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NICE National Institute for Health and Care Excellence

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

Lead team presentation

2nd appraisal committee A meeting
Chair: Jane Adam
Lead team: Rita Faria, Roger Whittaker, Richard Ballerand
ERG: Southampton Health Technology Assessments Centre (SHTAC)
Technical team: Sarah Wilkes, Ewa Rupniewska, Henry Edwards
Company: Seagen inc
December 2021

Tucatinib combination not recommended

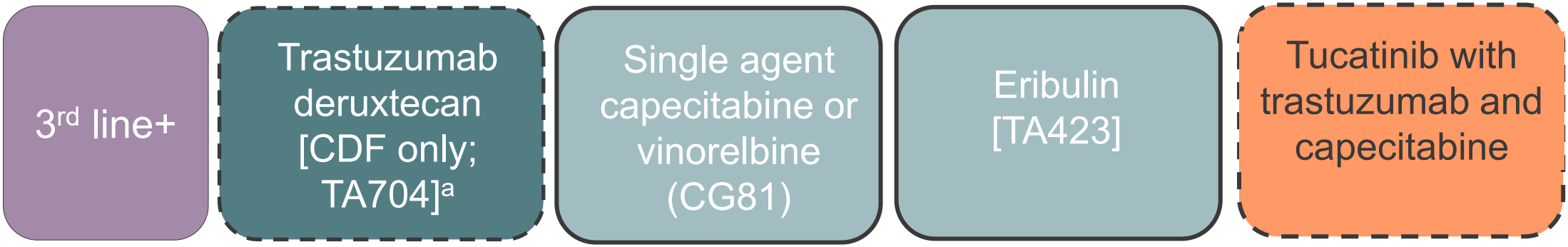
- Comparator of the key clinical trial of tucatinib combination (tucatinib with trastuzumab and capecitabine) was trastuzumab with capecitabine – not standard care in the NHS
- No direct evidence comparing tucatinib combination with eribulin, capecitabine or vinorelbine
- Indirect comparison suggests tucatinib combination increases overall and progression-free survival vs. NHS standard care, but uncertain because of differences between the trials, especially in including or not people with brain metastases
  - Outcomes in comparator trials might have been worse if they had included patients with active brain metastases as in tucatinib trial
- Cost-effectiveness estimates for tucatinib combination are higher than what NICE normally considers an acceptable use of NHS resources

Recap from 1st meeting

Tucatinib (Tukysa)

Full Marketing authorisation	Combined with trastuzumab and capecitabine for people with HER2-positive advanced breast cancer **who have received at least 2 prior anti-HER2 treatment regimens**.
Dosage and administration	• Tucatinib 300 mg orally twice daily until progression • Capecitabine 1000 mg/m^2 orally twice daily for 2 weeks of 3week cycle • Trastuzumab loading dose of 8 mg/kg intravenous infusion followed by 6 mg/kg once every 21 days **(trastuzumab can also be given subcutaneously:** 600 mg every 21 days**)**
Mechanism of action	Tucatinib: oral tyrosine kinase inhibitor selective for the kinase domain of HER2
Average list price per course of treatment	Combination cost per cycle: £7,016.91 loading dose, then £6,677.14 • Tucatinib: 150 mg film-coated tablets; pack 84 tablets £5,636.84 • Trastuzumab: £366.65 per 150mg vial infusion • Capecitabine: 500 mg film-coated tablets; pack of 120 tablets £25.02 Patient Access Scheme (PAS) for tucatinib approved by NHS England • **Company improved its PAS in response to appraisal document consultation**

Treatment pathway- HER2-positive metastatic breast cancer



Key:

- **Current practice Non-targeted**
- **CDF only – not standard care**
- Under consideration

Note: Trastuzumab + chemotherapy is prescribed by some oncologists in the third line setting but not standard care across the NHS (not available in all trusts).

