NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

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

1 Recommendations

1.1 Tucatinib with trastuzumab and capecitabine is recommended, within its marketing authorisation, as an option for treating HER2-positive locally advanced or metastatic breast cancer in adults after 2 or more anti-HER2 treatment therapies only if the company provides tucatinib according to the commercial arrangement (see section 2).

Why the committee made these recommendations

Current treatment for HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 regimens is chemotherapy. Tucatinib with trastuzumab and capecitabine (tucatinib combination) is another anti-HER2 therapy that could be used after 2 or more anti-HER2 regimens. Trastuzumab can be given subcutaneously or intravenously. The subcutaneous injection is easier to administer but costs more than the intravenous infusion.

Clinical trial evidence shows that tucatinib combination increases the time people have before their cancer gets worse and how long they live compared with trastuzumab with capecitabine. But trastuzumab with capecitabine is not standard care in the NHS. Comparing tucatinib combination indirectly with chemotherapy suggests it may increase the time people have before their cancer gets worse and how long they live. It is likely that tucatinib combination improves people's quality of life before and after their cancer gets worse compared with chemotherapy.

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The economic model does not take into account all of the benefits of tucatinib combination, particularly for people with brain metastases. Taking this into account, the cost-effectiveness estimates for tucatinib combination are likely to be within what NICE normally considers an acceptable use of NHS resources. So, tucatinib combination is recommended.

2 Information about tucatinib

Marketing authorisation indication

2.1 Tucatinib (TUKYSA, Seagen UK) has a marketing authorisation for use 'in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in tucatinib's summary of product characteristics.

Price

2.3 The list price is £5,636.84 per 84-pack of 150 mg film-coated tablets (excluding VAT; BNF online accessed February 2022). The average cost of a course of combination treatment at list prices is £7,016.91 for the loading dose and £6,677.14 for the following cycles (company submission).

The company has a commercial arrangement (simple discount patient access scheme). This makes tucatinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Seagen UK, a review of this submission by the evidence review group (ERG), responses from stakeholders and comments on the first appraisal consultation document. See the committee papers for full details of the evidence.

The committee discussed the following issues.

Clinical need and treatment pathway

HER2-positive breast cancer has a high disease burden

3.1 Some breast cancer cells have higher levels of a protein called HER2 on their surface, which stimulates them to grow. This is known as HER2-positive breast cancer. Around 1 in 5 breast cancers are HER2-positive. Patient experts explained that being diagnosed with locally advanced or metastatic breast cancer is extremely difficult for people and their family and friends. It can cause considerable anxiety and fear, with the uncertainty being the hardest part for many people. These feelings can negatively affect mental health. People with metastatic breast cancer must organise their lives around hospital appointments, which constrains their everyday activities. Brain metastases may develop in up to half of people with HER2-positive cancer, which negatively affects people's prognosis and quality of life. The patient experts explained they were not able to drive or work, and lost their independence. The committee concluded that there is a high disease burden for people with HER2-positive metastatic breast cancer, especially for those with brain metastases.

There is a need for anti-HER2 therapies after second-line treatment, especially for people with brain metastases

3.2 There is no cure for metastatic breast cancer. 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. First-line treatment of HER2-positive metastatic breast cancer includes the anti-HER2 therapies pertuzumab with trastuzumab and docetaxel, or trastuzumab with paclitaxel (see NICE's technology appraisal guidance on pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer and NICE's technology appraisal guidance on trastuzumab for treating advanced breast cancer). Trastuzumab emtansine is an anti-HER2 therapy used at second line (see NICE's technology appraisal guidance on trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane; from now referred to as TA458). Clinical experts explained that HER2-positive metastatic breast cancer that has progressed after 2 or more anti-HER2 regimens has a high symptom burden and is resistant to previous lines of therapy. The committee noted that, although some NHS trusts may offer third-line anti-HER2 therapy, it is not available across the NHS and cannot be considered standard care. Trastuzumab deruxtecan is only available through the Cancer Drugs Fund so is not considered standard care (see NICE's technology appraisal guidance on trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies; from now referred to as TA704). 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 (see NICE's clinical guideline on advanced breast cancer: diagnosis and management [from now referred to as CG81] and NICE's technology appraisal guidance on eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens, from now referred to as TA423). Brain metastases can be treated with stereotactic radiosurgery or radiotherapy (see NICE's clinical guideline on brain tumours and metastases). The clinical experts explained that there is a limit to the number of these treatments, and most people cannot have more than 2 courses of radiotherapy because of its neurological toxicity. Currently there are no

further treatment options that target brain metastases because most chemotherapy treatments have very limited capacity to cross from the blood into the brain. The committee concluded that there is a high unmet need for anti-HER2 treatment after second-line anti-HER2 treatment. This is particularly important for the significant proportion of people who have brain metastases, because tucatinib can cross an intact blood-brain barrier and treat brain metastases.

