NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

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 depends on whether the cancer is hormone-receptor negative or positive. Sacituzumab govitecan is a possible treatment for triple-negative breast cancer. 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. Because of a lack of evidence, it is not possible to reliably compare trastuzumab deruxtecan with sacituzumab govitecan.

Despite accounting for the condition's severity, by applying a severity modifier, and accounting for innovation and uncaptured benefits, the most likely cost-effectiveness estimate are above the upper end of 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 June 2024).

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.

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. Trastuzumab deruxtecan binds to HER2 expressed on these cells. The HER2 status of breast cancer is defined by immunohistochemistry (IHC) testing to determine the presence of HER2 protein and in situ hybridisation (ISH) to detect HER2 gene amplification. Breast cancer has traditionally been categorised as HER2-positive (tumours scoring 3+ or 2+ by IHC and ISH-positive for gene amplification) or HER2-negative (tumours scoring 2+ by IHC and ISH-negative, or tumours scoring 1+ or 0 by IHC). But because some HER2-negative breast cancers do express HER2 protein, those with an IHC score of 1+ or 2+ are now categorised as HER2-low. 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. 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 over time. There are more treatment options for HER2-positive cancer, including trastuzumab deruxtecan

which is recommended by NICE for use with managed access. They explained that having targeted, individualised, tolerable treatments that can extend and improve quality of life is important to people with the condition. Stakeholders commented on the draft guidance that many people with the condition are of working age and are carers for young children and older relatives. They also noted that the condition mostly affects women. 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 for HER2-low metastatic or unresectable breast cancer. The company positioned it as a second- or third-line option, after chemotherapy in the metastatic setting or after recurrence during or within 6 months of completing adjuvant chemotherapy. This is for both hormone-receptor positive and negative breast cancer. The clinical experts explained that trastuzumab deruxtecan is a targeted treatment that may delay the need for subsequent chemotherapy. They agreed with the company, explaining that healthcare professionals and people with breast cancer would like the flexibility to have trastuzumab deruxtecan at different points in the treatment pathway. They suggested that they may prefer to use it after sacituzumab govitecan in people with triple-negative breast cancer. 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 (see section 3.2). The committee concluded that there is an unmet need for targeted treatments for HER2-negative and HER2-low breast cancer. It concluded that positioning trastuzumab deruxtecan at second and third line 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, and 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 clinical experts 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. The committee also concluded that the trial evidence was suitable for decision making.

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 clinical trial for sacituzumab govitecan (ASCENT). 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. 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. 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 committee's concern about the generalisability of the TPC arm to NHS clinical practice (see section 3.6), the company's revised base case at the second committee meeting used a cohort of the full DESTINY-Breast04 population (from here called the DB04 cohort). In the DB04 cohort, both efficacy and costs related to second-line eribulin and gemcitabine were removed from the modelling. 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. Efficacy and costs related to third-line eribulin were kept in both arms to reflect eribulin use in NHS clinical practice. Across both groups, the number of people decreased by more than 30% (247 people had trastuzumab deruxtecan, 118 had TPC). The EAG noted the smaller sample size of the company's DB04 cohort. Also, it highlighted that more people were likely to have had 2 or more lines of chemotherapy in the DB04 cohort compared with the full DESTINY-Breast04 population. The clinical experts considered that the treatments used for the DB04 cohort represented the treatments used in the NHS. But there was a larger proportion of later-line use of these in the cohort than might be seen in clinical

practice. The company provided updated analyses on which survival distributions should be applied to the DB04 cohort (see sections 3.10 to 3.12) and updated the associated utility data (see section 3.13 and section 3.14). The EAG agreed with using the DB04 cohort population and applied it in its base case and associated analyses. The committee concluded that the company's updated approach to modelling TPC was suitable for decision making.