[a] Trastuzumab deruxtecan not considered a comparator

CDF, cancer drugs fund

Clinical trial evidence – HER2CLIMB

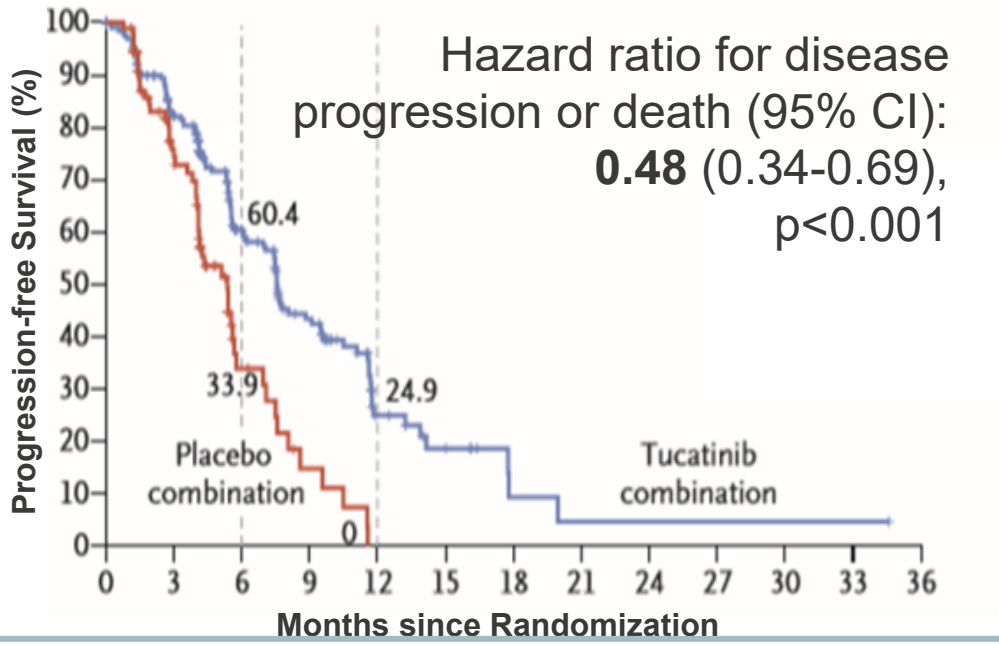
Study design	Phase II*, randomised (2:1 ratio), international, multicentre, double-blind, placebo-controlled, active-comparator trial.
Location	155 sites,15 countries (N America, Europe (including UK), Israel & Australia)
Population	Patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab and trastuzumab emtansine, **including patients with previously untreated or treated, stable or active brain metastases**
Analysis populations	**Primary endpoint population:** First 480 randomised patients **Total study population:** All 612 randomised patients **Patients with brain metastases:** All 291 randomised patients with brain metastases (48%) **Safety:** All 601 randomised who received at least 1 dose of study treatment
Intervention	Tucatinib in combination with trastuzumab and capecitabine
Comparator	Trastuzumab, capecitabine plus placebo – not a comparator in the scope
Outcomes	**Primary endpoint** • PFS per RECIST 1.1 in primary endpoint population **Key secondary endpoints** • PFS per RECIST 1.1 in patients with brain metastases at baseline • Overall survival in total population • Confirmed overall response rate in total population **Additional endpoints:** EQ-5D-5L (added at a later time point)

*HER2CLIMB originally registered as phase 2 study but sample size and trial conduct were consistent with phase 3 study; most received IV trastuzumab; ■ HER2CLIMB patients received subcutaneous trastuzumab. PFS: progression-free survival

Clinical trial evidence – HER2CLIMB

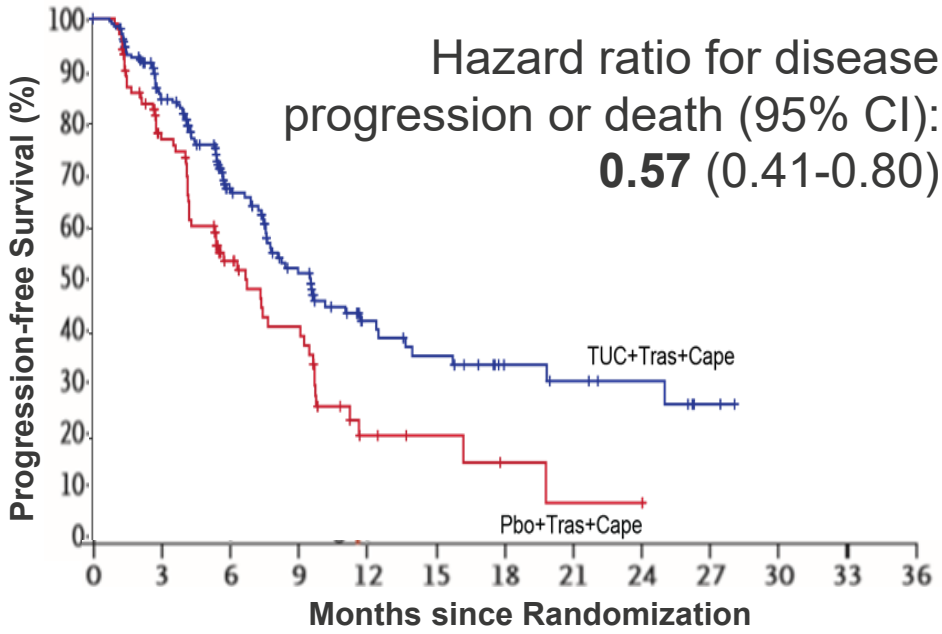
Progression-free survival (PFS) in patients with/without brain metastases

