does not seem that these areas of contribution are taken into account within cost effectiveness calculations.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I believe important areas of contribution are not recognised by the NHS (see above).

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

This drug is licensed for use in the US and Europe. Therefore, the NHS is in general discriminatory by approving the drug for use in the UK. Not providing a drug that has been evidenced as giving longer quality of life cannot be reduced to mere economic factors which does not take into account how those improved and longer lives contribute to society and the economy (see above).

Represents an organisation – No

Tobacco links – No

Respondent 254. [redacted]

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The evidence is not considering the average age of women with this form of cancer, nor how frequently they have young children

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Women under fifty with young children should surely be prioritised?

This is surely an acceptable use of resources if it offers up to two years of life to women with this form of cancer. The majority are young women, often with young children and even adding more months to longevity will have a huge benefit on women with this cancer. Please reconsider , taking in how frequently it affects women under fifty years old.

Represents an organisation – No

Tobacco links – No

Respondent 255. [redacted]
Has all of the relevant evidence been taken into account?

No

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, it clearly states that TD " delayed disease progression and improved overall survival in people".

Are the recommendations sound and a suitable basis for guidance to the NHS?

I strongly disagree. There is evidence suggesting improved survival rates in women with breast cancer and yes NICE are not prepared to fund this drug on the NHS. Countries such as the US and Europe are offering this drug to patients. NICE is playing God and it's unacceptable.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes WOMENS LIVES!!!!

Represents an organisation – No

Tobacco links – No

Respondent 256. [redacted]
I would like to urge you to change the decision of not supplying this drug. NICE states here that people using the drug have 'delayed disease progression and improved overall survival' - So it clearly works.

Represents an organisation – No

Tobacco links – No

Respondent 257. [redacted]
Has all of the relevant evidence been taken into account?

Unsure as not an expert.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Unsure.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No - they fail to consider patients lives and families.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Disability discrimination - you're effectively treating someone less favourably because you're not offering someone the same care and treatment in the UK, as you would treat someone who is fit and healthy.

That cost of treatment against effective clinical trials is favourable; it seems unfair to put a price on a patients head. It should be readily available for everyone no matter where they live. Other countries offer the drug for the same her 2 - low subgroup.

This affects my mum as she can't access it in the UK. My mum is suffering from stage 4 breast cancer and has done since I was 11 (I am now 23). This is her third course of treatment whilst being a stage 4 patient, and I would hate for her not to be able to return to me in the UK due to the unavailability of this treatment. This treatment works well with her whilst she lives abroad with my dad, but when my dad retires I hope for them both to be able to return to the UK and for my mum to continue a treatment that works well for her with very little side effects. Please reconsider.

Represents an organisation – No

Tobacco links – No

Respondent 258. [redacted]
I am quite frankly appalled that a drug used in US and EU and that is giving patients with secondary breast cancer (like me) an average of nearly 2 extra years of life if her2 low has been rejected for NHS use. Why are our lives not valued? Believe me 2 years is a lifeline to so many. Shame on you NICE

Represents an organisation – No

Tobacco links – No

Respondent 259. [redacted]
It is absolutely devastating to deny people this life extending drug. I urge a reconsideration of this for the sanity and care of those poor sufferers of breast cancer who, upon hearing his news, believe they have been prescribed instead a premature expiration date and have been thrown the to wayside.

Represents an organisation – No

Tobacco links – No

Respondent 260. [redacted]
Has all of the relevant evidence been taken into account?

I urge you to reconsider your decision not to recommend Transtuzumab Deruxtecan for routine use on the NHS in metestatic or unresectable HER2 low breast cancer patients.

Having reviewed the evidence from
The Destiny-Breast04 Trial you are aware that this drug improves overall survival and you are aware that this drug improves progression free survival in these patients. You are also aware that this is the first licensed treatment option for this type of breast cancer.

Treatment options are limited for this group of patients, current treatments are outdated and generic with multiple undesirable side effects.

You seem to have based your decision solely on the financial cost of this drug. While we are all aware that the NHS is under pressure - please tell me, what happens to the patients who simply need this drug to be able to survive or

lead a normal life for as long as possible? How will they get treatment? Do you expect them to somehow fund this privately themselves or to beg, borrow or steal to try to pay for it themselves? What happened to free access to healthcare at the point of use? How has it come to this?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I urge you to reconsider your decision not to recommend Transtuzumab Deruxtecan for routine use on the NHS in metestatic or unresectable HER2 low breast cancer patients.

Having reviewed the evidence from
The Destiny-Breast04 Trial you are aware that this drug improves overall survival and you are aware that this drug improves progression free survival in these patients. You are also aware that this is the first licensed treatment option for this type of breast cancer.

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Are the recommendations sound and a suitable basis for guidance to the NHS?

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Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I urge you to reconsider your decision not to recommend Transtuzumab Deruxtecan for routine use on the NHS in metestatic or unresectable HER2 low breast cancer patients.

Having reviewed the evidence from
The Destiny-Breast04 Trial you are aware that this drug improves overall survival and you are aware that this drug improves progression free survival in these patients. You are also aware that this is the first licensed treatment option for this type of breast cancer.

Treatment options are limited for this group of patients, current treatments are outdated and generic with multiple undesirable side effects.

You seem to have based your decision solely on the financial cost of this drug. While we are all aware that the NHS is under pressure - please tell me, what happens to the patients who simply need this drug to be able to survive or lead a normal life for as long as possible? How will they get treatment? Do you expect them to somehow fund this privately themselves or to beg, borrow or steal to try to pay for it themselves? What happened to free access to healthcare at the point of use? How has it come to this?

Represents an organisation – No

Tobacco links – No

Respondent 261. [redacted]
Absolutely 100% do not agree with the decision. You are putting a price on the life of a woman (and a man). I do not support your decision and compel you to reverse it and support the use of this drug routinely on the NHS. Cost is not an acceptable reason to reject it. YOU MUST SUPPORT THE USE OF THIS DRUG FOR ROUTINE USE ON THE NHS

Represents an organisation – No

Tobacco links – No

Respondent 262. [redacted]
Has all of the relevant evidence been taken into account?

I can see that this document has looked at various evidences, but I think there are elements that haven't been fully explored, especially in respect of the long term benefits and quality of life issues for people living with secondary breast cancer.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I don't agree that the summaries presented take account of the real world costs of people living with cancer. Additionally improved patient outcomes will reduce the costs of repeated hospitalisations and patient care.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I don't agree that the recommendations here are an accurate description of the value that such a drug could bring to people living with cancer. More in-depth analysis with longer timelines would offer a more accurate basis for NHS guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am concerned that these recommendations do disproportionally affect patients with limited treatment options. It is really important for NICE to ensure fair access to innovative treatments without discrimination based on cost alone.

Represents an organisation – No

Tobacco links – No

Respondent 263. [redacted]
Has all of the relevant evidence been taken into account?

