For Public - redacted

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

1st appraisal committee A meeting
Chair: Jane Adam
Lead team: Rita Faria, Roger Whittaker, Richard Ballerand
ERG: Southampton Health Technology Assessments Centre (SHTAC)
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Company: Seagen inc
October 2021

Key clinical issues

- Are capecitabine, eribulin and vinorelbine equally relevant comparators?
- HER2CLIMB showed effectiveness for brain metastases whereas patients with active brain metastases were excluded from other trials. Is there a biological reason for this, and would it replace other treatments such as surgery and radiotherapy?
- Is the percentage of patients with brain metastases in HER2CLIMB trial representative of UK practice?
- What is the prognostic difference of ‘stable’ and ‘active’ or untreated brain metastases?
- Are the results of the indirect treatment comparison with capecitabine, vinorelbine and eribulin robust considering the clinical heterogeneity across trials in the network meta-analysis (including differences in the numbers of patients with brain metastases, different prior treatments etc.)?
- Is there evidence that comparator therapies are less effective for treating brain metastases compared with tucatinib combination? If all trials in the network included patients with brain metastases, would outcomes for the comparators be worse? If so, by how much?

Background and decision problem

Tucatinib (Tukysa)

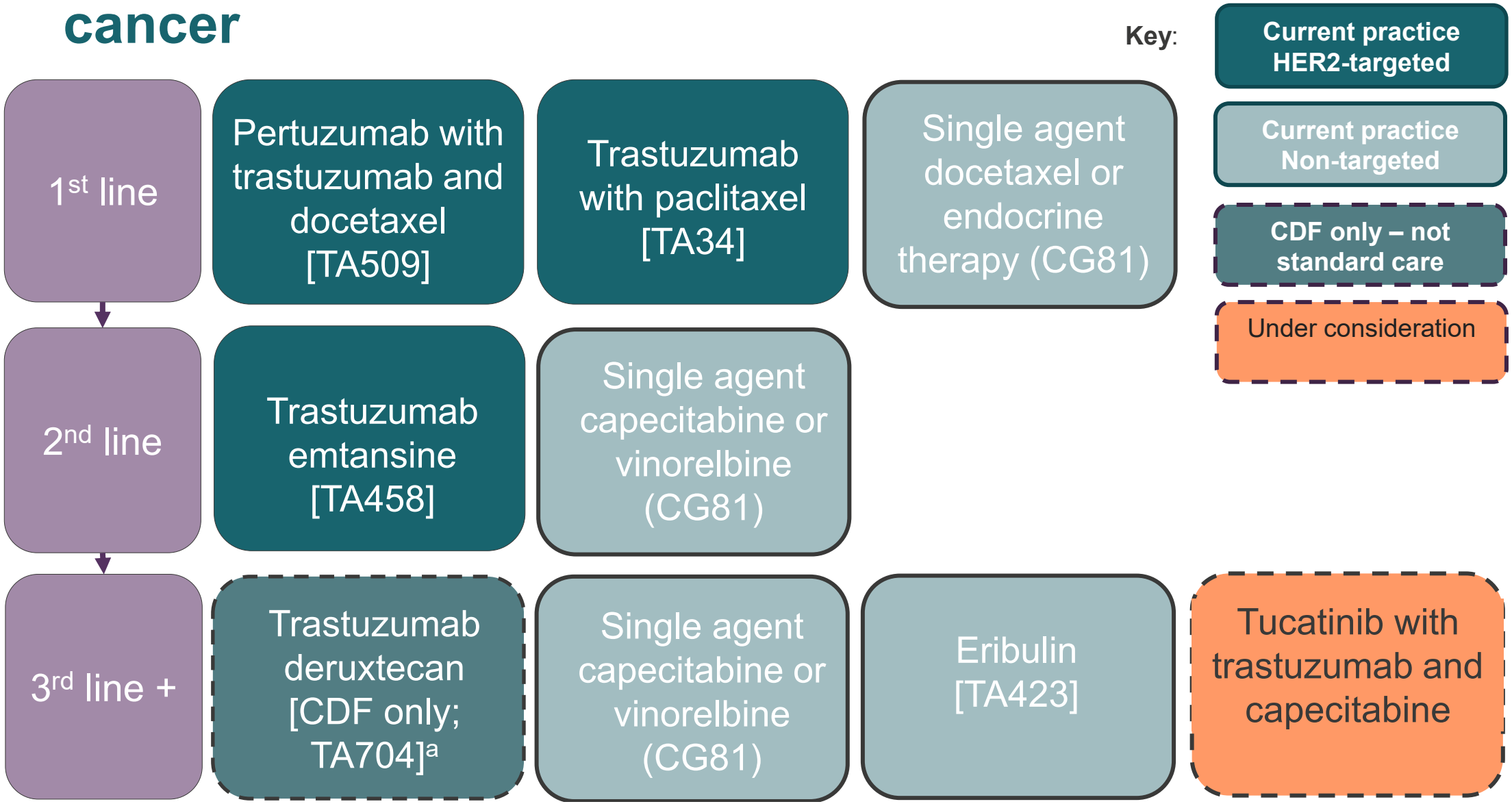
Full Marketing authorisation	Indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer **who have received at least 2 prior anti-HER2 treatment regimens**.
Dosage and administration	• Tucatinib 300 mg orally twice daily until progression • Capecitabine 1000 mg/m^2 orally twice daily on days 1–14 of each 21-day cycle • Trastuzumab loading dose of 8 mg/kg intravenous infusion followed by 6 mg/kg once every 21 days
Mechanism of action	Tucatinib is an oral tyrosine kinase inhibitor highly selective for the kinase domain of HER2
Average list price per course of treatment	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 Combination cost per cycle: £7,016.91 loading dose, following cycles £6,677.14 Patient Access Scheme (PAS) approved by NHS England

Disease background

- Approximately **2,300 people** with metastatic breast cancer in the UK in 2016 (National Cancer Registration and Analysis Service).[1]
- Human epidermal growth factor receptor 2 (**HER2**) is a receptor for a growth factor which occurs naturally in the body and is **overexpressed** in approximately **15-20%** of breast cancer tumours: HER2-positive or HER2+ cancers.[2]
- Brain metastases may develop in **up to half of patients** with HER2-positive cancer.[3]
- Patients with HER2-positive metastatic breast cancer who have progressed on 2 or more prior HER2-targeted therapies have a **high symptom burden**, and built up **treatment resistance** to multiple previous lines of therapy.
- Treatments are needed that can delay progression and extend survival, while preserving patient's quality of life and managing symptoms. Currently no treatment options that target brain metastases – **high unmet need**

[1]ONS. Cancer registration statistics. 2017; [2]NCRAS. Death registrations summary statistics. 2016; [3]Murthy et al. NEJM 2020;382:597-609.

