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SMC2608

trastuzumab deruxtecan powder for concentrate for solution for infusion (Enhertu®)

Daiichi Sankyo UK Ltd

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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 use within NHSScotland.

Indication under review: as monotherapy 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.

In an open-label, randomised, phase III study, trastuzumab deruxtecan significantly improved progression-free survival compared with single-agent chemotherapy in patients with HER2-low, hormone receptor-positive, unresectable or metastatic breast cancer who had received one or two lines of prior chemotherapy in the metastatic setting.

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.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Trastuzumab deruxtecan is a 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 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, 2]

Trastuzumab deruxtecan is the first medicine to be licensed for the treatment of HER2-low breast cancer and provides the first HER2-targeted therapy for these patients. It is administered at a dose of 5.4 mg/kg by intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.[1] SMC has previously accepted trastuzumab deruxtecan for restricted use as monotherapy for the treatment of adult patents with unresectable or metastatic HER2-positive breast cancer who have received one prior anti-HER2-based regimen (SMC2545) and accepted on an interim basis subject to ongoing evaluation, as monotherapy for the treatment of adult patents with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens (SMC2388).

1.2. Disease background

Breast cancer is the most common cancer in women in Scotland. It has traditionally been categorised as HER2-positive (tumours scoring 3+ or 2+ by immunohistochemistry [IHC] and HER2 gene amplification by in situ hybridisation [ISH]) or HER2-negative (tumours scoring 2+ by IHC and no evidence of HER2 gene amplification by ISH or tumours scoring 1+ or 0 by IHC). However, around half of the patients with HER2-negative breast cancer have tumours with some HER2 proteins on their cell surfaces and these can be classified as having HER2-low status (defined as tumours scoring 2+ or 1+ by IHC and no evidence of HER2 gene amplification). This includes a heterogeneous group of patients with hormone receptor-positive and hormone receptor-negative disease, including those with triple-negative breast cancer (TNBC).[2]

1.3. Treatment pathway and relevant comparators

Patients with HER2-low, advanced or metastatic breast cancer are currently treated in the same way as patients with HER2-negative breast cancer, based on tumour hormone receptor status, PD-L1 and BRCA mutation status, visceral disease, menopausal status and previous treatment. For patients with hormone receptor-positive metastatic disease, first-line standard of care is generally endocrine therapy plus a cyclin-dependent kinase (CDK) 4/6 inhibitor. Guidelines recommend at least two lines of endocrine-based therapy. Other second-line endocrine therapy currently includes fulvestrant (if not used previously) plus a CDK4/6 inhibitor, or everolimus plus exemestane or fulvestrant, or fulvestrant monotherapy. Patients with endocrine-resistant disease should be considered for chemotherapy and sequential single-agent is generally preferred over combination regimens unless a rapid response is needed. Available single-agent chemotherapy options include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine and platinum. European guidelines have recently been updated for patients with hormone receptor-positive and HER2-negative disease to include trastuzumab deruxtecan as a second or later line of treatment for patients with HER2-low disease.[2-5]

The poly-ADP ribose polymerase (PARP) inhibitors, olaparib and talazoparib, are licensed for the treatment of breast cancer; however, they have not been recommended for use by SMC as monotherapy for patients with germline BRCA1/2 mutations who have HER2-negative locally advanced or metastatic breast cancer due to non-submission (SMC2436 and SMC2325 respectively).

For patients with metastatic TNBC, first-line treatment is generally chemotherapy with specific treatments dependent on PD-L1 and BRCA mutation status. In the second-line, ESMO updated guidelines recommend sacituzumab govitecan or further chemotherapy and, in the third- and subsequent lines, trastuzumab deruxtecan is recommended for patients with HER2-low disease.[3, 4] Sacituzumab govitecan has been accepted by SMC for the treatment of adult patients with unresectable locally advanced or metastatic TNBC who have received two or more prior lines of systemic therapies (SMC2466).

The submitting company considered single-agent chemotherapy to be the most relevant comparator.

1.4. 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 Innovative Licensing and Access Pathway and has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency.

