NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using trastuzumab deruxtecan in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation 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 recommendations sound and a suitable basis for guidance 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?

Issue date: September 2023

Note that this document is not NICE's final guidance on trastuzumab deruxtecan. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using trastuzumab deruxtecan in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 17 October 2023.
- Second evaluation committee meeting: 7 November 2023.
- Details of the evaluation committee are given in section 4.

1 Recommendations

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.

1.2 This recommendation is not intended to affect treatment with trastuzumab deruxtecan that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

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. They are offered treatments for HER2-negative cancer. Which type of treatment may depend on whether their cancer is hormone-receptor negative or positive. Trastuzumab deruxtecan is the first licensed treatment for HER2-low metastatic or unresectable breast cancer, and it specifically targets HER2.

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.

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.

2 Information about trastuzumab deruxtecan

Marketing authorisation indication

2.1 Trastuzumab deruxtecan (Enhertu, Daiichi Sankyo) is indicated for 'the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for trastuzumab deruxtecan.

Price

2.3 The list price of trastuzumab deruxtecan is £1,455 per 1 vial containing 100 mg powder for concentrate for solution for infusion (excluding VAT; BNF online accessed September 2023).

2.4 The company has a commercial arrangement. This makes trastuzumab deruxtecan available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Daiichi Sankyo, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

HER2-low classification

3.1 Some breast cancer cells have a protein called human epidermal growth factor receptor 2 (HER2) on their surface, which stimulates them to grow. An immunohistochemistry test (IHC) determines the presence of this protein. If the IHC score is more than 3, the tumour is HER2-positive. An IHC score lower than 3 was previously considered to be HER2-negative. But more detailed testing of tumours with an IHC score of 2 using fluorescence in situ hybridisation (FISH), have further classified HER2-negative cells as either HER2-low or HER2-negative. HER2-low includes cells that have an IHC score of 1 or an IHC score of 2 plus a negative FISH test. HER2-negative cells have an IHC score of 0. The committee acknowledged that HER2-low is a subgroup of the previously classified HER2-negative group.

Effects on quality of life

3.2 The patient organisation submissions emphasised that metastatic breast cancer can affect all aspects of a person's life: physical, psychological, social and financial. They emphasised that there can be considerable anxiety, fear and uncertainty because treatments only delay disease progression. Moreover, they explained that the change in categorisation had led to uncertainty about treatment options based on HER2 status. The patient experts highlighted that disease classification may also change from HER2-positive to HER2-negative. There are more treatment options for HER2-positive cancer. They explained that having targeted, individualised, tolerable treatments that can extend and improve quality of life are important to people with the condition. The committee concluded that metastatic or unresectable 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.

Clinical management

Treatment pathway

3.3 HER2-low breast cancer is managed with treatments for HER2-negative breast cancer. For metastatic or unresectable breast cancer after chemotherapy, available options also depend on hormone-receptor status. Hormone-receptor positive cancer cells can have either oestrogen or progesterone receptors or both. Hormone-receptor negative cancer cells do not have either receptors. For metastatic breast cancer regardless of hormone-receptor status, NICE recommends:

- anthracyclines or docetaxel at first line (see NICE's guideline on advanced breast cancer)
- gemcitabine plus paclitaxel at first line (see NICE's technology appraisal guidance on gemcitabine)
- offering vinorelbine or capecitabine at second line, and at third line, offering whichever of these was not used at second line (see NICE's guideline on advanced breast cancer)
- eribulin at third line (see NICE's technology appraisal guidance on eribulin).

For triple negative metastatic breast cancer, that is, cancer that is both HER2 and hormone-receptor negative, NICE recommends:

- atezolizumab plus nab-paclitaxel at first line but only for tumours expressing PD-L1 (see NICE's technology appraisal guidance on atezolizumab with nab-paclitaxel)
- pembrolizumab plus paclitaxel or nab-paclitaxel at first line but only for tumours expressing PD-L1 (see NICE's technology appraisal guidance on pembrolizumab plus chemotherapy)
- sacituzumab govitecan after 2 or more systemic therapies, either at second or third line (see NICE's technology appraisal guidance on sacituzumab govitecan).