Treatment pathway- HER2-positive metastatic breast cancer



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

Patient and carer perspectives (Breast Cancer Now)

- Being diagnosed with metastatic breast cancer is extremely difficult to come to terms with both for patients and their family and friends. It affects patients mental health and day-to-day activities

- Patients want treatment that will halt progression, extend life for as long as possible, have good safety profile and give them good quality of life

- There is unmet need for further anti-HER2 treatments (after 2 or more lines), especially for people whose breast cancer has spread to the brain

"It is scary. I am permanently scared about my future and what my family will have to deal with without me"

"It totally and completely affects your life after diagnosis. Endless doctors' appointments can begin to wear you down in no time at all"

"I could not work, needed constant care and I ended up hospitalised with infections […]"

"I lost my independence with not being able to drive. It really did feel like this was the end"

"I was eligible for the HER2CLIMB trial … I have had no progression or reoccurrence in the brain metastasis which has enabled me to resume driving which has a positive impact on my mental well-being and independence"

"I was accepted on the HER2 climb trial … After 6 weeks my metastasis shrunk everywhere in my body and for last 2 years I have remained stable. This trial has in no doubt extended my life"

Decision problem

	Final scope issued by NICE	Evidence used in the model
Population	People with HER2-positive, unresectable locally advanced or metastatic breast cancer who have had 2 or more prior anti-HER2 therapies	Aligned with marketing authorisation: people with HER2-positive, locally advanced or metastatic breast cancer who have had 2 or more prior anti-HER2 therapies
Intervention	Tucatinib with trastuzumab and capecitabine	As per final scope
Comparators	• eribulin • capecitabine • vinorelbine	As per final scope
Outcomes	• progression-free survival • overall survival • response rate • duration of response • adverse effects of treatment • health-related quality of life	As per final scope

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Q: Are capecitabine, eribulin and vinorelbine equally relevant comparators?

Clinical effectiveness

Clinical trial evidence – HER2CLIMB

Study design	Phase II*, randomised (2:1 ratio), international, multicentre, double-blind, placebo-controlled, active-comparator trial.
Location	155 sites in 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, progressing 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 **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 was originally registered as a phase 2 study but the sample size and trial conduct were consistent with a phase 3 study; PFS: progression-free survival

HER2CLIMB trial - Baseline characteristics

All patients had ECOG 0 or 1; all but one received trastuzumab, pertuzumab and trastuzumab emtansine ie. 3 HER2 agents in total, in 2 rounds of treatment (trastuzumab given with pertuzumab 1st line); approximately 50% of patients had brain metastases

Characteristic	Primary endpoint population (N=480)		Total study population (N=612)	
	Tucatinib combination (N=320)	Placebo combination (N=160)	Tucatinib combination (N=410)	Placebo combination (N=202)
Median age, years	54	54	55	54
ECOG 0 or 1, n (%)	320 (100)	160 (100)	410 (100)	202 (100)
Presence or history of brain metastases, n (%)	**148 (46)**	**71 (44)**	**198 (48)**	**93 (46)**
Prior lines of therapy in the metastatic setting, median (range)	**3 (1,14)**	**3 (1,13)**	**3 (1,14)**	**3 (1,13)**
Previous systemic cancer therapy, n (%)				
Trastuzumab	320 (100)	160 (100)	410 (100)	202 (100)
Pertuzumab	320 (100)	159 (99)	409 (100)	201 (100)
Trastuzumab emtansine	320 (100)	160 (100)	410 (100)	202 (100)
Lapatinib	22 (7)	10 (6)	24 (6)	10 (5)

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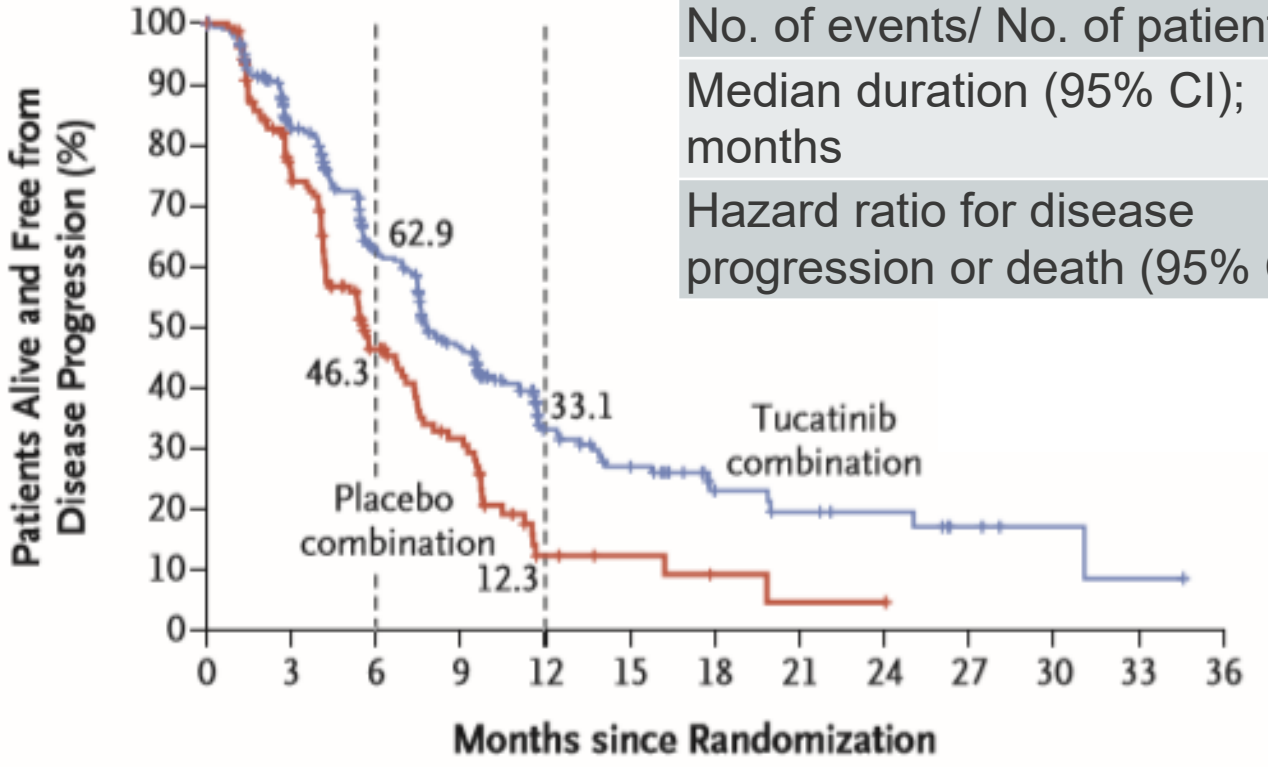
Source: Company submission, Table 6.

