NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tucatinib with trastuzumab and capecitabine for treating HER2-positive unresectable locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies [ID3828]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tucatinib with trastuzumab and capecitabine for treating HER2-positive unresectable locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies [ID3828]

Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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 number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
NA	Consultee (company)	Seagen	Seagen is grateful for the opportunity to respond to feedback from the NICE appraisal committee summarized within the Appraisal Consultation Document (ACD). While we are disappointed that tucatinib with trastuzumab and capecitabine did not receive an initial positive recommendation for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies, we are pleased that the appraisal committee recognized the high unmet medical need for better treatment in this poor prognosis patient population and appreciated the significant value of tucatinib with trastuzumab and capecitabine (hereafter referred to as the tucatinib combination) in this population. Currently in England there are limited approved treatment options for patients who have received 2 or more anti-HER2 therapies, especially amongst the roughly 50% of patients who will develop brain metastases (BM). There is also inequality of treatment across England as only some centres can access trastuzumab through local funding mechanisms in this later line setting. The HER2CLIMB study is the first to demonstrate significant efficacy in the whole of this population (PFS, OS and ORR), including the hardest to treat patient population with active BM (PFS only), a population which has been systematically excluded from historical clinical trials, due to their poor survival outcomes. We are encouraged that the committee has recognized that, by not including these hard to treat active BM patients, the clinical trial data from the comparators in this appraisal is not representative of the population in HER2CLIMB and the true patient population in clinical practice. There is therefore a bias in the current network against the tucatinib combination. We have addressed in our response the key committee requests summarised in the ACD in the following sections, with particular focus on the two biggest drivers of uncertainty in **Error! Reference source not found.** (treatment effect modification) and **Error! Reference source not found.** (utility differences post progression): 1. Exploration of a treatment effect modifier for brain metastases (**Error! Reference source not found.**): • Seagen conducted three approaches to derive a treatment effect modifier. • A review of the literature and feedback from the NICE clinical experts, has shown that the combination of chemotherapy with trastuzumab improved survival, even after	Thank you for your comment. Please see responses to individual comments below.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the development of brain metastases. • An analysis using the HER2CLIMB data is therefore expected to be a conservative approach given that it would not have captured any additional effect modification arising from the addition of HER2-targetted therapy (trastuzumab) in the whole population, but also specifically in the BM population. • Seagen believes the average of the estimates obtained from clinical experts to be a reasonable estimation of an effect modifier and has therefore included these in the revised company base case. 2. Subgroup and threshold analyses for people with and without brain metastases (**Error! Reference source not found.** and **Error! Reference source not found.**) 3. Justification for any differences in post-progression utility values for tucatinib combination and its comparators (**Error! Reference source not found.**) • There is clear evidence from both clinicians and carers that treatments given pre-progression have an impact on HRQoL post-progression and Seagen has therefore revised the company base case to include different post-progression utilities for the tucatinib combination and the single-agent chemotherapies. 4. Additional analyses using subcutaneous (SC) trastuzumab (**Error! Reference source not found.**) • Choice of SC vs IV trastuzumab should not be a relevant decision driver in this assessment as the choice of route of administration is a local decision influenced by the HCP, the patient and the local budget holder, as recommended by NICE Evidence Summary (ESNM13). • Due to the uncertainty of what clinical practice may be, Seagen has carried out two scenario analyses, one to reflect the usage of SC trastuzumab in the HER2CLIMB study and the second which we believe to be a higher estimate of SC usage than current clinical practice. Accepting all the committee's preferences and reflecting the above results of the additional analyses requested by the committee, Seagen have revised the company base case assumptions as follows: • using random effects network meta-analysis (see section 3.7 of the ACD) • extrapolating progression-free and overall survival directly from HER2CLIMB data ('within-trial' approach) (see section 3.10 of the ACD) • using clinician feedback as a basis for adjusting the modelling survival outcomes on the single-agent chemotherapies, in the absence of alternative unbiased estimates	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• assuming different pre-progression utility values for tucatinib and its comparators (see section 3.12 of the ACD) • assuming different post-progression utilities by treatment, using the HER2CLIMB utility value for the tucatinib combination and the ERG preferred mean value for the comparators • adjusting utility values for ageing (see section 3.12) • including drug wastage for trastuzumab and capecitabine (see section 3.14). Please refer to company's response to ACD for further details	
1	Consultee (company)	Seagen	**ACD section 3.8** *"The company should further explore the relative efficacy of the tucatinib combination in people with and without brain metastases"* **Company response:** • Seagen has conducted three approaches to derive an estimate of the magnitude of treatment effect modification due to brain metastases. These include a review of the literature, eliciting estimates of overall survival (OS) for single-agent chemotherapy from key opinion leaders (KOLs), and use of the HER2CLIMB data to derive an effect. • A review of the literature and feedback from the NICE clinical experts, has shown that the combination of chemotherapy with trastuzumab improved survival, even after the development of brain metastases. • The analysis of the HER2CLIMB data to derive a treatment effect modifier is therefore expected to be a conservative approach given that it would not have captured any additional effect arising from the addition of HER2-targetted therapy (trastuzumab) in the whole population, but also specifically in the BM population. • Seagen believes the average of the estimates obtained from clinical experts to be a reasonable estimation of an effect modifier and has therefore included these in the revised company base case. Please refer to company's response to ACD for further details	Comment noted. At its second meeting, the committee considered additional evidence related to treatment-modifying effect of brain metastases submitted by the company. The committee concluded that a treatment-modifying effect based on the HER2CLIMB data was most appropriate but noted it was highly uncertain and probably conservative (Final Appraisal Determination sections 3.8 and 3.9).
2	Consultee (Company)	Seagen	**ACD section 3.11** *"Subgroup and threshold analyses could help better understand uncertainty around the effectiveness of tucatinib in people with and without brain metastases"* **Company response:** • The HER2CLIMB study was designed to review efficacy and safety in the ITT population with some power to show PFS benefit in the BM subgroup. • However, as requested by NICE, Seagen has carried out an assessment of clinical effectiveness in the subgroup of patients with BM coupled with a cost-effectiveness	Comment noted. At its second meeting, the committee considered subgroup analyses provided by the company in its response to consultation. It concluded subgroup analyses were not suitable for decision

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			analysis of this subgroup. • These analyses demonstrate tucatinib combination to be even more cost-effective in the BM subgroup than in the ITT analysis, though this analysis is still subject to bias against the tucatinib combination and there is a high level of uncertainty. • Seagen was not able to carry out subgroup analyses for the non-BM subgroup within the response timeframe, however an estimate of cost-effectiveness has been generated using a weighted average approach. • As highlighted above, HER2CLIMB study was not powered to show a significant benefit in the non-BM subgroup and the size of the population assessed means there is greater uncertainty in this population. Therefore, the cost-effectiveness results in this subgroup are not relevant for decision making. Please refer to company's response to ACD for further details	making because of methodological limitations (Final Appraisal Determination section 3.12).
3	Consultee (company)	Seagen	**ACD section 3.11** "Subgroup and threshold analyses could help better understand uncertainty around the effectiveness of tucatinib in people with and without brain metastases" **Company response:** • Seagen has carried out a threshold analysis to determine the relative effects. (HRs) that would be required between tras-cape and the single agent chemotherapies to achieve an ICER of £50,000/QALY. • The analyses indicate that these HRs would need to be between 20-40% times worse than the current random effects HRs to achieve a £50,000/QALY ICER • This is within the range of estimates that were obtained via the supplementary analyses carried out as part of Topic 1 Please refer to company's response to ACD for further details	Comment noted. The committee discussed the threshold analyses but not used them in its decision making as they did not help resolve uncertainty.
4	Consultee (company)	Seagen	**ACD section 3.12** *"Some differences in pre-progression health state utilities are plausible, but post-progression utility differences are not justified"* **Company response:** • Seagen has carried out a literature search on the effect of treatment received pre-progression on health-related quality of life (HRQoL) post-progression.	Comment noted. The committee considered justifications for differences in post-progression utilities between tucatinib combination and comparators provided by the company. It concluded that some differences

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• As part of the KOL survey of survival estimates carried out for **Error! Reference source not found.**, Seagen also questioned KOLs regarding effect of prior treatments on HRQoL post-progression and the effect of BM on HRQoL. • These sources were further supported by feedback from patient groups regarding the impact of BM on their daily lives. • Due to the novel ability of the tucatinib combination to reduce the impact of BM both pre and post-progression, especially compared to single agent chemotherapy, Seagen believes that different post-progression utilities are plausible • In summary, there is clear evidence from both clinicians and carers that treatments given pre-progression have an impact on HRQoL post-progression. At least some of this is due to a larger proportion of patients receiving single-agent chemotherapies progressing with BM and its impacts • Seagen has therefore revised the company base case to include different post-progression utilities for the tucatinib combination and the single-agent chemotherapies. Please refer to company's response to ACD for further details	in post-progression health state utilities are plausible, but uncertain. (Final Appraisal Determination sections 3.13 and 3.14)
5	Consultee (company)	Seagen	**ACD section 3.13** *"Trastuzumab can be given subcutaneously or intravenously and both administration routes need to be considered"* **Company response:** • While Seagen agrees that SC trastuzumab is a treatment option in the UK, it is unclear in what proportion. As highlighted previously and recognized by the committee, in this setting, trastuzumab, either as an IV and even more so for the SC formulation, is not equally available across the NHS to patients • The choice of SC vs IV trastuzumab should therefore not be a relevant decision driver in this assessment as the choice of route of administration is a local decision influenced by the HCP, the patient and the local budget holder, as recommended by NICE Evidence Summary (ESNM13). • Due to the uncertainty of what clinical practice may be, Seagen has carried out two scenario analyses, one to reflect the usage of SC trastuzumab in the HER2CLIMB study and the second which we believe to be a higher estimate of SC usage than current clinical practice. Please refer to company's response to ACD for further details	Comment noted. The committee discussed the use of subcutaneous and intravenous trastuzumab in its second meeting. It concluded that subcutaneous trastuzumab is the standard of care in the NHS and could have unaccounted benefits for patients and service delivery. However, the committee acknowledged that the patient and clinical experts expressed a desire to have access to tucatinib combination, even if it could only be given with intravenous trastuzumab (Final Appraisal Determination section 3.15)

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
6	Consultee	[Breast Cancer Now]	We are incredibly disappointed that NICE has been provisionally unable to recommend tucatinib in combination with trastuzumab and capecitabine. This news was particularly devastating as we are concerned that this treatment could remain out of reach for people whose breast cancer has spread to the brain who have limited treatment options and who may have potentially shorter prognoses and a poorer quality of life. We urge the pharmaceutical company, Seagen and NICE to work together during this consultation period to consider every possible solution so that the drug can be recommended for routine use on the NHS.	Comment noted. The committee considered new PAS discount, additional evidence and revised base case submitted by the company during consultation. The committee concluded tucatinib combination, when administered with intravenous trastuzumab, is within what NICE normally considers an acceptable use of NHS resources (Final Appraisal Determination section 1.1)
7	Consultee	[Breast Cancer Now]	We are pleased that the committee recognised that the tucatinib combination had significant potential benefits for patient and recognised the unmet need for anti-HER2 treatments after second-line HER2 treatment. We reiterate our points from our earlier submissions and comments at the committee meeting about the importance of this treatment for this group of patients. A patient current receiving this treatment option explains that: 'It was really hard to come to terms with my diagnosis and the fact that there was no cure. It felt like a death sentence hanging over my head. While treatments helped shrink the tumours, it was at the cost of my quality of life. No treatment worked for long and when my cancer started to grow I felt I was fast running out of options. 'Then, the cancer spread to my brain. It felt like this was the end, as my lung and ancillary tumours had also started to grow more rapidly. 'Luckily, I found out I was eligible for a trial for tucatinib with trastuzumab and capecitabine and within six weeks of starting all of my tumours started to shrink and I've had no progression. This was so much more than I'd hoped for. The treatment not only works very effectively and has helped keep the cancer at bay for the past two and a half years, it's enabled me to have a better quality of life. 'I've seen too many young women tragically die of this disease and the tucatinib combination offers the opportunity to extend life. No price can be put on the additional time I've had with my family and the memories we've made thanks to this drug. That's why I want other women	Comment noted. The committee acknowledged HER2-positive breast cancer has a high disease burden and there is an unmet need for new treatment options such as tucatinib combination. (Final Appraisal Determination sections 3.1 and 3.2)

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			to be able to access this treatment too and hope this provisional rejection can be reversed.' Another patient who has HER2 positive secondary breast cancer who wants to ensure the tucatinib combination is made available on the NHS so it's there to access it when she needs it explains: 'When I was first diagnosed with secondary which was 'incurable and inoperable' in my liver and bones, I thought my life was likely over. But I responded well to Herceptin and chemotherapy and things got under control. I had been able to enjoy life and to make the most of it wherever and whenever I can. 'Then, three years later, I found it had spread to my brain. This provided a whole new level of fear because drugs struggle to cross the blood/brain barrier. 'When there are treatment options, there is always hope. At the moment I have options, but they are running out. There is definitely an unmet need in treatments for HER2 positive cancer. In fact, there is an urgent need to get life-prolonging treatment into the brain. But as yet approval hasn't happened and so I continue to wait and time continues to pass by, while hope begins to dwindle. 'A few precious years or even months may not seem much to people not faced with death, but to me, my family and my friends, it is everything. It's crucial that this treatment is now quickly made available on the NHS.'	
8	Consultee	[Breast Cancer Now]	Whilst we understand that the Committee would like to see further modelling of the cost-effectiveness of tucatinib combination relative to its comparators separately for people with and without brain metastases, we would urge the Committee to consider what flexibilities can be utilised here, given the lack of evidence for the comparators in people with brain metastases. We feel this is an area where a more reasonable approach could be explored. For many years patients with progressive brain metastases have been excluded from clinical trial and there has been a fear that as brain metastasis can lead to poorer outcome, that trials didn't want results influenced by this patient population. As the committee has recognised the network may be biased against tucatinib because if more patients with brain mets, particularly active mets, had been included in the comparator trials, the outcomes in those trials may have been worse. We are pleased the tucatinib trial included this patient group and flexibility must be used during this appraisal as this treatment would be a huge step forward for this patient group and it would not be fair for tucatinib combination to be penalised for this and worryingly there must not be a disincentive for trials including this population group.	Comment noted. The committee acknowledged HER2-positive breast cancer has a high disease burden, especially for people with brain metastases. It also acknowledged the unmet need for new treatment options such as tucatinib combination, especially for the significant proportion of people who have brain metastases. It agreed that trials of single agent chemotherapy would have had worse outcomes if they had included people with brain

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Brain metastases can have a huge impact on the patient and their family and people are fearful of breast cancer spreading to the brain. Symptoms can include seizures, nausea and vomiting, fatigue, pain and headaches. It can negatively impact quality of life, function, and independence for the patient, but also be difficult for the family to cope with. Brain metastases remains a treatment challenge as many existing treatments are unable to effectively cross the blood-brain barrier. That's why new treatments are desperately needed which can offer important PFS and OS improvements for patients, including those with brain metastases, whilst still offering a good quality of life. A patient receiving the tucatinib combination explains: "I have had no progression or reoccurence in the brain metastasis which has a positive impact on my mental well-being and independence". Another patient tells us: "I do not feel there are enough options available for secondary breast cancer patients, especially targeted treatments and specifically for treating brain metastasis".	metastases. Therefore in its decision making, it considered analysis that tries to adjust for this bias, using one of the methods proposed by the company. (Final Appraisal Determination sections 3.1, 3.2, 3.8 and 3.9)
9	Consultee	[Breast Cancer Now]	We also want to reflect on the point of whether any earlier discussions could have taken place between NICE and the company on the areas of uncertainty outlined in the ACD which could have avoided a second committee meeting.	Comment noted. NICE and the company engaged in discussions during the Technical Engagement stage of the Technology Appraisal process. Only issues unresolved after Technical Engagement were discussed by the committee in its first meeting, while only issues unresolved after ACD consultation were discussed in its second meeting.
10	Consultee	[Breast Cancer Now]	The tucatinib combination is recognised in international guidelines such as ESO-ESMO international consensus guidelines for advanced breast cancer and the ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. It references that continued HER2 blockade beyond disease progression is considered standard clinical practice and it is clear from the testimony of both patient and clinical experts the strength of feeling behind wanting to see tucatinib recommended for routine use on the NHS.	Comment noted. The committee acknowledged there is an unmet need for new treatment options such as tucatinib combination (Final Appraisal Determination section 3.2)
11	Commentator	Clinical expert	I am concerned that a group of patients with a high unmet need are missing out on an important treatment because capecitabine plus trastuzumab is not currently funded by NICE,	Comment noted. The committee acknowledged HER2-positive

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			therefore the comparator arm used in the HER2Climb 2 trial of the technology is not a standard NHS treatment.	breast cancer has a high disease burden and there is an unmet need for new treatment options such as tucatinib combination. It also acknowledged the comparator arm of HER2CLIMB (trastuzumab with capecitabine) is not a standard treatment in NHS practice. Instead ,it considered results of an indirect treatment comparison, in which tucatinib combination was compared with capecitabine, vinorelbine and eribulin currently used in the NHS. It also acknowledged that trials of single agent chemotherapy would have had worse outcomes if they had included people with brain metastases. Therefore it considered analysis that tries to adjust for this bias in its decision making, using one of the methods proposed by the company. (Final Appraisal Determination sections 3.1, 3.2, 3.8 and 3.9)
12	Commentator	Clinical expert	As discussed in the meeting, the indirect comparison to trials of single agent chemotherapy which largely excluded patients with brain metastases lead to better outcomes with these agents than would be expected if 50% of patients had brain metastases, as in the HER2Climb trial.	Comment noted. The committee acknowledged that trials of single agent chemotherapy would have had worse outcomes if they had included people with brain metastases. Therefore it considered analysis that tries to adjust for this bias in its decision making, using one of the methods proposed by the company. (Final Appraisal Determination sections 3. 6, 3.8,

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				and 3.9)
13	Commentator	Clinical expert	Patients with progressive brain metastases experience very difficult symptoms including seizures, headaches, nausea, visual disturbance and worsening mobility, leading to loss of independence and increasing care needs. They may also experience personality change as a result of their brain disease. Furthermore, these patients frequently become dependent on dexamethasone (due to brain oedema) and suffer the side effects of prolonged treatment with this drug, including weight gain, appearance changes, mood disturbance, glucose intolerance and hypertension. The benefit of controlling patients' brain disease for longer and delaying the onset of these awful symptoms which impact hugely on both the patient and their family cannot be overstated.	Comment noted. The committee acknowledged HER2-positive breast cancer has a high disease burden, especially in people with brain metastases, and there is an unmet need for new treatment options such as tucatinib. (Final Appraisal Determination sections 3.1 and 3.2)
14		METUPUK	• Has all of the relevant evidence been taken into account? METUPUK is the only charity in England and Wales solely dedicated to patient advocacy for metastatic breast cancer. We note that reading the 489 page committee papers makes contributing to this appraisal inaccessible to the majority of patients. Approving multiple combinations of drugs are always going to be a problem for double and triple drugs indicated together. The combined costs of the regimen are more likely to breach NICE limits for cost effectiveness. The individual effect of each drug is difficult to determine, not least because in combination the drugs may potentiate each other. We are disappointed that the NICE committee cited the fact that the comparator arm, trastuzumab with capecitabine, is not standard care in the NHS and therefore is reason to not recommend tucatinib. ESMO guidelines produced in 2021 state that "Continued HER2 blockade beyond disease progression is considered standard clinical practice". We are campaigning that all NHS patients should have access to anti-HER2 beyond progression of two treatment lines, reflecting clinical practice in high income countries. Too many NHS patients currently self fund trastuzumab beyond two/three treatment lines, causing financial instability for terminally ill patients. To use current undertreatment of NHS patients as a reason to not recommend a new therapeutic is an additional blow to patients who already do not have parity of care. The HER2CLIMB trial was a multicentre randomised control trial conducted across multiple countries. Without HER2 blockade in the control arm, the trial would have failed ethical approval because international guidelines state HER2 blockade plus chemotherapy is a minimum standard of care. The question must now be asked, will a NICE committee EVER approve a novel therapeutic for heavily pre-treated HER2 positive patients with MBC if having HER2 blockade in the comparator arm is a reason to discount the findings?	Comment noted. NICE provides all relevant Technology Appraisal documents for transparency. Key information is summarised on the slides presented during committee meetings and will be published on the website as part of the committee papers. Tucatinib is indicated in combination with capecitabine and trastuzumab. The committee considers new interventions in agreement with their marketing authorisation, so can only consider cost-effectiveness of tucatinib combination. The committee's remit is to appraise a new technology against standard care in NHS practice. The committee acknowledged the comparator arm of HER2CLIMB, trastuzumab with capecitabine, is not part of standard care in the NHS. Therefore, it considered results of indirect treatment

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Up to 50% of patients with metastatic HER2 positive breast cancer go on to develop brain metastases but there is no targeted drug treatment funded by the NHS which is known to cross an intact blood brain barrier. Although radiotherapy is an important treatment, it has limitations for patients. Access to stereotactic radiotherapy is inconsistently applied across the NHS, specifically with regard to total number and total volume of tumours which can be treated. Whole brain radiotherapy is typically only carried out once and has considerable short term and long term reductions in quality of life. There are also geographical barriers in accessing radiotherapy centres for patients living in remote areas or with disabilities. The unmet need for patients with HER2 positive MBC and brain involvement should be weighted highly by the committee. It is worth emphasising that no tyrosine kinase inhibitor is available on the NHS for patients with MBC. The drug lapatinib, which is currently used in most high income countries, was not deemed cost effective for NHS patients. As noted by the committee tyrosine kinase inhibitors are small molecules with the potential to breach the blood brain barrier. Therefore this class of drugs has the potential to provide disease control in patients with brain metastases. The HER2CLIMB trial data shows that the capecitabine and tucatinib combination increases progression free survival. Cancer progression is correlated with poorer quality of life, and so delaying progression gives patients longer time in better health. The capecitabine and tucatinib combination also increases overall survival, which is the most important metric to patients.	comparison against single-agent chemotherapy, capecitabine, vinorelbine and eribulin, which are used in NHS practice. (Final Appraisal Determination section 3.8 and 3.9) The committee acknowledged that trials of single agent chemotherapy would have had worse outcomes if they had included people with brain metastases. Therefore it considered analysis that tries to adjust for this bias in its decision making, using one of the methods proposed by the company (Final Appraisal Determination sections 3.8 and 3.9) Radiotherapy and stereotactic radiotherapy are not comparator therapies in this appraisal and are expected to be used alongside the tucatinib combination. Therefore, the committee considered addressing this inequality is beyond its remit. The committee acknowledged there is an unmet need for new treatment options such as tucatinib (Final Appraisal Determination section 3.1 and 3.2)
15		METUPUK	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	The committee considered both results of HER2CLIMB and an

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			It is unreasonable to dismiss trial data because the comparator arm, which is standard of care in similar GDP countries, is not available in the NHS. Using this logic, no new treatments for patients who have received at least two prior anti-HER2 treatment regimens can ever be approved, because no clinical trial will be ethically conducted without HER2 blockade in the comparator arm. Cancer care should not be a race to the bottom. The clinical summary from the HER2CLIMB trial reflected real world patients within the NHS because patients with active brain metastases were included. Controlling brain metastases not only increases survival but increases the quality of the additional months of life. As patient advocates at METUPUK we note that the NICE committee and Seagen Inc. both attempted to model the HER2CLIMB data to chemotherapy regimens without HER2 blockade. We question the utility of these models which are retrospective and based on patient populations with different characteristics. We also question if the models can determine the extent to which the three drugs in the capecitabine and tucatinib combination potentiate each other. We would prefer the actual trial data to be given the greatest weight since it is prospective, has been peer reviewed and has fewer inbuilt biases and assumptions than the models. The redaction of large portions of the committee papers relating drug cost means no meaningful comments can be made on cost effectiveness.	indirect treatment comparison, in which tucatinib combination was compared with capecitabine, vinorelbine and eribulin currently used in the NHS. It also acknowledged that trials of single agent chemotherapy would have had worse outcomes if they had included people with brain metastases. Therefore it considered analysis that tries to adjust for this bias in its decision making, using one of the methods proposed by the company. (Final Appraisal Determination sections 3.1, 3.2, 3.8 and 3.9) The committee's remit is to consider both clinical- and cost-effectiveness of new therapeutic interventions. Please see Final Appraisal Determination sections 3.4 to 3.9 for committee's discussion of clinical effectiveness evidence, including HER2CLIMB trial, and sections 3.10 to 3.16 for its discussion of cost-effectiveness results.
16		METUPUK	Are the recommendations sound and a suitable basis for guidance to the NHS? The recommendations are not a sound guidance for the NHS. They fail to consider the existing treatment pathway for patients who have had at least two prior anti-HER2 treatment regimens. There is an unmet need for HER2 blockade in later lines of treatment, and specifically an unmet need for ongoing treatment for brain metastases. NHS patients with HER2 positive MBC do not have access to any tyrosine kinase inhibitors, despite this class of medication being a mainstay treatment in most developed healthcare	The committee acknowledged there is an unmet need for new treatment options such as tucatinib combination, especially for people with brain metastases (Final Appraisal Determination section 3.2) Comment noted. The committee

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			systems. The EMA patent of lapatinib will expire in June 2023, and potentially cheaper generic versions will be available. However, NICE has rejected lapatinib on cost, and without drug company sponsorship there is no mechanism to overturn this decision. Tucatinib is modelled to be superior to lapatinib, and if this drug is rejected NHS patients will once again be let down. We note that many publicly funded healthcare systems including those in Australia, Canada, and many EU countries have approved tucatinib.	considered new PAS discount, additional evidence and revised base case submitted by the company during consultation. The committee concluded tucatinib combination, when administered with intravenous trastuzumab, is within what NICE normally considers an acceptable use of NHS resources (Final Appraisal Determination section 1.1)
17		METUPUK	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Breast cancer predominantly affects women. Although men can get breast cancer, 99% of cases occur in women. Therefore women will be disproportionately affected by this ruling. HER2 positive (along with triple negative) breast cancer occurs at a higher frequency in younger women and in black women. Therefore this ruling will disproportionately impact on younger people and on black people. The alternative treatment for patients with brain metastases is radiotherapy. Access to radiotherapy sites across England and Wales is inequitable, depending on the patient's geographical location. There are considerably fewer sites offering stereotactic radiotherapy than conventional radiotherapy, and many more patients will be required to travel more than 45 minutes to access care. The geographical disparities will disproportionately impact on people with disabilities and people with limited English who may struggle to travel long distances. In addition, some people with disabilities would struggle with the physical demands of radiotherapy and planning MRI scans, such as lying flat for protracted periods of time. The capecitabine and tucatinib combination gives the possibility for people with brain metastases to receive treatment closer to their homes.	Comment noted. Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. Radiotherapy and stereotactic radiotherapy are not comparator therapies in this appraisal and are expected to be used alongside the tucatinib combination. Therefore, the committee considered addressing this inequality is beyond its remit.

