National Institute for Health and Care Excellence

Health Technology Evaluation

Trastuzumab deruxtecan for treating HER2-low unresectable or metastatic breast cancer after chemotherapy ID3935

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	Action
Appropriateness of an evaluation and proposed evaluation route	Daiichi Sankyo UK (Company)	Daiichi Sankyo agrees that it is appropriate to refer trastuzumab deruxtecan (T-DXd) for evaluation via the NICE Single Technology Appraisal (STA) process.	Comment noted. No action required.
	Breast Cancer Now	Yes, a single technology appraisal for tratsuzumab deruxtecan in this indication is appropriate.	Comment noted. No action required.
	METUPUK	We welcome the single technology appraisal for trastuzumab deruxtecan for treatment of HER2-low metastatic breast cancer after chemotherapy. We agree that a STA is the most appropriate evaluation route.	Comment noted. No action required.
Wording	Daiichi Sankyo UK (Company)	Daiichi Sankyo agrees that the wording reflects the issues of clinical and cost-effectiveness of this technology. To align with the proposed label for the technology, Daiichi Sankyo propose a minor wording change to the order of 'metastatic or unresectable' in the title of the scope, draft remit, and throughout the scope, as follows:	Comment noted. The scope has been amended as suggested.

Section	Stakeholder	Comments	Action
		"To appraise the clinical and cost effectiveness of trastuzumab deruxtecan within its marketing authorisation for treating HER2-low unresectable or metastatic breast cancer after chemotherapy".	
	Breast Cancer Now	Yes the remit accurately reflects the issue.	Comment noted. No action required.
	METUPUK	Yes, the current remit reflects the priorities of patients with HER2-low disease. We welcome in particular that there are no treatment line restrictions specified and would like this to be preserved.	Comments noted. The positioning of the technology in the treatment pathway will be considered during the appraisal process. No action required.
Timing Issues	Daiichi Sankyo UK (Company)	Daiichi Sankyo considers the NICE STA route to be appropriate to deliver timely guidance to the NHS for this topic. There is relative urgency of this evaluation to the NHS given that there are currently no targeted treatments available for HER2-low unresectable or metastatic breast cancer (u/mBC) after prior chemotherapy in the UK. Under the current breast cancer (BC) treatment paradigm, patients are classified as either human epidermal growth factor receptor 2 (HER2)-positive or HER2-negative.[1,2] This is despite a significant proportion of patients (~58%) currently classified as HER2-negative with tumours expressing low levels of HER2 (HER2-low).[3] These HER2-low u/mBC patients may potentially be able to benefit from HER2-targeted therapies. Patients with HER2-low u/mBC aire currently treated according to the HER2-negative pathway. After exhausting targeted therapies, the only treatment options available for these patients are non-targeted chemotherapies,[4,5] which are associated with poor outcomes.[6–10] According to data from randomised clinical trials, patients currently classified as having HER2-negative u/mBC receiving non-targeted chemotherapies have a poor prognosis, with a median progression-free survival	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10813. No action required.

Section	Stakeholder	Comments	Action
		(PFS) of 3.7–4.2 months and a median overall survival (OS) of 13.2–16.1 months.[6–10] There is, therefore, a high unmet need for patients with HER2-low u/mBC who have received one line of chemotherapy in the metastatic setting to have timely access to effective targeted therapies that delay disease progression, prolong survival, and maintain quality of life (QoL) compared with the current standard of care. **References** 1. Montemurro F, Cosimo SD & Arpino G. Human epidermal growth factor receptor 2 (HER2)-positive and hormone receptor-positive breast cancer: new insights into molecular interactions and clinical implications. Annals of Oncology 2013. 24: 2715–2724. 2. Gradishar WJ, Moran MS, Abraham J, et al. NCCN Clinical Practice Guidelines in Oncology, Breast Cancer. Version 4.2022. 2022. at <https://www.nccn.org/patients/guidelines/cancers.aspx> 3. Dodson A, Parry S, Ibrahim M, et al. Breast cancer biomarkers in clinical testing: analysis of a UK NEQAS ICC & ISH database containing results from 199 300 patients. J Pathol Clin Res 2020. 6: 227–227. 4. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021. 32: 1475–1495. 5. NICE. Recommendations | Advanced breast cancer: diagnosis and treatment | Guidance | NICE. at	