Overall survival extrapolation

3.10 The company provided a log-cumulative hazard plot of overall survival in the DB04 cohort. It noted that this showed there was no clear evidence to support an assumption of proportional hazards between the trial arms (the curves were not parallel over time). Also, that standard parametric survival distributions could be fitted to Kaplan–Meier data from the DB04 cohort to model overall survival. In the company's updated base case, it preferred the log-logistic distribution because it had better statistical and visual fit for both treatment arms. The company noted this provided clinically plausible long-term estimates that were aligned with clinical opinion and similar to those observed in the real-world Flatiron study. This observational study included people with HER2-low metastatic breast cancer who had standard care and had 1 or 2 prior lines of chemotherapy. The company considered that the proportion of people alive in the Flatiron cohort at 5 years supported its selection of the log-logistic distribution in its updated base case. The EAG agreed and used the log-logistic distribution for the TPC arm in its preferred base case. But it considered that the size of the treatment effect for trastuzumab deruxtecan after 5 years predicted by the log-logistic distribution was uncertain and unsupported. So, the EAG explored using different survival distributions for the trastuzumab deruxtecan arm. It noted that the log-logistic or log-normal distribution predicted a survival benefit for trastuzumab deruxtecan that lasted for more than 10 years (the hazard ratio compared with TPC remains below 1). The EAG considered this clinically implausible because almost all people in the trastuzumab deruxtecan arm stopped treatment and had disease progression years earlier. It noted that the gamma fit for trastuzumab deruxtecan had a 5-year overall survival estimate between the log-logistic and the more pessimistic Weibull distribution. But the EAG noted that when it combined the log-logistic for TPC with the gamma for trastuzumab deruxtecan, the risk of death becomes higher for trastuzumab deruxtecan than TPC after 3.5 years,

which it considered implausible. So, the EAG capped the gamma fit so that the risk of death for those on trastuzumab deruxtecan stays equal or below that in the TPC arm. The company suggested that the overall survival predicted by the gamma fit for trastuzumab deruxtecan was only slightly higher than the Flatiron estimates for standard care. The EAG added that the Flatiron estimates were lower than that observed in the TPC arm in the DB04 cohort (year 1 and 2), but generally higher than predicted in the TPC arm extrapolations from 3 years onwards. The clinical experts considered it was difficult to provide a view on which curves gave more plausible survival estimates, particularly for 10 years. This is because they see very few people with this condition still alive at this point, so there is limited available data. They suggested that estimates for the 2 treatment arms that are closest to the real-world Flatiron study should be used. But the EAG explained that the Flatiron estimates were for standard care only, not for trastuzumab deruxtecan. The clinical experts had concerns about selecting different distributions for the 2 arms. The EAG noted the company showed that the proportional hazards assumption did not hold. So, it is acceptable to explore independent distributions for the 2 treatments because they are expected to have different hazard (risk of death) profiles over time. The committee considered that the company's approach to extrapolate the trastuzumab deruxtecan arm was too optimistic and uncertain. The company extrapolating both arms with the log-logistic assumed a survival benefit lasting more than 10 years. The committee considered this clinically implausible because almost all people had stopped trastuzumab deruxtecan and had disease progression a long time before this. The committee also considered that the gamma distribution selected by the EAG for extrapolating trastuzumab deruxtecan had some limitations. But, the committee thought that the resulting 5 year survival estimate likely more realistic than the estimate from the log-logistic distribution. So overall, the committee preferred the EAG's approach of using log-logistic for TPC and a modified gamma distribution for trastuzumab deruxtecan.

Progression-free survival extrapolation

3.11 The company provided a log-cumulative hazard plot of progression-free survival in the DB04 cohort. It noted that this showed there was no clear evidence of a constant hazard of progression. So, it considered that it was not appropriate to assume proportional hazards between the trial arms. It fitted parametric survival