Summary of comments received from members of the public

Theme	Response
Do not agree with the ACD decision to not recommend tucatinib combination	Comment noted.
Disease impact	
There is a crucial unmet need for patients with HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies, particularly those with brain metastases	Comment noted. The committee acknowledged there is an unmet need for new treatment options such as tucatinib, particularly for people with brain metastases. (Final Appraisal Determination section 3.1)
Stopping progression and maintaining quality of life is very important	Comment noted. The committee recognised that HER2-positive metastatic breast cancer has a high disease burden and can adversely affect patients' quality of life, especially for people with brain metastases. (Final Appraisal Determination sections 3.1, 3.13 and 3.14)
Controlling brain metastases improves quality of life	Comment noted. The committee recognised that brain metastases have particular burden for patients and can adversely affect patients' quality of life. (Final Appraisal Determination sections 3.1, 3.13 and 3.14)
Impact on social activities	Comment noted. The committee recognised that HER2-positive metastatic breast cancer has a high disease burden and can adversely affect patients' quality of life, especially for people with brain metastases. (Final Appraisal Determination sections 3.1, 3.13 and 3.14)
Current treatments	
High unmet need for new treatment options	Comment noted. The committee recognised high unmet need for additional treatment options after 2 or more anti-HER2 therapies. It also recognised the unmet need is particularly high for people with brain metastases. (Final Appraisal Determination section 3.2)
Chemotherapy drugs can have severe side effects	Comment noted. The committee recognised high unmet need for additional treatment options after 2 or more anti-HER2 therapies. It noted that tucatinib combination has a favourable safety profile compared with single agent chemotherapies. (Final Appraisal Determination sections 3.2 and 3.13)
Limited treatments that cross the blood-brain barrier	Comment noted. The committee recognised there are limited treatment options for people with brain metastases. (Final Appraisal Determination section 3.2)
Shortage of current treatments	Comment noted. The committee recognised high unmet need for additional treatment options after 2 or more anti-HER2 therapies. (Final Appraisal Determination section 3.2)
Lapatinib + capecitabine was used in the network-meta analysis but this is not routinely offered on the NHS	Comment noted. The committee considered results of an indirect treatment comparison, in which tucatinib combination was compared with capecitabine, vinorelbine and eribulin currently used in the NHS. (Final Appraisal Determination sections 3.6, 3.8 and 3.9)

Theme	Response
Tucatinib disadvantaged as trastuzumab and capecitabine not NHS standard of care	Comment noted. Committee acknowledged that trials of single agent chemotherapy would have had worse outcomes if they had included people with brain metastases. Therefore it considered analysis that tries to adjusts for this bias in its decision making, using one of the methods proposed by the company. (Final Appraisal Determination sections 3.6, 3.8 and 3.9)
Current treatment is worse than other countries including similar GDP countries	Comment noted. NICE technology appraisals committees appraise the clinical- and cost-effectiveness of new health technologies compared with current standard care in NHS practice. Comparing current NHS practice with practice in other countries is outside of committee's remit.
Trastuzumab deruxtecan has efficacy in brain metastases population.	Comment noted. Trastuzumab deruxtecan is not a comparator in this appraisal. The committee did not see any evidence of trastuzumab deruxtecan efficacy in people with brain metastases and could not comment on this. However, Trastuzumab deruxtecan is currently being scoped for a potential technology appraisal.
Trastuzumab deruxtecan efficacy in stable brain metastases	Comment noted. Trastuzumab deruxtecan is not a comparator in this appraisal. The committee did not see any evidence of trastuzumab deruxtecan efficacy in people with brain metastases and could not comment on this. However, Trastuzumab deruxtecan is currently being scoped for a potential technology appraisal.
Confidentiality and transparency	
Unable to comment on cost-effectiveness due to redacted data	Comment noted. NICE is dedicated to transparency of its decision-making. However, it has responsibility to respect confidentiality of data submitted in confidence by the company.
Long committee papers are not patient or public friendly	Comment noted. NICE provides all relevant Technology Appraisal documents for transparency. Key information is summarised on the slides presented during committee meetings.
Tucatinib	
Tucatinib was shown to be effective with few side effects	Comment noted. Committee noted that tucatinib combination has been shown to be effective and has a favourable safety profile compared to single agent chemotherapies. (Final Appraisal Determination section 3.5 and 3.13)
Overall risks of hospital admission are reduced	Comment noted. Risk of hospital admissions was considered in the economic model.
Tucatinib especially effective in brain metastases	Comment noted. Committee acknowledged the efficacy of tucatinib combination, including in people with brain metastases. (Final Appraisal Determination section 3.5)

Theme	Response
Tucatinib can improve quality of social and work lives, can be “life-changing” for some patients	Comment noted. The committee recognised that HER2-positive metastatic breast cancer has a high disease burden and can adversely affect quality of life, particularly for people with brain metastases. The committee concluded tucatinib combination may improve patients’ quality of life before and after progression of their disease (Final Appraisal Determination section 3.1, 3.13 and 3.14)
Need access to treatments that can cross the blood-brain barrier	Comment noted. The committee recognised there are limited treatment options for people with brain metastases, because standard treatments do not cross an intact blood-brain barrier, in contrast to tucatinib. (Final Appraisal Determination section 3.2 and 3.8)
Drug can possibly reduce the risk of brain metastases	Comment noted. Committee concluded tucatinib combination provides clinical benefit to people with and without brain metastases (Final Appraisal Determination sections 3.5 and 3.6)
Relevant evidence	
ESMO guidelines recommend sequential trastuzumab-based strategies if anti-HER2 therapies are not an option	Comment noted. The committee’s remit is to compare new therapeutic interventions (tucatinib combination) with current standard of care in the NHS. Trastuzumab plus capecitabine is not routinely available in the NHS beyond progression after 2 or more HER2-targeted therapies, and therefore is not a relevant comparator in this appraisal (Final Appraisal Determination sections 3.2 and 3.3).
ASCO guidelines recommended HER2 directed treatment beyond progression after two or more lines of therapy	Comment noted. The committee’s remit is to compare new therapeutic interventions (tucatinib combination) with current standard of care in the NHS. Trastuzumab plus capecitabine is not routinely available in the NHS beyond progression after 2 or more HER2-targeted therapies, and therefore is not a relevant comparator in this appraisal (Final Appraisal Determination sections 3.2 and 3.3).
Not all relevant evidence has been collated - Department of Health/NHS secondary breast cancer survey on prevalence of secondary breast cancer	Comment noted. Following its standard processes, NICE invited all stakeholders to submit all evidence relevant to the appraisal of tucatinib combination for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies. Survey on prevalence of secondary breast cancer would not have helped to resolve uncertainty in this appraisal.
Cost-effectiveness	
Putting a price on life	Comment noted. In accordance with NICE’s charter and principles, the committee’s remit is to consider both clinical- and cost-effectiveness of new therapeutic interventions. Please see Final Appraisal Determination sections 3.4 to 3.9 for committee’s discussion of clinical effectiveness evidence, including HER2CLIMB trial, and sections 3.10 to 3.16 for its discussion of cost-effectiveness results.

Theme	Response
Issues with NICE approval methods	Comment noted. The committee's remit is to consider both clinical- and cost-effectiveness of new therapeutic interventions. Please see Final Appraisal Determination sections 3.4 to 3.9 for committee's discussion of clinical effectiveness evidence, including HER2CLIMB trial, and sections 3.10 to 3.16 for its discussion of cost-effectiveness results.
Equality	
Affects more women than men – particularly black women	Comment noted. Higher prevalence of a disease among people with particular characteristics is not considered in and of itself an equality issue. However, the committee will consider if its recommendation has the potential to directly or indirectly discriminate an groups of people and they make amendments if necessary to avoid any inequality.
Younger people can be outliers regarding survival	Comment noted. There are no sub-group populations within this guidance so no group within the population of people with HER2-positive advanced breast cancer has been treated less favourably.
Should not be regional variation in availability of trastuzumab with capecitabine	Comment noted. The technology appraisal committee's remit is to compare new therapeutic interventions with current standard of care in the NHS. It is beyond its remit to make judgements about appropriateness of standard care in the NHS.
Trastuzumab is too expensive for private treatment – some people don't have access to care	Comment noted. In accordance with NICE's social value judgement principles, no priority is given based on individuals' income, social class, position in life or social roles in guidance developed for the NHS. NICE's standard approach to economic modelling (the 'reference case') does not compare NHS healthcare with privately funded healthcare.

Seagen response to NICE Appraisal consultation document

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

Contents

List of Tables

List of figures

Executive summary

Seagen is grateful for the opportunity to respond to feedback from the NICE appraisal committee summarized within the Appraisal Consultation Document (ACD). While we are disappointed that tucatinib with trastuzumab and capecitabine did not receive an initial positive recommendation for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies, we are pleased that the appraisal committee recognized the high unmet medical need for better treatment in this poor prognosis patient population and appreciated the significant value of tucatinib with trastuzumab and capecitabine (hereafter referred to as the tucatinib combination) in this population. Currently in England there are limited approved treatment options for patients who have received 2 or more anti-HER2 therapies, especially amongst the roughly 50% of patients who will develop brain metastases (BM). There is also inequality of treatment across England as only some centres can access trastuzumab through local funding mechanisms in this later line setting.

The HER2CLIMB study is the first to demonstrate significant efficacy in the whole of this population (PFS, OS and ORR), including the hardest to treat patient population with active BM (PFS only), a population which has been systematically excluded from historical clinical trials, due to their poor survival outcomes. We are encouraged that the committee has recognized that, by not including these hard to treat active BM patients, the clinical trial data from the comparators in this appraisal is not representative of the population in HER2CLIMB and the true patient population in clinical practice. There is therefore a bias in the current network against the tucatinib combination.

We have addressed in our response the key committee requests summarised in the ACD in the following sections, with particular focus on the two biggest drivers of uncertainty in Topic 1 (treatment effect modification) and Topic 4 (utility differences post progression):

1. Exploration of a treatment effect modifier for brain metastases (Topic 1):
    - Seagen conducted three approaches to derive a treatment effect modifier.
    - A review of the literature and feedback from the NICE clinical experts, has shown that the combination of chemotherapy with trastuzumab improved survival, even after the development of brain metastases.

- An analysis using the HER2CLIMB data is therefore expected to be a conservative approach given that it would not have captured any additional effect modification arising from the addition of HER2-targetted therapy (trastuzumab) in the whole population, but also specifically in the BM population.
- Seagen believes the average of the estimates obtained from clinical experts to be a reasonable estimation of an effect modifier and has therefore included these in the revised company base case.

2. Subgroup and threshold analyses for people with and without brain metastases (Topic 2 and Topic 3)

3. Justification for any differences in post-progression utility values for tucatinib combination and its comparators (Topic 4)

- There is clear evidence from both clinicians and carers that treatments given pre-progression have an impact on HRQoL post-progression and Seagen has therefore revised the company base case to include different post-progression utilities for the tucatinib combination and the single-agent chemotherapies.

4. Additional analyses using subcutaneous (SC) trastuzumab (Topic 5)

- Choice of SC vs IV trastuzumab should not be a relevant decision driver in this assessment as the choice of route of administration is a local decision influenced by the HCP, the patient and the local budget holder, as recommended by NICE Evidence Summary (ESNM13).
- Due to the uncertainty of what clinical practice may be, Seagen has carried out two scenario analyses, one to reflect the usage of SC trastuzumab in the HER2CLIMB study and the second which we believe to be a higher estimate of SC usage than current clinical practice.

Accepting all the committee's preferences and reflecting the above results of the additional analyses requested by the committee, Seagen have revised the company base case assumptions as follows:

- using random effects network meta-analysis (see section 3.7 of the ACD)

- extrapolating progression-free and overall survival directly from HER2CLIMB data ('within-trial' approach) (see section 3.10 of the ACD)
- using clinician feedback as a basis for adjusting the modelling survival outcomes on the single-agent chemotherapies, in the absence of alternative unbiased estimates
- assuming different pre-progression utility values for tucatinib and its comparators (see section 3.12 of the ACD)
- assuming different post-progression utilities by treatment, using the HER2CLIMB utility value for the tucatinib combination and the ERG preferred mean value for the comparators
- adjusting utility values for ageing (see section 3.12)
- including drug wastage for trastuzumab and capecitabine (see section 3.14).

Furthermore, to show our commitment to ensuring patient access to the tucatinib combination, Seagen has significantly increased the PAS initially offered at submission from [redacted]

As part of our response, Seagen have submitted an updated version of the ERG model with all changes/additions highlighted in yellow.

The revised company base case cost effectiveness results are presented in Table 1, including the revised PAS. Although these are presented by individual comparator, there is varied usage of the single agent chemotherapies across England and Wales and Seagen believes that blended scenarios should also be considered in NICE's decision making. We therefore include within our base case results:

- A blended ICER, that is likely to reflect the current treatment practice, by assuming [redacted] of the comparators in the NHS (ie [redacted]). This takes a more conservative approach than the scenario which was included in the original company submission, which assumed [redacted] usage of capecitabine, [redacted] of eribulin and [redacted] of vinorelbine, based on feedback as part of an advisory board from clinicians. In this scenario, at the revised base case and PAS, the blended ICER is £[redacted].

It can be seen that the blended ICER lies below the end-of-life threshold of £50,000/QALY, demonstrating that the tucatinib combination not only has significant

benefits for patients in terms of improved survival and HRQoL, but is a cost-effective alternative for the NHS in England and Wales. It is therefore vital that both clinicians and patients have access to this innovative treatment, which, if approved, will provide the additional service benefit to the NHS of helping to address the current inequality of access for trastuzumab.

Table 1: Seagen ACD response base case cost-effectiveness estimates

Technology	Total costs (£)	Total QALYs	Pairwise ICER
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	[redacted]
Blended ICER assuming average of all three comparators			
Blended comparator	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years			

Note: While adapting the current model, Seagen noticed that an additional trastuzumab discount had been erroneously incorporated into the model (Cost sheet cell E27). This has been removed and all results within this response document are inclusive of this correction.

Topic 1 Exploration of a treatment effect modifier for brain metastases

ACD section 3.8 *"The company should further explore the relative efficacy of the tucatinib combination in people with and without brain metastases"*

Company response:

- Seagen has conducted three approaches to derive an estimate of the magnitude of treatment effect modification due to brain metastases. These include a review of the literature, eliciting estimates of overall survival (OS) for single-agent chemotherapy from key opinion leaders (KOLs), and use of the HER2CLIMB data to derive an effect.
- A review of the literature and feedback from the NICE clinical experts, has shown that the combination of chemotherapy with trastuzumab improved survival, even after the development of brain metastases.
- The analysis of the HER2CLIMB data to derive a treatment effect modifier is therefore expected to be a conservative approach given that it would not have captured any additional effect arising from the addition of HER2-targetted therapy (trastuzumab) in the whole population, but also specifically in the BM population.
- Seagen believes the average of the estimates obtained from clinical experts to be a reasonable estimation of an effect modifier and has therefore included these in the revised company base case.

1.1 Summary

In the HER2CLIMB study, we enrolled a large percentage of patients with untreated or previously treated BM, a population typically excluded from clinical trials despite this condition being a common clinical problem. Though it is believed that up to 50% of patients will develop BM, unfortunately, in current NHS practice, patients do not routinely undergo routine screening of the brain. This is mainly due to a lack of effective treatments and guidelines for the treatment of central nervous system (CNS) metastasis but may also be due to the extra burden on radiological services that active screening would require in a very stretched service. Once a diagnosis is confirmed,

treatment is at the discretion of a patient's oncology team (1) and is usually a combination of local therapies (surgery and radiotherapy) and systemic treatments such as high dose steroids. KOL feedback confirmed that only symptomatic patients are currently diagnosed with brain metastasis in NHS practice, making patients with brain metastasis an under-reported population and further highlighting the unmet medical need in this setting.

Having HER2-positive disease (amplification/overexpression) is a significant negative prognostic factor (2). This has changed with the advances in HER2-targeted therapies leading to improved survival of these patients. This is especially true of patients with BM, even though it is believed that current treatment options do not cross the blood brain barrier. Several clinical studies have shown that the combination of chemotherapy with trastuzumab improved survival, even after the development of brain metastases (3–5). This benefit is presumed to be mainly due to improved control of systemic disease, highlighting the importance of targeting HER2 regardless of location of disease (6). It is therefore likely that any in-trial comparison carried out in HER2CLIMB, comparing the different hazards ratios (HRs) between the BM and non-BM populations will underestimate the benefit that tucatinib combination would bring versus single-agent chemotherapy. This is echoed in the feedback from the NICE clinical experts, who noted: *"that good control of disease and metastases in other parts of the body may delay brain metastases development and progression, so treatments that are more effective in controlling other metastases are also believed to be more effective for people with brain metastases*."

The HER2CLIMB study was the only study in the network-meta-analysis (NMA) to recruit patients with active BM. While some other studies included patients with stable or treated BM, the proportions were either not reported or were extremely low. Thus, without anchored evidence from comparator trials recruiting BM patients, an effect modifier cannot be estimated using robust methods such as meta-regression.

Therefore, *a priori*:

Any effect modification observed in the HER2CLIMB trial, that is, the poorer hazard ratio (HR) of tras-cape observed in BM patients, is likely to be an underestimate of any treatment effect modifier and other approaches are required to quantify the larger

effect modification expected in the single-agent chemotherapies. Seagen has therefore also sought input from clinical experts and has taken the following approaches to calculate an effect modifier:

1 A review of the literature, to identify any evidence on relative effectsbetween HER-2-targeted and untargeted regimens in patients with BM.
2 Via clinician elicitation of expected OS following treatment with single-agent chemotherapy in patients with the same characteristics as those recruited to HER2CLIMB.
3 Deriving an interaction effect of BM from HER2CLIMB and using it to adjust the OS and PFS NMAs. This is expected to be a conservative approach, given there is some effect on BM expected from trastuzumab.

These three approaches and their results are summarised below:

1.2 Review of the published literature for relative effects in HER2-positive BM patients

A number of historic real-world evidence studies of HER2+ patients with BM, show the stark difference in survival outcomes seen with the addition of targeting HER2, with improvements ranging from 9.9 to 13.8 months. These studies support the theory that the targeting of HER2, is important for patients with BM further reinforcing the hypothesis that any effect modifier derived from the HER2CLIMB study in section 1.4 is likely to underestimate the likely effect modification when comparing against single-agent chemotherapies.

In a retrospective analysis of 1,712 breast cancer patients identified as having BM from the Breast Cancer Network Registry in Germany, 47.8% (n=732) were HER2- positive. Those that received anti-HER2 treatment after diagnosis with BM had a median OS of 17.1 months (95% CI: 14.4-19.5) versus 7.2 months without treatment (95% CI: 5.8-8.7; $p < 0.0001$)(7). In the registHER, prospective observational study inthe US (8), for those patients who received trastuzumab following diagnosis of CNS disease (n = 258), the median survival was 17.5 months, compared with 3.7 months for patients who did not receive trastuzumab (n = 119) with a HR of 0.25 (95% CI: 0.20-0.33, <0.001).

Furthermore, a retrospective analysis of 280 HER2-positive breast cancer patients diagnosed with BM, across 6 Asian countries, showed a median OS of 18.5 months (95% CI: 12.9-21.8) versus 5.7 months (95% CI: 4.2-8.9), for patients receiving trastuzumab (n=56) versus receiving no anti-HER2 therapy (n=166) leading to a crude HR (0.57 (0.39–0.84), p=0.005) and adjusted HR (0.73 (0.49–1.10), p=0.13)(4). All of these results point to a notably larger improvement than those obtained for tras-cape vs. the single-agent chemotherapies (HR range 0.85-0.9) in the ERG's preferred base case.

These data support the fact that targeting HER2 is particularly crucial in increasing survival for HER2-positive patients with BM and by not accounting for this we would expect outcomes to be substantially worse than in the ERG's preferred base case indirect comparison, which excludes BM patients in the single-agent chemotherapy arms.

1.3 Application of an effect modifier using estimates from a clinician survey

Seagen conducting 10 clinician surveys, with KOLs who treat HER2-positive breast cancer from a wide range of teaching hospitals across England. We asked the clinicians to estimate the survival outcomes for single agent chemotherapies, if they had been included in the HER2CLIMB study at various timepoints (1, 2, 3 and 5 years), so for patients who had received 2 or more anti-HER2 therapies. As a reference point, the clinicians were provided with the predicted survival estimates at those timepoints for the tucatinib combination and tras-cape patients from the economic model (ERG's preferred estimates). The questions asked and the results by clinician are summarized in Appendix B. The OS predictions from the KOLs were then used to adjust the ERG model OS and PFS survival curves for singe agent chemotherapy comparators as follows:

- The worst, best and average survival estimates from the KOLs at each timepoint were tabulated, alongside those predicted for the single-agent chemotherapies from the current ERG model. The mean, upper and lower confidence levels (CIs) of the estimates were calculated for each timepoint. Note that a blinded assumption was also provided by the clinical expert at technical engagement, who gave survival estimates of <50%, <20% and 0% at

1, 2 and 5 years respectively. However, it was noted that when these were compared to the modelled outcomes during the committee meeting, these were considered the “best possible expected outcomes”.

A relative effect (calculated as a HR) was derived, based on the average clinician OS prediction at each timepoint compared with the average of the ERG OS survival curve predictions for the three single-agent chemotherapies (see Table 2). This can be considered a method of deriving an effect modifier based on clinical opinion.

- The HRs were applied to the ERG model survival curves (PFS, OS and time on treatment, assuming proportionality), tapering the HR between adjacent estimates and eventually down to 1 (no relative effect) by year 5. This had the effect of adjusting the ERG survival curves downwards to fit the clinician estimates.
- Although this comprises a crude adjustment that leads to some ‘kinking’ of the survival curves, it provides a reasonable approximation of life years and QALYs for the single-agent chemotherapies based on the clinician estimates.

The KOL OS estimates, original ERG model predictions and the relative difference (HR) calculated using this approach are shown in Table 2 and the cost-effectiveness estimates are summarized in Table 3 (other than this change, Table 3 reflects the revised company base case assumptions as stated previously).