Section	Stakeholder	Comments	Action
		<https://www.nice.org.uk/guidance/cg81/chapter/Recommendations> 6. Pivot X, Im SA, Guo M, et al. Subgroup analysis of patients with HER2-negative metastatic breast cancer in the second-line setting from a phase 3, open-label, randomized study of eribulin mesilate versus capecitabine. Breast Cancer 2018. 25: 370–374. 7. Pivot X, Marmé F, Koenigsberg R, et al. Pooled analyses of eribulin in metastatic breast cancer patients with at least one prior chemotherapy. Ann Oncol 2016. 27: 1525–1531. 8. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011. 377: 914–923. 9. Twelves C, Awada A, Cortes J, et al. Subgroup Analyses from a Phase 3, Open-Label, Randomized Study of Eribulin Mesylate Versus Capecitabine in Pretreated Patients with Advanced or Metastatic Breast Cancer. Breast Cancer (Auckl) 2016. 10: 77–84. 10. Decker T, Marschner N, Muendlein A, et al. VicTORia: a randomised phase II study to compare vinorelbine in combination with the mTOR inhibitor everolimus versus vinorelbine monotherapy for second-line chemotherapy in advanced HER2-negative breast cancer. Breast Cancer Res Treat 2019. 176: 637–647.	
	Breast Cancer Now	As the NICE scope identifies, there are currently no recommended treatments for HER2-low unresectable or secondary (metastatic) breast cancer. Currently, only people whose tumours produce high levels of HER2 and are classified as HER2-positive, can access anti-HER2 therapies.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/inde

Section	Stakeholder	Comments	Action
		Recent research on HER2-low suggests around 50% of all breast cancers show low levels of HER2, this would be around 27,500 cases each year in the UK. Around 80% of secondary breast cancers are HER2 negative with 55-60% of these having low levels of HER2. A phase 3 clinical trial has shown that trastuzumab deruxtecan could give an additional 4.8 months on average before disease progression compared to placebo, as well as improving overall survival by 6 months compared to placebo – two significant outcomes for this population, enabling them to have extra precious time to the things that matter most to them.	velopment/gid-ta10813. No action required.
	METUPUK	This evaluation is urgent. HER2-low is a subtype which has no treatments currently available to NHS patients. Therefore there is an unmet need and the evaluation should be prioritised.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10813. No action required.
Additional comments on the draft remit	Daiichi Sankyo UK (Company)	None	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Daiichi Sankyo UK (Company)	Daiichi Sankyo broadly agrees with the wording proposed by NICE. For clarification, Daiichi Sankyo proposes that the last two sentences in the first paragraph are amended as follows:	Comments noted. This section of the scope aims to provide a brief overview of the background for the appraisal. Amendments have been made to the information on the classification of

Section	Consultee/ Commentator	Comments	Action
		"HER2 status is defined according to immunohistochemistry (IHC) and in situ hybridisation (ISH) criteria.[11] The current classification is as follows: • HER2-positive: IHC 3+ **or** IHC 2+ and ISH+ • HER2-negative: IHC 0 **or** IHC 1+ **or** IHC2+ and ISH- The introduction of HER2-low redefines HER2 classification to: • HER2-positive: IHC 3+ **or** IHC 2+ and ISH+ • HER2-low: IHC 1+ **or** IHC 2+ and ISH- • HER2-negative: IHC 0" Daiichi Sankyo also proposes that the first sentence of the third paragraph is amended to fully capture the goals of treatment: "Current treatments for advanced breast cancer aim to relieve symptoms, prolong survival and maintain a good quality of life with minimal adverse events" to "Current treatments for advanced breast cancer aim to relieve symptoms, prolong *progression-free and overall* survival*,* and maintain a good quality of life *while managing* adverse events.". Daiichi Sankyo proposes adding the following text after the third sentence in the fourth paragraph: "Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate[5,12] i.e. as a first-line chemotherapy in the metastatic setting." **References**	HER2-low and HER2-negative. Details about NICE technology appraisal 116 have been added to this section.

