National Institute for Health and Care Excellence

Health Technology Evaluation

Trastuzumab deruxtecan for neoadjuvant treatment of HER2-positive early breast cancer [ID6620]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Daiichi Sankyo	Daiichi Sankyo agrees that the proposed evaluation of trastuzumab deruxtecan (T-DXd) for neoadjuvant treatment of HER2-positive early breast cancer as part of the NICE Single Technology Appraisal (STA) process is appropriate.	Comment noted. No action required.
	Breast Cancer Now	The topic and proposed evaluation route are appropriate.	Comment noted. No action required.
	Roche Products	No comment	Comment noted. No action required.
Wording	Daiichi Sankyo	The draft scope states that the remit/evaluation objective is “to appraise the clinical and cost effectiveness of trastuzumab deruxtecan within its marketing authorisation for neoadjuvant treatment of HER2-positive early breast cancer.”	Thank you for your comment. The remit has been kept broad to ensure that it captures possible wording of the

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		Daiichi Sankyo proposes that the remit is updated to reflect the population evaluated in the phase III DESTINY-Breast11 trial used to inform this appraisal, namely previously untreated patients with HER2-positive early breast cancer who are at high risk of recurrence (Tumour stage ≥ T3 or node-positive or inflammatory breast cancer).	marketing authorisation from the MHRA.
	Breast Cancer Now	Yes	Comment noted. No action required.
	Roche Products	The wording of the remit is appropriate	Comment noted. No action required.
Additional comments on the draft remit	Daiichi Sankyo	Daiichi Sankyo considers the timing of this evaluation to be appropriate, particularly in the context of ensuring timely access to innovative treatments in the neoadjuvant setting for patients with HER 2-positive early breast cancer. The company is seeking marketing authorisation via the ORBIS pathway to support the early availability of T-DXd for UK patients and would be very keen to work with stakeholders to ensure timely patient access. The current standard of care for neoadjuvant treatment of HER2-positive early breast cancer comprises dual HER2-targeted therapy with trastuzumab and pertuzumab administered concurrently or sequentially with multi-agent chemotherapy. Despite this, pathological complete response (pCR) is only achieved in approximately 39–64% of the patients, indicating that many patients have residual disease following neoadjuvant treatment. Patients with residual disease are at an increased risk of disease recurrence and poorer long-term outcomes, highlighting a continued unmet clinical need in this population. However, despite this clear unmet need there have been no new therapeutic advancements in the neoadjuvant treatment setting over the past decade.	Thank you for your comment. This evaluation has been scheduled into the Medicines Evaluation programme.

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		Achieving pCR following neoadjuvant therapy is an important clinical outcome in early breast cancer as: • It may influence subsequent adjuvant treatment decisions, allowing for potential de-escalation, whereas patients with residual disease may require more intensive adjuvant therapy. • For patients with large tumours (i.e, ≥ T3) and/or axillary nodal involvement, achieving pCR may reduce the need for axillary lymph node dissection and enable the use of less extensive approaches such as sentinel lymph node biopsy, thereby lowering the risk of surgical morbidity. Based on a meta-analysis, the prevalence of lymphoedema and pain was higher with axillary lymph node dissection than with sentinel lymph node biopsy (13.7% and 24.2%, respectively). • It may enable breast-conserving surgery, which is less invasive and associated with better physical function compared with mastectomy. A meta-analysis reported lower postoperative tissue ischaemic necrosis rates (mean difference = 0.37, $P < 0.00001$), and higher postoperative body image scores (mean difference = 21.41, $P < 0.05$) with breast-conserving surgery compared to mastectomy. • Additionally, pCR is an established individual-level prognostic factor in early breast cancer, and achievement of pCR is associated with improved long-term survival and disease control. Evidence from a meta-analysis of real-world data showed that patients who achieved pCR had improved disease-free survival and overall survival, with improvements of approximately 20% and 14%, respectively, compared with patients with residual disease. Consistent with this, a meta-analysis by Spring et al. reported a hazard ratio for event-free survival of 0.31 for patients who achieved pCR compared with those with residual disease in the HER2-positive subgroup. In the same subgroup, patients who achieved pCR had a 5-year event-free survival of 86%, compared with 63% in those who did not achieve pCR. Similarly, 5-year overall survival was 95% in patients who achieved pCR versus 76% in those without pCR.	