Clinical trial evidence – HER2CLIMB

Progression-free survival in first 480 patients enrolled

Primary analysis (company submission; median follow-up: 14.0 months)

	Placebo combination	Tucatinib combination
No. of events/ No. of patients	97/160	178/320
Median duration (95% CI); months	5.6 (4.2-7.1)	7.8 (7.5-9.6)
Hazard ratio for disease progression or death (95% CI)		0.54 (0.42-0.71) p<0.001



No. at Risk

Tucatinib combination	320	235	152	98	40	29	15	10	8	4	2	1	0
Placebo combination	160	94	45	27	6	4	2	1	1	0	0	0	0

ASCO updated data 2021* (median follow-up: 29.6 months)
Median PFS: 4.9 vs 7.6 for placebo vs. tucatinib combination; hazard ratio: 0.57 (p<0.001)

*Clinical expert responses to technical engagement; ASCO 2021.

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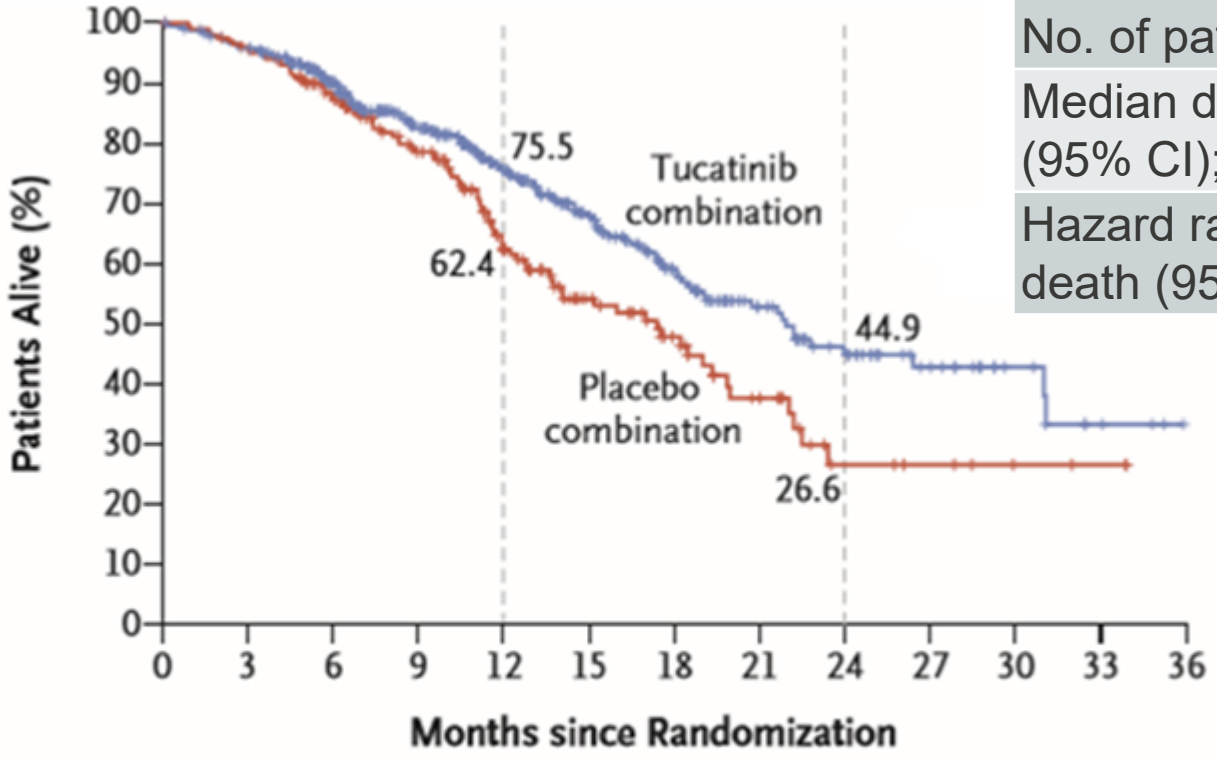
Source: Company submission, Figure 4. CI, confidence interval.

Clinical trial evidence – HER2CLIMB

Overall survival in all 612 randomised patients

Primary analysis (company submission; median follow-up: 14.0 months)

	Placebo combination	Tucatinib combination
No. of events/ No. of patients	85/202	130/410
Median duration (95% CI); months	17.4 (13.6-19.9)	21.9 (18.3-31.0)
Hazard ratio for death (95% CI)		0.66 (0.50-0.88) p=0.005



No. at Risk

Tucatinib comb	410	388	322	245	178	123	80	51	34	20	10	4	0
Placebo comb	202	191	160	119	77	48	32	19	7	5	2	1	0

ASCO updated data 2021* (median follow-up: 29.6 months)
Median OS: 19.3 vs 24.7 for placebo vs tucatinib combination; hazard ratio: 0.73 (95% CI, 0.59-0.90; p=0.004)

*Clinical expert responses to technical engagement; ASCO 2021. After primary analysis, crossover from placebo to tucatinib allowed; 12.9% patients crossed

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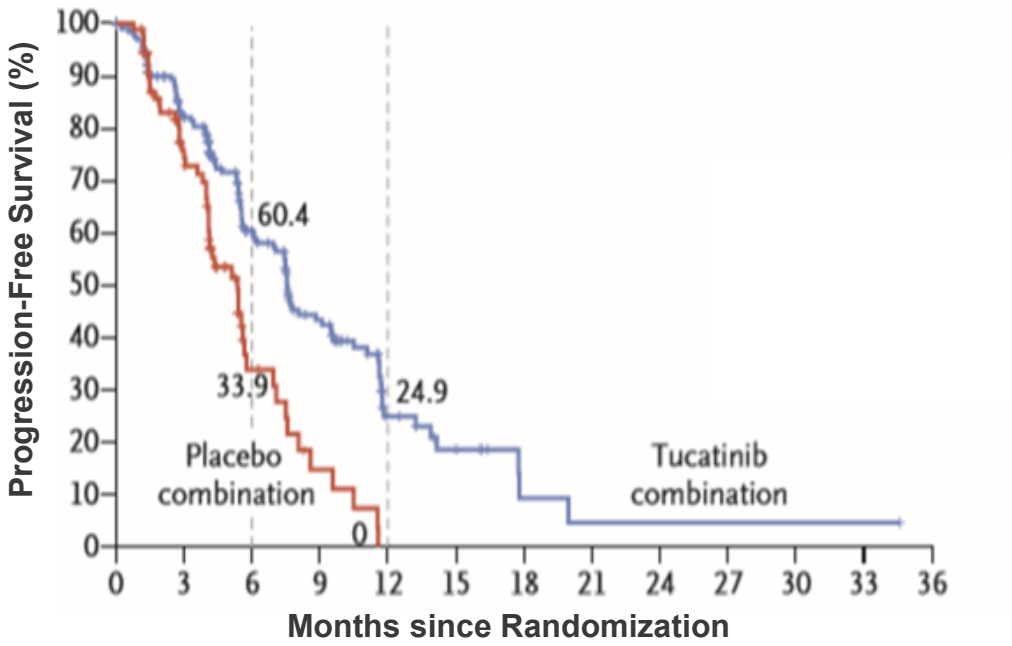
Source: Company submission, Figure 5. CI, confidence interval.

