National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tucatinib with trastuzumab and capecitabine for treating HER2-positive unresectable locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies

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

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Seagen Inc.	Yes	Comment noted. No action required.
	Pierre Fabre Ltd	Yes	Comment noted. No action required.
	Breast Cancer Now	Yes, the wording is appropriate.	Comment noted. No action required.
	Roche Products Ltd	No comment	Comment noted. No action required.
	National Cancer Research Institute-Association of Cancer	No comment	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Physicians-Royal College of Physicians-Royal College of Radiologists (NCRI-ACP-RCP-RCR)		
Timing Issues	Seagen Inc.	The urgency relates to the unmet need and has been outlined in 'Innovation' section of Comment 2.	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	Pierre Fabre Ltd	No comment	Comment noted. No action required.
	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 and overall survival are highly valued by patients with incurable breast	Comments noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.

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		cancer. We therefore believe this appraisal should be progressed quickly.	
	Roche Products Ltd	No comment	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
Additional comments on the draft remit	Seagen Inc.	None	Comment noted. No action required.
	Pierre Fabre Ltd	None	Comment noted. No action required.
	Breast Cancer Now	No comment	Comment noted. No action required.
	Roche Products Ltd	No comment	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Seagen Inc.	The following clause in the first paragraph, “When human epidermal growth factor attaches itself to HER2 receptors on breast cancer cells” is not entirely accurate in terms of description. We therefore suggest amending this to: “The changes in the tumour environment enables the activation of HER2 receptors, irrespective of ligand or without the heterodimerization needed for its normal functioning.”	Comment noted. The background section is written, as far as possible, using lay language. No action required.
	Pierre Fabre Ltd	No comment	Comment noted. No action required.
	Breast Cancer Now	The information is accurate.	Comment noted. No action required.
	Roche Products Ltd	No comment	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
The technology/ intervention	Seagen Inc.	We would like to update the medicine brand name to include a registered trademark symbol and the company name from “(Tukysa, Seattle Genetics Inc.)” to “(Tukysa®, Seagen Inc.)“	Comment noted. The company name has been updated in the scope as suggested. However, NICE does not use registered trademark symbols, “Inc” etc in any scoping documents, therefore this change has not been made to the scope.

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	Pierre Fabre Ltd	Yes	Comment noted. No action required.
	Breast Cancer Now	Yes to the best of our knowledge.	Comment noted. No action required.
	Roche Products Ltd	In addition to being administered intravenously, trastuzumab (Herceptin, Roche) can also be given subcutaneously. Patients were able to receive both formulations in the HER2Climb trial (1). 1. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. New England Journal of Medicine. 2019;382(7):597-609.	Comment noted. The technology section has been updated to include that trastuzumab can be given subcutaneously.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
Population	Seagen Inc.	No further comments	Comment noted. No action required.
	Pierre Fabre Ltd	The population is appropriately defined	Comment noted. No action required
	Breast Cancer Now	Yes to the best of our knowledge.	Comment noted. No action required.
	Roche Products Ltd	'People with HER2-positive, unresectable locally advanced or metastatic breast cancer who have had 2 or more prior anti-HER2 therapies'	Comment noted. The scope has been kept broad to ensure that NICE can appraise the technology

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		should be 'People with HER2-positive, unresectable locally advanced or metastatic breast cancer who have had 2 or more prior anti-HER2 therapies in the metastatic setting'	within its marketing authorisation. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
Comparators	Seagen Inc.	Seagen agree that the comparators included in the scope are appropriate for consideration. In addition, evidence shows that the combination of trastuzumab with capecitabine and monotherapy with trastuzumab emtansine (TDM1) are relevant comparators to the tucatinib combination and should therefore be included in this appraisal. Trastuzumab with capecitabine could be included as a comparator as over 50% of centres in the United Kingdom (UK) currently use this combination in patients with HER2+ metastatic breast cancer (MBC) who have received two prior anti HER2 treatment regimens (1). TDM1 monotherapy could also be included for consideration since it is also used to treat patients with HER2+ MBC who have received two prior anti HER2 treatment regimens, including treatment with trastuzumab in the neoadjuvant or adjuvant setting (2). Data on file show that the use of TDM1 in second line is high in the UK and there continues to be more use of chemotherapy without a HER2+ agent in later lines. 1. Robinson T, Palmieri C, Braybrooke JP. Trastuzumab Beyond Progression in Advanced Human Epidermal Growth Factor	Comments noted. Trastuzumab with capecitabine is not licensed for this indication. In addition, NICE recommends trastuzumab emtansine at second line (TA458). Therefore, these 2 options have not been added as comparators to the scope. No action required.

