Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2545

trastuzumab deruxtecan, 100mg powder for concentrate for solution for infusion (Enhertu®)

Daiichi Sankyo UK Ltd

10 March 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

trastuzumab deruxtecan (Enhertu®) is accepted for restricted use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

SMC restriction: in patients who have received one prior anti-HER2-based regimen.

In a phase III study, trastuzumab deruxtecan was associated with significantly improved progression-free survival compared with an antibody-drug conjugate medication.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

SMC has previously issued advice (SMC2388) accepting trastuzumab deruxtecan (Enhertu®) for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens. This advice remains valid.

Chair, Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Trastuzumab deruxtecan is a human epidermal growth factor receptor 2 (HER2)-targeted antibody-drug conjugate. Trastuzumab (an anti-HER2 IgG1 antibody) is attached to deruxtecan, a topoisomerase I inhibitor, by a cleavable linker. After the antibody portion binds to HER2 expressed on the surface of certain tumour cells, the trastuzumab deruxtecan complex enters the cell and intracellular lysosomal enzymes release deruxtecan, which causes DNA damage and apoptotic cell death.[1]

Trastuzumab deruxtecan 5.4 mg/kg is given as an intravenous (IV) infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.[1]

1.2. Disease background

Breast cancer is the most common cancer in women in Scotland and approximately 20% of patients with breast cancer have HER2-positive tumours. Treatment with anti HER2-targeted therapies has improved disease outcomes, but they are not curative in the unresectable or metastatic setting, and the disease invariably progresses. [2-4]

1.3 Proposed position in treatment pathway

The indication under review is for a licence extension to a previous indication. SMC has already accepted trastuzumab deruxtecan for use, on an interim basis subject to ongoing evaluation and future reassessment, as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens (SMC2388). This submission focused on patients who have received one prior anti-HER2-based regimen.

1.4. Treatment pathway and relevant comparators

Standard of care for unresectable or metastatic HER2-positive breast cancer is a combination of a taxane with trastuzumab, which can be administered alongside the anti-HER2 medicine, pertuzumab. On progression of disease, in the second-line setting, trastuzumab emtansine is used. SMC issued advice (990/14) in 2017 that trastuzumab emtansine is accepted for use within NHSScotland as a single agent, for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: received prior therapy for locally advanced or metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy.

1.5. Category for decision-making process

- Eligibility for interim acceptance decision option

Trastuzumab deruxtecan received an Innovation Passport allowing entry into the Medicines and Healthcare Products Regulatory Agency (MHRA) Innovative Licensing and Access Pathway (ILAP) and has conditional marketing authorisation from the MHRA.

- Eligibility for a PACE meeting

Trastuzumab deruxtecan meets SMC end of life and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of trastuzumab deruxtecan for this indication comes from the ongoing study, DESTINY-Breast03. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study[3, 5]

Criteria	DESTINY-Breast03
Study design	International, randomised, open-label, active-controlled, phase III study
Eligible patients	• Adults with pathologically documented breast cancer that is unresectable or metastatic • Confirmed HER2-positive expression as determined according to American Society of Clinical Oncology – College of American Pathologists guidelines evaluated at a central laboratory • Previously treated with trastuzumab and taxane in the advanced/metastatic setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane • Documented radiologic progression (during or after most recent treatment or within 6 months after completing adjuvant therapy) • HER2-positive as confirmed by central laboratory assessment of most recent tumour tissue sample available • Patients with brain metastases were eligible for enrolment only if they had clinically stable, previously treated brain metastases (but not if they had brain metastases that were symptomatic or required treatment)
Treatments	Patients were randomised equally to receive trastuzumab deruxtecan 5.4mg/kg (n=261) or trastuzumab emtansine 3.6mg/kg (n=263), intravenously (IV) every 3 weeks. Treatment was continued until withdrawal of consent, progressive disease or unacceptable toxicity.
Randomisation	Randomisation was stratified according to hormone receptor status (positive or negative), prior treatment with pertuzumab (yes or no) and history of visceral disease (yes or no).
Primary outcome	The primary outcome was Progression Free Survival (PFS), defined as the time between date of randomisation to the earliest date of the first objective documentation of radiographic disease progression, based on blinded independent central review [BICR]) assessed using the modified Response Evaluation Criteria in Solid Tumours Version 1.1 (mRECIST v1.1) criteria, or death due to any cause, whichever occurred first.
Secondary outcomes	The key secondary outcome was overall survival, defined as the time from the date of randomisation to the date of death due to any cause. Other secondary outcomes were PFS based on investigator assessment, objective response rate (ORR; defined as the proportion of patients with best overall response of confirmed complete response or partial response according to mRECIST version 1.1 criteria based on BICR and investigator assessment), and duration of response (DoR; defined as the time from date of initial objective response [complete or partial response] to the date of progression or death by any cause based on BICR)