distributions to Kaplan–Meier data from the DB04 cohort to model progression-free survival. It considered both the generalised gamma and log-logistic curves gave similar 1- to 2-year progression-free survival estimates to the observed data in DB04. But when using the generalised gamma for both arms the curves crossed before 3 years, which the company considered clinically implausible. Based on this, and statistical and visual fit, the company selected the log-logistic distribution for both the trastuzumab deruxtecan and TPC arms in its updated base case. The EAG preferred the log-normal distribution for the TPC arm, based on it having the best statistical fit scores and good visual fit. The EAG noted that exploring different distributions for the 2 arms was appropriate because the assumption of proportional hazards was not held. For the trastuzumab deruxtecan arm it noted that the log-logistic and log-normal distributions overestimated progression-free survival beyond the observed data, and the Weibull and Gompertz fits underestimated it. So, the EAG preferred to use the generalised gamma for trastuzumab deruxtecan in its base case. It noted that this distribution provided an estimate of 2-year progression-free survival that was closer to the observed data for trastuzumab deruxtecan than the company's log-logistic. The EAG noted that the log-logistic predicts a progression-free benefit for trastuzumab deruxtecan that lasts for more than 10 years. It considered this clinically implausible because almost all people in the trastuzumab deruxtecan arm stopped treatment and had disease progression years earlier. The EAG noted that when it combined log-normal for TPC with generalised gamma for trastuzumab deruxtecan, the risk of progression becomes higher for trastuzumab deruxtecan than TPC after 2 years, which is implausible. So, it preferred to cap the generalised gamma fit for trastuzumab deruxtecan so that the risk of progression stays equal to or below that in the TPC arm. The clinical experts could not provide a view on which curves provided more plausible estimates. The committee considered that the EAG's use of the generalised gamma provided closer estimates to the observed trial data for the trastuzumab deruxtecan arm. It concluded it preferred the EAG's approach of using log-normal for TPC and a modified generalised gamma for trastuzumab deruxtecan.

Time-to-treatment stopping extrapolation

3.12 The company provided a log-cumulative hazard plot of time-to-treatment stopping in the DB04 cohort. It noted that there was no clear evidence or strong

clinical rationale for the proportional hazards assumption to hold. It fitted parametric survival distributions to Kaplan–Meier data from the DB04 cohort to model time-to-treatment stopping. The company preferred the generalised gamma distribution because it provided a good statistical and visual fit for both treatment arms, and clinically plausible long-term estimates. Taking account of the long-term predictions, the EAG considered that the generalised gamma distribution was reasonable for the TPC arm and used this in its preferred base case. But it noted that with generalised gamma for both arms, the risk of treatment stopping becomes higher for trastuzumab deruxtecan than TPC after 42 months. The EAG considered this clinically implausible because in the trial, people having TPC stopped and had disease progression earlier than those having trastuzumab deruxtecan. So, the EAG preferred to cap the generalised gamma fit for trastuzumab deruxtecan so that the risk of stopping treatment stays equal to or below that in the TPC arm. It noted that this had minimal impact because very few people were still having trastuzumab deruxtecan at 42 months. Because of clinical plausibility, the committee concluded that it preferred the EAG's approach of using generalised gamma for TPC and a modified generalised gamma distribution for trastuzumab deruxtecan.

Utility values

Progression-free utilities

3.13 The company updated its approach to calculating progression-free utilities after consultation on the draft guidance. These were based on the EQ-5D-5L trial data mapped to EQ-5D-3L. The company used the linear mixed-effects model approach preferred by the EAG. Both the company and the EAG used the same utility value estimates and these were updated for the DB04 cohort. The estimates are considered confidential so cannot be reported here. The clinical experts considered that the updated utility values were plausible. The committee concluded that the company and EAG estimates for progression-free utilities were suitable for use in the modelling.

Post-progression utilities

3.14 In the company's original 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. But, in the company's updated base case for the DB04 cohort, it did use trial-based data in a linear mixed-effects model to estimate post-progression utility values by treatment arm. It noted that this is consistent with the method it used to estimate progression-free utilities (see section 3.13). The EAG considered that the trial-based estimates were uncertain because most of the post-progression EQ-5D data was collected within 3 months of progression. It noted that many of the observations of post-progression utility were for people still having treatment, with relatively few observations occurring between progression and death. So, these estimates may not properly represent the average utility across the whole post-progression period. The EAG did not change its preferred approach after consultation except to use the DB04 cohort. It estimated treatment-specific post-progression utilities by applying the utility decrement from the Lloyd algorithm for progressed disease, adjusted for mean cohort age, to the trial-based progression-free utilities (see section 3.13). The EAG preferred this approach for its base case but noted that the resulting post-progression utility values for the DB04 cohort were low compared with those accepted in previous technology appraisals. So, it explored a scenario where the post-progression utilities were midpoint values of those assumed in the EAG and updated company base cases. The committee considered the differing approach of the company and EAG used to calculate post-progression utilities. The utility value estimates are considered confidential so cannot be reported here. It noted that in the company's updated approach, the values were high but were within the range of those accepted in previous technology appraisals in advanced or metastatic breast cancer. It added that the company's updated values were closer than the EAG's to the post-progression utility values accepted for sacituzumab govitecan, which it considered may offer similar quality of life benefits to trastuzumab deruxtecan. The committee concluded that the company's updated post-progression utility values were high but were within an acceptable range.