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		Receptor 2-Positive Breast Cancer: UK Practice now and in the Future. Clin Oncol (R Coll Radiol). 2020;32(10):636-8. 2. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, Andre F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)(dagger). Ann Oncol. 2020.	
	Pierre Fabre Ltd	The comparators are appropriate based on current NICE recommendations	Comment noted. No action required.
	Breast Cancer Now	The exact treatment for patients who have already received 2 or more anti HER2 therapies may differ. For the population being considered in this appraisal, eribulin is an appropriate comparator as it is recommended by NICE for treating secondary 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.	Comments noted. No action required.
	Roche Products Ltd	No comment	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
Outcomes	Seagen Inc.	The listed outcomes are appropriate and include the pre-defined primary (PFS in the intention-to-treat [ITT] population) and secondary endpoints (which includes OS in the ITT population).	Comment noted. No action required.

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	Pierre Fabre Ltd	Yes – the outcomes listed are appropriate	Comment noted. No action required.
	Breast Cancer Now	Yes	Comment noted. No action required.
	Roche Products Ltd	No comment	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
Economic analysis	Seagen Inc.	No further comments	Comment noted. No action required.
	Pierre Fabre Ltd	No comment.	Comment noted. No action required.
	Breast Cancer Now	No comment	Comment noted. No action required.
	Roche Products Ltd	No comment	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
Equality and Diversity	Seagen Inc.	No issues relating to equality have been identified.	Comment noted. No action required.

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	Pierre Fabre Ltd	No comment	Comment noted. No action required.
	Breast Cancer Now	The scope does not appear to promote discrimination	Comment noted. No action required.
	Roche Products Ltd	No comment	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
Other considerations	Seagen Inc.	No comment	Comment noted. No action required.
	Pierre Fabre Ltd	None	Comment noted. No action required.
	Breast Cancer Now	No comment	Comment noted. No action required.
	Roche Products Ltd	No comment	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
Innovation	Seagen Inc.	Despite recent advances in the management of HER2+ MBC, current treatment options for patients with disease progression provide limited benefits. There are currently no NICE-	Comments noted. Innovation will be considered by the appraisal committee when formulating its

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		recommended therapies demonstrating an OS benefit for patients with HER2+ MBC after two prior anti HER2 treatment regimens (3). Because of the lack of a safe and efficacious regimen for these patients, current European School of Oncology (ESO)-European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines recommend continued/recurrent use of HER2-directed agents (e.g. trastuzumab) (2, 4, 5). Treatments are needed that offer meaningful increases in PFS and OS, while preserving HRQoL and managing symptoms. Current therapies for patients who have received two prior anti HER2 treatment regimens are associated with frequent adverse events, including gastrointestinal, cardiovascular, pulmonary, and haematological toxicities. This highlights the need for novel therapies that can delay disease progression, particularly among women who have been treated with several systemic regimens. The tucatinib combination offers an innovative, effective treatment option for patients with HER2+ MBC who have received at least two prior anti-HER2 treatment regimens. • Tucatinib addresses multiple high unmet medical needs for HER2+ MBC patients, including patients with brain metastases • HER2CLIMB is the first randomised trial in patients with HER2+ MBC that included patients with untreated or previously treated, progressing brain metastases • HER2CLIMB demonstrated that tucatinib in combination with trastuzumab and capecitabine provides statistically significant and clinically meaningful improvement in PFS, OS, PFS in subjects with brain metastases, and confirmed ORR	recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.