Eligibility for a PACE meeting

Trastuzumab deruxtecan meets SMC end of life criteria 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 the treatment of HER2-low breast cancer comes from the DESTINY-Breast04 study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	DESTINY-Breast04[1, 2, 6]
Study design	An open-label, randomised, multicentre, phase III study
Eligible patients	• Adults, aged ≥18 years, with unresectable or metastatic breast cancer • low HER2 disease (defined as IHC2+/ISH- or IHC1+ (ISH- or untested) and never previously HER2-positive (IHC 3+ or ISH+) • hormone receptor-positive or -negative disease • received one or two lines of chemotherapy in the recurrent or metastatic setting. If recurrence occurred <6 months after (neo) adjuvant chemotherapy, then (neo) adjuvant therapy counted as one line of chemotherapy. • hormone receptor-positive patients had progressed on and would no longer benefit from endocrine therapy • documented radiologic progression during or after most recent treatment

	• had at least one measurable lesion according to RECIST version 1.1 • patients with treated brain metastases that were no longer symptomatic and who required no treatment with corticosteroids or anticonvulsants were eligible if they had recovered from acute toxic effect of radiotherapy. • ECOG performance status of 0 or 1.
Treatments	Trastuzumab deruxtecan 5.4 mg/kg intravenously every 21-day cycle or physician's choice of chemotherapy from: • capecitabine 1000 to 1250 mg/m^2 orally twice daily on days 1 to 14 every 21 days • eribulin 1.4 mg/m^2 intravenously on days 1 and 8 every 21 days • gemcitabine 800 to 1200 mg/m^2 intravenously on days 1 and 8 every 21 days or 800 to 1200 mg/m^2 intravenously on days 1, 8 and 15 every 28 days • paclitaxel 175 mg/m^2 intravenously on day 1 every 21 days or 80 mg/m^2 intravenously on day 1 every week • nab-paclitaxel 260 mg/m^2 intravenously every 21 days or 100 or 125 mg/m^2 intravenously on days 1, 8 and 15 every 28 days.
Randomisation	Patients were randomised in a ratio of 2:1, stratified by central HER2 IHC status, number of prior lines of therapy and hormone receptor/CDK4/6 status.
Primary outcome	PFS assessed by BICR in the cohort of patients with hormone receptor positive disease
Secondary outcomes	Key secondary outcomes: • PFS assessed by BICR in the full analysis set • OS in the cohort of patients with hormone receptor positive disease • OS in the full analysis set Additional secondary outcomes: • ORR by BICR • duration of response
Statistical analysis	A hierarchical testing procedure was applied to the primary and key secondary outcomes of the study with no formal testing after the first non-significant outcome in the hierarchy.

IHC= immunohistochemistry; ISH= in situ hybridisation; ECOG=Eastern Co-operative Oncology Group; CDK=cyclin-dependent kinase; PFS=progression-free survival; BICR=blinded independent committee review; OS=overall survival; ORR=objective response rate; RECIST = Response Evaluation Criteria in Solid Tumours

At the time of the primary PFS analysis (data cut-off 11 January 2022), median PFS was significantly improved in the trastuzumab deruxtecan group compared with the physician's choice of chemotherapy group in the hormone receptor positive cohort. Results for the key secondary outcomes, assessing PFS in the full analysis set (FAS) and OS in the hormone receptor-positive cohort and FAS also significantly favoured trastuzumab deruxtecan over chemotherapy. Details are presented in Table 2.2.

Table 2.2: Results for the primary and key secondary outcomes in the hormone receptor-positive cohort and FAS of DESTINY-Breast04[2, 6, 7]

	Hormone receptor-positive cohort		FAS	
	Trastuzumab deruxtecan (n=331)	**Physician choice of chemotherapy (n=163)**	**Trastuzumab deruxtecan (n=373)**	**Physician choice of chemotherapy (n=184)**
PFS by BICR				
Median duration of follow-up, months	*	*	16.1	13.5
Number of patients with a PFS event	211	110	243	127
Median PFS, months	10.1	5.4	9.9	5.1
Hazard ratio (95% CI)	0.51 (0.40 to 0.64) p<0.001		0.50 (0.40 to 0.63) p<0.001	
OS				
Median duration of follow-up, months	18.4			
Number of deaths	126	73	149	90
Median OS, months	23.9	17.5	23.4	16.8
Hazard ratio (95% CI)	0.64 (0.48 to 0.86) p=0.0028		0.64 (0.49 to 0.84) p=0.001	
KM estimates of survival at 12 months	81%	70%	79%	66%
KM estimates of survival at 24 months	49%	37%	48%	32%