The committee concluded that because HER2-low is a subgroup of what was previously classified as HER2-negative cancer, treatment options

used to manage HER2-negative metastatic breast cancer after chemotherapy are relevant to this appraisal.

Positioning of trastuzumab deruxtecan

3.4 Trastuzumab deruxtecan is the first licensed treatment option for people with HER2-low metastatic or unresectable breast cancer. 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 clinical experts explained that trastuzumab deruxtecan is a first-line targeted treatment that may mean a person does not have to have chemotherapy. They agreed with the company, explaining that clinicians and people with breast cancer would like the flexibility to use trastuzumab deruxtecan at different points in the treatment pathway. 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.

Clinical effectiveness

Data sources and generalisability

3.5 The main evidence for trastuzumab deruxtecan is from DESTINY-Breast04, an international, multicentre (7 UK centres), randomised, open-label trial comparing trastuzumab deruxtecan with 'treatment of physician choice' (TPC; see section 3.6). People in the trial had HER2-low metastatic or unresectable breast cancer and previously had at least 1, and a maximum of 2, lines of chemotherapy in the metastatic setting or after recurrence. Everyone had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0

or 1. Of the 557 people included, 89% had hormone-receptor positive breast cancer, while 11% had hormone-receptor negative breast cancer. The EAG considered that the trial population was unlikely to be representative of the people in NHS clinical practice who would have trastuzumab deruxtecan. This was because they were younger and there was a higher proportion of people with Asian ethnicity than would be expected in NHS practice. Also, the trial did not include people with an ECOG PS score of 2. The EAG noted that some of these characteristics may be treatment effect modifiers. The clinical experts explained that trastuzumab deruxtecan is standard care for people with HER2-positive metastatic breast cancer. 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.

Composition of TPC

3.6 The comparator arm in DESTINY-Breast04, TPC, included 184 people. Of these people, 52% had eribulin, 21% had capecitabine, 10% had nab-paclitaxel, 9% had gemcitabine and 8% had paclitaxel. The EAG considered that the TPC arm in the trial may not reflect NHS clinical practice. In particular, gemcitabine is not used alone and eribulin is only recommended by NICE at third line, not second line. Also, the TPC arm did not include anthracyclines and carboplatin, which can be used at second line. It also did not include sacituzumab govitecan, which can be used at second or third line for hormone-receptor negative breast cancer. 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. They noted that anthracyclines are usually used early in the treatment pathway. In the metastatic setting, they would be used at first line. They explained that

carboplatin may be used for triple-negative breast cancer. The company explained that the DESTINY-Breast04 trial started about 1 year after the ASCENT trial for sacituzumab govitecan. Because of this overlap, sacituzumab govitecan was not standard care and did not appear in the TPC group for DESTINY-Breast04. 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.

Effects on survival

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. Similar trends were seen for the hormone-receptor negative subgroup, although the hazard ratios were not statistically significant because of its small sample size (n=58). 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.

Economic model

Company's model for trastuzumab deruxtecan compared with TPC

3.8 To compare trastuzumab deruxtecan with TPC in people with HER2-low metastatic or unresectable breast cancer, the company used a partitioned survival model that had 3 health states (progression-free, post-progression and death), a 3-week model cycle and a 30-year time horizon. Everyone enters the model in the progression-free state and starts treatment. Trial-based progression-free and overall survival curves

inform the proportion of people in the progression-free and death states. All remaining people are in the post-progression state. During each model cycle, people in the progression-free state can be on-treatment or off-treatment depending on whether they stopped treatment for reasons such as side effects. The proportion of people in the progression-free state who are on treatment is estimated from the trial-based time-to-treatment stopping curve. The committee concluded that the company's partitioned survival model structure is appropriate for decision making.