It can be seen that the cost-effectiveness results produce ICERs for tucatinib combination close to or below the NICE WTP threshold for EoL therapies and even lower than the ICERs generated using an effect modifier derived from HER2CLIMB (see 1.4). This is not unexpected, given that the latter analysis would not have captured any additional effect modification on BM arising from the addition of HER2-targeted therapy. Seagen therefore believes these estimates to be a more reasonable estimation of an effect modifier and has therefore included these in the revised company base case.

Table 2: Calculation of relative effect applied to ERG single-agent chemotherapy survival curves from KOL elicitation

% alive	1 year	2 year	3 year	5 year	Model undiscounted LYs
KOL OS estimates					
Mean estimate	43%	20%	6%	1%	1.38
Lower CI	36%	17%	5%	0%	1.22
Upper CI	50%	23%	8%	1%	1.55
ERG model estimates					
Capecitabine	60%	24%	8%	0%	1.84
Vinorelbine	62%	27%	9%	1%	1.71
Eribulin	61%	26%	9%	1%	1.75
Average of 3 agents	61%	26%	9%	1%	1.77
Hazard ratio, KOL mean estimate versus ERG estimate (average of 3 comparators)					
Mean HR[1]	1.64	1.11	1.07	0.93[2]	
HR, lower	1.99	1.22	1.17	1.02[2]	
HR, upper	1.34	1.02	0.99	0.87[2]	

Key: LYs, Life years
[1]Hazard ratio calculated as -LN(% alive at year t)$_{KOL}$/-LN(% alive at year t)$_{ERG}$
[2]Set to an HR of 1 in the model at this timepoint given ≤1% of patients alive in all estimates.

Table 3: Cost-effectiveness results applying an effect modifier derived from KOL elicitation

Technology	Total costs (£)	Total QALYs	Pairwise ICER
Assuming different post-progression utilities by comparator			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	[redacted]
Assuming different post-progression utilities by comparator – lower CI HR			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]

Tucatinib combination	[redacted]	[redacted]	[redacted]
Assuming different post-progression utilities by comparator – upper CI HR			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years, CI, confidence interval; HR, hazard ratio			

Note: While adapting the current model, Seagen noticed that an additional trastuzumab discount had been erroneously incorporated into the model (Cost sheet cell E27). This has been removed and all results within this response document are inclusive of this correction.

1.4 Application of an effect modifier using analysis of the HER2CLIMB BM subgroup

Seagen has attempted to modify the ERG's preferred modelling approach through an adjustment factor of the HRs applied to the tras-cape survival curve, by deriving a treatment effect modifier from the BM patients recruited to the HER2CLIMB study.

The approach, briefly, was to:

- Fit Cox proportional hazards model to intent-to-treat (ITT) patient-level data from HER2CLIMB:
    - Include model terms for treatment (T), brain metastases (BM) and T*BM interaction
    - T*BM hazard ratio (HR_i) =

      Ratio of (HR of tras-cape vs. tucatinib combination arms in BM=1) *vs.* (HR of tras-cape vs. tucatinib combination arms in BM=0)
- Adjust each HR (HR_o) from the NMA posterior distribution as follows:
    - $HR_a = Exp(LN[HR_o] + (LN[HR_i] \times BM\ proportion))$

      Where HR_i is the HR of the BM interaction term; HR_0 is the original (unadjusted) HR between treatments and HR_a is the new HR adjusted using the BM interaction term and BM proportion of HER2CLIMB = 291/612 = 48%.

Other than this adjustment, the methodological approach of the NMA was identical to the ERG and committee's preferred random-effects proportional hazards model

- Carry out a cost-effectiveness analysis whereby the revised HRs are applied to the tras-cape baseline survival curves.

This approach relies on two key assumptions:

- The effect modification of BM estimated from the comparison of tras-cape versus tucatinib combination is applicable to the comparison of single-agent chemotherapies versus tucatinib combination. As previously discussed, this is a conservative estimate given that the addition of an anti-HER2 regimen such as trastuzumab has some effect on progression of BM (6).
- There are no (or negligible numbers of) BM patients that were on capecitabine, vinorelbine or eribulin in the clinical trials included in the NMA network. These include:
  - Kaufman et al., 2015 (9) (eribulin vs. capecitabine): Not reported;
  - Yuan et al., 2019 (10) (eribulin vs. vinorelbine): 0;
  - EGF100151 (12) (lapatinib-capecitabine vs. capecitabine): 23/399

1.4.1 NMA including an effect modifier derived from HER2CLIMB

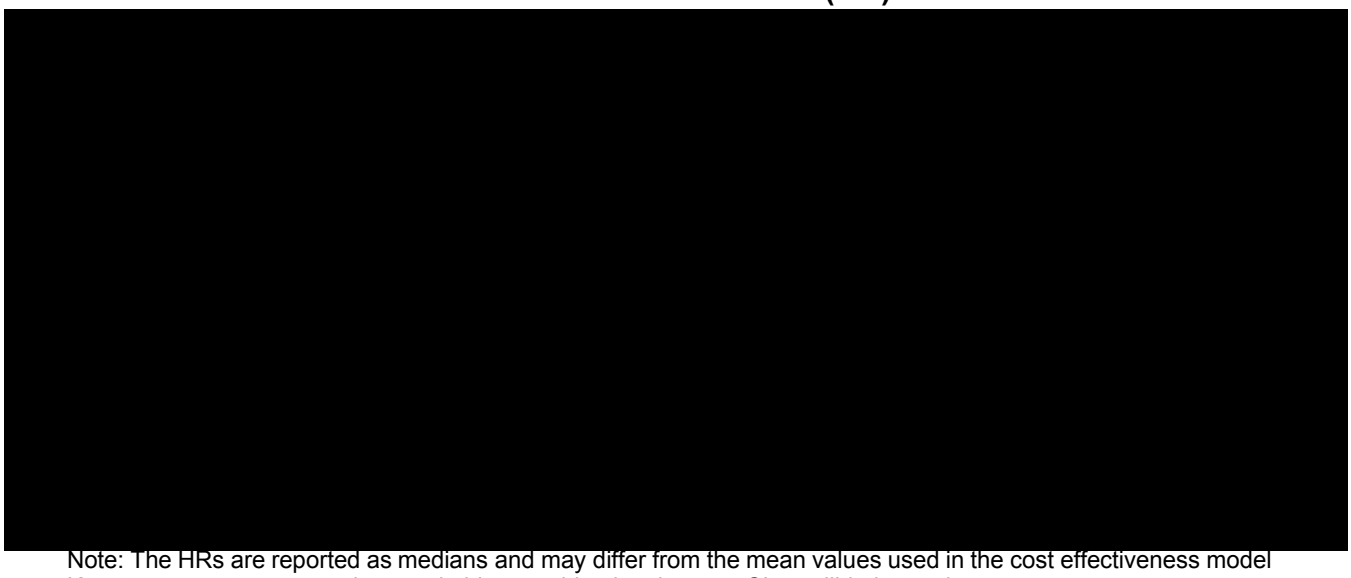
The results of the OS NMA including the treatment effect modification due to BM derived from HER2CLIMB are presented in Table 4. These are reported as median HRs with their credible intervals. The unadjusted results are presented in Table 5 for comparison. Those for progression-free survival (PFS) can be found in Appendix A. From these results, it can be concluded that with the application of a treatment effect modification from BM estimated using HER2CLIMB data:

- Tucatinib combination is numerically superior to capecitabine (borderline significant relative effect versus capecitabine) eribulin and vinorelbine, with death over twice as likely for all three groups.
- Tucatinib combination generates numerically better HRs vs. the single-agent chemotherapies than in the ITT analysis. That is, tucatinib combination

demonstrates better relative efficacy vs. the single-agent chemotherapies once the BM effect modifier is incorporated.

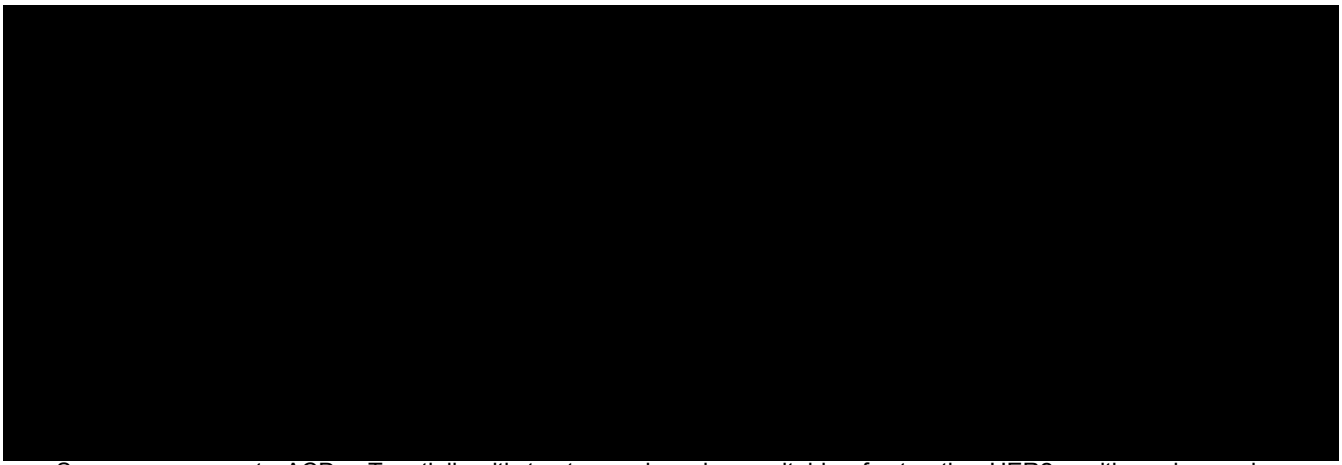
As previously stated in 1.2, targeting HER2 is likely to have an effect on outcomes for patients with BM. The results of this analysis are therefore likely to underestimate the treatment effect of the tucatinib combination versus single-agent chemotherapies because effect modification is estimated using HER2CLIMB data, in which both arms included the HER2-targeting agent trastuzumab. Treatment effect modification due to BM can be expected to be greater in a scenario comparing tucatinib combination to single-agent chemotherapies in a similar population with BM, due to absence of a HER2-targeting agent.

Table 4: NMA results of HER2CLIMB ITT population after application of treatment modification effect of brain metastases (OS)



Note: The HRs are reported as medians and may differ from the mean values used in the cost effectiveness model
Key: tras-cape; trastuzumab-capecitabine combination therapy, CI, credible interval

Table 5: NMA results of HER2CLIMB ITT population (OS)



[redacted]

Note: The HRs are reported as medians and may differ from the mean values used in the cost effectiveness model
Key: tras-cape; trastuzumab-capecitabine combination therapy

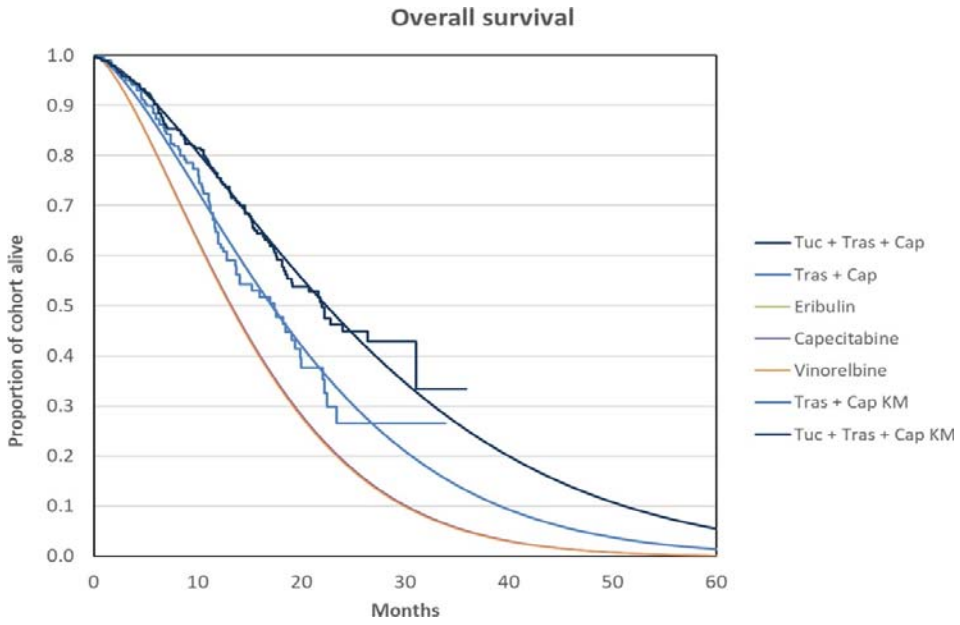
1.4.2 Cost-effectiveness analysis using an effect modifier derived from HER2CLIMB

Seagen has performed a cost-effectiveness analysis that utilizes the NMA results adjusted by the effect modifier (Table 6). Other than this change, the analysis reflects the revised company base case assumptions, as outlined previously.

The adjusted curves following incorporation of the effect modifier and the ERG's preferred analysis are presented in Figure 1A and B, respectively. It can be seen that the cost-effectiveness results produce ICERs for tucatinib combination close to or below the NICE willingness-to-pay (WTP) threshold for End-of-Life (EoL) therapies and lower than the results without the effect modifier applied in Table 6. Again, Seagen wishes to emphasize that this analysis still retains some bias against tucatinib combination, being underpinned by an effect modifier that does not account for the absence of HER2-targeted therapy.

Figure 1: Modelled overall survival results applying an effect modifier derived from the HER2CLIMB BM subgroup

A: OS results including the effect modifier



B: Original OS results excluding the effect modifier

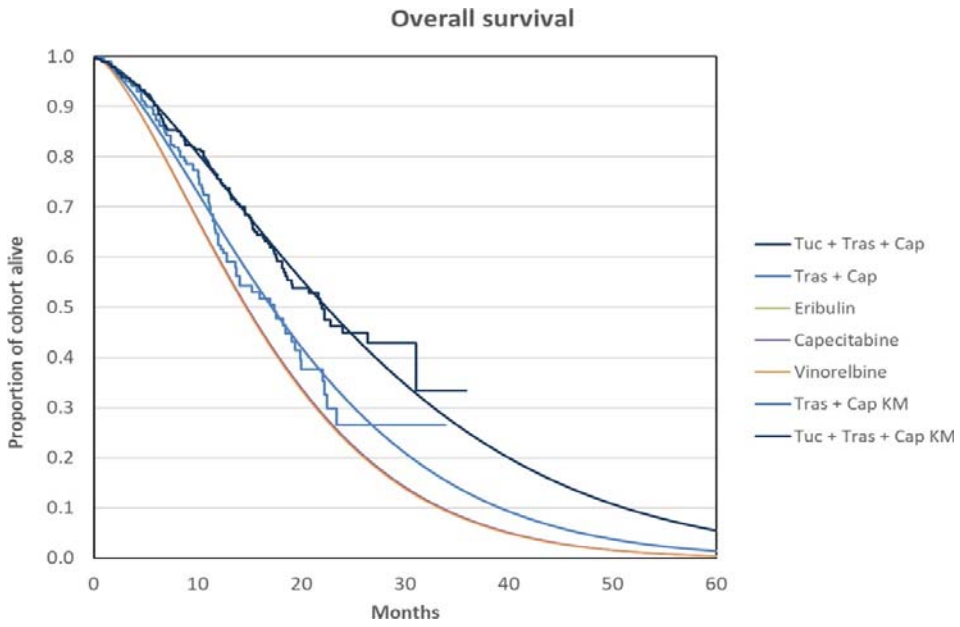
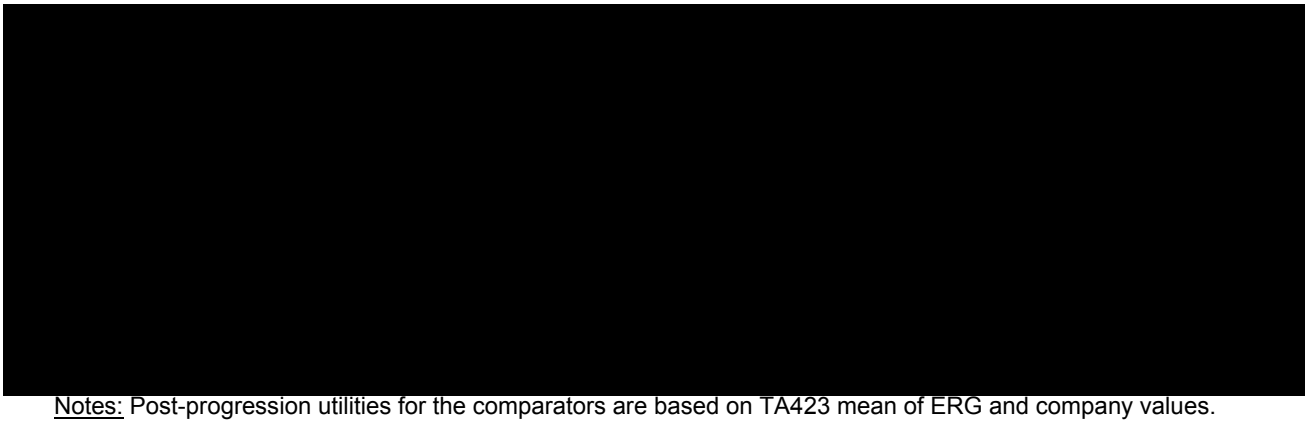


Table 6: Cost effectiveness results incorporating an effect modifier from HER2CLIMB

Notes: Post-progression utilities for the comparators are based on TA423 mean of ERG and company values. While adapting the current model, Seagen noticed that an additional trastuzumab discount had been erroneously incorporated into the model (Cost sheet cell E27). This has been removed and all results within this response document are inclusive of this correction.

Table 7: Cost effectiveness results without the effect modifier



Notes: Post-progression utilities for the comparators are based on TA423 mean of ERG and company values. While adapting the current model, Seagen noticed that an additional trastuzumab discount had been erroneously incorporated into the model (Cost sheet cell E27). This has been removed and all results within this response document are inclusive of this correction.

Topic 2 Subgroup analyses of people with and without brain metastases

ACD section 3.11 *"Subgroup and threshold analyses could help better understand uncertainty around the effectiveness of tucatinib in people with and without brain metastases"*

Company response:

- The HER2CLIMB study was designed to review efficacy and safety in the ITT population with some power to show PFS benefit in the BM subgroup.
- However, as requested by NICE, Seagen has carried out an assessment of clinical effectiveness in the subgroup of patients with BM coupled with a cost-effectiveness analysis of this subgroup.
- These analyses demonstrate tucatinib combination to be even more cost-effective in the BM subgroup than in the ITT analysis, though this analysis is still subject to bias against the tucatinib combination and there is a high level of uncertainty.
- Seagen was not able to carry out subgroup analyses for the non-BM subgroup within the response timeframe, however an estimate of cost-effectiveness has been generated using a weighted average approach.
- As highlighted above, HER2CLIMB study was not powered to show a significant benefit in the non-BM subgroup and the size of the population assessed means there is greater uncertainty in this population. Therefore, the cost-effectiveness results in this subgroup are not relevant for decision making.

2.1 NMA of the BM subgroup

While noting that BM are not routinely screened for in UK clinical practice, Seagen has performed an NMA of the BM subgroup of patients from HER2CLIMB compared to the full populations of the other trials in the network, as requested by NICE. The methodological approach of the NMA is identical to the ERG and committee's preferred random-effects proportional hazards model, with one exception: the HER2CLIMB ITT HR is replaced with that from the BM subgroup.

The results of the OS NMA from this subgroup analysis, reported as medians with their credible intervals, are presented in Table 8, alongside the original results from the ITT analysis in Table 9. Additional analysis results, including those for progression-free survival (PFS) can be found in Appendix C. It can be seen that:

- In the original ITT analysis, tucatinib combination is numerically superior to all comparators. It is worth noting that the uncertainty increases proportionately to the increase in the number of bridges (links) between pairwise comparisons. A more closely connected network for the comparators of interest would reduce this uncertainty, which will only be possible if more relevant trial data becomes available.
- In the NMA using the BM subgroup data from HER2CLIMB, point estimates further improve in favour of the tucatinib combination. The tucatinib combination has the greatest numerical superiority over capecitabine with death twice as likely in the capecitabine group.

These results are underpinned by the same comparator trial data as the ITT analysis, therefore any biases against tucatinib combination arising from the imbalance in BM in the ITT analysis will be present in this analysis.

Table 8: NMA results of HER2CLIMB BM subgroup (OS)

[redacted]

Note: The HRs are reported as medians and may differ from the mean values used in the cost effectiveness model
Key: tras-cape; trastuzumab-capecitabine combination therapy

Table 9: NMA results of HER2CLIMB ITT population (OS)

Note: The HRs are reported as medians and may differ from the mean values used in the cost effectiveness model
Key: tras-cape; trastuzumab-capecitabine combination therapy

2.2 Survival analyses of the BM subgroup

Survival analyses were performed to determine survival curves for the tucatinib and control arm for the BM subgroup. A wide range of survival models were fitted to data from the HER2CLIMB trial. Survival models fitted to PFS and OS data included parametric models, flexible spline-based models, and hybrid models. The following sets of functions were fitted:

- Treatment included as a covariate (scale parameter allowed to vary by treatment).
- Stratified models in which all parameters (scale and shape) can vary by treatment. This approach is equivalent to fitting separate models by treatment, but it enables the creation of a single fit statistic that allows model comparisons to be made with simpler models.

To determine the most appropriate survival functions, model fit was assessed as follows:

- Estimation of smoothed hazard rates to investigate how the hazard rates and ratios change over time
- Testing of −log(−log(survival)) plot and significance to assess the proportional hazards assumptions

- Graphic comparison of the predicted curve from a given parametric function to the Kaplan-Meier curve from the patient data
- Comparison of Akaike information criterion (AIC) statistics and Bayesian information criterion (BIC) statistics
- Assessment of the clinical validity of the extrapolated portion of the survival curves and comparison with other external data

Further details can be found in Appendix C. Models were not fitted to the non-BM subgroup nor were models fitted that included external data.

2.2.1 Summary of selected models

Twenty-one models without external data extrapolation were fitted to the PFS data and 13 provided a reasonable fit to the data and gave long-term plausible predictions.The stratified Weibull model was selected as the most likely PFS model and was usedin the BM subgroup analysis.

Twenty-three models without external data extrapolation were fitted to the OS data and 9 of these models provided a reasonable fit to the data and gave long-term plausible predictions. The Weibull model was selected as the most likely OS model and was used in the BM subgroup analysis. This aligns with the model selected for the ITT population.

2.3 Cost-effectiveness analyses of the BM subgroup

The results of the cost-effectiveness analysis of the BM subgroup are presented in Table 10 (see Table 7 for the ITT results). Charts of the extrapolated OS analyses are provided in Figure 2 and Figure 3, with those for PFS presented in Appendix C.

From these results, it can be seen that tucatinib combination is more cost-effective in the subgroup of patients with BM, while still not accounting for the bias due to comparing with single-agent chemotherapy studies that excluded BM patients.

Figure 2: Modelled overall survival results in the subgroup with brain metastases

[redacted]

Figure 3: Modelled overall survival results in the ITT population

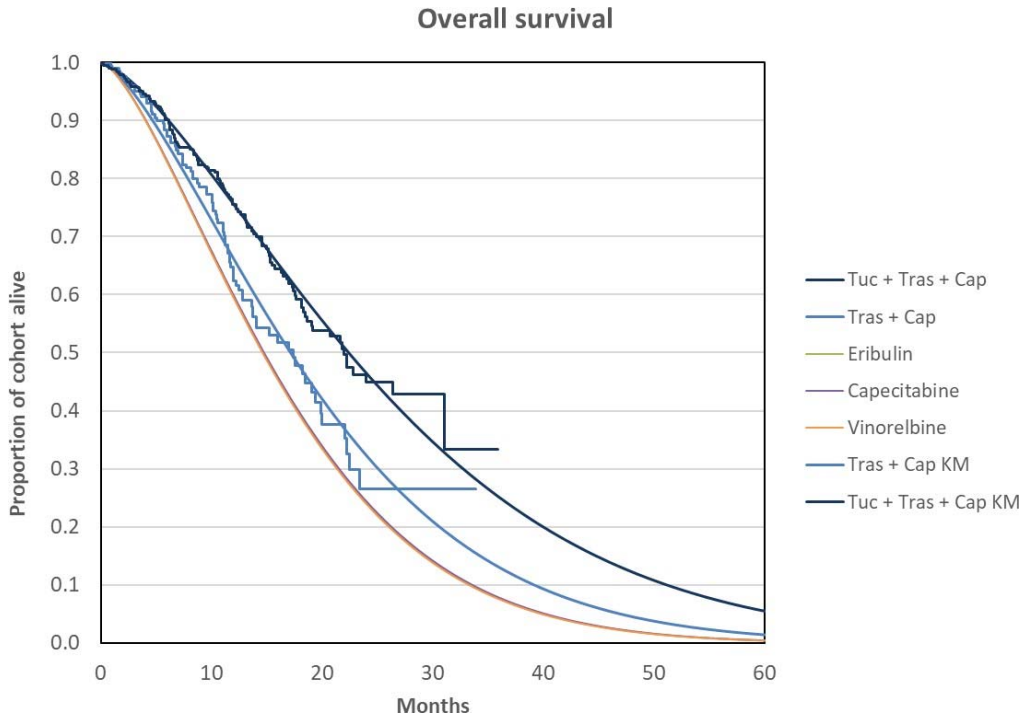


Table 10: Cost-effectiveness results in the subgroup of patients with brain metastases

Note: While adapting the current model, Seagen noticed that an additional trastuzumab discount had been erroneously incorporated into the model (Cost sheet cell E27). This has been removed and all results within this response document are inclusive of this correction.

