National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Breast Cancer Now	Yes, the topic is appropriate for a NICE appraisal.	Thank you for your comment. No action needed.
	METUPUK	Yes trastuzumab deruxtecan is a step-change drug which provides greater PFS and OS than the comparators in second and third/later line treatment of HER2 positive metastatic breast cancer.	Thank you for your comment. No action needed.
	Daiichi Sankyo UK Ltd	Yes.	Thank you for your comments. No action needed.
Wording	Breast Cancer Now	Yes, the wording seems appropriate.	Thank you for your comment. No action needed.

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	METUPUK	The marketing authorisation is not stated so it is difficult to make meaningful comments. The conditional marketing authorisation on the CDF is 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. ie. Third line and beyond. The draft scope is for patients who have received one (or more?) prior anti-HER2-based regimens.	Thank you for your comment. No action needed. The proposed marketing authorisation is not yet in the public domain. The clinical trial for this evaluation is for people with HER2-positive, unresectable or metastatic breast cancer previously treated with trastuzumab and taxane. TA704 appraised trastuzumab deruxtecan in patients who have received two or more prior anti-HER2-based regimens.
	Daiichi Sankyo UK Ltd	Daiichi Sankyo propose the wording of the remit is aligned to the anticipated regulatory wording: "To appraise the clinical and cost effectiveness of trastuzumab deruxtecan within its Marketing Authorisation for patients with HER2-positive unresectable or metastatic breast cancer [redacted]	Thank you for your comment. The anticipated regulatory wording is not in the public domain. The trial for this indication is in the public domain and is for people with HER2-

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			positive, unresectable or metastatic breast cancer previously treated with trastuzumab and taxane.
Timing Issues	Breast Cancer Now	Metastatic (secondary) breast cancer is incurable and there is an urgent need for new treatment options which can improve outcomes for this patient group. We hope this appraisal can be progressed in a timely manner.	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	METUPUK	Trastuzumab deruxtecan should remain available to all eligible NHS patients on the cancer drug fund pending a NICE decision. As long as trastuzumab deruxtecan remains available the urgency of the appraisal is reduced.	Thank you for your comment. No action needed.
	Daiichi Sankyo UK Ltd	Daiichi Sankyo considers the NICE Single Technology Appraisal (STA) route is appropriate to deliver timely guidance to the NHS for this topic. Despite the availability of trastuzumab emtansine (T-DM1), a high unmet need for improved survival outcomes still exists for patients with HER2-positive, unresectable or metastatic breast cancer [redacted]. Treatments shown to increase progression-free survival (PFS) are highly valued by patients with incurable breast cancer.[1]	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this

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			topic into its work programme. No action needed.

Comment 2: the draft scope

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Background information	Breast Cancer Now	The information appears to be accurate	Thank you for your comment. No action needed.
	Daiichi Sankyo UK Ltd	For completeness, Daiichi Sankyo proposes that it should be made clear that HER2-positive breast cancer is not defined only by higher expression of HER2 receptors, but by specific criteria related to HER2 receptor expression (assessed by immunohistochemistry [IHC]) and HER2 gene copy number (assessed by gene fluorescence in situ hybridisation [FISH] amplification).[2] Positivity for HER2 is defined as a score of 3+ on IHC analysis or as IHC score of 2+ and a positive ISH result.[2] Daiichi Sankyo propose the following wording to replace the final two sentences in the first paragraph. “Positivity for HER2 is defined as a score of 3+ on immunohistochemistry [IHC] analysis (i.e. substantially overexpress the HER2 receptor) or as IHC score of 2+ and a positive in situ hybridisation [ISH] result (i.e. multiple copies of the HER2 gene).” For completeness, Daiichi Sankyo would propose to replace the sentence “Current treatments for advanced breast cancer aim to relieve symptoms, prolong survival and maintain a good quality of life with few adverse events”	Thank you for your comment. The background section was updated. The scope is a brief document. This level of detail can be included in the submission.