The relevant comparators are capecitabine, vinorelbine and eribulin

3.3 In its initial submission, the company used eribulin as its base-case comparator. It stated that eribulin is the only third-line treatment approved by NICE for HER2-positive locally advanced or metastatic breast cancer and has clinical equivalence to capecitabine and vinorelbine. The ERG noted that CG81 recommends that people may also have treatment with other non-HER2-targeted chemotherapies such as capecitabine or vinorelbine. The clinical experts confirmed that current NHS third-line standard care is non-targeted chemotherapy, including capecitabine, vinorelbine or eribulin. The clinical experts explained that although some people have trastuzumab with capecitabine, there is wide regional variation in its availability. As it is not available to all patients in the NHS, the committee agreed that trastuzumab with capecitabine is not a relevant comparator. The committee concluded that the relevant comparators for tucatinib with trastuzumab and capecitabine (from now referred to as tucatinib combination) are capecitabine, vinorelbine and eribulin.

Clinical evidence

The HER2CLIMB population is generalisable to UK clinical practice

3.4 The clinical evidence was based on HER2CLIMB, a randomised, double-blind, placebo controlled, active comparator trial for HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab, pertuzumab and trastuzumab emtansine. Approximately 50% of people in HER2CLIMB had brain metastases. The clinical experts

explained that HER2CLIMB represents patients in the NHS in terms of characteristics and previous treatment, including the proportion of people who will go on to develop brain metastases. The committee concluded that the population in HER2CLIMB was generalisable to the eligible population in clinical practice in the UK.

Tucatinib combination is more effective than trastuzumab with capecitabine, but this comparison does not reflect NHS practice

3.5 HER2CLIMB assessed tucatinib combination compared with placebo plus trastuzumab and capecitabine (from now referred to as placebo combination). However, trastuzumab with capecitabine is not used in NHS practice (see section 3.3). People who had tucatinib combination had a median progression-free survival of 7.8 months compared with 5.6 months for people who had placebo combination. The hazard ratio for disease progression or death was 0.54 (95% confidence interval [CI], 0.42 to 0.71; p<0.001). People who had tucatinib combination had a median overall survival of 21.9 months compared with 17.4 months for people who had placebo combination. The hazard ratio for death was 0.66 (95% CI, 0.50 to 0.88; p=0.005). 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 pass through an intact blood-brain barrier. The clinical experts also explained that the clinical data in the company submission was supported by some longer follow-up data from the trial, which was 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. The committee also noted that the impact on brain metastases is important because brain metastases are associated with a poor prognosis and reduced quality of life (see sections 3.1 and 3.2).

Indirect treatment comparison

Results of the network meta-analysis are uncertain because of heterogeneity across trials

3.6 There was no head-to-head evidence comparing tucatinib combination against the relevant comparators, capecitabine, vinorelbine or eribulin (see section 3.3). Therefore, the company did a network meta-analysis to allow for an indirect treatment comparison. The results showed increased progression-free and overall survival for tucatinib combination compared with other treatments (the exact numbers are academic in confidence and cannot be reported here). However, the ERG explained that these results are uncertain because there were differences between patient populations in the trials included. The HER2CLIMB trial included people with and without brain metastases. Approximately 29% had active brain metastases (that is, either treated and progressing, or untreated) and 19% had stable brain metastases. 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 or was lower than in HER2CLIMB (see sections 3.8 and 3.9 for further discussion of brain metastases). Other differences between patient populations were the number of previous therapies, prior anti-HER2 treatment, HER2 positivity status, Eastern Cooperative Oncology Group performance status and family background. The committee concluded that tucatinib is likely to improve clinical outcomes relative to eribulin, capecitabine and vinorelbine, but the size of the effect is uncertain. This is because there was clinical heterogeneity in several areas, particularly that people with active brain metastases were included in the HER2CLIMB trial but not in the other trials.