2.4 Cost-effectiveness analyses of the non-BM subgroup

Seagen has not been able to carry out a cost-effectiveness analysis of the non-BM subgroup using formal health economic methods within the required timeframe. Instead, we estimate an ICER in this subgroup assuming a weighted average approach. That is, we assume that the ICER of the ITT population represents the weighted average of the ICERs of the BM and non-BM subgroups. The ICER for the non-BM subgroup is therefore calculated as per the following formula:

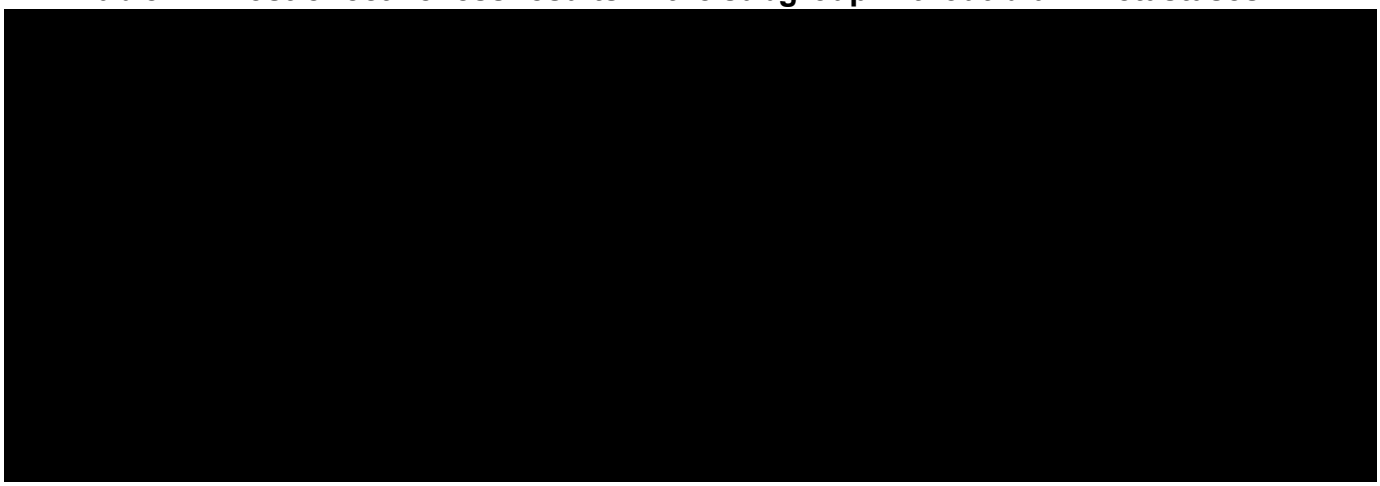
$$ICER_{NBM} = \frac{ICER_{ITT} - (\%\,\mathrm{BM} \times ICER_{BM})}{\%\,\mathrm{NBM}}$$

Where NBM = non-BM subgroup; ITT = intent-to-treat population

These results are presented in Table 11.

Though the HER2CLIMB study showed efficacy benefit in all subgroups, including non-BM patients, the study was only powered to show a benefit (OS, ORR and PFS) in the whole population and also PFS for those patients with BM. The lack of power and size of the population adds greater uncertainty to the analyses. As discussed previously, the study has also shown in a post-hoc analysis the potential ability that the tucatinib combination also reduced the risk of new CNS lesions or death by 46% (HR 0.52 (95% CI 0.33, 0.82) p=0.005) compared to the placebo arm (13).

Table 11: Cost-effectiveness results in the subgroup without brain metastases



Topic 3 Threshold analyses

ACD section 3.11 *"Subgroup and threshold analyses could help better understand uncertainty around the effectiveness of tucatinib in people with and without brain metastases"*

Company response:

- Seagen has carried out a threshold analysis to determine the relative effects. (HRs) that would be required between tras-cape and the single agent chemotherapies to achieve an ICER of £50,000/QALY.
- The analyses indicate that these HRs would need to be between 20-40% times worse than the current random effects HRs to achieve a £50,000/QALY ICER
- This is within the range of estimates that were obtained via the supplementary analyses carried out as part of Topic 1.

3.1 Estimation of the relative effects for single-agent chemotherapies that would generate a cost-effective ICER

For this analysis, Seagen followed the lead of the ERG who incorporated a table into the model which enabled the HRs from the preferred random effects NMA to be overridden.

As a reminder, the ERG and committee's preferred approach to modelling the single-agent chemotherapy survival curves was to apply the HRs from the NMA to the HER2CLIMB tras-cape survival curve. Using the Excel '*Goal Seek*' function, the model was queried to determine the magnitude of the OS HR required between tras-cape and the single-agent chemotherapies to reduce their respective ICERs versus tucatinib combination to £50,000/QALY (with the PFS HRs left unchanged). The results of this threshold analysis are summarized in Table 12. It can be seen that an additional factor of 1.6 and 1.8 needs to be applied to the existing HRs vs. tras-cape for vinorelbine and capecitabine, respectively, to achieve an ICER of £50,000/QALY. Eribulin, already being cost-effective at a WTP of £50,000/QALY, does not require further adjustment.

Table 12: Threshold analysis of required HRs to achieve £50,000/QALY

Topic 4 Justification for any differences in post-progression utility values for tucatinib combination and its comparators

ACD section 3.12 *"Some differences in pre-progression health state utilities are plausible, but post-progression utility differences are not justified"*

Company response:

- Seagen has carried out a literature search on the effect of treatment received pre-progression on health-related quality of life (HRQoL) post-progression.
- As part of the KOL survey of survival estimates carried out for Topic 1, Seagen also questioned KOLs regarding effect of prior treatments on HRQoL post-progression and the effect of BM on HRQoL.
- These sources were further supported by feedback from patient groups regarding the impact of BM on their daily lives.
- Due to the novel ability of the tucatinib combination to reduce the impact of BM both pre and post-progression, especially compared to single agent chemotherapy, Seagen believes that different post-progression utilities are plausible
- In summary, there is clear evidence from both clinicians and carers that treatments given pre-progression have an impact on HRQoL post-progression. At least some of this is due to a larger proportion of patients receiving single-agent chemotherapies progressing with BM and its impact.
- Seagen has therefore revised the company base case to include different post-progression utilities for the tucatinib combination and the single-agent chemotherapies.

4.1 Summary

As recognised by the committee, the HER2CLIMB study is representative of the current UK population due to the inclusion of around 50% with BM. Seagen therefore proposes that the post-progression utilities from the tucatinib combination should be used by the committee, whilst a lower utility should be used for the single agent chemotherapy. Though NICE has not previously accepted a difference in post-progression utilities, Seagen believe the unique trial design and outcomes of

HER2CLIMB show that a difference is plausible. This is because in the HER2CLIMB study, the combination with tucatinib showed the ability to not only reduce the burden of disease including BM, but it also appears to reduce the risk of developing new BM. This reduced impact of BM can have a positive impact on a patient's quality of life and is likely to lead to different utilities post-progression compared to the impact of single agent chemotherapies.

4.2 Literature review on the effect of treatment received pre-progression on health-related quality of life (HRQoL) post-progression.

Despite treatment advances over the past 20 years, the vast majority of patients with HER2-positive metastatic breast cancer (MBC) ultimately succumb to their disease. Furthermore, up to 50% of patients with HER2-positive MBC develop brain metastases over the course of the disease (14,15), which is associated with a 1-year survival of 50% and a 3-year survival of only 16% (7). As patients progress through lines of therapy they experience deterioration in HRQoL due to both the disease and treatment-related adverse events (16–20).

A diagnosis of BM even with the "best" care, will lead to a worse prognosis, disproportionate treatment response and a lower survival than patients with metastases in other organs. Treatment options are limited to invasive interventions that can cause debilitating side effects and seriously impact the quality of life. One of the major contributors to this deterioration in quality of life is progression in the brain, which can have a multifaceted impact on a patient's life. Symptoms that will all have an impact on HRQoL can include; headaches, feeling or being sick, weakness of a part of the body, seizures (fits), personality or mood changes, changes to your eyesight such as loss of sight (vision), confusion and difficulty understanding and difficulty speaking (21).

A prospective, observational registry of 977 newly diagnosed HER2-positive breast cancer patients, showed the impact of BM, with patients who were diagnosed with BM having a significantly lower quality of life that those diagnosed without as measured by FACT-B (median score 94.5 vs. 103.5 out of a possible 148, P = 0.002) and FACT-B TOI (median score 56.5 vs. 62.0 out of 96, P= 0.009 They also showed a greater impairment in daily activity per RSC-ALS (Rotterdam Symptom Checklist–Activity

Level Scale) (median score 77.1 vs. 87.5 out of 100, P=0.002), as well as greater severity of cognitive dysfunction per MDASI-BT (cognitive symptoms, median score 2.3 vs. 0.8 out of 10, P <0.001; and brain tumor-related interference in daily life, median score 3.9 vs. 2.0 out of 10, P ¼ 0.004) (13).

The impact of the location of progression for patients with HER2+ breast cancer, is therefore an important consideration for their post-progression quality of life or utility. This is supported by feedback from the 10 clinical surveys (see below), where it is highlighted that BM generally has the worse quality of life compared to other sites (visceral) of progression. This is driven, by a number of factors, including the treatment of BM (ie high dose steroids), but more importantly BM impact, usual daily activities, mobility and self-care, therefore making patients dependent on family and friends for care.

The potential ability of the tucatinib combination to reduce the risk of progression in the brain is therefore a key driver of an improved post-progression utility compared to single agent chemotherapy. In the HER2CLIMB study, tucatinib combination showed the ability to not only reduce the burden of BM, but it also appears to reduce the risk of developing new BM:

- Among the 291 patients with BM, the risk of progression in the brain or death was reduced by 68% in the tucatinib arm versus the control arm (HR, 0.32; 95% CI, 0.22 to 0.48; P < .0001).
- The 1-year CNS-PFS (progression in the CNS only), was 40.2% (95% CI, 29.5% to 50.6%) in the tucatinib arm and 0% in the control arm.
- For the 75 patients with active BM and measurable intracranial disease at baseline, the confirmed ORR-IC was 47.3% (95% CI, 33.7% to 61.2%) in the tucatinib arm versus 20.0% (95% CI, 5.7% to 43.7%) in the control arm (P = .03) (22).
- In the whole study population (n=612), tucatinib combination also reduced the risk of new CNS lesions or death by 46% (HR 0.52 (95% CI 0.33, 0.82) p=0.005) compared to the placebo arm.

As previously noted, targeting HER2 systemically can have a positive efficacy impact for patients with BM compared to single-agent chemotherapy. Hence the benefit shown in HER2CLIMB in reducing the burden of BM (pre and post progression) is likely to be even greater if the tucatinib combination were to be compared to single agent chemotherapy.

Retrospective real-world evidence, points to the improvement seen by the addition of trastuzumab to chemotherapy. One study comparing 251 HER2-positive breast cancer patients, treated with or without trastuzumab, showing that development of BMbetween the two treatment groups was significantly different (37.8% for trastuzumab vs 25.0% for without trastuzumab, P=0.028). Time to death (TTD) from BM was significantly longer in the trastuzumab group than in the group without trastuzumab (median 14.9 vs 4.0 months, P=0.0005) (6).

On top of this, it was noted during the clinical surveys, that being HER2-positive is a negative prognostic risk factor, that now has improved outcomes due to the targeting of HER2-positive. Treatments such as the tucatinib combination offer greater disease control, including reducing the overall disease burden, on treatment, which can lead to better HRQoL upon progression.

In the HER2CLIMB study of the 511 patients with measurable disease at baseline, the percentage who had a confirmed objective response was 40.6% (95% CI, 35.3 to 46.0) in the tucatinib-combination group and 22.8% (95% CI, 16.7 to 29.8) in the placebo-combination group (P<0.001) (14). When this response rate is compared to the historical single agent chemotherapy studies, that did not generally include patients with BM (eribulin 11.0%, capecitabine 11.5% -(9)), there is a large and significant difference in the burden of the disease at the point of progression. It was noted during the clinical surveys that progression on single agent chemotherapy is likely to be symptomatic, ie with an aggressive multi-site progression leading to poorer HRQoL. On the other hand, progression on a HER2 targeted therapy is usually asymptomatic due to better disease control. It is not picked up as part of routine screening, and so will not be impacting on a patient's quality of life.

The ability of tucatinib, to reduce the potential negative impact of brain metastasis and reduce the disease burden before the point of progression, compared to single agent

chemotherapy therefore provides justification for there to be different post-progression utilities.

4.3 Clinician survey on the effect of prior treatments on HRQoL post-progression and the effect of BM on HRQoL.

As mentioned above, and to support the literature search, Seagen undertook 10 clinician surveys, which included asking for their views regarding post-progression in HRQoL.

The survey questions and a summary of the feedback is below:

- "*In your experience, do patients experience different quality of life after discontinuing treatment due to disease progression when progressing on different treatment options (chemotherapy vs anti-HER2)*
- *If there are differences, what aspects of these treatments lead to this difference (Eg neuropathy, hair loss, fatigue, immunity, daily activities including work and leisure etc.)*
- *Does the location of progression impact on a patients QoL i.e. would progression in the brain lead to worse QoL versus progression elsewhere (bone/lung etc.)"*

The majority of clinical experts (7/10) agreed that quality of life after discontinuation due to disease progression differed by treatment (chemotherapy vs. anti-HER2). This was attributed both to the toxicity of the regimen and to more aggressive, and more frequently symptomatic, progression on single agent chemotherapies compared to with HER2 targeting therapies. Several experts (4/10) specifically identified treatment induced neuropathy (associated with eribulin) as a driver of poor post progression quality of life.

The majority of experts (8/10) identified BM as having a significant impact on post progression quality of life. The brain was highlighted by healthcare professionals as 'the worst area to progress' due to a variety of factors. These included cognitive decline, loss of independence, neurological death and side effects of treatments such as radiotherapy and steroids. Fits and the inability to walk, drive, and loss of physical

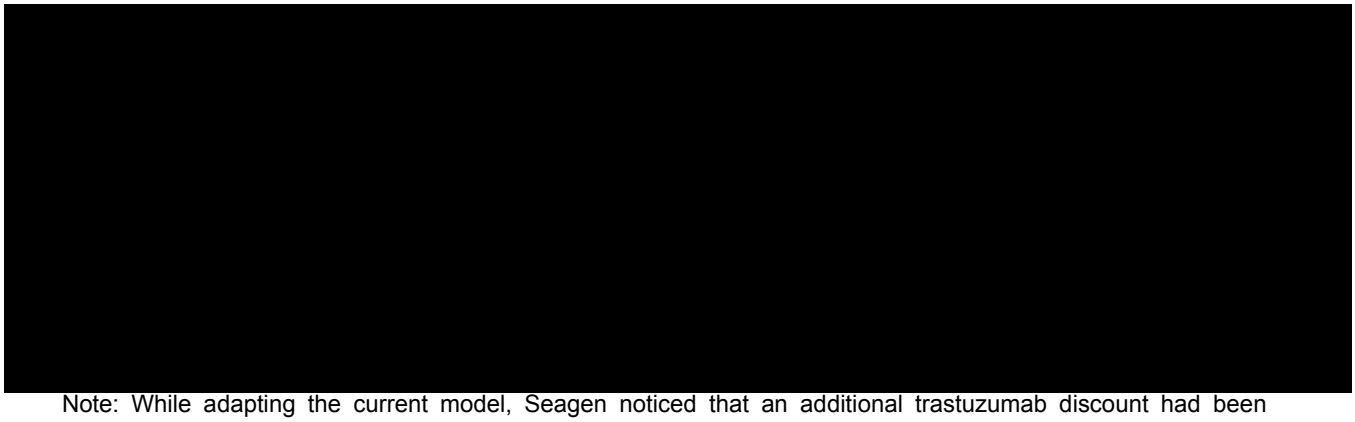
function (e.g. arms) were also underscored as key aspects of progression in the brain. Furthermore, it was emphasised that treatment of visceral metastases with HER2 therapies where brain progression is also present can lead to prolonged periods of very poor quality of life preceding death by brain metastases.

Seagen have therefore included in our revised base case and all the tables in this response, the following different post progression utilities:

- 0.698 for the tucatinib combination taken directly from the HER2CLIMB study
- 0.588 for the comparators (the ERG's preferred mean value and one which was used in TA704)

As NICE has conducted appraisals of the single agent chemotherapies in TA423, we have also included a scenario with the post progression value used in this appraisal below (0.496) (Table 13).

Table 13 Cost effectiveness results using post progression value from TA423



Note: While adapting the current model, Seagen noticed that an additional trastuzumab discount had been erroneously incorporated into the model (Cost sheet cell E27). This has been removed and all results within this response document are inclusive of this correction.

Topic 5 Additional analyses using subcutaneous trastuzumab

ACD section 3.13 *"Trastuzumab can be given subcutaneously or intravenously and both administration routes need to be considered"*

Company response:

- While Seagen agrees that SC trastuzumab is a treatment option in the UK, it is unclear in what proportion. As highlighted previously and recognized by the committee, in this setting, trastuzumab, either as an IV and even more so for the SC formulation, is not equally available across the NHS to patients
- The choice of SC vs IV trastuzumab should therefore not be a relevant decision driver in this assessment as the choice of route of administration is a local decision influenced by the HCP, the patient and the local budget holder, as recommended by NICE Evidence Summary (ESNM13).
- Due to the uncertainty of what clinical practice may be, Seagen has carried out two scenario analyses, one to reflect the usage of SC trastuzumab in the HER2CLIMB study and the second which we believe to be a higher estimate of SC usage than current clinical practice.

As highlighted previously and acknowledged by the committee, trastuzumab in this setting, is not equally available across the NHS to patients, but access is dependant on local decisions.

NICE Evidence Summary (ESNM13) for subcutaneous trastuzumab, states that subcutaneous trastuzumab was not considered appropriate for a NICE technology appraisal. It notes that the subcutaneous formulation of trastuzumab is a potential alternative to intravenous trastuzumab in people for whom trastuzumab treatment is appropriate and offers a quicker, less invasive mode of administration. At the time of the publication, NICE stated that there was a potential cost saving, however local decision makers will need to estimate the potential savings for their organisations, as there were a number of factors that might affect this (biosimilars and local usage of IV trastuzumab). Though we understand that SC is available in some trusts, biosimilars are now in the market across the UK and a recent Freedom of Information request in Scotland (23), showed a potential switch back to IV with biosimilar use (see Table 14)

Table 14: trastuzumab switch back to IV biosimilar, NHS Lothian

Treatment	Number of patients in last 3 months (dated June 2020)
Herceptin IV	0
Herceptin SC	<5
Trastuzumab biosimilar IV	104
Trastuzumab biosimilar SC	0

COVID-19 has biased the current treatment pattern towards subcutaneous route of administration and home treatment. Current usage in England is therefore unclear due to the impact of the NHSE Covid treatment guidance, recommending the use of treatments that keep patients out of hospital and also the recent approval of the subcutaneous combination of trastuzumab and pertuzumab (Phesgo) in an earlier line setting (24). It is therefore unclear what the uptake of SC would be in this setting, however, Seagen believe the usage of SC may be less common in the later setting, and that this usage will decline as the impact of COVID becomes more effectively managed.

Seagen has therefore found it hard to quantify the potential impact on the ICER, as whilst it is clear that subcutaneous trastuzumab can provide a cost saving in the range of £111.81 per treatment for reduced healthcare practitioner time and consumables, there are savings/benefits that are not captured such as an improvement in the patient experience, as well as creating opportunity for other cancer treatments at stretched oncology day units to be fitted into schedules by the time and resource savings (25). There is also currently the additional unquantifiable system benefit of patients not catching COVID-19 if they don't come into hospital for their treatment.

The clinical and patient experts in the NICE committee meeting explained that subcutaneous administration is preferred because patients may be able to self-administer, avoiding unnecessary hospital visits. Yet, both the clinical and patient experts explained that if subcutaneous administration was not possible, they would accept intravenous administration if it allowed people to receive tucatinib combination.

Seagen believe that due to the uncertainty of usage, true cost and cost savings in the NHS, by including subcutaneous trastuzumab in the model, there could be an unrealised increase in the ICER by these additional costs that would not be seen in clinical practise. We therefore believe that NICE should follow its Evidence Summary documentation and allow local decision makers to decide what is the best use of their local resources.

We have, however, provided two scenarios that explore the impact on the revised company base case ICER, one in line with usage information and outcomes from HER2CLIMB (Table 15) [redacted] patients received SC trastuzumab in the study) and the other which is an estimate of the upper end of usage within clinical practice (

Table 16). Seagen are aware that subcutaneous trastuzumab is made available at a discounted price to NHSE (26) and therefore have assumed a discount for both scenarios which we believe to be in line with the current average discount applied to cancer medicines assessed by NICE. We have also assumed a [redacted] discount to administration costs to reflect some savings associated with using the sc formulation versus IV. This is as per NICE TA509 (Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer).

Further modelling assumptions underpinning the scenarios (unit costs, dosing etc.) are detailed in Appendix D.

Table 15: [redacted]% use of SC trastuzumab, [redacted]% discount off list price

[redacted]

Note: While adapting the current model, Seagen noticed that an additional trastuzumab discount had been erroneously incorporated into the model (Cost sheet cell E27). This has been removed and all results within this response document are inclusive of this correction.

Table 16: [redacted]% use of SC trastuzumab, [redacted]% discount off list price

[redacted]

Note: While adapting the current model, Seagen noticed that an additional trastuzumab discount had been erroneously incorporated into the model (Cost sheet cell E27). This has been removed and all results within this response document are inclusive of this correction.

