National Institute for Health and Care Excellence

STA

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies ID2697

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Roche	None	Thank you for your comment. No action required.
	Breast Cancer Now	Yes, the wording is appropriate.	Thank you for your comment. No action required.
	Pierre Fabre	Yes.	Thank you for your comment. No action required.
	Daiichi Sankyo	Yes – no further comment.	Thank you for your comment. No action required.
Timing Issues	Roche	None	Thank you for your comment.

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	Breast Cancer Now	Although in recent years there has been the welcome introduction of new HER2 targeted therapies in the first and second line setting, there are currently no targeted treatments recommended for use after 2 prior lines of therapy. There is an urgent need for new and clinically effective treatments for pre-treated patients who progress on current treatments. Treatments shown to increase progression free survival are highly valued by patients with incurable breast cancer. We therefore believe this appraisal should be progressed quickly.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No changes to the remit required.
	Pierre Fabre	No comment.	Thank you for your comment.
	Daiichi Sankyo	Daiichi Sankyo considers the NICE Single Technology Appraisal (STA) route is appropriate to deliver timely guidance to the NHS for this topic. There exists a very high unmet need in patients with HER2-positive, unresectable or metastatic breast cancer who have received 2 or more prior anti-HER2 therapies.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.

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			No changes to the remit required.
Additional comments on the draft remit	Roche	None	Thank you for your comment. No action required.
	Pierre Fabre	None.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Roche	None	Thank you for your comment. No action required.
	Breast Cancer Now	The information is accurate.	Thank you for your comment. No action required.
	Pierre Fabre	No comment.	Thank you for your comment. No action required.
	Daiichi Sankyo	For completeness, Daiichi Sankyo proposes that it should be made clear that 'unresectable' includes 'advanced disease'. Additionally, the explanation of	Thank you for your comment. The scope is intended to provide a

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		'HER2-positive' should also refer to 'immunohistochemistry 3 (IHC3) and IHC2/fluorescent in situ hybridisation (FISH)+ gene amplification'. For completeness, Daiichi Sankyo proposes that it should be made clear that lapatinib does not have funding for this patient population in England.	brief description of the disease area and epidemiology data.
The technology/ intervention	Roche	None	Thank you for your comment. No action required.
	Breast Cancer Now	Yes to the best of our knowledge.	Thank you for your comment. No action required.
	Pierre Fabre	Yes.	Thank you for your comment. No action required.
	Daiichi Sankyo	Daiichi Sankyo proposes the wording is updated based on the following: Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate (ADC) composed of three components: 1) a humanized 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. The scope is intended to provide a brief description of the technology. Some further detail has been added.
Population	Roche	"People with HER2-positive, unresectable or metastatic breast cancer who have received 2 or more prior anti-HER2 therapies" should be 'People with HER2-positive, unresectable or metastatic breast cancer who have received 2 or more prior anti-HER2 therapies in the metastatic setting'	Thank you for your comment. The population section of the scope is intended to cover the population

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			that is likely to be the marketing authorisation of the technology.
	Breast Cancer Now	Yes to the best of our knowledge.	Thank you for your comment. No action required.
	Pierre Fabre	No comment	Thank you for your comment. No action required.
	Daiichi Sankyo	Yes the population is defined appropriately; i.e. people with HER2-positive, unresectable or metastatic breast cancer who have received 2 or more prior anti-HER2 therapies. No relevant subgroups identified within the trial that should be considered separately. Trial outcomes are homogenous across protocol pre-specified subgroups.	Thank you for your comment. No action required.
Comparators	Roche	Trastuzumab + chemotherapy should be a comparator because 50% centres in England have access and use it in the third-line setting (source).	Thank you for your comment. NICE does not recommend trastuzumab in combination with chemotherapy in the 3rd line setting, as a result it is not included in the comparators.
	Breast Cancer Now	The exact treatment for patients who have already received 2 or more anti HER2 therapies may differ.	Thank you for your comment. Lapatinib has been removed from the