Section	Consultee/ Commentator	Comments	Action
		5. NICE. Recommendations | Advanced breast cancer: diagnosis and treatment | Guidance | NICE. at <https://www.nice.org.uk/guidance/cg81/chapter/Recommendations> 11. Eiger D, Agostinetto E, Saúde-Conde R, et al. The Exciting New Field of HER2-Low Breast Cancer Treatment. Cancers (Basel) 2021. 13: 1015. 12. NICE. Gemcitabine for the treatment of metastatic breast cancer | NICE [TA116]. at <https://www.nice.org.uk/guidance/ta116>	
	Breast Cancer Now	The following statistic used - "Around 35% of people with early or locally advanced disease will progress to metastatic breast cancer in the 10 years following diagnosis" – is based on regional data from the West Midlands which is nearly 30 years old so should be used with caution. Furthermore, the scope currently points towards the NICE Clinical Guideline 81, however, this is significantly out of date and does not reflect a number of new treatments that are available for patients, including CDK 4/6 inhibitors.	Comments noted. The sentence has been removed from the scope. "Cyclin-dependent kinase (CDK) 4/6 inhibitors are recommended in NICE technology appraisals 495, 496 and 563, alongside endocrine therapy for HER2-negative locally advanced or metastatic breast cancer. After endocrine therapy, NICE technology appraisals 687 and 725 recommend in combination with fulvestrant, ribociclib and abemaciclib for treating hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer if exemestane with everolimus is the most appropriate alternative to a CDK 4/6 inhibitor. For hormone receptor-positive, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer that has progressed after a CDK 4/6 inhibitor

Section	Consultee/ Commentator	Comments	Action
			and endocrine therapy, NICE technology appraisal 816 recommends alpelisib with fulvestrant." The technology being evaluated is likely positioned after chemotherapy when CDK 4/6 inhibitors are not options.
	METUPUK	No comments	Comment noted. No action required.
Population	Daiichi Sankyo UK (Company)	Yes, Daiichi Sankyo agrees that the population is defined appropriately.	Comment noted. No action required.
	Breast Cancer Now	Yes it appears correct. We understand from the clinical trial that patients will have received one or two previous lines of chemotherapy.	Comments noted. No action required.
	METUPUK	No comments	Comment noted. No action required.
Technology / Intervention	Daiichi Sankyo UK (Company)	Daiichi Sankyo proposes that the first sentence in the first paragraph is replaced with the following wording to align with the company description of the technology: "Trastuzumab deruxtecan (T-DXd; Enhertu®, Daiichi Sankyo) 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.[13]". For completeness, Daiichi Sankyo proposes specifying the clinical trial in the second sentence of the second paragraph: "It has been compared with chemotherapy comprising capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel in *the DESTINY-Breast04* clinical trial in *adult patients* with	Comments noted. The scope is a brief document, outlining the question for the appraisal. The technology section of the scope no longer includes a description of the technology. The company will have an opportunity to provide a detailed description of the technology in its submission. The company will have an opportunity to provide further details of the clinical trial in its submission. No action required.

Section	Consultee/ Commentator	Comments	Action
		HER2-low, unresectable or metastatic breast cancer previously treated with chemotherapy.". Daiichi Sankyo proposes the wording in the final paragraph is updated as follows: "T-DXd as monotherapy is *currently* indicated for the treatment of *adult patients* with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.". **Reference** 13. NICE. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies | NICE [TA704]. at <https://www.nice.org.uk/guidance/ta704>	For the current indication 'people' has been amended to 'adults'.
Subgroups	Daiichi Sankyo UK (Company)	Daiichi Sankyo can confirm that there are no subgroups to be considered separately as part of the cost-effectiveness analysis and this appraisal should be based on the full analysis set (FAS) from DESTINY-Breast04. In the FAS, treatment with T-DXd led to a statistically significant benefit for the primary endpoint (PFS by blinded independent central review [BICR]) compared with treatment of physician's choice (TPC; hazard ratio [HR]=0.50; P<0.001), which was consistent across analysed pre-specified subgroups.[14] There is a high unmet need for T-DXd to be made available for all eligible patients with HER2-low u/mBC as these patients are currently treated within the HER2-negative u/mBC pathway where non-targeted chemotherapies are the only options after one line of prior chemotherapy in the metastatic setting.[15] **References**	Comment noted. No action required.