Please do not withdraw this drug

Represents an organisation – No

Tobacco links – No

Respondent 264. [redacted]
Has all of the relevant evidence been taken into account?

Relevant evidence has been considered but not taken into account. There is considerable evidence that Enhertu offers another treatment line, it has uccess in other countries and is being offered as a treatment line, so it's not understandable why the NHS would not offer this. Why is the NHS behind on medical advances?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I don't think you can put a price on potentially saving someone's life.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I think this is clear discrimination, putting a cost on people's lives when there is evidence to support that Enhertu could offer people another chance. Majority of people diagnosed with breast cancer are women. Why is this not being taken seriously? The study has shown that the drug works, but you can't offer it because it's too expensive? Does women's health have a cost to it? If this had been a drug for specifically male cancers, would the outcome have been the same? I somehow can't believe it would.

Represents an organisation – No

Tobacco links – No

Respondent 265. [redacted]
Has all of the relevant evidence been taken into account?

I believe that should have been value should have been more consideration of the benefits for patients. Qualative accounts of patients who have or would have received the drug should be given value.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I disagree with the findings as they they give insufficient weight to the value of the additional life that patients would receive from this drug.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I believe the patient's voice has been given too little value. In addition short term cost cutting removes the possibility of assessing, researching and developing further treatments for this cohort of patients.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

As women are more effected by breast cancer more opportunities to provide treatments should be made available.

I appreciate the considerable thought and effort that has gone into this document. I however, disagree with the conclusion. I believe that the additional life this medication can give has been undervalued. The sum of time and cost doesn't fully appreciate how valuable a person's life is. The extra months not only means a person may spend valuable time with loved ones, but that extra time could ensure patients are alive to try out new more effective drugs that come on the market.

My personal connection to the area of treatment is through my very good friend. She has previously been given treatment that is only supposed to be affect for 18 months yet on number of occasions the treatment was effective for many many months longer. By approving funding for this medication you not only allow people to live, but give researchers time to develop treatment programs that will extend the effectiveness of the drug.

Represents an organisation – No

Tobacco links – No

Respondent 266. [redacted]
Has all of the relevant evidence been taken into account?

Have you spoken to real women living with this disease who will do anything to continue living?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Avoid unlawful discrimination against the thousands of women in the UK who will benefit from this drug, their children, families and friends who want to see them alive for as long as possible, without a committe putting a price on their heads and concluding theyare not worth the money.

1.2
Evidence shows that people live longer with this drug but you are not going to reccommend it due to cost? As I understand it, this costs £1400 a vial. at the moment I am taking ribociclib, which costs £3000 a month - it doesn't make sense?

3.2
I am one of the women with HER - low. There are fewer treatments for my sub group. You acknowledge the stress of living with secondary breast cancer, I am on my first line of treatment but even reading this consultation is scaring me, to think I will be denied life because of money. I have an 18 year old daughter I want to live for. Please reconsider.

3.2
I agree with this - I have recently found out that i am her2 low and previously thought that there were lots of treatment lines open to me. To hear that there aren't, and you are closing off a treatment that has been proven to extend lives, is unfathomable.
committee-discussion

3.4
It seems to me that this drug is vital as you said there are fewer if any other options for this sub group of sbc. Why do the research and find out about this new sub group if you aren't going to treat it?

Represents an organisation – No

Tobacco links – No

Respondent 267. [redacted]
The extra time this drug would give my friend, a wife, a mum, a daughter, a sister… would be invaluable and for all her family, life changing. A mum of 3 girls being denied access to more time to live and love her girls and those who love her seems disproportionately unfair and cruel. Time might also buy the option to try other, innovative treatments. Please reconsider this decision. There is no price on life.

Represents an organisation – No

Tobacco links – No

Respondent 268. [redacted]
I haven't watched the video to find out how to comment. I believe that if you want people to comment on a consultation, it should be easy and accessible for all.
If I had read your reasoning to why you were not approving this drug for patients with low HER 2 four years ago, I would have understood and accepted your reasoning. However I got diagnosed with inflammatory breast cancer 4 years ago
With a positive HER 2 status. I progressed
To stage 4 within 18 months. So for the last 2 1/2 years I have been on kadcyla. I think your trials showed this was effective for an average of 9 months. I am still on it. I continue to work full time, run half marathons, see my son go to university, my daughter start secondary. 6 months, 9 months, 12 months seems an insignificant amount of time when you are not living through this, but it so is. And not everybody is average. There are many of us with this cancer that are young, healthy, managing with treatment pretty well. Please don't treat us as average.
In addition, you have incredible oncologists who are prescribing this treatment, they do this on an evidence basis, trust their judgement and who they prescribe this to.

Represents an organisation – No

Tobacco links – No

Respondent 269. [redacted]
Surely these women's lives are more important than the cost here? Many of these women are young with young families and any extension in life should be provided.
I totally understand the cost implications to the NHS and there would need to be specific criteria in place but This must be looked at again.

Represents an organisation – No

Tobacco links – No

Respondent 270. [redacted]
This is incredibly disappointing and feels like discrimination. Why would this so positive and useful drug be excluded from HER2 low patients? Other than money I don't see the rationale

Represents an organisation – No

Tobacco links – No

Respondent 271. [redacted]
As I have been diagnosed with stage 4 breast cancer, taking an option off the table away from a stage 4 cancer patient can mean quality and quantity of life remaining. Also I think this discriminate against people with stage 4 cancer.

Represents an organisation – No

Tobacco links – No

Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]. A Single Technology Appraisal

Second addendum: EAG response to the company's draft guidance consultation comments.

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Date completed	03/11/2023

1. Introduction

In October 2023, the company commented on the Draft Guidance Consultation (DGC) document for the appraisal of trastuzumab deruxtecan (T-DXd) as monotherapy for treating adult patients with unresectable or metastatic breast cancer (u/mBC) with low levels of human epidermal growth factor receptor 2 (HER2), and who have had at least one prior chemotherapy.[1] The company's DGC response includes a written response form which presents discussion of each of the key issues identified in the DGC document. This involved a change in the company's base case in terms of efficacy data used and some of the costs and utility values.

The response also includes a new version of the model which had been used to generate updated cost-effectiveness estimates, and an updated model version of the cost minimisation analysis (CMA) comparing T-DXd to sacituzumab govitecan (SG).

This addendum provides a brief external assessment group (EAG) commentary on the company's DGC response and should be read in conjunction with the EAG report,[2] and the EAG response to the technical engagement process.[3] Section 2 presents a description of the issues raised by the company's response and new analyses suggested by the company in addition to the EAG's critique. Section 3 provides a brief description of the changes in the updated model submitted by the company. Section 4 presents the methods for additional exploratory analyses undertaken by the EAG. Section 5 presents the results of additional exploratory analyses undertaken by the EAG.