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		with “Current treatments for advanced breast cancer aim to relieve symptoms, prolong survival and maintain a good quality of life *while managing adverse event*s.”	
The technology/ intervention	Breast Cancer Now	Yes to the best of our knowledge	Thank you for your comment. No action needed.
	METUPUK	It is correct to state that trastuzumab deruxtecan has been compared to trastuzumab emtansine (DESTINY-Breast03 trial). It has also been compared to investigator’s choice of chemotherapy in patients who have received two or more prior anti-HER2 based regimens (DESTINY-Breast02 trial). Indeed, this is the indication that trastuzumab deruxtecan is currently being used for on the CDF.	Thank you for your comment. No action needed. TA704 appraised trastuzumab deruxtecan in patients who have received two or more prior anti-HER2-based regimens.
	Daiichi Sankyo UK Ltd	For consistency with TA704 for trastuzumab deruxtecan (T-DXd) as treatment for patients with HER2-positive unresected of metastatic breast cancer after 2 or more anti-HER2+ therapies,[3] Daiichi Sankyo proposes the wording is updated as follows: “Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate (ADC) composed of three components: 1) a humanised anti-HER2 IgG1 monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab, covalently linked to 2) a topoisomerase I inhibitor, an exatecan derivative, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of the linker and the topoisomerase I inhibitor.”	Thank you for your comment. No action needed. The scope is a brief document. This detail can be included in the submission.

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		Daiichi Sankyo would propose amending the wording around the proposed Marketing Authorisation for T DXd as described immediately below.	
Population	Breast Cancer Now	It appears to be defined accurately.	Thank you for your comment. No action needed.
	METUPUK	For trastuzumab deruxtecan in the second line setting, this is the correct population. It should be noted trastuzumab deruxtecan is also effective in later lines.	Thank you for your comment. No action needed.
	Daiichi Sankyo UK Ltd	Daiichi Sankyo would like to advise that the anticipated indication is as follows: "Enhertu as monotherapy for patients with HER2-positive unresectable or metastatic breast cancer [redacted] Please update the wording throughout in line with the anticipated indication wording. No relevant subgroups have been identified within the trial that should be considered separately. Trial outcomes for the primary endpoint, PFS, are homogenous across pre-specified subgroups in DESTINY-Breast03.	Thank you for your comment. The anticipated regulatory wording is not in the public domain. The trial for this indication is in the public domain and is for people with HER2-positive, unresectable or metastatic breast cancer previously treated with trastuzumab and taxane.

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Comparators	Breast Cancer Now	Yes trastuzumab emtansine (Kadcyla) is routinely approved for use on the NHS for progression of HER2-positive metastatic breast cancer after previous treatment with a taxane or trastuzumab.	Thank you for your comment. No action needed.
	METUPUK	For patients who have received one or more prior anti-HER2-based regimens it is appropriate to compare trastuzumab deruxtecan to trastuzumab emtansine, in the second line setting. In the third line and beyond setting, trastuzumab deruxtecan is being evaluated by NICE TA704. It is currently offered to patients on the cancer drug fund 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 therapies.	Thank you for your comment. No action needed.
	Daiichi Sankyo UK Ltd	Yes. Daiichi Sankyo considers T-DM1 to be the relevant comparator for this decision problem. T-DM1 is the only NICE assessed and approved treatment at this point in the treatment pathway for patients with HER2-positive metastatic breast cancer [TA458],[4] and is the only licensed therapy recommended as a second-line treatment option for patients with HER2-positive metastatic breast cancer in the 2021 ESMO Clinical Practice Guidelines.[6] As stated in the ESMO Clinical Practice Guidelines, T DXd is expected to replace T DM1 as standard of care in the second-line setting.[6]	Thank you for your comments. No action needed.
Outcomes	Breast Cancer Now	Yes	Thank you for your comment. No action needed.

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	METUPUK	Yes we are satisfied with the stated outcomes.	Thank you for your comment. No action needed.
	Daiichi Sankyo UK Ltd	Daiichi Sankyo considers the outcome measures listed in the draft scope are appropriate, and comprise the important outcomes for the assessment of health-related benefits and harms. For completeness, the primary endpoint of DESTINY-Breast03 is PFS based on blinded independent central review (BICR).[7] Secondary endpoints include PFS based on investigator's assessment (IA), overall survival (OS), objective response rate (ORR) and duration of response (based on BICR and IA) and safety.	Thank you for your comments. No action needed.
Economic analysis	Daiichi Sankyo UK Ltd	No additional comments. Daiichi Sankyo intends to submit a cost effectiveness analysis of treatments expressed in terms of incremental cost per quality-adjusted life year, consistent with the NICE reference case.	Thank you for your comment. No action needed.
Equality and Diversity	Breast Cancer Now	The scope does not appear to promote discrimination	Thank you for your comment. No action needed.
	Daiichi Sankyo UK Ltd	Daiichi Sankyo are not aware of any issues of inequality in the management of breast cancer in England and Wales.	Thank you for your comment. No action needed.
Other considerations	METUPUK	In the draft scope, under Related NICE recommendations and NICE Pathways it is stated there are no related appraisals in development. This is incorrect, NICE TA704 is appraising trastuzumab deruxtecan for the	Thank you for your comments. TA704 is already completed and is for a later line of