Section	Consultee/ Commentator	Comments	Action
		14. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. New England Journal of Medicine 2022. 387: 9–20. 15. Daiichi Sankyo Inc. Clinical Study Report for DS8201-A-U303. Data cut-off date: 11 Jan 2022. Data on File. 2022.	
	Breast Cancer Now	We understand that there was a higher proportion of patients in the trial who had hormone receptor positive breast cancer, compared to triple negative breast cancer.	Comment noted. No action required.
	METUPUK	No comments	Comment noted. No action required.
Comparators	Daiichi Sankyo UK (Company)	DESTINY-Breast04 is a Phase III, randomised, open-label trial in patients with HER2-low unresectable or metastatic breast cancer assessing the safety and efficacy of T-DXd compared with TPC. The comparator arm comprised of capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel.[14] Based on NICE CG81, the European Society of Medical Oncology (ESMO) 2021 guidelines, and UK patient data, a broad range of non-targeted single agent chemotherapies are used in the UK and there is no single standard of care in the HER2-negative u/mBC pathway following one line of chemotherapy.[4,5,16] Daiichi Sankyo considers the TPC comparator arm of DESTINY-Breast04 to be representative of chemotherapies used after at least one line of prior chemotherapy in the metastatic setting in routine NHS practice. NICE Clinical Guideline 81 (CG81), which was last updated in 2017, recommends single-agent docetaxel as a first-line treatment, single-agent vinorelbine or capecitabine as a second-line treatment, and single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment) as a third-line treatment.[5] NICE TA116 recommends gemcitabine in combination with paclitaxel, within its licensed indication (i.e. in the first-line setting), as an option for the	Comments noted. The lines of therapy have been removed from the scope and the following comparators have been added: • anthracyclines • platinum therapies • taxanes For people whose disease is hormone receptor negative: • sacituzumab govitecan

Section	Consultee/ Commentator	Comments	Action
		treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.[12] In addition, based on TA423, NICE recommends eribulin as an option for treating locally advanced or metastatic breast cancer when it has progressed after at least two chemotherapy regimens.[17] The ESMO 2021 guidelines were updated more recently and provide further insight into clinical treatment recommendations for HER2-negative u/mBC patients after one line of chemotherapy. The guidelines are aligned with NICE CG81 in that they recommend sequential single-agent chemotherapy at later lines of therapy and state that, regardless of the line of therapy, single-agent chemotherapies include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine, platinum therapies, and other agents.[4] Crucially, ESMO 2021 guidelines state that the optimal chemotherapy sequence in mBC has not been established and available options should be discussed with the patient.[4] UK patient data from 2022 highlight that there is no optimal or standard treatment sequence and that the pathway is highly variable and fragmented in HER2-negative u/mBC, with a wide range of chemotherapies being used across both second and third line.[16] This indicates that UK treatment decisions are likely to be driven by individual patient needs and clinician choice. In addition, there is unlikely to be any significant difference in efficacy across non-targeted single-agent chemotherapies used in the metastatic BC setting.[17,18] Given the use of chemotherapies across lines and similar efficacy, Daiichi Sankyo considers it inappropriate for different comparators in the scope to be specified at different lines of therapy. It does not reflect clinical practice and introduces	