Modelling TPC

3.9 In the company's base case, the clinical effectiveness of the comparator was informed by the observed progression-free and overall survival data from the TPC arm in DESTINY-Breast04 (see section 3.6). The company assumed that all treatments were similarly clinically effective. The comparator costs were based on the observed distribution of treatments in the TPC arm of the trial. To address the EAG's concern about the generalisability of the TPC arm to NHS clinical practice, the company did an exploratory post-hoc analysis. It removed both efficacy and costs related to second-line eribulin and gemcitabine, but it kept efficacy and costs related to third-line eribulin. Because the decision about TPC treatments happened before randomisation, the company also removed people in the trastuzumab deruxtecan arm who would have had second-line eribulin or gemcitabine had they been randomised to TPC. Across both groups, the number of people decreased by more than 30%. The EAG had concerns that the company had not provided detailed analyses on which survival distributions should be applied using this truncated data set. Also, it had concerns about the smaller sample size. The EAG highlighted that keeping those who had eribulin at third line meant people were more likely to have had multiple lines of treatments before. It questioned whether this analysis was generalisable to the NHS, in which people will likely have trastuzumab deruxtecan at second line. In the EAG's base case, it removed all eribulin and gemcitabine costs and assumed that TPC efficacy was the same as in the trial. The EAG's TPC

arm included 54% capecitabine, 25% nab-paclitaxel and 21% paclitaxel. The committee considered that TPC should be modelled to reflect NHS clinical practice and should exclude second-line eribulin and gemcitabine. But it had concerns that the company's post-hoc analysis did not provide evidence for choosing survival distribution using the truncated data set. The committee recalled the clinical experts' comments that eribulin is the most clinically-effective option in the TPC arm (see section 3.6). It had concerns about the assumption of similar clinical efficacy in the company's and EAG's base case. The committee concluded that it preferred the EAG's base case for decision making. It 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.

Overall survival extrapolation

3.10 The company fitted parametric survival distributions (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma) to Kaplan-Meier data from DESTINY-Breast04 to model overall survival. In the company's base case, it preferred the log-logistic distribution because of its statistical and visual fit. The company considered that it provided clinically plausible, conservative, long-term estimates that were similar to those observed in the trial's TPC arm and in other real-world sources. The EAG considered that the log-logistic distribution overestimated overall survival. It preferred the Weibull distribution based on statistical and visual fit, and clinical plausibility of survival at 10 years. But it acknowledged that estimates using the Weibull distribution may be conservative. It considered that an exploration of the gamma distribution may provide an estimate between the log-logistic and Weibull. 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. The committee considered the log-logistic to be optimistic and the Weibull likely to be too conservative. It concluded that estimates are likely to be between the log-logistic and Weibull distributions. It further

concluded that it would like to see an exploration of the gamma distribution.

Progression-free survival extrapolation

3.11 The company fitted parametric survival distributions (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma) to Kaplan-Meier data from DESTINY-Breast04 to model progression-free survival. The company preferred the log-logistic distribution based on the statistical and visual fit and to be consistent with its overall survival distribution. The EAG considered that the log-logistic distribution overestimated the tail of the trastuzumab deruxtecan arm and preferred the generalised gamma. It acknowledged that the trastuzumab deruxtecan and TPC curves cross at 5 years when using the generalised gamma, and placed a cap on the fitted curves at the point of crossing. The clinical experts could not provide a view on which curves provided more plausible estimates. 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.

Time-to-treatment stopping extrapolation

3.12 The company fitted parametric survival distributions (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma) to Kaplan-Meier data from DESTINY-Breast04 to model time-to-treatment stopping. The company preferred the generalised gamma distribution because it provided a good statistical fit for both the trastuzumab deruxtecan and TPC arms. It also provided estimates that were in the middle of the range of all distributions. The EAG considered that the estimates using the generalised gamma were lower compared with the observed data from the trial for the TPC arm. It 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. But it noted that the company had not provided such analyses. The EAG provided scenarios

where the restricted mean treatment duration approach was used as the lower limit and the log-logistic time-to-treatment stopping extrapolation used as the upper limit. It noted that these scenarios had a large effect on the cost-effectiveness estimates. While the EAG considered the time-to-treatment stopping extrapolation to be uncertain, it used the company's generalised gamma distribution in its base case. The committee considered that there is uncertainty about the most appropriate way to model time-to-treatment stopping. It would like to see an exploration of the EAG's suggested analysis, that is, using the mature Kaplan-Meier data to directly estimate treatment stopping in the model.