A random effects model is appropriate because of heterogeneity in the network, but does not account for systematic differences between trials

3.7 In its initial submission, the company used a fixed effects model for the network meta-analysis. This was because random effects modelling had limitations such as convergence issues and a higher degree of uncertainty. The ERG used a random effects model, explaining that it better accounted for heterogeneity in the network meta-analysis and is preferred to fixed effects modelling, despite its limitations. The company agreed with the ERG's approach in its response to consultation and updated its base case accordingly. The committee noted that the results from using the 2 methods were similar, although the random effects model gave wider confidence intervals. The committee concluded that the random effects methodology was more appropriate because of heterogeneity in the network, and acknowledged it was used by the company in its updated base case. However, it noted that using a random effects model did not account for any systematic bias in the network related to differences in the proportions of people with brain metastases.

Network meta-analysis results should be adjusted for a treatment-modifying effect of brain metastases

3.8 The clinical experts explained that people with brain metastases have a poorer prognosis than those without. The committee noted that an anchored indirect treatment comparison can account for differences in prognostic factors between trials, but only if they have no effect on relative treatment outcomes (that is, they are not treatment effect modifiers). The clinical experts explained that tucatinib is the only treatment shown to cross the blood-brain barrier with demonstrated activity in brain metastases. But they highlighted that the impact of other treatment options on brain metastases is complex. Although comparator drugs generally cannot cross an intact blood-brain barrier, small amounts can cross when the barrier is compromised, for example, after whole-brain radiation therapy. The clinical experts also noted that good control of

disease and metastases in other parts of the body may delay the time to developing brain metastases or them reoccurring. This means that treatments that are more effective in controlling other metastases, such as trastuzumab with capecitabine, are also believed to be more effective for people with brain metastases compared with single-agent non-targeted chemotherapy. They also noted that lapatinib with capecitabine (not a relevant comparator but included in the network) was shown to have at least some activity for brain metastases. The committee understood that the network meta-analysis results may be biased because the presence of brain metastases may affect how well comparator treatments work for people with breast cancer. That is, had people with active brain metastases been included in the comparator trials, the outcomes would be expected to be worse. In its response to consultation, the company presented the results of a literature review suggesting that the trastuzumab component alone in both arms of the HER2CLIMB trial may give a survival benefit in people with brain metastases compared with no treatment or non-HER2-targeted therapy. Therefore, the non-tucatinib control arm in the trial may itself have had better outcomes than the 3 individual non-HER2-targeted therapies considered as comparators in this appraisal. However, the company acknowledged this represents a naive comparison between different populations in different studies. The committee concluded that the network meta-analysis results could be adjusted for a treatment-modifying effect of brain metastases. It noted that this analysis is still likely to be highly uncertain, but nevertheless useful for decision making (see section 3.9).

Adjustment based on HER2CLIMB data is preferred, but may be conservative

3.9 The company used 2 approaches to estimate how much worse outcomes would have been if the same proportion of people with brain metastases as in HER2CLIMB had been included in the comparator monotherapy trials.

- In its preferred approach, the company asked 10 clinicians to estimate overall survival at 1, 2, 3 and 5 years for single-agent chemotherapies if their respective trials had included the same proportion of people with brain metastases as HER2CLIMB. These estimates were lower than predicted by the ERG model (see section 3.11). Comparing the 2 sets of estimates, the company calculated by how much the network meta-analysis results would need to be adjusted to align with the survival predictions given by clinicians.
- In the alternative approach, the company used individual patient data from HER2CLIMB to estimate a treatment-modifying effect of brain metastases.

The ERG noted that the company's preferred approach (using clinician estimates) resulted in an upward kink in the survival estimates at year 2, which was unrealistic. It preferred the alternative, data-driven approach, using HER2CLIMB data. The company explained that the upward kink in survival estimates was because it relied on clinician predictions at specific timepoints, without smoothing out between these timepoints. However, it noted that if it had done so, the cost-effectiveness estimates would decrease slightly. The company explained that the approach using the HER2CLIMB data did not capture any additional treatment effect from HER2-targeted therapy (trastuzumab) in the placebo arm of the trial. The ERG recognised that its approach may be conservative. The committee noted that neither approach was robust. There was uncertainty about how much the comparator arms should be adjusted to account for the discrepancy in the proportion of people with brain metastases. However, despite its limitations, the committee's preference was for the HER2CLIMB data-driven approach, over the clinician's estimations. It concluded that this approach did not account for any benefit from trastuzumab and may be conservative, and acknowledged that the true cost-effectiveness estimates are likely to be lower than those estimated using the data-driven approach.