Post-progression utility benefit

3.15 Higher treatment response rates were seen with trastuzumab deruxtecan compared with TPC in the trial, so the utility values post-progression were also assumed to be higher in the trastuzumab deruxtecan arm. Originally the company had assumed this difference lasted for 12 months, after which everyone adopted the utility value for TPC post-progression. Without a strong justification from the company for the assumption of a 12-month benefit, the EAG preferred to assume this benefit lasted for 6 months because this was accepted previously for sacituzumab govitecan (see NICE's technology appraisal guidance on sacituzumab govitecan). Stakeholders commented on the draft guidance that it is reasonable to assume some utility benefit after progression on an effective treatment. The clinical experts noted that it is difficult to establish in a trial what the duration of utility benefit might be because another treatment is usually started after progression. 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 then likely be more fit to have subsequent lines of treatment after progression. In its response to the draft guidance consultation the company updated the duration of post-progression utility benefit to 6 months, which aligned with the EAG's position. The committee considered that there was uncertainty about the assumption of a differential effect in post-progression utilities. It noted that a 6-month benefit was accepted previously for sacituzumab govitecan. It concluded that it was reasonable to assume that the utility benefit for trastuzumab deruxtecan lasted 6 months.

Costs

Vial sharing

3.16 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 Cancer Drugs Fund clinical lead agreed with the company's estimate of 75% given the size of the HER2-low population. The EAG updated its base case after consultation to assume no wastage in 75% of administrations of trastuzumab deruxtecan and TPC. The committee agreed with this approach.

Administration costs

3.17 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 different cost codes should apply to the different treatments. He provided revised costs for these from the NHS England 2023-25 NHS Payment Scheme, which led to small reductions in the administration costs per treatment cycle. In addition, a medical review cost of £144 was needed for people on chemotherapy. The committee concluded that the revised costs were suitable for use in its decision making. The company and EAG updated these costs after the committee meeting so that the decision-making incremental cost-effectiveness ratios (ICERs) included them.

Severity

3.18 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 absolute and proportional QALY shortfall estimates. Both the company and EAG's estimates resulted in a severity weight of 1.2 being applied. The committee noted stakeholder comments that a higher severity weighting should be applied but understood that NICE's manual on health technology evaluations specified the approach for calculating the severity modifier. And, using this method resulted in a weighting of 1.2 to account for the impact of the

condition on quality and length of life. 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

3.19 The committee recalled that sacituzumab govitecan was not included in the TPC arm of DESTINY-Breast04 because it was not part of standard care for triple-negative advanced breast cancer at the time of the trial (see section 3.6). The company explained that a robust indirect treatment comparison of trastuzumab deruxtecan and sacituzumab govitecan was not possible because of:

- differences in trial populations and data reported between DESTINY-Breast04 and the ASCENT trial of sacituzumab govitecan
- the small number of people in the HER2-low and hormone-receptor negative subgroups of the trials
- limited data reporting in the HER2-low and hormone-receptor negative subgroup of the ASCENT trial.