FAS=full analysis set; PFS=progression free survival; BICR=blinded independent committee review; CI=confidence interval; KM=Kaplan Meier; OS=overall survival

**median duration of follow-up for PFS in the hormone receptive-positive cohort and KM estimates of PFS in all groups were considered confidential by the company.*

Additional secondary outcomes included confirmed objective response rate (ORR) which was higher in the trastuzumab deruxtecan group compared with the chemotherapy group (52% versus 16%) and duration of response (median of 10.7 months versus 6.8 months respectively) in the FAS. Exploratory analysis in the cohort of patients with hormone receptor-negative disease favoured trastuzumab deruxtecan (n=40) over chemotherapy (n=18); median PFS 8.5 months versus 2.9 months and median OS 18.2 months versus 8.3 months.[1, 2, 6]

2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed as exploratory outcomes using the generic EuroQoL-5 dimensions-5 levels of severity (EQ-5D-5L), the European Organisation for Research and Treatment of Cancer Quality of Life C-30 (EORTC QLQ-C30) for cancer patients and the breast cancer specific EORTC QLQ Breast Cancer-45 (BR45) questionnaires (since this was still being validated and analysis was performed based on QLQ-BR23 scoring comprising 23 questions). Questionnaires were completed at baseline, cycles 2 and 3, then every two cycles of study treatment, at the end of study treatment visit and at the 40-day follow-up visit as well as the first long-term follow up 3 months later.[6]

At baseline the questionnaires were completed by >92% of patients in both treatment groups and by >80% for cycles 2 to 27. In both treatment groups, results for the EORTC-QLQ-C30 global health

status/quality of life score remained stable up to cycle 21, suggesting that quality of life was maintained during treatment. Results for the median time to a clinically meaningful deterioration in global health, subscales and breast specific symptoms suggested this was generally longer with trastuzumab deruxtecan than with chemotherapy.[2]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

The submitting company assessed the feasibility of performing an indirect comparison of trastuzumab deruxtecan with sacituzumab govitecan, which is a relevant comparator for patients with unresectable locally advanced or metastatic TNBC who have received at least two prior lines of systemic therapies. However, feasibility assessments suggested that the results would be highly uncertain and an indirect comparison was not conducted. The company noted that the patient population who would be eligible for sacituzumab govitecan as a relevant comparator was likely to be small (11% of the HER2-low population).

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

3. Summary of Safety Evidence

During DESTINY-Breast04, there were no clinically significant changes to the known safety profile of trastuzumab deruxtecan and no new safety issues were identified. Safety data in patients >75 years, patients with severe renal impairment and patients with moderate or severe hepatic impairment remain limited.[2]

For the DESTINY-Breast04 safety analysis set at data cut-off 11 January 2022, the median duration of treatment in the trastuzumab deruxtecan group was 8.2 months and in the chemotherapy group was 3.5 months. Any treatment-emergent adverse event (AE) was reported by 99.5% (369/371) of patients in the trastuzumab deruxtecan group and 98% (169/172) in the chemotherapy group and these were considered treatment-related in 96% and 94% respectively. In the trastuzumab deruxtecan and chemotherapy groups respectively, patients reporting a grade 3 or higher AE were 53% versus 67%, patients with a reported serious AE were 28% versus 25%, patients with a dose reduction due to treatment emergent AEs were 23% versus 38%, the proportion of AEs that led to dose interruptions were 39% versus 42% and patients discontinuing therapy due to an AE was 16% versus 8.1%.[2, 6]