All results presented in this document include an updated Patient Access Scheme (PAS) discount which reduces the cost per 100 mg vial from a list price of £[redacted] to £[redacted]. This represents [redacted] discount of the list price compared to the [redacted] offered at the time of the committee meeting in September 2023.

2. Issues raised by the company's DGC response and EAG critique

Issue 1: The revised company base case excludes gemcitabine and eribulin when used second line

In the DGC document, the committee concluded that, "*the TPC arm was not fully generalisable to standard care in NHS clinical practice*" and considered that "*TPC should be modelled to reflect NHS clinical practice and should exclude second-line eribulin and gemcitabine*".[4] The committee, "*would like to see an analysis using the company's post hoc analysis, with its associated utility data and justification for its choice of survival distribution.*"[4]

In response, the company adopted the post hoc subgroup analysis of the DESTINY-Breast04 (DB-04) trial as its base case (hereon referred to as "DB-04 NHS cohort"). The EAG agrees that this is a better

approach than just excluding gemcitabine and eribulin costs because it does not assume similar clinical efficacy among the various TPC agents. The company presented an updated survival analysis for the extrapolations of the Kaplan-Meier (KM) data for overall survival (OS), progression-free survival (PFS), and time-to-treatment discontinuation (TTD), as well as an updated utility analysis from the DB-04 NHS cohort.

However, the EAG reiterates its concerns that the analysis "*reduces the sample size*" and "*biases the trial population towards those who have had more than one line of prior therapy,*" as the company noted "*a higher proportion of patients in the "DB-04 NHS cohort" received ≥2 prior lines of chemotherapy than in the FAS ("DB-04 NHS cohort" vs. FAS: [redacted]% vs [redacted]% in the T-DXd arm; [redacted]% vs [redacted]% in the TPC arm).*"[1]

Issue 2: OS extrapolations for the DB-04 NHS cohort

The company fitted independent models to the OS KM data from the T-DXd and TPC arms of the DB-04 NHS cohort because they did not consider that it was appropriate to assume proportional hazards between the trial arms based on inspection of the log-cumulative hazards plots. Seven parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma) were fitted, and the statistical goodness-of-fit scores were provided. The EAG would also have preferred to see the assessment of the empirical hazard, however this was not provided.

The company concluded that for the TPC arm, "*Weibull, log-logistic, log-normal, generalised gamma and gamma curves could be considered potential options,*" based on the statistical goodness-of-fit scores (Akaike information criterion [AIC] and Bayesian information criterion [BIC]). Among these models, log-normal and log-logistic provided 5-year survival predictions of >[redacted] for the TPC arm consistent with the clinical advice received by the company and the EAG that [redacted] of patients treated with TPC would remain alive at 5 years (Table 1). The Weibull, generalised gamma, and gamma gave lower 5-year predictions at [redacted], [redacted], and [redacted] respectively. The company conducted a re-analysis of the Flatiron study (an unpublished retrospective observational cohort study of US patients) where patients receiving more effective TPC components were excluded, and adjustments were made to align the subgroup of patients analysed with the DB-04 NHS cohort (hereon referred to as "Flatiron NHS cohort"). The 5-year survival rate was [redacted] in the Flatiron NHS cohort supporting the use of log-logistic and log-normal to extrapolate OS for the TPC arm. The company used log-logistic for its base case and explored the log-normal fit in a scenario analysis. The EAG prefers the log-logistic model over the log-normal model for its better statistical fit (company's response to the DGC, Table 17).

Table 1: Comparison of long-term predictions of OS from the DB-04 NHS cohort and the Flatiron NHS cohort versus the parametric fits from the KM data of the DB-04 NHS cohort (reproduced from the company's response to the DGC, Tables 2 and 3)[1]

Distribution	Median (months)*	1-Year OS	2-year OS	3-Year OS	5-Year OS	10-Year OS
TPC						
Observed KM data (DB-04 NHS cohort)	[redacted]	[redacted]	[redacted]	-	-	-
Observed KM data (Flatiron NHS cohort)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd						
Observed KM data (DB-04 NHS cohort)	[redacted]	[redacted]	[redacted]	-	-	-
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*OS in the extrapolated curves is estimated after OS has been adjusted to include general population mortality
Abbreviations: DB04, DESTINY-Breast04; KM, Kaplan-Meier; OS, overall survival.

For the T-DXd arm, the company concluded that "*log-logistic, Weibull, generalised gamma, gamma and Gompertz could be considered potential options*" and selected the log-logistic distribution as it "*generates a 5-year OS estimate for T-DXd of* [redacted]*, which appears to be clinically plausible given that clinical experts estimate 5-year survival of 5–10% for TPC.*" However, the EAG deems the size of treatment effect after 5 years to be uncertain and there is currently no evidence to support it.

On exploring the hazards of death calculated from the different extrapolations (Figure 7), it is shown that using the log-logistic or log-normal distributions to model T-DXd OS results in a favourable treatment effect for T-DXd persisting for more than 10 years as demonstrated by hazard ratios (HRs) being lower than 1. The EAG considers this to be clinically implausible as the results from the DB-04 NHS cohort show that almost all patients on T-DXd discontinue treatment and progress by [redacted] months.

Among the remaining potential options which provided good statistical fit for T-DXd, the gamma distribution showed the highest 5-year OS prediction ([redacted]) as shown in Table 1. The EAG also notes that the gamma fit provides estimates between Weibull ([redacted]) and log-logistic ([redacted]) distributions which the committee preferred. The EAG explored the effect of combining the gamma model for T-DXd with the log-logistic model for TPC on the HRs for death between both arms and

noted that the HR becomes greater than 1 after 3.5 years. The EAG did not believe that T-DXd could be associated with higher hazards of death at any given timepoint compared to TPC. Hence a cap was applied to the hazards predicted from the gamma fit for T-DXd to restrict the HR to a maximum of 1 and used this new modified fit as the EAG base case. The resulting extrapolations are shown in Figure 2. The EAG notes that the log-normal model for TPC aligned well with the Flatiron data and explored it as a scenario with the modified gamma fit for T-DXd.