Utility values

Progression-free utilities

3.13 The company's base case used EQ-5D-5L data from DESTINY-Breast04 mapped to EQ-5D-3L and a generalised linear mixed effect model to estimate progression-free utility values by treatment arms. The EAG considered that the utilities lacked face validity because they were higher than the general population value used in the severity modifier calculation. They were also high compared with utilities used in NICE's technology appraisal guidance on trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer. The EAG preferred to use progression-free utilities by treatment arms estimated from a linear mixed effect model, which the company provided in its technical engagement response. The clinical experts could not provide a view on the plausibility of the utility values. 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.

Post-progression utilities

3.14 In the company's base case, it did not use EQ-5D-5L trial data to estimate utilities for the post-progression state. This was because the utilities were high compared with previously accepted utilities for progressed disease in people with metastatic breast cancer in other NICE appraisals. The company used an algorithm published by Lloyd et al. (2006) to estimate the expected post-progression utility. It also assumed that the post-progression utility was higher in the trastuzumab deruxtecan arm than in the TPC arm because of higher treatment response rates. This difference lasted for 12 months, after which everyone adopted the utility value for TPC post-progression. The EAG disagreed with how the company estimated utilities using the Lloyd algorithm, by using treatment response to calculate post-progression disutility. This is because the algorithm was not developed to be able to to predict post-progression utility by inputting pre-progression response. The EAG preferred to estimate treatment-specific post-progression utilities by applying the utility decrement from the Lloyd algorithm for progressed disease adjusted for mean cohort age (0.243) to the trial progression-free utilities. It assumed that the difference in post-progression utilities between arms would last for 6 months, after which everyone adopts the TPC utility. The committee preferred the EAG's approach in calculating post-progression utilities using the Lloyd algorithm. But it had concerns about the assumption of a differential benefit after progression depending on treatment arm. 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 uncertainty about the assumption of a differential effect in post-progression utilities. It would like to see an analysis assuming no differential effect.

Costs

Vial sharing

3.15 The company assumed that vial sharing would lead to no wastage in 75% of administrations of intravenous treatments for both trastuzumab deruxtecan and TPC. This is because the HER2-low subgroup is much larger than the HER2-positive subgroup, for which trastuzumab deruxtecan is recommended with managed access. So, there would be an increased opportunity for vial sharing. The EAG considered that the company had provided no evidence to support its 75% estimate and preferred to use the 50% estimate assumed in NICE's technology appraisal guidance on trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer. 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.

Administrative costs

3.16 In the company's base case, it assumed that the cost per administration of all intravenous treatments was sourced from the National Schedule of NHS Costs 2020/21, Healthcare Resource Group (HRG) code SB12Z: deliver simple parenteral chemotherapy. For the first cycle, the day-case cost was applied. For all subsequent cycles, the outpatient cost was applied. The Cancer Drugs Fund clinical lead considered that the following costs would be more appropriate:

- £362 for all cycles of trastuzumab deruxtecan (HRG code SB12Z: simple parenteral at first attendance of each cycle)
- £245 per cycle for capecitabine (HRG code SB11Z: oral chemotherapy)
- £362 for day 1 and £471 for day 8 per cycle for eribulin and sacituzumab govitecan (HRG codes SB12Z: simple parenteral at first attendance of each cycle and SB15Z: subsequent elements of a chemotherapy cycle).

The Cancer Drugs Fund clinical lead noted that medical supervision usually happens at a different time to chemotherapy delivery. So, 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. The committee concluded that the administration costs of the treatments should be corrected in the model.

Severity

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). The committee may apply a greater weight to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity (a severity modifier). The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The EAG also provided QALY shortfall estimates. 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.

Company's exploratory analysis with sacituzumab govitecan

Cost-minimisation analysis

3.18 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. The cost-minimisation analysis implicitly assumed equivalent clinical effectiveness on all outcomes (progression-free and overall survival, time-to-treatment stopping and adverse events). To justify its assumption of equivalent clinical effectiveness, the company provided a naive, unadjusted comparison of the hazard ratios for progression-free and overall survival for trastuzumab deruxtecan and TPC from the DESTINY-Breast04 trial and sacituzumab govitecan and TPC from the ASCENT trial. It explained that an indirect treatment comparison was not possible because of:

- differences in trial populations between DESTINY-Breast04 and ASCENT
- the small number of people in the hormone-receptor negative subgroup in DESTINY-Breast04
- the post-hoc nature of the analyses from both trials of HER2-low and hormone-receptor negative subgroup
- limited data reporting in the ASCENT trial.