Cost-effectiveness evidence

The company's economic model is suitable for decision making

3.10 The company submitted a partitioned survival model to estimate the cost effectiveness of tucatinib combination compared with eribulin, capecitabine and vinorelbine. It had 3 health states: progression-free, progressed, and death. The committee considered that the partitioned survival model is a standard approach to estimate the cost effectiveness of cancer drugs and is suitable for decision making.

Directly extrapolating HER2CLIMB data is most appropriate for estimating progression-free and overall survival for tucatinib and the comparators

3.11 In its initial submission, 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. It used fractional polynomial curves to extrapolate survival data for the reference arm. It then used hazard ratios from its network meta-analysis to estimate survival for other treatments. The ERG explained that the company approach resulted in estimated survival data for tucatinib combination that had a poor visual fit to data from the HER2CLIMB trial, particularly for overall survival. Instead, it preferred to fit survival curves directly to the HER2CLIMB data using trastuzumab with capecitabine as the reference treatment. It chose the Weibull curve because it provided better visual fit and the best statistical fit. The company explained the ERG's approach created bias against tucatinib because HER2CLIMB included more people with brain metastases than the comparator trials (see section 3.6), and because these people have poorer outcomes than people without brain metastases (see section 3.8). The committee noted that because the HER2CLIMB population was representative of that in clinical practice (see

section 3.4), while the populations of other trials were not, it should be used to model survival that would be expected in NHS practice. It also noted that lapatinib with capecitabine is not a relevant comparator in this appraisal (see section 3.3). The committee agreed that the curves fitted to the HER2CLIMB data better fitted the outcomes observed in the trial and more closely matched the clinical expert estimates of progression-free survival and overall survival. However, it acknowledged that this did not address the underlying issues with the network meta-analysis (see sections 3.6 to 3.9). In its response to consultation, the company agreed with the ERG approach. It updated its base case to directly extrapolate HER2CLIMB data for progression-free and overall survival for trastuzumab with capecitabine. It applied hazard ratios from its network meta-analysis, adjusted for the treatment-modifying effect of brain metastases, to estimate survival for the other treatments. The committee acknowledged that the revised company approach aligned with its preference to directly extrapolate survival data from HER2CLIMB trial.

The subgroup analyses have methodological limitations and are not appropriate for decision making

3.12 The company did not model the cost effectiveness of tucatinib combination relative to its comparators separately for people with and without brain metastases because there was limited evidence on the efficacy of comparators in people with brain metastases. The ERG agreed that there was a lack of evidence for the comparators in people with brain metastases. The committee noted that the subgroup of people without brain metastases from HER2CLIMB better corresponded to the patient populations in the other trials included in the network meta-analysis (see section 3.6). It considered that modelling survival for tucatinib combination and its comparators separately for people with and without brain metastases could help to better understand the uncertainty in the cost effectiveness of tucatinib. This is because the presence of brain metastases may be a prognostic factor and have a treatment-modifying

effect. So the shape and extrapolation of survival curves would be likely to differ for people with and without brain metastases (see sections 3.6 to 3.9). In response to consultation, the company did a subgroup analysis for people with brain metastases, by directly extrapolating progression-free and overall survival data from the corresponding HER2CLIMB subgroup. It stated that this analysis showed that tucatinib combination is more cost effective in people with brain metastases than in those without brain metastases. However, it cautioned that the HER2CLIMB trial was not powered to show a significant benefit in overall survival in subgroups. The ERG noted that the company did not provide sufficient information on how the analysis was done and was unable to replicate the company's results. In particular, the company did not justify its selection of survival extrapolation curves, nor did it explore alternative survival extrapolations, so it was unclear if the method it chose was appropriate. The ERG ran exploratory analyses using the same assumptions as the company, and the results were generally aligned with the company estimates. The company further stated that it was not able to do subgroup analyses for people without brain metastases because of time constraints. Instead, it used a weighted average approach to estimate cost effectiveness in this subgroup. The ERG explained these estimates were not accurate because the survival curves were likely to differ between the 2 subgroups, which was not explored. It also explained that incremental cost-effectiveness estimates (ICERs) are ratios and cannot be directly used to estimate weighted averages. Instead, weighted averages of the total costs and total quality-adjusted life years would need to be estimated and used to calculate the ICER for the non-brain-metastases subgroup. It also noted that the results did not account for the cost of screening people for brain metastases. The committee concluded that the subgroup analyses had methodological limitations and were not described in sufficient detail for adequate scrutiny. Therefore, it concluded that the subgroup analyses were not appropriate for decision making.