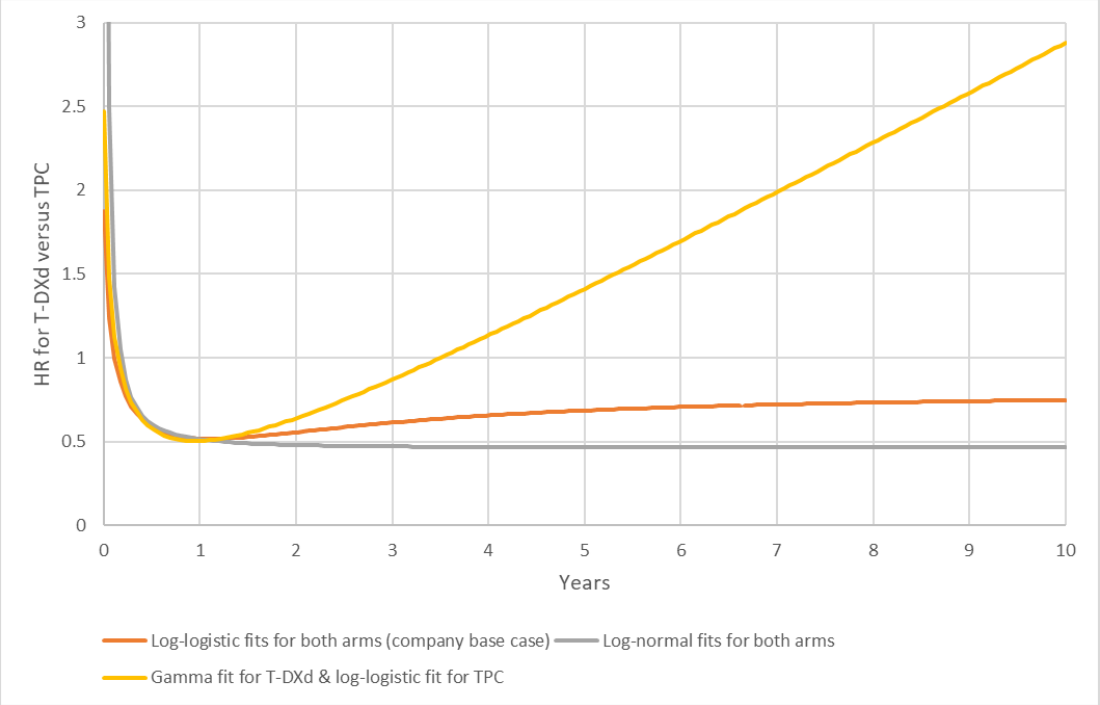

Figure 1: Predicted hazard ratios (T-DXd versus TPC) for different OS extrapolations

Figure 2: Base-case extrapolations for OS in the DB-04 NHS cohort

Issue 3: PFS extrapolations for the DB-04 NHS cohort

The company fitted independent models to the PFS KM data from the T-DXd and TPC arms of the DB-04 NHS cohort because they did not consider that it was appropriate to assume proportional hazards between the trial arms based on inspection of the log-cumulative hazards plots. Six parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma) were fitted, and the statistical goodness-of-fit scores were provided. The EAG would also have preferred to see the assessment of the empirical hazard, however this was not provided.

For the TPC arm, after considering the AIC and BIC scores of statistical goodness-of-fit the company concluded that the generalised gamma, log-normal and log-logistic models provided the best statistical fit (Table 2), however the EAG notes that the log-normal and log-logistic models had better visual fits than the generalised gamma as shown in Figure 3. The EAG preferred the log-normal distribution as it had lower AIC/BIC scores and explored the log-logistic in a scenario analysis. The company selected the log-logistic model for its base case based on the similarity of its 1-year estimate ( ) to the observed PFS ( ) in the DB-04. However, the EAG notes that all the other models provided better aligned 1-year estimates in the range of (company's response to the DGC, Table 4).

Table 2: Statistical goodness-of-fit scores (PFS, independent models) in the DB-04 NHS cohort (reproduced from the company's response to the DGC, Table 18)[1]

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates best statistical fit

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TPC, treatment of physician's choice; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan

Figure 3: Observed KM versus predicted PFS for TPC in the DB-04 NHS cohort (reproduced from the company's response to the DGC, Figure 14)[1]

For T-DXd as shown in Table 2, the Weibull, Gompertz, log-logistic, log-normal, and generalised gamma models provided similar AIC/BIC scores within the 5-point range.[5] As shown in Figure 4, the log-logistic and log-normal distributions are overestimating the PFS beyond the KM data whereas the Weibull and Gompertz fits may be considered underestimates. Hence the EAG preferred the generalised gamma in its base case. The company selected the log-logistic curve for its base case based on the similarity of its 1-year ([redacted]) and 2-year estimates ([redacted]) to the observed PFS ([redacted] and [redacted] respectively) in the DB-04. However, the EAG notes that the generalised gamma provided a better aligned 2-year estimate of [redacted] (company's response to the DGC, Table 4).

Figure 4: Observed KM versus predicted PFS for T-DXd in the DB-04 NHS cohort (reproduced from the company's response to the DGC, Figure 15)[1]

On exploring the hazards of progression calculated from the different extrapolations (Figure 5), it is shown that using the log-logistic distributions to model PFS results in a favourable treatment effect for T-DXd persisting for more than 10 years as demonstrated by hazard ratios (HRs) being lower than 1. The EAG considers this to be clinically implausible as the results from the DB-04 NHS cohort show that almost all patients on T-DXd discontinue treatment by [redacted] months. The EAG explored the effect of combining the generalised gamma model for T-DXd with the log-normal model for TPC on the HRs for progression between both arms, and noted that the HR becomes greater than 1 after 2 years. The EAG did not believe that T-DXd could be associated with higher hazards of progression at any given timepoint compared to TPC. Hence a cap was applied in the EAG base case to restrict the HR to a maximum of 1. The resulting extrapolations are shown in Figure 6.

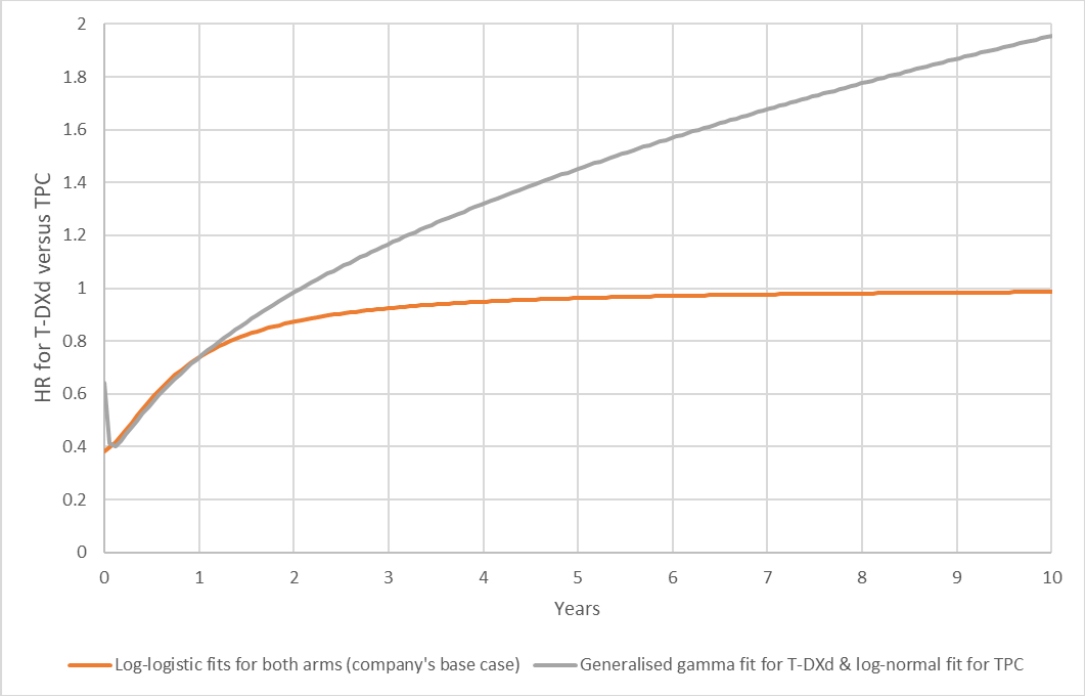

Figure 5: Predicted hazard ratios (T-DXd versus TPC) for different base case PFS extrapolations