References

1. Joe NS, Hodgdon C, Kraemer L, Redmond KJ, Stearns V, Gilkes DM. A common goal to CARE: Cancer Advocates, Researchers, and Clinicians Explore current treatments and clinical trials for breast cancer brain metastases. npj Breast Cancer 2021 71 [Internet]. 2021 Sep 14 [cited 2021 Nov 11];7(1):1–10. Available from: https://www.nature.com/articles/s41523-021-00326-5

2. Ménard S, Fortis S, Castiglioni F, Agresti R, Balsari A. HER2 as a Prognostic Factor in Breast Cancer. Oncology [Internet]. 2001 [cited 2021 Nov 11];61(Suppl. 2):67–72. Available from: https://www.karger.com/Article/FullText/55404

3. Brufsky AM, Mayer M, Rugo HS, Kaufman PA, Tan-Chiu E, Tripathy D, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res [Internet]. 2011 Jul 15 [cited 2021 Nov 11];17(14):4834–43. Available from: https://pubmed.ncbi.nlm.nih.gov/21768129/

4. Yap YS, Cornelio GH, Devi BCR, Khorprasert C, Kim SB, Kim TY, et al. Brain metastases in Asian HER2-positive breast cancer patients: anti-HER2 treatments and their impact on survival. Br J Cancer 2012 1077 [Internet]. 2012 Aug 23 [cited 2021 Nov 11];107(7):1075–82. Available from: https://www.nature.com/articles/bjc2012346

5. Bartsch R, Rottenfusser A, Wenzel C, Dieckmann K, Pluschnig U, Altorjai G, et al. Trastuzumab prolongs overall survival in patients with brain metastases from Her2 positive breast cancer. J Neurooncol [Internet]. 2007 Dec [cited 2021 Nov 11];85(3):311–7. Available from: https://pubmed.ncbi.nlm.nih.gov/17557136/

6. Park YH, Park MJ, Ji SH, Yi SY, Lim DH, Nam DH, et al. Trastuzumab treatment improves brain metastasis outcomes through control and durable prolongation of systemic extracranial disease in HER2-overexpressing breast cancer patients. Br J Cancer [Internet]. 2009 Mar 24 [cited 2021 Nov 11];100(6):894. Available from: /pmc/articles/PMC2661774/

7. Witzel I, Laakmann E, Weide R, Neunhöffer T, Park-Simon TJ, Schmidt M, et al.

Treatment and outcomes of patients in the Brain Metastases in Breast Cancer Network Registry. Eur J Cancer [Internet]. 2018 Oct 1 [cited 2021 Nov 11];102:1–9. Available from: https://pubmed.ncbi.nlm.nih.gov/30099223/

8. Brufsky AM, Mayer M, Rugo HS, Kaufman PA, Tan-Chiu E, Tripathy D, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res [Internet]. 2011 Jul 15 [cited 2021 Nov 15];17(14):4834–43. Available from: https://pubmed.ncbi.nlm.nih.gov/21768129/

9. Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol [Internet]. 2015 Feb 20 [cited 2021 Nov 10];33(6):594–601. Available from: https://pubmed.ncbi.nlm.nih.gov/25605862/

10. Yuan P, Hu X, Sun T, Li W, Zhang Q, Cui S, et al. Eribulin mesilate versus vinorelbine in women with locally recurrent or metastatic breast cancer: A randomised clinical trial. Eur J Cancer [Internet]. 2019 May 1 [cited 2021 Nov 10];112:57–65. Available from: https://pubmed.ncbi.nlm.nih.gov/30928806/

11. Von Minckwitz G, Du Bois A, Schmidt M, Maass N, Cufer T, De Jongh FE, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol [Internet]. 2009 Apr 20 [cited 2021 Nov 10];27(12):1999–2006. Available from: https://pubmed.ncbi.nlm.nih.gov/19289619/

12. Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat [Internet]. 2008 Dec [cited 2021 Nov 10];112(3):533–43. Available from: https://pubmed.ncbi.nlm.nih.gov/18188694/

13. Hurvitz SA, O'Shaughnessy J, Mason G, Yardley DA, Jahanzeb M, Brufsky A, et al. Central Nervous System Metastasis in Patients with HER2-Positive Metastatic Breast Cancer: Patient Characteristics, Treatment, and Survival from SystHERs. Clin Cancer Res [Internet]. 2019 Apr 15 [cited 2021 Nov 11];25(8):2433–41. Available from: https://clincancerres.aacrjournals.org/content/25/8/2433

14. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med [Internet]. 2020 Feb 13 [cited 2021 Nov 11];382(7):597–609. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa1914609

15. Seagen Inc - Data on file. Tucatinib UK advisory board meeting (virtual meeting, March 2021). In 2021.

16. pan-Canadian Oncology Drug Review. Final Clinical Guidance ReportLapatinib (Tykerb) with letrozole for Metastatic Breast Cancer. 2013.

17. Reyes C, Engel-Nitz NM, DaCosta Byfield S, Ravelo A, Ogale S, Bancroft T, et al. Cost of Disease Progression in Patients with Metastatic Breast, Lung, and Colorectal Cancer. Oncologist [Internet]. 2019 Sep [cited 2021 Nov 11];24(9):1209–18. Available from: https://pubmed.ncbi.nlm.nih.gov/30796156/

18. Cacho-Díaz B, Spínola-Maroño H, Arrieta VA, Granados-García M, Wegman-Ostrosky T, Mendoza-Olivas LG, et al. Diagnosis of brain metastases in breast cancer patients resulting from neurological symptoms. Clin Neurol Neurosurg [Internet]. 2018 Oct 1 [cited 2021 Nov 11];173:61–4. Available from: https://pubmed.ncbi.nlm.nih.gov/30086430/

19. Müller V, Nabieva N, Häberle L, Taran FA, Hartkopf AD, Volz B, et al. Impact of disease progression on health-related quality of life in patients with metastatic breast cancer in the PRAEGNANT breast cancer registry. Breast [Internet]. 2018 Feb 1 [cited 2021 Nov 11];37:154–60. Available from: https://pubmed.ncbi.nlm.nih.gov/29237546/

20. Walker MS, Hasan M, Mi Yim Y, Yu E, Stepanski EJ, Schwartzberg LS.

Retrospective study of the effect of disease progression on patient reported outcomes in HER-2 negative metastatic breast cancer patients. Health Qual Life Outcomes [Internet]. 2011 Jun 20 [cited 2021 Nov 11];9. Available from: https://pubmed.ncbi.nlm.nih.gov/21689425/

21. Cancer Research UK. What is secondary brain cancer? [Internet]. 2021 [cited 2021 Nov 11]. Available from: https://www.cancerresearchuk.org/about-cancer/secondary-cancer/secondary-brain-cancer/about

22. Lin NU, Borges V, Anders C, Murthy RK, Paplomata E, Hamilton E, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. J Clin Oncol. 2020 Aug 10;38(23):2610–9.

23. Lothian NHS board. Response to FoI request re. medication prescribing [Internet]. 2020. Available from: https://org.nhslothian.scot/FOI/RequestAndResponseRegister/FOIs/4358.pdf

24. European Medicines Agency. Phesgo [Internet]. 2021 [cited 2021 Nov 15]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/phesgo

25. Burcombe R, Chan S, Simcock R, Samanta K, Percival F, Barrett-Lee P, et al. Subcutaneous Trastuzumab (Herceptin®): A UK Time and Motion Study in Comparison with Intravenous Formulation for the Treatment of Patients with HER2-Positive Early Breast Cancer. Adv Breast Cancer Res [Internet]. 2013 Sep 9 [cited 2021 Nov 11];2(4):133–40. Available from: http://www.scirp.org/Html/5-2470046_36732.htm

26. NHS dm+d browser. Actual Medicinal Product pack (AMPP) - Herceptin 600mg/5ml solution for injection vials 1 vial Roche Products Ltd [Internet]. 2021 [cited 2021 Nov 15]. Available from: https://services.nhsbsa.nhs.uk/dmd-browser/ampp/view/104482?ref=YW1wTmFtZT10cmFzdHV6dW1hYitpbmplY3Rpb24mc2VhcmNoVHlwZT1BTVAmc2hvd0ludmFsaWRJdGVtcz1mYWxzZSZoaWRlUGFyYWxsZWxJbXBvcnQ9ZmFsc2UmaGlkZVNwZWNpYWxPcmRlcj1mYWxzZSZoaWRlRGlzY29udGludWVkSXRlbXM9ZmFsc2U

Appendix A. Application of an effect modifier from analysis of the HER2CLIMB BM subgroup: methodology

Table 17: NMA results of HER2CLIMB ITT population after application of treatment modification effect of brain metastases (PFS)

Key: tras-cape; trastuzumab-capecitabine combination therapy

Appendix B. Details of clinician survey on effectiveness of single-agent chemotherapies

Methods

10 UK clinicians who treat HER2-positive MBC cancer patients were asked the following questions via a video-call:

"*The current modelled outcomes for single-agent chemotherapies were based on an indirect treatment comparison (ITC) between HER2CLIMB (~50% brain metastases) and trials of single-agent chemotherapies that excluded patients with brain metastases.*

Below we present the modelled survival outcomes for the tucatinib-tras-cape and placebo-tras-cape arms of HER2CLIMB.

What would be your survival estimates if these patients had instead received single-agent chemotherapies?"

Treatment	1 year OS	2 year OS	3 year OS	5 year OS
Tucatinib-tras-cape	76%	47%	25%	5%
Placebo-tras-cape	66%	33%	13%	1%
Eribulin				
Capecitabine monotherapy				
Vinorelbine				
All				

Table 18: Survey results – survival estimates by clinician

Initials	Role	Disclosure	Location	1y	2y	3y	5y
[redacted]	Medical Oncologist	[redacted]	Mount Vernon	30%	15%	5%	1%
[redacted]	Consultant Clinical Oncologist	[redacted]	Imperial	30%	20%	8%	2%
[redacted]	Consultant Clinical Oncologist	[redacted]	Christie	50%	25%	9%	1%
[redacted]	Consultant Medical Oncologist	[redacted]	Leeds	29%	13%	5%	1%
[redacted]	Consultant Medical Oncologist	[redacted]	Newcastle	50%	20%	5%	1%
[redacted]	Breast Physician	[redacted]	Mount Vernon	43%	21%	8%	1%
[redacted]	Consultant Medical Oncologist	[redacted]	Clatterbridge	45%	20%	6%	1%
[redacted]	Consultant Medical Oncologist	[redacted]	Maidstone and Tunbridge Wells	65%	30%	10%	1%
[redacted]	Clinical Oncologist	[redacted]	Truro	50%	20%	6%	1%
[redacted]	Consultant Medical Oncologist	[redacted]	Royal Free	38%	20%	2%	0%

Note: in cases where a range was provided, the average of the range was used

.

Appendix C. Methods and results of BM subgroup analyses

Table 19: NMA results of HER2CLIMB BM subgroup (PFS)

Key: tras-cape; trastuzumab-caprecitabine combination therapy

Table 20: NMA results of HER2CLIMB ITT population (PFS)

Key: tras-cape; trastuzumab-capecitabine combination therapy

Survival Analyses

Progression-Free Survival

Figure 4 presents the Kaplan-Meier estimates for PFS from the HER2CLIMB trial for the brain metastases subgroup. The shape of the Kaplan-Meier curves is similar to the total population data.

Figure 4 Kaplan-Meier Estimates for Progression-Free Survival From the HER2CLIMB Trial: Brain Metastases Subgroup

Cape = capecitabine; Pbo = placebo; Tras = trastuzumab; TUC = tucatinib.

Figure 5 presents the log-(log) survival chart for the two treatment arms in the HER2CLIMB trial for the brain metastases subgroup. The chart shows that the two survival lines cross. Lines that cross typically indicate nonproportional hazards.

Figure 5 Log-(log) Survival Plot From the HER2CLIMB Trial Data—Progression-Free Survival: Brain Metastases Subgroup

Cape = capecitabine; Pbo = placebo; Tras = trastuzumab; TUC = tucatinib.

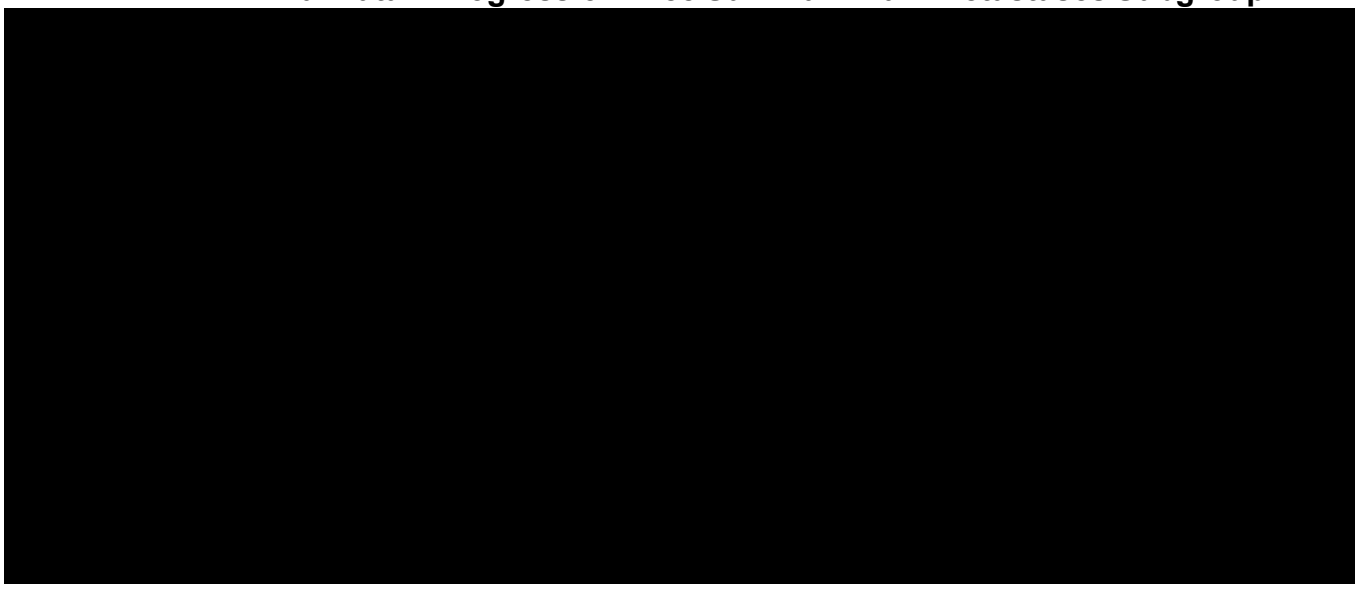
Figure 6 presents the smoothed hazard rates, with bootstrap intervals, for the two treatment arms of the HER2CLIMB trial for the brain metastases subgroup. The chart shows that the hazard rates were approximately proportional between the two arms for the first 7 months of the study.

Figure 6 Smoothed Hazard Rates From the HER2CLIMB Trial Data—Progression-Free Survival: Brain Metastases Subgroup

Cape = capecitabine; Pbo = placebo; Tras = trastuzumab; TUC = tucatinib

Figure 7 presents the hazard ratios estimated from the smoothed hazard rates for the brain metastases subgroup. The hazard ratios appear to change with time, although the bootstrap intervals are large.

Figure 7 Hazard Ratio Plot Derived From the Smoothed Hazard Rates From the HER2CLIMB Trial Data—Progression-Free Survival: Brain Metastases Subgroup



Cape = capecitabine; HR = hazard ratio; Pbo = placebo; Tras = trastuzumab; TUC = tucatinib.

Figure 8 presents the model fit statistics (AIC, BIC, and associated weights) from models fitted to the HER2CLIMB PFS data for the brain metastases subgroup. The gamma (nonstratified and stratified), Weibull (nonstratified and stratified), generalized gamma (nonstratified and stratified), and flexible spline–based model with 1 knot (nonstratified and stratified) gave the best fit.

Figure 8 Model Fit Statics for the Models Fitted to the HER2CLIMB Data and Associated Weights for (A) AIC and (B) BIC—Progression-free Survival: Brain Metastases Subgroup

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 9 presents the standard parametric models fitted to the HER2CLIMB PFS data for the brain metastases subgroup. Only the exponential, log-normal, and log-logistic models did not provide a good visual fit with the Kaplan-Meier estimates.

Figure 10 presents the flexible spline–based Weibull models fitted to the HER2CLIMB PFS data for the brain metastases subgroup. All the spline-based models provided a good visual fit with the Kaplan-Meier estimates.

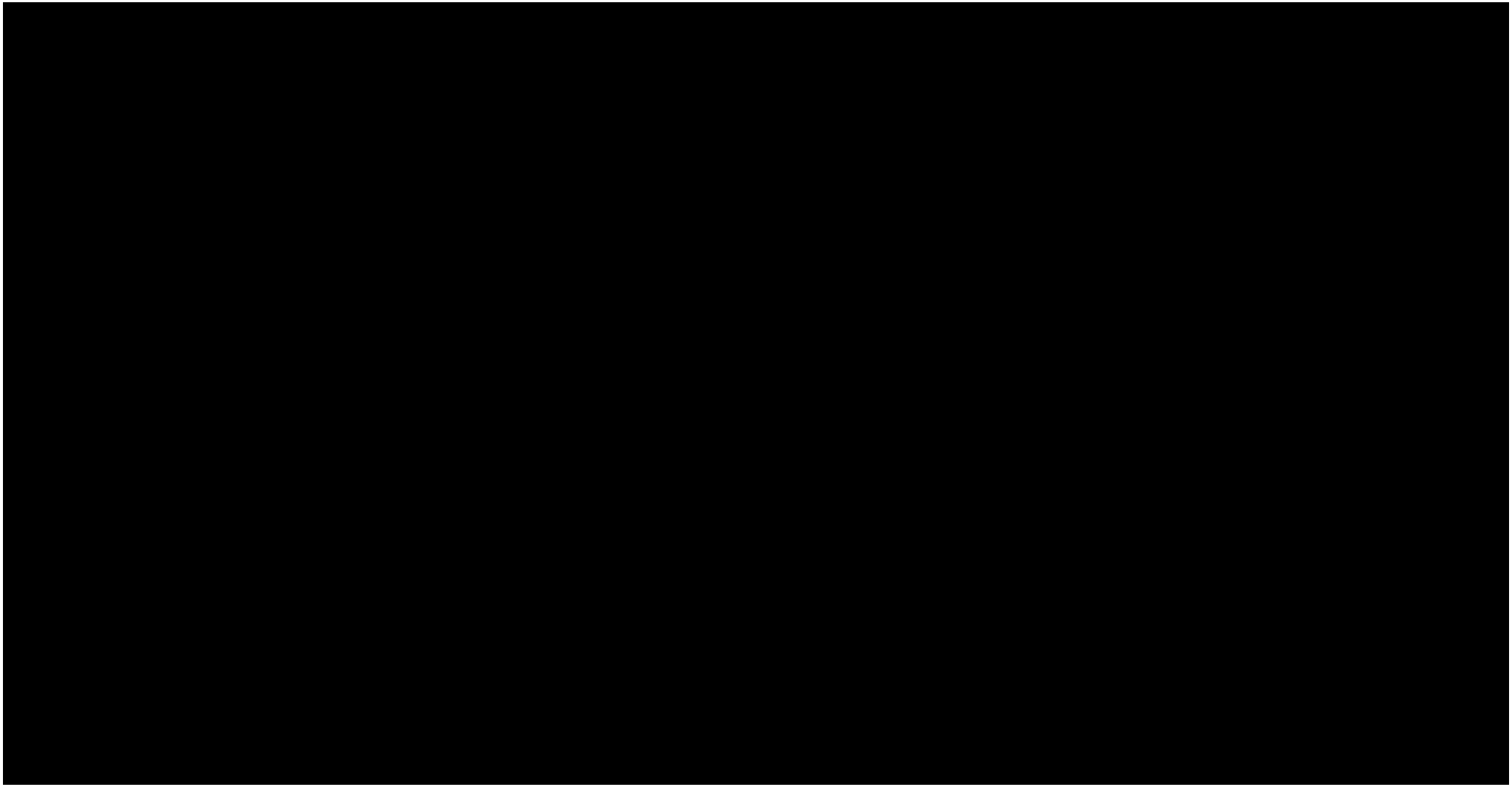
Table 21 presents the mean survival estimates for the extrapolated models (calculated as the area under the curve between 0 and 100 years). Of the 21 models fitted, 13 produced predictions that provided a good fit with the trial data and extrapolations that did not exceed those from the models fitted to the Kaufman et al. (2015) data. These 13 models are highlighted in green in Table 21. Overall, the models that gave plausible predictions gave a fairly narrow range of predictions. The stratified Weibull model (difference in mean survival = [redacted] months) was selected as the most likely.

Figure 9 Parametric Models Fitted to the HER2CLIMB Trial Data—Progression-free Survival: Brain Metastases Subgroup

Figure 10 Flexible Spline–based Models Fitted to the HER2CLIMB Trial Data—Progression-free Survival: Brain Metastases Subgroup

Cape = capecitabine; Pbo = placebo; Tras = trastuzumab; TUC = tucatinib.

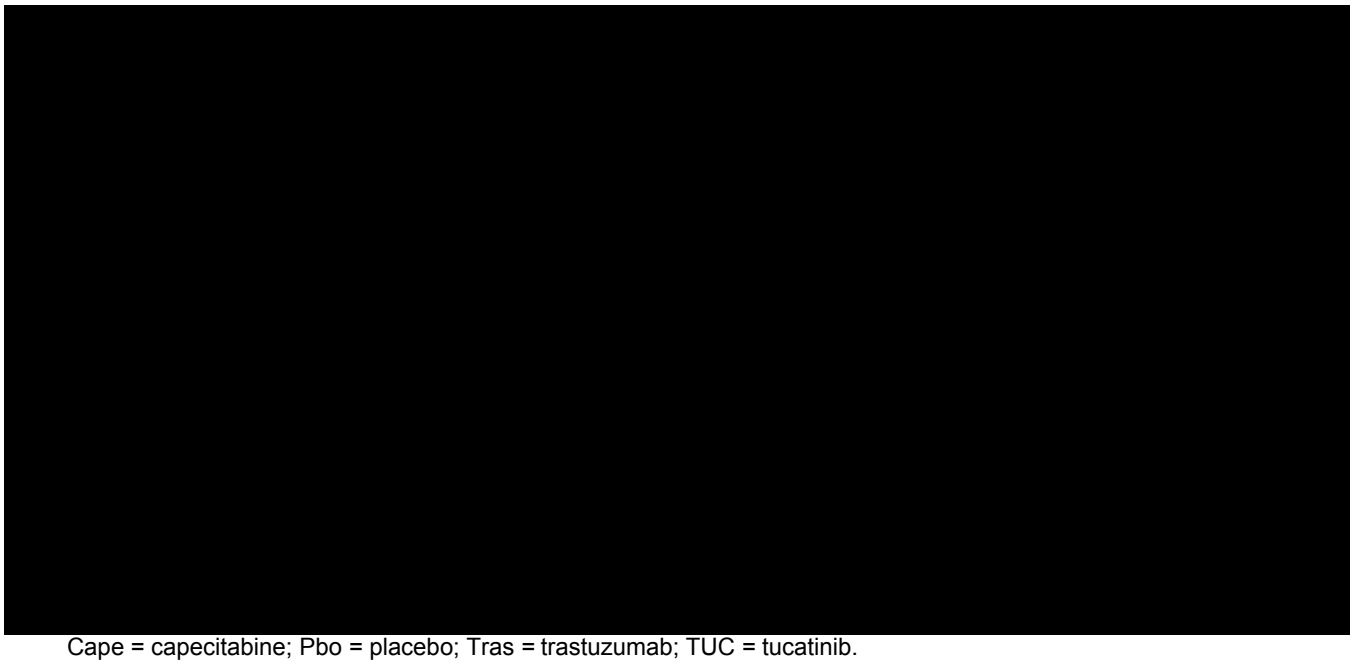
Table 21 Predicted Mean Progression-Free Survival Times in Months for Models Fitted to the HER2CLIMB Data: Brain Metastases Subgroup



Overall Survival

Figure 11 presents the Kaplan-Meier estimates for OS from the HER2CLIMB trial for the brain metastases subgroup.

Figure 11 Kaplan-Meier Estimates for Overall Survival From the HER2CLIMB Trial: Brain Metastases Subgroup



Cape = capecitabine; Pbo = placebo; Tras = trastuzumab; TUC = tucatinib.

The shape of the Kaplan-Meier curve for the tucatinib arm is similar to the total population data. However, the Kaplan-Meier estimates for the control arm show a significant drop at 11 months.

Figure 12 presents the log-(log) survival chart for the two treatment arms in the HER2CLIMB trial for the brain metastases subgroup. The chart shows that the two survival lines cross but are also approximately parallel. Lines that cross typically indicate nonproportional hazards. However, lines that are close to parallel indicate that the proportional hazard assumption may have been met.

Figure 12 Log-(log) Survival Plot From the HER2CLIMB Trial Data—Overall Survival: Brain Metastases Subgroup

Cape = capecitabine; Pbo = placebo; Tras = trastuzumab; TUC = tucatinib.

Figure 13 presents the smoothed hazard rates, with bootstrap intervals, for the two treatment arms of the HER2CLIMB trial for the brain metastases subgroup. The chart shows that the hazard rates were approximately proportional between the two arms.

Figure 13 Smoothed Hazard Rates From the HER2CLIMB Trial Data—Overall Survival: Brain Metastases Subgroup

Cape = capecitabine; Pbo = placebo; Tras = trastuzumab; TUC = tucatinib.

Figure 14 presents the hazard ratios estimated from the smoothed hazard rates for the brain metastases subgroup. The hazard ratios remained close to 0.6 for most of the follow-up period. Although they drop close to 0.3 toward the end of follow-up, theyare only borderline significantly different from 0.6.

Figure 14 Hazard Ratio Plot Derived From the Smoothed Hazard Rates From the HER2CLIMB Trial Data—Overall Survival: Brain Metastases Subgroup

Cape = capecitabine; HR = hazard ratio; Pbo = placebo; Tras = trastuzumab; TUC = tucatinib.

Figure 15 presents the model fit statistics (AIC, BIC, and associated weights) from models fitted to the HER2CLIMB OS data for the brain metastases subgroup. The log-logistic (nonstratified and stratified), Weibull (nonstratified and stratified), gamma (nonstratified and stratified), generalized gamma (nonstratified and stratified), and flexible spline–based model with 1 knot (nonstratified and stratified) provided the best fit.