The company provided a naive, unadjusted comparison of the hazard ratios for progression-free and overall survival for trastuzumab deruxtecan compared with TPC from the DESTINY-Breast04 trial, and sacituzumab govitecan compared with TPC from the HER2-low subgroup of the ASCENT trial. Because trastuzumab deruxtecan and sacituzumab govitecan had a similar treatment effect compared with TPC, the company considered that an assumption of equal clinical effectiveness between trastuzumab deruxtecan and sacituzumab govitecan was justified. So, the company considered a cost-minimisation analysis was appropriate. This implicitly assumed equal clinical effectiveness of trastuzumab deruxtecan and sacituzumab govitecan on all outcomes (progression-free and overall survival, time-to-treatment stopping and adverse events). After consultation on the draft guidance, the company provided an unadjusted Bucher indirect treatment comparison of

trastuzumab deruxtecan and sacituzumab govitecan in the HER2-low subgroup. The company acknowledged that the results of the unadjusted indirect treatment comparison were highly uncertain, potentially biased, and not robust for decision making. But it considered that the results supported its assumption of equal clinical effectiveness for trastuzumab deruxtecan and sacituzumab govitecan. The EAG noted that the results of the unadjusted treatment comparison were inconclusive. It considered that the relative efficacy of trastuzumab deruxtecan and sacituzumab govitecan remains highly uncertain. The clinical experts considered that trastuzumab deruxtecan and sacituzumab govitecan each have their own benefit and they would prefer to have both options in clinical practice. 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 unadjusted comparisons of trastuzumab deruxtecan with sacituzumab govitecan were highly uncertain. It acknowledged the company's reasons for difficulty in providing a more robust comparison. The committee thought that the unadjusted comparisons were too uncertain to support the assumption that trastuzumab deruxtecan and sacituzumab govitecan were clinically equivalent. It also recalled clinical experts' possible preference for using sacituzumab govitecan first in practice (see section 3.4), so it may not be a comparator for subsequent trastuzumab deruxtecan. The committee concluded that because of the high level of uncertainty, the cost-minimisation approach was not appropriate for decision making on the cost effectiveness of trastuzumab deruxtecan compared with sacituzumab govitecan.

Data sources for costs

3.20 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 company suggested that if time on treatment is used, it should be based on the HER2-low subgroup of the ASCENT sacituzumab govitecan arm. The company provided a scenario that calculated the ratio of median progression-free survival in the full ASCENT population compared with the HER2-low subgroup. This increased the time-on-treatment estimate from 6.1 months to 7.9 months. The EAG agreed with the approach in the company's scenario and updated its time-on-treatment estimate for sacituzumab govitecan to reflect the HER2-low subgroup of ASCENT. The committee accepted that this was the best approach for reflecting treatment-related costs.

Cost-effectiveness results

Committee's preferred assumptions

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

- DB04 cohort that removed the efficacy and costs of second-line eribulin and gemcitabine (see section 3.9)
- log-logistic extrapolation of overall survival for TPC and the EAG's approach of a modified gamma distribution for trastuzumab deruxtecan (see section 3.10)
- EAG's approach to extrapolating progression-free survival using log-normal for TPC and a modified generalised gamma for trastuzumab deruxtecan (see

section 3.11)

- generalised gamma extrapolation of time-to-treatment stopping for TPC and the EAG's approach of a modified generalised gamma distribution for trastuzumab deruxtecan (see section 3.12)
- company's revised estimates for post-progression utility values (see section 3.14)
- updated treatment administration costs and a medical review cost (see section 3.17)
- severity weight of 1.2 applied to the QALYs (see section 3.18).

Acceptable ICER

3.22 NICE's manual on health technology evaluations notes that above a most plausible 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 that after consultation on the draft guidance, the company and EAG's updated approaches had reduced some of the uncertainty in the modelling of trastuzumab deruxtecan compared with TPC. But some remained, especially around these 2 issues:

- overall survival extrapolation (see section 3.10)
- post-progression utility values (see section 3.14).