Figure 6: Base-case extrapolations for PFS in the DB-04 NHS cohort

Issue 4: TTD extrapolations for the DB-04 NHS cohort

The company fitted independent models to the TTD KM data from the T-DXd and TPC arms of the DB-04 NHS cohort because they did not consider that it was appropriate to assume proportional hazards between the trial arms based on inspection of the log-cumulative hazards plots, consideration of data

maturity and likely independence of treatment discontinuation across arms. The same set of six parametric models previously considered for PFS were also considered for TTD. The EAG would also have preferred to see the assessment of the empirical hazard, however this was not provided.

After considering the AIC and BIC measures of statistical goodness-of-fit the company concluded that the log-logistic model provided the best statistical fit for both arms (Table 3) followed by the log-normal and generalised gamma models. When comparing long-term estimates from the models with observed KM data for TTD from the DB-04 NHS cohort, the company concluded that "*all curves provide plausible long-term estimates for TTD … due to the maturity and completeness of the TTD data*".[1] The EAG notes that the log-logistic, log-normal, and generalised gamma distributions provide the same median TTD prediction, however the AIC/BIC of the generalised gamma model is over 5 points higher than the AIC/BIC of the log-logistic model for the TPC arm indicating that the log-logistic model provides better statistical fit to the TPC KM data.

Table 3: Statistical goodness-of-fit scores (TTD, independent models) in the DB-04 NHS cohort (reproduced from the company's response to the DGC, Table 19)[1]

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates best statistical fit

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TPC, treatment of physician's choice; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan

On exploring the hazards of treatment discontinuation calculated from the different extrapolations (Figure 7), it is shown that T-DXd has higher hazards of discontinuation than TPC after 42 months (HR > 1) when a generalised gamma distribution is used in contrast to when using log-normal or log-logistic models where the hazards are lower for T-DXd for at least 10 years. The EAG did not believe that the hazards predicted by the generalised gamma model after 42 months are plausible considering that patients discontinued treatment and progressed earlier in the TPC arm compared to the T-DXd arm in the DB-04 trial. Nonetheless, the long-term predictions from the log-normal and log-logistic curves are not plausible either as the HR remains below 1 for more than 10 years. Hence, the EAG preferred the generalised gamma fit and applied a cap to the HR at 42 months so that hazards are the same between both arms afterwards. The log-logistic had the best AIC/BIC scores and was explored in a scenario analysis by the EAG. The resulting extrapolations are shown in Figure 8. The EAG notes that applying

the cap to the generalised gamma fit at 42 months had a minimal impact as [redacted] of patients are still on T-DXd treatment at that time.

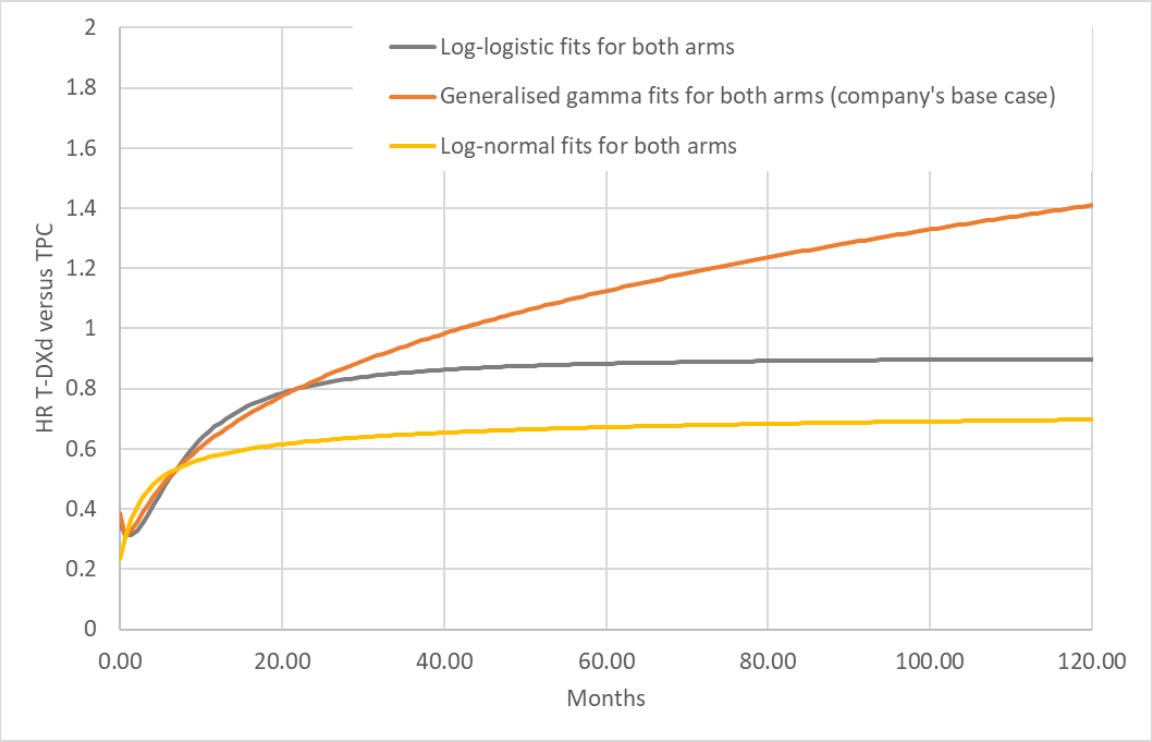

Figure 7: Predicted hazard ratios (T-DXd versus TPC) for different TTD extrapolations

Figure 8: Base-case extrapolations for TTD in the DB-04 NHS cohort

The company provided a scenario where KM data are used until arbitrary time points (23 and 14 months for T-DXd and TPC, respectively) and then the fitted parametric models are used beyond. The EAG believes the choice of the time points adds more uncertainty and explored this as a scenario. In addition, the EAG believes the switching between the KM curve and the fitted parametric models was not applied correctly by the company because the survival probabilities from the parametric model were used directly instead of applying the hazards from the fitted parametric model to the KM curve. The company's approach results in a sudden jump at the point where the KM curve is joined with the fitted model. The EAG applied a fix for this scenario where the hazards from the survival extrapolations were applied to the survival estimates from the timepoint of switch from the KM curves onwards.