Patients with brain metastases (44-48%)



Hazard ratio for disease progression or death (95% CI): **0.48** (0.34-0.69), p<0.001

Patients without brain metastases



Hazard ratio for disease progression or death (95% CI): **0.57** (0.41-0.80)

ASCO 2020:

- 68% reduction in risk of central nervous system (CNS) PFS - median CNS PFS, tucatinib 9.9 vs placebo 4.2 months
- 42% reduction in risk of death: median overall survival, tucatinib 18.1 vs placebo 12.0 months

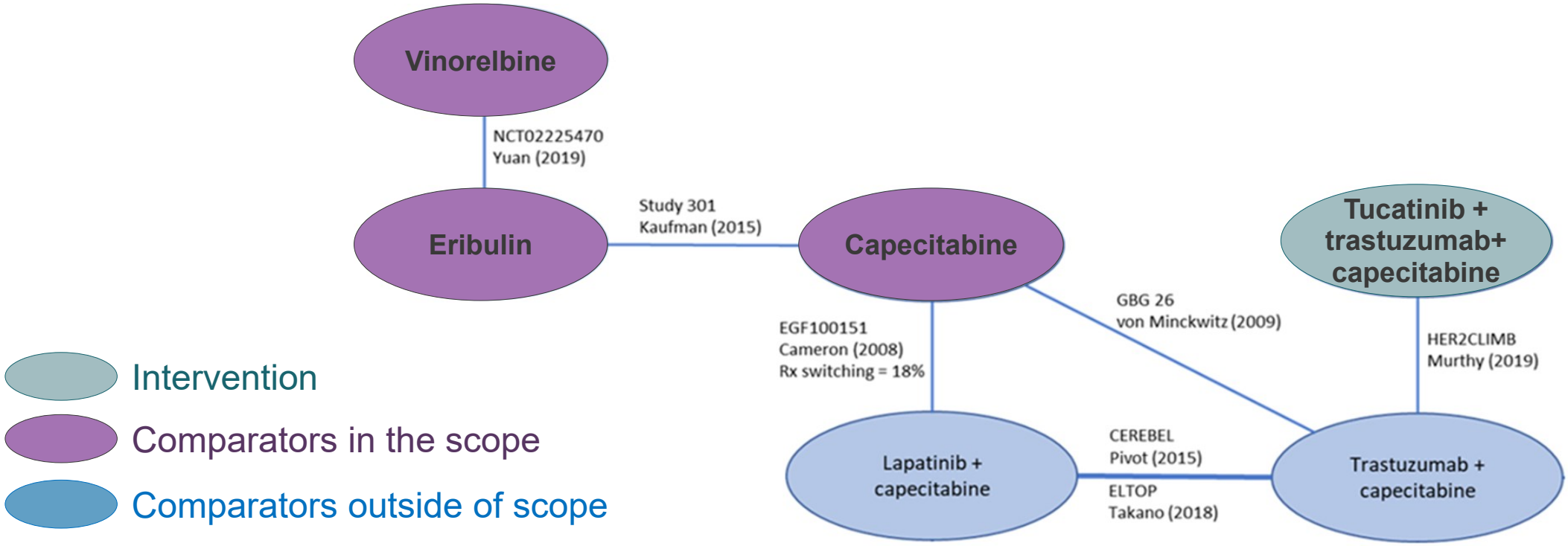
Committee's conclusions summary:

- Brain metastases are a prognostic factor: people with brain metastases have a poorer prognosis than those with metastases to other organs
- Brain metastases are likely a treatment effect modifier: Tucatinib showed some benefit in people with and without brain metastases, but those with brain metastases may not have done as well if they had had other treatments (tucatinib can cross blood-brain barrier; other treatments do not).

Source: Company submission, Figures 6 and 7. CI, confidence interval.