Statistical analysis	A hierarchical statistical testing strategy was applied in the study for the primary and key secondary outcomes (PFS tested first then overall survival) with no formal testing of outcomes after the first non-significant outcome in the hierarchy.

Table 2.2. Primary and selected secondary outcomes of DESTINY-Breast03 (data cut off: 21 May 2021)[3, 5]

	trastuzumab deruxtecan (n=261)	trastuzumab emtansine (n=263)
Median follow-up	16.2 months	15.3 months
Progression free survival assessed by BICR		
Patients with event, n (%)	87 (33%)	158 (60%)
Median PFS (95% CI), months	NE (18.5 to NE)	6.8 (5.6 to 8.2)
Stratified HR (95% CI)	0.28 (0.22 to 0.37)	
p-value	<0.001	
KM estimate at 12 months	76%	34%
Overall survival		
Number of deaths, n (%)	33 (13%)	53 (20%)
Median overall survival (95% CI), months	NE (NE, NE)	NE (NE, NE)
HR (95% CI)	0.55 (0.36 to 0.86)[a]	
KM estimate at 12 months	94%	86%
Response outcomes by BICR		
ORR, n %	208 (80%)	90 (34%)
Patients with DoR event (progressive disease or death), n (%)[b]	58/208 (28%)	31/90 (34%)
Median DoR, months	NE	NE

[a] The difference between treatment groups did not reach the prespecified cut off for statistical significance.
[b] calculated using number of patients with objective response.
Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; KM, Kaplan-Meier; NE, not estimable; ORR, objective response rate; PFS, progression-free survival

Results from a second interim analysis of DESTINY-Breast03, pre-specified for overall survival (with descriptive analysis for the other efficacy outcomes), were recently published (data cut off: 25 July 2022).[6] This second interim analysis demonstrated a statistically significant improvement in overall survival with trastuzumab deruxtecan compared with trastuzumab emtansine (median overall survival not estimable in either group, HR: 0.64 [95% CI: 0.47 to 0.87], p-value=0.0037).

2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the EuroQoL Five Dimensions Five Levels (EQ-5D-5L) and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and BR45. Higher scores in the EQ-5D-5L correspond to better health states, and high scores in the EORTC QLQ-C30 and QLQ-BR45 represent a greater response level. Regulators noted that HRQoL of patients in the trastuzumab deruxtecan group was either maintained or numerically improved compared with patients in the trastuzumab emtansine group; however due to the lack of preplanned/defined analysis for these outcomes and the open-label study design, firm conclusions on HRQoL could not be made.[3, 5]

3. Summary of Safety Evidence

Overall, regulators concluded that there were no clinically significant changes in the known safety profile of trastuzumab deruxtecan nor any new safety findings. In the second-line metastatic treatment setting, the toxicities observed with trastuzumab deruxtecan were described as clinically significantly different from those observed with trastuzumab emtansine and tolerability of trastuzumab deruxtecan appears lower; however, they were considered acceptable and manageable. The remaining major safety concern is the risk of interstitial lung disease/pneumonitis. [3]