Issue 5: Progression-free utilities

The company has updated its approach to use the utilities derived from applying a linear mixed model (LMM) regression to data from the "DB-04 NHS cohort," for the progression-free (PF) health state. Using the estimates from the LMM is consistent with the approach taken by the EAG to estimate PF utilities at technical engagement,[3] and is also consistent with the committee's preferences stated in the DGC (paragraph 3.13).[4] Using data from the "DB-04 NHS cohort," for both efficacy and utility estimates is also consistent with the committee's preferences stated in the DGC (paragraph 3.9).[4] The EAG has previously commented on how the use of this cohort affects the proportion of the population with two rather than one previous lines of treatment (see Issue 1). The EAG therefore makes no further comment on the company's choice of PF utility values.

Issue 6: Post-Progression utilities

The company has updated its approach to estimating post-progression (PP) utilities. It had previously argued that the PP utility estimates from the DB-04 trial were uncertain due to limited follow-up and collection of EQ-5D outcomes in the DB-04 trial, and for this reason it proposed using estimates derived from the Lloyd *et al.* algorithm.[6] However, now the company is using PP utility estimates from the DB-04 NHS cohort in its updated base case.

The EAG considers that these estimates should be treated with caution for the reason previously explained by the company. This was that the collection of EQ-5D data was limited to 3 months after the first follow-up assessment, which occurred on day 40 after last study drug administration. In addition, as previously described in the EAG's critique of the company's technical engagement response, many of the observations of PP utility ([redacted] in the T-DXd arm and [redacted] in the TPC arm for the FAS) were in patients still classed as being on treatment at the time of the observation.[3] This was either due to the patient being classed as on-treatment for 21 days after treatment administration, or as a result of a discrepancy between the progression status based on the investigator assessment of progression, used to determine end of treatment, and the progression status later applied by blinded

independent central review (BICR), which was used when classifying patients as progressed for the utility analysis. The EAG previously estimated that the mean number of PP observations per patient falling after the end of treatment is expected to be fairly low ([redacted] for TPC and [redacted] for T-DXd using the FAS).[3] This means that the estimates of PP utilities derived from the trial data will be biased towards reflecting utility around the time of progression and may fail to properly represent the average utility between the time of progression and the death. Median PFS was 5.1 months for TPC in the FAS, and median OS was 17.5 months, meaning that median PP survival is likely to be around 1 year.[2] Therefore, the limited duration of EQ-5D follow-up in the DB04 trial is unlikely to fully capture the average utility between time of progression and death. The EAG notes that the utility decrement associated with progression is [redacted] when using the LMM applied to the DB-04 NHS cohort.[1] This is much smaller than the 0.243 estimate for the utility decrement associated with progression provided by the Lloyd *et al.* algorithm (estimated by the EAG using patient characteristics from DB-04 FAS).[3 7] Applying the progression-decrement from Lloyd *et al.* to the PF utilities estimated for the DB-04 NHS cohort gives PP utility values of [redacted] for TPC and [redacted] for T-DXd (see Table 4). These values have been applied in the EAG's post-DGC base case.

The company provided a table of PP utility values applied in relevant previous NICE appraisals (Company response to DGC, Table 6). In Table 5, the EAG has added PF utility values to the company's table to allow a comparison of both absolute PP values and decrements for progression. The EAG accepts that the absolute utility values obtained by applying the decrement estimated from the Lloyd *et al.* algorithm to the LMM PF utility values are lower than those applied in previous appraisals, as can be seen from Table 5. The majority of appraisals in Table 5, which did not use the trial data directly to calculate PP utility, applied a PP utility value of 0.588, which was commonly reported as being the value applied in TA423.[1 8 9] This estimate from TA423 was estimated as the midpoint between the trial-based estimate of PP utility (0.679; equivalent to a 3% decrement) which the committee considered to be implausible, and an estimate based on Lloyd *et al.* (0.496; equivalent to a 20% decrement),[1] which the committee considered to have limitations.[10] The EAG notes that those previous appraisals which used trial-based values for both pre- and post-progression utilities had smaller progression-related decrements than those that used the estimate from TA423 (see Table 5). To provide the committee with an alternative scenario to consider, the EAG has presented a scenario analysis in which the progression-related decrement has been taken to be the average of that predicted by the Lloyd *et al.* algorithm and that predicted by the LMM regression using the DB-04 NHS cohort ([redacted] = [0.243-[redacted]]/2). The EAG acknowledges that this is a fairly arbitrary midpoint between the EAG and the company's preferred base-case PP utility values.

The EAG maintained the 6-month PP utility benefit assumption in its base case, whereby patients progressing on T-DXd have higher utility values post-progression than patients progressing on TPC for

6 months, after which both patient sets assume the same utilities as the TPC arm. The EAG have also provided a scenario analysis in which there is no difference in PP utilities and the PP utility values for the TPC arm are applied to patients progressing on either TPC or T-DXd.

Overall, the EAG considers that the company's approach in their updated base case should be treated with caution because the PP utility estimates may be overestimates, given that they are based on measurements of EQ-5D close to the time of progression. However, the EAG's base case approach of applying the utility decrement for progression from Lloyd et *al.* results in absolute PP utility values that are low relative to values used in previous appraisals. Whilst neither sources are ideal, the EAG prefers its base case values because they maintain the decrement associated with progression predicted by the Lloyd et *al*. algorithm, whilst incorporating the absolute PF utility values, which the company and the EAG both agree are appropriate.

Table 4 Comparison of utility values used in the company and EAG analyses

Scenario	Sources for utility values	Progression-free (PF)		Δ between arms in PFS	Progressed disease (PD) - short-term		Δ between arms in PD short-term	Switch from short- to long-term	PD both arms long-term	Δ PF to PD For TPC
		T-DXd	TPC		T-DXd	TPC				
Company post-TE-base case	PF: GLMM regression (FAS) PD: Lloyd algorithm	[redacted]	[redacted]	[redacted]	0.6101	0.5655	0.0447	12 months	0.5655	[redacted]
Company post-TE - Table 26, scenario 6	PF: GLMM regression (FAS) PD: GLMM regression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12 months	[redacted]	[redacted]
EAG pre-TE – base case	PF: Mean by trial arm (FAS) PD = PFS-0.272; Lloyd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 months	[redacted]	0.2716
EAG post-TE – base case	PF: LMM (FAS) PD = PFS-0.243; Lloyd - age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 months	[redacted]	0.2429
Company post ACM1 – base case	PF: LMM (NHS) PP TPC: LMM (NHS) PP T-DXd: PP TPC + ΔPF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 months	[redacted]	[redacted]
Company post ACM1 – scenario analysis	PF: LMM (FAS) PP TPC: LMM (FAS) PP T-DXd: PP TPC + ΔPF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 months	[redacted]	[redacted]
EAG updated base case	PF: LMM (FAS) PD = PFS-0.243; Lloyd - age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 months	[redacted]	0.2429
EAG – scenario analysis	PF: LMM (FAS) PD = PF – (0.243-[redacted])/2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 months	[redacted]	[redacted]