Figure 15 Model Fit Statics for the Models Fitted to the HER2CLIMB Data and Associated Weights for (A) AIC and (B) BIC—Overall Survival: Brain Metastases Subgroup

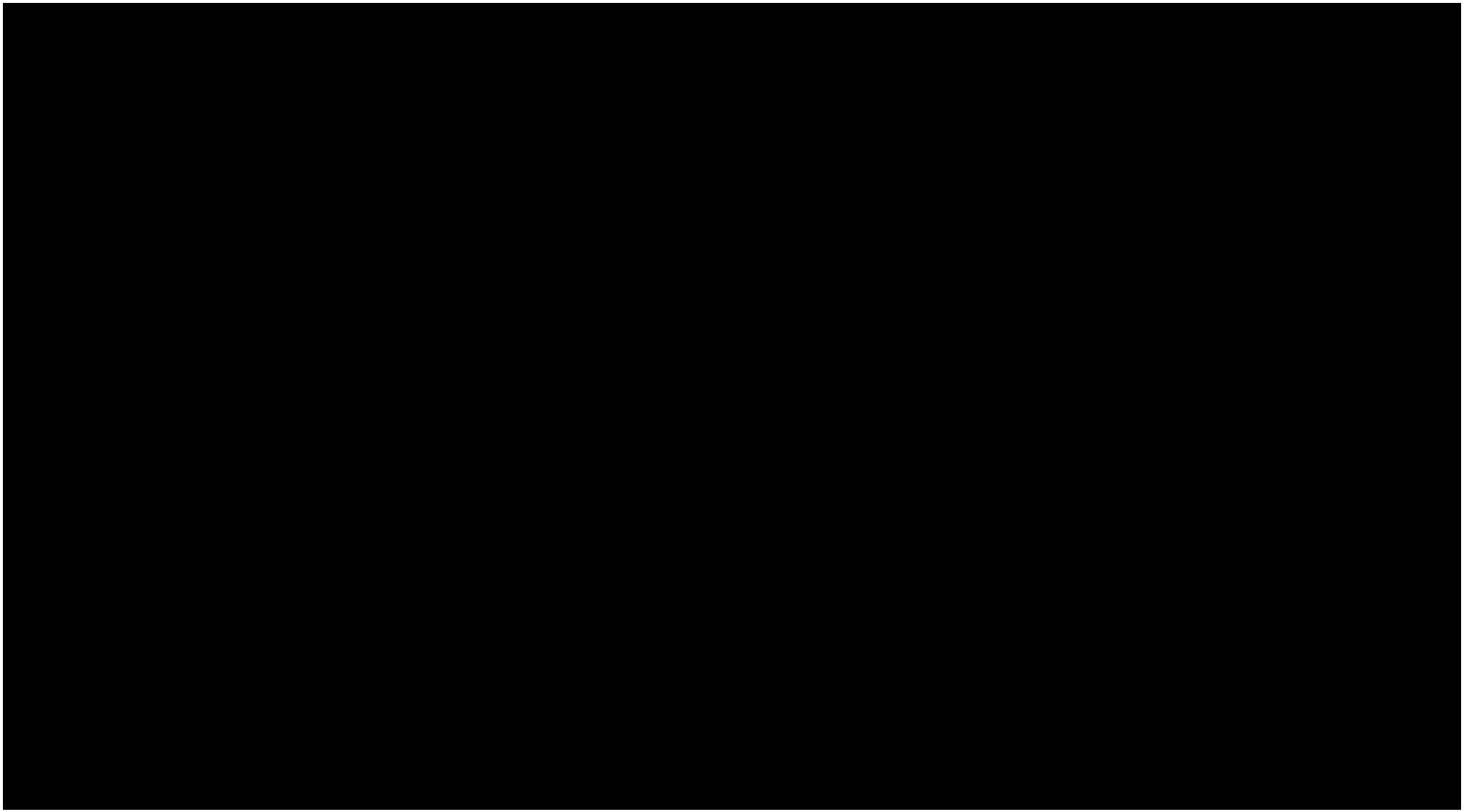
AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 16 presents the standard parametric models fitted to the HER2CLIMB OS data for the brain metastases subgroup. Only the exponential, nonstratified log-normal model and nonstratified log-logistic models did not provide a good visual fit with the Kaplan-Meier estimates.

Figure 17 presents the flexible spline–based Weibull models fitted to the HER2CLIMB OS data for the brain metastases subgroup. All the spline-based models provide a good visual fit with the Kaplan-Meier estimates.

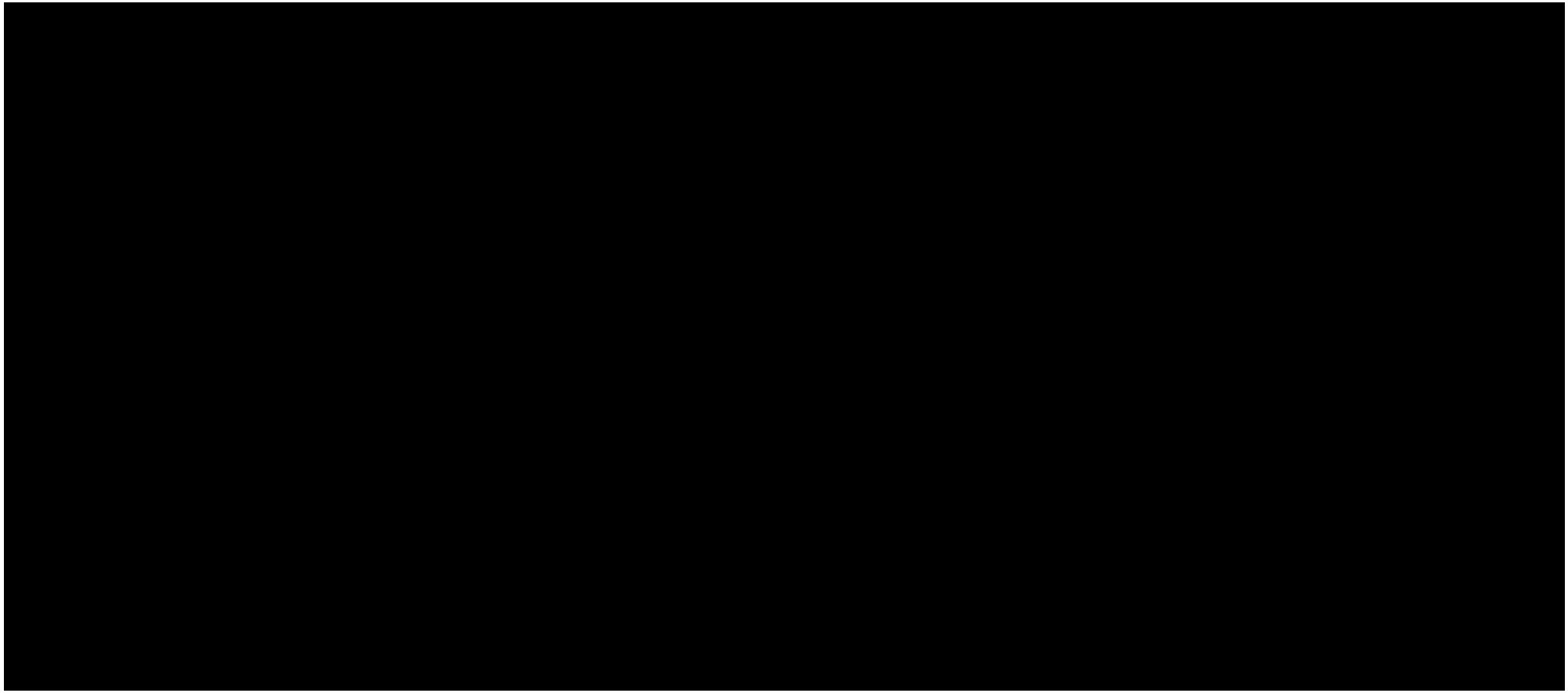
Table 22 presents the mean survival estimates the extrapolated models (calculated as the area under the curve between 0 and 100 years). Of the 21 models fitted, 9 produced predictions that produced a good fit with the trial data and extrapolations that did not exceed those from the models fitted to the Kaufman et al. (2015) and general-population data. These 9 models are highlighted in green in. The differencesin the point estimates for the mean survival from these models for tucatinib versus placebo ranged from [redacted] to [redacted] months. These predicted differences are larger than those from the total population and are likely the result of the large drop in survival at 11 months in the control arm. The Weibull model (difference in mean survival = [redacted] months) was selected as the most likely.

Figure 16 Parametric Models Fitted to the HER2CLIMB Trial Data—Overall Survival: Brain Metastases Subgroup



[redacted]

Figure 17 Flexible Spline–Based Models Fitted to the HER2CLIMB Trial Data—Overall Survival: Brain Metastases Subgroup


[redacted]

Cape = capecitabine; Pbo = placebo; Tras = trastuzumab; TUC = tucatinib.

Table 22 Predicted Mean Overall Survival Times in Months for Models Fitted to the HER2CLIMB Data: Brain Metastases Subgroup

[redacted]

Cape = capecitabine; CrI = credible interval; Pbo = placebo; RCT = randomized controlled trial; Tras = trastuzumab; TUC = tucatinib.

Note: Models in green provided a good fit to the HER2CLIMB data and produced plausible predictions (i.e., did not exceed the predicted survival from the models fitted to the external data) (Kaufman et al., 2015).

Appendix D. Methods of the SC trastuzumab analysis

As requested by the committee, the subcutaneous formulation of trastuzumab has been included in the company's updated model as follows:

- A price for subcutaneous trastuzumab has been included in the Costs sheet and is applied to the tucatinib combination, as well as subsequent anticancer therapy
- The model includes an option to include a discount to the list price
- A flat dose of 600mg irrespective of the patient's body weight is applied in all cycles (no loading dose), as per the SPC and the dosing used in the HER2CLIMB study
- The dose intensity is assumed to be 100%, because there are no dose adjustments, but the RDI may be lower due to patients missing planned doses
- The default setting in the model for administration costs is to assume the same cost as for IV administration of £241.06. This is taken from the NHS reference costs, HRG code SB12Z ("Deliver Simple Parenteral Chemotherapy at First Attendance"). This is applied in the same way as for IV; i.e., per cycle.
- The ERG control sheet has been updated to allow the user to run scenarios changing the proportion of sc vs IV trastuzumab (applied to both acquisition and administration costs) and to apply a relevant discount to reflect the true cost to the NHS
- The ERG control sheet also allows the user to amend the administration cost to reflect any savings to the NHS vs the IV costs

NICE National Institute for Health and Care Excellence

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [ID3828]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example 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 provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Breast Cancer Now
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]

Comment number	**Comments**

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [ID3828]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2021. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are incredibly disappointed that NICE has been provisionally unable to recommend tucatinib in combination with trastuzumab and capecitabine. This news was particularly devastating as we are concerned that this treatment could remain out of reach for people whose breast cancer has spread to the brain who have limited treatment options and who may have potentially shorter prognoses and a poorer quality of life. We urge the pharmaceutical company, Seagen and NICE to work together during this consultation period to consider every possible solution so that the drug can be recommended for routine use on the NHS.
2	We are pleased that the committee recognised that the tucatinib combination had significant potential benefits for patient and recognised the unmet need for anti-HER2 treatments after second-line HER2 treatment. We reiterate our points from our earlier submissions and comments at the committee meeting about the importance of this treatment for this group of patients. A patient current receiving this treatment option explains that: 'It was really hard to come to terms with my diagnosis and the fact that there was no cure. It felt like a death sentence hanging over my head. While treatments helped shrink the tumours, it was at the cost of my quality of life. No treatment worked for long and when my cancer started to grow I felt I was fast running out of options. 'Then, the cancer spread to my brain. It felt like this was the end, as my lung and ancillary tumours had also started to grow more rapidly. 'Luckily, I found out I was eligible for a trial for tucatinib with trastuzumab and capecitabine and within six weeks of starting all of my tumours started to shrink and I've had no progression. This was so much more than I'd hoped for. The treatment not only works very effectively and has helped keep the cancer at bay for the past two and a half years, it's enabled me to have a better quality of life. 'I've seen too many young women tragically die of this disease and the tucatinib combination offers the opportunity to extend life. No price can be put on the additional time I've had with my family and the memories we've made thanks to this drug. That's why I want other women to be able to access this treatment too and hope this provisional rejection can be reversed.' Another patient who has HER2 positive secondary breast cancer who wants to ensure the tucatinib combination is made available on the NHS so it's there to access it when she needs it explains: 'When I was first diagnosed with secondary which was 'incurable and inoperable' in my liver and bones, I thought my life was likely over. But I responded well to Herceptin and chemotherapy and things got under control. I had been able to enjoy life and to make the most of it wherever and whenever I can. 'Then, three years later, I found it had spread to my brain. This provided a whole new level of fear because drugs struggle to cross the blood/brain barrier. 'When there are treatment options, there is always hope. At the moment I have options, but they are running out. There is definitely an unmet need in treatments for HER2 positive cancer. In fact, there is an urgent need to get life-prolonging treatment into the brain. But as yet approval hasn't happened and so I continue to wait and time continues to pass by, while hope begins to dwindle. 'A few precious years or even months may not seem much to people not faced with death, but to me, my family and my friends, it is everything. It's crucial that this treatment is now quickly made available on the NHS.'

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [ID3828]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2021. Please submit via NICE Docs.

3	Whilst we understand that the Committee would like to see further modelling of the cost-effectiveness of tucatinib combination relative to its comparators separately for people with and without brain metastases, we would urge the Committee to consider what flexibilities can be utilised here, given the lack of evidence for the comparators in people with brain metastases. We feel this is an area where a more reasonable approach could be explored. For many years patients with progressive brain metastases have been excluded from clinical trial and there has been a fear that as brain metastasis can lead to poorer outcome, that trials didn't want results influenced by this patient population. As the committee has recognised the network may be biased against tucatinib because if more patients with brain mets, particularly active mets, had been included in the comparator trials, the outcomes in those trials may have been worse. We are pleased the tucatinib trial included this patient group and flexibility must be used during this appraisal as this treatment would be a huge step forward for this patient group and it would not be fair for tucatinib combination to be penalised for this and worryingly there must not be a disincentive for trials including this population group. Brain metastases can have a huge impact on the patient and their family and people are fearful of breast cancer spreading to the brain. Symptoms can include seizures, nausea and vomiting, fatigue, pain and headaches. It can negatively impact quality of life, function, and independence for the patient, but also be difficult for the family to cope with. Brain metastases remains a treatment challenge as many existing treatments are unable to effectively cross the blood-brain barrier. That's why new treatments are desperately needed which can offer important PFS and OS improvements for patients, including those with brain metastases, whilst still offering a good quality of life. A patient receiving the tucatinib combination explains: "I have had no progression or reoccurence in the brain metastasis which has a positive impact on my mental well-being and independence". Another patient tells us: "I do not feel there are enough options available for secondary breast cancer patients, especially targeted treatments and specifically for treating brain metastasis".
4	We also want to reflect on the point of whether any earlier discussions could have taken place between NICE and the company on the areas of uncertainty outlined in the ACD which could have avoided a second committee meeting.
5	The tucatinib combination is recognised in international guidelines such as ESO-ESMO international consensus guidelines for advanced breast cancer and the ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. It references that continued HER2 blockade beyond disease progression is considered standard clinical practice and it is clear from the testimony of both patient and clinical experts the strength of feeling behind wanting to see tucatinib recommended for routine use on the NHS.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [ID3828]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2021. Please submit via NICE Docs.

- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [ID3828]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example 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 provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**METUPUK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**
Name of commentator person completing form:	[redacted]

Comment number	**Comments**

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [ID3828]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2021. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	• Has all of the relevant evidence been taken into account? METUPUK is the only charity in England and Wales solely dedicated to patient advocacy for metastatic breast cancer. We note that reading the 489 page committee papers makes contributing to this appraisal inaccessible to the majority of patients. Approving multiple combinations of drugs are always going to be a problem for double and triple drugs indicated together. The combined costs of the regimen are more likely to breach NICE limits for cost effectiveness. The individual effect of each drug is difficult to determine, not least because in combination the drugs may potentiate each other. We are disappointed that the NICE committee cited the fact that the comparator arm, trastuzumab with capecitabine, is not standard care in the NHS and therefore is reason to not recommend tucatinib. ESMO guidelines produced in 2021 state that "Continued HER2 blockade beyond disease progression is considered standard clinical practice". We are campaigning that all NHS patients should have access to anti-HER2 beyond progression of two treatment lines, reflecting clinical practice in high income countries. Too many NHS patients currently self fund trastuzumab beyond two/three treatment lines, causing financial instability for terminally ill patients. To use current undertreatment of NHS patients as a reason to not recommend a new therapeutic is an additional blow to patients who already do not have parity of care. The HER2CLIMB trial was a multicentre randomised control trial conducted across multiple countries. Without HER2 blockade in the control arm, the trial would have failed ethical approval because international guidelines state HER2 blockade plus chemotherapy is a minimum standard of care. The question must now be asked, will a NICE committee EVER approve a novel therapeutic for heavily pre-treated HER2 positive patients with MBC if having HER2 blockade in the comparator arm is a reason to discount the findings? Up to 50% of patients with metastatic HER2 positive breast cancer go on to develop brain metastases but there is no targeted drug treatment funded by the NHS which is known to cross an intact blood brain barrier. Although radiotherapy is an important treatment, it has limitations for patients. Access to stereotactic radiotherapy is inconsistently applied across the NHS, specifically with regard to total number and total volume of tumours which can be treated. Whole brain radiotherapy is typically only carried out once and has considerable short term and long term reductions in quality of life. There are also geographical barriers in accessing radiotherapy centres for patients living in remote areas or with disabilities. The unmet need for patients with HER2 positive MBC and brain involvement should be weighted highly by the committee. It is worth emphasising that no tyrosine kinase inhibitor is available on the NHS for patients with MBC. The drug lapatinib, which is currently used in most high income countries, was not deemed cost effective for NHS patients. As noted by the committee tyrosine kinase inhibitors are small molecules with the potential to breach the blood brain barrier. Therefore this class of drugs has the potential to provide disease control in patients with brain metastases. The HER2CLIMB trial data shows that the capecitabine and tucatinib combination increases progression free survival. Cancer progression is correlated with poorer quality of life, and so delaying progression gives patients longer time in better health. The capecitabine and tucatinib combination also increases overall survival, which is the most important metric to patients.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [ID3828]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2021. Please submit via NICE Docs.

2	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? It is unreasonable to dismiss trial data because the comparator arm, which is standard of care in similar GDP countries, is not available in the NHS. Using this logic, no new treatments for patients who have received at least two prior anti-HER2 treatment regimens can ever be approved, because no clinical trial will be ethically conducted without HER2 blockade in the comparator arm. Cancer care should not be a race to the bottom. The clinical summary from the HER2CLIMB trial reflected real world patients within the NHS because patients with active brain metastases were included. Controlling brain metastases not only increases survival but increases the quality of the additional months of life. As patient advocates at METUPUK we note that the NICE committee and Seagen Inc. both attempted to model the HER2CLIMB data to chemotherapy regimens without HER2 blockade. We question the utility of these models which are retrospective and based on patient populations with different characteristics. We also question if the models can determine the extent to which the three drugs in the capecitabine and tucatinib combination potentiate each other. We would prefer the actual trial data to be given the greatest weight since it is prospective, has been peer reviewed and has fewer inbuilt biases and assumptions than the models. The redaction of large portions of the committee papers relating drug cost means no meaningful comments can be made on cost effectiveness.
3	• Are the recommendations sound and a suitable basis for guidance to the NHS? The recommendations are not a sound guidance for the NHS. They fail to consider the existing treatment pathway for patients who have had at least two prior anti-HER2 treatment regimens. There is an unmet need for HER2 blockade in later lines of treatment, and specifically an unmet need for ongoing treatment for brain metastases. NHS patients with HER2 positive MBC do not have access to any tyrosine kinase inhibitors, despite this class of medication being a mainstay treatment in most developed healthcare systems. The EMA patent of lapatinib will expire in June 2023, and potentially cheaper generic versions will be available. However, NICE has rejected lapatinib on cost, and without drug company sponsorship there is no mechanism to overturn this decision. Tucatinib is modelled to be superior to lapatinib, and if this drug is rejected NHS patients will once again be let down. We note that many publicly funded healthcare systems including those in Australia, Canada, and many EU countries have approved tucatinib.
4	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Breast cancer predominantly affects women. Although men can get breast cancer, 99% of cases occur in women. Therefore women will be disproportionately affected by this ruling. HER2 positive (along with triple negative) breast cancer occurs at a higher frequency in younger women and in black women. Therefore this ruling will disproportionately impact on younger people and on black people. The alternative treatment for patients with brain metastases is radiotherapy. Access to radiotherapy sites across England and Wales is inequitable, depending on the patient's geographical location. There are considerably fewer sites offering stereotactic radiotherapy than conventional radiotherapy, and many more patients will be required to travel more than 45 minutes to access care. The

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [ID3828]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2021. Please submit via NICE Docs.

	geographical disparities will disproportionately impact on people with disabilities and people with limited English who may struggle to travel long distances. In addition, some people with disabilities would struggle with the physical demands of radiotherapy and planning MRI scans, such as lying flat for protracted periods of time. The capecitabine and tucatinib combination gives the possibility for people with brain metastases to receive treatment closer to their homes.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [ID3828]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example 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 provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Direct – financial** I received a speakers fee (May 2020) and was compensated for my work on an advisory board panel (Jan 2020-March 2020) for Seagen. I have participated in an advisory board for Roche (September 2020) and Astra Zeneca/Daiichi Sankyo (December 2020-Jan 2021) also. **Direct – non-financial** I have received research funding (paid to my institution) from Pfizer (2019=current) and Roche (2020-current) I received travel support to attend ESMO 2019 from Leo Pharmaceuticals. **Indirect** None

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [ID3828]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2021. Please submit via NICE Docs.

Name of commentator person completing form:	[Dr Alicia Okines]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I am concerned that a group of patients with a high unmet need are missing out on an important treatment because capecitabine plus trastuzumab is not currently funded by NICE, therefore the comparator arm used in the HER2Climb 2 trial of the technology is not a standard NHS treatment.
2	As discussed in the meeting, the indirect comparison to trials of single agent chemotherapy which largely excluded patients with brain metastases lead to better outcomes with these agents than would be expected if 50% of patients had brain metastases, as in the HER2Climb trial.
3	Patients with progressive brain metastases experience very difficult symptoms including seizures, headaches, nausea, visual disturbance and worsening mobility, leading to loss of independence and increasing care needs. They may also experience personality change as a result of their brain disease. Furthermore, these patients frequently become dependent on dexamethasone (due to brain oedema) and suffer the side effects of prolonged treatment with this drug, including weight gain, appearance changes, mood disturbance, glucose intolerance and hypertension. The benefit of controlling patients' brain disease for longer and delaying the onset of these awful symptoms which impact hugely on both the patient and their family cannot be overstated.
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [ID3828]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2021. Please submit via NICE Docs.

reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Comments on the ACD:	
I am 53, a single mother and a Scientist who loves to go to the theatre, travel, run and spend time with family and friends. My life has value. But I have metastatic HER2+ breast cancer that has spread to my bones, liver and brain. Since diagnosis in 2017, my extra cranial metastases have been stable because of Herceptin. But last year, after a fit whilst running, I discovered I had 41 brain mets. I have had whole and targeted radiotherapy which have worked well so far to reduce and stabilise. But every scan shows some increase in number or size and I know it's only a matter of time before I need something else, something that can cross the blood brain barrier to good effect. Tucatinib. I have tracked Tucatinib's extremely promising results for nearly 2 years now. It has given me hope that there was this wonder-drug on the horizon if I could just keep my mets at bay. This decision has depleted my hope… According to this document 50% of HER2+ patients go on to get brain mets, surely the need for Tucatinib - the unmet need - is crucial? Getting to brain mets is the final frontier in metastatic HER2+ breast cancer treatment and this drug seems to do it better, and with fewer side effects, than any other targeted drug so far. Since an audit in to the actual numbers of secondary patients is upcoming, I don't know how the 'cost effectiveness' could even be calculated? What price more time with my family, my friends? What price my boys having me here for longer? Today I walked 9 miles and I'm going to the theatre tomorrow. How long before I can't do these things and I am left without options, and without hope? Please rethink and at least allow patients like me to have more options and a chance to be with their loved ones longer. Tucatinib offers that chance.	