Section	Consultee/ Commentator	Comments	Action
		additional complexity and uncertainty to the appraisal due to the limited published data for comparators at a specific line of therapy. Instead, comparators should be considered interchangeable at all lines of therapy in the metastatic setting in this appraisal. **References** 4. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021. 32: 1475–1495. 5. NICE. Recommendations | Advanced breast cancer: diagnosis and treatment | Guidance | NICE. at <https://www.nice.org.uk/guidance/cg81/chapter/Recommendations> 12. NICE. Gemcitabine for the treatment of metastatic breast cancer | NICE [TA116]. at <https://www.nice.org.uk/guidance/ta116> 14. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. New England Journal of Medicine 2022. 387: 9–20. 15. Daiichi Sankyo Inc. Clinical Study Report for DS8201-A-U303. Data cut-off date: 11 Jan 2022. Data on File. 2022. 16. Daiichi Sankyo Inc. Breast Cancer Treatment Landscape. Data on File. 2022. 17. NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens | NICE [TA423]. at <https://www.nice.org.uk/guidance/ta423> 18. NICE. Sacituzumab govitecan for treating unresectable triple-negative advanced breast cancer after 2 or more	

Section	Consultee/ Commentator	Comments	Action
		therapies | NICE [TA819]. at <https://www.nice.org.uk/guidance/ta819>	
	Breast Cancer Now	These appear correct to the best of our knowledge.	Comment noted. No action required.
	METUPUK	Comparators listed should include taxanes. Many patients will not choose a taxane as their first line of chemotherapy, preferring capecitabine which for most people is associated with better quality of life and no hair loss. Patients may then chose a taxane as an option at a later line.	Comments noted. Taxanes have been added to the list of comparators in the scope.
Outcomes	Daiichi Sankyo UK (Company)	Daiichi Sankyo agrees that the outcome measures listed in the draft scope are appropriate and comprise the important outcomes for the assessment of health-related benefits and harms of the technology.	Comments noted. No action required.
	Breast Cancer Now	Yes these are appropriate.	Comment noted. No action required.
	METUPUK	No comments	Comment noted. No action required.
Equality	Daiichi Sankyo UK (Company)	Daiichi Sankyo is not aware of any issues of inequality in the management of breast cancer in England and Wales.	Comment noted. No action required.
	Breast Cancer Now	None that we are aware of.	Comment noted. No action required.
	METUPUK	We understand that issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. Our concern is that the severity modifier does by definition categorise patients by age when determining the absolute shortfall. Age is also factored into the proportionate shortfall calculation, although less directly. In fact, metastatic breast cancer does remove decades from an average person's life, but the use of discounting at 3.5% and quality adjusted life expectancy fails to capture this. Metastatic breast cancer is the	Comments noted. The application of the severity modifier will be considered on a case-by-case basis by the committee, based on the totality of evidence, the condition and indication under consideration. No action required.

Section	Consultee/ Commentator	Comments	Action
		largest cause of death in women aged 35-50. If the severity modifier fails to capture this actual loss of life years at a level comparable to the end of life criteria it has replaced, it is failing patients.	
Economic Analysis	Daiichi Sankyo UK (Company)	Daiichi Sankyo intends to submit a cost-effectiveness analysis of treatments expressed in terms of incremental cost per quality-adjusted life year. The economic analysis will be developed in line with the NICE reference case.	Comments noted. No action required.
Other considerations	Daiichi Sankyo UK (Company)	T-DXd is an innovative ADC that is the first HER2-targeted treatment to show efficacy in HER2-low u/mBC. This has been demonstrated in DESTINY-Breast04, the pivotal, Phase III, randomised, open-label trial assessing the safety and efficacy of T-DXd compared with TPC in patients with HER2-low u/mBC.[14] In the FAS population, DESTINY-Breast04 demonstrated that: • T-DXd was associated with significantly longer PFS compared with TPC (9.9 vs. 5.1 months; HR: 0.50; 95% CI, 0.40, 0.63; P<0.001]). • T-DXd was associated with significantly longer OS compared with TPC (23.4 vs. 16.8 months; HR: 0.64; 95% CI: 0.49, 0.84; P=0.001).[14] Based on its significant clinical benefit versus non-targeted chemotherapies, T-DXd is a step-change and represents a shift in the treatment paradigm for a large proportion of patients currently classified as HER2-negative. It addresses a high unmet need by providing a novel, targeted and efficacious option for patients who would otherwise receive non-targeted chemotherapies, which are associated with poor outcomes.[14] ASCO rapid recommendations (2022) state that patients with HR+/HER2-low mBC who have received at least one prior	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.

