Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2298

trastuzumab emtansine 100mg and 160mg powder for concentrate for solution for infusion (Kadcyla®)

Roche Products Limited

9 October 2020

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

ADVICE: following a full submission

trastuzumab emtansine (Kadcyla®) is accepted for use within NHSScotland.

Indication under review: As a single agent, for the adjuvant treatment of adult patients with human epidermal growth factor-2 (HER2) positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2 targeted therapy.

Trastuzumab emtansine was associated with a statistically significant improvement in invasive disease-free survival compared with a HER2 targeted agent in patients with HER2 positive early breast cancer with residual invasive disease in the breast and/or axillary lymph nodes after completion of neoadjuvant treatment containing a HER2 targeted agent.

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.

Chairman
Scottish Medicines Consortium

Indication

Trastuzumab emtansine, as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.[1]

Dosing Information

The recommended dose of trastuzumab emtansine is 3.6mg/kg bodyweight administered as an intravenous infusion every 3 weeks (21-day cycle). The initial intravenous infusion should be given over 90 minutes; patients should be observed during the infusion and for at least 90 minutes following the initial infusion for fever, chills, other infusion-related reactions, and possible subcutaneous infiltration during administration. If the initial infusion was well tolerated, subsequent infusions can be administered over 30 minutes. Patients should be observed during the infusion and for at least 30 minutes after the infusion.

Patients should receive treatment for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity.

Trastuzumab emtansine should only be prescribed by a physician and administered as an intravenous infusion under the supervision of a healthcare professional who is experienced in the treatment of cancer patients.

For advice on adjusting doses and infusion rates according to adverse reactions, see the Summary of Product Characteristics (SPC).[1]

Product availability date

16 December 2019

Trastuzumab emtansine meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Trastuzumab emtansine is an antibody-drug conjugate. It contains the humanised anti-HER2 immunoglobulin, trastuzumab, covalently linked to the microtubule inhibitor DM1 via a stable thioether linker. The combination of DM1 and the linker is known as emtansine. Trastuzumab emtansine has the mechanisms of action of both trastuzumab and DM1. The conjugation of DM1 to trastuzumab allows the cytotoxic agent to selectively target HER2 overexpressing tumour cells. Trastuzumab inhibits shedding of the HER2 extracellular domain, inhibits signalling through the phosphatidylinositol 3-kinase (PI3-K) pathway, and mediates antibody-dependent cell-mediated cytotoxicity. Trastuzumab emtansine has previously been accepted by SMC for use in HER2 positive, unresectable locally advanced or metastatic breast cancer.[1]

KATHERINE was a phase III, open-label, randomised, multicentre study that evaluated the efficacy and safety of trastuzumab emtansine compared with trastuzumab in 1,486 patients with HER2-

positive primary breast cancer who had received neoadjuvant chemotherapy and HER2-targeted therapy (including trastuzumab), followed by surgery, and had a finding of pathologically documented residual invasive disease (RID) in the breast or axillary lymph nodes.[2]

Patients were randomised equally to receive trastuzumab emtansine 3.6mg/kg intravenously on day 1 of a 3 week cycle for 14 cycles (n= 743) or trastuzumab 6mg/kg (8mg/kg if a loading dose was required) intravenously on day 1 of a 3 week cycle for 14 cycles (n= 743). Treatment could be discontinued in the event of disease recurrence, unacceptable toxicity, or study termination by the sponsor. Dose reductions were permitted for the trastuzumab emtansine group only. Patients that discontinued treatment with trastuzumab emtansine due to toxicity were able to complete 14 cycles of treatment with trastuzumab at the discretion of the investigator. Radiotherapy and hormone therapy were administered concomitantly if indicated as per local guidance and trial protocol. Randomisation was stratified according to clinical stage at presentation, hormone receptor status, preoperative HER2 therapy, and pathological nodal status after neoadjuvant therapy.[2, 3]

The primary outcome, invasive disease–free survival (IDFS), was defined as the time from randomisation until the date of the first occurrence of one of the following IDFS events: recurrence of ipsilateral invasive breast tumour, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. Efficacy analyses were performed in the intention-to-treat population (ITT), which included all patients who underwent randomisation.[2, 3]

The KATHERINE study met its primary outcome; trastuzumab emtansine was associated with a statistically significant improvement in IDFS compared with trastuzumab in patients with HER2 positive early breast cancer with RID in the breast and/or axillary lymph nodes after completion of neoadjuvant treatment containing a HER2 targeted agent. The early reporting efficacy boundary was crossed at the pre-specified interim analysis, which triggered full trial analysis at a median follow-up of 41.4 months in the trastuzumab emtansine group and 40.9 months in the trastuzumab group.[2, 3] See Table 1.