Differences in health state utilities before progression are plausible, but the exact values are uncertain

3.13 For tucatinib combination, the company used EQ-5D-5L health-related quality of life data collected in HER2CLIMB, mapped to the EQ-5D-3L with UK preference weighting. Utilities for the comparator therapies were from TA423. This resulted in higher utility values for tucatinib combination compared with comparators in both pre- and post-progression health states. The company explained that tucatinib has better efficacy and safety profiles than eribulin or vinorelbine. It noted that in TA423, eribulin had higher pre-progression utilities than other single-agent chemotherapies. The ERG explained the company approach was inappropriate because the differences in utilities between tucatinib and comparators were not based on comparative evidence. It preferred to use the same utility values for all treatments for each health state, and to derive them all from HER2CLIMB data. The ERG noted that in the HER2CLIMB trial, there was no difference in utility values between the 2 trial arms. The clinical experts explained that the safety profile of tucatinib is good, but it is difficult to separate the effects on quality of life of disease progression and toxicity. The clinical experts also noted that disease control could support different pre-progression utility values because treatments offer different levels of overall response rate. The committee concluded that different pre-progression utility values are plausible, but noted the values used by the company were not evidence based, so were uncertain.

Differences in health state utilities after progression are plausible, but their extent is probably overestimated

3.14 In addition to the limitations of the company's approach highlighted in section 3.13, the ERG explained that the utility value used by the company was not accepted by the TA423 committee because it was too low. In response to consultation, the company corrected its post-progression utility value to align with the value the committee agreed on in

TA423. It also provided a literature review and results of a survey with clinicians to support differences in post-progression utilities between tucatinib combination, HER2-directed therapies, and standard single-agent chemotherapy. The ERG explained that the company's justification was reasonable, but it still had concerns about using different sources for post-progression utilities for different treatments. It noted that this resulted in large differences in post-progression utilities for tucatinib combination and the comparators, which may have overestimated the benefit of tucatinib combination. The clinical experts explained that:

- Brain metastases affect people's quality of life to a greater extent than metastases to other organs. So it is likely that if it takes longer for the disease to progress because of brain metastases, someone's quality of life after progression will be better than if the disease had progressed quickly.
- People with disease that is better controlled would have better quality of life before and after progression than those with disease that is less well controlled. This is because the decline in quality of life related to progression will start from a higher level than in people with disease that is less well controlled and with lower quality of life before progression.
- Some toxic effects of chemotherapy can be long lasting and affect a person's quality of life after progression.

The committee noted that:

- Differences in quality of life after progression between tucatinib combination and comparators were plausible. However, it noted that this difference may decrease once people's disease (and therefore quality of life) deteriorates further with time after progression on tucatinib combination.
- The toxicity of capecitabine on its own is expected to be similar or lower than the toxicity of tucatinib combination. Therefore, differences in

toxicity may not explain the large difference in utilities after disease progression between capecitabine and tucatinib combination.

- The company's approach was not methodologically robust because it used utility values from 2 different sources: the HER2CLIMB trial for tucatinib combination and TA423 for the comparators, in a 'naive comparison', that is, without adjusting for any differences between populations in these sources that might have affected the utility values. It also noted that the value from TA423 was based on the midpoint of 2 utility estimates from 2 different studies. Therefore, the results from the company's approach were uncertain.
- The company's approach may overestimate the extent of difference in post-progression utilities between tucatinib and comparators, so it may overestimate the benefit of tucatinib combination.
- The alternative approach of assuming equal post-progression utility after tucatinib and single-agent chemotherapy is most likely pessimistic.

The committee concluded that some differences in post-progression health state utilities are plausible, but uncertain. Although the ERG incorporated the company's revised utilities in its base case, the committee remained concerned that if the difference in post-progression utility was overestimated, the cost-effectiveness estimates would be slightly higher than those estimated by the company. It noted that in future it would prefer evidence-based utilities and additional scenarios to be explored.