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		• The tolerability profile and low discontinuation rate allows for continued dual HER2 inhibition until progression in heavily pre-treated patients; HRQoL was maintained throughout treatment • Tucatinib in combination with trastuzumab and capecitabine represents a new treatment option that has the potential to become a new standard of care in this population 2. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, Andre F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)(dagger). Ann Oncol. 2020. 3. NICE. NICE Pathways—advanced breast cancer: managing complications 2020. Available from: https://pathways.nice.org.uk/pathways/advanced-breast-cancer/advanced-breast-cancer-managing-complications. 4. Giordano SH, Temin S, Chandarlapaty S, Crews JR, Esteva FJ, Kirshner JJ, et al. Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018;36(26):2736-40. 5. NCCN. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Breast Cancer. Version 6.2020 2020 [updated September 8]. Available from: www.nccn.org/professionals/physician_gls/pdf/breast.pdf. 6. Lindegger N, Ike C, Schwartz NR, Surinach A, Liu YR, Debusk K. Trastuzumab use among patients with HER2-positive metastatic breast cancer in an electronic health records database (abstract 169P). Annals of Oncology. 2020;31:S62-S82.	

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		7. Baselga J, Cortes J, Kim SB, Im SA, Hegg R, Im YH, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366(2):109-19. 8. Blackwell KL, Burstein HJ, Storniolo AM, Rugo H, Sledge G, Koehler M, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol. 2010;28(7):1124-30. 9. Xu ZQ, Zhang Y, Li N, Liu PJ, Gao L, Gao X, et al. Efficacy and safety of lapatinib and trastuzumab for HER2-positive breast cancer: a systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2017;7(3):e013053.	
	Pierre Fabre Ltd	No comment	Comment noted. No action required.
	Breast Cancer Now	Yes we consider this treatment to be an innovative oral tyrosine kinase inhibitor that could provide a very important new treatment option to pre-treated HER2+ positive secondary breast cancer patients. Results published from the clinical trial suggest this treatment option improved progression free survival and overall survival compared to the placebo which are crucial outcomes for this patient group. When breast cancer spreads to the brain, it is incredibly hard to treat. New treatments such as tucatinib which may benefit a sub-group of patients with brain metastases are desperately needed. Traditionally, clinical trials have excluded patients with brain metastases so to now have potential positive data for this group would be a step-change in treatment.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.

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	Roche Products Ltd	No comment	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
Questions for consultation	Seagen Inc.	**Have all relevant comparators for tucatinib with trastuzumab and capecitabine been included in the scope?** As outlined in the section 'Comparators', Seagen believe there may be two additional relevant comparators used in UK clinical practice, namely combination of trastuzumab with capecitabine (which is included in the data package) and TDM1 monotherapy.	Comment noted. Trastuzumab with capecitabine is not licensed for this indication. In addition, NICE recommends trastuzumab emtansine at second line (TA458). Therefore, these 2 options have not been added as comparators to the scope. No action required.
		Would trastuzumab monotherapy or trastuzumab with chemotherapy be used in this population in clinical practice? Guidelines published by NICE do not recommend trastuzumab either alone or in combination with further chemotherapy for patients with disease progression (outside the central nervous system [CNS]) after two prior anti-HER2 treatment regimens. Moreover, the treatment is not funded centrally and there is not equitable access to such treatment. Despite the NICE guidance, a recent study has shown that over half (51.6%, n=32) of the 62 surveyed centres in the UK are using trastuzumab beyond	Comments noted. No further action required.