Clinical trial evidence – HER2CLIMB

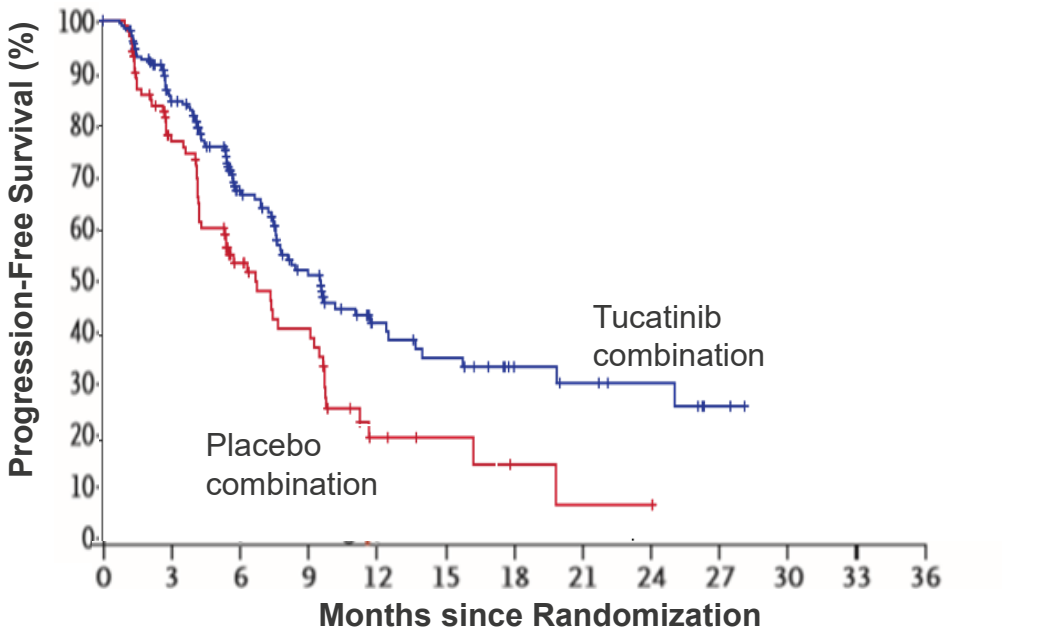
Progression-free survival in patients with/without brain metastases

Patients with brain metastases (44-48%)



	Placebo combination	Tucatinib combination
No. of events/ No. of patients	51/93	106/198
Median duration (95% CI) months	5.4 (4.1-5.7)	7.6 (6.2-9.5)
Hazard ratio for disease progression or death (95% CI)		0.48 (0.34-0.69), p<0.001

Patients without brain metastases



	Placebo combination	Tucatinib combination
No. of events/ No. of patients	60/108	91/211
Median duration (95% CI) months	6.8 (4.3-9.3)	9.6 (7.6-12.4)
Hazard ratio for disease progression or death (95% CI)		0.57 (0.41-0.80)

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

Median follow-up: 14.0 months

Clinical evidence – safety

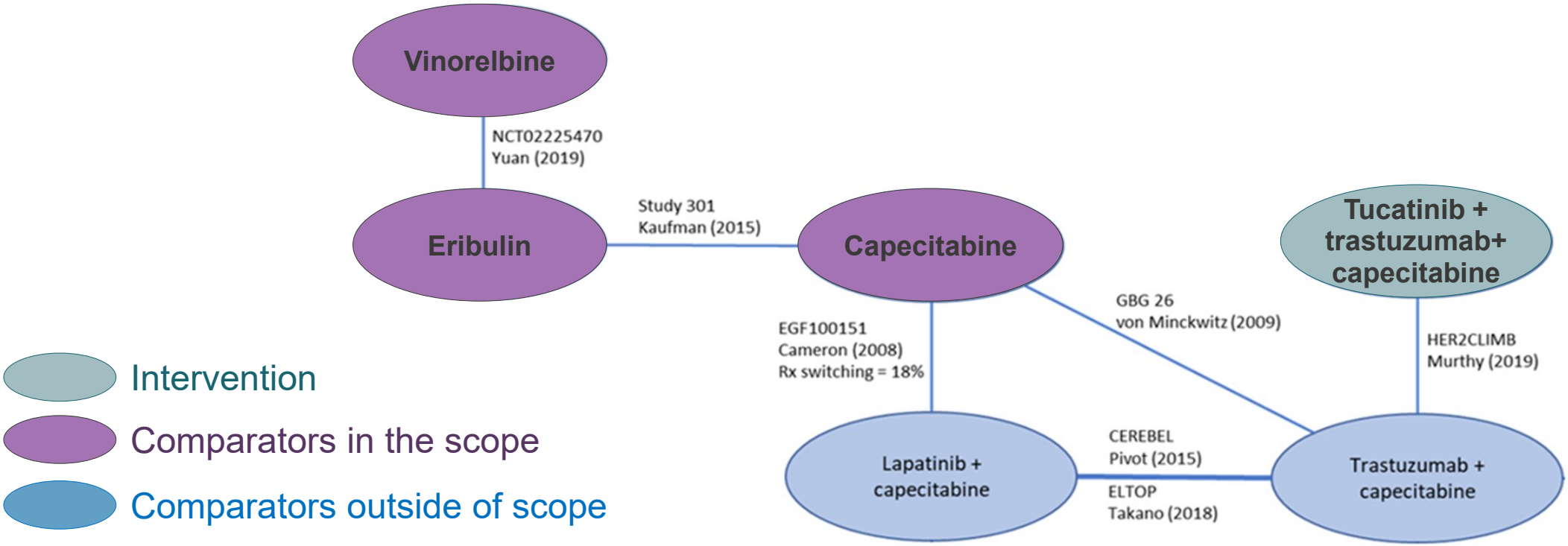
Tucatinib combination well tolerated with manageable safety profile

Type of treatment-emergent adverse event (TEAE), n (%)	Tucatinib combination (N=404)	Placebo combination (N=197)
Any TEAE	401 (99.3)	191 (97.0)
TEAEs Grade ≥3	223 (55.2)	96 (48.7)
Most common TEAEs Grade ≥3		
Diarrhoea	52 (12.9)	17 (8.6)
Hand-foot/PPE syndrome	53 (13.1)	18 (9.1)
Nausea	15 (3.7)	6 (3.0)
Fatigue	19 (4.7)	8 (4.1)
Vomiting	12 (3.0)	7 (3.6)
Stomatitis	10 (2.5)	1 (0.5)
Decreased appetite	2 (0.5)	0
Headache	2 (0.5)	3 (1.5)
AST increased	18 (4.5)	1 (0.5)
ALT increased	22 (5.4)	1 (0.5)

Source: Company submission, Tables 13 and 14

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 (1)

	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%

[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.