Standard NHS practice is subcutaneous trastuzumab

3.15 In HER2CLIMB, trastuzumab (as part of tucatinib combination) was administered either intravenously or subcutaneously, as allowed for in tucatinib's summary of product characteristics. But the initial company model assumed only intravenous administration of trastuzumab. The clinical experts explained that intravenous trastuzumab is no longer standard NHS practice. The clinical and patient experts explained that

subcutaneous administration is preferred because people can self-administer, avoiding unnecessary hospital visits. The committee noted that although biosimilar intravenous trastuzumab products exist, subcutaneous trastuzumab is only available as a branded product, so is more expensive. Therefore, the choice of administration method for trastuzumab as part of tucatinib combination has considerable cost implications. Both the clinical and patient experts explained that if subcutaneous administration was not possible, they would accept intravenous administration if it meant people could have tucatinib combination. In its response to consultation, the company presented scenario analyses assuming different levels of subcutaneous trastuzumab usage. The ERG provided an additional scenario analysis assuming 100% use of subcutaneous trastuzumab. The Cancer Drugs Fund clinical lead explained that over 90% of patients have trastuzumab subcutaneously in the NHS. Some people may choose to have intravenous trastuzumab if subcutaneous administration is not appropriate for them. He also noted that chemotherapy units have capacity issues with intravenous administration. The clinical experts noted that there are additional benefits from subcutaneous administration that have not been captured in the current modelling, such as fewer hospital visits, and convenience and quality of life benefits for patients. Fewer hospital visits may also help reduce COVID-19 transmission. The committee concluded that subcutaneous trastuzumab is standard care in the NHS and could have unaccounted-for benefits for patients and service delivery.

Drug wastage should be included in the analysis

3.16 In its initial submission, the company did not include drug wastage for intravenous trastuzumab in its base case because it is packaged in multi-use vials. The ERG preferred to include this because some wastage is expected in clinical practice. It noted this has a very small effect on overall costs and the cost-effectiveness estimates. It also noted that this applied to intravenous administration only and was not relevant for analyses

assuming subcutaneous administration of trastuzumab. The company agreed with the ERG in its response to consultation and updated its base case accordingly. The committee concluded that drug wastage should be included in the analysis and acknowledged this was done appropriately by the company in its revised base case.

End of life

Tucatinib combination meets the end of life criteria

3.17 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The clinical experts and the ERG agreed that the life expectancy for people with HER2-positive locally advanced or metastatic breast cancer having third-line treatment is less than 24 months. They also agreed that the gain in life expectancy with tucatinib combination is expected to be greater than 3 months. The committee also noted that the end of life criteria were accepted in TA423 and TA704 in a third-line setting, and in TA458 in a second-line setting. The committee concluded that tucatinib meets the end of life criteria.

Cost-effectiveness results

Tucatinib with trastuzumab and capecitabine is likely to be cost effective

3.18 Because of confidential commercial arrangements for tucatinib, trastuzumab, eribulin and post-progression therapies, the ICERs cannot be reported here. The company addressed a number of the committee's concerns in its response to consultation, including:

- using a random effects network meta-analysis (see section 3.7)
- exploring a treatment-modifying effect of brain metastases (see sections 3.8 and 3.9)
- extrapolating progression-free and overall survival directly from HER2CLIMB data ('within-trial' approach; see section 3.11)

- assuming different pre-progression utility values for tucatinib and its comparators (see section 3.13)
- justifying differences in post-progression utility values for tucatinib and its comparators (see section 3.14)
- adjusting utility values for ageing
- including drug wastage for trastuzumab and capecitabine (see section 3.16).

However, the committee noted that the company's updated base case was not fully aligned with its preferences and instead considered ERG scenarios in its decision making that:

- used HER2CLIMB data to derive a treatment-modifying effect for tucatinib combination (see section 3.9)
- assumed 100% subcutaneous administration of trastuzumab (see section 3.15)
- assumed different post-progression utility values for tucatinib combination or assumed the same post-progression utility values for tucatinib combination (see section 3.14).

Taking into account all of the confidential discounts, the committee concluded that, compared with chemotherapy, the cost-effectiveness estimates for tucatinib combination are likely to be within the range that NICE considers a cost-effective use of NHS resources.

Innovation

Tucatinib has a novel mechanism of action and not all of its benefits are captured in the model

3.19 The company and the clinical and patient experts considered tucatinib combination to be innovative. They explained this is because of its improved efficacy and tolerability in people with HER2-positive metastatic

breast cancer, including those with brain metastases, which are common at this stage of disease. The committee agreed that tucatinib combination has significant potential benefits. It acknowledged that not all of the potential benefits in relation to its effect on brain metastases were captured in the analyses (see section 3.9).

Conclusion

Tucatinib with trastuzumab and capecitabine is recommended for routine use

3.20 Having concluded that tucatinib combination is likely to be a cost-effective use of NHS resources, the committee recommended it for routine use.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-

date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies and the doctor responsible for their care thinks that tucatinib with trastuzumab and capecitabine is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee A
February 2022

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sarah Wilkes
Technical lead

Ewa Rupniewska
Technical adviser

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Project manager

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