The most frequently reported treatment-related AEs of any grade in the trastuzumab deruxtecan group versus the chemotherapy group were: nausea (73% versus 24%), fatigue (48% versus 42%), alopecia (38% versus 33%), vomiting (34% versus 9.9%), neutropenia (33% versus 51%), anaemia (33% versus 23%), decreased appetite (29% versus 16%), thrombocytopenia (24% versus 9.3%), leucopenia (23% versus 31%), increased aspartate aminotransferase (23% versus 23%), diarrhoea (22% versus 18%) and constipation (21% versus 13%). Drug-related interstitial lung disease or pneumonitis was more common in the trastuzumab deruxtecan group compared with chemotherapy (12% versus 0.6%).[2, 6]

In the trastuzumab deruxtecan group, there were two treatment-related deaths due to pneumonitis and one treatment-related death each due to ischaemic colitis, disseminated intravascular coagulation, dyspnoea, febrile neutropenia and sepsis. There were no treatment-related deaths in the chemotherapy group.[6]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Trastuzumab deruxtecan is the first medicine to be licensed for the treatment of HER2-low breast cancer and provides the first HER2-targeted therapy for these patients.[1, 2]
- The primary outcome of the DESTINY-Breast04 study was PFS assessed by BICR in the hormone receptor-positive cohort of patients. PFS by BICR in the FAS was a key secondary outcome as was OS in the hormone receptor-positive cohort and FAS. There were statistically significantly improvements in PFS and OS in the hormone receptor-positive cohort and FAS with trastuzumab deruxtecan compared with chemotherapy. The improvements were considered clinically relevant for this patient population.[2]

4.2. Key uncertainties

- The primary outcome of DESTINY-Breast04 was assessed in patients with hormone receptor-positive disease but the FAS, including hormone receptor-positive and -negative patients, represents the licensed population. The study hierarchy included PFS and OS in the hormone receptor-positive cohort and the FAS and the study was also powered to assess efficacy in terms of OS. ORR and quality of life outcomes were not included in the hierarchy and were not controlled for multiplicity.
- The study was of open-label design but PFS and ORR were assessed by BICR to minimise potential bias. Subjective outcomes including patient reported quality of life and safety may be prone to bias.
- The available OS results are based on the first interim analysis of OS performed at the time of the primary PFS analysis. At this point, 43% (239/557) of study patients had died. Final OS analysis was planned after 333 deaths in the hormone receptor-positive cohort anticipated in 2024 but the company has noted there is no requirement to perform further analysis as statistical significance has been shown. Some uncertainty remains over the longer term survival results but a later detriment in OS was considered unlikely. Further OS results may be confounded by subsequent cancer therapy.[2]
- The licensed indication includes patients with hormone receptor-positive and -negative disease. However the study only included a small number of patients with hormone receptor-negative disease (n=58), a proportion representative of the distribution in clinical practice, and analysis was exploratory. Due to this limited data, the size of the treatment effect is less robust in these patients.[2, 6]
- The physician's choice of chemotherapy in the comparator arm comprised eribulin 51%, capecitabine 20%, gemcitabine 10%, nab-paclitaxel 10% and paclitaxel 8.2%. The study compared trastuzumab deruxtecan with this chemotherapy group as a whole and the numbers

of patients receiving individual medicines were too small to allow meaningful comparison versus individual medicines. Clinical experts consulted by SMC considered that these comparators were reasonably reflective of clinical practice in Scotland although they noted that there may be more use of capecitabine and less use of eribulin which is restricted by SMC to use after the former. There may also be less use of gemcitabine and some use of vinorelbine in clinical practice. Anthracyclines were not included in the comparator arm and since approximately two-thirds of patients had received prior anthracyclines, the remainder may have been eligible for anthracycline-based treatment. However, a post hoc sensitivity analysis confirmed that the treatment effect of trastuzumab deruxtecan was shown regardless of prior anthracycline use. There are no comparative data (direct or indirect) with sacituzumab govitecan and therefore the relative efficacy and safety in the small number of patients for whom this may be a relevant comparator is unknown.[2, 6]

- In DESTINY-Breast04, 40% of study patients were Asian which would be higher than in patients in Scotland. This may affect the generalisability of study results to Scottish practice.
- There was a higher incidence of AEs with trastuzumab deruxtecan compared with chemotherapy, particularly gastrointestinal and haematological toxicity, interstitial lung disease/pneumonitis and left ventricular dysfunction. Despite the safety profile, the HRQoL outcomes did not detect a detrimental effect on quality of life but this may be limited by the open-label study design. Longer term safety data in this indication remains limited.[2, 6]