Network meta-analysis

- No head-to-head evidence for tucatinib in combination versus relevant comparators (eribulin, capecitabine and vinorelbine): indirect treatment comparison needed
- Network meta-analysis included 7 studies for comparison of PFS, and 6 for overall survival



Adapted from company submission, Figure 14

Studies included in the NMA differ in proportion of enrolled patients with brain metastases

	Inclusion criteria		% patients with any brain metastases at baseline
	Active brain metastases	Stable/inactive brain metastases	
HER2CLIMB	✓	✓	19% stable; 28% active
Study 301	X	✓	NR
NCT02225470	X	✓	NR
GBG 26	X	✓	1.9%[a]
EGF100151	X	✓	NR[b]
CEREBEL	X	X[c]	7%[c]
ELTOP	X	✓	15%

Committee's conclusions summary:

- Comparator trials did not include people with active brain metastases - HER2CLIMB did – and likely included lower % of people with stable brain metastases than HER2CLIMB
- Because brain metastases likely are both a prognostic factor and treatment effect modifier, indirect treatment comparison needs to be adjusted for these differences

Note: Brain metastases treated with radiotherapy and surgery, limit to the number of radiotherapy treatments

[a] Metastases to the central nervous system; [b] Reported as 5.7% in company submission, Table 10, but NICE was unable to verify this information; [c] No history or presence of CNS metastases at baseline was permitted; baseline brain MRI scans at screening to exclude asymptomatic metastases. Among first 199 patients, the central review identified abnormalities on baseline MRIs of 39 (19.6%) patients. The protocol was then amended to include an independent review of baseline and on-study brain MRI scans to confirm eligibility before random assignment.

Company's model

Model type	Partitioned survival model (progression-free, progressed, death)
Population	Adults with HER2-positive metastatic breast cancer who have received 2 or more prior anti-HER2 regimens
Intervention	Tucatinib with trastuzumab and capecitabine
Comparator	Eribulin, vinorelbine and capecitabine
Time horizon	20 years
Model cycle	7 days (no half-cycle correction applied)
Discount rates	3.5% costs/outcomes
Utility values	Tucatinib combination: HER2CLIMB trial EQ-5D-5L, mapped to EQ-5D-3L Comparators: Utilities from TA423 (eribulin)
Costs	- BNF costs 2021 - NHS Reference Costs 2018/2019 - eMIT PSSRU 2020
Perspective	NHS and Personal Social Services

eMIT: Drugs and pharmaceutical electronic market information tool; BNF: British National Formulary, PSSRU: Personal Social Services Research Unit,
Source: Company submission, Table 17, 18 and 19

Appraisal consultation document (ACD)

Conclusions and uncertainties (1)

	Committee conclusion	Discuss?	ACD
Comparators	• Regional variation in availability of trastuzumab with capecitabine but comparators are capecitabine, vinorelbine and eribulin	No	3.3
Clinical evidence	• HER2CLIMB participant characteristics generalisable to NHS, possibly also including rate of brain metastases	No	3.4
	• Tucatinib combination more effective than trastuzumab with capecitabine	No	3.5
Indirect treatment comparison	• Results of network meta-analysis uncertain because of heterogeneity across trials	No	3.6
	• Random effects model is appropriate	Updated	3.7
	• Company should further explore relative efficacy of tucatinib combination in people with and without brain metastases	Yes	3.8
Model	• Company model suitable for decision making	No	3.9

Appraisal consultation document (ACD)

Conclusions and uncertainties (2)

	Committee conclusion	Discuss?	ACD
Overall and progression-free survival modelling	• Directly extrapolating HER2CLIMB data most appropriate to estimate tucatinib progression-free and overall survival • Method did not address the underlying issues with network meta-analysis	Updated	3.10
	• Subgroup and threshold analyses could help better understand uncertainty around effectiveness of tucatinib in people with/without brain metastases	Yes	3.11
Utility values	• Differences in pre-progression health state utilities are plausible; differences after progression not justified	Yes	3.12
Trastuzumab administration	• Trastuzumab can be given subcutaneously or intravenously; both need to be considered	Yes	3.13
Drug wastage	• Drug wastage should be included in the analysis	Updated	3.14
End of life	• End of life is accepted	No	3.15
Cost effectiveness	• No analyses reflect committee's preferences	Yes	3.16
Other	• Tucatinib has a novel mechanism of action, and some benefits may not have been fully captured in the model	Yes	3.17

Consultation responses

ACD consultation responses:

Received consultation responses from:

- Company – Seagen Inc
- 2 patient organisations
  - Breast Cancer Now
  - MET UP UK
- 1 clinical expert
- Web comments (including clinicians, industry and patients) (n=7)