Table 5 Utility values from previous relevant NICE TAs (adapted from Table 6 of company's ACD response)

NICE TA	Disease	Treatment arm	PP utility value	Source	PF utility	Source	Decrement for progression
TA423[10]	Advanced or metastatic BC	Eribulin 3L	0.588*	Average of trial based estimate of 0.679 and estimate based on Lloyd *et al.* of 0.496[1]	0.706	Trial based estimate[11]	0.118
		TPC 3L	0.588*		0.701	Trial based estimate[11]	0.113
TA862[12]	Unresectable or metastatic HER2 positive BC	T-DXd 2L	0.596	Lloyd *et al.* based on pooled characteristics across both trial arms[13]	AIC	Trial based estimate[13]	NE
		T-DM1 2L	0.596		AIC	Trial based estimate[13]	NE
TA819[14]	Triple negative unresectable or metastatic BC	SG 3L	0.653**	Trial based/ same as TA639[15]	0.710	Trial based[15]	0.057
		TPC 3L	0.569**	Trial based[15]	0.626	Trial based[15]	0.057
TA704[16]	Unresectable or metastatic HER2 positive BC	T-DXd 3L	0.588	TA423[8]	0.750 (0.704 off treatment)	TA423[8]	0.116 from off treatment to PP
		SoC 3L	0.588	TA423[8]	0.715 to 0.728	TA423;Treatment dependent[8]	0.127 - 0.140
TA786[17]	Unresectable or metastatic HER2 positive BC	Tucatinib 3L	0.698**	Trial based[9]	0.762	Trial based[9]	0.063
		Eribulin/capecitabine/ vinorelbine 3L	0.588**	TA423[9]	0.701/0.706	TA423[9]	0.113 - 0.118

**Derived mid-point value – the committee agreed that a PP utility value between 0.496 and 0.679 was appropriate;[1] **Values are for the period of time when a treatment-specific PP utility difference is assumed.*

Abbreviations: 2L, second-line; 3L, third-line; NE, not estimable; NICE, National Institute for Health and Care Excellence; PP, post-progression; SG, sacituzumab govitecan; SoC, standard of care; TA, technology appraisal; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

Issue 7: The comparison versus sacituzumab govitecan (SG)

In response to the committee's request to "*see an indirect treatment comparison (ITC) of trastuzumab deruxtecan and sacituzumab govitecan rather than a naive, unadjusted comparison*", the company presented ITC results from a simple unadjusted Bucher analysis. The results show [redacted], and the company concluded that results "*confirm that* [redacted]". The EAG agrees with the company's assessment that these results are "*highly uncertain, potentially biased, and not robust for decision-making,*" based on the difference in study populations between the DB-04 and ASCENT trials, and the small sample sizes of HER2-low/HR-negative subgroups in them.

However, the EAG disagrees with the company that based on this uncertainty, "[redacted]" because absence of evidence for clinical inequivalence does not mean that both drugs have the same clinical effectiveness. Hence, the EAG considers that the relative efficacy of T-DXd and SG remains uncertain and this issue remains unresolved.

The company included a scenario to estimate time on treatment (ToT) for the ASCENT HER2-low subgroup for SG using the ratio of median PFS in the full ASCENT population vs the HER2-low trial subgroup. This increased the ToT estimate from 6.12 months to 7.9 months. The EAG accepts the change based on the assumption that an increase in PFS is likely to be associated with an increase in ToT and included the estimated ToT in its base case.

Issue 8: Administration costs

As recommended by the CDF clinical lead, the company updated the administration costs for TDX-d and TPC agents (DGC document, paragraph 3.16). The EAG confirms the correct values are being used in the model.

4. Summary on the changes of the updated economic analysis presented by the company

Table 6 summarises the preferences of the committee, the company's updated base case model which adopts the DB-04 NHS cohort, and the EAG updated base case for the new evidence from the DB-04 NHS cohort. The company updated its survival extrapolations to reflect the OS, PFS, and TTD data observed with the DB-04 NHS cohort. Utility values were updated to reflect those predicted by the LMM model for both pre- and post-progression states for the DB-04 NHS cohort. In addition, the administration costs were updated as per the advice received from the CDF lead, and the [redacted].

For the cost-minimisation analysis (CMA) model comparing T-DXd to SG, the company updated the administration costs, [redacted], and included the approach described in Issue 7 of calculating ToT for SG based on PFS.

Table 6: Summary of committee's preferences, company's updated base case (DGC response), and the EAG updated base case

Aspect of model/issue identified in the company's comment on the DGC document	Committee at ACM1	Company's DGC response	EAG's updated base case
Removing patients randomised to 2L eribulin and gemcitabine from both arms of the DB-04 trial (i.e., the NHS cohort)	Yes	Yes	Yes, with concerns
OS extrapolations	Estimates between log-logistic and Weibull with gamma to be explored	Log-logistic for both arms	Log-logistic for TPC and modified gamma for T-DXd
PFS extrapolations	Capped generalised gamma	Log-logistic for both arms	Log-normal for TPC and modified generalised gamma for T-DXd
TTD extrapolations	Mature KM data to be explored	Generalised gamma for both arms	Generalised gamma for TPC and modified generalised gamma for T-DXd
EAG's preferred utility values for pre and post progression	See Table 4	See Table 4	See Table 4
post progression utility difference	Uncertain	6 months	6 months
Comparison of T-DXd versus SG	Preferred to see ITC results	Uncertain naïve ITC results so assume equivalence	Uncertain naïve ITC results so can't assume equivalence
Sourcing the mean time on treatment for SG from ASCENT	Yes	Only as a scenario	Yes

Abbreviations: 2L - second line; DB-04 - DESTINY-Breast04 trial; ITC - indirect treatment comparison; OS - overall survival; PFS - progression free survival; RDI - relative dose intensity; SG - sacituzumab govetecan; T-DXd - trastuzumab deruxtecan; TEAE - treatment emergent adverse events; TPC - treatment of physician's choice; TTD - time-to-treatment discontinuation

5. Methods of the EAG's exploratory analyses

Company changes adopted by the EAG

The EAG base case is updated to reflect the DB-04 NHS cohort including the log-logistic fit for modelling OS for the TPC arm, the generalised gamma fits for modelling TTD for both arms, the PF utility values, and the updated administration costs.

Exploratory analyses 1 to 4

The EAG's post-DGC base case differs from the company's post-DGC base case in four ways explored individually using the company's post-DGC base case as the starting point (see Table 7). These six changes are as follows:

- The EAG preferred the modified gamma distribution for extrapolating OS for T-DXd.
- The EAG preferred the modified generalised gamma and log-normal distributions for extrapolating PFS for T-DXd and TPC respectively.
- The EAG preferred the modified generalised gamma distribution for extrapolating TTD for T-DXd.
- The EAG has maintained its preference of using Lloyd *et al*. algorithm to estimate PP utilities.