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		treatment of HER2-positive unresectable or metastatic breast cancer in adults after 2 or more anti-HER2 therapies.	therapy. No action needed.
	Daiichi Sankyo UK Ltd	None	Thank you for your comments. No action needed.
Innovation	Breast Cancer Now	Yes we consider this treatment to be innovative. Some breast cancer cells have a higher than normal level of a protein called HER2 on their surface, which stimulates them to grow. Trastuzumab works by attaching itself to the HER2 proteins so that the cancer cells are no longer stimulated to grow. It also helps the body's immune system destroy breast cancer cells. When the trastuzumab attaches to the proteins, it delivers deruxtecan directly into the breast cancer cells to kill them. Trastuzumab deruxtecan is already approved for use via the Cancer Drugs Fund for patients with HER2 positive unresectable or metastatic breast cancer after 2 prior anti-HER2 treatments. An ongoing clinical trial has now shown positive results earlier in the treatment pathway, showing an improved progression free survival when compared to trastuzumab emtansine. Treatments shown to increase progression free survival are highly valued by patients with incurable breast cancer. We understand that overall survival data is currently immature.	Thank you for your comments. The extent to which the technology may be innovative will be considered during the evaluation. No action needed.
	METUPUK	Yes, trastuzumab deruxtecan gives patients with HER2 positive MBC a valuable extra treatment line and confers a longer PFS and OS at both the second and third line. We note the extent of OS is not yet mature.	Thank you for your comments. The extent to which the technology may be innovative will be considered during

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			the evaluation. No action needed.
	Daiichi Sankyo UK Ltd	DESTINY-Breast03 is a head-to-head trial vs. the in-scope comparator, T-DM1, and will form the primary evidence source for this STA submission. Based on the data available from the DESTINY-Breast03 trial, Daiichi Sankyo considers T-DXd to be highly innovative and expects the technology to bring significant and substantial improvement in health benefits to patients' lives. Despite previous advances in treatments for unresectable or metastatic breast cancer, survival for patients with HER2-positive disease who have received trastuzumab and/or a taxane as first-line therapy remains limited. In the pivotal 2012 study for T-DM1 in this setting – EMILIA – median PFS in the T-DM1 treatment arm was 9.6 months.[8] This translated into a median OS of 29.9 months.[9] Subsequent clinical trials and real-world studies have demonstrated median PFS outcomes with T-DM1 in the range of 6–7 months.[10,11] Median PFS for T-DM1 in the randomised KATE2 study was 6.8 months, although median OS was not estimable at the second interim analysis.[10] In DESTINY-Breast03, treatment with T-DXd led to a significant 72% reduction in the risk of progression (PFS by BICR) vs. T-DM1 (hazard ratio [HR]=0.2840; P=7.8×10−22)[7] with consistent benefit observed across all pre-specified subgroups.7 Median PFS by BICR was not reached in the T-DXd arm and was 6.8 months in the T-DM1 arm. Median PFS by investigator assessment was 25.1 months vs 7.2 months for T-DXd and T-DM1, respectively (HR=0.27; P=6.5×10−24).[7] Confirmed responses were observed in 79.7% of those receiving T-DXd and 34.2% receiving T-DM1 (P<0.0001).[7] The estimated 12-month OS event rates were 94.1% vs 85.9% for T-DXd and T-DM1, respectively (HR=0.56;	Thank you for your comments. The extent to which the technology may be innovative will be considered during the evaluation. We encourage companies to submit all relevant and available evidence for consideration.

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		P=0.007172), although this did not cross the pre-specified boundary for significance as these data are immature.[7] Based on the DESTINY-Breast03 study, T-DXd has been recommended by ESMO in their 2021 Clinical Practice Guidelines as a second-line treatment option for patients with HER2-positive metastatic breast cancer.[6] Clinical experts have described the efficacy of T-DXd in DESTINY-Breast03 as "unprecedented", and that it will lead to a "paradigm shift in the treatment of HER2 positive metastatic breast cancer".[12] Daiichi Sankyo considers that T-DXd represents a step-change in management vs. the only effective targeted therapy approved by NICE for the target population, assessed via a head-to-head randomised controlled trial.	
Questions for consultation	Breast Cancer Now	***Have all relevant comparators for trastuzumab deruxtecan been included in the scope? Which treatments are considered to be established clinical practice in the NHS for HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane?*** Trastuzumab emtansine would be the key comparator here. ***Where do you consider trastuzumab deruxtecan will fit into the existing NICE pathway, Advanced breast cancer (2018)?*** Whilst the scope states that trastuzumab deruxtecan would be a treatment after trastuzumab and a taxane which may be as a result of the trial design, please note that this treatment would mostly likely following treatment with pertuzumab (Perjeta) in combination with trastuzumab and a taxane. Pertuzumab is the first line treatment for this group of patients.	Thank you for your comment. No action needed.
	METUPUK	The draft scope focused on trastuzumab deruxtecan use in the second line with trastuzumab emtansine as the comparator.	Thank you for your comment. No action needed.