Sources: Study 301: Kaufman et al. 2015; **NCT02225470**: clinicaltrials.gov, Yuan et al. 2019; **GBG 26**: clinicaltrial.gov; von Minckwitz et al. 2009; **EGF100151**: Cameron et al. 2008; **CEREBEL**: Pivot et al. 2015.; **ELTOP**: Takano et al. 2018

Studies included in the NMA differ in proportion of enrolled patients with brain metastases (2)

ERG

- Nearly 50% of total HER2CLIMB population had presence or history of brain metastases – higher % than in comparator trials
- ERG expert and recent network meta-analysis reported 31% brain metastases[a]

Company

- HER2CLIMB population generalisable to patients who will be treated with tucatinib in clinical practice in England
- Literature and experts support that ~50% brain metastases
- Limited evidence on efficacy of single-agent chemotherapy in patients with brain metastases

Clinical experts

- By the 3rd line setting, ~50% of patients will develop brain metastases
- HER2CLIMB within 3rd line setting is representative of NHS patients

Note: Patients in HER2CLIMB all had at least 3 prior anti-HER2 therapies, not the case for some of the comparator trials which did not require any prior anti-HER2 therapy[b]

NICE Is % brain metastases in HER2CLIMB trial representative of NHS practice?

[a] Kuksis M, et al. Neuro-oncology 2020;23(6):894-904; [b] For example, in CEREBEL, prior trastuzumab was allowed but not required.

Network meta-analysis results

Hazard ratios are similar between the company and ERG approach; random effects model has larger confidence intervals

	OS hazard ratio* (95% credible interval)		PFS hazard ratio (95% credible interval)	
Tucatinib combination versus	Bayesian hazard ratio NMA; fixed-effects model (company preferred)	Bayesian hazard ratio NMA; random effects model (ERG preferred)	Bayesian hazard ratio NMA; fixed-effects model (company preferred)	Bayesian hazard ratio NMA; random effects model (ERG preferred)
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]

Fixed effects model assumes true effect size is identical across studies
Random effects model assumes effects across studies are not identical, but follow some distribution

Source: Company submission, Page 46; Technical engagement appendices C and D; Clarification response, Figure A5c.
*OS results were updated due to a corrected error in Pivot et al. (2015)

Network meta-analysis limitations

Results uncertain due to clinical heterogeneity across trials; fixed vs random-effect NMA model: minimal impact on cost-effectiveness estimates

ERG

- NMA results uncertain due to heterogeneity between studies - direction and magnitude of bias is unclear
- Uneven distribution of brain metastases (main concern), number of prior lines of therapy, previous anti-HER2 treatment, HER2 status, performance status, race
- Company's fixed-effect NMA model inappropriate given heterogeneity; random-effects model more appropriate:
  - Insufficient evidence to reject proportional hazards assumption
  - Random effects model needed when heterogeneity despite its limitations

Company

- Network demonstrates bias against HER2CLIMB – No or few brain metastases in other studies
- Brain metastases linked to significant morbidity and mortality – supported by published literature and survey with experts
- Brain metastases is a prognostic modifier for all treatments; brain metastases not a treatment modifier for tucatinib regimen but are treatment modifier for comparators
- Random-effects model has convergence issues and higher degree of uncertainty; inconsistent with head-to-head data. Fixed-effects model most appropriate
- Alternative fractional polynomial NMA explored

Clinical experts: Comparator studies better prognosis population

- Including large high-risk patient group within HER2CLIMB disadvantages tucatinib combination

Q: Are the results of the indirect treatment comparison robust?
Q: Are brain metastases a treatment effect modifier, or only a prognostic factor?
Q: Is NMA biased against tucatinib because of differences in % brain metastases?

Key clinical issues

- Are capecitabine, eribulin and vinorelbine equally relevant comparators?
- HER2CLIMB showed effectiveness for brain metastases whereas patients with active brain metastases were excluded from other trials. Is there a biological reason for this, and would it replace other treatments such as surgery and radiotherapy?
- Is the percentage of patients with brain metastases in HER2CLIMB trial representative of UK practice?
- What is the prognostic difference of ‘stable’ and ‘active’ or untreated brain metastases?
- Are the results of the indirect treatment comparison with capecitabine, vinorelbine and eribulin robust considering the clinical heterogeneity across trials in the network meta-analysis (including differences in the numbers of patients with brain metastases, different prior treatments etc.)?
- Is there evidence that comparator therapies are less effective for treating brain metastases compared with tucatinib combination? If all trials in the network included patients with brain metastases, would outcomes for the comparators be worse? If so, by how much?

Cost-effectiveness

Key cost effectiveness issues

- Which trials (HER2CLIMB or lapatinib + capecitabine trials) better reflect % brain metastases in the NHS and should be used to model reference survival curves? Major impact on ICER
- If the comparator therapies are less effective in patients with brain metastases (see key clinical issues), how can the cost-effectiveness analysis reflect this?
- Should different health state utilities – before and after progression – be used for tucatinib combination and comparators? Greatest impact on ICER
- Should drug wastage be included for the tucatinib regimen? Minor impact on ICER

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% for both health and cost outcomes
Utility values	Tucatinib combination: HER2CLIMB trial EQ-5D-5L, mapped to EQ-5D-3L Comparators: Utilities from TA423
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

Company and ERG approaches to modelling overall and progression-free survival differ