Table 1. Primary outcome results for KATHERINE study (ITT population). Data cut-off: 25 July 2018.[2, 3]

	Trastuzumab emtansine (n= 743)	**Trastuzumab (n= 743)**
Median follow-up (months)	41.4	40.9
Number of IDFS events (%)	91 (12%)	165 (22%)
Hazard Ratio (95% CI)	0.50 (0.39 to 0.64) p<0.001	
Median time to event	NE	NE
3 year event-free estimate	88%	77%

CI = confidence interval; IDFS = invasive disease-free survival; NE = not estimable

Distant recurrence was the most common IDFS event reported in both study groups (82% versus 66% of total IDFS events in the trastuzumab emtansine and trastuzumab groups respectively).

Overall both treatment groups had similar numbers of CNS recurrences, however there was a greater number of CNS recurrences reported as the first IDFS event in the trastuzumab emtansine group than in the trastuzumab group (47% versus 18%). Sensitivity analyses of IDFS that censored for new anti-cancer treatment and discontinuation of study treatment were consistent with the primary analysis. Subgroup analyses of the primary outcome showed consistent benefit across subgroups with trastuzumab emtansine treatment compared with trastuzumab.[2, 3]

Secondary outcomes included overall survival, IDFS (STEEP definition, including second primary non-breast cancer events), disease free survival, and distant recurrence free interval, the results of which were generally supportive of treatment with trastuzumab emtansine. A hierarchical statistical testing strategy was applied in the study, however overall survival was the only secondary outcome included and therefore the only secondary outcome that was tested formally. Due to the immaturity of the data, no conclusions can be drawn on the effect of trastuzumab emtansine on overall survival. See Table 2.

Table 2. Secondary outcome results for KATHERINE study (ITT population). Data cut-off: 25 July 2018.[2, 3]

	Trastuzumab emtansine (n= 743)	**Trastuzumab (n= 743)**
Overall survival		
Number of events (%)	42 (5.7%)	56 (7.5%)
Hazard ratio (95% CI)	0.70 (0.47 to 1.05) p= 0.08	
Median time to event	NE	NE
3 year event-free estimate	95%	94%
IDFS (STEEP definition)		
Number of events (%)	95 (13%)	167 (22%)
Hazard ratio (95% CI)	0.51 (0.40 to 0.66)	
3 year event-free estimate	88%	77%
Disease-free survival		
Number of events (%)	98 (13%)	167 (22%)
Hazard ratio (95% CI)	0.53 (0.41 to 0.68)	
3 year event-free estimate	87%	77%
Distant recurrence-free interval		
Number of events (%)	78 (10%)	121 (16%)
Hazard ratio (95% CI)	0.60 (0.45 to 0.79)	
3 year event-free estimate	90%	83%

CI = confidence interval; IDFS = invasive disease-free survival; NE = not estimable; STEEP = standardised definitions for efficacy endpoints

Health Related Quality of Life (HRQoL) was assessed using 2 questionnaires: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30

(QLQ-C30) and QLQ–Breast Cancer (QLQ-BR23). These instruments were used at screening, at day 1 of cycles 5 and 11, within 30 days after study drug completion, and at 6 and 12 month follow-up.[4, 5] No mean change from baseline at any time point in either treatment group exceeded the threshold for a clinically meaningful deterioration. When comparing the proportion of patients that reported a clinically meaningful deterioration in selected scales at any time point, trastuzumab was favourable in 12 out of the 14 reported scales. The most notable differences between treatment groups were in the following scales: systemic therapy with side effects (13% more patients with clinically meaningful deterioration in the trastuzumab emtansine group), appetite loss (11% more in the trastuzumab emtansine group), constipation (9% more in the trastuzumab emtansine group), nausea/vomiting (9% more in the trastuzumab emtansine group), and role functioning (8% more in the trastuzumab emtansine group).[5]