Patient organisations, web comments and clinical expert

- Disappointment with preliminary recommendation
- Unmet need for HER2-targeted therapies after 2 prior lines (none routinely available in the NHS; standard internationally) – especially high in people with brain metastases
- Current treatment can have severe side effects and limited treatments can cross blood brain barrier
- HER2CLIMB showed tucatinib combination clinically effective
- Network meta-analysis biased against tucatinib because it's the only trial that included people with brain metastases which is representative of real world patients

Note: Trastuzumab deruxtecan, currently available via CDF cannot be considered as a comparator in this appraisal, but trial included patients with stable brain metastases

"Tucatinib would be huge step forward for this [brain metastases] patient group"

"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"

"All NHS patients should have access to anti-HER2 beyond progression of two treatment lines"

"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"

"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"

"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"

Company ACD response summary

Issue	Committee preferences	Company revised base case	Company additional analyses	ERG critique
Indirect treatment comparison	Use random effects network meta-analysis	Yes	N/A	N/A
	Explore treatment effect modifier for presence of brain metastases	Yes	Yes (alternative approach)	Prefers alternative approach
	Do threshold analyses around relative efficacy of tucatinib combination	N/A	Yes	Some issues
Overall and progression-free survival modelling	Extrapolate progression-free and overall survival directly from HER2CLIMB data ('within-trial' approach)	Yes	N/A	N/A
	Explore subgroup analyses for people with/without brain metastases	N/A	Yes	Some issues
Utilities	Justify differences in post-progression utilities	Yes	Yes (alternative approach)	Some concerns
	Adjust utilities for age	Yes	N/A	N/A
Trastuzumab administration	Include drug wastage for trastuzumab and capecitabine	Yes	N/A	N/A
	Consider both subcutaneous and intravenous administration	No	Yes	Additional scenario

Note: Company also adjusted approach to modelling subsequent treatments to align with ERG-preferred approach and improved confidential discount for tucatinib

Indirect treatment comparison: brain metastases as treatment effect modifier

Indirect treatment comparison

Company explores likely efficacy in comparator trials if they had included people with brain metastases

Committee's conclusions:

- Results of network meta-analysis are uncertain because of heterogeneity across trials → company should explore relative efficacy of tucatinib combination in people with/without brain metastases

Company:

- Review of literature → historic real-world evidence shows survival benefit of anti-HER2 therapies in patients with brain metastases compared with no treatment or non-HER2 targeted therapy (HR, 0.25 to 0.73)[a] *Note: the company did not report survival benefit of HER2 therapies in corresponding group of people without brain metastases → unclear if relative benefit of HER2 would be the same or lower than in people without brain metastases*
- 2 approaches to estimate treatment effect modifier due to brain metastases:
  1. Survey with 10 clinicians → estimated overall survival for single-agent chemotherapy if trials included same % of people with brain metastases as HER2CLIMB→ **company base case**
  2. HER2CLIMB → modifier estimated from brain metastases subgroup → **company scenario**

[a]Breast cancer Network Registry - anti-HER2 treatment after brain metastases diagnosis median OS 17.1 months (95% CI: 14.4-19.5) vs 7.2 months without treatment (95% CI: 5.8-8.7; p < 0.0001); RegistHER - trastuzumab after central nervous system diagnosis (n = 258), median survival 17.5 months, compared to 3.7 months for those did not receive trastuzumab (n = 119); HR 0.25 (95% CI: 0.20-0.33, <0.001); Retrospective analysis in 6 Asian countries; median OS of 18.5 months (95% CI: 12.9-21.8) vs 5.7 months (95% CI: 4.2-8.9), for people 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)

Approach based on clinician's survival estimates

Company preferred; clinicians expect lower overall survival with single-agent chemotherapy than predicted by ERG model

% alive	1 year	2 year	3 year	5 year	
NICE technical engagement: clinical expert estimates for non-HER2 therapy					
1 expert	<50%	<20%	-	0%	
Clinician survey: overall survival estimates for single agent chemotherapy					
Mean estimate	43%	20%	6%	1%	←1.38 life-years[a]
Lower CI	36%	17%	5%	0%	
Upper CI	50%	23%	8%	1%	
Overall survival estimates predicted by ERG model					
Capecitabine	60%	24%	8%	0%	
Vinorelbine	62%	27%	9%	1%	
Eribulin	61%	26%	9%	1%	
Average of 3 agents	61%	26%	9%	1%	←1.77 life-years[a]
Hazard ratios (HRs), expert mean estimate versus ERG model prediction (average of 3 agents)					
Mean HR (upper CI, lower CI)	1.64 (1.43, 1.99)	1.11 (1.02, 1.22)	1.07 (0.99, 1.17)	0.93[b] (0.87, 1,02)	