The committee recalled that in the updated model using the DB04 cohort (see section 3.9), both treatment arms had a greater proportion of later-line treatments than might be seen in clinical practice. The committee took this into account when considering the acceptable ICER. It also recognised the unmet need in HER2-low metastatic or unresectable breast cancer and that trastuzumab deruxtecan was innovative with some potential health effects uncaptured (see section 3.26). The committee agreed that an acceptable ICER would be around £30,000 per QALY gained, which is around the upper

end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Cost-utility analysis

3.23 Including all confidential discounts that applied to treatments in the model, and with the severity modifier 1.2 QALY weight applied, the company's updated base-case ICER presented at the second committee meeting was above £30,000 per QALY gained. After including the revised administration costs (see section 3.17), the company's base-case ICER was below £30,000 per QALY gained. The exact ICERs are confidential and cannot be reported here. Also, the EAG updated base-case ICER was substantially above £30,000 per QALY gained when including all confidential discounts for all relevant treatments and with the severity modifier 1.2 QALY weight applied. Taking account of the committee's preferred assumptions including the severity modifier (see section 3.21), the ICERs were considerably higher than £30,000 per QALY gained. So, the committee concluded that the cost effectiveness estimate for trastuzumab deruxtecan was above what it considered acceptable. The considerations with the biggest impact on the ICER were the overall survival extrapolation and the post-progression utility values.

Cost-minimisation analysis

3.24 The committee acknowledged that because of a lack of data it was not possible to establish the presence or absence of any incremental benefit between trastuzumab deruxtecan and sacituzumab govitecan. But it also considered that the evidence supporting the assumption of equal clinical effectiveness between trastuzumab deruxtecan and sacituzumab govitecan was highly uncertain (see section 3.19). So, it considered that the results of the cost-minimisation analysis were highly uncertain. The committee noted that if equal clinical effectiveness is assumed, trastuzumab deruxtecan and sacituzumab govitecan have different costs. Because of confidential commercial arrangements for both treatments, the amount and direction of the difference in costs cannot be reported here. Considering the uncertainty, the committee concluded it could not make a specific recommendation about trastuzumab deruxtecan compared with

sacituzumab govitecan in the population who would be eligible for both treatments. The committee also concluded that the cost-effectiveness of trastuzumab deruxtecan compared with sacituzumab govitecan would be considered within the broader cost-effectiveness results for trastuzumab deruxtecan compared with TPC (see section 3.23).

Other factors

Equality

3.25 Stakeholders commented on the draft guidance that not recommending trastuzumab deruxtecan may disadvantage women, who are more likely to have breast cancer than men. They also commented that people with African, Caribbean and Asian ethnicity are diagnosed with breast cancer later than people with White British ethnicity. The committee recognised that cancer can have a substantial and long-term adverse effect on a person's ability to do normal day-to-day activities. So people with HER2-low breast cancer may be covered under the disability provision of the Equality Act (2010). The committee acknowledged that there are more treatment options for HER2-positive cancer (see section 3.2). The committee considered the potential equality issues, noting that its recommendations apply to all people within the marketing authorisation indication for trastuzumab deruxtecan for HER2-low breast cancer. It concluded that its recommendations do not have a different impact on people protected by the equality legislation than on the wider population.

Innovation and uncaptured benefits

3.26 Because trastuzumab deruxtecan is the first licensed HER2-low targeted treatment option for metastatic or unresectable breast cancer, the clinical experts considered it to be a step-change in managing the condition. The committee acknowledged that there are benefits with trastuzumab deruxtecan and it is a potential new treatment option for people who have limited treatments available. The company considered there were benefits not captured in the QALYs. These included maintenance of body image, sexual function and social function, which

are captured in the European Organisation for Research and Treatment of Cancer's QLC-C30 (a questionnaire developed to assess the quality of life of people with cancer). The committee recalled that metastatic or unresectable breast cancer can have a profound impact on a person's quality of life (see section 3.1). It noted that non-health effects such as financial effects and impacts on work are outside the NICE reference case for health technology evaluations. To account for innovation and uncaptured benefits, the committee agreed an ICER around the upper end of the range normally considered a cost-effective use of NHS resources would be acceptable (see section 3.22).

Conclusion

Recommendation

3.27 With the severity weight of 1.2 applied, the committee's preferred ICERs were above £30,000 per QALY gained. Even after accounting for innovation and uncaptured benefits, the committee concluded that the most likely cost-effectiveness estimates were above what it considered to be a cost-effective use of NHS resources. 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.

Committee members are asked to declare any interests in the technologies being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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.

Catherine Spanswick, Sharlene Ting
Technical leads

Claire Hawksworth
Technical adviser

Thomas Feist
Project manager

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