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		progression (1). This is an indication of the huge unmet need for new effective treatments in this population. Outside of NICE, it is also important to note that European guidelines recommend anti-HER2 treatment regimens regardless of the line of therapy. **As trastuzumab is included in the NICE recommended combinations for both untreated HER2-positive breast cancer and after one prior therapy, would it be used again in a different combination after two prior therapies and beyond?** Given the lack of proven treatment options following two prior anti-HER2 treatment regimens, many patients continue therapy with trastuzumab-based regimens (6). While trastuzumab is a humanised anti-HER2 antibody considered to be the backbone of treatment in the (neo)adjuvant and first-line metastatic settings (usually in combination with a taxane) (5), dual targeting of HER2, such as in the tucatinib combination, can lead to further improvements in efficacy in metastatic disease (7-9). In the HER2CLIMB trial, one inclusion criterion was that patients should have received previous treatment with trastuzumab, pertuzumab and TDM1. Thus, all patients had at least two prior exposures to trastuzumab-based regimens in any setting. The efficacy of tucatinib in combination with trastuzumab + capecitabine was demonstrated in the trial and tucatinib in combination with trastuzumab + capecitabine has already been included in the ESMO guidelines pending marketing authorisation in Europe.	Comments noted. No further action required. Comment noted. No further action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are the outcomes listed appropriate? This has been addressed above in the Outcomes section. **Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom tucatinib with trastuzumab and capecitabine is expected to be more clinically effective and cost effective or other groups that should be examined separately?** This questions in the draft scope have been covered in the sections above. **Would the comparators for people with brain metastases differ to those listed in the scope?** No, as current guidelines recommend continuing systemic therapies despite progression of metastatic tumours in the CNS. Accordingly, Seagen is not aware of any robust evidence supporting the use of any specific treatment option in this patient population. Therefore, the comparators listed in the scope as well as the additional agents outlined in the 'Comparators' section should also be applicable for patients with brain metastases. **Where do you consider tucatinib with trastuzumab and capecitabine will fit into the existing NICE pathway, advanced breast cancer?** The tucatinib combination represents a suitable treatment option for patients with HER2+ MBC who progressed after two prior anti-HER2 treatment regimens. The tucatinib combination has	Comment noted. No further action required. Comments noted. No further action required. Comments noted. No further action required.

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		shown robust efficacy and safety data in a patient population reflective of clinical practice, importantly because it included patients with brain metastases who have historically been excluded from clinical trials. Including patients with active (untreated and progressing) brain metastases is unprecedented and reflects disease progression that is common among patients with MBC in clinical practice. Given the high incidence of brain metastases in MBC, referenced as up to half in the background section of the scope, and lack of routine screening, many patients in the UK may have undiagnosed brain metastases and could therefore benefit from the tucatinib combination. As the available treatment options have not shown robust evidence in providing benefit for patients previously treated with current standard of care, the tucatinib combination represents an effective and well-tolerated medical therapy in patients with HER2+ MBC, regardless of (known or unknown) presence of brain metastases. **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 tucatinib with trastuzumab and capecitabine will be licensed;**	Comment noted. No further action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		• **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.** Seagen is not aware of any equality concerns that would impact the submission. **Do you consider tucatinib with trastuzumab and capecitabine 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)?** The tucatinib combination has the potential to be a step-change in the management of HER2+ MBC due to the unprecedented survival benefits achieved in patients who represent the real world but are rarely included in clinical trials. Please see section 'Innovation'. **Do you consider that the use of tucatinib with trastuzumab and capecitabine can result in any potential significant and**	Comment 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. Comment noted. No further action required.

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		substantial health-related benefits that are unlikely to be included in the QALY calculation? This question in the draft scope has been covered in the section above ('Innovation'). **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** This has been covered in the sections above. *References provided but not listed here*	Comment noted. No further action required.
	Pierre Fabre Ltd	Responses to the additional consultation questions are provided below. ***Would trastuzumab monotherapy or trastuzumab with chemotherapy be used in this population in clinical practice?*** No comment ***As trastuzumab is included in the NICE recommended combinations for both untreated HER2-positive breast cancer and after one prior therapy, would it be used again in a different combination after two prior therapies and beyond?*** No comment	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are the subgroups suggested in 'other considerations appropriate'? Yes ***Are there any other subgroups of people in whom tucatinib with trastuzumab and capecitabine is expected to be more clinically effective and cost effective or other groups that should be examined separately?*** No comment ***Would the comparators for people with brain metastases differ to those listed in the scope?*** No ***Where do you consider tucatinib with trastuzumab and capecitabine will fit into the existing NICE pathway, advanced breast cancer?*** We anticipate the position to be within the 'Person with advanced (stage 4) breast cancer' flow diagram as a 3rd-line treatment for both hormone receptor negative /HER2 positive and hormone receptor positive/ HER2 positive ***Do you consider that the use of tucatinib with trastuzumab and capecitabine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?***	