Company base case applied these HRs to ERG's survival curve to model survival for single-agent chemotherapies

ERG:

- Overall survival based on clinical opinion has unrealistic kink at 2 years
  - Treatment effect modifier from HER2CLIMB more plausible

[a]Mean undiscounted life years predicated by the model; [b]Set to an HR of 1 in the model at this timepoint given ≤1% of patients alive in expert and ERG estimates. Source: Company ACD response, Table 2

Approach based on HER2CLIMB data

ERG preferred; applying treatment effect modifier improves relative efficacy of tucatinib vs. single-agent chemotherapy

Relative effect derived from people with/without brain metastases enrolled in HER2CLIMB. The approach, briefly, was to:

- Derive interaction term (treatment x presence of brain metastases) by fitting Cox proportional hazards model to intent-to-treat patient-level data from HER2CLIMB
- Adjust each hazard ratio from network meta-analysis using this interaction term and proportion of people with brain metastases from HER2CLIMB (48%)
- Carry out a cost-effectiveness analysis applying revised hazard ratios to trastuzumab-capecitabine baseline survival curves.

Company: approach does not capture additional treatment effect modification from HER2-targeted therapy

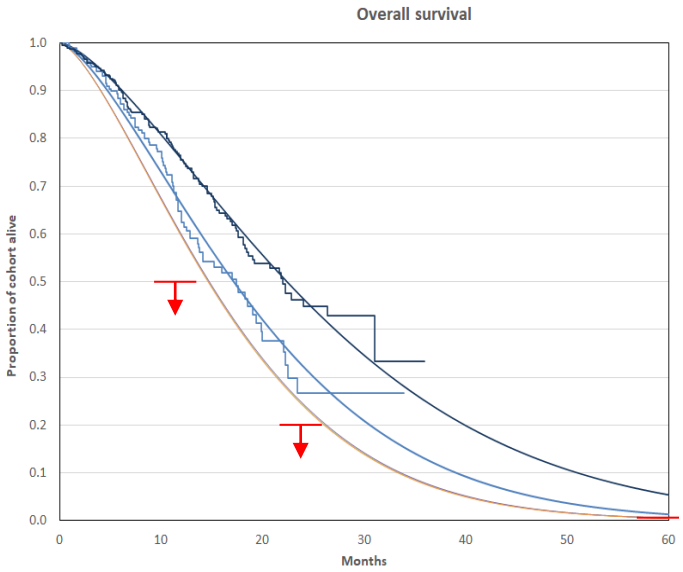
ERG:

- Recognised this approach may overestimate survival with single agent comparators if trastuzumab relatively more effective in people with brain metastases than those without, compared with single agent chemotherapy

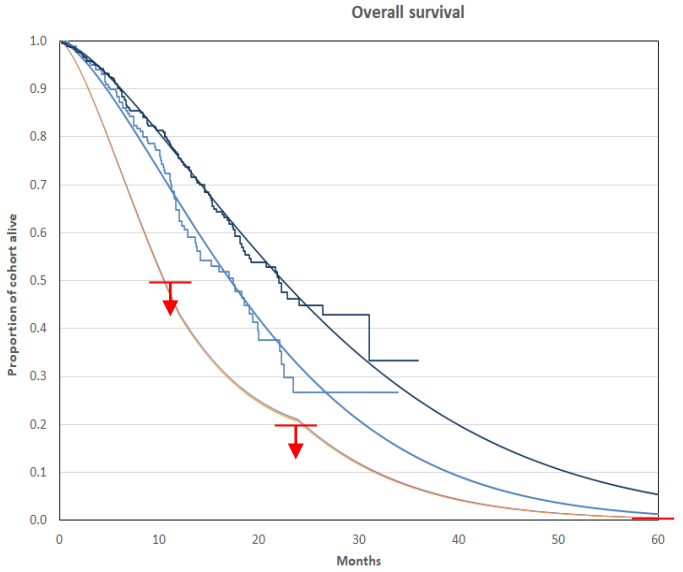
Source: ERG critique of company ACD response, table 3