Summary of evidence on comparative safety

In the KATHERINE study at data cut-off 25 July 2018, the median duration of treatment in both the trastuzumab emtansine group and the trastuzumab group was 10 months. Adverse events (AE) were reported by 99% (731/740) of patients in the trastuzumab emtansine group and 93% (672/720) in the trastuzumab group. In the trastuzumab emtansine and trastuzumab groups respectively, the proportion of patients reporting a grade 3 or higher AE was 26% versus 15%, patients with a reported serious AE was 13% versus 8.1%, and patients discontinuing therapy due to an AE was 18% versus 2.1%. Around 10% (71/743) of patients in the trastuzumab emtansine group switched to trastuzumab treatment during the study.[2, 3]

The most frequently reported AEs of any grade with an incidence >20% in the trastuzumab emtansine group versus the trastuzumab group were: fatigue (50% versus 34%), nausea (42% versus 13%), decreased platelet count (28% versus 2.4%), elevated aspartate aminotransferase (28% versus 5.6%), headache (28% versus 17%), arthralgia (26% versus 21%), radiation skin injury (25% versus 28%), elevated alanine aminotransferase (23% versus 5.7%), epistaxis (22% versus 3.5%), and hot flush (13% versus 20%). One death during the study was considered related to treatment with trastuzumab emtansine. The patient died of an intracranial haemorrhage after the first dose of trastuzumab emtansine.[3]

Summary of clinical effectiveness issues

Breast cancer is the most common cancer in women in Scotland, with 4,711 new cases diagnosed in 2017.[6] Around 15 to 20% of breast cancers have an overexpression of HER2, and if left untreated are associated with aggressive tumour growth and poor clinical outcomes. Treatment of HER2 positive early breast cancer involves loco-regional surgery, radiotherapy, and systemic anti-cancer treatment. The most common chemotherapy regimens contain anthracyclines and/or taxanes, which can be given with HER2-targeted therapies either in the neoadjuvant or adjuvant setting. In the neoadjuvant setting, high risk patients in Scotland receive chemotherapy plus

pertuzumab and trastuzumab. It is estimated that patients with HER2 positive early breast cancer who receive neoadjuvant therapy will achieve pathological complete response (pCR) in approximately 40 to 60% of instances, leaving the rest with RID. The amount of residual disease present following neoadjuvant treatment is an important prognostic factor. At present, patients with HER2 positive early breast cancer who have RID, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2 targeted therapy will receive adjuvant trastuzumab.[3] Clinical experts consulted by SMC considered that trastuzumab emtansine fills an unmet need in this therapeutic area as patients with RID are at high risk of relapse despite currently available treatments. Trastuzumab emtansine meets SMC orphan equivalent criteria.

In the KATHERINE study, trastuzumab emtansine was associated with a statistically significant and clinically meaningful improvement in IDFS compared with the most relevant comparator in clinical practice, trastuzumab. In patients with HER2 positive early breast cancer with RID, the risk of an IDFS event was reduced by 50%. The EMA state that IDFS is an appropriate primary outcome as it implies reduced probability of local or distant relapse and has previously been used to evaluate benefit in the adjuvant setting of early breast cancer.[3] However, one limitation of the IDFS definition used in the study was that it did not include second primary non-breast cancer as an event. A broader definition of IDFS, using STEEP criteria that includes second primary non-breast cancer events, was analysed as a secondary outcome and showed consistent results with the primary analysis.[2]

There were some limitations to the KATHERINE study that should be considered. Firstly, the median follow-up of 41.4 months and 40.9 months in the trastuzumab emtansine and trastuzumab groups respectively can be considered a limited time period for a study in the adjuvant breast cancer setting. Consequently, overall survival data were immature, and when coupled with the fact that the study was underpowered to detect statistical differences in overall survival, conclusions are difficult to draw from the available data. Final analysis results are expected in June 2024.[3]

A further limitation of the study was the open-label design, which may have contributed to more patients in the trastuzumab group exiting the study before receiving first dose of study drug. However, the numbers involved were small (23 patients versus 4 patients in the trastuzumab and trastuzumab emtansine groups respectively) and were not expected to have a relevant impact on the results.[3] The open-label design may also have biased the reporting of safety and quality of life outcomes.