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		For the population being considered in this appraisal, eribulin is an appropriate comparator as it is recommended for treating metastatic breast cancer after 2 or more chemotherapy regimens. It is also correct to include other chemotherapies such as capecitabine or vinorelbine as comparators for this treatment. Breast Cancer Now recommends NICE discusses with clinical experts about including lapatinib in combination with capecitabine as a comparator. Although this treatment is licensed, it was removed from the old Cancer Drugs Fund and is not recommended for routine use on the NHS for this patient population and we therefore understand it is not widely used in England	comparators. Further detail about the recommendation for eribulin has been added.
	Pierre Fabre	The only relevant comparator is eribulin. Only eribulin has been appraised and recommended by NICE in the 3rd line setting. NICE TA423 recommends eribulin as an option for treating locally advanced or metastatic breast cancer in adults, only when it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine). Eribulin is also the only treatment included in the NICE pathway '*Managing advanced breast cancer*' for the 3rd line treatment of HER2 positive patients (both hormone-receptor positive and hormone receptor negative). The chemotherapy agents capecitabine and vinorelbine are not relevant comparators and if required in the 3rd line setting would be used in combination with trastuzumab deruxtecan and not instead of.	Thank you for your comment. Lapatinib has been removed from the comparators. Further detail about the recommendation for eribulin has been added. NICE clinical guideline (CG81) recommends that patients may have non-targeted chemotherapies such as capecitabine or vinorelbine and are also included as comparators.

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	Daiichi Sankyo	Daiichi Sankyo considers eribulin to be the only relevant comparator for decision making in the final decision problem. Eribulin is the only NICE approved treatment at this point in the treatment pathway [TA423], and the only treatment option included in the existing NICE pathway [Advanced breast cancer (2018)] in this setting. Clinical expert feedback sought by Daiichi Sankyo reinforces eribulin as the only NICE approved, and thus, routinely used therapy in NHS practice in England. Lapatinib in combination with capecitabine is not a relevant comparator for this appraisal as it is not NICE approved (see FAD) nor included in Guidance. We are concerned to see that lapatinib remains listed as a possible treatment option in the draft scope as it is not NICE recommended. The NICE appraisal of lapatinib [ID20] was suspended in 2010. In addition, lapatinib was delisted from the Cancer Drugs Fund (CDF) in January 2015. Without positive NICE guidance or inclusion in the new CDF, there is no routine funding mechanism for this medicine through the NHS. Clinical expert feedback sought by Daiichi Sankyo confirms that due to a lack of funding, this combination is not used in routine clinical practice in England. Daiichi Sankyo considers that lapatinib in combination with capecitabine should be removed as a comparator from the final scope for this appraisal.	Thank you for your comment. Lapatinib has been removed from the comparators. Further detail about the recommendation for eribulin has been added. NICE clinical guideline (CG81) recommends that patients may have non-targeted chemotherapies such as capecitabine or vinorelbine and are also included as comparators.
Outcomes	Roche	None	Thank you for your comment. No action required.
	Breast Cancer Now	Yes	Thank you for your comment. No action required.

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	Pierre Fabre	In addition to the outcomes listed the following should also be included: • Overall response rate • Duration of response • Clinical benefit rate (complete response, partial response, stable disease).	Thank you for your comment. The outcomes listed are not intended to be exhaustive. The scope has been updated to include response rate and duration of response.
	Daiichi Sankyo	Daiichi Sankyo considers the outcome measures listed in the draft scope are appropriate. For completeness, the primary endpoint of DESTINY-Breast-01 (U201) was Objective Response Rate (ORR) as confirmed by Independent Central Review. Secondary endpoints included: • Best Overall Tumour Response as Confirmed By the Investigator • Disease Control Rate and Clinical Benefit Rate as Confirmed by Independent Central Review • Duration of Response (Complete Response or Partial Response) as Confirmed by Independent Central Review • Progression-Free Survival Estimate As Confirmed by Independent Central Review • Percent Change From Baseline in Sum of Diameters Over Time as Determined by Independent Central Review.	Thank you for your comment. The outcomes listed are not intended to be exhaustive. The scope has been updated to include response rate and duration of response. Progression-free survival has already been included in the scope