Name	[redacted]
Comments on the ACD:	
Has all of the relevant evidence been taken into account? Yes. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** I do not feel the argument for cost-effectiveness is appropriate. A lot of the data also has not been divulged due to confidentiality so unable to comment on cost-effectiveness argument. Any drug that can give a person extra life which is of quality (note chemotherapy drugs currently offered have substantial side effects and can be worse than the cancer itself!), is surely of better benefit to the patient. Admissions to hospital due to chemotherapy side effects have not been mentioned. Due to being a targeted	

therapy, the overall risks of hospital admission are reduced which is also cost effective in the long run.

Are the recommendations sound and a suitable basis for guidance to the NHS?
See previous answer. There is not complete information offered. How do you put a price on a life? The extra 6 months could give a young mother a chance to see their child turn 18, go to nursery or other huge life milestones.
One drug combo used as comparison (lapatinib and capecitabine), is not routinely offered on the NHS. This alone is not sound basis for comparison as how many patients were used for this drug comparison.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Age. There are a lot of younger breast cancer patients who can be outliers regarding survival. I was 32 at diagnosis with MBC spread to lungs. I have been on my 1st line treatment for almost 7 years. The data suggests that my drug combo (herceptin and pertuzumab) will only give an extra few months. This targeted therapy combo has allowed me to live a relatively normal life, I still work full time. If I was on chemotherapy I would almost certainly be unable to work as I am now. People need to be given a chance and an opportunity to thrive with this disease and it needs to be treated as a chronic illness rather than people being written off due to it being metastatic.

Section 3.1: Treatment aims to stop progression of the disease, extend life, and maintain or improve quality of life for as long as possible. Treatment is continued for as long as it works. The committee concluded that there is a high disease burden for people with HER2-positive metastatic breast cancer, especially for those with brain metastases.
Stopping progression and maintaining QOL is very important and if this medication is not approved the only option is harsh chemo which is much more detrimental to quality of daily living and has much harsher side effects. Disease burden is individual and many people with HER2+ disease have 1 small area of disease which could be easily controlled with this medication.

Section 3.2: The committee noted that, although some trusts may offer third-line anti-HER2 therapy, it is not available across the NHS and cannot be considered standard care.
There should not be a difference or post code lottery as to what treatments are available. If some Trusts offer a 3rd anti her2 therapy then ALL should.

Section 3.2: Instead, standard care for people whose disease has progressed on or after 2 anti-HER2 therapies is non-targeted chemotherapy, including capecitabine, vinorelbine or eribulin
These are harsh chemotherapies and affect quality of life with severe side effects.

Section 3.2: The committee concluded that there is an unmet need for anti-HER2 treatment after second-line HER2 treatment. This is particularly important for the significant proportion of people who have brain metastases because all the existing HER2 and chemotherapy treatments have limited penetration through the blood-brain barrier and are not of proven benefit for brain metastases.

There is an UNMET need. Patients require further treatments to be made available to allow them to live a quality life.

Section 3.3: there was wide regional variation in its availability.
There should not be areas where some treatments are available and others not. This is devastating for patients who do not live in certain areas. Patients are being severely let down by this and patients are DYING due to this.

Section 3.5: An improvement in progression-free and overall survival was observed in people with and without brain metastases. The clinical experts explained that this is because, unlike existing treatments, tucatinib is a small molecule that can readily pass through the blood-brain barrier. The clinical experts also explained that the clinical data in the company submission is supported by some longer follow-up data from the trial presented at the American Society of Clinical Oncology annual meeting. The committee concluded that tucatinib combination is more effective than trastuzumab with capecitabine, but that this comparison does not reflect NHS practice.
Trials have shown that this drug is very effective at giving progression free survival including patients with brain mets. It is targeted so less systemic side-effects and QOL. Longer term studies have also shown effectiveness. This drug should be available to UK patients.

Section 3.6: The clinical experts explained that tucatinib is the only treatment shown to cross the blood-brain barrier with demonstrated activity in people with brain metastases.
Access to medications that cross the blood brain barrier must be available. There are limited medications available that currently do this and evidence and trials have shown that this medication is effective at crossing the BBB and therefore a great treatment option for patients with brain mets - especially those who have had maximum radiotherapy and are not suitable for surgical removal.

Section 3.6: The clinical experts also noted that good control of disease and metastases in other parts of the body may delay brain metastases development and progression, so treatments that are more effective in controlling other metastases are also believed to be more effective for people with brain metastases.
This means that this drug can possibly help reduce the risk of brain metastasis from occurring in patient with other HER2+ disease. This can allow patients to live longer without possibly of developing brain mets.

Section 3.10: The company chose lapatinib with capecitabine as a reference treatment to model progression-free and overall survival because this was the most commonly used treatment in the network meta-analysis. It explained that lapatinib with capecitabine data was generated using an average of the evidence in the network.
Why use this drug combo?? Lapatanib and Capecitabine is NOT routinely available on the NHS so question the suitability of this data

Section 3.11: It considered that modelling survival for tucatinib combination and its comparators separately for people with and without brain metastases could help better understand the uncertainty in the cost effectiveness of tucatinib.
There appears to be questions regarding cost effectiveness of this drug so needs to be further researched.

Section 3.17
It has been shown that there is evidence to say that tucatinib is effective at treating HER+ metastatic breast cancer with limited effects on QOL compared to SOC chemotherapy treatment. This allows patients to have a longer progression free survival and allow them longer with their families. There is no price on life.
This drug is an option for me when my 2nd line treatment fails. I have been on 1st line treatment for almost 7 years. This drug may give me the same amount of time, and time with a good QOL.

Name	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
This information is not patient or public friendly and to have to read a document that is 489 pages long obstructs patients and public from getting involved and sharing their thoughts because many don't know where to start. There is full information from the clinical trials (even though information redacted) but I feel that there is a bias because of many issues surrounding approvals through NICE. England are NOT world class and the system isn't world class to review and approve drugs effectively.

Approving multiple combinations of drugs are always going to be a problem for double & triple drugs indicated together as they can't test a drug alone as it's the combination that's effective. I feel that the drug was comparable but some patients may respond differently to it and have better responses. Vicky has had an effective response for 2 years and continues that response. People are very individual. The system is always going to let us down due to the cost as using drugs together will always raise the price & we will be perpetually stuck going round in circles because its a small trial sample (?) and then doesn't replicate to 2300 individual peoples responses.

NICE state that brain mets is an "unmet need" therefore that should be a priority as an approval for a drug that targets that. The drug lapatinib was removed from NICE guidance a few years ago which is another drug that crossed the BBB and targets brain mets but we've had that drug taken away aswell. BUT NICE use lapatinib in clinical trials YET patients can't access it as SOC which is feel is a human rights issue. That's discrimination. We are unable to get a drug that is FALSLEY stated is SOC. That is wrong.

You CANT compare to chemo alone. And chemo alone won't give results as for ANYONE with HER2+ they need herceptin/traz included.. it's SOC in USA & ESMO just confirmed guidance on that YET the UK are STILL not giving herceptin/traztuzamab 4th+ line - so what happens to these patients? Some are now accessing herceptin PRIVATE at a cost from £500-£1000 every 3 weeks (based on your weight) but who can afford that? And this means if you don't get herceptin/traz you die. We need this drug as there's an unmet need 4th+ line.

The clinical experts say that HER2+ targeted products should be available at later line (that currently not) as chemo alone is not effective for her2 patients.

50% of HER2+ patients will develop brain mets. We are not stratified in a pathway OR have any intervention to keep a check of this. I was found to have a brain met incidentally 6 years after my SBC diagnosis & my Oncologist was aware that this could be a problem. Not everyone gets that support to have an scan "just

because" and they they develop side effects which then means that the metastasis will be bigger and more of a problem to treat. This is wrong and patients need intervention to increase survival and outcomes instead of having zero intervention when we know that 50% are at risk.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
There is information redacted so i cannot comment on that.
Some data compared to chemo alone but the trial was comparing against cape & herceptin but this is not routinely given in real life. The Standard of Care additionally has an UNMET need of herceptin/traztuzamab 4th+ line (after Enhertu 3rd line) and tucanitib is needed desperately to help support survival and better outcomes for patients with HER2+ disease.

Are the recommendations sound and a suitable basis for guidance to the NHS?
How can this be answered when patients will die because they don't get the opportunity to try this drug.
50% of HER2+ patients will go onto develop brain metastates and NICE have confirmed that there is an unmet need. So the only way to sort this is to approve a drug that supports patients with a drug/s that can target those specific issues.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
You need to consider that Tucatinib is very well tolerated when compared to other treatments. Thus Tucatinib enables people to live more normal and less disabled lives.

More women than men are affected by HER2 positive metastatic breast cancer. Women often put themselves last. NICE must fund Tucatinib and put women first.

Name	[redacted]
Comments on the ACD:	

Section 3.2: This is particularly important for the significant proportion of people who have brain metastases because all the existing HER2 and chemotherapy treatments have limited penetration through the blood-brain barrier and are not of proven benefit for brain metastases.
Please clarify that there is a lack of data for existing treatments showing CNS penetration and there is limited data available to demonstrate benefit specifically in active brain metastases. Some data is available in stable brain metastases.

Prespecified subgroup analyses of DESTINY-Breast01 showed consistent responses across demographic and prognostic subgroups including patients who had CNS metastases at baseline. T-DXd showed efficacy in a subgroup of patients who had stable, treated brain (CNS) metastases at baseline (n=24). Importantly, efficacy in patients with brain metastases seemed to be similar to the overall population.

Suggested text:

This is particularly important for the proportion of people who have active brain metastases because there is limited data for existing HER2 and chemotherapy treatments to show CNS penetration through the blood-brain barrier, and they are not of proven benefit for active brain metastases in metastatic breast cancer.

Section 3.2: Treatment options for people with brain metastases are stereotactic radiosurgery or radiotherapy (see NICE's clinical guideline on brain tumours and metastases). The clinical experts explained that these treatments usually stop working after some time and most patients cannot have more than 2 courses of radiotherapy because of its neurological toxicity. Currently there are no further treatment options for these patients.
Please clarify that "there are no further treatment options" relates to localised options and/or refers specifically to patients with active brain metastases.

Suggested text:

Treatment options for people with brain metastases are stereotactic radiosurgery or radiotherapy (see NICE's clinical guideline on brain tumours and metastases). The clinical experts explained that these treatments usually stop working after some time and most patients cannot have more than 2 courses of radiotherapy because of its neurological toxicity. Currently there are no further localised treatment options for patients with active brain metastases.

Section 3.6: The clinical experts explained that tucatinib is the only treatment shown to cross the blood-brain barrier with demonstrated activity in people with brain metastases. But they highlighted that the impact of other treatment options on brain metastases is complex.
The statement is correct for active brain metastases not stable and active. Data for activity in stable brain metastases is available from a sub-group analysis of DESTINY-Breast01 where T-DXd showed efficacy in stable brain metastases.

Suggested text:

The clinical experts explained that tucatinib is the only treatment shown to cross the blood-brain barrier with demonstrated activity in people with active brain metastases. But they highlighted that the impact of other treatment options on brain metastases is complex.

Section 3.6: It concluded that tucatinib is likely to improve clinical outcomes relative to eribulin, capecitabine and vinorelbine, but the size of effect is uncertain because of clinical heterogeneity in several areas, particularly the inclusion of people with brain metastases in the HER2CLIMB trial.
Page 9 of the ACD states that "None of the comparator trials included people with active brain metastases. All but one included people with stable or inactive brain metastases, but the proportion was usually not reported". Comparator trials did include patients with stable brain metastases and so this statement is correct only if it is in reference to inclusion of active brain metastases in HER2CLIMB specifically. The ACD should text should reflect this distinction.

Suggested text:

It concluded that tucatinib is likely to improve clinical outcomes relative to eribulin, capecitabine and vinorelbine, but the size of effect is uncertain because of clinical heterogeneity in several areas, particularly the inclusion of people with active brain metastases in the HER2CLIMB trial.

Section 3.8
Page 9 of the ACD states that:

“None of the comparator trials included people with active brain metastases. All but one included people with stable or inactive brain metastases, but the proportion was usually not reported”.

It should be noted that while the suggested subgroup analysis would be informative this analysis will compare patients without brain metastases in HER2CLIMB with comparator trials which include patients with stable brain metastases. Given stable and active brain metastases are prognostic for poorer outcomes this would be expected to favour tucatinib. The wording in the ACD should reflect this point.

Section 3.10: The company explained the ERG's approach created bias against tucatinib because HER2CLIMB included people with brain metastases who have poorer outcomes than people without brain metastases.
Please clarify that HER2CLIMB included patients with active brain metastases which comparator trials did not. Comparator trials did include patients with stable brain metastases as acknowledged on p9 of the ACD. Both stable and active brain metastases are prognostic for poorer outcomes.

Suggested text:

The company explained the ERG’s approach created bias against tucatinib because HER2CLIMB included people with active brain metastases who have poorer outcomes than people without brain metastases or with stable brain metastases.

Section 3.11
It should be noted that while the suggested subgroup analysis would be informative this analysis will compare patients without brain metastases in HER2CLIMB with comparator trials which include patients with stable brain metastases. Given stable and active brain metastases are prognostic for poorer outcomes this would be expected to favour tucatinib. The wording in the ACD should reflect this point.

Section 3.17: They explained this is because of its improved efficacy and tolerability in patients with HER2-positive metastatic breast cancer, including those with brain metastases.
Request wording clarifies that this refers to active brain metastases as other trials have shown benefit in stable brain metastases. This includes a subgroup analysis of DESTINY-Breast01.

Suggested text:
They explained this is because of its improved efficacy and tolerability in patients with HER2-positive metastatic breast cancer, including those with active brain metastases.

Name	[redacted]
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
At the moment the dept health / NHS are undertaking a survey to see how many patients have SBC , therefore the number of patients with Herplus and other subsets is unknown , therefore the benefit of doubt should be given and the drug given to those who need it ,as all relevant evidence has not been collated and by allowing the treatment patients will benefit greatly

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
I don't think the clinical cost effectiveness is reasonable ,
As at the moment the actual cost if the drug was accepted by NICE has not been made public and would be less than the price shown , also if the drug was accepted and used by more patients the cost to the public purse would go down in time,

Section 3.1
There is a shortage of therapies for patients going forward and all these treatments are like life rafts , going on treatment to treatment all put together elongates life and surely that is the aim.

Name	[redacted]
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
A reason cited by the committee to not recommend tucatinib with trastuzumab and capecitabine is because the comparator arm trastuzumab with capecitabine is not standard care in the NHS. As a patient with metastatic HER2 positive breast cancer I am aware that the NHS standard of care for patients after at least 2 prior anti-HER2 treatment regimens falls short of what is standard in high income countries with similar healthcare systems. The guidelines produced by ESMO in 2021 are as follows:
Continued HER2 blockade beyond disease progression is considered standard clinical practice. If the anti-HER2 therapies [discussed above] have been exhausted, are not considered suitable or are not available, sequential trastuzumab-based strategies (in combination with different ChTs) should be considered.
Looking further afield at ASCO guidelines, HER2 directed treatment is also recommended beyond progression after two or more lines of therapy.
The HER2CLIMB trial was a multicentre randomised control trial conducted across multiple countries. Without HER2 blockade in the control arm, the trial would have failed ethical approval in most countries because ESMO/ASCO guidelines consider HER2 blockade plus chemotherapy to be standard of care. It is concerning that NICE determined that the minimum ethical standard of care comparator arm as a reason to consider the results inapplicable to the NHS because we do not match this level of treatment.
Up to 50% of patients with metastatic HER2 positive breast cancer go on to develop brain metastases. There is no HER2 directed treatment funded by the NHS which is known to cross an intact blood brain barrier. This leaves only radiotherapy options which cannot be repeated. Access to stereotactic

radiotherapy is inconsistently applied across the NHS, specifically with regard to total number and total volume of tumours which can be treated. Whole brain radiotherapy can only be carried out once and has considerable short term and long term reductions in quality of life.
The unmet need for patients with HER2 positive MBC and brain involvement should be weighted highly by the committee. It is worth emphasising that no tyrosine kinase inhibitor is available on the NHS for patients with MBC. The drug lapatinib, which is currently used in most high income countries, was not deemed cost effective for NHS patients, although it is widely used in the UK for privately treated patients. The drug neratinib is only given to NHS patients with primary breast cancer who are also hormone positive. As noted by the committee tyrosine kinase inhibitors are small molecules with the potential to breach the blood brain barrier. Therefore this class of drugs has the potential to provide disease control in patients with brain metastases.
The committee should take into account treatment pathways within the NHS for patients with HER2 positive MBC who have at least 2 prior anti-HER2 treatment regimens, both with and without brain mets. The HER2CLIMB trial data shows that the capecitabine and tucatinib combination increases progression free survival. Cancer progression is correlated with poorer quality of life. The capecitabine and tucatinib combination also increases overall survival, which is the most important metric to patients.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
It is not reasonable to consider trial data inapplicable to NHS care because the comparator arm, which is standard of care in publically funded healthcare systems in similar GDP countries, is not available in the NHS. Using this logic, no new treatments for patients who have received at least 2 prior anti-HER2 treatment regimens can ever be approved, because no clinical trial will be ethically conducted without HER2 blockade in the comparator arm.
Cancer care should not be a race to the bottom.
The clinical summary from the HER2CLIMB trial reflected real world patients within the NHS because active brain metastases were not an exclusion criteria. Controlling brain mets not only increases survival, but increases the quality of the additional months of life. Attempts to capture quality of life in models will always be flawed, and cannot fully quantify how much life will be improved if brain mets are controlled. Attempts to model the HER2CLIMB data to chemotherapy regimens without HER2 blockade will also be flawed because they are retrospective and based on different patient populations. The extent to which treatment combinations potentiate each other cannot easily be mathematically modelled without human assumption and bias.

Are the recommendations sound and a suitable basis for guidance to the NHS?
The recommendations are not a sound guidance because they do not take into account treatment options that patients who have had at least 2 prior anti-HER2 treatment regimens can access. There is an unmet need for access to HER2 blockade in later line treatment, and specifically an unmet need for ongoing treatment for brain metastates.
As previously noted, NHS patients with HER2 positive MBC do not have access to any tyrosine kinase inhibitors, despite this class of medication being a mainstay treatment in most developed healthcare systems. The EMA patent of lapatinib will expire in June 2023, and potentially cheaper generic versions will be available. However, NICE has rejected lapatinib on cost, and without drug company sponsorship there is no mechanism to overturn this decision.

Tucatanib is modelled to be superior to lapatinib, and if this drug is rejected NHS patients will once again be let down.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Breast cancer predominantly affects women. Although men can get breast cancer, 99% of cases occur in women. Therefore women will be disproportionately affected by this ruling. HER2 positive (along with triple negative) breast cancer occurs at a higher frequency in younger women and in black women. Therefore this ruling will disproportionately impact on younger people and on black people. Please note the younger a person is diagnosed with MBC, the more life years they lose. Increasing the length and quality of life by providing the most up to date treatments will make a huge difference both to the patients and their families. The HER2CLIMB trial data shows that capecitabine and tucatinib combination not only increases progression free survival, it also increases overall survival, which is the most important metric to patients.

Name	[redacted]

Comments on the ACD:
I am extremely disappointed that this has not been approved. In trials this drug has been my wonder drug and has allowed my life to be extended with minimal side effects. This drug would allow other families to lead a normal life and to be able to live longer. No price can be put on the opportunities for longer survival and the hope this drug will give breast cancer patients especially those with her2 and brain mets. We are at a disadvantage compared to other countries that have already approved this drug for general use.

CONFIDENTIAL

Evidence Review Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

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

Evidence Review Group's summary and critique of the company's response to the appraisal consultation document

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	David Alexander Scott, Principal Research Fellow, SHTAC Lorna Hazell, Senior Research Assistant, SHTAC Neelam Kalita, Senior Research Fellow, SHTAC Joanne Lord, Director, SHTAC Jonathan Shepherd, Principal Research Fellow.
Correspondence to	Jonathan Shepherd Southampton Health Technology Assessments Centre (SHTAC) Wessex Institute Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	30 November 2021

[redacted]

Contents

List of tables

List of figures

LIST OF ABBREVIATIONS

ACD	Appraisal Consultation Document
AE	Adverse event
AIC	Academic in confidence
CI	Confidence interval
CIC	Commercial in confidence
CrI	Credible interval
CS	Company submission
ERG	Evidence Review Group
HER2	Human epidermal growth factor receptor 2
HER2-	Human epidermal growth factor receptor 2-negative
HER2+	Human epidermal growth factor receptor 2-positive
HER2CLIMB	A Study of Tucatinib vs Placebo in Combination with Capecitabine & Trastuzumab in Patients with Advanced HER2+ Breast Cancer
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
KM	Kaplan-Meier
NHS	National Health Service
NMA	Network meta-analysis
NICE	National Institute for Health and Care Excellence
NR	Not reported
OS	Overall survival
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
QoL	Quality of life
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error

1 Introduction

This document is the Evidence Review Group's (ERG) summary and critique of the response by the company, Seagen, to the Appraisal Consultation Document (ACD) for the NICE Single Technology Appraisal (STA) of 'Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies' [ID3828].The ERG received the company's response on 17th November 2021. The company also submitted an updated version of their cost-effectiveness model, dated 16 November 2021.

The company's ACD response document contains a revised base case for the cost-effectiveness analysis and additional information and analyses relating to five topics as requested in the ACD.

Table 1 Summary of topics addressed by the company

Topic number	Summary of topic	Does this response contain new evidence, data or analyses?
1	Exploration of a treatment effect modifier for brain metastases	Yes
2	Subgroup analyses for people with and without brain metastases	Yes
3	Threshold analyses to explore relative effects of comparators	Yes
4	Justification for differences in post-progression utility	Yes
5	Additional analyses using subcutaneous trastuzumab	Yes

In this report we present a brief critique of the company's revised base case analysis (section 2) and their response to each of the five topics (section 3). We provide a discussion and overview of ERG conclusions in section 4, and revised analysis for the ERG's preferred assumptions and scenarios in section 5.

2 Company's ACD response revised base case analysis

The company report a revised base case analysis in Table 1 of their ACD response, which they say accepts all of the committee's preferences and reflects the results of the additional analyses requested by the committee. The changes in assumptions are not described in detail in the company's ACD response. However, the ERG replicated the company's previous base case results (model dated 25/08/21 submitted with their response to technical engagement) using the revised version of their model (model dated 16/11/21 with their ACD response). Table 2 below shows the results of this analysis, presented as cumulative changes from the previous to revised company base case for a series of changes to the assumptions. Note that each successive set of results in Table 3 includes a change in assumptions applied to the previous set of results. This indicates that the revised company base case includes the following changes:

- Correction to assumed price discount for trastuzumab in previous versions of the model, as noted in the footnote to Table 1 in the company's ACD response. The assumed discount of [redacted] had been applied twice (equivalent to a discount of [redacted]).
- Random effects NMA, rather than fixed-effect. This includes the corrected confidence interval for the overall survival (OS) hazard ratio (HR) confidence interval from the Pivot et al. paper, as discussed in technical engagement.
- PFS and OS for the tucatinib combination arm extrapolated directly from HER2CLIMB data ('within-trial' approach). This replaces extrapolations based on fractional polynomial curves fitted to NMA data in the previous base case.
- Application of an effect modifier to adjust comparator OS, PFS and time to treatment discontinuation (TTD) for differences in the trial populations compared with HER2CLIMB. HR estimate of 1.64 (95% CI: 1.34 to 1.99) derived from clinical expert opinion tapered to 1.00 from year 2 to year 5, as described in section 1.3 of the company's ACD response.
- Post-progression utilities for the comparators based on the mean of the TA423 ERG and company estimates (0.588), rather than the TA423 ERG estimate alone (0.496). Other utilities have not changed from the previous base case: tucatinib combination pre-progression [redacted] and post-progression [redacted] (HER2CLIMB EQ-5D-5L pooled arms); eribulin and capecitabine/vinorelbine pre-progression 0.706 and 0.701 respectively (as in TA423).
- Utilities adjusted for ageing (Ara and Brazier 2010 equation).
- Including drug wastage for trastuzumab and capecitabine, as estimated in the company model.

- ERG scenario for use of subsequent treatments: 50% trastuzumab IV, 10% each for capecitabine and vinorelbine and 30% no treatment. The previous base case included use of trastuzumab IV, lapatinib, neratinib, pertuzumab and T-DM1.
- PAS price discount for tucatinib of [redacted], increased from [redacted] in previous analysis.