4.3. GB/EMA conditional marketing authorisation specific obligations

The MHRA has not made any specific obligations on the clinical evidence for this licensed indication for trastuzumab deruxtecan and there appears to be no further planned analysis of OS in DESTINY-Breast04.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that trastuzumab deruxtecan fills an unmet need in this therapeutic area, namely offering a HER2-targeted treatment option for these patients and is a therapeutic advancement due to the improvements in PFS and OS over standard chemotherapy in this setting.

4.5. Service implications

SMC clinical experts advise that trastuzumab deruxtecan is likely to be associated with service implications, including clinic, nursing and pharmacy time. They also suggest that there may be an increased requirement for toxicity management. Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information**.**

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:

- Advanced or metastatic breast cancer is a devastating diagnosis for patients and their families and is described as life-changing. There is no cure and treatment aims to control and slow down the spread of the cancer, relieve symptoms and maintain best quality of life for as long as possible. It has a substantial physical impact with patients suffering disease symptoms including fatigue, pain, breathlessness and as well as toxicities from previous treatments. There is the constant worry and anxiety of ongoing treatment and monitoring and the fear of running out of available treatment options. HER2-low breast cancer is a newly defined subset of HER2-negative breast cancer, which accounts for approximately half of breast cancer cases.
- Patients with unresectable or metastatic HER2-low breast cancer are currently treated as HER2-negative patients, guided at initial stages by hormone receptor status. Following endocrine therapy plus targeted agents in patients with hormone receptor positive disease and chemotherapy in all patients, further effective treatment options are limited, particularly in patients with triple negative disease. Further chemotherapy at later lines of treatment is of limited efficacy and side effects may negatively impact quality of life. Therefore, there is a considerable unmet need for further treatment options at the early stages of metastatic disease which offer improved efficacy for patients with HER2-low breast cancer following prior chemotherapy.
- Trastuzumab deruxtecan is the first HER2-targeted therapy for this patient population opening a new therapeutic option and filling an unmet need by offering a further, specifically targeted, effective treatment option. PACE participants described this additional option as a “life-line”. Compared with chemotherapy, trastuzumab deruxtecan significantly improved progression-free survival and overall survival while maintaining quality of life. This may allow patients more time to spend with their families and friends and to continue to enjoy normal life, while feeling more secure that they have options with their treatment.
- By controlling the disease symptoms, trastuzumab deruxtecan may allow patients increased time to spend in good quality of life compared with standard treatment. This may lead to patients continuing to enjoy normal life, remain independent and to care for dependents. It may allow those, who are able to and wish to, to continue to work and contribute to society. The availability of trastuzumab deruxtecan may relieve some of the anxiety around disease progression and running out of treatment options and offer the potential to bridge to a time when other new and effective medicines become available. PACE participants noted that patients prefer targeted therapy, which they considered optimal, to untargeted chemotherapy.
- Patients would need to attend hospital clinics every 3 weeks for administration of trastuzumab deruxtecan but for patients who respond, they may need fewer clinic visits or hospital admissions for symptom management. The side effect profile of trastuzumab deruxtecan is not negligible but for many patients this is considered to be outweighed by potential benefits of the medicine. Trastuzumab deruxtecan is associated with interstitial lung disease and patients should be warned about potential symptoms and monitored closely. PACE clinicians noted that they have had good experience of managing this risk while treating patients with HER2-positive disease.