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Economic analysis	Roche	None	Thank you for your comment. No action required.
	Breast Cancer Now	No comment.	Thank you for your comment. No action required.
	Pierre Fabre	No comment.	Thank you for your comment. No action required.
	Daiichi Sankyo	No comments.	Thank you for your comment. No action required.
Equality and Diversity	Roche	None	Thank you for your comment. No action required.
	Breast Cancer Now	The scope does not appear to promote discrimination.	Thank you for your comment. No action required.
	Pierre Fabre	No comment.	Thank you for your comment. No action required.

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	Daiichi Sankyo	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 required.
Other considerations	Roche	None	Thank you for your comment. No action required.
	Pierre Fabre	None.	Thank you for your comment. No action required.
Innovation	Roche	None	Thank you for your comment. No action required.
	Breast Cancer Now	Yes we consider this treatment to be innovative. It works in a similar way to trastuzumab emtansine by delivering substances capable of destroying cells directly to breast cancer cells, while leaving normal cells relatively untouched. The main difference between the treatments is the substances they deliver. In reports from an early clinical trial it is suggested that on average patients taking this treatment had 16.7 months before their disease got worse which would be a significant outcome for this group of patients. We look forward to seeing further data from the trial.	Thank you for your comment. The innovative nature of trastuzumab deruxtecan will be considered by the NICE appraisal committee during the appraisal. No action required.
	Pierre Fabre	No comment.	Thank you for your comment. No action required.

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	Daiichi Sankyo	Based on the data available from the DESTINY-Breast01 trial, Daiichi Sankyo considers T-DXd to be highly innovative and expects the compound to bring significant and substantial improvement in health-benefits to patient's lives. Approximately a quarter of heavily pre-treated patients with HER2+ 3L+ mBC do not respond to current therapy, exhibiting low objective response rates (9 to 31%) and rarely achieve a complete response (<1%). , Despite previous advances in mBC treatment, outcomes for HER2+ 3L+ patients remain poor (mPFS ranging from 3-6 months).ii Patients suffering from advanced mBC face debilitating symptoms and poor QoL. , Patients cycle through minimally efficacious and/or poorly tolerated treatments (median time to treatment discontinuation is 4 months).i T-DXd is a targeted monotherapy that offers significant objective response rate (ORR [61%]) across all sub-groups and a complete response in 6% of patients.ii, T-DXd has demonstrated a substantial delay in progression of disease (mPFS 16 months) and is expected to achieve a significant improvement in overall survival.ii,v Due to this significant increase in progression free survival and substantial improvements in health-related benefits. To note, the dosing schedule of T-DXd is half that of the frequency of eribulin, resulting in 1 versus 2 hospital visits for treatment administration over a 21 day period.	Thank you for your comment. The innovative nature of trastuzumab deruxtecan will be considered by the NICE appraisal committee during the appraisal. No action required.
Questions for consultation	Roche	None	Thank you for your comment. No action required.

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	Breast Cancer Now	The question regarding lapatinib has been addressed in the comparator section of this response.	Thank you for your comment. Lapatinib has been removed from the comparators.
	Pierre Fabre	**Have all relevant comparators for trastuzumab deruxtecan been included in the scope?** See above response. **Which treatments are considered to be established clinical practice in the NHS for HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies?** Eribulin is the only relevant comparator. See above response. **Is lapatinib in combination with trastuzumab a relevant comparator?** Eribulin is the only relevant comparator. See above response. **In a population that has already had 2 anti-HER2 therapies, which anti-HER2 therapies would remain as the comparators**? As stated above the only relevant comparator is eribulin. **Would trastuzumab deruxtecan be used only after progression on trastuzumab emtansine**? Yes, based on the available clinical trial data. Evidence from the key trastuzumab deruxtecan clinical trial DESTINY-Breast 01 (NCT03248492) only included patients who had been previously treated with trastuzumab emtansine.	Thank you for your comments. Lapatinib has been removed from the comparators. Further detail about the recommendation for eribulin has been added. NICE clinical guideline (CG81) recommends that patients may have non-targeted chemotherapies such as capecitabine or vinorelbine and are also included as comparators. The outcomes have been updated to include