At data cut-off May 2021, in DESTINY-Breast03, the median duration of treatment in the trastuzumab deruxtecan group was 14.3 months (range, 0.7 to 29.8) months and in the trastuzumab emtansine group was 6.9 months (range, 0.7 to 25.1) months. Any treatment-emergent adverse event (AE) was reported by nearly all (256/257) of the patients in the trastuzumab deruxtecan group and 95% (249/261) in the trastuzumab emtansine group; these were considered treatment-related in 98% and 87%, respectively. In the trastuzumab deruxtecan and trastuzumab emtansine groups respectively, patients reporting a grade 3 or higher AE were 52% versus 48%, patients with a reported serious AE were 19% versus 18%, patients with an AE associated with a dose reduction were 21% versus 13%, patients with an AE associated with study drug interruption were 44% versus 23% (considered treatment-related in 35% versus 13%), and patients with an AE associated with study drug discontinuation were 14% versus 7% (considered treatment-related in 13% versus 5.0%). The most frequently reported treatment-related AEs of any grade in the trastuzumab deruxtecan group versus the trastuzumab emtansine group were (>40% in any group): nausea (73% versus 28%), fatigue (45% versus 30%), vomiting (44% versus 5.7%), neutropenia (43% versus 11%), and thrombocytopenia (25% versus 52%). Treatment-related interstitial lung disease or pneumonitis was more common with trastuzumab deruxtecan than trastuzumab emtansine (11% versus 1.9%).[3]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In DESTINY-Breast03, trastuzumab deruxtecan significantly reduced the risk of disease progression or death in comparison to the current standard of care in the second line setting, trastuzumab emtansine, in adults with HER2-positive unresectable or metastatic breast cancer that was previously treated with trastuzumab plus taxane chemotherapy in the metastatic setting (or who had progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen that included trastuzumab and taxane). This was considered clinically relevant.[3]
- The most recently available results have suggested a significant overall survival benefit associated with trastuzumab deruxtecan over trastuzumab emtansine, although the median overall survival has not yet been reached in either group.

4.2. Key uncertainties

- Uncertainty remains for the long-term effectiveness of trastuzumab deruxtecan. Overall survival data are still immature. The median overall survival was still not reached at the later data cut in both groups (with 28 and 37% of events, respectively). [6] Duration of response data were also not mature (28% and 34% of events, respectively). [3]
- There is some uncertainty about the generalisability of DESTINY-Breast03 data to the population that may receive treatment in practice. Patients in the study potentially were more heavily pre-treated. In addition, there was a lower proportion of patients who have previously received pertuzumab as part of first line treatment and a higher proportion of Asian patients than would be expected in Scotland. Only patients with an ECOG PS of 0 or 1 were included in the clinical study so efficacy and tolerability of trastuzumab deruxtecan in patients with a poorer performance status is unknown.
- Some other factors affected the interpretability of secondary and exploratory outcomes. There were differences in subsequent therapies received between treatment groups, mainly due to the differences in progression rates.[5] DESTINY-Breast03 is an open-label study, which design may affect the assessment of subjective outcomes, such as HRQoL and adverse events. [3] HRQoL and response outcomes (ORR and DoR) were not part of a statistical hierarchy and not adjusted for multiplicity.

4.3. MHRA/EMA conditional marketing authorisation specific obligations / Innovative Licensing and Access Pathway (ILAP) and ongoing studies

The specific obligation, for additional data in third or later lines of treatment, is unlikely to address the key uncertainties in the clinical evidence presented for this submission against trastuzumab emtansine, the current standard of care in the second line setting.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that trastuzumab deruxtecan is a therapeutic advancement due to an improved efficacy compared with the current standards of care; and they considered that its place in therapy is as second line treatment of adult patients with unresectable or metastatic HER2-positive breast cancer.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine may impact on the service delivery as increased monitoring is required, especially radiographic monitoring due to the increased risk of lung toxicity.