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. The clinical experts explained that both trastuzumab deruxtecan and sacituzumab govitecan each have their own benefit. They explained that they would prefer to use trastuzumab deruxtecan and sacituzumab govitecan sequentially in clinical practice. But the NICE technical team explained that the company's model had not been set up this way. The clinical experts also noted that the trial populations for DESTINY-Breast04 and ASCENT were different in terms of line in the treatment pathway. In general, they noted that chemotherapy treatments have not been compared with each other. The committee considered that the comparison of trastuzumab deruxtecan with sacituzumab govitecan is highly uncertain. It acknowledged the company's reasons for difficulty in providing a more robust comparison. But it would like to see an indirect treatment comparison of trastuzumab deruxtecan and sacituzumab govitecan rather than a naive, unadjusted comparison.

Data sources for costs

3.19 In the EAG's base case, to estimate treatment-related costs, it used:

- the DESTINY-Breast04 trial for the average weight of people in the hormone-receptor negative subgroup

- NICE's technology appraisal guidance on sacituzumab govitecan for relative dose intensity estimates, and time-on-treatment for sacituzumab govitecan from the ASCENT trial.

The company agreed with the EAG's base case except for the use of time-on-treatment data from NICE's guidance on sacituzumab govitecan. It also considered that using the proportion of grade 3 or above treatment-emergent adverse events from DESTINY-Breast04 for trastuzumab deruxtecan and from ASCENT for sacituzumab govitecan is more appropriate. The company preferred this approach because time on treatment may affect various clinical factors, including toxicity and efficacy, and the populations are different for DESTINY-Breast04 and ASCENT. The committee considered that the EAG's base case using time on treatment best reflects treatment-related costs. But given the uncertainty, it preferred to see a scenario in which the company applied grade 3 or above treatment-emergent adverse events.

Cost-effectiveness estimates

Committee's preferred assumptions

3.20 The committee's preferred assumptions for the cost-effectiveness modelling of trastuzumab deruxtecan compared with TPC were for the model to use the:

- log-logistic and Weibull distributions to assume that the overall survival extrapolated estimates lie between the estimates (see section 3.10)
- EAG's approach to extrapolating progression-free survival using the generalised gamma capped at the point of crossing (see section 3.11)
- EAG's estimates for progression-free utilities (see section 3.13)
- company's assumption of 75% vial sharing (see section 3.15)
- corrected administration costs for all treatments (see section 3.16).

The committee considered that none of the analyses reflected their preferred assumptions.

Uncertainties in the model

3.21 NICE's manual on health technology evaluation notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the high level of uncertainty, specifically around the following issues:

- modelling TPC (see section 3.9)
- overall survival extrapolation (see section 3.10)
- time-to-treatment stopping extrapolation (see section 3.12)
- post-progression utilities modelling (see section 3.14)
- comparison of trastuzumab deruxtecan and sacituzumab govitecan for the hormone-receptor negative subgroup (see sections 3.18 and 3.19).

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).

Further analyses

3.22 The committee recalled the uncertainties in the evidence base and in the company's modelling assumptions (see section 3.21). 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:

- Justification for survival extrapolation of the TPC arm in the truncated dataset of the company's exploratory post-hoc analysis (see section 3.9).

- Overall survival extrapolation using the gamma distribution (see section 3.10).
- Time-to-treatment stopping using the EAG's suggested approach of applying Kaplan-Meier data directly to estimate treatment stopping in the model and limit parametric extrapolations to the time period beyond this (see section 3.12).
- Justification for a differential post-progression utility benefit and a scenario assuming no differential benefit between arms (see section 3.14).
- Further analyses to show the clinical effectiveness of trastuzumab deruxtecan compared with sacituzumab govitecan for the hormone receptor-negative subgroup (see section 3.18).

Other factors

Equality

3.23 The committee did not identify any equality issues.

Innovation

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.

Conclusion

Recommendation

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.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Radha Todd

Chair, technology appraisal committee A

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Sharlene Ting

Technical lead

Claire Hawksworth

Technical adviser

Thomas Feist

Project manager

ISBN: [to be added at publication]