Section	Consultee/ Commentator	Comments	Action
		chemotherapy for metastatic disease should be offered treatment with T-DXd.[19] In recognition of its innovation, T-DXd was awarded the Innovation Passport designation by the UK Medicines and Healthcare Regulatory Agency (MHRA) in May 2022. **References** 14. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. New England Journal of Medicine 2022. 387: 9–20. 19. Moy B, Rumble RB, Carey LA, et al. Chemotherapy and Targeted Therapy for Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer That Is Either Endocrine-Pretreated or Hormone Receptor–Negative: ASCO Guideline Rapid Recommendation Update. Journal of Clinical Oncology 2022. doi:10.1200/JCO.22.01533	
	Breast Cancer Now	Under the section “related NICE recommendations”, only treatments for hormone receptor positive breast cancer have been included. However, although we understand the study was not designed to look primarily at people with triple negative breast cancer, some patients with triple negative breast cancer could be considered HER2-low and were in the trial. Therefore, other appraisals may be relevant to include, such as atezolizumab with nab-paclitaxel, pembrolizumab with chemotherapy and sacituzumab govitecan.	Comments noted. NICE technology appraisal 819 on sacituzumab govitecan for treating unresectable triple-negative advanced breast cancer after 2 or more therapies has been added to the list. However, NICE technology appraisals 639 (atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer) and 801 (pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic

Section	Consultee/ Commentator	Comments	Action
			breast cancer) are recommended for untreated advanced breast cancer.
	METUPUK	If a patient has hormone negative and HER2-low MBC, will the patient still be considered to have triple negative breast cancer? Will the patient still be eligible for drugs on the triple negative pathway such as sacituzumab govitecan or immune checkpoint inhibitors if appropriate? Do we have an accepted definition of and reproducible test for HER2-low? Can all patients be certain they will get an accurate and consistent test result? Will all Trusts across the country implement testing for HER2-low ensuring that patients can access timely and accurate results regardless of where they live?	Comments noted. This group of people would currently be considered HER2 negative so would likely still be eligible for previously recommended triple negative therapies. HER2 testing is completed as standard during diagnosis so no additional testing requirements are needed for this treatment. No action required.
Questions for consultation	Daiichi Sankyo UK (Company)	**Q. Are taxanes relevant comparators for people with HER2-low metastatic or unresectable breast cancer after chemotherapy?** A: Yes, as per the ESMO 2021 guidelines and UK patient data, taxanes are recommended and used in clinical practice.[4,16] Please refer to the 'Comparators' section above for further information. **Q. Where do you consider trastuzumab deruxtecan will fit into the treatment pathway for HER2-low metastatic or unresectable breast cancer?** A: T-DXd is anticipated to be used as an alternative to non-targeted chemotherapies in adult patients with HER2-low u/mBC who have received a prior chemotherapy, in accordance with the anticipated licensed indication.	Comments noted. Taxanes have been added to the list of comparators in the scope. Comments noted. No action required.