Table 2 Cumulative change to company's base case

Technology	Total costs (£)	Total QALYs	Pairwise ICER	Incremental ICER
Previous company base case (technical engagement model dated 25/08/21)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
+ Correction to assumed price discount for trastuzumab ([redacted] applied once)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
+ Random effects network meta-analysis, including Pivot correction				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
+ OS and PFS extrapolated from HER2CLIMB data ('within trial' analysis)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
+ Effect modifier for comparator OS from clinical experts (HR 1.64, tapered year 2-5)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]

+ Post-progression utility for comparators TA423 mean 0.588 (no change to other utilities)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
+ Utilities adjusted for age				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
+ Drug wastage for trastuzumab and capecitabine included				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
+ ERG subsequent treatment scenario [a]				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
+ Increased PAS discount for tucatinib (from [redacted] to [redacted])				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Revised company base case				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]

Source: ERG analysis using company model submitted with ACD response (dated 16 Nov 2021)
[a] Company's original subsequent treatment scenario included trastuzumab IV, lapatinib, neratinib, pertuzumab and T-DM1. ERG scenario used in revised base case includes 50% trastuzumab IV, 10% each for capecitabine and vinorelbine and 30% no treatment.

3 Scenario analyses conducted on the company's revised base case

Topic 1 Exploration of a treatment effect modifier for brain metastases

Effect modifier estimates based on clinical expert opinion

The company report their approach to estimating an effect modifier to adjust survival outcomes (PFS, TTD and OS) for the comparator arms based on clinical expert opinion (section 1.3 of their ACD response). Mean HR estimates and 95% confidence intervals at 1 year, 2 years and 3 years are reported in Table 2 of the ACD response, and the impact of these estimates on the cost-effectiveness results in Table 3 of the ACD response. We replicated the company's estimates in Table 2 of the company ACD response.

Effect modifier estimates based on HER2CLIMB data

The company explain their approach to estimating an effect modifier based on HER2CLIMB data in section 1.4 of their ACD response. The model includes treatment x brain metastases interaction terms of [redacted] for OS and [redacted] for PFS, which are applied to the random effects NMA HR estimates for the proportion of patients with brain metastases in HER2CLIMB of 47.5%. The estimated treatment effects (HR versus trastuzumab + capecitabine) from this approach are shown alongside the unmodified estimates in Table 3 below. We replicated the company's cost-effectiveness scenarios with no effect modifiers and with HER2CLIMB based effect modifiers (from ACD response Tables 6 and 7 respectively) in Table 4 below. The company emphasises that the HER2CLIMB based estimates of effect modification do not take account of any benefit for people with brain metastases from the trastuzumab + capecitabine control arm in HER2CLIMB. If trastuzumab + capecitabine is more effective for people with brain metastases than the decision problem comparators (capecitabine, vinorelbine or eribulin), then ICERs for the tucatinib combination with the HER2CLIMB based effect modifiers will be over-estimates.

Table 3 Effect of HER2CLIMB effect modifiers on model treatment effect estimates (hazard ratios compared with trastuzumab + capecitabine)

Technology	PFS		OS	
	No modifier	With modifier	No modifier	With modifier
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]

Table 4 Scenarios with no effect modifiers and HER2CLIMB based modifiers

Technology	Total costs (£)	Total QALYs	Pairwise ICER	Incremental ICER
Revised company base case (KOL HR 1.64 tapered to 1.00 between year 2 and 5)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
No effect modifiers				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Effect modifiers estimated from HER2CLIMB data				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]

Source: ERG analysis using company model submitted with ACD response (dated 16 Nov 2021).
KOL Key opinion leader

Topic 2 Subgroup analyses for people with and without brain metastases (BM)

The company report cost-effectiveness results for the subgroup of people with brain metastases (BM) in Table 10 of their ACD response. We were unable to replicate this analysis from the company's model as there is insufficient information on which combination of assumptions the company used for this subgroup analysis, although we obtained similar results with the following model options:

- Population: Brain metastases subgroup (ERG!C25)
- OS survival model: Weibull (ERG!C42)

- PFS survival model: Stratified Weibull (ERG!C58)
- HR NMA: HER2CLIMB brain mets subgroup (ERG!C29)
- HR taper KOL effect modifier: excluded (ERG!C94)
- HER2CLIMB subgroup data for adverse events (ERG!C34)
- HER2CLIMB subgroup data for use of antidiarrheals (ERG!C35)
- HER2CLIMB subgroup data for dose intensity (ERG!C36)
- HER2CLIMB subgroup data for treatment exposure (ERG!C37)

The company report estimated ICERs for the remaining HER2CLIMB population without brain metastases in Table 11 of their ACD response. We note that for this calculation, ICERs for the non-BM subgroup are back-calculated from the ICERs for the BM subgroup and the ICERs for the ITT population without the effect modifier to adjust the comparator results for the absence of patients with BM. Hence, the ICER for the tucatinib combination compared with capecitabine in the ITT population cited in Table 11 is [redacted] per QALY gained (rather than the revised base case [redacted] per QALY gained). This is appropriate bit means that the weighted average of the company's ICER estimates for the BM and non-BM subgroups does not equal their revised base case ICER.

We also note that the method that the company used to estimate the ICER for the non-BM subgroup from the ICERs for the BM subgroup and ITT population is not accurate: as a ratio, the ICER is very sensitive to small differences in the denominator (incremental QALYs). A more accura method is to first calculate the costs and QALYs for each intervention for the non-BM subgroup (using the same formula as in section 2.4 of the company's ACD response but applied to costs and QALYs, rather than ICERs). Then the ICERs can be calculated directly.

Table 5 below shows ERG estimates of cost-effectiveness for the subgroup with brain metastases (based on the changes to the company's base case model listed in the above bullet points) and for the subgroup without brain metastases (calculated from residual estimates of costs and QALYs). The results are similar to those reported by the company (ACD response Tables 10 and 11).

The company's estimated ICERs for the tucatinib combination are below the usual NICE end of life threshold of £50,000 per QALY gained for the subgroup with BM but not for the subgroup without BM. The company note that BM are not routinely screened for in UK clinical practice. Thus, if tucatinib were to be recommended only for use in the subgroup with

brain metastases, additional costs would be incurred that are not included in the above calculations.

Table 5 ERG analysis for subgroups with and without brain metastases

Technology	Total costs (£)	Total QALYs	Pairwise ICER	Incremental ICER
ITT population (revised company base case without effect modifier for comparators)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
ERG subgroup with brain metastases (changes in assumptions as reported above)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
ERG subgroup without brain metastases (differences between ITT and BM subgroup)				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]		[redacted]
Source: ERG analysis using company model submitted with ACD response (dated 16 Nov 2021)				

Topic 3 Threshold analyses to explore relative effects of comparators

In response to the committee's request for a threshold analysis, the company report HR thresholds for capecitabine, vinorelbine and eribulin at which the ICER for the tucatinib combination versus each comparator would fall below the usual NICE end of life threshold of £50,000 per QALY gained (see ACD response Table 12).

However, we note that these calculations ignore dominance and extended dominance between the treatment options, which are key components of a correct incremental analysis. We show the impact of the company's estimated thresholds with full incremental ICERs as well as pairwise ICERs in Table 6 below. These show that the full incremental ICERs for the tucatinib combination (excluding dominated comparators) do not fall below the £50,000 per QALY gained threshold for any of the company's reported thresholds applied for individual comparators. We also show a combined threshold analysis, in which the OS HRs for all

comparators were increased by a single multiplier. The full incremental ICER for the tucatinib combination fell below £50,000 per QALY gained with a multiplier of [redacted] applied to all comparator OS HRs (approximately [redacted] for all comparators).

Table 6 ERG threshold analysis

Technology	Total costs (£)	Total QALYs	Pairwise ICER	Incremental ICER
Revised company base case without effect modifier (OS HR [redacted], [redacted], [redacted] for capecitabine, vinorelbine and eribulin respectively)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
OS HR for capecitabine [redacted]				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
OS HR for vinorelbine [redacted]				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
OS HR for eribulin [redacted]				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
OS HR multiplier for all comparators [redacted] ([redacted], [redacted], [redacted] for capecitabine, vinorelbine and eribulin respectively)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Source: ERG analysis using company model submitted with ACD response (dated 16 Nov 2021)				

Topic 4 Justification for differences in post-progression utility

The company provide discussion to support the use of different post-progression utilities for the tucatinib combination (0.698, based on EQ-5D data from the HER2CLIMB trial) than for the comparators (0.588, reflecting the TA423 committee's preference for a value between the TA423 ERG and TA423 company estimates). In Table 13 of their ACD response, the company report cost-effectiveness results using the value of 0.496, which was the TA423 ERG's estimate. We note that this does not align with the TA423 committee preferences.

We show the impact of two alternative scenarios in Table 7 below. First, we report results using the same post-progression utility (0.588) for all interventions. This shows the impact on the ICERs of this more conservative approach. The second scenario shows the effect of aligning utility estimates with the approach in the NICE appraisal of trastuzumab deruxtecan (TA704 ERG report Table 21). This included response-based estimates prior to progression, and 0.588 for all treatments post-progression. For the tucatinib combination, the estimated utility is 0.735 (=0.704 + 0.076 * 0.406).

Table 7 Scenarios with alternative utility estimates

Technology	Total costs (£)	Total QALYs	Pairwise ICER	Incremental ICER
Revised company base case (pre-progression 0.762 tucatinib, 0.706 eribulin, 0.701 capecitabine/ vinorelbine; post-progression 0.698 tucatinib, 0.588 comparators)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Same post-progression utility (0.588 all comparators)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Response based utilities based on TA704 (pre-progression 0.725 capecitabine, 0.717 vinorelbine, 0.713 eribulin, 0.735 tucatinib; post-progression for all treatments 0.588)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Source: ERG analysis using company model submitted with ACD response (dated 16 Nov 2021)				

Topic 5 Additional analyses using subcutaneous trastuzumab

Finally, the company address the committee's request for additional analysis using costs for subcutaneous trastuzumab. The committee requested analyses for "both routes of administration" (ACD paragraph 3.13). However, the company argues that due to differences in availability of subcutaneous and intravenous trastuzumab across the NHS, this cost should not be a decision driver. They present two scenarios with different proportions subcutaneous trastuzumab ([redacted] and [redacted]), with an assumed price discount of [redacted] (compared with the company's assumption of [redacted] price discount for intravenous trastuzumab) (ACD response tables 15 and 16). The company also assumed a 100% relative dose intensity for subcutaneous trastuzumab, compared with 100% for the first dose of IV trastuzumab and 73.9% for subsequent doses. We show the results of the company's scenarios in Table 8 below, with the revised base case (100% intravenous trastuzumab) and an additional ERG scenario with costs for 100% subcutaneous trastuzumab (other assumptions are the same as in the company's scenarios). We report results for this and all other analyses in this report with all available PAS and CMU NHS price discounts for concurrent, comparator and subsequent treatments in a separate confidential addendum.

Table 8 Scenarios with subcutaneous trastuzumab

Technology	Total costs (£)	Total QALYs	Pairwise ICER	Incremental ICER
Revised company base case (100% IV trastuzumab)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Company scenario ([redacted] subcutaneous trastuzumab, assumed [redacted] price discount)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Company scenario ([redacted] subcutaneous trastuzumab, assumed [redacted] price discount)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]

ERG scenario ([redacted] subcutaneous trastuzumab, assumed [redacted] price discount)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Source: ERG analysis using company model submitted with ACD response (dated 16 Nov 2021)				

4 ERG discussion and conclusions

The company's revised base case reflects the committee's preferred assumptions, as specified in section 3.16 of the ACD.

4.1 Modelling of survival outcomes

Survival outcomes for the tucatinib combination are estimated by direct extrapolation from HER2CLIMB trial data (Weibull for OS, flexible Weibull with two knots for PFS), which provide a good fit to the observed data. OS and PFS for the comparators are estimated using hazard ratios from the random effects NMA, with appropriate correction of results from the Pivot et al. trial.

There is high remaining uncertainty over the relative effects from the NMA, due to important differences in the patient populations in the included trials, particularly the low proportion of patients with brain metastases in the comparator trials. In their revised base case, the company adjust the comparator extrapolations using survival estimates elicited from 10 clinical experts. The experts were asked to estimate survival for the HER2CLIMB population if they had received single-agent chemotherapies. The resulting effect modifier (1.64) reduced survival outcomes (OS, PFS and treatment duration) for the comparators over a period of five years (the modifier was reduced from the end of year 1 down to 1.00 at year 5). The methods and results of the expert elicitation process were sparsely reported but appear reasonable (although the ERG could not replicate the upper and lower limits for the effect modifier reported by the company).

The company also reported results for a scenario using an interaction term for treatment effect with brain metastases estimated from HER2CLIMB data. This was used to adjust HR estimates from the NMA for the proportion of patients with brain metastases from the HER2CLIMB trial (48% which is thought to be representative of clinical practice). The company note that this approach assumes that the effectiveness of the control arm in HER2CLIMB (trastuzumab with capecitabine) for people with brain metastases is the same

as the single agent comparators, which might not be true. We agree that this approach is likely to be conservative, underestimating survival differences between the tucatinib combination and included comparators.

Overall survival curves with no treatment effect modifier for brain metastases, effect modification based on clinical expert opinion, and effect modification based on HER2LCIMB data are shown in Figure 1, Figure 2 and Figure 3 respectively.

We conclude that it is appropriate to adjust the single-agent comparator arms for the lower expected treatment effect for people with brain metastases. The extrapolation based on the HER2CLIMB treatment effect modifier appears more plausible than that based on clinical expert opinion, which has an unrealistic kink at two years. However, we recognise that the trial-based effect modifier may overestimate survival with the single agent comparators, due to a possible treatment effect of trastuzumab for people with brain metastases. We therefore consider that the clinical expert modifier provides a reasonable alternative scenario.

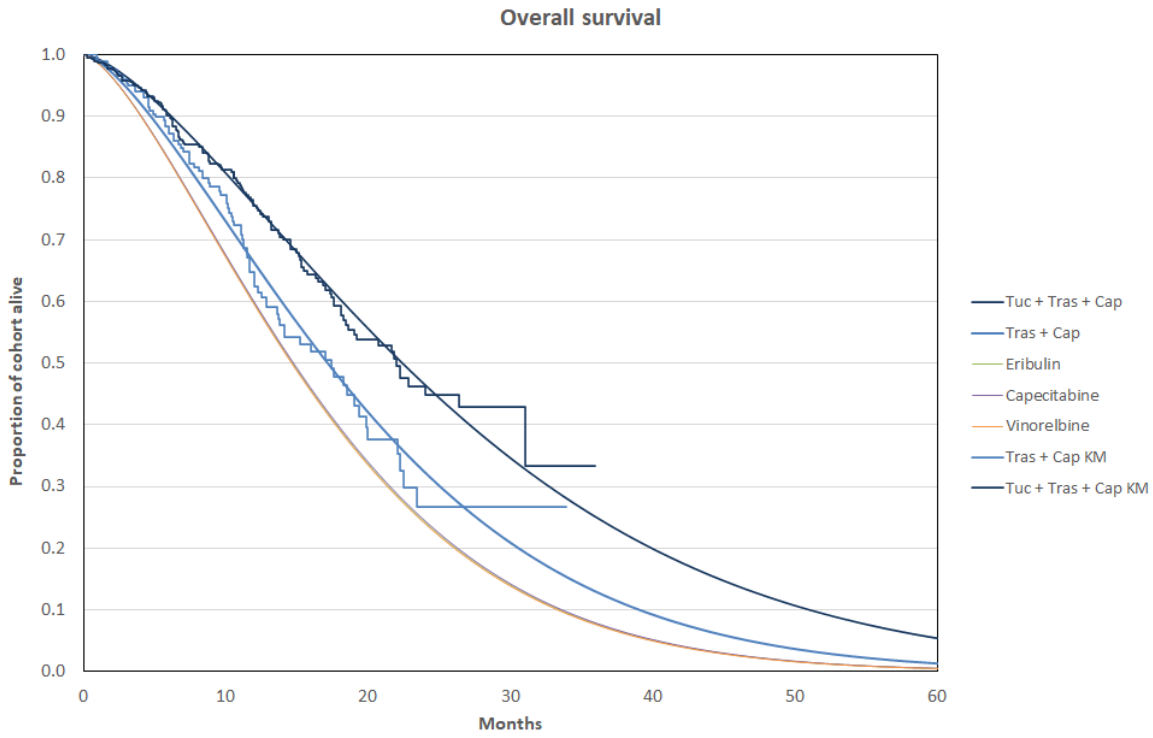


Figure 1 Modelled OS with no treatment effect modifier for brain metastases

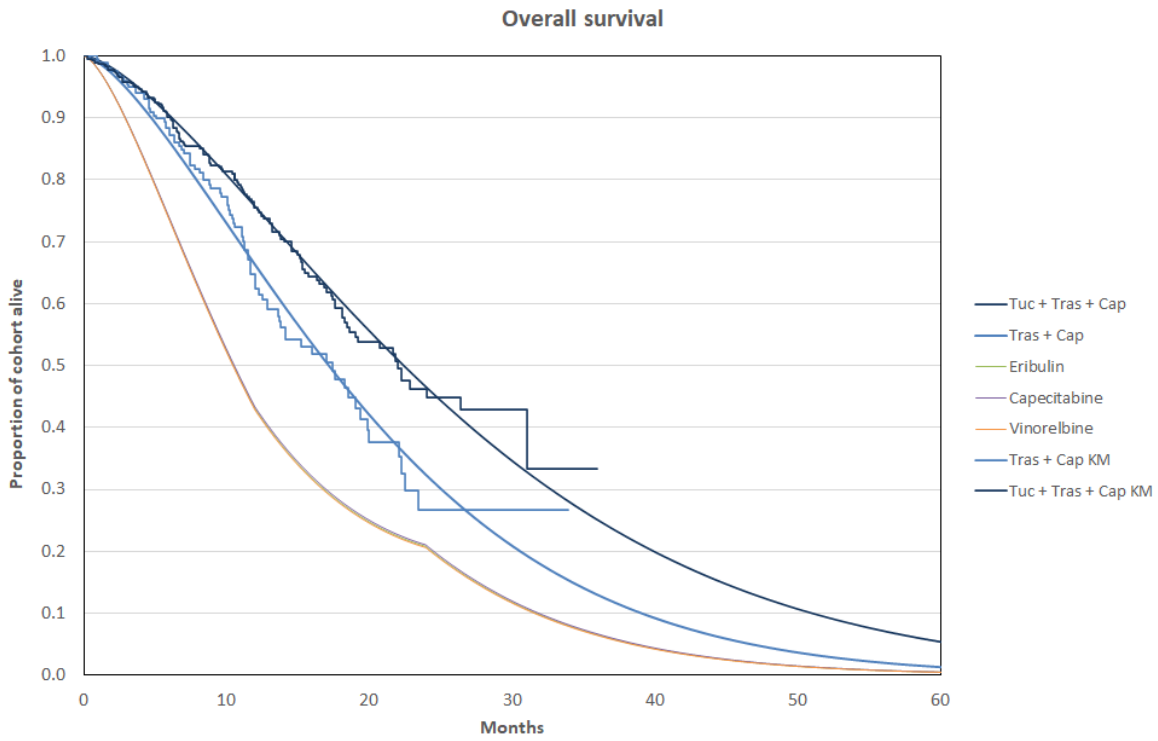


Figure 2 Modelled OS with treatment effect modifier based on clinical opinion

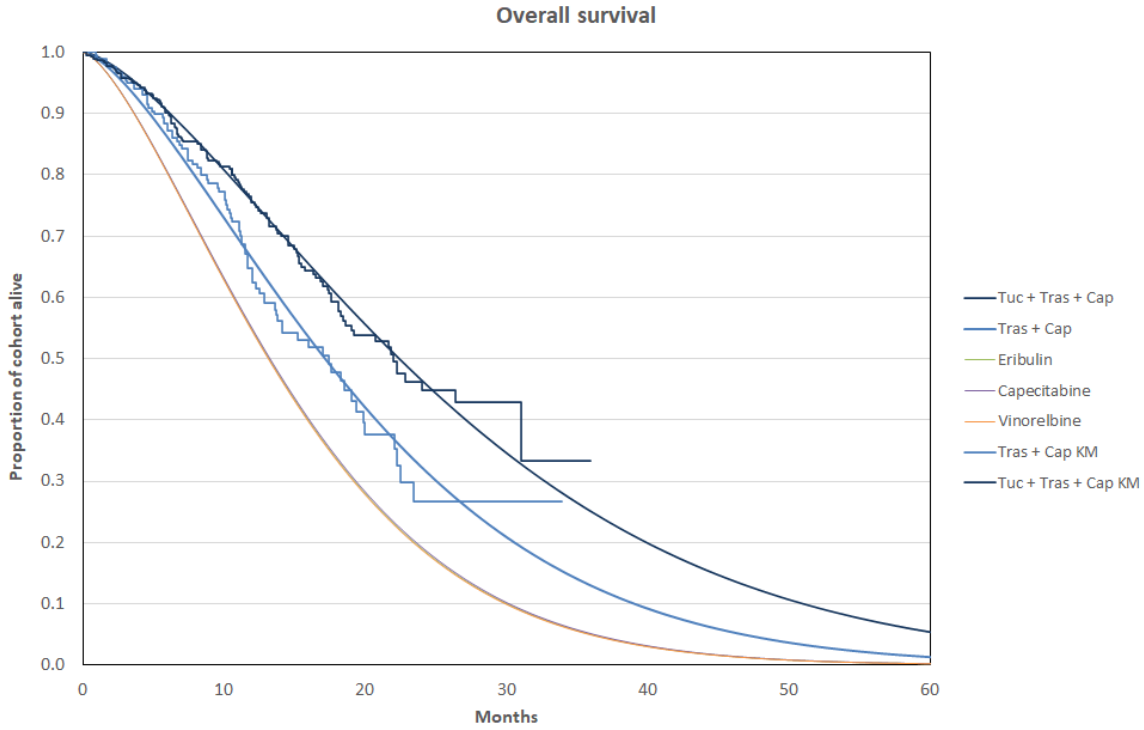


Figure 3 Modelled OS with treatment effect modifier estimated from HER2CLIMB

4.2 Subgroup analysis for people with and without brain metastases

Survival extrapolations for people with brain metastases have a poor fit to the trial data (see company ACD response Figure 2). We also could not replicate the company's reported results for this subgroup – further information on how to run this subgroup would be helpful. The lack of survival extrapolations for the subgroup without brain metastases is also problematic. We note that the reported cost-effectiveness results for these subgroups do not take account of the cost of testing for brain metastases.

4.3 Utility estimates

The company use different pre-progression utilities for the tucatinib arm (0.762, based on EQ-5D data from the HER2CLIMB trial) and for comparators (0.706 for eribulin and 0.701 for capecitabine and vinorelbine, as used in TA432). They also assume different post-progression utilities for tucatinib (0.698, based on HER2CLIMB EQ-5D data) and comparators (0.588, based on committee preferences in TA432). In response to the committee's request for justification of the difference in post-progression utilities, the company report evidence from HER2CLIMB and a retrospective study that HER2 targeted therapy (trastuzumab and the tucatinib and trastuzumab combination) appear to reduce or mitigate the effects of brain metastases, and that evidence from registry data and clinical expert opinion that brain metastases have an additional impact on patients' quality of life. This is a reasonable argument, although we do still have concerns over the very large difference in post-progression utilities for the tucatinib arm and the comparators, based on different evidence sources. We present results for scenarios with equal post-progression utilities (0.588) as well as response-based pre-progression utilities, as used in TA704.

4.4 Cost of subcutaneous and intravenous trastuzumab

In their base case, the company assumes that trastuzumab is delivered intravenously. They present scenarios with costs for [redacted] and [redacted] of trastuzumab delivered subcutaneously. We present analyses for both routes of administration, as requested in the ACD.

5 ERG preferred analysis and scenarios

The ERG preferred analysis is therefore the same as the company's revised base case, except for the use of the treatment effect modifier for brain metastases based estimated from HER2CLIMB data (rather than clinical opinion as in the company's base case).

Table 9 ERG preferred analysis and scenarios

Technology	Total costs (£)	Total QALYs	Pairwise ICER	Incremental ICER
ERG preferred analysis (including treatment effect modifier from HER2CLIMB)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Treatment effect modifier for brain metastases based on clinical opinion				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Same post-progression utilities (0.588 for all treatments)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Response based utilities based on TA704 (pre-progression 0.725 capecitabine, 0.717 vinorelbine, 0.713 eribulin, 0.735 tucatinib; post-progression for all treatments 0.588)				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Subcutaneous trastuzumab				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Source: ERG analysis using company model submitted with ACD response (dated 16 Nov 2021)				

We report results for the company's revised base case other scenarios reported above with all available PAS and CMU NHS price discounts for concurrent, comparator and subsequent treatments in a separate confidential addendum.