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		We note that the ESMO guidelines published in 2021 also recommend trastuzumab deruxtecan in the second line setting, and we agree with second line use. However, as a patient group, we would like oncologists to use their clinical judgement in deciding whether to deploy trastuzumab deruxtecan in the second or third/later line. Where trastuzumab deruxtecan is used in the second line setting we would like trastuzumab emtansine to remain available in the third line setting. Any patients who have already been treated with trastuzumab emtansine in the second line should be eligible upon progression for trastuzumab deruxtecan in the third (or later) line.	
	Daiichi Sankyo UK Ltd	***Have all relevant comparators for trastuzumab deruxtecan been included in the scope? Which treatments are considered to be established clinical practice in the NHS for HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane?*** Yes. As outlined above, T DM1 is the only NICE assessed and approved therapy in this treatment line, and is considered established NHS clinical practice in this setting following publication of NICE TA458.[4] T DM1 is therefore the relevant comparator for this appraisal. ***Would trastuzumab deruxtecan be used as an alternative to trastuzumab emtansine?*** Yes, T-DXd is intended to be positioned as an alternative to T-DM1 based on the head-to-head clinical trial, DESTINY-Breast03. ESMO 2021 Clinical Practice Guidelines state that "it is reasonable to consider trastuzumab deruxtecan the new standard second-line therapy in regions where this drug is available [I, A], moving T-DM1 to a later-line setting".[6] ***Are the outcomes listed appropriate?*** Daiichi Sankyo considers the outcome measures listed in the draft scope appropriate. ***Are there any subgroups of people in whom trastuzumab deruxtecan is expected to be more clinically effective and cost effective or other***	Thank you for your comments. No action needed.

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		groups that should be examined separately? Daiichi Sankyo is not currently aware of any subgroups of people in whom T-DXd is expected to be more clinically effective and cost effective. Trial outcomes for the primary endpoint, PFS, are homogenous across protocol pre-specified subgroups. ***Where do you consider trastuzumab deruxtecan will fit into the existing NICE pathway, Advanced breast cancer (2018)?*** As an alternative treatment option to T-DM1 within its Marketing Authorisation, i.e. as an option for patients with HER2-positive unresectable or metastatic breast cancer who have received one or more prior anti-HER2 regimens. ***NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:*** • ***could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which trastuzumab deruxtecan will be licensed;*** • ***could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*** • ***could have any adverse impact on people with a particular disability or disabilities.*** ***Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*** Daiichi Sankyo is not aware of any such factors.	

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		Do you consider trastuzumab deruxtecan to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Daiichi Sankyo considers T-DXd to represent a step-change in the management of patients with HER2-positive unresectable or metastatic breast cancer [redacted] T-DXd is a targeted monotherapy that offers unprecedented efficacy vs T-DM1, the only NICE-approved therapeutic option at second line for the target patient population. In the phase 3, head-to-head randomised clinical trial DESTINY-Breast03, T DXd significantly and substantially delayed progression of disease (median PFS by BICR; not reached vs 6.8 months for T-DM1; HR=0.2840) – across all pre-specified subgroups.7 Median PFS by investigator assessment was 25.1 months vs 7.2 months for T-DXd and T-DM1, respectively.[7] While median OS was not reached in either arm, the PFS benefit is anticipated to translate into an OS benefit. 12-month OS rates were 94.1% and 85.9% in the T-DXd and T-DM1 arms, respectively.[7] T-DXd also offers significantly improved objective response rates compared with T-DM1 (79.7% vs 34.2%, respectively; P<0.0001).7 Clinical experts have described the efficacy of T-DXd in DESTINY-Breast03 as "unprecedented", and that it will lead to a "paradigm shift in the treatment of HER2 positive metastatic breast cancer".[12] ***Do you consider that the use of trastuzumab deruxtecan can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*** At the time of writing, analysis of the DESTINY-Breast03 trial data is ongoing. The extent to	

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		which T DXd may provide significant and substantial health-related benefits that are not included in the QALY calculation is yet to be determined. ***To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.*** Daiichi Sankyo is not aware of any barriers to adoption. T-DXd is already available within the NHS via the Cancer Drugs Fund for patients with HER2-positive unresectable or metastatic breast cancer who have received two or more anti-HER2 therapies [NICE TA704]. ***NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. Would it be appropriate to use the cost comparison methodology for this topic?*** Daiichi Sankyo believes that a cost effectiveness analysis is the appropriate comparison methodology. ***Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?*** As above, data from DESTINY-Breast03 demonstrates that T-DXd is clinically superior to T DM1, the only NICE assessed and approved therapeutic option at second line for the target patient population. T-DXd significantly and substantially delayed progression of disease (median PFS by BICR; not reached vs 6.8 months for T-DM1; HR=0.2840) – across all pre-specified subgroups.[7] Median PFS by	

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		investigator assessment was 25.1 months vs 7.2 months for T-DXd and T-DM1, respectively.[7] The PFS benefit is anticipated to translate into an OS benefit. 12-month OS rates were 94.1% and 85.9% in the T-DXd and T-DM1 arms, respectively.[7] Clinical experts have described the efficacy of T-DXd in DESTINY-Breast03 as "unprecedented", and that it will lead to a "paradigm shift in the treatment of HER2 positive metastatic breast cancer".[12] ***Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?*** Yes, the primary outcomes measure for DESTINY-Breast03, PFS assessed by BICR, is a clinically relevant endpoint in metastatic breast cancer. ***Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?*** DESTINY-Breast03 is a head-to-head trial vs. the in-scope comparator, T-DM1, and will form the primary data source in the economic evaluation. Daiichi Sankyo is not aware of any other important studies – for T-DXd or T-DM1 – that would provide data in a relevant timeframe for this appraisal.	
Additional comments on the draft scope	METUPUK	As a patient group, we are very excited by the prospect of trastuzumab deruxtecan being available on the NHS. We have several members and supporters who are currently accessing it through the CDF, and it has been transformative for them. We understand that the DESTINY-Breast trial has several arms, testing trastuzumab deruxtecan in the second line and also in the third/later lines. We hope that the committee will give oncologists the clinical freedom to determine where best to deploy trastuzumab deruxtecan, supported but not constrained by evidence based guidelines.	Thank you for your comment. No action needed. TA704 appraised trastuzumab deruxtecan in patients who have received two or more

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		We are aware that trastuzumab deruxtecan is not suitable for every patient, and that some patients experience toxicity, in particular interstitial pneumotitis. For most but not all patients with HER2 positive MBC, trastuzumab deruxtecan is a very promising drug. However, we strongly believe that trastuzumab emtansine should remain an option at third line for all patients with metastatic HER2-positive breast cancer, after trastuzumab deruxtecan at second line. As NHS patients, we are aware that we have fewer targeted anti-HER2 treatment lines than patients with HER2-positive MBC in similar income countries. We welcome an additional line of treatment, but are concerned the committee are considering putting trastuzumab deruxtecan in the place of trastuzumab emtansine. We very much hope trastuzumab deruxtecan will be offered in addition to trastuzumab emtansine. This concern is particularly highlighted by the fact that NHS patients cannot yet access the tucatinib combination, and cannot access trastuzumab beyond progression of second/third line of anti-HER2 therapy. We believe that trastuzumab beyond progression is an unmet need which needs to be addressed. As an aside, we also note that TA34 for trastuzumab dates from 2002. We believe that NICE may be twenty years out of date in their recommendations on the use of trastuzumab, because they do not take into account that cheaper biosimilar products are now available. We note that the 2021 ESMO guidelines recommend use of trastuzumab plus chemotherapy as the current clinical standard beyond progression at second/third line. We hope that no HER2 positive patient who may benefit from trastuzumab deruxtecan will be denied it because they fall between rigid treatment line rules. We would like the committee to consider the pathway every patient with metastatic HER2 positive breast cancer takes, as they work towards providing personalised medicine within the NHS.	prior anti-HER2-based regimens. The evaluation will consider trastuzumab deruxtecan for people with HER2-positive, unresectable or metastatic breast cancer previously treated with trastuzumab and a taxane.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Roche Products Ltd.

References – for comments from Daiichi Sankyo UK Ltd

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