Section	Consultee/ Commentator	Comments	Action
		Q. Would trastuzumab deruxtecan be a candidate for managed access? A: Daiichi Sankyo consider that the proposed clinical evidence base is suitable to support a recommendation for routine commissioning. PFS data in DESTINY-Breast04 are mature, as [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%) had a progression event as assessed by BICR in the FAS population at data cut-off in the T-DXd and TPC cohorts, respectively.[15] OS data are also mature, as [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%) had died in the FAS population at data cut-off in the T-DXd and TPC cohorts, respectively.[15] [redacted] as T-DXd demonstrated a statistically significant PFS and OS benefit compared with TPC (PFS in FAS population: HR: 0.50; 95% CI: 0.40, 0.63; P<0.001; OS in FAS population: HR: 0.64, 95% CI: 0.49, 0.84, P=0.001).[14,20]	Comments noted. No action required.
		Q. 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.** A: All substantial health-related benefits are expected to be captured in the QALY calculations. T-DXd has demonstrated a significant improvement in PFS and OS in HER2-low u/mBC compared with non-targeted chemotherapies and offers the first HER2-targeted treatment in this population, representing a shift in the treatment paradigm of BC.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments	Action
		u/mBC poses a substantial clinical and socioeconomic burden on patients and a major physical, emotional, and financial burden on their caregivers.[21,22] As well as patients, the disease also negatively impacts employers which results in unemployment for the majority of patients.[23] Given that HER2-low u/mBC patients are often of working age,[24] T-DXd is likely to generate wider societal benefits in terms of lost productivity (i.e. presenteeism and absenteeism) and delaying retirement in both patients and carers. **Q. 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.** A: Daiichi Sankyo is not aware of any equality considerations.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments	Action
		Q. NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. A: Daiichi Sankyo agrees that it is appropriate to evaluate T-DXd via the NICE STA process. **References** 4. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021. 32: 1475–1495. 14. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. New England Journal of Medicine 2022. 387: 9–20. 15. Daiichi Sankyo Inc. Clinical Study Report for DS8201-A-U303. Data cut-off date: 11 Jan 2022. Data on File. 2022. 16. Daiichi Sankyo Inc. Breast Cancer Treatment Landscape. Data on File. 2022. 20. Daiichi Sankyo Inc. Statistical Analysis Plan Version 2.0 for DS8201-A-U303. 04 January 2022. Data on File. 2022. 21. Grunfeld E, Coyle D, Whelan T, et al. Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. CMAJ 2004. 170: 1795–1801. 22. Mayer M, Sampayo I, Dickson R, et al. Abstract P1-11-06: The experience of caregivers of women with metastatic breast cancer: Insights from the Make Your Dialogue Count survey. Cancer Research 2016. 76: P1-11.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments	Action
		23. Islam T, Dahlui M, Majid HA, et al. Factors associated with return to work of breast cancer survivors: a systematic review. BMC Public Health 2014. 14: S8. 24. Miglietta F, Griguolo G, Bottosso M, et al. Evolution of HER2-low expression from primary to recurrent breast cancer. npj Breast Cancer 2021. 7: 1–8.	
	METUPUK	Patients would welcome there to be flexibility for where trastuzumab deruxtecan fits into the treatment pathway. Most likely it will be after targeted hormonal therapy (if patient has hormone positive MBC) and in the second line of chemotherapy, after a taxane or capecitabine. For all patients we would prefer oncologists to be given freedom to use their clinical acumen to decide where to use trastuzumab deruxtecan in the treatment pathway. We consider that trastuzumab deruxtecan would be a candidate for managed access for HER2-low MBC. This is a new subtype of cancer for which there is limited data. A period of managed access could be used to address any uncertainties.	Comments noted. NICE can appraise the technology within its marketing authorisation. The positioning of the technology in the treatment pathway will be considered during the appraisal process. Managed access may be considered by the company if needed. No action required.
Additional comments on the draft scope	Daiichi Sankyo UK (Company)	No further comments	Comment noted. No action required.
	METUPUK	As a patient group we have had a huge amount of interest in trastuzumab deruxtecan for HER2-low. Many patients would like to know if they have HER2-low MBC, particularly those that had equivocal HER2 results that went on to be classified as negative. We welcome this TA because trastuzumab deruxtecan gives hope for patients with this newly identified class of breast cancer. As the only drug available for HER2-low, trastuzumab	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10813. No action required.

Section	Consultee/ Commentator	Comments	Action
		deruxtecan addresses an unmet need for patients who often respond poorly to standard of care untargeted treatments. The UK lags behind similar income countries in cancer outcomes, and we hope that approval of this leading edge cancer technology can go some way to address this.	

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

Eisai Limited