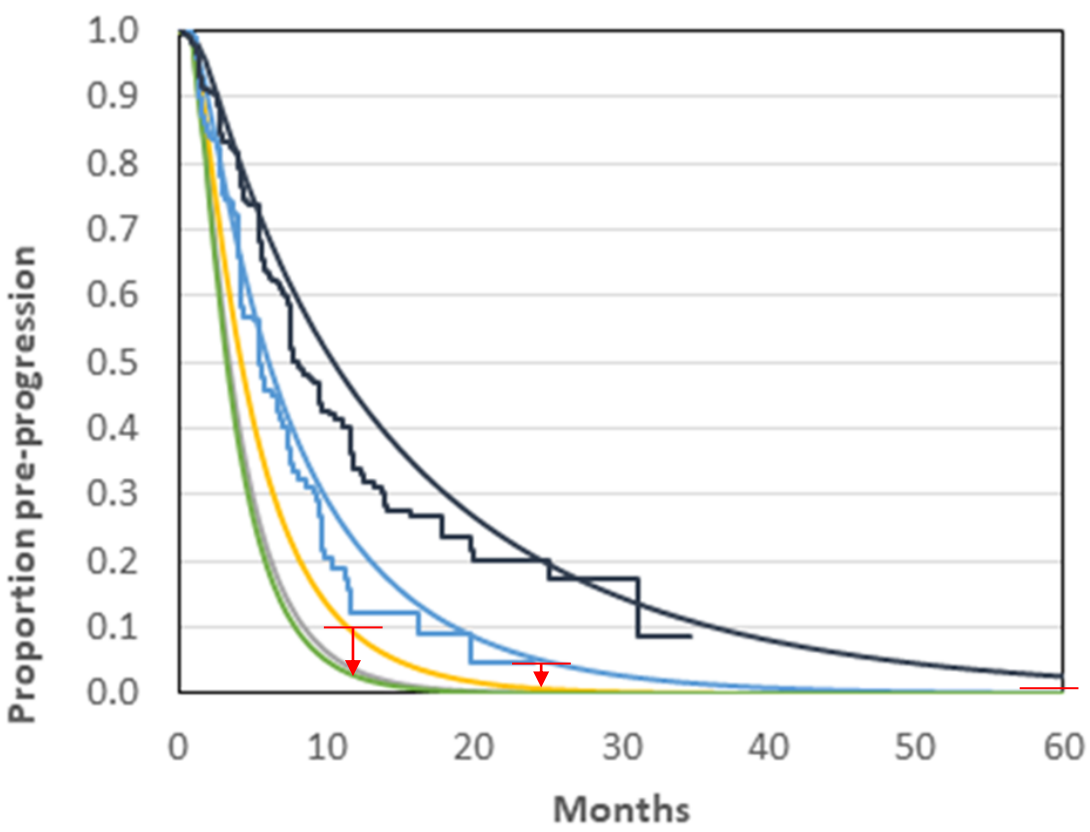
Major impact on cost-effectiveness estimates

	Company base case	ERG 'within trial' approach
Reference arm	Lapatinib + capecitabine	Trastuzumab + capecitabine (from HER2CLIMB trial)
Extrapolation curves	Fractional polynomial	Weibull[a]
Relative effects	Fixed-effects NMA	Random-effects NMA

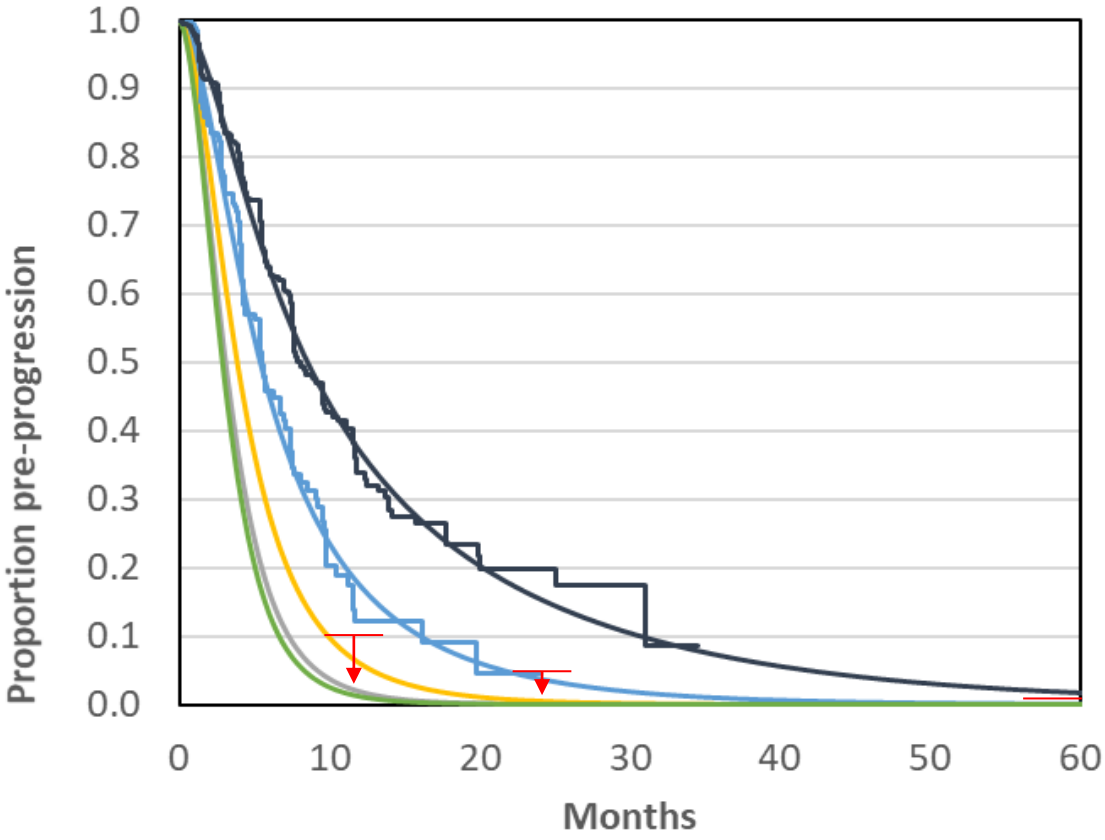
[a]Alternative curves explored in sensitivity analyses

Progression-free survival modelling

Company base case



ERG 'within trial' approach



- Tucatinib combination (fitted / Kaplan-Meier)
- Trastuzumab + capecitabine (fitted / Kaplan-Meier)
- Eribulin
- Capecitabine
- Vinorelbine