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **trastuzumab deruxtecan**, as an **orphan-equivalent and end of life** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Metastatic HER2 positive breast cancer limits patients' life expectancy and severely affects their physical and mental health. Symptoms vary depending on site of metastases, and can be painful and debilitating. Patients often experience fear, anxiety, and depression. There are also major implications for their families.
- It is an incurable disease with limited treatment options. There is an unmet need for additional well-tolerated treatments to control the disease and improve survival of patients with this condition.
- Trastuzumab deruxtecan data are very promising. Compared with the current standard of care in second line, trastuzumab emtansine, it is expected to increase response rates, extend PFS and potentially survival, which could significantly improve the patients' quality of life. It would offer patients and their families hope, and would undoubtedly improve the mental health of all involved. It could allow patients to lead near-normal lives for longer. Patients could continue to work for longer and the potential burden on carers could be reduced. This could lessen the potential for financial hardship.
- Trastuzumab deruxtecan and trastuzumab emtansine have distinct side effect profiles. Although generally well tolerated, trastuzumab deruxtecan could be considered more toxic. More cases of interstitial lung disease have been reported with trastuzumab deruxtecan. Despite this different and possibly less favourable side effect profile, patients are willing to accept an increased risk of side effects for the potentially significant improvements in progression-free survival and overall survival.
- It would be preferable to use trastuzumab deruxtecan as early as possible, which is in second line. Patients who would not have received trastuzumab deruxtecan as second line may be unfit for further therapy after progression on second line treatment, and they may miss the opportunity to receive it. As patients tend to become less fit as their cancer advances, a higher toxicity may be better tolerated at an earlier stage.

Additional Patient and Carer Involvement

We received patient group submissions from Breast Cancer Now and METUP UK, both organisations are registered charities. Breast Cancer Now has received 0.65% pharmaceutical company funding in the past two years, including from the submitting company. METUP UK has not received any pharmaceutical company funding in the past two years. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1. Description of economic analysis

Analysis type	Cost-utility analysis
Time horizon	Lifetime (30 years, based on a median starting age of 54 years)
Population	The economic submission aligned with the company's proposed position and focused on the use of trastuzumab deruxtecan as second-line treatment for unresectable or metastatic HER2-positive breast cancer.
Comparators	Trastuzumab deruxtecan is compared with trastuzumab emtansine.
Model description	The economic analysis used a partitioned survival model with three health states (progression free, progressed, and death).
Clinical data	The relative efficacy of trastuzumab deruxtecan and trastuzumab emtansine was estimated from the randomised, phase III, open-label DESTINY-Breast03 study, which informed patient baseline characteristics, clinical variables, treatment duration, utilities, and adverse events for the economic analysis.[3, 5]
Extrapolation	To estimate long-term efficacy, independent parametric curves were fitted to overall survival (OS), PFS and time to treatment discontinuation (TTD) data from the DESTINY-Breast03 study. The best fitting curves were selected based on statistical fit, visual fit and clinical expert validation. For both treatment arms, the generalised gamma function was chosen for OS, whilst the Weibull function was chosen for PFS and TTD, with TTD capped at PFS. General population background mortality is included in the model to ensure the risk of death for patients does not fall below general population mortality.
Quality of life	Utility estimates for progression free disease were based on the EQ-5D data collected in the DESTINY-Breast03 study. Due to a limited number of observations from the study, utility values for progressive disease were taken from a published source.[7] Utility values were applied in the model were dependent on health state and treatment arm. Disutilities for adverse events were not included in the base case having been assumed captured in the health state utility values.
Costs and resource use	Costs included medicine acquisition, medicine administration, subsequent therapies, treatment of adverse events and terminal care. Vial sharing was assumed for 50% of patients in the base case, applied to both treatment arms. Non-medicine costs associated with health state monitoring and end-of-life care were included.
Patient Access Scheme (PAS)	A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. The results presented do not take account of the PAS for trastuzumab deruxtecan or the PAS for trastuzumab emtansine but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for trastuzumab emtansine due to commercial confidentiality and competition law issues.