Fewer than a quarter of patients received a HER2 targeting medicine (such as pertuzumab) in addition to trastuzumab (20%) as part of neoadjuvant therapy in the study, which is now considered standard practice for patients with “high risk” disease. This was not standard practice when the study was designed. Subgroup analysis of patients who received dual HER2 targeting therapies produced consistent central estimates of treatment effect compared with the primary results.[3]

Trastuzumab emtansine was considerably more toxic than trastuzumab. Both the frequency and severity of AEs were greater in the early breast cancer setting than what has been reported previously with trastuzumab emtansine use. The SPC has been updated to warn of safety risks, mainly related to thrombocytopenia, haemorrhage, hepatotoxicity, and peripheral neuropathy.[3]

Clinical experts consulted by SMC considered that trastuzumab emtansine is a therapeutic advancement due to the IDFS benefit over treatment with trastuzumab, and would be the new standard of care for patients with HER2-positive early breast cancer who have RID following neoadjuvant therapy. The route of administration of trastuzumab emtansine (intravenous infusion) may be less favourable than that of trastuzumab, which is available both as a subcutaneous injection or intravenous infusion. Consequently, this could have implications for patients and oncology day units.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of trastuzumab emtansine versus trastuzumab as adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2 targeted therapy. SMC clinical expert feedback was that trastuzumab is the most relevant comparator, as included in the economic analysis.

The economic analysis used a Markov model with seven health states: IDFS – on treatment, IDFS – off treatment, non-metastatic recurrence, remission, first-line treatment for metastatic breast cancer (mBC), subsequent treatment lines for mBC (second+ line mBC), and death. The model used a 6-monthly cycle with half cycle correction applied, and adopted a lifetime horizon of 51 years, with patients entering the model at a median age of 49 years.

The clinical data for trastuzumab emtansine and trastuzumab were taken from the randomised, phase 3 KATHERINE study, which informed the patient baseline characteristics, clinical variables, treatment duration, utilities, and adverse events for the economic model. As direct head-to-head data were available no indirect comparison was conducted.

The estimation of long-term efficacy to (non-metastatic) recurrence and transition to metastatic breast cancer were based on observed KATHERINE data for IDFS and extrapolated to 10 years fitting the Generalised gamma parametric function to the Kaplan-Meier data for both treatment arms. Adjustments were made to the fitted curves to account for a decreasing risk of recurrence over time, based on long-term trastuzumab published data. From 10 years it is assumed that only 5% of patients are at risk of recurrence (95% assumed ‘cured’) with risk rate for these patients derived from KATHERINE, and applied to both treatment arms. Patients were assumed to transition to remission after receiving one-year of adjuvant therapy due to a non-metastatic recurrence. Rate of progression from first-line mBC to later lines was based on was based on published literature or additional clinical trials, with patients receiving different rates of transitioning to second+ line metastatic breast cancer dependent on time to relapse.

Mortality is based on general population background mortality, with an increased risk of dying without recurrence based on the KATHERINE study in the early breast cancer health states, and an increased risk of death based on additional clinical studies in the metastatic disease states.

Time on treatment for trastuzumab emtansine and trastuzumab was based on the KATHERINE study, with a maximum of 14 cycles for each therapy. Treatment effect of trastuzumab emtansine is assumed to be maintained for 7 years with a linear decreasing to no treatment effect at 10 years.

Utility values were derived using EQ-5D-3L data collected in the KATHERINE clinical trial using UK preference-based scores. In the IDFS health states utilities were specified by treatment and were assumed to account for disutilities due to adverse events. Utility values for the other health states were assumed equivalent to the IDFS utilities or sourced from published literature. Utility values were age adjusted.

Costs included medicine acquisition, medicine administration, subsequent therapies, and treatment of adverse events. Resource usage for health state monitoring and adverse event management whilst on subsequent therapies were based on previous NICE technology appraisals and validated via an advisory board with expert clinicians.

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 NHS Scotland. Under the PAS, a discount was offered on the list price of trastuzumab emtansine. A confidential price discount for the comparator trastuzumab (Herceptin) in intravenous formulation is also available.