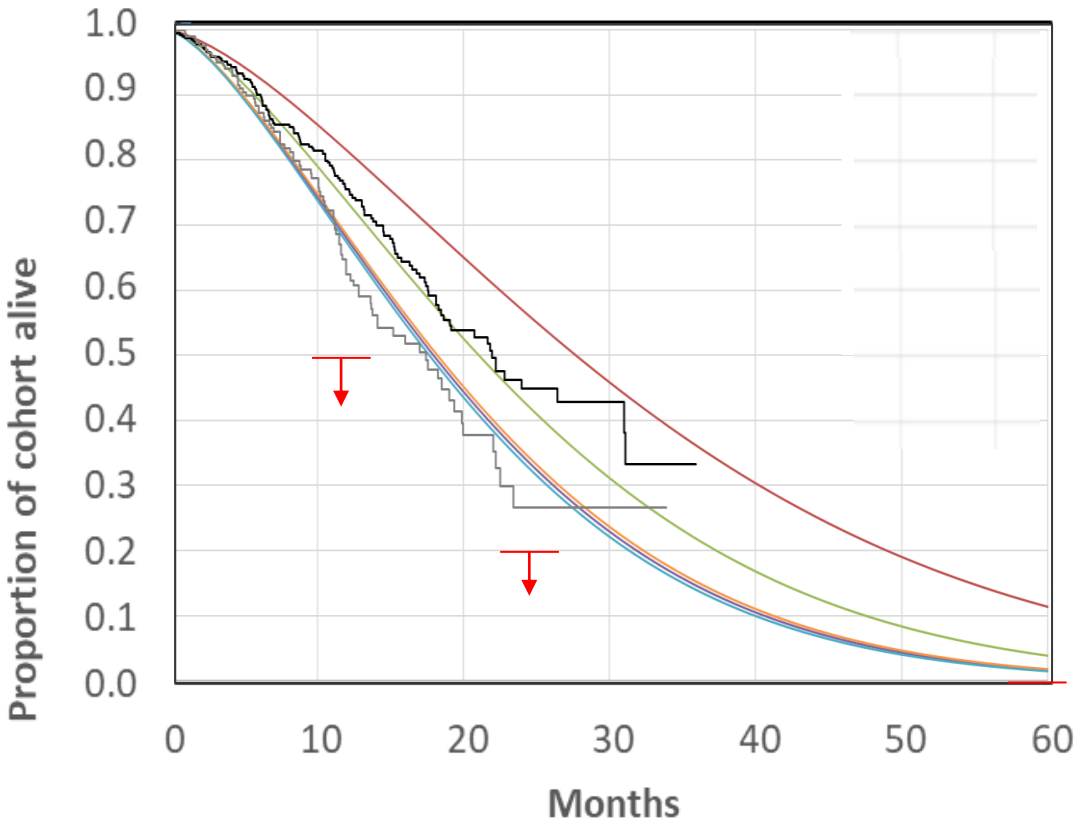
(Eribulin, Capecitabine, Vinorelbine: non-HER2 therapies)

- Clinical expert estimates for non-HER2 therapies (1 year: <10%; 2 years: <5%; 5 years: 0%)

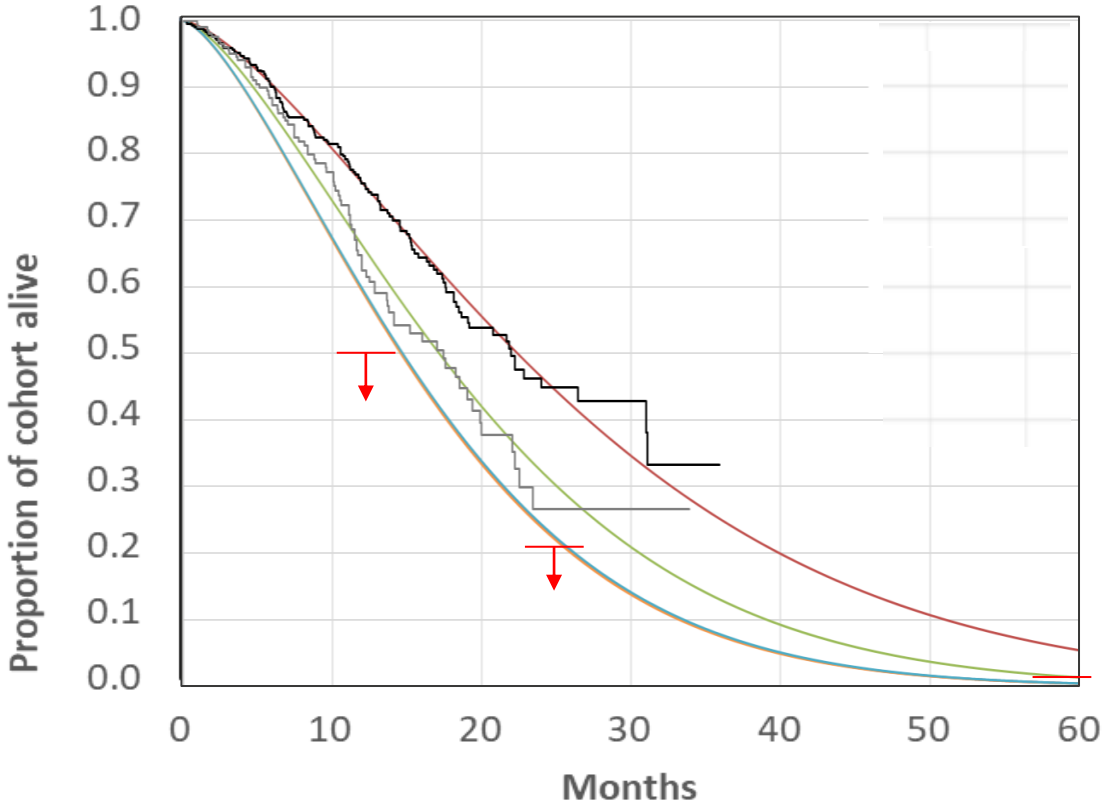
Sources: ERG report, Figures 6 and 14; response to technical engagement from one clinical expert

Overall survival modelling

Company base case



ERG 'within trial' approach



- Tucatinib combination (fitted)
- Trastuzumab + capecitabine (fitted)
- Eribulin
- Capecitabine
- Vinorelbine

non-HER2 therapies

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

Source: ERG critique of company response to technical engagement, Figures 1 and 3 (include correction of Pivot et al study); response to technical engagement from one clinical expert

Modelling of progression-free and overall survival for tucatinib combination and comparator treatments

ERG

- Company's base case approach has poor fit to HER2CLIMB data due to differences between HER2CLIMB population and other trials
- Prefers 'real-world' baseline for survival extrapolations or weighted average for HER2CLIMB patients with and without brain metastases
- Prefers 'within-trial' approach:
  - Better face validity
  - More generalisable results if HER2CLIMB (~50% brain metastases) representative of the NHS
  - Unclear how much uncertainty associated with fractional polynomial; company did not explore any alternative fractional polynomial functional forms
- In absence of subgroup-specific relative effects estimate, current model could be used

Company

- Literature and experts support ~50% brain metastases –HER2CLIMB generalisable to NHS practice:
  - No subgroup analyses required
  - No external data sources required to provide alternative baseline survival curves to which results of network meta-analysis are applied
- Its base case approach most appropriate
  - Approach more favourable than 'within-trial' as represents average of trial evidence
  - ERG does not appropriately adjust for inclusion of harder to treat, real-world, population in HER2CLIMB
- Treatment differences represent differences in real-world outcomes

Q: Which reference arm better reflects 'real-world' baseline for survival modelling?
Q: If the comparator therapies are less effective in patients with brain metastases (see key clinical issues), how can the cost-effectiveness analysis reflect this?
Q: Is subgroup analysis necessary and feasible?