For the CMA of T-DXd versus SG, the EAG included the ToT calculated by the company as described in Issue 7.

EAG post-DGC scenario analyses

EAG scenario analyses are then provided, in Table 7 using the EAG preferred base case as the starting point. These scenarios explore the impact of using alternative curves for OS, PFS and TTD extrapolations, using post-progression utilities midway between those estimated from the DB-04 trial and from Lloyd *et al.*, and assuming no utility benefit for T-DXd after progression.

6. Results of the EAG's exploratory analyses

The results in Table 7 show that the key driver of the difference in the ICER between the EAG's base case and the company's base case is the curve choice for OS extrapolation, as implementing this alone increases the ICER from [redacted] to [redacted] per QALY (all reported ICERs in-text are using the 1.2x QALY weight as this was considered appropriate in paragraph 3.17 of the DGC document). Estimating post-progression utilities using the Lloyd algorithm had the second largest impact increasing the ICER by ~[redacted]. The curve choices for PFS and TTD had less impact on the ICER increasing it by less than [redacted].

The scenario analyses confirmed that assuming other OS curves significantly impact the ICER. However, using different extrapolations for PFS and TTD and different utility assumptions varied the ICER in the range of ±[redacted].

For the CMA, when calculating treatment costs using the treatment-specific mean time on treatment for T-DXd from DESTINY-Breast04 and SG from ASCENT as per the calculation described under Issue 7, T-DXd is associated with a total cost of £[redacted] (compared to £[redacted] in the company's base case) and SG a total cost of £[redacted] (compared to £[redacted] in the company's base case), meaning that T-DXd is associated with a savings of £[redacted] (compared to £[redacted] in the company's base case) over a lifetime time horizon. The EAG notes that this analysis uses the list price for SG and the cost differences was re-estimated in the confidential appendix using the PAS price for SG.

Table 7: Results of the EAG's exploratory analyses with QALY weighing of 1x and 1.2x

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
Company base case (Deterministic)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 1: Assuming the modified gamma distribution for extrapolating OS for T-DXd						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 2: Assuming the modified generalised gamma distribution for extrapolating PFS for T-DXd and the log-normal for TPC						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 3: Assuming the modified generalised gamma curve for extrapolating TTD for T-DXd						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 4: Estimating post-progression utilities from the Lloyd algorithm						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-4 (Deterministic)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-4 (Probabilistic)						
TPC	[redacted]	[redacted]	-	-		

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 1 (Assuming a log-normal curve for OS extrapolations of TPC)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 2 (Assuming a log-logistic curve for PFS extrapolations of TPC)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 3 (KM data used to model TTD followed by generalised gamma fits)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 4 (using post-progression utilities midway between those estimated from the DB-04 trial and from Lloyd et al.)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 5 (Assuming no utility benefit after progression with T-DXd)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG - evidence assessment group, OS - overall survival, PD - progressed disease, PFS - progression-free survival, T-DXd – trastuzumab deruxtecan, TPC - treatment of physician's choice, TTD - time to treatment discontinuation

7. Discussion

The EAG considers that there remains significant uncertainty regarding three key issues. The first issue is the OS extrapolation for T-DXd where the company's base case assumes a persistent treatment effect for over 10 years which the EAG deemed not sensible considering that DB-04 data show treatment discontinuation and progression for almost all of the trial population after around [redacted] years.

Secondly, for utility values after progression the company opted to the LMM model to derive trial-based utilities; an approach that deemed previously unreasonable by the company. The EAG does not think that trial-based PP utility estimates are reliable and prefers to maintain their approach of applying the progression decrement from Lloyd *et al.* to the PF utilities.

The third key issue was the CMA of T-DXd versus SG where the company conducted a naïve ITC analysis that showed highly uncertain and inconclusive results. The EAG believes there is no evidence available to support clinical equivalence between T-DXd and SG, hence the EAG still interprets the results from the CMA with caution.

The probabilistic ICER based on the EAG's preferred data and assumptions is [redacted] with a 1.2x QALY weight. However, as was shown in the scenario analyses the EAG's base case ICER can range between [redacted] when a log-logistic curve is used for PFS extrapolations of TPC, and [redacted] when a log-normal curve is assumed for extrapolating OS for TPC.

8. References

1. Daiichi Sankyo Inc. Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]. Draft guidance comment form. (Company response), 2023.
2. Metry A, Davis S, Carroll C, et al. Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]. A Single Technology Appraisal. London, UK, 2023.
3. Metry A, Davis S, Carroll C, et al. Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]. A Single Technology Appraisal. Addendum: EAG comments of the company's technical engagement response. London, UK: National Institute for Health and Care Excellence,, 2023.
4. National Institute for Health and Care Excellence. Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935]. Draft Guidance Consultation document. London, UK: National Institute for Health and Care Excellence,, 2023.
5. Burnham KP, Anderson DR, Huyvaert KP. AIC model selection and multimodel inference in behavioral ecology: some background, observations, and comparisons. *Behav Ecol Sociobiol* 2011;65:23-35. doi: https://doi.org/10.1007/s00265-010-1029-6
6. Daiichi Sankyo Inc. Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy. Company response to technical engagement, 2023.

7. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. *Br J Cancer* 2006;95(6):683-90. doi: 10.1038/sj.bjc.6603326
8. Daiichi Sankyo Inc. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]: Company submission. London, UK: National Institute for Health and Care Excellence,, 2020.
9. Scott et al. Tucatinib with trastuzumab and capecitabine for treating HER2-positive unresectable locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies. ERG report. London, UK: National Institute for Health and Care Excellence,, 2021.
10. National Institute for Health and Care Excellence. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens [TA423], 2016.
11. Eisai. Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]: Company submission. London, UK: National Institute for Health and Care Excellence,, 2016.
12. National Institute for Health and Care Excellence. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 therapies [TA862]. London, UK: National Institute for Health and Care Excellence,, 2023.
13. Daiichi Sankyo Inc. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909] Company submission. London, UK: National Institute for Health and Care Excellence,, 2022.
14. National Institute for Health and Care Excellence. Sacituzumab govitecan for treating unresectable triple-negative advanced breast cancer after 2 or more therapies [TA819]. London, UK: National Institute for Health and Care Excellence,, 2022.
15. Gilead. ID3942: Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after two or more therapies: Company Submission London, UK: National Institute for Health and Care Excellence, , 2021.
16. National Institute for Health and Care Excellence. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [TA704]. London, UK: National Institute for Health and Care Excellence,, 2021.
17. National institute for Health and Care Excellence. Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [TA786]. London, UK: National Institute for Health and Care Excellence,, 2022.