Additional patient and carer involvement

We received patient group submissions from Breast Cancer Now and METUP UK. Breast Cancer Now is a registered charity and METUP UK is a charitable incorporated organisation. Breast Cancer Now has received 0.7% pharmaceutical company funding in the past two years, including from the submitting company. METUP UK has received 23% pharmaceutical company funding in the past two years, including from the submitting company. 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 economic case is summarised in the Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (30 years)
Population	Adult patients with unresectable or metastatic HER2-low breast cancer (HER2-low u/mBC) who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
Comparators	The comparator in the model is the TPC arm from DESTINY-Breast04, which comprises of a basket of single-agent chemotherapies: • eribulin (52%) • capecitabine (21%) • nab-paclitaxel (10%) • gemcitabine (9%) • paclitaxel (8%)
Model description	The submitting company presented a partitioned survival model using three health states; 'progression free', 'post-progression' and 'death'. The model had a cycle length of 3 weeks to align with the dosing schedule of trastuzumab deruxtecan with a half-cycle correction applied. The proportion of patients in each health state at any time point was calculated as follows: • Progression-free = PFS • Post-progression = OS – PFS • Death = 1 – OS.
Clinical data	Clinical data were taken from the DESTINY-Breast04 study.
Extrapolation	As the submitting company's model applied a lifetime horizon of 30 years, OS, PFS and time to treatment discontinuation (TTD) had to be extrapolated. Kaplan Meier (KM) curves from DESTINY-Breast04 were used and a visual fit assessment, examination of the log-cumulative hazard plots, and goodness-of-fit scores using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were used to determine the most appropriate approach to fit the various parametric models. Finally, clinical expert validation of the fitted models was included. The submitting company applied independent log-logistic models to both treatment arms for OS and PFS in the base case. For PFS, although generalised gamma seemed to be the better fit visually and statistically, there were some issues with its long-term clinical outcomes. For TTD the generalised gamma curve was selected to inform the model base case as it provides a good statistical fit and good visual fit to the KM data.
Quality of life	Quality of life was captured through utility values applied to the progression-free and post-progression health states. The progression-free utility values were derived from DESTINY-

	Breast04. For the post-progression health state the submitting company applied a previously accepted published algorithm from Lloyd et al using DESTINY-Breast04 response data. This resulted in a value of 0.6101 for trastuzumab deruxtecan and 0.5655 for TPC post-progression. The company did not apply any AE disutilities in the base case. Scenarios incorporating AE disutilities were provided.
Costs and resource use	Medicine costs included were medicine acquisition costs, administration costs, adverse event costs and subsequent treatment costs. A 50% vial sharing was also applied. Other costs and savings included were health-state unit costs and terminal care costs. The submitting company assumed the same resource use across health state and treatment arms. After uplifting, the cost applied for terminal care was £4,856.
PAS	A patient access scheme (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. A PAS discount is in place for eribulin and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

Base case results are presented below in Table 6.2. The biggest driver of costs in the model is the medicine acquisition cost, with resource use in the progression-free state being the second largest driver of costs. The results presented do not take account of the PAS for trastuzumab deruxtecan or the PAS for eribulin 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 eribulin due to commercial confidentiality and competition law issues.

Table 6.2. Base case results (list prices)

Technologies	ICER(£/QALY)
TPC	-
trastuzumab deruxtecan	£89,772

TPC = treatment of physician's choice; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year

6.3. Sensitivity analyses

A number of sensitivity analyses were provided, and the key scenarios are summarised in Table 6.3.

Table 6.3. Selected scenario analyses (list prices)

	Scenario	Base case	ICER (£/QALY)
Base case result			**£89,772**
1	0% Vial sharing (with Scottish weight and height: 70kg + 1.64m)	Vial sharing 50%	£104,383
2	100% RDI for T-DXd (with Scottish weight and height)	RDI from DESTINY-Breast04 study	£106,360
3	OS benefit stops at 5 years (with Scottish weight and height)	OS benefit assumed to continue	£104,223

4	Generalised gamma PFS curve (with Scottish weight and height)	Log-logistic PFS curve	£110,565
5	OS distribution: Weibull	Log-logistic OS curve	£127,972
6	Post-progression utilities from DESTINY-Breast04 trial (with Scottish weight and height)	Post-progression utilities from Lloyd et al. 2006	£96,757
7	10 year time horizon	30 year time horizon	£102,859
8	Comparator basket: • capecitabine (46.7%) • paclitaxel (35.5%) • eribulin (10.2%) • vinorelbine (6.1%) • gem-carbo (1%) • nab-paclitaxel (0.5%)	TPC arm from DESTINY-Breast04 study • eribulin (52%) • capecitabine (21%) • nab-paclitaxel (10%) • gemcitabine (9%) • paclitaxel (8%)	£97,808
9	Comparator basket as following (with Scottish weight and height): • eribulin (60%) • capecitabine (25%) • nab-paclitaxel (5%) • gemcitabine (0%) • paclitaxel (10%)		£98,051
Combined scenario analyses			
10	Combined scenario: • 0% vial sharing • RDI 100% for T-DXd • OS benefits of T-DXd stop at 5 years • AE disutilites are applied • Scottish weight and height		£118,863
11	Combined scenario: • 0% vial sharing • RDI of 100% for T-DXd • AE disutilities • PFS curve set to generalised gamma • Basket of comparators from scenario 9. • Scottish weight and height		£125,147

RDI = relative dose intensity; AE = adverse events; PFS = progression-free survival; OS = overall survival; TPC = treatment of physician's choice; T-DXd = trastuzumab deruxtecan; ICER =incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

6.4. Key strengths

- The model type was appropriate for decision making.
- The DESTINY-Breast04 study reached its primary outcome and key secondary outcomes were also favourable to trastuzumab deruxtecan.
- The handling of resource use and costs were good.

6.5. Key uncertainties

- Vial sharing is unlikely to be at 50% in NHS Scotland due to few patients. 0% was indicated as realistic by clinicians.
- The generalised gamma function was identified as a potentially plausible way of extrapolating PFS. Scenario analysis shows that the ICER increases when this is applied (see scenario 4). A combined scenario with the alternative extrapolation was also explored (scenario 11).
- It is uncertain if the proportions in the comparator basket represents the likely proportions of comparators in real practice in NHS Scotland. Additional scenarios exploring this were provided (scenarios 8 and 9).
- The utility values from the DESTINY-Breast04 study were high for the disease population of interest, which could have been influenced by bias in the open-label study. Sensitivity analysis was provided using lower median PFS utility values from the study which resulted in a small increase in the ICER.
- The study cohort population may not be an accurate representation of the patient population in NHSScotland, and this was evidenced in the average weight and height used in the model when based on the patient population. A number of scenarios were provided in table 6.3 using Scottish population weight and height.

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

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 and agreed that the criterion for a substantial improvement in life expectancy was satisfied. In addition, 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 modifiers, the Committee accepted trastuzumab deruxtecan for use in NHSScotland.

8. Guidelines and Protocols

The European Society of Medical Oncology (ESMO) published clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer in 2021. In May 2023, an update provides recommendations for patients with oestrogen receptor positive and HER2-negative metastatic breast cancer.[3, 4]

The National Institute of Health and Care Excellence (NICE) clinical guideline number 81: Advanced breast cancer: diagnosis and treatment was published in February 2009 and updated in August 2017.[8]

9. Additional Information

9.1. Product availability date

March 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
trastuzumab deruxtecan	**5.4 mg/kg intravenously every 21 days**	**5,820**

Costs from BNF online on 7 August 2023. Costs calculated based on a 70kg patients 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 125 patients eligible for treatment with trastuzumab deruxtecan in Year 1 and 139 in Year 5, to which confidential uptake rates were applied.

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.

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

References

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3. Gennari A, Andre F, Barrios CH, Cortes J, de Azambuja E, DeMichele A*, et al.* ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32(12):1475-95. Epub 2021/10/23.
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5. Gilead Sciences Limited. Sacituzumab govitecan 180 mg powder for concentrate for solution for infusion (Trodelvy). Summary of product characteristics. Electronic Medicines Compendium. available at: www.medicines.org.uk/ Last updated: 29 June 2023.
6. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E*, et al.* Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. New England Journal of Medicine. 2022;387(1):9-20.
7. Daiichi Sankyo I. Clinical Study Report for DS8201-A-U303. Data cut-off date: 11 Jan 2022. Data on File. 2022.
8. The National Institute of Health and Care Excellence (NICE). Clinical guideline number 81: Advanced breast cancer: diagnosis and treatment, updated in August 2017. www.nice.org.uk/.

This assessment is based on data submitted by the applicant company up to and including 15 September 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.