Company uses different health state utilities for tucatinib combination and comparators

Key driver of cost-effectiveness estimates

Background:

- Company base case uses utilities from HER2CLIMB for tucatinib (mapped from EQ-5D-5L) and TA423 for comparator therapies
- ERG approach uses HER2CLIMB EQ-5D utilities for all treatments

ERG

- Same utilities should be used for all treatments in pre- and post-progression health states
  - TA423 used same post-progression utility across treatments (recommended by NICE guidelines)
  - Differences in utilities between tucatinib and comparators are not based on comparative evidence
- Prefers HER2CLIMB utilities derived from EQ-5D data in relevant trial population

Company

- Pre- and post-progression utility higher for tucatinib combination compared to comparators - due to tucatinib efficacy and toxicity
- After disease progression, quality-of-life benefits related to disease response, particularly the central nervous system response could continue
- TA423 eribulin had higher pre-progression utilities than other single agent chemotherapies, related to differences in treatment response rates

Clinical experts

- Safety profile of tucatinib is good – similar to capecitabine alone, and better than with eribulin or vinorelbine
- Difficult to separate out effects on quality of life of disease progression and toxicity
- Disease control could support different pre-progression utility values because treatments offer different levels of overall response rate

Utility values used in the model

Treatment	Company base case		ERG base case		ERG scenario	
	Pre-progression	Post-progression	Pre-progression	Post-progression	Pre-progression	Post-progression
Tucatinib combination	0.762[a]	0.698[a]	0.762[a]	0.698[a]	0.762[a]	0.588[d]
Eribulin	0.706[b]	0.496[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]TA423 (Lloyd et al. 2006) [d]Midpoint from TA423. Note: Company provided 2 scenario analyses against eribulin with same post-progression utilities for both treatments. Post-progression utility values were 0.698 in one scenario; 0.496 in second scenario.

In TA423, the committee did not agree with post-progression utility value of 0.496: it agreed plausible post-progression utility lies between the Lloyd et al. and Study 301 estimates (0.496 and 0.679, respectively; midpoint: **0.588**).Clinical experts: 20% deterioration in quality of life on progression was too high and implausible.

TA704: 'progression-free, on-treatment' utility values were a function of TA423 utility values (0.704) and overall response rate for each treatment

Health state	Utility value
Progression-free, on-treatment, trastuzumab deruxtecan	0.750
Progression-free, on-treatment, comparators[a]	0.713-0.725
Progression-free, off treatment, all treatments	0.704
Progressed, all treatments	0.588

[a]Eribulin, vinorelbine, capecitabine; **ERG used these utility values in new scenario analysis**

Q: Is it plausible that people have different quality of life before disease progression? And after progression? Q: Which approach to model utility values is most appropriate?

Company did not include drug wastage for tucatinib regimen

Minor impact on cost-effectiveness estimates

ERG

- Company model includes wastage estimates for intravenous trastuzumab and trastuzumab emtansine; company does not include these estimates in base case or scenario analysis
- Prefers including drug wastage cost in analysis – small impact on overall costs or cost-effectiveness estimates

Company

- Tucatinib and capecitabine are both oral therapies available in multiple pill doses
  - In previous NICE appraisals of oral metastatic breast cancer treatments, wastage was not applied to oral therapies
- Trastuzumab is packaged in multi-use vials to allow the same vial to be used with multiple patients and ensure it is not wasted.
- Therefore, wastage does not apply to the tucatinib regimen

NICE

Q: Should drug wastage be included?

Key assumptions in company and ERG analyses

Parameter	Base case	
	Company	ERG
Comparators	Capecitabine, eribulin and vinorelbine	Capecitabine, eribulin and vinorelbine
Survival modelling: reference curve	Lapatinib + capecitabine	Trastuzumab + capecitabine (control arm of HER2CLIMB)
Survival modelling: extrapolations	Fractional polynomial curve	Weibull curve
Survival modelling: relative treatment effects	Fixed-effect network meta-analysis	Random effect network meta-analysis
Treatment specific utilities	Different pre- and post-progression utilities for tucatinib and comparators	Same pre- and post-progression utilities across all treatments
Age adjusted utilities	No	Yes
% subsequent treatments	Based on HER2CLIMB[a]	Based on clinical opinion[b]
Drug wastage	No drug wastage	Drug wastage

[a]Includes treatments not used in the NHS; [b] includes trastuzumab + capecitabine.

Does tucatinib meet the end-of-life criteria?

- Both criteria must be met:
    1. Treatment is indicated for patients with a short life expectancy, normally less than 24 months
    2. Sufficient evidence to indicate that treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

- In addition, committee should be satisfied that:
    - estimates are robust
    - assumptions used in the reference case economic modelling are plausible, objective and robust

- Company and ERG agree that both criteria are met, that is, short life expectancy + tucatinib combination is life extending.
- In TA423 and TA704, committee agreed that end of life criteria were met for eribulin and trastuzumab deruxtecan in the same indication

Key cost effectiveness issues

- Which trials (HER2CLIMB or lapatinib + capecitabine trials) better reflect % brain metastases in the NHS and should be used to model reference survival curves? Major impact on ICER
- If the comparator therapies are less effective in patients with brain metastases (see key clinical issues), how can the cost-effectiveness analysis reflect this?
- Should different health state utilities – before and after progression – be used for tucatinib combination and comparators? Greatest impact on ICER
- Should drug wastage be included for the tucatinib regimen? Minor impact on ICER

Innovation and Equality

Innovation:

- Use of currently available treatment options is limited by inconsistent efficacy and poor tolerability.
- Tucatinib granted Promising Innovative Medicine designation by the Medicines and Healthcare Products Regulatory Agency (MHRA) due to efficacy and tolerability in patients with HER2-positive metastatic breast cancer, including those with brain metastases.
- First treatment targeting brain metastases

Equality issues:

- Use of tucatinib not expected to raise any equality issues.

Cost-effectiveness results

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