In the base case for trastuzumab emtansine versus trastuzumab the incremental cost-effectiveness ratio (ICER) is estimated at £3,250 per quality adjusted life year (QALY), with the PASs for both treatments applied. Compared to trastuzumab, trastuzumab emtansine was estimated to increase survival by 1.33years. The driver of cost differences is the medicine acquisition costs for trastuzumab emtansine.

Table 3: Base case results for trastuzumab emtansine versus trastuzumab (discounted, with PASs applied for both treatments)

Analysis	Treatment	Total LYs	ICER (cost/QALY)
Base case	Trastuzumab emtansine	17.03	£3,250
	Trastuzumab	15.69	-

LY= life year; PAS= patient access scheme; QALY = quality adjusted life year

In one-way sensitivity analysis the ICER was most sensitive to varying the utility value in the IDFS off-treatment health state for trastuzumab emtansine, followed by varying the same parameter but for the trastuzumab arm. The next most influential parameter was the proportion of metastatic events after the early recurrence threshold for trastuzumab. A range of scenario analyses were performed, with the potentially most plausible scenarios presented in the table below alongside scenarios which had the greatest impact on the ICER. The scenario analyses which had the greatest upward impact on the ICER was the time horizon, 'cure' rate, treatment duration

and the proportion of patients receiving subcutaneous trastuzumab compared with intravenous therapy.

Table 4: Selected scenario analysis results for trastuzumab emtansine

	Trastuzumab emtansine versus trastuzumab scenario analysis	**Incremental LYs**	**ICER**
1	Treatment duration: administered until disease recurrence (per label)	1.33	£5,262
2	Early breast cancer utilities pooled (KATHERINE)	1.33	£3,153
3	Trastuzumab subcutaneous market share 70% (84% in base case)	1.33	£5,828
4	IDFS: parametric distribution applied as KM + log-logistic	1.65	Trastuzumab emtansine dominant
5	IDFS: parametric distribution applied as Generalized gamma	1.38	£2,999
6	Treatment effect maintained over time [limited to 7 years in base case with waning to 10 years]	1.28	£4,330
7	Incremental treatment effect decreases from 48 months [84 months in base case]	1.31	£3,523
8	Time horizon 10 years	0.30	£27,029
9	Time horizon 30 years	1.10	£4,096
10	Definition of early relapsers as 24 months [18 months in base case]	1.36	£3,698
11	Treatment effect decreases from 48 months with waning until 8 year, no benefit assumed beyond this point, 20 year time horizon, 70% patients receive SC trastuzumab	NR	£8,724
12	A 20 year time horizon, 70% patients receive subcutaneous trastuzumab, and a maximum 'cure' proportion of 80% [95% in base case];	NR	£9,465

IDFS = invasive disease-free survival; LY = life year; NR = not reported; PAS = patient access scheme; QALY = quality adjusted life year

The main weakness of the economic analysis is the immaturity of the data which led to uncertainties and challenges in the modelling relating to:

- The median follow-up period in the ITT population was 41.43 months and 40.94 months in the trastuzumab emtansine and trastuzumab arms, respectively. At the time of the primary analysis of IDFS, only 12.2% and 22.2% IDFS events had occurred in the trastuzumab emtansine and trastuzumab arms, respectively, necessitating long extrapolation over a lifetime horizon for all health states, and requiring assumptions of long-term treatment effect duration.
- The lack of observed data leads to uncertainties particularly in the mid to long term. The duration of follow up, and lack of events, leads to uncertainty in the rate of recurrence for

patients over the long-term resulting in additional extrapolation uncertainty due to the fitting of parametric function to early data (around 4 years) where patients are at higher risk of disease recurrence than in the longer-term, where risk of disease recurrence is expected to decrease. Hence, the company adjusted the extrapolated data based on long-term trastuzumab data.

- The duration of follow up leads to overall survival data immaturity (93% alive at end of KATHERINE follow up), with the study underpowered to detect differences in overall survival, and limiting survival analysis options in the economic model.
- The economic analysis could be strengthened through greater (more long-term) evidence of trastuzumab emtansine, versus trastuzumab, in patients with early breast cancer. The KATHERINE trial is ongoing, therefore the uncertainty associated with extrapolations and treatment effect duration in the medium term is likely to be lessened with later study data cuts.

Despite the above limitations the economic case was demonstrated.