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		Are the outcomes listed appropriate? See above comment. **Are there any subgroups of people in whom trastuzumab deruxtecan is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No comment. **Where do you consider trastuzumab deruxtecan will fit into the existing NICE pathway, Advanced breast cancer (2018)?** 3rd line.	response rate and duration of response. The comment on subgroups is noted.
	Daiichi Sankyo	**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 2 or more anti-HER2 therapies?** As outlined above, Daiichi Sankyo considers eribulin to be the appropriate comparator for decision-making. It is the only NICE assessed and recommended therapy for this patient population and forms established clinical practice in the NHS for HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies. **Is lapatinib in combination with trastuzumab a relevant comparator?** Daiichi Sankyo does not consider lapatinib in combination with trastuzumab to be a relevant comparator. This combination is not NICE approved for HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER 2 therapies and is not routinely funded.	Thank you for your comment. Thank you for your comment. Lapatinib has been removed from the comparators. Further detail about the recommendation for eribulin has been added. NICE clinical guideline (CG81) recommends that patients may have non-targeted chemotherapies such

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		In addition, lapatinib was delisted from the Cancer Drugs Fund (CDF) in January 2015. Clinical expert opinion sought by Daiichi Sankyo supports that this combination is not used routinely in this population due to lack of funding. **In a population that has already had 2 anti-HER2 therapies, which anti-HER2 therapies would remain as the comparators?** As outlined above, eribulin is the only NICE assessed and recommended treatment option in this patient population. Daiichi Sankyo considers eribulin to be the relevant comparator for decision making. **Would trastuzumab deruxtecan be used only after progression on trastuzumab emtansine?** Based on the current proposed label wording, no. T-DXd would be used after progression of 2 anti-HER2 therapies, which in some cases may not be trastuzumab emtansine. **Are the outcomes listed appropriate?** As outlined above, for completeness, the primary endpoint of the DESTINY-Breast-01 trial was Objective Response Rate (ORR) as Confirmed by Independent Central Review. **Are there any subgroups of people in whom trastuzumab deruxtecan is expected to be more clinically effective and cost effective or other 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 are homogenous across protocol pre-specified subgroups.	as capecitabine or vinorelbine and are also included as comparators. The outcomes have been updated to include response rate and duration of response. The comment on subgroups is noted. No action required. The comment on equality is noted. No action required. The comment on innovation is noted. The innovative nature of trastuzumab deruxtecan will be considered by the NICE appraisal

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		Where do you consider trastuzumab deruxtecan will fit into the existing NICE pathway, Advanced breast cancer (2018)? As an alternative treatment option to Eribulin in line with Marketing Authorisation, i.e. patients with HER2-positive, unresectable or metastatic breast cancer who have received 2 or more prior anti-HER2 therapies. **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. **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)?**	committee during the appraisal. No action required.

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		Daiichi Sankyo considers T-DXd to be a step-change in the management of patients with HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies. There are currently no approved targeted therapies in this population, with patient prognosis poor, and hence a high unmet need. T-DXd is a targeted monotherapy that offers significant ORR (61%) across all sub-groups and a complete response in 6% of patients.[Error! Bookmark not defined.,Error! Bookmark not defined.] T-DXd has demonstrated a substantial delay in progression of disease (mPFS 16 months) in a heavily pre-treated patient population that has received a median of 6 prior line of therapy in metastatic setting and is on track to achieve a significant improvement in overall survival.[Error! Bookmark not defined.,Error! Bookmark not defined.] **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.** **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.	
Additional comments on the draft scope	Roche	None	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Pierre Fabre	None	Thank you for your comment. No action required.

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

- **Novartis**