Overall survival using different approaches

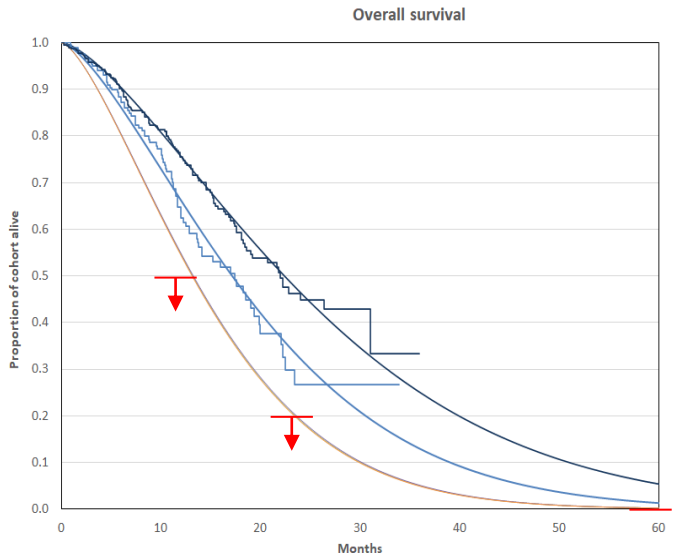
Original ERG approach: no modifier



Modifier based on clinical opinion



Modifier based on HER2CLIMB



- Tucatinib combination (fitted / Kaplan-Meier)
- Trastuzumab + capecitabine (fitted / Kaplan-Meier)
- Eribulin
- Capecitabine
- Vinorelbine
- Clinical expert estimates for non-HER2 therapies (1 year: <50%; 2 years: <20%; 5 years: 0%)

◉ *Which approach is most plausible?*

Source: ERG critique of company ACD response, Figure 1, Figure 2 and Figure 3

Intravenous versus subcutaneous trastuzumab

Trastuzumab administration

Company provided scenario analyses for subcutaneous treatment

Committee's conclusions:
- Trastuzumab can be given subcutaneously (SC) or intravenously (IV)
- Both administration routes need to be considered

Company:
- Agrees that SC trastuzumab used in NHS practice - unclear what proportion
- Trastuzumab, IV and SC, is not equally available across the NHS - therefore should not be a factor in decision making. Clinicians choose the route of administration
- Provided 2 scenario analyses:
  - Reflect the usage of SC trastuzumab in the HER2CLIMB study (n=[redacted])
  - Estimate of the upper end of usage of SC within clinical practice (note: unclear how this was calculated)

ERG:
- Provides scenario assuming 100% subcutaneous trastuzumab use

◉ *Is subcutaneous trastuzumab used in NHS practice?*

IV: intravenous; SC; subcutaneous

Post-progression utility values

Post-progression utilities (1)

Committee's conclusions:

- Different pre-progression utilities plausible - exact values not evidence based and uncertain
- Large post-progression utility differences not plausible, more evidence needed to justify difference

Company: Literature review and survey with clinicians support different post-progression utilities due to tucatinib's impact on brain metastases, objective response rate (ORR) and toxicity

Literature review and survey with 10 clinicians:

People with **brain metastases** have worse quality of life than those with metastases to other organs

HER2-targeted therapy has positive impact in brain metastases; 1 retrospective real-world study: trastuzumab added on to chemotherapy reduced frequency of brain metastases vs. chemotherapy only (37.8% vs. 25.0% respectively, p=0.028), and delayed time to death from brain metastases (median 14.9 vs 4.0 months, respectively, p=0.0005)[1]

8 clinicians agreed brain metastases have significant impact on post-progression quality of life

ORR for eribulin 11.0%; capecitabine 11.5%[2]

7 clinicians agreed quality of life after disease progressing on chemotherapy and anti-HER2 differs due to toxicity (e.g. neuropathy after eribulin) and more aggressive and more frequently symptomatic progression on chemotherapy

HER2CLIMB study data:

Tucatinib combination reduced burden of brain metastases and appeared to reduce risk of developing new brain metastases:

- People with brain metastases (n=291): tucatinib combination reduced risk of progression in brain or death by 68% vs control arm (HR, 0.32; 95% CI, 0.22 to 0.48; P < .0001); 1-year CNS-PFS was 40.2% (95% CI, 29.5% to 50.6%) in tucatinib arm and 0% in control arm
- ITT population (n=612): tucatinib combination reduced risk of new CNS lesions or death by 46% vs control arm (HR 0.52; 95% CI 0.33, 0.82; p=0.005)

ORR for tucatinib combination: 40.6% (95% CI, 35.3 to 46.0); control arm: 22.8% (95% CI, 16.7 to 29.8) (p<0.001)

[1]Park et al. 2009; Br J Cancer; 100(6):894: [2]Kaufman et al, 2015; J Clin Oncol;33(6)594-601: CNS, central nervous system; ITT, intention-to-treat analysis; Source: Company ACD response, Topic 4