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		• Furthermore, pCR is highly valued by patients with HER2-positive early breast cancer as it reflects aspects of treatment benefit that are meaningful to patients, particularly in the context of immature survival data. In a patient preference study of 334 patients with HER2-positive early breast cancer, achieving pCR was identified as the most important attribute, relative to all other attributes (mean relative attribute importance [mRAI] = 31%, SE = 2.50). T-DXd has demonstrated a statistically significant and clinically meaningful improvement in pCR compared with the current standard of care (pertuzumab with trastuzumab and chemotherapy) in the phase III DESTINY-Breast11 study and is characterised by a distinct safety profile. Specifically, pCR rates were 67.3% with T-DXd followed by THP (n = 216), and 56.3% with dose-dense doxorubicin plus cyclophosphamide(ddAC) followed by THP (n = 180), with a ΔpCR of 11.2% [95% confidence interval (CI) 4.0% to 18.3%, P = 0.003], which met the prespecified significance threshold of 0.03. The differentiated benefit–risk profile of T-DXd offers a meaningful alternative neoadjuvant treatment option for clinicians and patients, supporting the selection of an effective therapy that is aligned with individual patient characteristics and tolerability considerations.	
	Breast Cancer Now	There is a need for patients to access improved anti-HER2 therapies. Approximately 15-20% of breast cancer cases are HER2 positive. HER2 positive early breast cancer is also associated with a 20% rate of disease recurrence. The clinical trials for trastuzumab deruxtecan have shown that it demonstrated a statistically significant and clinically meaningful improvement in the pathologic complete response (pCR) rate. There are significant toxicities in the current standard of care with additional combination chemotherapy. Current regimes have risks of acute and long-	Thank you for your comment. This evaluation has been scheduled into the Medicines Evaluation programme.

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		term adverse effects. Patients who achieve pCR after neoadjuvant therapy have the option to receive less aggressive adjuvant therapy, so with improved outcomes trastuzumab deruxtecan could reduce overall toxicity burden and quality of life from less aggressive treatment regimes. Patients also need to be able to access treatments that will significantly reduce their chances of recurrence so that they can live well beyond a breast cancer diagnosis.	

Comment 2: the draft scope

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Background information	Daiichi Sankyo	Comment 1 Section: The technology The draft scope states that “trastuzumab deruxtecan has a marketing authorisation in the UK for treating unresectable or metastatic HER2-positive breast cancer in adults who have received one or more prior anti-HER2-based regimens.” Daiichi Sankyo does not consider this statement to be relevant for this appraisal and would propose to have it removed from the scope. Comment 2 Section: Intervention The draft scope states the intervention as “Neoadjuvant trastuzumab deruxtecan as monotherapy or followed by a taxane, trastuzumab and pertuzumab”	Thank you for your comment. Related existing marketing authorisations are regularly included in NICE technology appraisal scopes. Following your comment, this reference has been removed from this scope. Thank you for your comment. The intervention has been

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		Daiichi Sankyo will not submit an evaluation for trastuzumab deruxtecan as monotherapy and therefore proposes that the intervention wording is amended to align with the anticipated regulatory approval and the intervention to be assessed within this appraisal: "T-DXd followed by taxane, trastuzumab and pertuzumab (THP) as a neoadjuvant treatment for HER2-positive early breast cancer."	updated in line with your comment.
	Breast Cancer Now	The background information is accurate and complete.	Comment noted. No action required.
Population	Daiichi Sankyo	The draft scope states: Adults with HER2-positive early breast cancer. Daiichi Sankyo proposes that the population in the scope is updated to reflect the population enrolled in the pivotal phase III clinical trial (DESTINY-Breast11), which also represents the relevant population for this appraisal. This population includes previously untreated patients with HER2-positive early breast cancer who are at a high risk of recurrence (Tumour stage ≥ T3 or node-positive or inflammatory breast cancer). Evidence indicates that node-positive disease and greater tumour burden are associated with an increased risk of recurrence in early breast cancer. In the neoadjuvant setting, people presenting with node-positive disease are less likely to achieve a pCR and are at a higher risk of subsequent recurrence compared with those with node-negative disease. Subgroup analyses from the phase 3 TRAIN-2 trial, which evaluated chemotherapy regimens in combination with dual HER2-targeted therapy (trastuzumab and pertuzumab), showed that people presenting with node-positive disease had pCR rates (ypT0/Tis ypN0) that were 6% to 13% lower than those observed in node-	Thank you for your comment. The population has been kept broad to ensure that it captures possible wording of the marketing authorisation from the MHRA.

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		negative patients. This represented one of the largest differences in pCR rates across subgroups, second only to hormone receptor status. Higher tumour stage (T3–T4) was also associated with lower pCR rates, with reductions of up to 5%. In addition to worse long-term outcomes, this population has a greater treatment burden and unmet need. People with node-positive disease are more likely to require more extensive surgery, including axillary lymph node dissection, which is associated with clinically significant morbidity such as lymphoedema, chronic pain, and functional impairment. Therefore, patients with node-positive disease or high tumour burden represent a clinically relevant population with both high risk of recurrence and significant unmet need, for whom improved neoadjuvant treatment options would be of particular value.	
	Breast Cancer Now	Yes	Comment noted. No action required.
Subgroups	Daiichi Sankyo	Daiichi Sankyo does not believe that any subgroups need to be considered separately as the treatment effect is expected to be consistent, with no clinically meaningful differences anticipated between patient subgroups. As such, subgroup analyses are unlikely to influence the relative effectiveness or cost-effectiveness of the technology.	Comment noted. No action required.
	Breast Cancer Now	None that we are aware of	Comment noted. No action required.
	Roche Products	No additional subgroups are relevant for this appraisal.	Comment noted. No action required.
Comparators	Daiichi Sankyo	The draft scope states the comparators as: • “Neoadjuvant pertuzumab with trastuzumab and chemotherapy	Thank you for your comment. The

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		• Neoadjuvant chemotherapy” Daiichi Sankyo proposes that the comparator wording is refined to align with current NHS clinical practice. The current neoadjuvant standard of care in the UK for HER2 positive early breast cancer, as recommended by NICE (TA424), is trastuzumab and pertuzumab (dual HER2 blockade) in combination with chemotherapy. This is the only relevant NICE technology appraisal recommending a neoadjuvant treatment regimen in this patient population. This regimen is widely recognised as the standard of care in clinical practice both internationally and within the UK, and therefore represents the most appropriate comparator for this appraisal. Neoadjuvant chemotherapy alone is not aligned with current UK clinical practice or ESMO guidelines and would be considered suboptimal, given that HER2 positive early breast cancer is routinely managed with HER2 targeted therapy in combination with chemotherapy. Daiichi Sankyo would therefore propose removing “neoadjuvant chemotherapy” as a comparator, as it is not representative of standard care in the UK.	comparators have been kept broad to ensure that the whole population in the possible wording of the marketing authorisation from the MHRA is represented.
	Breast Cancer Now	Yes	Comment noted. No action required.
	Roche Products	Neoadjuvant trastuzumab with chemotherapy is another option for this patient population.	Thank you for your comment. The comparators section of the scope has been

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			updated in line with your comment.
Outcomes	Daiichi Sankyo	The draft scope states the outcomes to be considered as: • "overall survival • event-free survival • rate of pathological complete response • adverse effects of treatment • health-related quality of life." Daiichi Sankyo regards the outcomes to be largely appropriate as they reflect the clinical trial endpoints and are aligned with the endpoints considered in the previous TA424 appraisal. Daiichi Sankyo also proposes the addition of invasive disease-free survival as an outcome of interest, having been assessed in the pivotal clinical trial as a secondary endpoint.	Thank you for your comment. The outcomes have been updated in line with your comment.
	Breast Cancer Now	Yes	Comment noted. No action required.
	Roche Products	All relevant outcomes are included.	Comment noted. No action required.
Equality	Daiichi Sankyo	Daiichi Sankyo is not aware of any inequalities and does not consider that the draft remit and scope require modification.	Comment noted. No action required.
	Breast Cancer Now	No inequalities that we are aware of	Comment noted. No action required.

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Other considerations	Daiichi Sankyo	Daiichi Sankyo does not wish to raise any further considerations.	Comment noted. No action required.
Questions for consultation	Daiichi Sankyo	**Question. Where do you consider trastuzumab deruxtecan will fit into the existing care pathway for early breast cancer?** T-DXd followed by THP is anticipated to be used as a neoadjuvant treatment option for patients with HER2-positive early breast cancer who are at high risk of recurrence (Tumour stage ≥ T3 or node-positive or inflammatory breast cancer). **Question: In clinical practice in the NHS, is trastuzumab deruxtecan likely to be used?** • **as monotherapy** • **followed by a taxane, trastuzumab and pertuzumab?** In NHS clinical practice, neoadjuvant T-DXd is expected to be used as part of a sequential treatment strategy, rather than as monotherapy. Specifically, T-DXd followed by THP is anticipated to be used as a neoadjuvant treatment option for patients with HER2-positive early breast cancer. **Question: Please select from the following, will trastuzumab deruxtecan be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):**	Thank you for your comments. The intervention has been updated in the scope to reflect the consultation comments.

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		The proposed route for prescribing and routine follow-up care align with option “C”. In summary: T-DXd is expected to be initiated and prescribed in secondary care by specialists within hospital settings. Ongoing monitoring and follow-up will also be conducted in secondary care, reflecting standard clinical practice. **Question: Would trastuzumab deruxtecan be a candidate for managed access?** Relevant time-to-event outcomes, including event-free survival, will be immature at the time of submission; however, event-free survival will be re-analysed once all patients have either completed 3 years of follow-up or are censored due to loss to follow-up or death. While the data are expected to remain relatively immature at this point, the extended follow-up may provide important insight into the trajectory of events and support more robust extrapolations in the cost-effectiveness analysis. This approach could help reduce uncertainty, making T-DXd in this indication a potential candidate for managed access. **Question: Do you consider that the use of trastuzumab deruxtecan can result in any potential 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 committee to take account of these benefits.** In early breast cancer, axillary management has increasingly shifted towards de-escalation, particularly in patients receiving neoadjuvant systemic therapy. Achievement of pCR may enable the de-escalation of subsequent adjuvant treatment, therefore reducing overall treatment burden. Furthermore, improved tumour response, including higher rates of pCR, increases the	

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		likelihood of axillary downstaging, enabling less extensive surgical approaches such as sentinel lymph node biopsy or targeted axillary dissection, in place of axillary lymph node dissection. Avoidance of axillary lymph node dissection is associated with a lower risk of surgical morbidity, most notably lymphoedema, a chronic and potentially progressive condition that can have a substantial and long-term impact on patients' functional status and quality of life. These impacts are heterogeneous and may not be fully reflected in standard utility values used in economic evaluations. Furthermore, improved response to neoadjuvant therapy may reduce the need for more extensive breast surgery, such as mastectomy and complex reconstruction, with associated benefits for recovery, patient experience, and healthcare resource use. Evidence to support these associations is expected to be available from published literature and clinical opinion	
	Breast Cancer Now	In clinical practice in the NHS, is trastuzumab deruxtecan likely to be used • as monotherapy • followed by a taxane, trastuzumab and pertuzumab? In clinical trials, trastuzumab deruxtecan was followed by taxane, trastuzumab and pertuzumab, so that would be the likely plan for administration in practise. We feel unable to comment on whether trastuzumab deruxtecan could also be used as a monotherapy, as the monotherapy arm was closed early in the Destiny-Breast 11 trial due to lower pCR rates.	Thank you for your comments. The intervention has been updated in the scope to reflect the consultation comments.

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		Please select from the following, will trastuzumab deruxtecan be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care **C. Prescribed in secondary care with routine follow-up in secondary care** **Would trastuzumab deruxtecan be a candidate for managed access?** Yes. Overall survival data is not yet available, so it could be a candidate for managed access.	
	Roche Products	Where do you consider trastuzumab deruxtecan will fit into the existing care pathway for early breast cancer? *High-risk neoadjuvant HER2-positive early breast cancer population in-line with population studied in the clinical trial.* In clinical practice in the NHS, is trastuzumab deruxtecan likely to be used • as monotherapy • followed by a taxane, trastuzumab and pertuzumab? *This is accurate.* Are there any subgroups for whom the clinical and cost effectiveness is expected to differ and who should be considered separately? *Not applicable – no relevant subgroups* Please select from the following, will trastuzumab deruxtecan be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care	Thank you for your comments. No action required.

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		C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): *C. Prescribed in secondary care with routine follow-up in secondary care* For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. *The comparators will be prescribed and routinely followed-up in the same setting for neoadjuvant treatment.* *Subcutaneous trastuzumab and pertuzumab (PHESGO) can be offered after neoadjuvant treatment (if pathological complete response is achieved) which can be administrated outside of the SACT unit with routine follow up in secondary care.* Would trastuzumab deruxtecan be a candidate for managed access? *No comment* Do you consider that the use of trastuzumab deruxtecan can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? *No comment* Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. *Not applicable* **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**	

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		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.** ***No comment*** NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation). *No comment*	
Additional comments on the draft scope	Daiichi Sankyo	The draft scope lists the following related technology appraisals: **"Related technology appraisals:**	Thank you for your comment. The 'Related NICE

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		Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (2016) NICE technology appraisal guidance 424. Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy (2024) NICE technology appraisal guidance 992 Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 treatments (2023) NICE technology appraisal guidance 862. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies (2021) NICE technology appraisal guidance 704. **Related technology appraisals in development:** Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 therapies (MA review TA704 and TA862) NICE technology appraisal guidance ID5121. Publication expected May 2026. **Related NICE guidelines:** Early and locally advanced breast cancer: diagnosis and management (2018 updated 2025) NICE guideline NG101. Last reviewed April 2025. Several areas for update. **Related quality standards:**	recommendations' section of the scope has been updated in line with your comments.

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		Breast cancer (2011 updated 2016) NICE quality standard 12” Daiichi Sankyo proposes that the metastatic T-DXd technology appraisals listed in the draft scope be excluded, as they are not relevant to the decision problem for this evaluation, which focuses on T-DXd for early breast cancer in the neoadjuvant setting. Daiichi Sankyo further proposes that the following, relevant to early breast cancer, are included to ensure alignment with the decision problem: **Related technology appraisals:** Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (2016) NICE technology appraisal guidance 424. **Related NICE guidelines:** Early and locally advanced breast cancer: diagnosis and management (2018 updated 2025) NICE guideline NG101. Last reviewed April 2025. Several areas for update. **Related quality standards:** Breast cancer (2011 updated 2016) NICE quality standard 12	

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

None