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

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Breast Cancer Now, which is a registered charity.
- Breast Cancer Now has received 5% pharmaceutical company funding in the past two years, including from the submitting company.
- A diagnosis of breast cancer can cause considerable anxiety to patients. The initial diagnosis can be shocking and in the longer-term, the fear of breast cancer returning or spreading to other parts of the body can be extremely frightening. Around a quarter of people with HER2-positive breast cancer experience a recurrence within 10 years.
- Trastuzumab emtansine provides improvements in invasive disease-free survival in patients who have residual disease after neoadjuvant HER2-targeted therapy, compared to the current standard of care in Scotland, trastuzumab.
- Around 40-60% of patients have residual invasive breast cancer following neoadjuvant HER2-targeted therapy. These patients have a significantly worse prognosis, and adjuvant trastuzumab emtansine could offer them a valuable new treatment option
- The improvements offered by trastuzumab emtansine would be welcomed by breast cancer patients. Many patients find that fear of recurrence has a big impact on their quality of life, and the possibility of recurrence can be extremely frightening to patients in the longer-term, once treatment has finished.
- As with any breast cancer treatment, trastuzumab emtansine does have some side effects which can negatively impact patients' quality of life and may cause them to discontinue

treatment. However, a patient consulted by the patient group who had recently begun taking trastuzumab emtasine, found the side effects of the treatment minimal and easier to manage than her neoadjuvant, trastuzumab, pertuzumab and docetaxel treatment.

Additional information: guidelines and protocols

The European Society of Medical Oncology (ESMO) Clinical practice guidelines on early breast cancer (2019) state that patients with HER2 positive early breast cancer should receive chemotherapy (sequential anthracycline/taxane-based regimen is the standard for the majority of patients) plus trastuzumab ± pertuzumab. One year of (neo) adjuvant trastuzumab remains a standard for the vast majority of HER2-positive patients. Trastuzumab plus pertuzumab can be considered in high-risk patients, defined as N-positive or oestrogen receptor negative, for the duration of 1 year, starting before or after surgery.[7]

Additional information: comparators

Trastuzumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per cycle (£)
trastuzumab emtansine	3.6mg/kg bodyweight administered as an intravenous infusion every 3 weeks for 14 cycles	£4,267

Cost based on a patient bodyweight of 70kg. Costs from BNF online on 30 July 2020. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 107 patients treated with trastuzumab emtansine in year 1, rising to 162 in year 5.

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 budget impact template includes the PAS for both trastuzumab emtansine and trastuzumab, as both PASs are known by the submitting company.

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

References

1. Roche Products Ltd. Trastuzumab emtansine (Kadcyla) 100mg and 160mg powder for concentrate for solution for infusion. Summary of product characteristics. Electronic Medicines Compendium. www.medicines.org.uk Last updated 28 January 2020.
2. von Minckwitz G, Huang C-S, Mano MS, Loibl S, Mamounas EP, Untch M*, et al.* Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. New England Journal of Medicine. 2019;380(7):617-28.
3. European Medicines Agency (EMA). European Public Assessment Report. Trastuzumab emtansine (Kadcyla). EMA/652550/2019. 14 November 2019. www.ema.europa.eu.
4. Schneeweiss A, Loibl S, Mamounas EP, von Minckwitz G, Mano M, Untch M*, et al.* ASCO 2019. Poster 513. Patient-Reported Outcomes from KATHERINE: A Phase III Study of Adjuvant Trastuzumab Emtansine vs Trastuzumab in Patients with Residual Invasive Disease after Neoadjuvant Therapy for HER2-Positive Breast Cancer.
5. Conte P SA, Loibl S, et al.,. Patient-reported outcomes from KATHERINE: A phase 3 study of adjuvant trastuzumab emtansine versus trastuzumab in patients with residual invasive disease after neoadjuvant therapy for human epidermal growth factor receptor 2-positive breast cancer. Cancer. 2020;126(13):3132-3139. doi:10.1002/cncr.32873.
6. Scotland PH. Cancer Statistics - Breast Cancer - available here: https://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Breast.
7. Cardoso F, Committee obotEG, Kyriakides S, Committee obotEG, Ohno S, Committee obotEG*, et al.* Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2019.

This assessment is based on data submitted by the applicant company up to and including 11 September 2020.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.