Section	Consultee/ Commentator	Comments [sic]	Action
		No	
	Breast Cancer Now	**Would trastuzumab monotherapy or trastuzumab with chemotherapy be used in this population in clinical practice?** Trastuzumab is not licensed with chemotherapy for use as a later line treatment for patients who have progressed on earlier treatments such as trastuzumab emtansine (Kadcyla). However, off-label prescribing of trastuzumab may happen in some circumstances across the NHS in England, so , access to this treatment is variable. Also as set out in a recent paper (T.Robinson, C.Palmieri, J.P Braybrooke, Tratuzumab beyond progression in advanced HER2 positive breast cancer: UK practice now and in the future, Clinical Oncology), of centres that responded to the research, just over 50% (51.6%) centres were prescribing trastuzumab beyond progression	Comments noted. NICE recommends pertuzumab with trastuzumab and docetaxel (TA509), and trastuzumab with paclitaxel (TA34) only at the first-line setting. Therefore, trastuzumab with chemotherapy has not been added as a comparator at third line in the scope. No action required.
	Roche Products Ltd	**Would trastuzumab monotherapy or trastuzumab with chemotherapy be used in this population in clinical practice?** Trastuzumab + chemotherapy would be used in this population because 50% centres in England have access and use it in the third-line setting (2) 2. Robinson T, Palmieri C, Braybrooke JP. Trastuzumab Beyond Progression in Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: UK Practice now and in the Future. Clinical Oncology. 2020;32(10):636-8.	Comment noted. NICE recommends pertuzumab with trastuzumab and docetaxel (TA509), and trastuzumab with paclitaxel (TA34) only at the first-line setting. Therefore, trastuzumab with chemotherapy has not been added as a comparator at third line in the scope. No action required.

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	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
Additional comments on the draft scope	Seagen Inc.	Wording of appraisal should be updated to reflect expected indication (see Comment 3 section below)	Comment noted. The wording of the scope has been updated in line with the expected indication in the marketing authorisation.
	Pierre Fabre Ltd	None	Comment noted. No action required.
	Breast Cancer Now	No comment	Comment noted. No action required.
	Roche Products Ltd	No further comments.	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above draft scope. Please see our comments as follows. This is an effective and very well tolerated combination which demonstrated remarkable efficacy after a taxane, pertuzumab and T-DM1, in terms of improved response rate, PFS and overall survival in women with HER2 positive advanced breast cancer, including those with brain metastases.	Comments noted. NICE recommends pertuzumab with trastuzumab and docetaxel (TA509), and trastuzumab with paclitaxel (TA34) only at the first-line setting. Therefore, trastuzumab with chemotherapy has not been added as a comparator at third line in the scope. Other stakeholder comments state that treatment would not be expected to differ due to the presence of brain metastases in this population.

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		The chemotherapy regimens cited are appropriate comparators. However, although trastuzumab is not routinely commissioned beyond progression in HER2 positive breast cancer, a survey at a meeting of the UK breast cancer group demonstrated that it is available to approximately 50% of clinicians around the UK. As such, chemotherapy plus trastuzumab is an important comparator to use for the appraisal. Trastuzumab monotherapy would not be used in clinical practice, except in very exceptional circumstances. In terms of NICE approved comparators for women with brain metastases, the chemotherapy regimens described are again appropriate comparators, although combination with trastuzumab should again be included. Carboplatin is an additional agent that is used for these patients. As no HER2 tyrosine kinase inhibitors (TKIs) are currently funded for NHS patients, compassionate access to lapatinib or neratinib is commonly requested and used for patients with HER2 positive advanced breast cancer, in particular for those with brain metastases, as there is a genuine unmet need for these patients. Most commonly, these TKIs are used in combination with capecitabine, although neratinib monotherapy is also used (in patients who have already received capecitabine with or without trastuzumab). At the Royal Marsden Hospital, we have treated approximately 70 women over the past 3 years with neratinib, with or without capecitabine. We presented our interim results at ESMO Breast 2019 (Shepherd S et al., 2019). Unfortunately, this treatment is often complicated by side effects, in particular diarrhoea, as reported in the literature. In contrast, my experience	Therefore, carboplatin, lapatinib and neratinib are not included as comparators in the scope. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		with tucatinib in the HER2 Climb trial was consistent with the published study results that the side effect profile is easily manageable. The combination of capecitabine, tucatinib and neratinib will fit well into the existing NICE pathway after treatment with T-DM1 and before eribulin. This is an effective treatment for a group of patients for whom the current NICE approved treatments have only modest and short-lived benefit.	

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

Amgen