6.2. Results

In the base case for trastuzumab deruxtecan versus trastuzumab emtansine the incremental cost-effectiveness ratio (ICER) is estimated at £72,684 per quality adjusted life year (QALY) when the list price was used for each medicine. The main driver of cost differences was the medicine

acquisition costs for trastuzumab deruxtecan. The life years/QALYs differences were mainly driven by the occupancy of the pre-progression state for trastuzumab deruxtecan patients, although there were also additional QALYs generated in the post progression state.

6.3. Sensitivity analysis

The company conducted a variety of analysis to help explore areas of uncertainty. One-way sensitivity analysis (OWSA) suggested that the ICER was most sensitive to variation in the utility value for the progressed disease health state, followed by the proportion of patients in each treatment arm receiving subsequent treatment.

The company also presented a variety of exploratory scenarios, a selection of which have been presented below. These results do not take into account the PAS discounts available on trastuzumab deruxtecan or trastuzumab emtansine.

Table 6.3 Selected scenario analysis results (list prices)

#	Scenario analysis description	Base case description	ICER
1	Time horizon - 20 years	Time horizon - 30 years	£75,007
2	OS extrapolation – log-logistic	OS extrapolation – Generalised gamma	£73,336
3	OS extrapolation – Weibull		£82,369
4	OS extrapolation – Application of hazard ratio to survival data from EMILIA study[8]	OS extrapolation – Application of survival modelling to data from DESTINY-Breast03	£63,810
5	PFS extrapolation – log-logistic	PFS extrapolation – Weibull	£67,561
6	PFS extrapolation – exponential		£65,451
7	Utility source – PFS = DESTINY-Breast03 PD = Lloyd et al (2006) [7] Utility values uniform across treatment arm	Utility source – PFS = DESTINY-Breast03 PD = Lloyd et al (2006) Utility values treatment arm dependent	£82,184
8	Utility source – PFS = Lloyd et al (2006) PD = Lloyd et al (2006) Utility values uniform across treatment arm		£81,426
9	0% vial sharing	50% vial sharing	£78,263
10	25% vial sharing + utility values equalised across treatment arm	50% vial sharing + utility values treatment arm dependent	£85,338

Abbreviations: HR, hazard ratio; ICER, incremental cost effectiveness ratio; LY, life year; OS, overall survival; PFS, Progression free survival; PD, progressive disease; QALY, quality adjusted life year; RDI, relative dose intensity

*Other data were also assessed but remain confidential.**

6.4. Key strengths

The main strengths of the analysis were:

- The clinical data on the efficacy of trastuzuman deruxtecan was informed by a head-to-head study comparing it with a relevant comparator.
- The employed model structure was appropriate.
- Uncertainty was adequately explored through a wide range of sensitivity and scenario analyses.

6.5. Key uncertainties

The main weakness of the economic analysis were:

- The immaturity of OS data from DESTINY-Breast03 combined with the long time horizon of 30 years contributed to uncertainty in economic results. While varying the parametric curve has an upward impact on the ICER (see Scenarios 2 and 3, Table 6.3), the company did take appropriate steps to validate their predictions. Further, the company provided a scenario exploring an alternative method of predicting OS, where they modelled survival for trastuzumab emtansine patients from data from the EMILA study.[8] A hazard ratio, estimated from the DESTINY-Breast03 study, was applied to estimate treatment effect versus trastuzumab deruxtecan (scenario 4). This led to a reduction in the estimated ICER but, again, was associated with uncertainty.
- In line with clinical case, there were some concerns on the generalisability of the data from the DESTINY-Breast03 study to Scottish clinical practice. As a result, there was some associated uncertainty on how reflective the economic results are of trastzumab deruxtecan use in Scotland.
- The company assumed that trastuzumab deruxtecan patients have a higher quality of life in both the pre-progressed and progressed health states, despite treatment terminating at the point of progression. This was a point of uncertainty, and assuming equal utility values within health states between the treatment arms led to an increase in the ICER (Scenarios 7 and 8). The company justified differential utility values based on the observed outcomes of the DESTINY-Breast03 study for the pre-progressed state and the principle that even after progression tumour burden would be reduced in trastuzumab deruxtecan patients. This approach has been used in other breast cancer submissions to SMC.
- In the base case, vial sharing was assumed in 50% of patients receiving both trastuzumab deruxtecan and trastuzumab emtansine. However, it was uncertain to what extent this would happen in clinical practice. While the 50% vial sharing assumption was in line with other SMC submissions for breast cancer, alternative lower proportions were felt relevant. An exploratory scenario assuming no vial sharing increased the ICER (Scenario 11).

7. Conclusion

The Committee considered the benefits of trastuzumab deruxtecan in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios. As trastuzumab deruxtecan is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifier, the Committee accepted trastuzumab deruxtecan for restricted use in NHSScotland.

8. Guidelines and Protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published recommendations in 2013 for primary breast cancer (SIGN134), however this excluded patients with metastatic disease.[2]

The European Society of Medical Oncology (ESMO) clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer, published in 2021, recommend a combination of pertuzumab, trastuzumab and docetaxel (or an alternative taxane) as standard first line. Endocrine therapy can be added to the pertuzumab and trastuzumab combination for maintenance after completion of chemotherapy for hormone receptor positive tumours. If patient comorbidities, performance status, or personal preference make chemotherapy unsuitable, additional therapeutic options suggested by ESMO are HER2-targeted therapy without chemotherapy (such as trastuzumab or trastuzumab + pertuzumab) or with another less toxic chemotherapy if taxane is contraindicated (such as capecitabine or vinorelbine), or trastuzumab and lapatinib, or lapatinib monotherapy (with endocrine therapy added if the patient also has hormone receptor-positive disease). It is suggested that patients with metastatic recurrence within 6 to 12 months of receiving adjuvant trastuzumab + pertuzumab should follow second-line therapy recommendations. However, patients who experience distant metastatic recurrence within 12 months of adjuvant trastuzumab (without pertuzumab) may receive first-line trastuzumab + pertuzumab + taxane or second-line therapy. As second line, trastuzumab deruxtecan for patients with HER2+ mBC after progression on trastuzumab and a taxane is the preferred treatment option. When trastuzumab deruxtecan is not available, trastuzumab emtansine is recommended as an alternative. For selected patients with brain metastases, tucatinib with capecitabine plus trastuzumab may be considered. The ESMO guideline recommends tucatinib with capecitabine plus trastuzumab, trastuzumab emtansine or trastuzumab deruxtecan for third line treatment depending on previous therapy, patient suitability, safety profile and availability. The guidelines also suggest lapatinib-based regimens, neratinib, and margetuximab as possible options in a late-line setting. [4]

9. Additional Information

9.1. Product availability date

17 August 2022

9.2. Summary of product characteristics

See the SPC for further information including dosing and safety. Available from: trastuzumab deruxtecan, 100mg powder for concentrate for solution for infusion (Enhertu®)

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
trastuzumab deruxtecan	**5.4mg/kg IV once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity**	**5,820**

Costs from BNF online on 25 November 2022. Costs calculated using an adult bodyweight of 70kg, and using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 32 patients eligible for treatment with trastuzumab deruxtecan in each year.

Based on clinical expert responses, there was concern that the number of patients eligible for treatment and the estimated uptake of trastuzumab deruxtecan may be higher in Scottish practice than predicted by the submitting company.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 17 January 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a

patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.