Post-progression utilities (2)

Company:
- Updated its base case – used post-progression utility values from ERG scenario (utilities from HER2CLIMB for tucatinib; from TA423 for comparators)

ERG:
- Justification for differences in post-progression utilities reasonable but concerns over very large difference in post-progression utilities for tucatinib and comparators, based on using evidence from different sources (may overestimate the difference in post-progression utilities)
  - Presents scenario using the same utilities for all treatments, including tucatinib (from TA423; may be conservative)

	Company revised base case		ERG scenario	
	Pre-progression	Post-progression	Pre-progression	Post-progression
Tucatinib combination	0.762[a]	0.698[a]	0.762[a]	0.588[c]
Eribulin	0.706[b]	0.588[c]	0.706[b]	
Capecitabine	0.701[b]		0.701[b]	
Vinorelbine				

Source: ERG report, Tables 23 and 39. [a]HER2CLIMB EQ-5D; [b]TA423 (study 301, eribulin, mapped using Crott and Briggs 2010); [c]Midpoint from TA423; [d]TA704 baseline + TA704 incremental utility of response * overall response rate = (0.704 + 0.076 * 0.406); [e]TA704 utilities.

- Is it plausible there is difference in QoL after progression?
- Is the difference in QoL as modelled by the company plausible, considering not evidence-based?

Subgroup analyses for people with/without brain metastases

Subgroup analyses for people with brain metastases

Committee's conclusions:

- Subgroup analyses could help better understand uncertainty around the effectiveness of tucatinib in people with and without brain metastases

Company:

- HER2CLIMB study was not powered to show a significant benefit in the non-brain metastases subgroup and the size of population assessed means there is greater uncertainty in this population
- Used HER2CLIMB subgroup data from people with brain metastases in network meta-analysis (note: seems unadjusted for treatment effect modifier of brain metastases; ERG could not replicate)
- Directly extrapolated overall and progression-free survival data from this subgroup
    - Tucatinib combination is more cost-effective in brain metastases subgroup than ITT analysis
    - Approach still subject to bias against tucatinib due to comparing with single-agent chemotherapy studies that excluded brain metastases patients

ERG:

- Survival extrapolations for people with brain metastases have poor fit to trial data – no other survival curves explored
- Company did not provide sufficient information to replicate results – but exploratory ERG analyses aligned with company estimates (not able to explore alternative extrapolation curves)

Subgroup analyses for people without brain metastases

Committee's conclusions:

- Subgroup analyses could help better understand uncertainty around the effectiveness of tucatinib in people with and without brain metastases

Company:

- Not able to carry out subgroup analyses for the non-brain metastases subgroup in timeframe – alternative weighted average approach used
  - Assume cost-effectiveness estimates for ITT population represent weighted average of cost-effectiveness estimates for subgroups with and without brain metastases

ERG:

- Survival extrapolations for people without brain metastases not explored meaning cost-effectiveness estimates not accurate
- Results do not account for cost of testing for brain metastases

Subgroup analysis for people with brain metastases

Overall survival: Weibull curve

Progression-free survival: Stratified Weibull

Tucatinib combination (fitted / Kaplan-Meier)

Trastuzumab + capecitabine (fitted / Kaplan-Meier)

Eribulin

Capecitabine

Vinorelbine

◉ Is subgroup analysis robust enough for decision making (considering methodological issues flagged by ERG)?

◉ *Does it resolve some uncertainty?*

Equalities and innovation re-cap

Committee's conclusions:

- **Equalities:**
  - Use of tucatinib not expected to pose any equality issues.
- **Innovation:**
  - Tucatinib combination has significant potential benefits for patients
  - Could not be confident all potential benefits in relation to the effect on brain metastases had been explored or captured in analyses

Consultation comments:

- HER2-positive breast cancer more frequent in younger women and in Black women
- Access to radiotherapy varies across regions
- People with disabilities could struggle with the physical demands of current treatment

Cost-effectiveness issues

- *Which approach to estimate treatment effect modifier is most appropriate?*
- *Is subcutaneous trastuzumab used in NHS practice?*
- *Is it plausible there are differences in QoL after progression with tucatinib and single-agent chemotherapy?*
  - *Is the difference in QoL as modelled by the company plausible, considering not evidence-based?*
- *Is subgroup analysis robust enough for decision making (considering methodological issues flagged by ERG)?*
  - *Does it resolve some uncertainty?*

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts