NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Seagen

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Breast Cancer Now
   b. NCRI-ACP-RCP-RCR
   c. NHS England and Improvement
   d. NHS England and Improvement

4. **Evidence Review Group report** prepared by **Southampton Health Technology Assessments Centre**

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from **Seagen**

7. **Technical engagement responses & expert statements from experts:**
   a. Dr Alicia Okines, Consultant medical oncologist – Clinical expert, nominated by **Seagen**
   b. Dr Sheeba Irshad, Consultant medical oncologist – Clinical expert, nominated by **NCRI-ACP-RCP-RCR**
   c. Vicki McGinn, Patient – Patient expert nominated by **Breast Cancer Now**
   d. Holly Heath – Policy Manager – Patient expert nominated by **Breast Cancer Now**

8. **Technical engagement response from consultees and commentators:**
   a. Roche – No comments

9. **Evidence Review Group critique of company response to technical engagement** prepared by **Southampton Health Technology Assessments Centre**

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

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Single technology appraisal

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

Document B

Company evidence submission

April 2021

File name	Version	Contains confidential information	Date
ID3828 Tucatinib Company Evidence Submission Document B [redacted]	3	Yes	09 August 2021

Contents

Tables and figures

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Abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
3L	Third line
AE	Adverse event
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ANA	Anastrozole
AST	Aspartate aminotransferase
BAS	Body area surface
BC	Breast cancer
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
BIM	Budget-impact model
BM	Brain metastases
BNF	British National Formulary
BSA	Body surface area
CADTH	Canadian Agency for Drugs and Technologies in Health
Cap	Capecitabine
Cape	Capecitabine
CBR	Clinical benefit rate
CEA	Cost-effectiveness analysis
CG	Clinical guideline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Confidence limit
CMA	Cost-minimisation analysis
CMS	Centeris for Medicare & Medicaid Services
CNS	Central nervous system
CNS-PFS	Central nervous system progression-free survival

cORR	Confirmed objective response rate
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible intervals
CT	Computed tomography
CUA	Cost-utility analysis
DHHS	Department of Health and Human Services
DIC	Deviance information criterion
DOC	Docetaxel
DoH	Department of Health
DOR	Duration of response
EBC	Early breast cancer
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EGP	Economic guidance panel
ELTOP	Early switch to Lapatinib versus Trastuzumab beyond Progression
EMA	European Medicines Agency
EMBRACE	Epidemiological Study of Familial Breast Cancer
eMIT	Electronic market information
EQ-5D-3L	EuroQoL 5-Dimensions 3-Levels
EQ-5D-5L	EuroQoL 5 Dimensions 5-Levels
ER	Oestrogen receptor
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
ESO	European School of Oncology
FE	Fixed effects
FISH	Fluorescence *in situ* hybridisation
GBG	German Breast Group
GP	General practitioner
GVD	Global Value Dossier
HER2	Human epidermal growth factor receptor 2
HER2-	Human epidermal growth factor receptor 2-negative
HER2+	Human epidermal growth factor receptor 2-positive

HER2CLIMB	A Study of Tucatinib vs Placebo in Combination with Capecitabine & Trastuzumab in Patients with Advanced HER2+ Breast Cancer
HES	Hospital Episode Statistics
HIV	Human immunodeficiency virus
HmR	Hormone receptor
HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Healthcare resource utilisation
HSUV	Health state utility value
HTA	Health technology assessment
IC50	Half maximal inhibitory constant
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
IHC3	Immunohistochemical score 3+
ILD	Interstitial lung disease
IMSS	Mexican Institute of Social Security
ISH	*In situ* hybridisation
ISSSTE	*Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado*
ITC	Indirect treatment comparison
ITT	Intent to treat
ITT-OS	Total study population: intent to treat overall survival population in HER2CLIMB
$ITT\text{-}PFS_{brain\ metastases}$	All randomised patients with brain metastases in HER2CLIMB
IV	Intravenous
JDMC	JDMC, Inc.
LAP	Lapatinib
LET	Letrozole
LY	Life-year
MBC	Metastatic breast cancer
MHRA	Medicines and Healthcare Products Regulatory Agency
mo	Months
MRI	Magnetic resonance imaging
NA	Not applicable
NCCN	National Comprehensive Cancer Network

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
No	Number
NR	Not reported
ORR	Objective response rate
ORR-IC	Intracranial objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
Pbo	Placebo
pCR	Pathologic complete response
PD	Progressive disease
PER	Pertuzumab
PET	Positron emission tomography
PF	Progression free
PFS	Progression-free survival
PgR	Progesterone receptor
PI	Prescribing information
PI3K	Phosphoinositide 3-kinase
PICO	Population, interventions, comparators, outcomes
PIM	Promising Innovative Medicine
PO	Orally
PPE	Palmar-plantar erythrodysesthesia
PR	Partial response
PS	Performance status
PSS	Personal social services
PSSRU	Personal social services research unit
Pub	Publication
QALY	Quality-adjusted life years
RCT	Randomised clinical trial
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumours

SC	Subcutaneous
SD	Stable disease
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
SLR	Systematic literature review
SMC	Scottish Medicine Consortium
SmPC	Summary of Product Characteristics
SP	*Seguro Popular*
T-DM1	Ado-trastuzumab emtansine or trastuzumab emtansine
TA	Technology appraisal
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TH	Docetaxel + trastuzumab
THP	Docetaxel + trastuzumab + pertuzumab
TKI	Tyrosine kinase inhibitor
Tras	Trastuzumab
TSD	Technical Support Document
TTD	Time-to-treatment discontinuation
TUC	Tucatinib combination
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
WBRT	Whole brain radiotherapy

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. The decision problem as per final scope is outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with HER2-positive locally advanced or metastatic breast cancer who have had 2 or more prior anti-HER2 therapies	As per final scope	Whilst we recognise that NICE included 'unresectable' in the final scope, the licensed indication of tucatinib does not mention the term and therefore we have removed 'unresectable' from the title of this appraisal.
Intervention	Tucatinib with trastuzumab and capecitabine	As per final scope	Not applicable
Comparator(s)	• eribulin • capecitabine • vinorelbine	As per final scope	Not applicable
Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rate • duration of response • adverse effects of treatment • health-related quality of life	As per final scope	Not applicable
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • people with brain metastases	As per final scope	The overall population of tucatinib's HER2CLIMB trial is closely representative of patients seen in clinical practice, as it included those with untreated and previously treated brain metastases. Thus, clinical evidence for this subgroup will be presented alongside patient demographics and status of brain metastases in Appendix E. However, this subgroup will not be explored in the economic analysis due to the lack of available evidence for potential comparators including a similar subgroup of patients. Patients with brain metastases, particularly those with active or progressing brain lesions included in HER2CLIMB, have been excluded from prior clinical trials; thus, it is not possible to conduct indirect comparisons of the tucatinib combination with other comparators in patients with brain metastases.

B.1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Tucatinib, brand name: TUKYSA®
Mechanism of action	**Tucatinib** is an oral tyrosine kinase inhibitor (TKI) highly selective for the kinase domain of HER2 and with minimal inhibition of epidermal growth factor receptor (EGFR) (1). In vitro, tucatinib inhibits phosphorylation of the tyrosine kinase domain of the HER2 receptor, resulting in inhibition of downstream cell signalling and cell proliferation, and induces death in HER2-driven tumour cells (2-4). **Trastuzumab** is a recombinant humanised IgG1 monoclonal antibody against HER2 that binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. It inhibits the proliferation of human tumour cells that overexpress HER2 and is a potent mediator of antibody-dependent cell-mediated cytotoxicity (5). **Capecitabine** is an anti-metabolite chemotherapy that inhibits DNA synthesis and slows growth of tumour tissue (6).
Marketing authorisation/CE mark status	At the time of this submission, April 2021, tucatinib has been approved in the United Kingdom (UK), European Union, United States (US), Switzerland, Singapore, Canada, and Australia. Tucatinib has been granted a Promising Innovative Medicine (PIM) Designation by the Medicines and Healthcare products Regulatory Agency (MHRA). • The date of the Committee for Medicinal Products for Human Use (CHMP) positive opinion is 10 December 2020 • The UK regulatory approval was granted on 22 February 2021 • The anticipated date of launch of the technology is [redacted] Both medicinal products trastuzumab and capecitabine are approved by the MHRA for the treatment of HER2+ MBC.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Approved indication in the UK: TUKYSA is 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 two prior anti-HER2 treatment regimens. The SmPC is shown in Appendix C.
Method of administration and dosage	• Tucatinib 300 mg taken orally twice daily continuously until progression Capecitabine 1000 mg/m^2 orally twice daily on days 1–14 of each 21-day cycle, mean body surface area (BSA) 1.8 m^2 • Trastuzumab loading dose of 8 mg/kg intravenous infusion followed by 6 mg/kg once every 21 days, mean weight 69.5 kg
Additional tests or investigations	Not applicable
List price and average cost of a cycle of treatment	Tucatinib: 150 mg film-coated tablets; pack 84 tablets [redacted]; tucatinib 50 mg, pack 88 tablets [redacted] (at the time of submission,

	the price submitted to the Department of Health [DoH], but is not yet listed) Trastuzumab: £366.65 per vial for infusion (150 mg) (7) Capecitabine: per 500 mg film-coated tablets, pack of 120 tablets £25.02 (8) Average list price per cycle of TUKYSA, trastuzumab and capecitabine (21 days): [redacted] loading dose, following cycles [redacted]
Patient access scheme (if applicable)	Tucatinib 150 mg, pack 84 tablets [redacted] Tucatinib 50 mg, pack 88 tablets [redacted]

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

HER2-positive metastatic breast cancer (HER2+ MBC) is a biologically aggressive form of breast cancer that is likely to progress, remains difficult to treat, and is associated with a poor prognosis. Breast cancer arises from the tissues of the ducts or lobules of the breast. In MBC, the cancer has spread beyond the breast and nearby lymph nodes to other organs in the body. Human epidermal growth factor receptor 2 (HER2) is a receptor for a growth factor which occurs naturally in the body. Breast cancer cells that have higher than normal levels of HER2 receptors are described as being HER2-positive (HER2+). There is no cure for HER2+ MBC, and less than half of patients survive 5 years following diagnosis (9).

HER2+ MBC places a substantial burden on patients. Patients experience deterioration in health-related quality of life (HRQoL) due to both the disease and treatment-related adverse events, including increased physical, emotional and caregiver burden (10). As the disease progresses and patients receive later lines of systemic therapy, this burden increases; survival and HRQoL deteriorate further (11-14).

B.1.3.1.1 Brain metastases in HER2+ MBC

Patients with HER2+ MBC are among those at highest risk for developing metastases to the brain, with up to 50% developing brain metastases over the course of the disease (15, 16). The brain may represent a sanctuary site for HER2+ disease because current treatments, such as anti-HER2 monoclonal antibodies, have limited ability to penetrate an intact blood-brain barrier, and thus, have variable levels of activity in the brain. As patients live longer due to better control of non-central nervous system (CNS) disease, there is more time for brain metastases to develop (17). Despite treatment, survival after the development of brain metastases in patients with HER2+ MBC is poor, with a 1-year survival of 50% and a 3-year survival of only 16% (18).

B.1.3.1.2 Global epidemiology

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths among women worldwide (19). Metastatic breast cancer is either identified at first breast cancer diagnosis (*de novo*) or recurs in those originally diagnosed with early breast cancer. Approximately 75% of MBC is due to early breast cancer that has progressed to distant disease (20-23).

Patients with HER2+ MBC are a small, but important subgroup of breast cancer patients (24, 25). In 2016, there were approximately 2,300 cases of metastatic breast cancer in the UK according to the National Cancer Registration and Analysis Service (26). It is estimated that approximately 15–20% of women with breast cancer will have HER2+ tumours (27). Evidence from population-based studies, multi-national clinical trials, and autopsy studies in the United States (US), Europe and Asia suggests that brain metastases can occur in up to 50% of patients with HER2+ MBC throughout the course of the disease (28-38).

B.1.3.1.3 Breast cancer in the UK and England

One in seven women in the UK will develop breast cancer in their lifetime (39). Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases. In 2017, there were 45,790 new diagnoses of breast cancer in England (40). Concerning mortality, breast cancer is the second most common cause of cancer death in women in the UK, with around 11,500 deaths in 2018 alone. Breast cancer mortality rates are consistent across the UK nations, therefore this rate is expected to be applicable to England (41).

B.1.3.2 Treatment options in HER2+ MBC

Current treatments in the metastatic setting focus on palliation (42), with goals of delaying disease progression, extending survival, and preventing further metastases, while maintaining HRQoL. Use of specific agents for HER2+ MBC depends on whether the cancer cells have particular receptors (hormone receptor status), the extent of the disease, and previous treatments (43).

In addition to chemotherapy and hormone therapy (for hormone receptor-positive breast cancer), systemic therapy for HER2+ MBC may include directed therapy, such as monoclonal antibodies, that target the extracellular domain of the HER2 receptor (trastuzumab [Herceptin®], pertuzumab [Perjeta®]), anti-HER2 antibody-drug conjugates (T-DM1 [Kadcyla®]), and small molecule tyrosine kinase inhibitors (TKIs), which target the tyrosine kinases located in the internal domain of the HER2 receptor (lapatinib [Tyverb®], neratinib [Nerlynx®]). Recently licensed in the UK, trastuzumab deruxtecan (Enhertu®) is an anti-HER2 antibody-drug conjugate (44) that is currently being appraised by NICE (NICE ID2697), with an expected publication date of 19 May 2021 (45).

There is currently no standard of care for people with HER2+ MBC whose disease has progressed on or after second-line treatment with T-DM1. NICE clinical guideline 81 (NICE CG81) recommends that patients may receive treatment with non-targeted chemotherapies such as capecitabine or vinorelbine (46). Also as a non-targeted option, NICE technology appraisal guidance TA423 recommends eribulin for locally advanced or metastatic breast cancer after two or more lines of chemotherapy regimens (47). New targeted therapies are warranted for people with HER2+ MBC in the third-line setting.

B.1.3.2.1 International guidelines

International guidelines for the treatment of HER2+ MBC generally recommend chemotherapy plus trastuzumab and pertuzumab or chemotherapy plus trastuzumab as first-line regimens (48-50). Recommended second-line metastatic therapy is typically trastuzumab emtansine (T-DM1) (48-50).

The treatment landscape for HER2+ MBC in the third-line setting is highly fragmented with no clear standard of care (48). Current European School of Oncology (ESO)-European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines recommend continued use or retreatment with anti-HER2 therapies (e.g., trastuzumab combined with different chemotherapies) (48, 49, 51). However, in England, no anti-HER2 therapies are approved by NICE for use in the

third-line setting and retreatment with trastuzumab with chemotherapy is not recommended for use in patients who have progressed (43).

The latest ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 5) include tucatinib as a potential treatment in the third-line metastatic setting, if locally approved (48). Similarly, trastuzumab deruxtecan (Enhertu®) is also considered, despite its associated risk of fatal interstitial lung disease (ILD) (44).

B.1.3.2.2 Treatment pathway for HER2+ MBC in England

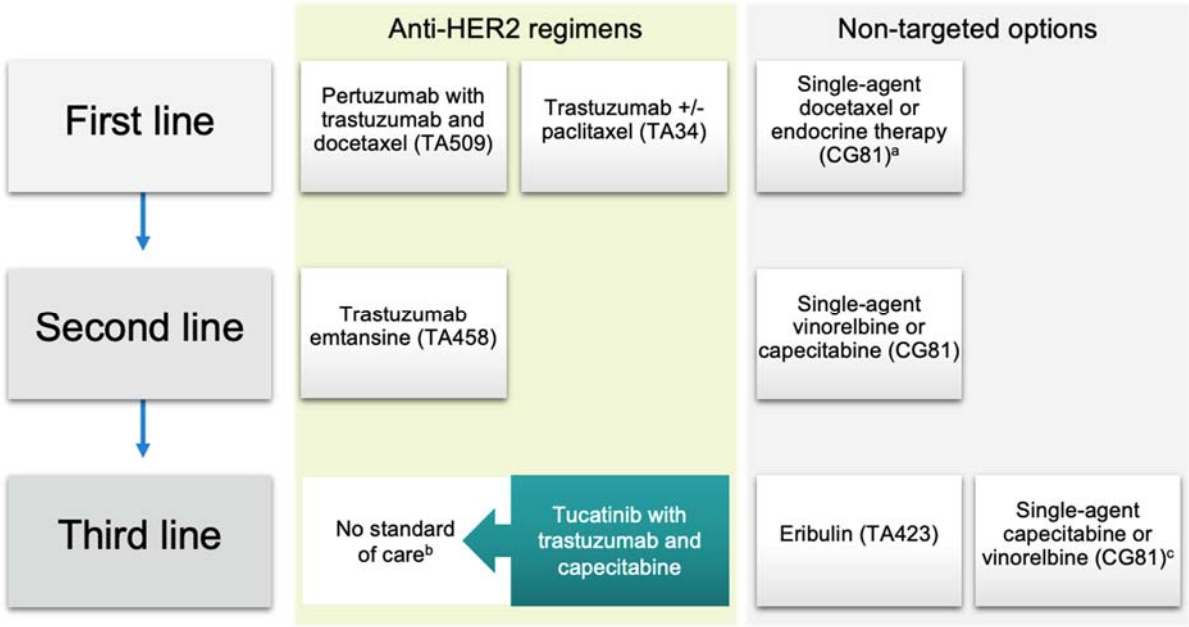
First-line

As first-line options in the metastatic setting, NICE recommends chemotherapy or, for patients whose tumours express hormone receptors, endocrine therapy (NICE CG81) (Figure 1). Other first-line options for patients with HER2+ MBC include the combination of pertuzumab with trastuzumab and docetaxel (NICE TA509) and trastuzumab alone or in combination with paclitaxel (NICE TA34).

Second-line

T-DM1 is recommended as a second-line option for HER2+ MBC patients who have previously received trastuzumab and a taxane, separately or in combination (NICE TA458) (52). Patients should have either received prior therapy for locally advanced or metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. Chemotherapy may also be used in this setting (NICE CG81) (46).

Figure 1: Treatment pathway in HER2+ MBC in England and tucatinib positioning



HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; NICE, National Institute for Health and Care Excellence
[a] Endocrine therapy is recommended for patients with hormone receptor-positive tumours.
[b] As NICE stated in the final scope of this appraisal, there is currently no standard of care for anti-HER2 therapy in people with HER2+ MBC whose disease has progressed on or after trastuzumab emtansine.
[c] Whichever was not used as second-line treatment.
The treatment pathway presented in this figure has been validated by clinicians in England.
Source: NICE pathways (43), NICE CG81 (46), NICE TA509 (53), NICE TA34 (54), NICE TA458 (52), NICE TA423 (47), Seagen Data on File 2021 (16)

Third-line

There are no NICE-recommended therapies that have demonstrated an overall survival (OS) benefit for patients with HER2+ MBC following two prior anti-HER2 therapies (43). As NICE stated in the final scope of this appraisal, there is currently no standard of care for people with HER2+ MBC whose disease has progressed on or after T-DM1 (55).

Because of the lack of a clear standard of care in later lines of therapy, Seagen explored Hospital Episode Statistics (HES) data. However, the HES datasets in the third-line setting were inconclusive, with some evidence suggesting frequent usage of trastuzumab in third-line setting.

NICE does not recommend use of trastuzumab beyond progression. Although trastuzumab with chemotherapy (e.g., capecitabine) is not licensed in this setting, off-label prescribing in later lines of therapy may occur in some circumstances. In addition, such use is not centrally funded or routinely available in clinical practice. Access to trastuzumab is not equitable across the National Health Service (NHS) in England and the regimen is not included in the final decision problem for this appraisal.

In the scope for this appraisal, NICE identified three single-agent chemotherapies, eribulin, capecitabine, and vinorelbine, as comparators for the tucatinib combination in the third-line setting (55). Seagen also recently commissioned an advisory board with seven expert clinicians who provided insights on the treatment pathway for HER2+ MBC in England (16). The clinical experts agreed that these three single-agent treatments are currently used in England in this setting (as further described in B2). Clinicians also confirmed that the three relevant comparators of eribulin, capecitabine and vinorelbine are clinically equivalent. In extensive advisory board discussions, physicians agreed that in their experience, capecitabine is typically used in combination with trastuzumab. As such, clinicians agreed that eribulin is the most plausible standard of care as it is used as a single agent and is the only treatment approved by NICE for use in the third-line setting (NICE TA423) (47). However, the consensus of the advisory board was that a significant unmet need exists for new and efficacious treatments in this setting (16). Based on this advice, eribulin is the base-case comparator in the evidence submission and economic model, with additional analyses conducted against capecitabine and vinorelbine for completeness.

Within the NICE pathway, the combination of tucatinib with trastuzumab and capecitabine (tucatinib combination) is expected to be positioned as an effective third-line treatment for patients with HER2+ MBC who have received at least two prior anti-HER2 therapies in the metastatic setting (Figure 1).

B.1.3.3 Current unmet need

Patients with HER2+ MBC who have progressed after second-line therapy represent a high unmet need in England. Despite recent advances in the treatment of HER2+ MBC, patients ultimately progress and there is no clear established standard of care in later lines of therapy. Although single-agent chemotherapies are recommended in third-line regardless of HER2 status, patients with HER2+ breast cancer could achieve greater clinical benefit with targeted treatment, as per international guideline recommendations (48, 49, 51).

Treatments are needed that offer meaningful increases in progression-free survival (PFS) and OS, while preserving HRQoL and managing symptoms. Currently available therapies in the third-line setting (e.g., eribulin) are associated with frequent adverse events, including fatigue, alopecia, peripheral neuropathy, nausea, neutropenia, leukopenia and anaemia (NICE TA423). Median OS with eribulin ranged from 13.1 to 15.9 months in three clinical trials including patients with HER2+ and HER2-negative (HER2-) MBC (56-58). The unmet need in HER2+ MBC is reflected in the following quote by Breast Cancer Now, a patient advocacy group, provided as comments to the decision problem meeting of the present appraisal, dated February 2021, “There is an urgent need for new and clinically effective treatments for pre-treated patients who progress on current treatments. Treatments shown to increase PFS and OS are highly valued by patients with incurable breast cancer.”

The unmet need is pronounced in HER2+ MBC patients with brain metastases. Systemic therapies are effective in treating early HER2+ breast cancer; however, they have little effect on brain metastases (59). There are few systemic treatment options for HER2+ MBC patients with brain metastases following two anti-HER2 regimens, and none have demonstrated an OS benefit in this population. Data assessing a benefit from anti-HER2 therapies in treatment-experienced patients with brain metastases are not robust as patients with brain metastases, particularly those with active or progressing brain lesions included in HER2CLIMB, have been excluded from prior clinical trials. Additionally, results of current clinical trials of anti-

HER2 therapies are not generalisable to real-world MBC patients because they include small numbers of individuals with stable brain metastases previously treated with local therapies (e.g., surgery, radiation therapy) and do not include those with active or progressing brain metastases (34, 60).

Treatment options that offer clinically meaningful efficacy in a real-world population, and have tolerable safety profiles, are needed for patients with HER2+ MBC in the third-line setting. This evidence submission aims to address these unmet needs in third-line treatment of patients with HER2+ MBC with tucatinib, an orally bioavailable, reversible, small molecule TKI that is highly specific to HER2. When used in combination with trastuzumab and capecitabine, tucatinib provides unparalleled efficacy and a manageable safety profile while maintaining HRQoL in treatment-experienced patients with HER2+ MBC (15).

Giving eligible patients access to the tucatinib combination represents a step-change in the management of HER2+ MBC in the third-line setting in England. As will be discussed in the next sections, the tucatinib combination can ultimately offer patients with HER2+ MBC, including those with brain metastases, hope to fight this aggressive disease and change its devastating prognosis.

B.1.4 Equality considerations

The use of tucatinib is not expected to raise any equality issues.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

The clinical evidence base for tucatinib was established using a systematic literature review (SLR) of publications (abstracts, manuscripts) in literature databases (e.g., PubMed, EMBASE), trial registries, and major scientific/medical congresses from inception through November 23, 2020. The search strategy identified clinical and safety studies with available treatments for unresectable, locally advanced, or metastatic HER2+ breast cancer, including patients with brain metastases; with progression after previous treatment with at least one prior anti-HER2 regimen in any

setting. As such, the search included a broader patient population than that of the licensed indication of TUKYSA. Initially the search was conducted for studies that included HER2+ MBC patients who had received at least two prior anti-HER2 regimens; however, due to the limited number of studies identification criteria were expanded and articles that had been excluded based on population were rescreened against the amended criteria. Appendix D describes the process and methods used to identify and select clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

One randomised, global, pivotal phase 2* clinical trial of tucatinib in combination with trastuzumab and capecitabine (jointly referred to as “tucatinib combination”), HER2CLIMB, was identified and is summarised in detail in this submission (15). HER2CLIMB evaluated the efficacy and safety of tucatinib in combination with trastuzumab and capecitabine versus placebo with trastuzumab and capecitabine (Table 3).

HER2CLIMB was unique among large, randomised trials in that it included patients with active brain metastases (previously untreated or treated, progressing brain metastases) who have historically been excluded from clinical trials (15). Because it included patients with active or stable brain metastases, HER2CLIMB is more representative of the patient population seen in real-world clinical practice (outlined in Section B1.3.1.2).

Although the combination of trastuzumab with capecitabine is a clinically relevant treatment combination used in some markets, it is not licensed (or recommended by NICE in this clinical setting) for HER2+ MBC in the UK. In the absence of head-to-head trial evidence comparing the tucatinib combination versus UK-relevant single-agent chemotherapies of interest as per the final scope (i.e., eribulin, capecitabine and vinorelbine), an indirect treatment comparison (ITC) was employed for the

* As described in Section B.2.3.1 and depicted in Figure 2, HER2CLIMB was originally registered as a phase 2 study but the sample size and rigorous trial conduct are consistent with a phase 3 study.

purposes of this submission. Section B.2.9 presents the relevant ITC for this appraisal.

Table 3: Clinical effectiveness evidence

<table>
<tr><td>Study</td><td colspan="5">HER2CLIMB (NCT02614794, Murthy et al. 2020) (15)</td></tr>
<tr><td>Study design</td><td colspan="5">Phase 2,* randomised, double-blind, controlled clinical trial involving 612 patients at 155 sites across 15 countries, including 10 centres in the UK

* As described in Section B.2.3.1 below and depicted in Figure 2, HER2CLIMB was originally registered as a phase 2 study but the sample size and trial conduct were consistent with a phase 3 study.</td></tr>
<tr><td>Population</td><td colspan="5">Patients with HER2+ MBC previously treated with trastuzumab, pertuzumab and T-DM1, including patients with previously untreated or treated, progressing brain metastases</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Tucatinib in combination with trastuzumab and capecitabine</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo in combination with trastuzumab and capecitabine</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>X</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>X</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">Pivotal trial providing robust, relevant evidence in this indication.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• PFS
• OS
• Response rate
• Duration of response
• Adverse effects of treatment
• HRQoL</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Clinical laboratory assessments
• Vital signs and other relevant safety variables
• Frequency of dose holding, dose reductions and discontinuations of tucatinib, capecitabine and trastuzumab
• Cumulative incidence of healthcare resource utilisation, including hospitalisations, length of stay and emergency department visits</td></tr>
<tr><td>Relevant amendments after trial commencement</td><td colspan="5">• Collection of HRQoL (EQ-5D-5L) data was added to the trial protocol when HER2CLIMB was amended and expanded to become a global, pivotal, randomised clinical trial (see Section B.2.3.1)</td></tr>
</table>

BICR, blinded independent central review; CBR, clinical benefit rate; DOR, duration of response; EQ-5D-5L, EuroQoL 5 Dimensions 5 Levels; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; ITT, intent to treat; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DM1, trastuzumab emtansine; UK, United Kingdom
Source: Murthy et al. 2020 (15)

HER2CLIMB was the only relevant study identified that assessed the tucatinib combination and was therefore used in the economic model. External studies with

the relevant comparators for this submission were identified in the SLR and included in the network meta-analysis (NMA) presented in Section B.2.9.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

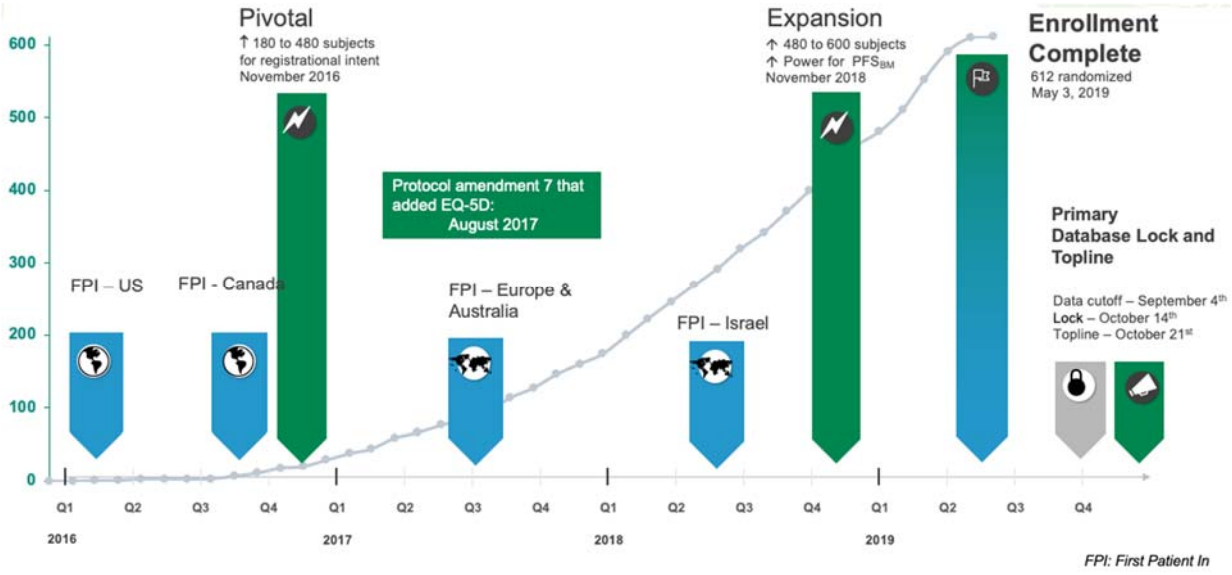
B.2.3.1 Evolution of clinical trial design

The HER2CLIMB study is a robust, multicentre, randomised, double-blind, placebo-controlled, active-comparator trial that included 612 patients with HER2+ MBC who were previously treated with trastuzumab, pertuzumab and T-DM1. Nearly half (48%) of patients had confirmed brain metastases, including stable and active (untreated or progressing) lesions at baseline. HER2CLIMB is the only randomised clinical trial to-date to evaluate treatment efficacy in a population of HER2+ MBC patients that included patients with active brain metastases, which closely represent patients who would be seen in clinical practice (15).

HER2CLIMB was initiated as a phase 2 study with a sample size of 180 subjects. During the study, the sample size was increased on two occasions to improve the statistical robustness of the study design; both increases occurred prior to unblinding and without knowledge of the study results. First, HER2CLIMB was amended soon after study initiation to increase the sample size to 480 subjects, with the intent of transforming it into a pivotal study to potentially support registration. Importantly, these changes were applied to the study protocol without any interim analysis or unblinding of the data. In addition to the other amendments, the EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) was added, and data collected from patients who were subsequently enrolled in the trial. Second, the total sample size was increased to 600 subjects to provide greater power for the key secondary endpoint of PFS in patients with brain metastases ($PFS_{brain\ metastases}$), since the analysis set for this endpoint includes approximately half of the total sample size. PFS remained the primary endpoint for the first 480 subjects enrolled, as this sample size provided sufficient statistical power for the expected treatment effect. Furthermore, limiting the primary analysis only to the first 480 subjects avoided potential bias from early

progression events in the overall population, where many of the subjects would have had a shorter follow-up. In addition, the statistical testing for the key secondary endpoints was amended from a hierarchical to parallel structure to ensure ability to test both OS and $PFS_{brain\ metastases}$. Again, these changes were applied to the study protocol without any interim analysis or unblinding of the data.

Figure 2: HER2CLIMB history and milestones



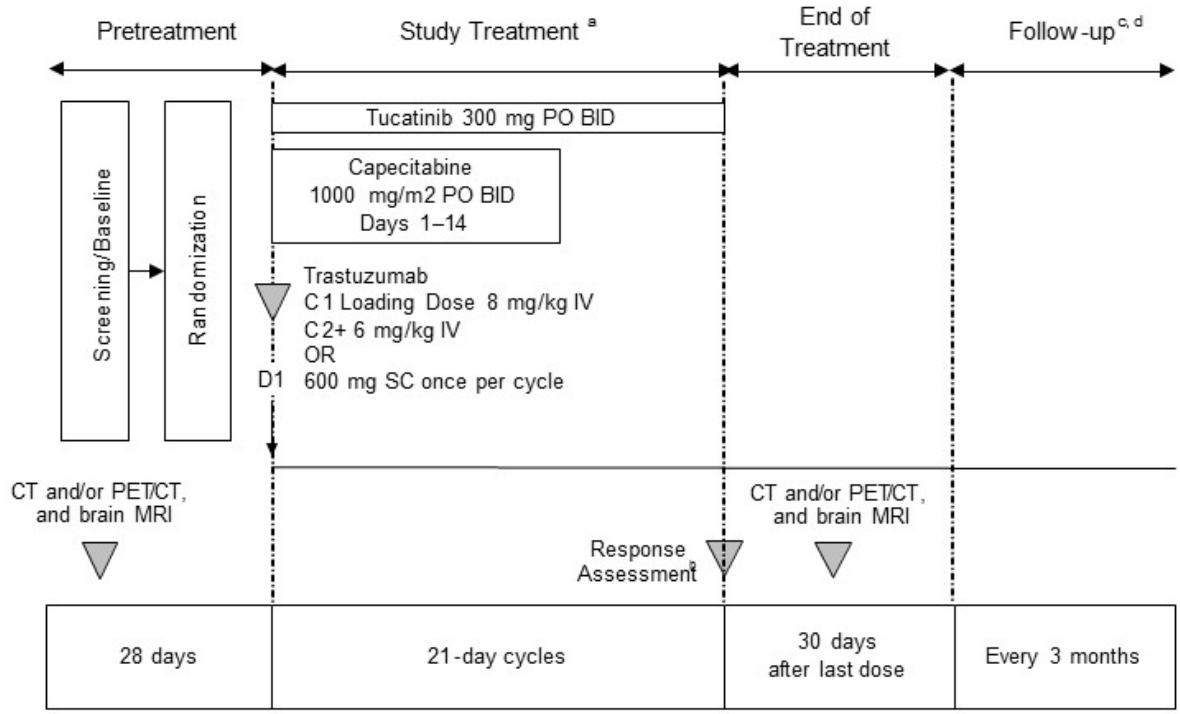
EQ-5D, EuroQoL 5 Dimensions; FPI, first patient in; PFS, progression-free survival; US, United States
Source: Seagen Data on File 2020 (61)

Patients were randomised 2:1 to receive either tucatinib or placebo in combination with trastuzumab and capecitabine, and treatment continued until unacceptable toxicity, disease progression, withdrawal of consent, or study closure (Figure 3). Patients were stratified by known history of treated or untreated brain metastases† (yes or no), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1) and geographic region (US, Canada or rest of world). Contrast-enhanced spiral CT, positron emission tomography (PET)/CT and/or contrast-enhanced magnetic

† In the literature, the terminology CNS metastases refer to brain and leptomeningeal metastases. HER2CLIMB included a subset of these patients, as those with leptomeningeal metastases were excluded, which is typically done in clinical trials. HER2CLIMB is unique in that it included patients with stable brain metastases (patients who had received prior therapy for their brain metastases with no progression and symptoms at the time of study enrolment) and active brain metastases (those previously treated with progression detected at the time of study consideration and also those with newly diagnosed lesions with no prior therapy for brain metastases). No pivotal, randomised, controlled trial of this size has included patients with active brain metastases.

resonance imaging (MRI) were obtained at baseline, every 6 weeks for 24 weeks and every 9 weeks thereafter. Brain MRI at baseline was required for all patients (15).

Figure 3: Schematic of study design for HER2CLIMB



BID, twice daily; CNS, central nervous system; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; PD, progressive disease; PET, positron emission tomography; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumours; SC, subcutaneous

[a] Treatments continued until unacceptable toxicity, disease progression, withdrawal of consent or study closure. Patients with CNS progression may have undergone local therapy to CNS lesions and continued on study treatment with approval from the medical monitor for clinical benefit.

[b] Contrast CT, PET/CT (CT must have been of diagnostic quality), and/or MRI and brain contrast MRI scan at baseline, every 6 weeks for the first 24 weeks, and then every 9 weeks thereafter until PD, initiation of a new therapy, withdrawal of consent, or study closure. Patients without brain metastases at baseline did not require brain contrast MRIs while on treatment. A brain contrast MRI was required at the 30-day follow-up visit for all patients.

[c] Assessment of overall survival and/or disease recurrence, as well as collection of information regarding any additional anti-cancer therapies administered after completion of study treatment.

[d] If study treatment was discontinued for reasons other than disease progression (per RECIST 1.1) or death, every reasonable effort was made to obtain contrast CT, PET/CT and/or MRI, and contrast brain MRI (only in patients with known brain metastases) approximately every 9 weeks until disease progression (per RECIST 1.1), death, withdrawal of consent or study closure.

Source: Seagen, HER2CLIMB Clinical Study Report, 2019 (4)

B.2.3.2 Trial methodology

Table 4: Summary of methodology

Trial name	HER2CLIMB (4, 15)
Trial design	Randomised (2:1 ratio), international, multicentre, double-blind, placebo-controlled, active-comparator trial

Patient population	Unresectable locally advanced or metastatic HER2+ breast carcinoma previously treated with trastuzumab, pertuzumab and T-DM1
Locations	155 sites in 15 countries across the US, Canada, Europe (Austria, Belgium, Czechia, Denmark, France, Germany, Italy, Portugal, Spain, Switzerland, and UK), Israel and Australia
Eligibility	**Key inclusion criteria** • Histologically confirmed HER2+ breast carcinoma, with HER2+ defined by ISH or FISH or IHC methodology • Previous treatment with trastuzumab, pertuzumab and T-DM1 • Progression of unresectable locally advanced or MBC after last systemic therapy (as confirmed by investigator), or was intolerant of last systemic therapy • Measurable or non-measurable disease assessable by RECIST 1.1 • ≥18 years of age at time of consent • ECOG PS 0 or 1 • Life expectancy of at least 6 months, in the opinion of the investigator • CNS inclusion o No evidence of brain metastases (no brain metastases) o Untreated brain metastases not needing immediate local therapy. For patients with untreated CNS lesions >2.0 cm on screening contrast brain MRI, discussion with and approval from the medical monitor is required prior to enrolment (active brain metastases) o Previously treated brain metastases (stable brain metastases) **Key exclusion criteria** • Prior treatment in the metastatic setting with capecitabine, lapatinib within 12 months of starting study treatment (except in cases where lapatinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity), neratinib, afatinib or other investigational HER2/EGFR or HER2 TKI at any time • Clinically significant cardiopulmonary disease, hepatitis B or C or other known chronic liver disease, HIV or dihydropyrimidine dehydrogenase deficiency • Unable to undergo brain MRI • Have used a strong CYP3A4 or CYP2C8 inhibitor within 5 half-lives of the inhibitor, or a strong CYP3A4 or CYP2C8 inducer within 5 days prior to first dose of study treatment CNS exclusions: • Untreated brain lesions >2.0 cm in size, unless discussed with medical monitor • Ongoing use of systemic corticosteroids for control of symptoms of BM at a total daily dose of >2 mg of dexamethasone (or equivalent) • Any brain lesion thought to require immediate local therapy • Known or suspected leptomeningeal disease as documented by the investigator • Poorly controlled (>1/week) seizures
Trial drugs	• Tucatinib: 300 mg PO BID continuously during treatment period Trastuzumab: 8 mg/kg IV loading dose then 6 mg/kg (or 600 mg SC) once every 21 days Capecitabine: 1000 mg/m^2 PO BID days 1–14 of each 21-day cycle • Placebo PO BID continuously during treatment period Trastuzumab: 8 mg/kg IV loading dose then 6 mg/kg (or 600 mg SC) once every 21 days Capecitabine: 1000 mg/m^2 PO BID days 1–14 of each 21-day cycle

	Treatments continued until unacceptable toxicity, disease progression, withdrawal of consent or study closure. Patients with CNS progression may have undergone local therapy to CNS lesions and continued on study treatment with approval from the medical monitor for clinical benefit.
Permitted and disallowed concomitant medication	Standard supportive care measures, including anti-emetics, anti-diarrhoeal medications, and hematopoietic growth factors, were permitted but not required. The following medications were prohibited: • Strong CYP3A4 or CYP2C8 inducers or inhibitors • Warfarin • Corticosteroids for control of symptoms of CNS metastases at study entry
Endpoints[a]	• **Primary endpoint:** PFS per RECIST 1.1 in primary endpoint population • **Key secondary (alpha-controlled) endpoints:** PFS per RECIST 1.1 in patients with BM at baseline ($PFS_{brain\ metastases}$); OS in total population; confirmed ORR in total population • **Other secondary endpoints:** PFS by investigator assessment in total population; DOR and CBR in total population • **Safety endpoints:** adverse events; clinical laboratory assessments; vital signs and other relevant safety variables; frequency of dose holding, dose reductions and discontinuations of tucatinib and capecitabine; frequency of dose holding and discontinuations of trastuzumab • **Health economics and outcomes endpoints:**[b] cumulative health resource utilisation, including length of stay, hospitalisations, and emergency room visits; HRQoL/health status using the EQ-5D-5L
Outcomes used in the economic model	• PFS • OS • Adverse effects of treatment • HRQoL
Pre-planned subgroups	• Age (≥65 or <65 years) • Race (white or non-white) • Hormone receptor status (HmR+ or HmR-) • Baseline brain metastases (yes or no) • ECOG performance-status score (0 or 1) • Geographic region (US and Canada or rest of world)

BICR, blinded independent central review; BID, twice daily; BM, brain metastases; CBR, clinical benefit rate; CNS, central nervous system; CYP2C8, cytochrome P450 2C8; CYP3A4, cytochrome P450 3A4; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EQ-5D-5L, EuroQoL 5 Dimensions 5 Levels; HER2, human epidermal growth factor receptor 2; HmR, hormone receptor; HRQoL, health-related quality of life; FISH, fluorescence *in situ* hybridisation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridisation; IV, intravenously; MBC, metastatic breast cancer; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor; UK, United Kingdom; US, United States

[a] Disease response and progression were evaluated in accordance with RECIST criteria version 1.1 by BICR.

[b] HRQoL and health economics endpoints were added in protocol amendment 7 (30 August 2017). Thus, analyses for these endpoints only include patients who consented to this protocol amendment; consequently, the number of patients is smaller compared with the total ITT population.

Source: Murthy et al. 2020 (15), Seagen, HER2CLIMB Clinical Study Report, 2019 (4); Clinicaltrials.gov, NCT02614794 (62)

As shown in Table 5, HER2CLIMB included several different analysis populations.

Table 5: HER2CLIMB analysis populations

Analysis population	Definition	Analyses where used
Primary endpoint population	First 480 patients randomised	Primary endpoint of PFS per BICR

ITT-OS	Total study population (N=612)	Secondary endpoints of OS and confirmed ORR
ITT-$PFS_{brain\ metastases}$	All randomised patients with BM (N=291)	Secondary endpoint of $PFS_{brain\ metastases}$ per BICR
Safety	All randomised who received at least 1 dose of study treatment (N=601)	Safety analyses

BICR, blinded independent central review; BM, brain metastases; ITT, intent to treat; OS, overall survival, ORR, objective response rate; PFS, progression-free survival
Source: Murthy et al. 2020 (15); Seagen, HER2CLIMB Clinical Study Report, 2019 (4)

B.2.3.3 Baseline characteristics

Between February 23, 2016 and May 3, 2019, 612 patients were enrolled at 155 sites in 15 countries across the US, Canada, Europe (including 10 sites in the UK), Israel and Australia. A total of 410 patients were randomised to the tucatinib combination group (tucatinib in combination with trastuzumab and capecitabine) and 202 to the placebo combination group (placebo in combination with trastuzumab and capecitabine). In the primary endpoint population (N=480), 320 patients were randomised to the tucatinib combination group and 160 to the placebo combination group. Median follow-up for the total population was 14.0 months.

The baseline patient demographics and disease characteristics are presented in Table 6 and were, overall, balanced between the treatment groups in both primary endpoint population and total study population. In the total population, the median age of all randomised patients was 54 years, and the majority (81%) were <65 years of age. Bone was the most frequent site of metastasis (55%) and 48% of patients had a presence or history of metastases to the brain. Among those patients with brain metastases, approximately 60% had active (untreated or progressing) lesions (15). Other stratification factors (ECOG performance status and region of the world) were balanced between the two treatment arms (15).

A total of [redacted] patients from UK centres were randomised to receive either tucatinib ([redacted]) or placebo ([redacted]) in combination with trastuzumab and capecitabine. Of those, [redacted] patients had brain metastases at baseline ([redacted] in the tucatinib combination group and [redacted] in the placebo combination group).

Table 6: Baseline demographics and disease characteristics of patients in HER2CLIMB

	Primary endpoint population[a] (N=480)		Total study population[a] (N=612)	
Variable, no. (%) if not otherwise stated	**Tucatinib combination (n=320)**	**Placebo combination (n=160)**	**Tucatinib combination (n=410)**	**Placebo combination (n=202)**
Female sex	317 (99.1)	158 (98.8)	407 (99.3)	200 (99.0)
Age				
<65 years	252 (78.8)	132 (82.5)	328 (80.0)	168 (83.2)
≥65 years	68 (21.3)	28 (17.5)	82 (20.0)	34 (16.8)
Median – years	54.0	54.0	55.0	54.0
Race				
Asian	17 (5.3)	3 (1.9)	18 (4.4)	5 (2.5)
Black/African American	30 (9.4)	13 (8.1)	41 (10.0)	14 (6.9)
White	225 (70.3)	125 (78.1)	287 (70.0)	157 (77.7)
Unknown/other	48 (15.0)	19 (11.9)	64 (15.6)	26 (12.9)
Region				
US/Canada	204 (63.8)	103 (64.4)	246 (60.0)	123 (60.9)
Rest of world	116 (36.3)	57 (35.6)	164 (40.0)	79 (39.1)
Hormone receptor status				
ER and/or PgR-positive	190 (59.4)	99 (61.9)	243 (59.3)	127 (62.9)
ER and PgR-negative	126 (39.4)	61 (38.1)	161 (39.3)	75 (37.1)
Other	4 (1.3)	0	6 (1.5)	0
ECOG performance status[b]				
0	159 (49.7)	76 (47.5)	204 (49.8)	94 (46.5)
1	161 (50.3)	84 (52.5)	206 (50.2)	108 (53.5)
Stage IV at initial diagnosis	108 (33.8)	67 (41.9)	143 (34.9)	77 (38.1)
Presence or history of brain metastases	148 (46.3)	71 (44.4)	198 (48.3)	93 (46.0)
Previously treated stable	[c]	[c]	80 (40.4)	37 (39.8)
Previously treated progressing	[c]	[c]	44 (22.2)	22 (23.7)
Untreated	[c]	[c]	74 (37.4)	34 (36.6)
Location of other metastases				
Lung	160 (50.0)	82 (51.3)	200 (48.8)	100 (49.5)
Liver	108 (33.8)	64 (40.0)	137 (33.4)	78 (38.6)
Bone	178 (55.6)	85 (53.1)	223 (54.4)	111 (55.0)
Prior lines of therapy, median (range)	4.0 (2, 14)	4.0 (2,17)	4.0 (2, 14)	4.0 (2,17)
Prior lines of therapy in the metastatic setting, median (range)	3.0 (1, 14)	3.0 (1, 13)	3.0 (1, 14)	3.0 (1, 13)
Prior therapies				
Trastuzumab	320 (100)	160 (100)	410 (100)	202 (100)
Pertuzumab	320 (100)	159 (99.4)	409 (99.8)	201 (99.5)
T-DM1	320 (100)	160 (100)	410 (100)	202 (100)
Lapatinib[d]	22 (6.9)	10 (6.2)	24 (5.9)	10 (5.0)

ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; ITT, intent to treat; no, number; OS, overall survival; PgR, progesterone receptor; T-DM1, trastuzumab emtansine; US, United States

[a] The primary endpoint analysis population included the first 480 patients who were randomly assigned to the tucatinib combination group or to the placebo combination group, and the total population included 612 patients who underwent randomisation. Randomisation stratification factors included geographic region (US, Canada or the rest of the world), presence or history of brain metastases (yes or no) and ECOG performance-status score (0 or 1).

[b] ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability.

[c] Data not available because brain metastases analyses included all patients with brain metastases from the total study population (ITT-OS).
[d] Patients received lapatinib more than 12 months before initiating a trial regimen were eligible for inclusion.
Source: Murthy et al. 2020 (15)

Baseline demographics and characteristics for patients with brain metastases (intent to treat [ITT]-$PFS_{brain\ metastases}$ population) are consistent with those from the primary endpoint population (HER2CLIMB patient populations are defined in Table 5). Baseline patient characteristics were also balanced between the subset of patients with HRQoL data at baseline and the full study population (ITT-OS population).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The primary objective of HER2CLIMB was to compare the PFS between the two treatment arms in the primary endpoint population (i.e., first 480 randomised patients, Table 5) (4). The null hypothesis for this comparison was that the assignment of patients to the two treatment arms had no effect on PFS. The two treatment arms were compared for PFS using a stratified, log-rank test controlling for the randomisation stratification factors (i.e., history of brain metastases or presence of brain metastases or lesions of equivocal significance on screening MRI [yes, no], ECOG performance status [0, 1] and region of the world [North America, rest of world]).

As per the prespecified statistical analysis plan, the primary endpoint analysis was to be performed after approximately 288 PFS events in the primary endpoint population, which would provide 90% power to detect a hazard ratio (HR) of 0.67 using a two-sided log-rank test at alpha of 0.05 (15). If the primary endpoint PFS in the primary endpoint population was statistically significant, OS in the total population and PFS in patients with brain metastases ($PFS_{brain\ metastases}$) were to be parallel tested at significance levels (alpha) of 0.02 and 0.03, respectively, in the first interim analysis. The final analyses for OS and $PFS_{brain\ metastases}$ were to be performed with 361 and 220 events, respectively. Approximately 600 patients were to be randomised for the required number of events. If both OS and $PFS_{brain\ metastases}$

were statistically significant, the difference in confirmed objective response rate (ORR) between treatment arms was to be tested at a two-sided alpha level of 0.05.

Kaplan-Meier methodology was used to estimate PFS and OS time curves, median PFS and OS and 95% confidence intervals (CIs) for the treatment arms. Stratified Cox proportional-hazards models were used to estimate HRs and 95% CIs.

At the 4 September 2019 data cutoff, there were 275 PFS events in the primary endpoint population, and 215 deaths and 157 PFS events in patients with brain metastases in the total population. Based on the observed number of events, the multiplicity-adjusted, two-sided alpha levels at the first interim analysis were 0.0074 for OS and 0.008 for $PFS_{\text{brain metastases}}$ (15).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A summary of the quality assessment for HER2CLIMB is presented in Table 7, and the full details of all studies included in this submission are presented in Appendix D.

HER2CLIMB is of high quality as it was conducted with accepted standards of good clinical practice, and all applicable federal, state and local laws, rules, regulations, requirements and guidelines (including all foreign laws and governmental requirements as applicable) relating to the conduct of the clinical trial.

The study was supported by Seagen and the main authors of the study declared they received consulting fees from pharmaceutical companies, including Seagen. No other potential conflict of interest relevant to the study publication was reported by the authors (15).

Table 7: Quality assessment of HER2CLIMB

HER2CLIMB (NCT02614794)	
Was randomisation carried out appropriately?	Yes – patients were randomised in a 2:1 ratio using a dynamic hierarchical randomisation scheme to receive tucatinib or placebo in combination with capecitabine and trastuzumab
Was the concealment of treatment allocation adequate?	Yes – adequate blind allocation was achieved with the applied randomisation scheme

Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – baseline patient characteristics were balanced between the treatment arms
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – the first part of the study was carried out blindly for the investigator, study centre personnel, clinical research organisation staff and sponsor personnel (except for prespecified Safety personnel)
Were there any unexpected imbalances in dropouts between groups?	No – balanced, low rates of dropouts were observed in both treatment arms: 23/404 (5.7%) patients discontinued tucatinib and 6/197 (3.0%) patients discontinued placebo
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all predefined endpoints were reported
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – the primary endpoint was assessed in the first 480 enrolled patients (primary endpoint population), and patients without outcomes for PFS and OS were censored and those with missing data considered non-responders for ORR and CBR outcomes

CBR, clinical benefit rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival
Source: Murthy et al. 2020 (15)

B.2.6 Clinical effectiveness results of the relevant trials

The efficacy and tolerability of the tucatinib combination has been demonstrated in HER2CLIMB, a pivotal randomised, double-blind, placebo-controlled, active-comparator trial in patients with HER2+ MBC, including those with brain metastases, who have previously been treated with trastuzumab, pertuzumab and T-DM1 (15).

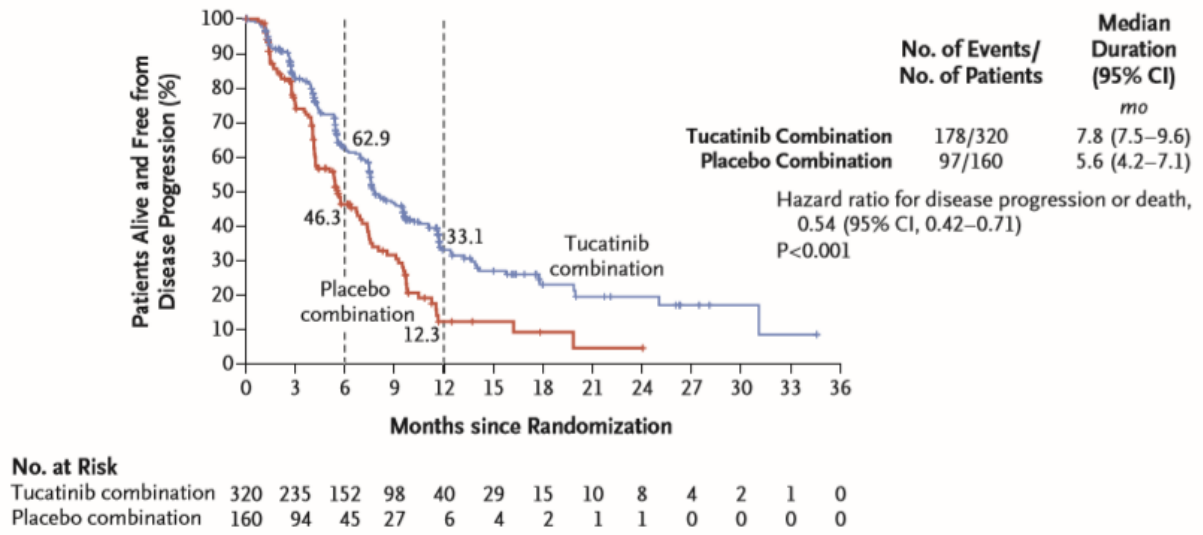
In HER2CLIMB, the tucatinib combination successfully met all key efficacy endpoints in addition to demonstrating a well-tolerated safety profile. In addition, the clinical benefit of the tucatinib combination was also achieved in patients with previously untreated or treated, progressing brain metastases at baseline. Given the robust design of HER2CLIMB, and the inclusion of patients with brain metastases who are routinely seen in UK clinical practice, its results support the use of the tucatinib combination in patients with HER2+ MBC (15).

B.2.6.1 PFS in the primary endpoint population (primary endpoint)

As of 4 September 2019, 275 of the first 480 randomised patients (57.3%) had experienced a PFS event (disease progression or death): 178 patients (55.6%) in the tucatinib combination group and 97 (60.6%) in the placebo combination group

(Figure 4). The tucatinib combination reduced the primary endpoint of risk of disease progression or death by 46% compared with the placebo combination (HR=0.54; 95% CI 0.42, 0.71; p<0.001) and led to a more than 2-month improvement in median PFS. A landmark analysis showed at 1 year, the estimated PFS was 33.1% (95% CI 26.6%, 39.7%) in the tucatinib combination group compared with 12.3% (95% CI 6.0, 20.9%) in the placebo combination group (15).

Figure 4: Kaplan-Meier estimate of PFS per BICR (primary endpoint population)



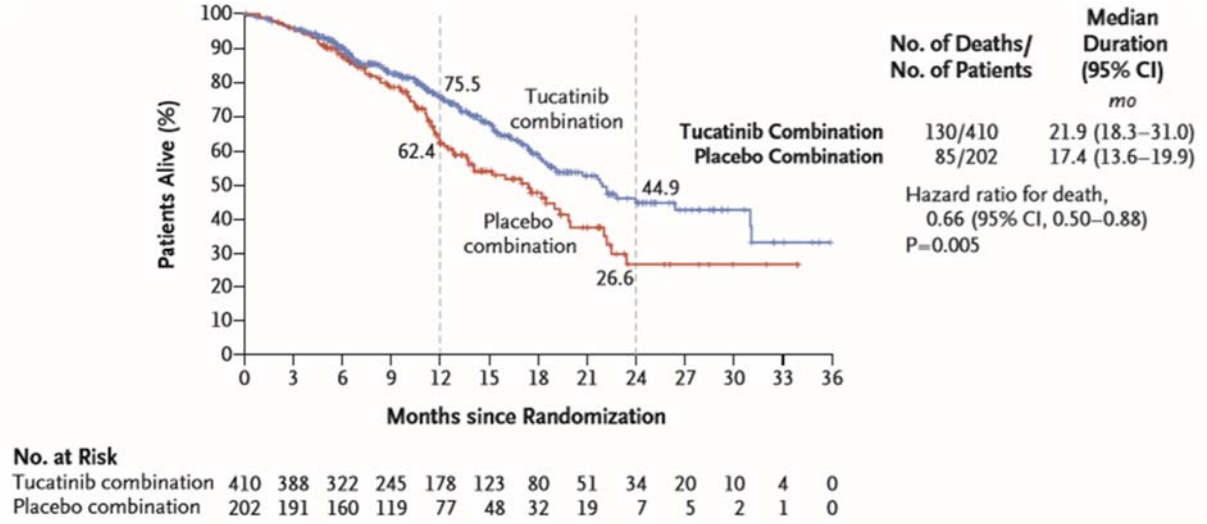
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; No, number
Source: Murthy et al. 2020 (15)

In the primary endpoint population, results of the PFS by investigator analysis were consistent with the primary efficacy endpoint (PFS by blinded independent central review [BICR]). Similarly, the improvement in PFS by BICR with the tucatinib combination in the total study population (ITT-OS, N=612) was also consistent with the primary efficacy endpoint in the primary endpoint population with a 46% reduction in the risk of disease progression or death for the tucatinib combination group compared with the placebo combination group (HR=0.54; 95% CI 0.42, 0.68) (15).

B.2.6.2 OS in the total study population (key secondary endpoint)

In the total study population (N=612), the tucatinib combination reduced the key secondary endpoint of risk of death by 34% compared with the placebo combination group (HR=0.66; 95% CI 0.50, 0.88; p=0.005) (Figure 5). Landmark analyses showed that at 1 year, estimated OS was 75.5% (95% CI 70.4%, 79.9%) in the tucatinib combination group and 62.4% (95% CI 54.1%, 69.5%) in the placebo combination group. At 2 years, estimated OS was 44.9% (95% CI 36.6%, 52.8%) in the tucatinib combination group and 26.6% (95% CI 15.7%, 38.7%) in the placebo combination group. The tucatinib combination extended median OS by 4.5 months over the placebo combination group (15).

Figure 5: Kaplan-Meier estimate of OS per BICR (total study population; ITT-OS)



BICR, blinded independent central review; CI, confidence interval; mo, months; ITT, intent to treat; No, number; OS, overall survival

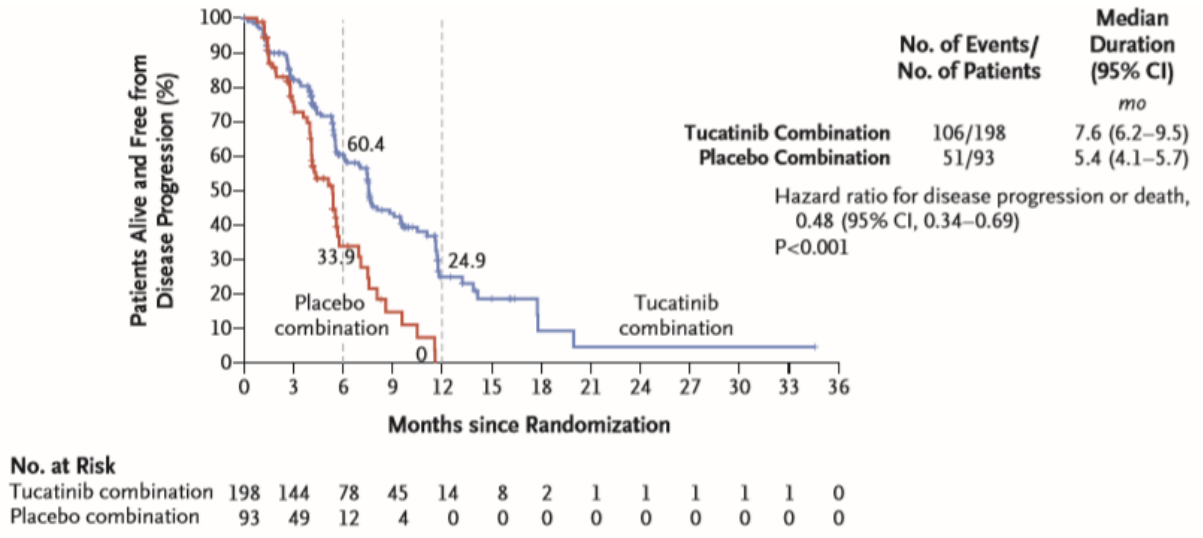
Source: Murthy et al. 2020 (15)

B.2.6.3 PFS in patients with brain metastases (key secondary endpoint)

In patients with active or stable brain metastases, including those with untreated, previously treated stable, and previously treated progressing lesions at baseline, the tucatinib combination reduced the key secondary endpoint of risk of disease progression or death by 52% compared with trastuzumab and capecitabine alone (HR=0.48; 95% CI 0.34, 0.69; p<0.001) and led to a more than 2-month improvement in median PFS (Figure 6).

A landmark analysis showed at 1 year, the estimated PFS was 24.9% (95% CI 16.5%, 34.3%) in the tucatinib combination group compared with 0% in the placebo combination group (15).

Figure 6: Kaplan-Meier estimate of PFS per BICR ($PFS_{brain\ metastases}$ population)

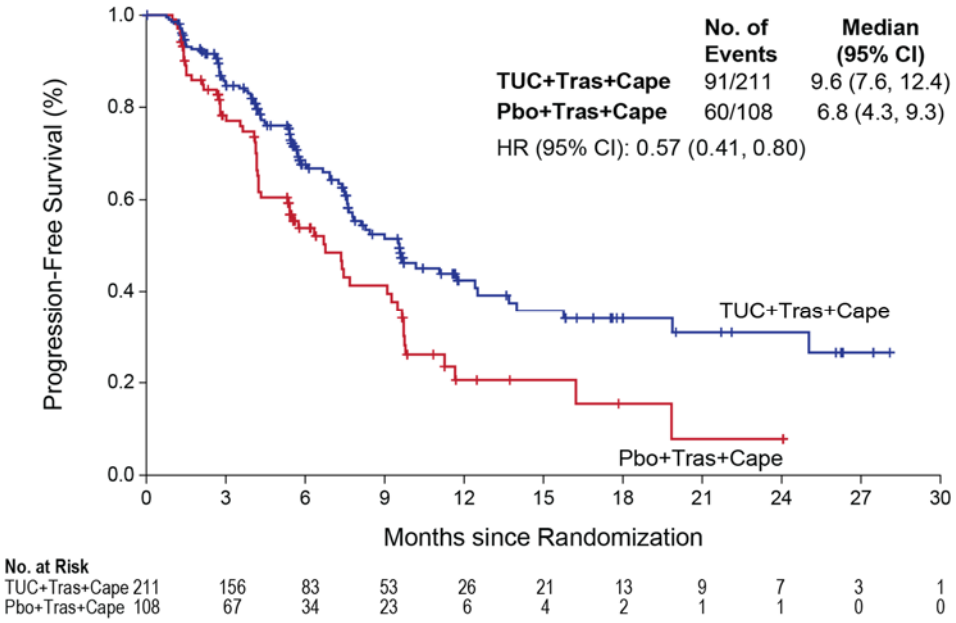


BICR, blinded independent central review; CI, confidence interval; mo, months; No, number; PFS, progression-free survival
Source: Murthy et al. 2020 (15)

B.2.6.4 PFS in patients without brain metastases

In a pre-specified exploratory analysis of patients without brain metastases at study entry (n=319; 211 tucatinib combination group and 108 placebo combination group), the tucatinib combination reduced the risk of disease progression or death by 43% compared with trastuzumab and capecitabine alone (HR=0.57; 95% CI 0.41, 0.80; p<0.001) (Figure 7) (4, 15). These results are consistent with those from the primary efficacy endpoint and the key secondary endpoint in patients with brain metastases (ITT-$PFS_{brain\ metastases}$), showing that the tucatinib combination has superior efficacy in HER2+ MBC in patients with and without brain metastases.

Figure 7: Kaplan-Meier estimate of PFS per BICR in patients without brain metastases (total study population; ITT-OS)

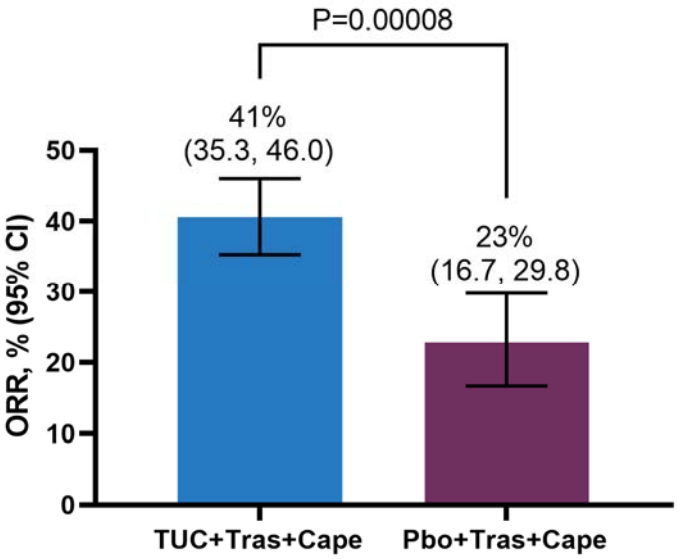


BICR, blinded independent central review; Cape, capecitabine; CI, confidence interval; ITT, intent to treat; HR, hazard ratio; No, number; Pbo, placebo; PFS, progression-free survival; OS, overall survival; TUC, tucatinib; Tras, trastuzumab
Source: Murthy et al. 2020 (15)

B.2.6.5 Overall response rate

In the total study population (ITT-OS), including patients with brain metastases, almost twice as many patients responded to the tucatinib combination compared with trastuzumab and capecitabine alone, as measured by confirmed ORR (Figure 8). Table 8 shows the best overall response achieved among 511 patients with measurable disease at baseline by BICR. More patients who received the tucatinib combination had a partial response (PR) and fewer had progressive disease (PD) compared with the placebo combination group (15).

Figure 8: Confirmed objective response[a] per BICR in patients with measurable disease (total study population; ITT-OS)



BICR, blinded independent central review; Cape, capecitabine; CI, confidence interval; ITT, intent to treat; ORR, confirmed objective response rate; OS, overall survival; Pbo, placebo; Tras, trastuzumab; TUC, tucatinib
[a] ORR defined as the percentage of patients with measurable disease at baseline (n=511) who had a confirmed complete response or partial response, as assessed by BICR.
Source: Murthy et al. 2020 (15)

Table 8: Confirmed objective response per BICR in patients with measurable disease (total study population; ITT-OS)

	Tucatinib combination (N=340)	Placebo combination (N=171)
Objective response, n (%)	138 (40.6)	39 (22.8)
95% CI[a]	35.3, 46.0	16.7, 29.8
Stratified CMH p-value[b]	<0.00008	
Best confirmed overall response[c], n (%)		
Complete response	3 (0.9)	2 (1.2)
Partial response	135 (39.7)	37 (21.6)
Stable disease	155 (45.6)	100 (58.5)
Progressive disease	27 (7.9)	24 (14.0)
Not evaluable	0	1 (0.6)
Not available[d]	20 (5.9)	7 (4.1)

BICR, blinded independent central review; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ITT-OS, intent-to-treat overall-survival population; RECIST, Response Evaluation Criteria in Solid Tumours; US, United States
[a] Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934).
[b] Cochran-Mantel-Haenszel test controlling for stratification factors (presence or history of BM: yes/no, ECOG performance status: 0/1, and region of world: US/Canada/rest of world) at randomisation.
[c] Confirmed best overall response assessed per RECIST 1.1.
[d] Patients with no post-baseline response assessment.
Source: Murthy et al. 2020 (15)

B.2.6.6 Clinical benefit rate

The clinical benefit rate was defined as achieving stable disease or non-complete response/non-PD for ≥6 months (i.e., no documented PD or death within 6 months from date of randomisation) or a best overall response of complete response (CR) or PR as determined by BICR review using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. In the total study population, the clinical benefit rate per BICR was 59.8% (95% CI 54.8, 64.5) for the tucatinib combination group compared with 38.1% (95% CI 31.4, 45.2) for the placebo combination group (nominal $p<0.00001$) (4).

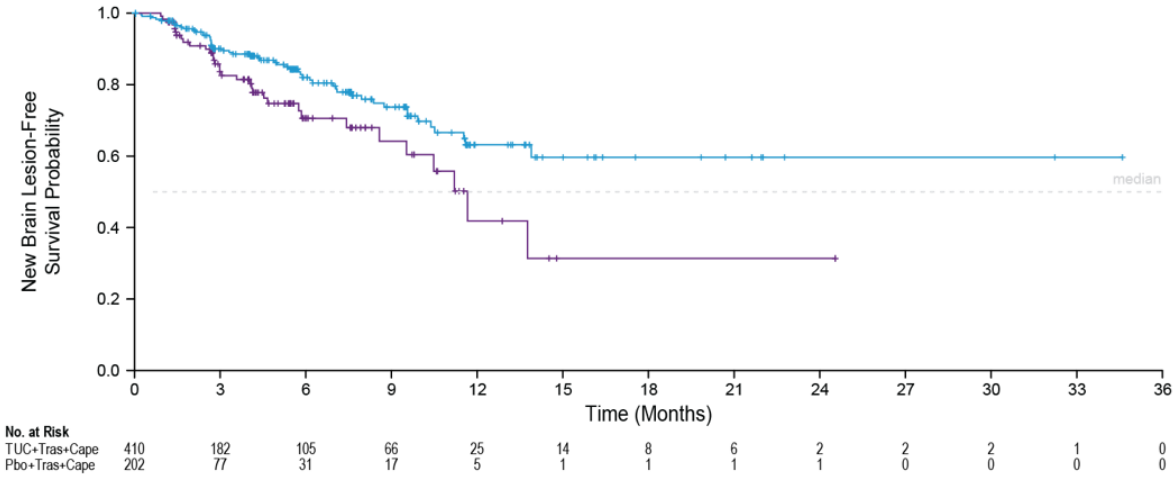
B.2.6.7 Duration of response (DOR)

DOR was defined as the time from the first objective response (CR or PR that is subsequently confirmed) to documented disease progression per RECIST 1.1 or death from any cause, whichever occurs first. The median DOR for patients with measurable disease at baseline per BICR was 8.3 months (95% CI 6.2, 9.7) for the tucatinib combination group and 6.3 months (95% CI 5.8, 8.9) for the placebo combination group (4).

B.2.6.8 Time to new brain lesions or death (post-hoc analysis)

Among all patients with HER2+ MBC in HER2CLIMB, with or without brain metastases, the tucatinib combination reduced the risk of developing new brain lesions or death from any cause by 48% (Figure 9) (59, 63). The rate of new brain lesions in all patients was lower in the tucatinib combination group (n=25/410; 6.1%) compared with the placebo combination group (n=19/202; 9.4%) (63).

Figure 9: Time to new brain lesions or death in patients with HER2+ MBC (total study population; ITT-OS)



Treatment arm	Events	HR (95% CI)	P value	Median new brain lesion-free survival (95% CI)
Tucatinib combination	52/410	0.52 (0.33, 0.82)	0.005	Not reached (13.9, -)
Placebo combination	33/202			11.7 months (9.5, -)

Cape, capecitabine; CI, confidence interval, CNS, central nervous system; HER2+ MBC, human epidermal growth factor receptor 2-positive metastatic breast cancer; HR, hazard ratio; ITT-OS, intent-to-treat overall-survival population; Pbo, placebo; Tras, trastuzumab; TUC, tucatinib
Source: Lin et al. 2020 (59); Lin et al. 2020 (60)

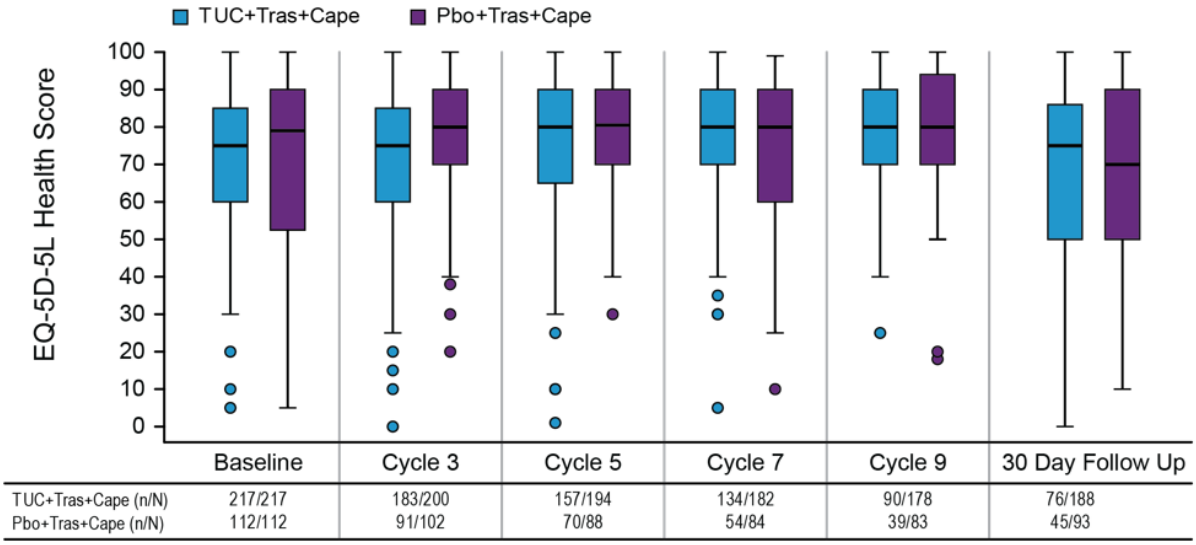
B.2.6.9 Patient-reported outcomes

As discussed in Section B.2.3.1, after Seagen acquired Cascadian Therapeutics, HER2CLIMB was expanded to enrol a larger number of patients around the world, including sites in the UK. Shortly thereafter, protocol amendment 7 added the assessment of HRQoL using the EQ-5D-5L, which consists of the EQ-5D descriptive system and the EQ visual analogue scale (VAS). Consequently, only a subset of patients has baseline HRQoL data (n=217 in the tucatinib combination group and n=112 in the placebo combination group) (64), including [redacted] patients from UK centres ([redacted] in the tucatinib combination group and [redacted] in the placebo combination group). However, baseline patient characteristics were consistent between the full study population (ITT-OS, as defined in Table 5) and those who had baseline HRQoL data.

During study treatment, no clinically meaningful differences in HRQoL were observed between the two treatment arms in any of the 5 domains: anxiety/depression, mobility, pain/discomfort, self-care, and usual activities (4). The

mean EQ-5D-5L VAS score was similar between treatment arms and stable throughout the trial, suggesting maintenance of HRQoL in both arms (Figure 10). Thus, no clinically meaningful declines in EQ-5D score from baseline to end of treatment were observed with the addition of tucatinib to trastuzumab and capecitabine.

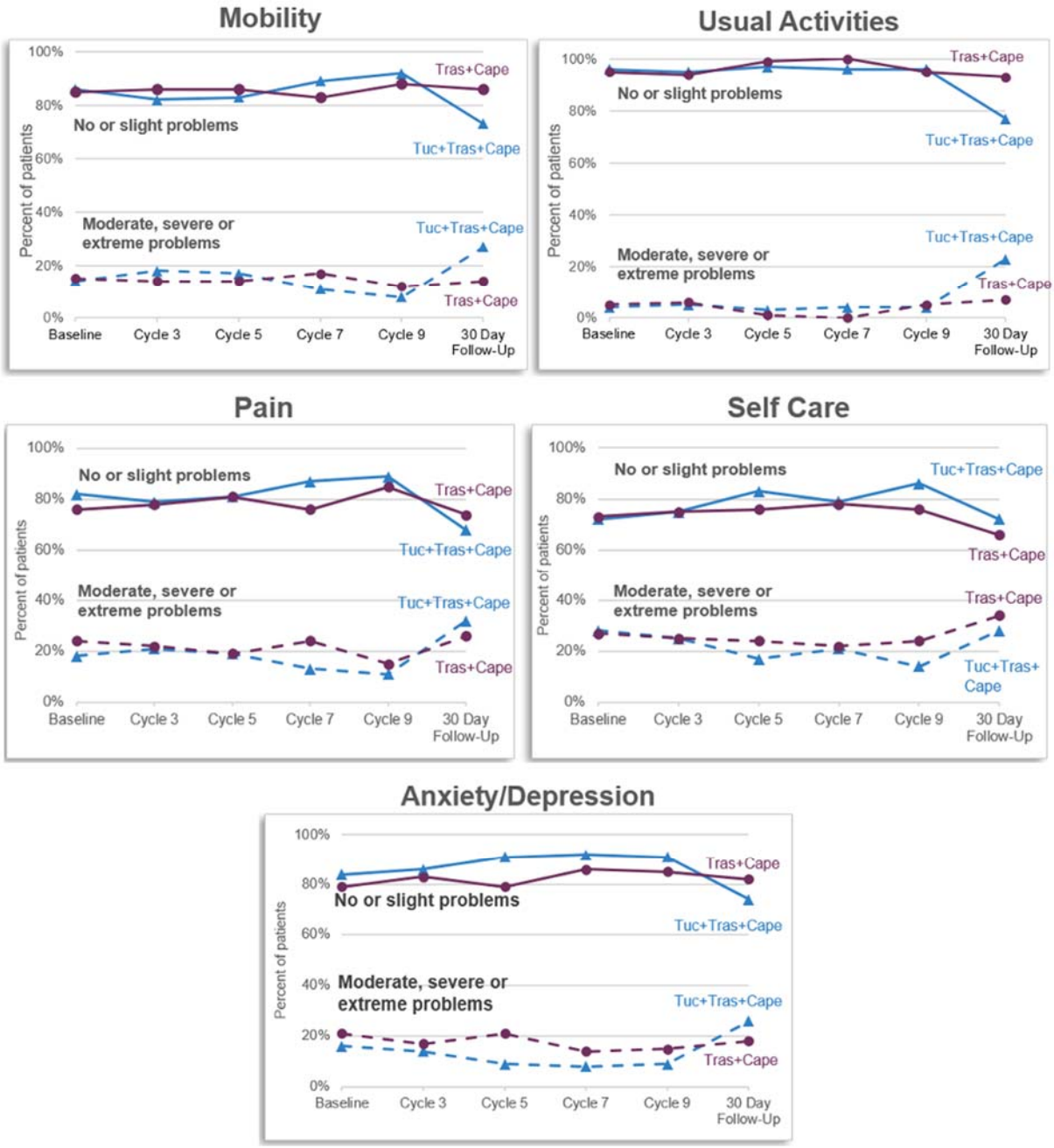
Figure 10: EQ-5D-5L VAS score over the course of treatment (full study population; ITT-OS[a])



Cape, capecitabine; EQ-5D-5L, EuroQol 5 dimensions 5 levels; HRQoL, health-related quality of life; ITT-OS, intent-to-treat overall-survival population; Pbo, placebo; Tras, trastuzumab; Tuc, tucatinib; VAS, visual analog scale
[a] HRQoL was evaluated in the full study population (ITT-OS); however, the EQ-5D-5L was implemented in protocol amendment 7; consequently, there were fewer patients with baseline HRQoL data (N=331, 218 in the tucatinib combination group and 113 in the placebo combination group) than in the full ITT-OS.
Baseline was defined as eventsmost recent non-missing assessment on or before first dose date.
n/N: n is the number of patients who completed the survey. N is the number of patients who completed baseline survey and are still on study. Cycles where the number of patients in each treatment group remained ≥20% of initial cohort size are presented. The length of the box represents the interquartile range (the distance between the 25th and 75th percentiles). The horizontal line in the box interior represents the group median. The whiskers extend to the group minimum and maximum values.
Source: Mueller et al. 2020 (64)

EQ-5D-5L subscale scores were maintained throughout the course of treatment and further confirm that adding tucatinib to trastuzumab plus capecitabine does not have a detrimental impact on HRQoL (Figure 11).

Figure 11: EQ-5D-5L subscale scores over the course of treatment (full study population; ITT-OS[a])



Cape, capecitabine; EQ-5D-5L, EuroQol 5 dimensions 5 levels; HRQoL, health-related quality of life; ITT-OS, intent-to-treat overall-survival population; Tras, trastuzumab; Tuc, tucatinib
Source: Mueller et al. 2020 (64)

B.2.7 Subgroup analyses

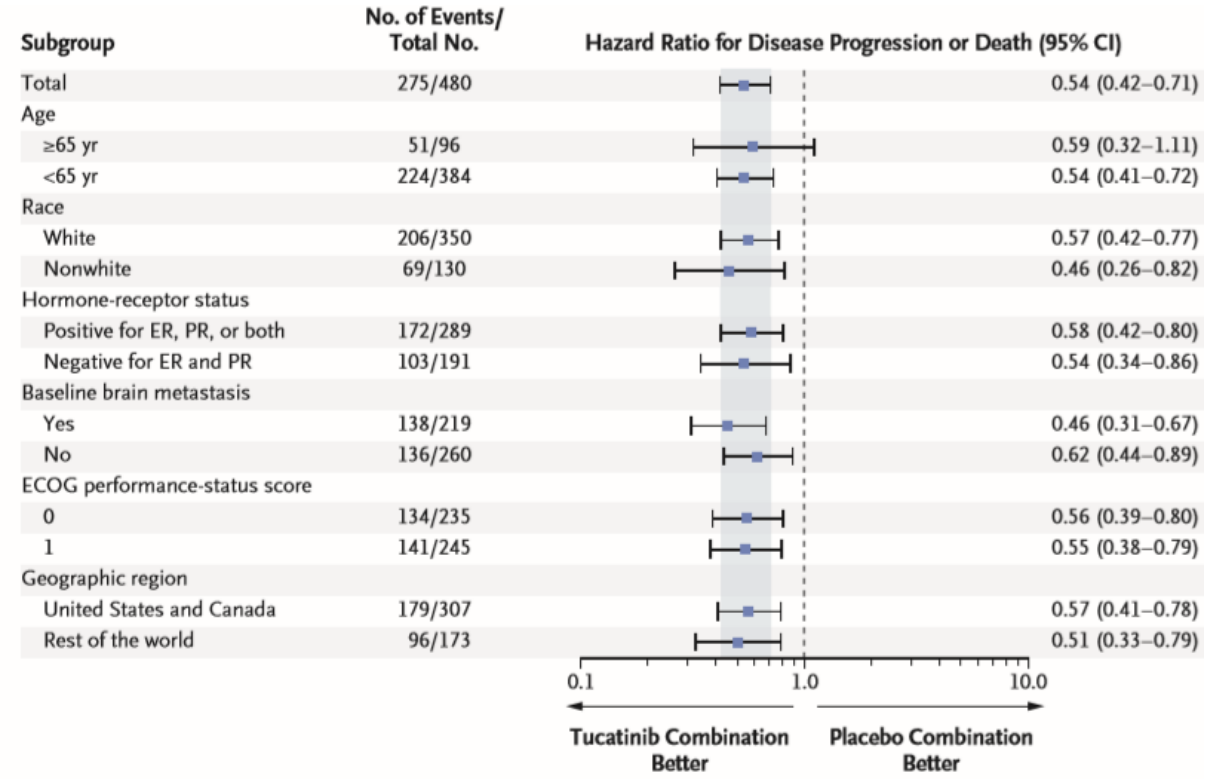
The tucatinib combination met all efficacy endpoints with consistent benefit across all pre-specified subgroups, including presence or absence of brain metastases, patient age, ECOG status, and hormone receptor status.

Consistent with the results in the total population, the tucatinib combination demonstrated a clinical benefit in patients with brain metastases in HER2CLIMB. Patients with active brain metastases not requiring immediate local therapy were eligible to enter HER2CLIMB and were classified as having either treated progressing or untreated brain metastases (Appendix E-Figure 1). Those requiring local therapy during screening could be eligible after washout and were considered to have treated stable brain metastases. Exploratory intracranial efficacy analyses in these subgroup of patients are presented in Appendix E for the endpoints of CNS-PFS, OS, confirmed intracranial ORR, and DOR in brain, along with HRQoL.

B.2.7.1 Subgroup analyses: PFS

Analyses of PFS by selected pre-specified subgroups (age ≥65 or <65 years, race, hormone receptor status, baseline brain metastases, ECOG status and geographic region) in the primary endpoint population (Figure 12) and brain metastases population (ITT-$PFS_{brain\ metastases}$, data not shown) show results that were generally consistent with the overall results from each of the respective populations (15). The PFS in the full ITT-OS population (N=612) was consistent with the primary endpoint PFS.

Figure 12: PFS per BICR by subgroups (primary endpoint population, n=480)

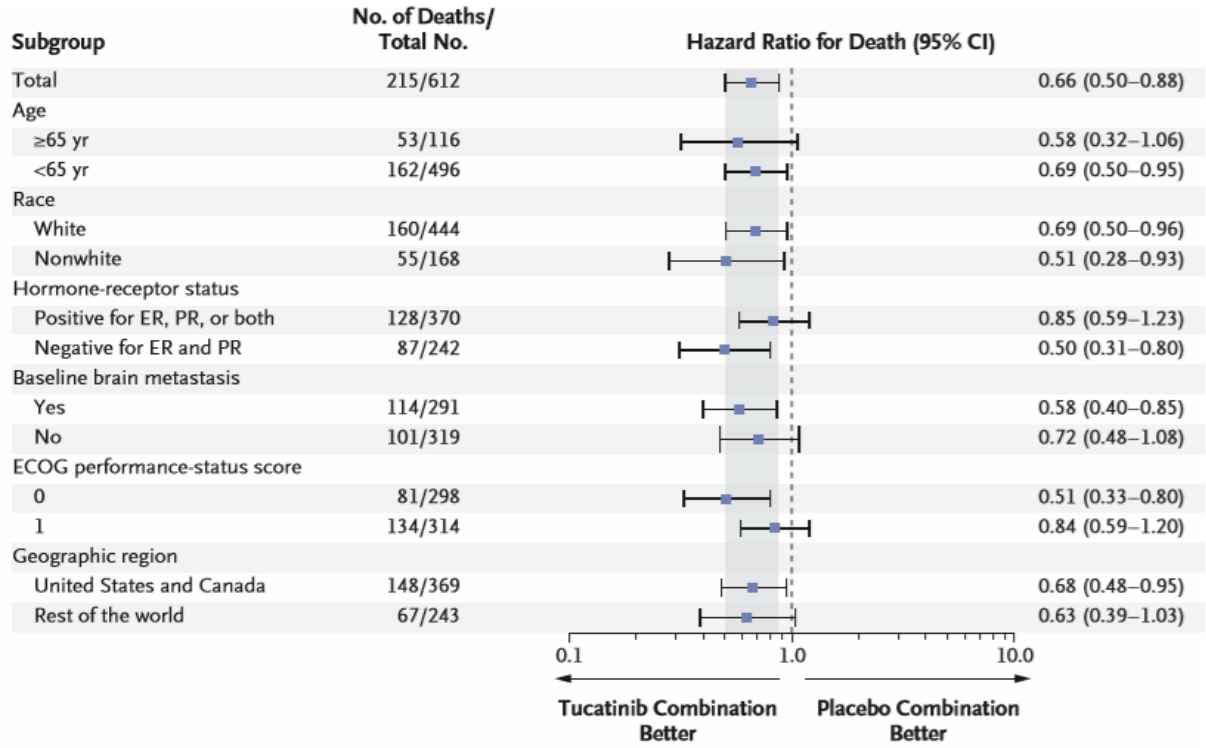


BICR, blinded independent central review; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; No, number; PFS, progression-free survival; PR, progesterone receptor; yr, year
Source: Murthy et al. 2020 (15)

B.2.7.2 Subgroup analyses: OS

The analysis of OS by selected pre-specified subgroups (age ≥65 or <65 years, race, hormone receptor status, baseline brain metastases, ECOG status and geographic region) show results that were generally consistent with the overall results from the total study population (ITT-OS) (Figure 13) (15).

Figure 13: OS per BICR by subgroups (ITT-OS population)



BICR, blinded independent central review; CI, confidence interval; ER, oestrogen receptor; ECOG, Eastern Cooperative Oncology Group; ITT, intent to treat; OS, overall survival; PR, progesterone receptor; yr, year
Source: Murthy et al. 2020 (15)

B.2.8 Meta-analysis

As there is only one relevant study (HER2CLIMB) for this submission, a meta-analysis could not be conducted. Instead, an ITC was performed.

B.2.9 Indirect and mixed treatment comparisons

Summary

- In the absence of head-to-head evidence for the tucatinib combination versus the single-agent chemotherapy agents included as relevant comparators in the decision problem (eribulin, capecitabine and vinorelbine), an NMA was conducted to enable ITCs for the tucatinib combination with the currently available third-line treatment options in England
- For the three comparisons of interest, seven relevant studies were used to compare PFS and six were used for OS comparisons

- The tucatinib combination demonstrated a [redacted] (eribulin monotherapy, capecitabine monotherapy and vinorelbine monotherapy):

Tucatinib combination versus	OS hazard ratio (95% credible interval)	PFS hazard ratio (95% credible interval)
Eribulin	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]

OS, overall survival; PFS, progression-free survival

- Eribulin is the only single-agent chemotherapy appraised and recommended by NICE in the third-line setting (NICE TA423), [redacted].
  - [redacted]eribulin, capecitabine and vinorelbine [redacted]
- Due to the uniqueness of HER2CLIMB with respect to the inclusion of patients with brain metastases, and that the pivotal single-agent chemotherapy trials excluded patients with active brain metastases, the evidence does not allow for a methodologically robust subgroup analysis in patients with brain metastases.

Indirect treatment comparisons

HER2CLIMB and the SLR outputs provided no direct head-to-head evidence comparing the tucatinib combination versus the single-agent chemotherapy agents included as relevant comparators in this submission (eribulin, capecitabine and vinorelbine). Thus, an NMA was conducted to enable indirect treatment comparisons for the tucatinib combination with the currently available options in third-line in England.

The results presented here are aligned with the decision problem of this appraisal and although the conducted NMA included treatments and combination treatments that are not licensed in the UK in the subpopulation of interest in this appraisal (Table 9), this submission only reports on comparisons of the tucatinib combination versus either eribulin, capecitabine or vinorelbine as monotherapy in patients with

HER2+ MBC. In order to create a viable network of evidence to perform an NMA that included comparators of interest, it was necessary to compare trials conducted in HER2+ MBC patients conducted in either:

- HER2+ patients who had received at least one anti-HER2 regimen (typically containing trastuzumab), or
- Mixed populations of patients with respect to HER2-status who had received at least one prior chemotherapeutic regimen

Key components of the NMA methodology include:

- HR analyses of PFS and OS – the analyses assume proportionality between the hazard rates over time for the two treatment arms being compared. An HR is a representative measure of PFS or OS only if it is constant over time (i.e., the hazard rates are proportional between treatment arms). If this assumption holds, an NMA of the HRs may be performed
- Fractional polynomial analyses – given the evidence of non-proportional HRs noted in some trials and heterogeneity of the populations, fractional polynomial NMA models were fitted to the network of evidence for PFS and OS. Since patient-level data were not reported in publications, they were reconstructed using Kaplan-Meier survival curves and the numbers at risk

Table 9: Summary of the trials used to carry out the indirect treatment comparison

References of trial	Tucatinib + trastuzumab + capecitabine	Eribulin alone	Capecitabine alone	Vinorelbine alone	Trastuzumab + capecitabine	Lapatinib + capecitabine
HER2CLIMB (NCT02614794) (15)	Yes				Yes	
Study 301 (NCT00337103)[a] (57)		Yes	Yes			
NCT02225470[a] (56)		Yes		Yes		

References of trial	Tucatinib + trastuzumab + capecitabine	Eribulin alone	Capecitabine alone	Vinorelbine alone	Trastuzumab + capecitabine	Lapatinib + capecitabine
GBG 26 (65)			Yes		Yes	
EGF100151[b] (66)			Yes			Yes
CEREBEL (NCT00820222) (67)					Yes	Yes
ELTOP (68)					Yes	Yes

Only trials contributing to the network of evidence for the relevant comparators are presented in this table. Full details of the methodology are presented in Appendix D.
[a] Data in subgroups of patients with HER2+ tumours were considered.
[b] Permitted treatment switching from capecitabine alone to lapatinib with capecitabine post-progression.

B.2.9.1 Methodology of the NMA

B.2.9.1.1 Systematic literature review

An SLR was conducted to identify relevant studies to inform indirect comparisons between the interventions of interest. The search strategy was prespecified in terms of population, interventions, comparisons, outcomes and study design, and is outlined in Appendix D.

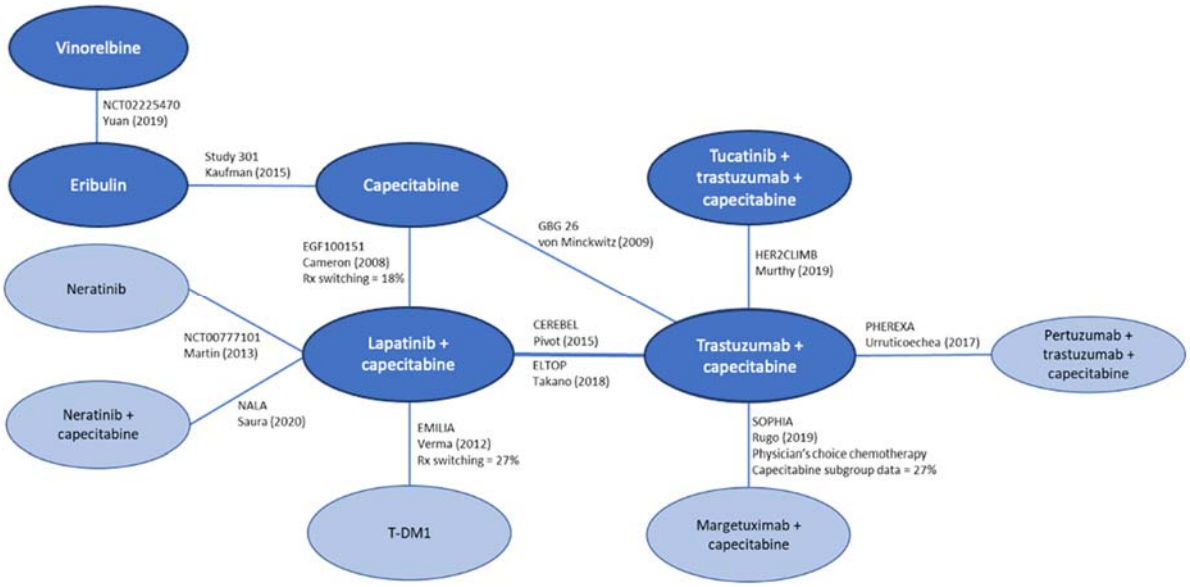
B.2.9.1.2 Comparators of interest

The comparators of interest included in the SLR reflect the comparators considered in the decision problem addressed in this submission (Section B.1.1). The comparison of the tucatinib combination with eribulin, capecitabine and vinorelbine are of particular interest in HER2+ MBC settings with prior exposure to either one or at least two anti-HER2 regimens.

In total, 11 treatments were included in the network, allowing for the comparison between the tucatinib combination and monotherapy with either eribulin, capecitabine or vinorelbine. The results of these three comparisons are reported in

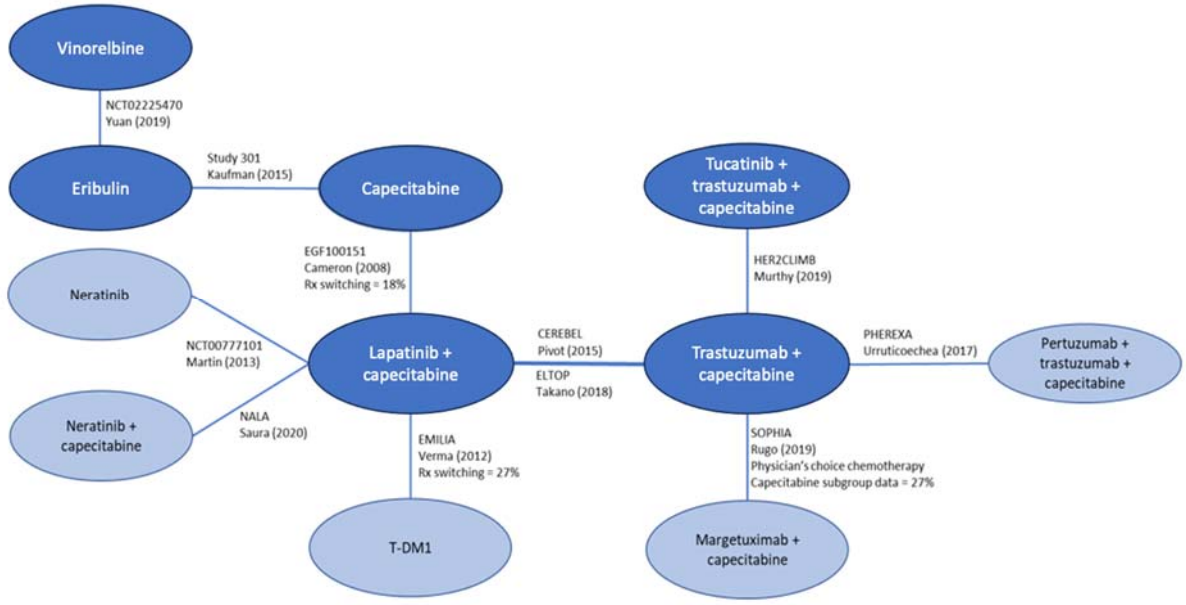
this submission. Seven relevant studies were used to compare PFS and best tumour response (Figure 14) and six were used for OS comparisons (Figure 15).Although the EMBRACE trial was a large, global, phase 3 trial evaluating eribulin in MBC, it was excluded from the NMA because it did not create a link between tucatinib and the treatments of interest (detailed methods in Appendix D).

Figure 14: Network of evidence informing the NMA – highlighted relevant nodes for PFS and best tumour response comparisons



Rx, treatment; T-DM1, trastuzumab emtansine
Blue ovals denote treatment of interest in the NMA; with relevant nodes for this submission highlighted in dark blue.
Source: Wardley et al. 2020 (69)

Figure 15: Network of evidence informing the NMA – highlighted relevant nodes for OS comparisons



Rx, treatment; T-DM1, trastuzumab emtansine
Blue ovals denote treatment of interest in the NMA, with relevant nodes for this submission highlighted in dark blue.
Source: Wardley et al. 2020 (69)

B.2.9.1.3 Study characteristics and patient demographics

All trials were randomised and controlled. Only HER2CLIMB was double-blinded; the remaining 11 studies were open label. The quality assessment of the studies included in the network is shown in Appendix D.

Trial design was predominantly parallel arm; however, treatment switching was permitted in EGF100151. GBG 26 re-randomised patients from both arms to either third-line chemotherapy or third-line chemotherapy with an anti-HER2 therapy (either trastuzumab or lapatinib).

Two trials, NCT02225470 and Study 301, investigated eribulin and included patients who previously received at least one chemotherapy regimen, regardless of their experience with anti-HER2 therapies like trastuzumab. NCT02225470 included few patients who received any prior anti-HER2 therapy. It is likely that Study 301 included a high proportion of trastuzumab-naïve patients; however, the proportion of patients with prior experience with trastuzumab, or other anti-HER2 therapies, was

not reported. These two trials included patients with HER2+ and HER2- tumours but only data from the former subgroup was included in the NMA.

Trial-level and treatment arm-level characteristics for the relevant studies are presented in Table 10. Study populations were broadly balanced and predominantly Caucasian; however, NCT02225470 and ELTOP were conducted in Chinese and Japanese populations, respectively.

Population mean age was broadly consistent across trials and, except for NCT02225470 and Study 301, all trials included HER2+ patients. It was difficult to assess heterogeneity across the other characteristics due to sparse and inconsistent reporting.

Due to differences across trials with respect to inclusion criteria for patients with brain metastases (unlike HER2CLIMB, most clinical trials included patients with stable brain metastases only and excluded those with active, progressing lesions), it was not possible to conduct a robust subgroup analysis in HER2+ MBC patients with brain metastases.

Table 10: Trial-level and treatment arm-level characteristics for the relevant studies included in the NMA

Trial (citation)	Blinding	Treatment	Line of therapy (MBC)	ITT N	Brain mets N	Median time since diagnosis (months)	Mean age (years)	ECOG = 1 (%)	HER2+ (%)	ER+ and/or PgR+ (%)	Race
HER2CLIMB (15)	Double-blind	Tucatinib + trastuzumab + capecitabine	≥2	410	198	48.1	53.8	50.2	100	59.3	Mixed – mainly Caucasian
		Trastuzumab + capecitabine		202	93	49.1	54.2	53.5	100	62.9	
Study 301 (57)	Open label	Eribulin	≤2[a]	554	NR[b]	NR	54.0[c]	52.9	15.5	46.8/41.0[d]	Mixed – mainly Caucasian
		Capecitabine		548	NR[b]	NR	53.0[c]	54.9	15.1	50.7/42.7[d]	
NCT02225470 (56)	Open label	Eribulin	≥3[e]	264	NA[e]	NR	50.3	74.2	19.7	61	Chinese
		Vinorelbine		266	NA[e]	NR	49.2	77.1	19.5	62	
GBG 26 (65)	Open label	Trastuzumab + capecitabine	2[f]	78	1[g]	NR	52.5[c]	NR	100	56	NR
		Capecitabine		78	2[g]	NR	59[c]	NR	100	62	
EGF100151 (66)	Open label	Lapatinib + capecitabine	≥1	198	23[h]	45.6 (N=207)	54[c]	38	100	48	NR
		Capecitabine		201		49.2	51[c]	41	100	46	
CEREBEL (67)	Open label	Lapatinib + capecitabine	≥1	271	20[g]	31.2 (N=253)	53.4	96[l]	100	49/36[d]	Mixed – mainly Caucasian
		Trastuzumab + capecitabine		269	19[g]	36 (N=246)	55.8	98[l]	100	45/30[d]	
ELTOP (68)	Open label	Lapatinib + capecitabine	NR	43	7	NR	59[c]	28	100	63	Japanese
		Trastuzumab + capecitabine		43	6	NR	57[c]	42	100	63	

ECOG, Eastern Cooperative Oncology Group performance score; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; ITT, intention to treat; MBC, metastatic breast cancer setting; Mets, metastases; NA, not applicable; NR, not reported; PgR, progesterone receptor

[a] Prior treatments comprised either up to three prior chemotherapy regimens or up to two prior chemotherapy regimens for advanced and/or metastatic disease.

[b] Patients with controlled and symptomatically stable brain metastases were eligible, but the number of such patients included was NR.

[c] Median age in years.

[d] Hormone receptor status reported separately ER+ (%)/PgR+ (%).

[e] Patients with brain metastases were excluded as part of the eligibility criteria.

[f] 96% to 100% of patients.

[g] Central nervous system metastases.

[h] Data unavailable by treatment arm.

[l] ECOG performance status 0 or 1.

B.2.9.1.4 Heterogeneity and inconsistency

In this NMA, heterogeneity for all endpoints was assessed via i) comparison of inclusion and exclusion criteria and study designs of the trials included in the meta-analyses, ii) evaluation of the similarity of endpoint definitions and iii) comparison of the response rates of a common reference treatment. When the network of evidence for an endpoint consisted of duplicate comparisons and/or closed loops, heterogeneity and inconsistency were also assessed using Higgins's I^2 (70) (to estimate the percentage of variance explained by heterogeneity), Cochran's Q (to test significance of the overall heterogeneity and where any duplicate comparisons exist) and node splitting (forest plots showing heterogeneity between the direct and indirect evidence where any closed loops existed in the network).

The main source of heterogeneity across trials was the difference in prior exposure to specific anti-HER2 therapies between trial populations, which would not be mitigated through covariate-adjustment. Thus, inclusion of covariates was not considered suitable for this NMA. In addition, it was not deemed necessary to use fractional polynomial adjustments for multi-parameter models. Sensitivity analyses involving exclusion of studies was not employed for any endpoints. A strong rationale was required if some studies that contribute relevant information for the interventions of interest are to be removed from an NMA.

This network contained information on heterogeneity in the form of one closed loop (between three treatments: capecitabine, lapatinib plus capecitabine, and trastuzumab plus capecitabine) and one duplicate comparison (two trials provided data comparing lapatinib plus capecitabine with and trastuzumab plus capecitabine). The node splitting analysis of inconsistency suggested that there was no significant difference ($p>0.05$) between the direct and indirect evidence for the three treatment comparisons within the closed loop.

The HRs for trastuzumab plus capecitabine versus lapatinib plus capecitabine (based on reconstructed data of the two trials that compared the regimens) indicated no significant difference between the treatments. The point estimate from ELTOP suggested that lapatinib plus capecitabine performed better than trastuzumab plus

capecitabine, while the point estimate from CEREBEL suggested the opposite. The Cochran's Q for the duplicate comparison was not significant (p=0.171). For the overall network, Higgins I^2 was 30.6% (95% CI 0.0%, 92.8%), which suggested there was moderate heterogeneity. However, the Cochran's Q was not significant (p=0.237). As there was no evidence of high heterogeneity, it was considered appropriate to include all trials in this analysis.

B.2.9.1.5 Sensitivity analysis

No sensitivity analyses were performed for the NMAs described in this submission. In the HR NMA and the fractional polynomial NMA no evidence of significant heterogeneity or inconsistency was observed that would warrant the exclusion of studies in sensitivity analyses. It must be noted though that the networks of evidence for these NMAs may not have had sufficient closed loops and/or duplicate comparisons to estimate the heterogeneity accurately.

B.2.9.1.6 Assessment of the proportional hazards assumption

Figure 16 and Figure 17 present the log(-log(Survival)) plot for PFS and for OS, respectively, where data that follow the proportional hazard assumption produce parallel lines. All relevant studies included in the NMA met the proportional hazards assumption for both PFS and OS, therefore HR NMAs were conducted.

Figure 16: Log(-log(Survival)) plot for PFS

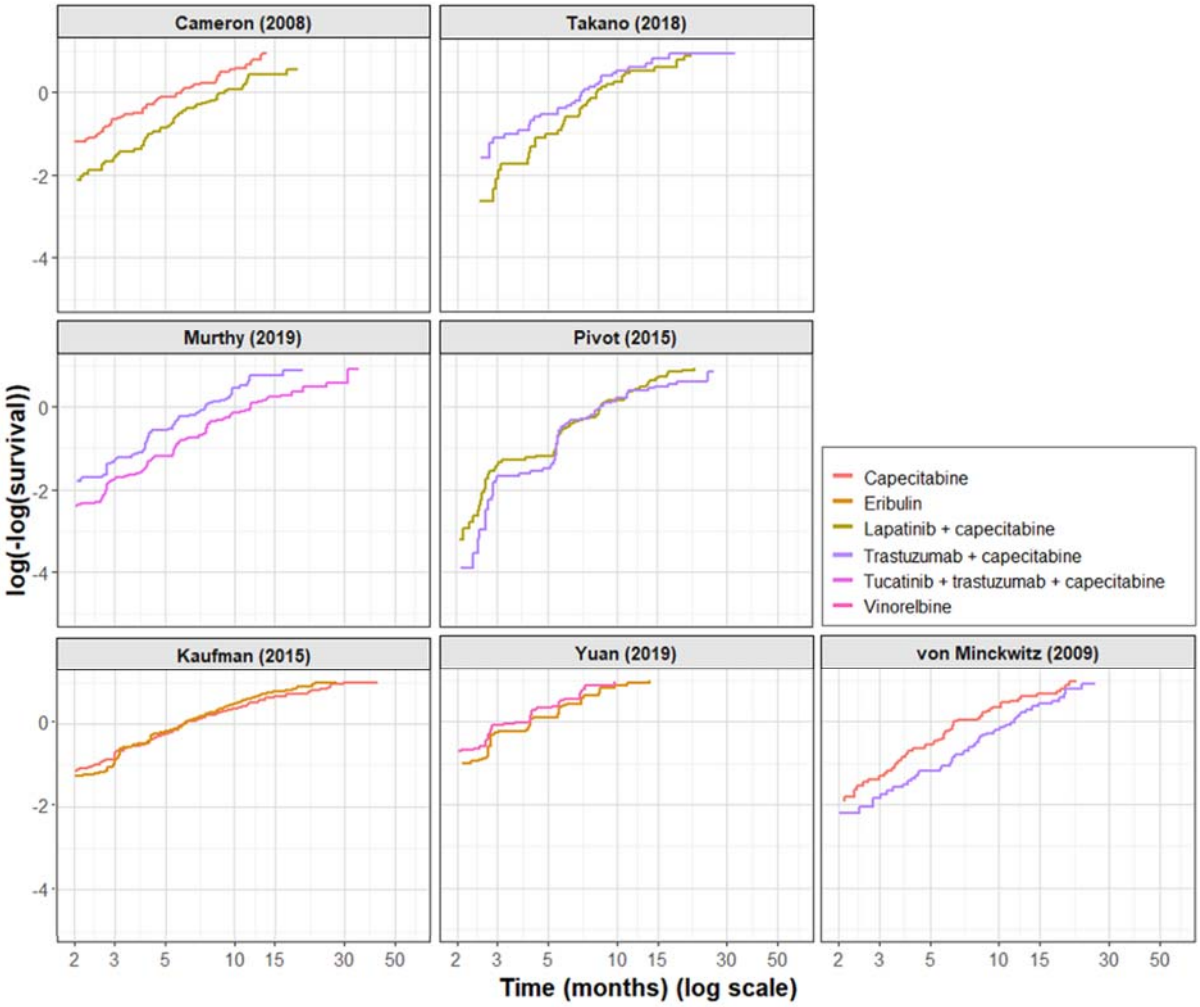
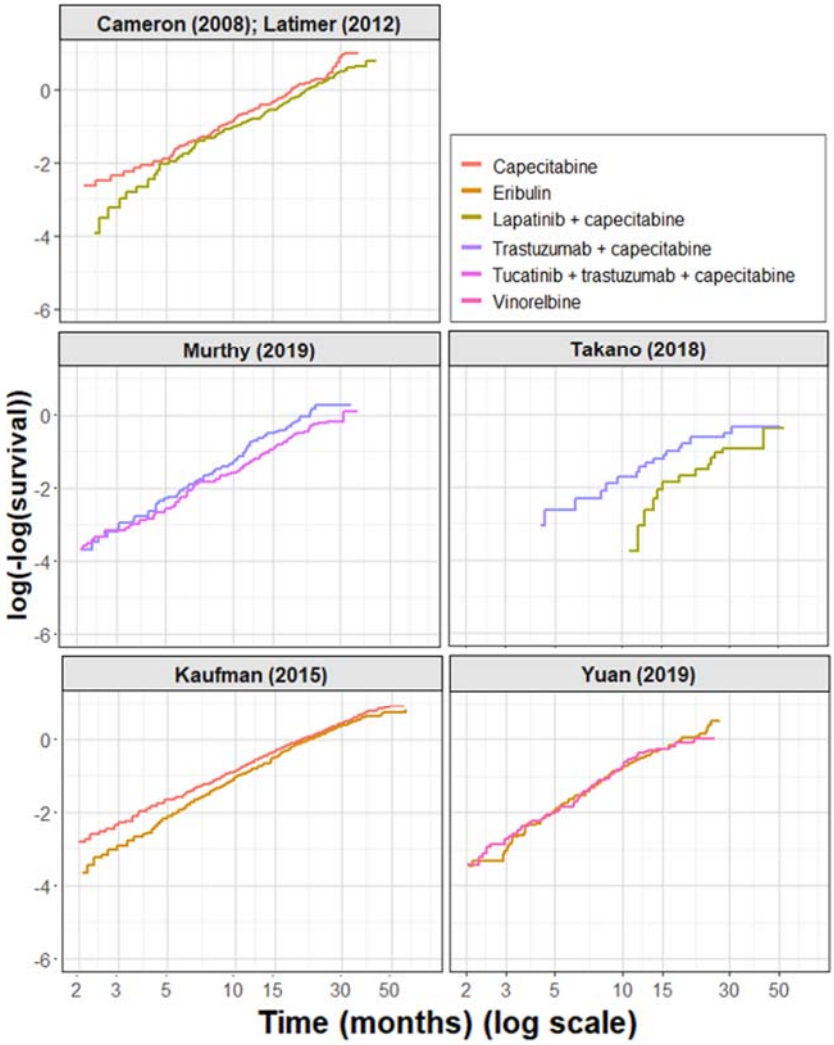


Figure 17: Log(-log(Survival)) plot for OS



B.2.9.1.7 Anchoring distribution

The most commonly used treatment was lapatinib plus capecitabine, therefore this was used as the reference treatment and the anchor for extrapolations.

Forest plots with the results for the OS and PFS HR NMAs are presented as the corresponding summary measure for each treatment relative to lapatinib plus capecitabine.

B.2.9.2 Hazard ratio results

B.2.9.2.1 PFS results

This network, shown in Figure 14, contained minimal information on heterogeneity in the form of one closed loop (between three treatments: capecitabine, lapatinib plus capecitabine, and trastuzumab plus capecitabine) and one duplicate comparison (two trials provided data to compare lapatinib plus capecitabine with trastuzumab plus capecitabine). [redacted]

The Bayesian fixed-effects (FE) model was run with a large number of iterations to ensure minimal correlation between draws. The iteration plots showed random noise, indicating model convergence. Results were consistent with head-to-head trial data in terms of significant treatment effects. Although the Bayesian random-effects (RE) model relied on an informative prior, the iteration plots from this model showed multiple peaks, suggesting the model had difficulty converging. There were inconsistencies between results from the Bayesian RE model and the head-to-head trial data in terms of significant treatment effects. [redacted]

The HRs and 95% credible intervals (CrIs) for each pairwise comparison are presented in Figure 18. The results are expressed as the HR (95% CrIs) for the

intervention listed on the vertical axis versus the intervention listed on the horizontal axis. Compared to eribulin, the tucatinib combination resulted in significantly better PFS ([redacted]). Eribulin, capecitabine and vinorelbine [redacted] for eribulin versus capecitabine, and [redacted] for eribulin versus vinorelbine.

Figure 18: Pairwise treatment comparisons for the PFS HR analysis

CrI, credible interval; HR, hazard ratio; PFS, progression-free survival; NMA, network meta-analysis; T-DM1, trastuzumab emtansine

Values are HR and 95% CrIs for the intervention listed on the vertical axis versus the intervention listed on the horizontal axis. If the cell is not coloured, then there is no statistical significance (threshold p value: 0.05). Where the treatment listed on the left side of the table was significantly better compared with treatments on the horizontal axes of the table, the results are coloured yellow to red, and where treatments on the bottom of the table were significantly worse versus those on the left, the results are coloured blue. The darker the shading of the colour in the cell, the larger the relative difference.

In total, 11 treatments were included in the network and allowed the comparison between the treatments of interest for this appraisal, namely the tucatinib combination versus monotherapy with either eribulin, capecitabine or vinorelbine.

Results from the Bayesian and Frequentist FE analyses were consistent, as evidenced by the combined forest plot of HRs (Figure 19). [redacted] (eribulin, capecitabine and vinorelbine) [redacted]

Figure 19: Bayesian versus Frequentist forest plots for the PFS HR analysis

HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; T-DM1, trastuzumab emtansine
In total, 11 treatments were included in the network and allowed the comparison between the treatments of interest for this appraisal, namely the tucatinib combination versus monotherapy with either eribulin, capecitabine or vinorelbine. Lapatinib plus capecitabine was the most commonly used therapy across the trials included in the network and was therefore employed as the reference treatment and the anchor for extrapolations.

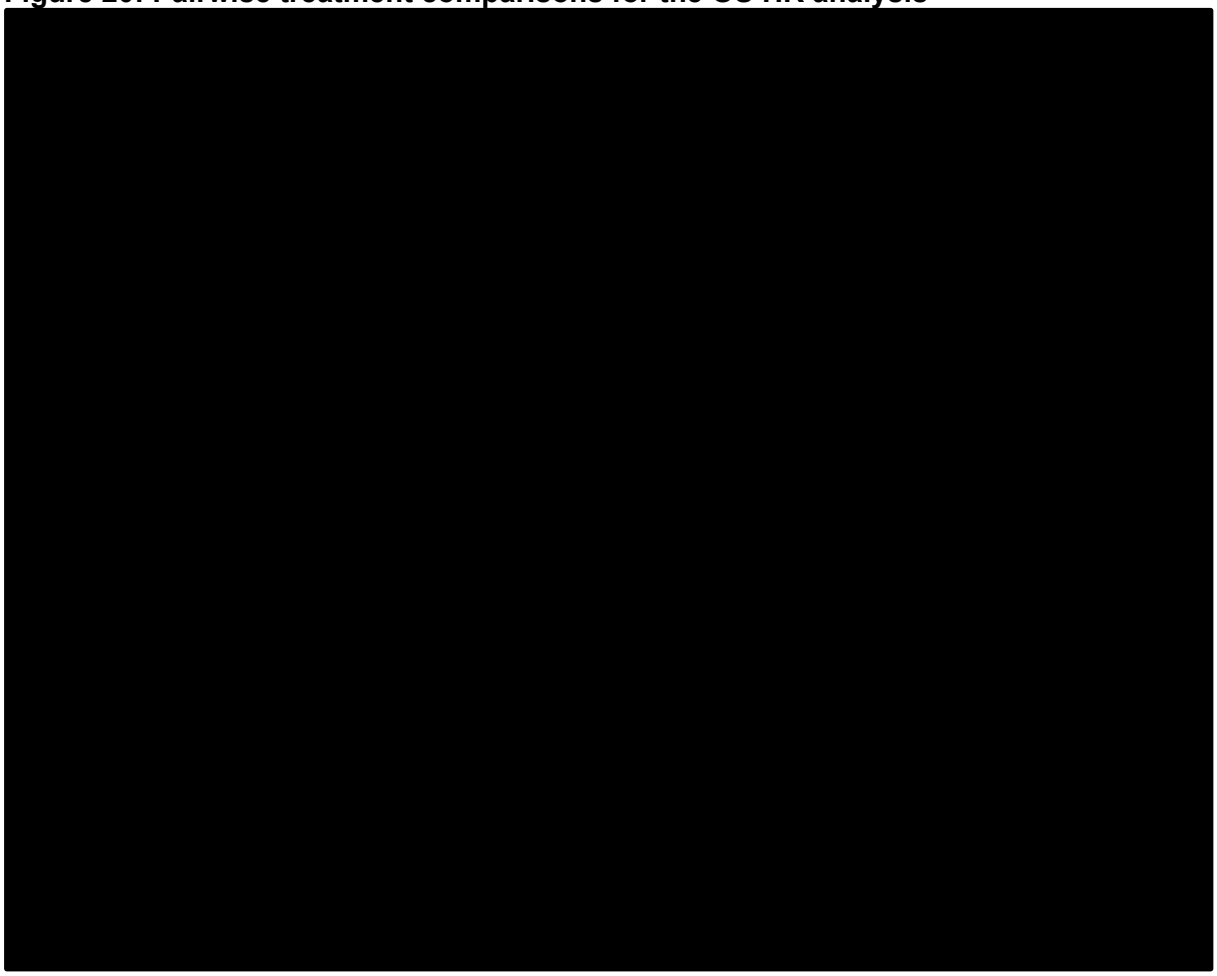
B.2.9.2.2 OS results

This network, shown in Figure 15, contained limited information on heterogeneity; although there was one duplicate comparison, there were no closed loops. Among the two trials that provided OS HRs for lapatinib plus capecitabine versus trastuzumab plus capecitabine (duplicate comparison), neither indicated a significant difference in OS between the treatments. [redacted]

The HRs and 95% CrIs for each pairwise comparison are shown in Figure 20. The tucatinib combination resulted in significantly greater OS versus eribulin ( ), capecitabine ( ) and vinorelbine ( ).

Results indicated that the three single-agent chemotherapies eribulin, capecitabine and vinorelbine were .

Figure 20: Pairwise treatment comparisons for the OS HR analysis



CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; T-DM1, trastuzumab emtansine
Values are HR and 95% CrIs for the intervention listed on the vertical axis versus the intervention listed on the horizontal axis. If the cell is not coloured, then there is no statistical significance (threshold p value: 0.05). Where the treatment listed on the left side of the table was significantly better compared with treatments on the horizontal axes of the table, the results are coloured yellow to red, and where treatments on the bottom of the table were significantly worse versus those on the left, the results are coloured blue. The darker the shading of the colour in the cell, the larger the relative difference.
In total, 11 treatments were included in the network and allowed the comparison between the treatments of interest for this appraisal, namely the tucatinib combination versus monotherapy with either eribulin, capecitabine or vinorelbine.

Results from the Bayesian and Frequentist FE analyses were consistent, as evidenced by the combined forest plot of HRs (Figure 21). [redacted] (eribulin, capecitabine and vinorelbine) [redacted]

Figure 21: Bayesian versus Frequentist forest plots for the OS HR analysis

NMA, network meta-analysis; T-DM1, trastuzumab emtansine
In total, 11 treatments were included in the network and allowed the comparison between the treatments of interest for this appraisal, namely the tucatinib combination versus monotherapy with either eribulin, capecitabine or vinorelbine. Lapatinib plus capecitabine was the most commonly used therapy across the trials included in the network and was therefore employed as the reference treatment and the anchor for extrapolations.

B.2.9.3 Fractional polynomial results

Due to violation of the proportional hazards assumption in some trials in the network, fractional polynomial analyses were conducted, and the results were compared to the HR analyses. Results were consistent for all comparisons relevant to the current decision problem. Subsequent sections discuss the consistency between results from the HR and fractional polynomial NMAs for PFS and OS.

B.2.9.3.1 Consistency between results of the PFS HR and fractional polynomial analyses

With the exception of a couple of minor differences the results of the HR and fractional polynomial NMAs were consistent (Figure 18). [redacted] compared with eribulin, capecitabine and vinorelbine. [redacted]

[redacted]

B.2.9.3.2 Consistency between results of the OS HR and fractional polynomial analyses

[redacted]

B.2.9.4 Uncertainties in the indirect treatment comparisons

Due to the small number of studies in the network, there is uncertainty as to how much heterogeneity exists with the network of evidence. The use of informative priors in the random-effects NMAs resulted in convergence issues with inflated credible intervals and there are currently no published methods to use informative priors with the fractional polynomial NMA or the ordinal probit NMA. Although fitting such models produced reasonable results, the [redacted] were considered to constitute the key results across all analyses due to better convergence and model fit.

B.2.10 Adverse reactions

B.2.10.1 Safety population and treatment exposure and discontinuations

In the primary endpoint population of the pivotal HER2CLIMB trial, patients had a longer median treatment exposure to tucatinib (7.3 months) compared with placebo (4.4 months) (see Table 11). Among the 601 patients who received at least one dose of any study drug in the safety analysis population, the median duration of exposure to tucatinib or placebo was 5.8 months and 4.4 months, respectively. The median

duration of exposure to capecitabine was 5.7 months (range, 0.3 to 35.4) in the tucatinib combination group versus 4.4 months (range, 0.3 to 24.1) in the placebo combination group. The median duration of exposure to trastuzumab was 6.0 months (range, 0.7 to 35.4) in the tucatinib combination group versus 4.6 months (range, 0.7 to 24.3) in the placebo combination group (15).

Table 11: Duration of tucatinib and placebo exposure in HER2CLIMB

	Primary endpoint safety population (N=474)		Safety analysis population (N=601)	
	Tucatinib combination (n=317)	Placebo combination (n=157)	Tucatinib combination (n=404)	Placebo combination (n=197)
Duration of tucatinib or placebo exposure, months				
Mean (standard deviation)	8.4 (6.9)	5.9 (4.6)	7.6 (6.3)	5.6 (4.3)
Median	7.3	4.4	5.8	4.4
Minimum, maximum	<0.1, 35.1	<0.1, 24.0	<0.1, 35.1	<0.1, 24.0
Number of treatment cycles[a] initiated				
Mean (standard deviation)	12.0 (9.7)	8.4 (6.5)	10.9 (9.0)	7.9 (6.0)
Median	10.0	6.0	8.0	6.0
Minimum, maximum	1, 51	1, 35	1, 51	1, 35
Median relative dose intensity[b], %	NR	NR	93.6	97.0

NR, not reported
[a] One treatment cycle was 3 weeks in duration.
[b] Relative dose intensity was computed as 100 × (absolute dose intensity/intended dose intensity), where the intended dose intensity was 600 mg/day.
Source: Seagen, HER2CLIMB Clinical Study Report, 2019 (4)

At the data cut off, 118 (28.8%) patients in the tucatinib combination group and 27 (13.4%) patients in the placebo combination group remained on treatment. Frequency of dose modification, including dose reduction, dose withheld by investigator, dose missed by patient, and treatment discontinuation due to adverse event, was higher in the tucatinib combination group compared with the placebo combination group (Table 12). Adverse events led to discontinuation of tucatinib in 5.7% of patients, placebo in 3.0% of patients and capecitabine in 9.8% of patients (10.1% in the tucatinib combination group and 9.1% in the placebo combination group) (15).

Table 12: Discontinuation of study drug due to adverse events (safety analysis population)

	Tucatinib combination (N=404)	Placebo combination (N=197)
Patients who discontinued any study treatment due to TEAE, n (%)	45 (11.1)	19 (9.6)
Patients who discontinued tucatinib/placebo	23 (5.7)	6 (3.0)
Patients who discontinued capecitabine	41 (10.1)	18 (9.1)
Patients who discontinued trastuzumab	18 (4.5)	5 (2.5)
Patients with TEAEs resulting in tucatinib/placebo dose modification, n (%)	220 (54.5)	81 (41.1)
Dose withheld	216 (53.5)	80 (40.6)
Dose reduced	84 (20.8)	21 (10.7)
Patients with TEAEs resulting in capecitabine dose modification, n (%)	313 (77.5)	122 (61.9)
Dose withheld	276 (68.3)	113 (57.4)
Dose reduced	243 (60.1)	77 (39.1)
Patients with TEAEs resulting in trastuzumab dose modification[a], n (%)	104 (25.7)	38 (19.3)
Dose withheld[b]	104 (25.7)	38 (19.3)

TEAE, treatment-emergent adverse event
[a] Dose reduction for trastuzumab was not allowed per protocol.
[b] Dose withheld for trastuzumab included interruption during infusion.
Source: Murthy et al. 2020 (15); Seagen, HER2CLIMB Clinical Study Report, 2019 (4)

B.2.10.2 Treatment-emergent adverse events (TEAEs)

When tucatinib was added to a regimen of trastuzumab and capecitabine, no unanticipated adverse events were observed compared with the safety profile of each agent in the combination.

Overall, tucatinib in combination with trastuzumab and capecitabine was well tolerated, with a manageable safety profile. Even with the addition of tucatinib to trastuzumab and capecitabine, no unanticipated adverse events were observed (Table 13). Rates of any, Grade ≥3 or serious TEAEs were balanced between treatment arms.

Table 13: Summary of TEAEs (safety analysis population)

Adverse event, n (%)	Tucatinib combination (N=404)	Placebo combination (N=197)
Any TEAE[a]	401 (99.3)	191 (97.0)
Grade ≥3 TEAE	223 (55.2)	96 (48.7)
Any TE serious adverse events	104 (25.7)	53 (26.9)
TEAE leading to death	8 (2.0)	6 (3.0)

TE, treatment-emergent; TEAE, treatment-emergent adverse event
[a] TEAEs are defined as events that are new or worsened on or after receiving the first dose of study treatment (tucatinib/placebo, capecitabine, or trastuzumab and up through 30 days after the last dose of study treatment (i.e., last dose of tucatinib/placebo).

Source: Murthy et al. 2020 (15); Seagen, HER2CLIMB Clinical Study Report, 2019 (4)

The most common adverse events observed in patients in the tucatinib combination group were diarrhoea, hand-foot syndrome, nausea, fatigue and vomiting (Table 14). Most adverse events were Grade 1 and 2 in severity.

Table 14: Most common (≥20% in the tucatinib combination) adverse events (safety analysis population)

	Tucatinib combination (N=404)		Placebo combination (N=197)	
Adverse event	**Any (N, %)**	**Grade ≥3 (N, %)**	**Any (N, %)**	**Grade ≥3 (N, %)**
Diarrhoea	327 (80.9)	52 (12.9)	105 (53.3)	17 (8.6)
Hand-foot/PPE syndrome	256 (63.4)	53 (13.1)	104 (52.8)	18 (9.1)
Nausea	236 (58.4)	15 (3.7)	86 (43.7)	6 (3.0)
Fatigue	182 (45.0)	19 (4.7)	85 (43.1)	8 (4.1)
Vomiting	145 (35.9)	12 (3.0)	50 (25.4)	7 (3.6)
Stomatitis	103 (25.5)	10 (2.5)	28 (14.2)	1 (0.5)
Decreased appetite	100 (24.8)	2 (0.5)	39 (19.8)	0
Headache	87 (21.5)	2 (0.5)	40 (20.3)	3 (1.5)
AST increased	86 (21.3)	18 (4.5)	22 (11.2)	1 (0.5)
ALT increased	81 (20.0)	22 (5.4)	13 (6.6)	1 (0.5)

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; PPE, palmar-plantar erythrodysesthesia
Source: Murthy et al. 2020 (15)

Adverse events of interest assessed in HER2CLIMB show no additional safety issues with the tucatinib combination versus the control arm (4, 15):

- Most diarrhoea events were grade 1 (43.3% and 32.0%) or grade 2 (24.8% and 12.7%) in the tucatinib combination group and placebo combination group and were generally manageable with supportive care and dose modification. Permanently discontinuing due to diarrhoea was infrequent with tucatinib and placebo (1.0% vs 0.5%). Anti-diarrhoeal prophylaxis was not required with the tucatinib protocol.
- Elevated liver enzymes, alanine transaminase (ALT) and aspartate transaminase (AST), occurred early in treatment, were mostly low-grade, transient, and reversible.
- Increases in serum creatinine occurred early, remained clinically insignificant with no development of renal injury during therapy, were reversible, and no patients discontinued therapy due to these events. Tucatinib has been shown to inhibit the

multidrug and toxin extrusion protein 1 and 2-K (MATE1 and MATE2-K) transporters, which increases the serum creatinine level without affecting glomerular function.

- Rates of left ventricular ejection fraction/cardiac failure TEAEs leading to tucatinib/placebo dose modifications or discontinuation were infrequent and similar between treatment arms (1.7% in the tucatinib combination group and 2.0% in the placebo combination group).
- No patients in the tucatinib combination group reported cerebral oedema-related TEAEs compared with two patients (1.0%) in the placebo combination group.

Additional information on adverse events of interest is available in Appendix F.

B.2.10.3 Safety overview

In vitro, tucatinib is highly selective for HER2 versus EGFR. When used in combination with trastuzumab and capecitabine for the treatment of HER2+ MBC in the third-line setting, the tucatinib combination has a well-tolerated safety profile:

- When tucatinib was added to a regimen of trastuzumab and capecitabine, no unanticipated adverse events were observed compared with the safety profile of each agent in the combination.
- There was a low rate of discontinuation due to adverse events, with the majority being low-grade in severity.
- Diarrhoea was manageable and anti-diarrheal prophylaxis is not required with the tucatinib combination.
- Transient, reversible elevations in liver enzymes and increases in serum creatinine occurred early in treatment, were mostly low-grade, and reversible.
- The tolerability of tucatinib is further demonstrated by its maintenance of patient HRQoL. Even with the addition of tucatinib to trastuzumab and capecitabine, patients did not experience a reduction in HRQoL over the course of therapy compared with trastuzumab and capecitabine alone.

B.2.11 Ongoing studies

HER2CLIMB is currently ongoing as patients continue to be followed in the open-label extension phase of the trial, where those who received placebo in the blinded

phase are allowed to switch to tucatinib (62). Additional protocol specified analysis may be conducted.

B.2.12 Innovation

Tucatinib was granted a Promising Innovative Medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency (MHRA) in January 2021 because of its unprecedented efficacy and tolerability in patients with HER2+ MBC, including those with brain metastases, who closely represent patients in real-world clinical practice. These patients have a high unmet need as there is no recognised standard of care in the third-line setting and use of currently available treatment options is limited by inconsistent efficacy and poor tolerability.

B.2.12.1 Unprecedented efficacy

Patients with HER2+ MBC previously treated with two anti-HER2 regimens have limited evidence-based treatment options once their disease progresses. In England, the only NICE-recommended third-line treatment is the single-agent chemotherapy eribulin, which is limited by moderate efficacy and side effects. HER2+ status is associated with increased risk of brain metastases over the course of disease (71), however, until now, most systemic therapies had minimal levels of activity in the brain due to limited ability to penetrate the blood-brain barrier. Additionally, clinical trials for currently available therapies have excluded patients with active brain metastases, as these patients are typically associated with a very poor prognosis and increased risk of toxicity.

The tucatinib combination provides a unique balance of efficacy and tolerability for HER2+ MBC patients both with and without brain metastases. Adding tucatinib to trastuzumab and capecitabine significantly reduces the risk of death by approximately one-third, which is unprecedented in this population of treatment-experienced patients, including patients with brain metastases (15). The magnitude of clinical benefit with the tucatinib combination was consistently observed across all patients in HER2CLIMB, including patients with confirmed active or stable brain metastases.

The tucatinib combination is the first regimen to offer clinically meaningful efficacy both systemically and in the brain, which is particularly important for patients with HER2+ MBC who may develop brain metastases over the course of disease. Due to lack of routine screening in clinical practice, it is estimated that 20% to 40% of MBC patients have asymptomatic brain metastases that remain undetected and untreated (72-74). In HER2CLIMB, the tucatinib combination reduced the risk of developing new brain lesions or death by 48% (59, 63). Receiving treatment with the tucatinib combination before symptoms of brain metastases arise could therefore delay the occurrence or progression of CNS disease in patients with HER2+ MBC.

B.2.12.2 Tolerability

In England, the currently available third-line treatment appraised and recommended by NICE, eribulin, is associated with several adverse events including fatigue, alopecia, peripheral neuropathy, nausea, neutropenia, leukopenia and anaemia (75), which can limit its use (16). In this setting, other single-agent chemotherapies are available with either capecitabine or vinorelbine, but these also provide limited efficacy with considerable side effects (16).

Tucatinib is highly selective for HER2 (76) and, when used in combination with trastuzumab and capecitabine, has a well-tolerated safety profile. There was a low rate of discontinuation due to adverse events in HER2CLIMB, whist the majority of adverse events were low-grade in severity. Diarrhoea and transient, reversible elevations in liver enzymes were both manageable and anti-diarrhoeal prophylaxis is not required with the tucatinib combination. The tolerability of tucatinib is further demonstrated by the maintenance of patient HRQoL. In HER2CLIMB, patients did not experience a negative impact on HRQoL with the tucatinib combination over the course of therapy compared with trastuzumab and capecitabine alone.

B.2.12.3 Representative patient population

The design of HER2CLIMB is also unprecedented compared with trials of other treatments for HER2+ MBC. HER2CLIMB is the first randomised, double-blind trial to enrol a large (48%) proportion of patients with brain metastases at baseline, with approximately 60% of these patients having active or progressing brain metastases

(15). In contrast, as shown in Table 10, other trials in this setting rarely included patients whose disease spread to the brain. Some trials do include a small number (<15%) of patients with stable brain metastases, however patients with active brain metastases have been excluded from clinical trials of other systemic treatments for HER2+ MBC due to poor prognosis, even though brain metastases are a common clinical problem among these patients. Additionally, HER2CLIMB enrolled patients who were heavily pre-treated, having received at least two prior anti-HER2 regimens before enrolment. HER2CLIMB, which included patients with and without brain metastases, is more representative of the real-world third-line MBC patient population than prior trials.

Among pre-treated HER2+ MBC patients, there is no current third-line standard of care and use of currently available treatment options is limited by minimal efficacy and poor tolerability. The tucatinib combination has the potential to be a step-change in the management of HER2+ MBC due to its unprecedented OS and PFS benefits and manageable safety profile.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Evidence from HER2CLIMB

The efficacy and safety of tucatinib was demonstrated in HER2CLIMB, the first and only randomised, double-blind, placebo-controlled, active-comparator global trial of HER2+ MBC to include patients with and without brain metastases at baseline (15). The dual HER2 blockade achieved with tucatinib in combination with trastuzumab and capecitabine, met all key efficacy endpoints with consistent benefit across all subgroups. Compared with the placebo combination, the tucatinib combination (15):

- Reduced the risk of death by 34% (HR=0.66; 95% CI 0.50, 0.88; p=0.005) over trastuzumab and capecitabine alone, leading to an unprecedented 4.5-month improvement in median OS
- Reduced the risk of disease progression or death by 46% (HR=0.54; 95% CI 0.42, 0.71; p<0.001), leading to a more than 2-month improvement in median PFS

- Is the first and only regimen to show a significant improvement in PFS in patients with brain metastases (HR=0.48; 95% CI 0.34, 0.69; p<0.001)
- Provided durable efficacy with landmark survival analyses showing:
  - 2-year OS was 44.9% (95% CI 36.6, 52.8) in the tucatinib combination group and 26.6% (95% CI 15.7, 38.7) in the placebo combination group
  - 1-year PFS was 33.1% (95% CI 26.6, 39.7) in the tucatinib combination group and 12.3% (95% CI 6.0, 20.9) in the placebo combination group
  - In patients with brain metastases, 1-year PFS was 24.9% (95% CI 16.5, 34.3) in the tucatinib combination group compared with 0% in the placebo combination group
- Reduced the risk of developing new brain lesions or death by almost half (HR=0.52; 95% CI 0.33, 0.82; p=0.005) (59, 63)
- Maintained HRQoL throughout the course of the study
- Is well-tolerated with adverse events that were manageable, reversible, and led to low rates of discontinuation

Because of the robust design and broad patient population enrolled, the findings from HER2CLIMB are generalisable to real-world patients with HER2+ MBC. The HER2CLIMB population is more representative of the real-world MBC patient population than prior trials in HER2+ MBC by including patients with brain metastases. Tucatinib's has demonstrated clinically meaningful improvements in OS and PFS in a population of pre-treated MBC patients, including those with stable and active brain metastases, that closely reflects patients treated in current clinical practice.

The clinical data strongly support the use of the tucatinib combination in patients with HER2+ MBC who have been received two prior anti-HER2 regimens. The large magnitude of clinical benefit with the tucatinib combination was consistently observed across all subgroups in HER2CLIMB, including patients with brain metastases. The tucatinib combination provides unparalleled efficacy and a manageable safety profile while maintaining HRQoL in patients with HER2+ MBC, which could have a significant impact in clinical practice.

B.2.13.2 Evidence from indirect comparisons

Since commonly used therapies for third-line MBC in England were not included as comparators in HER2CLIMB, an ITC was conducted to enable comparisons between the tucatinib combination and eribulin, capecitabine and vinorelbine. An SLR was performed to identify relevant studies (Section B.2.9 and Appendix D for further details) and an NMA was subsequently conducted.

Based on the results of [redacted], the tucatinib combination demonstrated superior OS and PFS benefit than monotherapy with either eribulin, capecitabine or vinorelbine. Additionally, the NMA results suggest that eribulin, capecitabine and vinorelbine have [redacted].

Seagen commissioned an advisory board in March 2021 where seven clinical experts in England agreed that the three single-agent chemotherapies are clinically equivalent, but that eribulin is the most appropriate comparator for this submission (16).

Eribulin is the only single-agent chemotherapy included in the final scope that is recommended by NICE in this setting. The clinical experts pointed out that inconsistencies in treatment exist across centres in England, and patients may receive capecitabine especially in combination with trastuzumab, where the latter is available. As trastuzumab plus capecitabine is not licensed or recommended by NICE in the UK as a third- or later-line therapy, and access to trastuzumab varies across centres, this submission uses eribulin as the base-case comparator in the economic model.

The tucatinib combination demonstrated superior OS and PFS outcomes compared with all three comparators in both the HR and fractional polynomial analyses. For the remaining endpoint analyses, a similar efficacy should be assumed between the tucatinib combination and these other key treatments until more data become available. In the two eribulin trials included in the NMA, eribulin was given at a slightly higher dose (i.e., 1.4 mg/m^2) (56, 57) than that indicated in its SmPC (i.e., 1.23 mg/m^2) (75). This minor discrepancy is not expected to meaningfully bias the

results and could indicate that the benefit observed with the tucatinib combination would potentially be greater in clinical practice.

As discussed previously, HER2CLIMB enrolled HER2+ MBC patients who closely represent the real-world patient population, including those with active brain metastases at baseline. Patients with active brain lesions were excluded from the comparator trials in the network. While some studies permitted patients with controlled and asymptomatic brain metastases, they did not report the number of such patients included. Therefore, it was not deemed appropriate to perform a meta-regression that explored the influence of either brain metastases status or proportion of patients with brain metastases on treatment effect.

B.2.13.3 End-of-life criteria

The tucatinib combination meets the NICE end-of-life criteria (Table 15). This is in line with previous NICE appraisals for third-line treatment in the metastatic setting (eribulin [NICE TA423]) as well as in second-line (T-DM1 [NICE TA458]). Clinical experts in England agreed that the life expectancy under the available treatment at third-line is less than 24 months and the gain in life extension with the tucatinib combination is expected to be greater than 3 months (16).

Table 15: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The median OS achieved with the single-agent chemotherapy currently available in the third-line setting (eribulin) is less than 16 months	Section B.1.3.3 (page 20)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The median OS difference between the tucatinib combination and the placebo combination in HER2CLIMB exceeds 3 months (21.9 versus 17.4 months)	Section B.2.6.2 (page 36)

NHS, National Health Service; OS, overall survival

B.2.13.4 Strengths and limitations

The HER2CLIMB trial was rigorously designed as a large, double-blind, placebo-controlled, active-comparator trial with the primary endpoint assessed by BICR. Most study endpoints were also assessed via investigator and there was consistency across assessment methods.

Patients in HER2CLIMB were enrolled globally, including from UK sites, and were required to have received prior treatment with trastuzumab, pertuzumab and T-DM1. These three therapies were considered the standard of care at the time of study initiation and are recommended in the first- (pertuzumab with trastuzumab and docetaxel [NICE TA509]) and second-line (T-DM1 [NICE TA458]) settings in England (Section B.1.3.2.2, Figure 1) (43). Thus, patients enrolled in HER2CLIMB received the best treatment available, allowing the benefit of tucatinib to be observed in patients who received 'gold standard' care. The clinical data strongly support the use of the tucatinib combination in patients with HER2+ MBC who have been previously treated with the trastuzumab, pertuzumab and T-DM1.

The strength of the HER2CLIMB results is also reflected in the consistency of benefit observed in the total population and across all pre-specified subgroups. The PFS benefit seen with the tucatinib combination was consistent across all study populations including all patients enrolled, those with brain metastases, and those without brain metastases. Similarly, the tucatinib combination demonstrated substantial OS and PFS benefits across pre-specified subgroups stratified by age, ECOG status and geographic region (15).

HER2CLIMB provides robust efficacy and safety evidence that is generalisable to the patient population seen in clinical practice in England. The inclusion of patients with active (untreated and progressing) brain metastases reflects the real-world experience, as it is estimated that up to 50% of HER2+ MBC patients will develop brain metastases throughout the course of disease (28, 77-79). Additionally, given the lack of routine screening, it is estimated that 20% to 40% of MBC patients have asymptomatic brain metastases that remain undetected and untreated (72-74). Thus, many HER2+ MBC patients in England may be living with brain metastases

(diagnosed and undiagnosed), further underscoring the importance of the tucatinib combination's systemic and CNS efficacy and the relevance of HER2CLIMB in clinical practice.

As HER2CLIMB did not include a comparator arm aligned with the final scope of this submission, an NMA was conducted to indirectly compare outcomes with the tucatinib combination versus eribulin, capecitabine and vinorelbine. The NMA demonstrated that the tucatinib combination provides an OS and PFS benefit versus all three relevant comparators, reaching a statistically significant OS and PFS benefit versus capecitabine and eribulin across both the HR and fractional polynomial analyses. Eribulin, which is currently recommended by NICE through the NHS in third-line MBC, shows clinical equivalence to the other two single-agent comparators and is therefore used in the economic model presented in Section B.3. Clinical experts in England validated the results of the NMA as representative of their clinical practice, as well as the use of eribulin as the base-case comparator in this setting (16).

Inherent to indirect analyses, the NMA is limited by the availability of evidence, including the comparability of patient populations and the small number of duplicate comparisons and closed loops in the network. Due to the uniqueness of HER2CLIMB with respect to the inclusion of patients with brain metastases, the evidence does not allow for a methodologically robust subgroup analysis in brain metastases.

Overall, the robust clinical data from HER2CLIMB and results from the NMA strongly support the use of the tucatinib combination in patients with HER2+ MBC who have received two prior anti-HER2 regimens in England.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An economic SLR was conducted to identify published economic evaluations of targeted therapies for locally advanced unresectable, or metastatic HER2+ breast cancer after progression on previous anti-HER2 treatment. As such, the search included a broader patient population than that of the licensed indication for TUKYSA to ensure all relevant literature in HER2+ MBC was identified. In addition, given the limited evidence in HER2+ MBC, additional targeted searches of previous NICE appraisals of HER2- MBC were considered. These economic evaluations were used to obtain a range of nonclinical data to support the development an economic model to assess the cost-effectiveness of the tucatinib combination (tucatinib with trastuzumab and capecitabine).

The economic SLR identified relevant studies in adults published prior to 11 December 2019 and an update is currently in progress with an anticipated submission before the NICE Technical Engagement step date on 7 May 2021, with no changes in the scope. Please see Appendix G for the economic SLR methodology, a description of each cost-effectiveness study identified, and quality assessments for each study.

In line with guidance from the Centre for Reviews and Dissemination (CRD), the population, interventions, comparators, outcomes, and study type (PICO) principle are described in further detail in Appendix G. The PICO framework was applied to define the following review question to identify:

- Published economic evaluations of relevant treatments for unresectable, locally advanced or metastatic HER2+ breast cancer with progression after previous treatment
- Utility data for unresectable, locally advanced or metastatic HER2+ breast cancer with progression after previous treatment

This systematic review identified 16 cost-effectiveness and/or cost-utility analyses that met the PICO as per Appendix G for patients with HER2+ MBC. Of these, five

were health technology assessment (HTA) appraisals identified through internet searches. The studies included perspectives from the UK, Canada, Spain, Italy, the US, Mexico, Brazil and Japan, but none evaluated the treatments included in the decision problem. Table 16 summarises each of the economic evaluations identified.

Table 16: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Pertuzumab						
Uechi et al (80) (Japan) TRAS+PER+ docetaxel (THP) vs TRAS and docetaxel (TH)	2018	CEA, partitioned survival model to predict costs and QALY, with a 10-year time horizon. Cycle length: 1 month Sources: cost parameters were estimated by using the JMDC claims database. Utilities were derived from published sources other than Japan.	Patients with HER2+MBC or recurrent BC	Additional 0.770 QALY THP vs TH	THP vs TH: Additional cost of ¥14,890,623	THP ICER: ¥19,337,853/ QALY gained
Durkee et al. (81) (US) THP vs TH	2016	CEA, Decision-analytic Markov model with a time horizon of a lifetime Health states: stable disease, progressing disease, hospice, and death Cycle: weekly Sources: costs from listed national payment amount in Medicare and published data from the SEER and linked Medicare data and a claims database. Utilities were same as published CEA of TRAS and PER.	HER2+ MBC or recurrent breast cancer with Eastern Cooperative Oncology Group performance Status of 0 or 1 and had received no more than one hormonal treatment for metastatic disease (n=17,450)	Additional QALYs (THP vs TH): 0.62 Utilities: base-case and modeled distribution (95% CI) Stable state: 0.65 (0.50-0.80) Progressing state: 0.29 (0.16-0.41) Hospice state: 0.48 Toll for major toxicity: −0.28	Additional costs (THP vs TH): $294,747	ICER: $472,668 per QALY gained

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Trastuzumab emtansine						
NICE (TA458) (52) (UK) T-DM1 vs LAP+CAP LAP+CAP vs CAP	2017	CEA, 3 Health states model Time horizon: 10 y Sources: NR	HER2+ unresectable, locally advanced, or MBC in adults who previously received TRAS and a taxane, separately or in combination	NR	NR	T-DM1 vs LAP+ CAP = £167,200 per QALY gained LAP+CAP vs CAP = £49,800 per QALY gained
SMC (990/14) (82) (UK) T-DM1 vs CAP	2016	Partitioned survival model Health states: PFS, progressed disease, and death with a time horizon of 15 years. Sources: resource use from published sources and utilities from Lloyd et al. (2006)	HER2+ unresectable, locally advanced, or MBC previously received TRAS and a taxane separately or in combination	T-DM1 vs CAP; QALY gain: 0.89	T-DM1 vs CAP; Incremental cost: £87,177	Base-case comparison with CAP Cost/QALY: £96,185
Le et al. (US) (83) T-DM1 vs LAP+CAP T-DM1 vs CAP	2016	CEA, 4 Markov models for advanced BC with a time horizon of a lifetime. Health states: stable or progression-free, respond to therapy, disease progression, and death Cycle length: 6 wk Sources: direct costs	HER2+ advanced BC previously treated with TRAS and a taxane Baseline patient in the models was a woman aged 53 y, with a height of	T-DM1: 1.803 LAP+CAP: 1.467 CAP: 0.894	T-DM1: $276,447 (1.803) LAP+CAP: $214,541 (1.467) CAP: $161,866 (0.894)	Societal perspective ICER (T-DM1 vs LAP+CAP): $183,828/ QALY ICER (T-DM1 vs CAP): $126,001/ QALY Payer

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		derived from published literature, indirect costs from Wan et al. (2013). Utility values derived from Lloyd et al. (2006) and other similar studies of advanced BC	162 cm and weight of 74 kg			perspective ICER (T-DM1 vs LAP+CAP): $220,385/ QALY ICER (T-DM1 vs CAP): $168,355/QAL Y
CADTH (84) (Canada) T-DM1 vs LAP+CAP T-DM1 vs TRAS+CAP	2014	CEA and CUA with a time horizon of 7 years, Sources: costs source not reported. Utility values based on adverse events and an algorithm from a standard gamble utility study	HER2+ unresectable, locally advanced, or MBC previously treated with TRAS and a taxane.	T-DM1 vs LAP+CAP (incremental QALYs); Manufacturer's estimate: 0.433 EGP's estimate: 0.398 T-DM1 vs TRAS+CAP (incremental costs); Manufacturer's estimate: 0.762 EGP's estimate: 0.725	T-DM1 vs LAP+CAP (incremental costs); Manufacturer's estimate: $55,015 EGP's estimate: $57,835 T-DM1 vs TRAS+CAP (incremental costs); Manufacturer's estimate: $65,750 EGP's estimate: $65,618	T-DM1 vs LAP+CAP (costs per QALY); Manufacturer's estimate: $127,015 EGP's estimate: $145,403 T-DM1 vs TRAS+CAP (costs per QALY); Manufacturer's estimate: $86,304 EGP's estimate: $90,540
Trastuzumab						
Poquet-Jornet et al.	2018	Budget-impact analysis	HER2+ BC	NR	Direct cost was higher	NA

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
(Spain) (85) TRAS (IV) vs TRAS SC		with a time horizon of 11 months. Direct costs included drugs, clinicians and materials. Indirect costs included patient and caregiver. Data sources were electronic medical records, data claims and costs for 58 patients from Denia Hospital.	treated with TRAS IV (n=38) or (n=20) TRAS SC based on medical criteria (total n=58)		for TRAS IV (€71.553) TRAS IV +TRAS SC total cost = €466.480 TRAS SC only total cost = €393.654	
SMC (928/13), (86) (UK) TRAS SC vs TRAS IV	2013	CMA with a time horizon of 1 year. Sources: used UK population weight distribution data to calculate the medicine costs associated with TRAS IV.	HER2+ early BC and MBC	NR	Base case, overall cost saving/patient over 1 y: EBC: £3,454.33 MBC: £3,162.67	NR
Matter-Walstra et al. (Switzerland) (87) CAP (control) vs CAP+continuation of TRAS (treatment)	2010	CUA, Markov cohort simulation with a time horizon of a lifetime Health states: stable or responsive disease, disease progression, and death Cycle length: 3 weeks Sources: medical resource use based on the BIG 03-05 study and on a study of the	Women with HER2+ MBC who progressed during treatment with TRAS	Base-case QALYs Control: 1.17 Treatment: 1.51 Incremental QALYs:0.35 Utility Stable disease: 0.7 (range, 0.5-0.8) Time in progression: 0.5 (range, 0.45-0.72).	Base-case costs Control: €23,217 Treatment: €57,198 Incremental costs: €33,980	Base-case analysis for CAP +continuing TRAS vs CAP ICER: €98,329/QALY

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		resource use and costs for patients with MBC conducted at the University Hospital of Zurich. Utilities derived from published literature.				
Garrison et al. (88) (US) TRAS vs No TRAS	2009	CUA, dynamic life-cycle modelling. The base-case MBC and EBC cost-effectiveness ratios for TRAS were based on the trials described by Slamon et al. (2001) and Romond et al. (2006) Sources: EBC = Garrison et al. (2007), MBC = Based on current drug costs, survival estimates from Hornberger et al. (2002) and utility weights from Elkin et al. (2004).	HER2+v EBC and MBC, approved in 2006 and 1998, respectively. The female population was divided into 5 age groups: <21, 21-39, 40-54, 55-64, and >64 years	EBC; QALYs (no TRAS): 10.08 QALYs (with TRAS): 11.78 MBC; QALYs (no TRAS): 0.70 QALYs (with TRAS): 1.26	EBC; Total costs (no TRAS): $28,749 Total costs (with TRAS): $73,672 MBC; Total costs (no TRAS): $40,000 Total costs (with TRAS): $87,728	EBC; ICER: $26,417 MBC; ICER: $85,676 Combined ICER: $35,600
Trastuzumab and Lapatinib						
CADTH (89) Canada LAP+LET vs LET LAP+LET vs TRAS+ANA	2013	CEA, partitioned survival model Sources: NR	Postmenopausal women with hormone receptor-positive and HER2+ MBC	LAP+LET vs LET (incremental QALYs) Manufacturer's estimate: 0.440 EGP's estimate:0.218 LAP+LET vs TRAS+ANA (incremental QALYs) Manufacturer's estimate:	LAP+LET vs LET (incremental costs) Manufacturer's estimate: $67,029 EGP's estimate: $59,838 LAP+LET vs TRAS+ANA (incremental costs) Manufacturer's estimate:	LAP+LET vs LET (incremental costs) Manufacturer's estimate: $152,344 EGP's estimate:

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				0.236 EGP's estimate: No increase	$5,805 EGP's estimate: $2,536	$274,261 LAP+LET vs TRAS+ANA (incremental costs) Manufacturer's estimate: $24,561 EGP's estimate: not estimated
Lapatinib						
Ballali et al. (90) (Italy) TRAS+paclitaxel vs Paclitaxel vs LAP+CAP	2013	Markov state decision model with a time horizon of 3 years. Cycle: 6 months Health states: stable disease, progressive disease, and death All data were obtained from published studies	HER2+ MBC TRAS as 1st line (stable at beginning, n=195) No TRAS as 1st line (stable at beginning, n=227) LAP as 2nd line (stable at beginning, not applicable)	Progression at 3 years (90% CI): TRAS as 1st line disease: 2 (0-4) No TRAS as 1st line: 2 (0-4) LAP as 2nd line: 0 (0-2) Death at 3 y (90% CI) TRAS as 1st line disease: 262 (229-296) No TRAS as 1st line: 253 (222-285) LAP as 2nd line: 43 (31-56)	6-month administration; 1st line TRAS+paclitaxel: €2,765,662 2nd line LAP+CAP: €100,000, costs Cumulative costs at 3 years; 1st line TRAS+paclitaxel: €8,934,821 2nd line LAP+CAP: €533,300 Note: Cumulative cost impact of anti-HER2 therapies in association with chemotherapy in MBC 1L and 2L treatments at 6, 12, 18, 24, 30 and 36 months presented	NR

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Machado et al. (91) (Brazil) LAP+CAP vs CAP LAP+CAP vs TRAS+CAP	2012	CEA, mathematical model (similar to a Markov model, but does not explicitly make use of transition probabilities) Time horizon of 5-years. Health states: PFS after TRAS failure, disease progression (supportive care), and death Sources: costs were derived from public reimbursement databases. Utilities derived from EGF100151 trial	HER2+ MBC previously treated with TRAS	Expected QALYs: CAP: 0.769 LAP/CAP: 0.958 TRAS/CAP: 0.827	Expected cost total: CAP: R$41,195 LAP+CAP: R$95,256 TRAS+CAP: R$113,686 Expected cost *Medications* CAP: R$14,345 LAP/CAP: R$66,775 TRAST/CAP: R$88,833 *Follow-up* CAP: R$57 LAP/CAP: R$85 TRAS/CAP: R$73 *Adverse events* CAP: R$255 LAP/CAP: R$201 TRAS/CAP: R$329 *Disease progression* CAP: R$26,739 LAP/CAP: R$28,195 TRAS/CAP: R$24,450	Incremental difference from LAP/CAP: CAP: R$284,864 TRAS/CAP: Dominant
Le et al. (92) (US) LAP+CAP CAP alone	2009	Markov model Health with a time horizon of a lifetime states: stable disease, response to therapy, disease progression, and death Sources: health care resource costs based on published data. Utilities adapted from prior MBC	Baseline patient age 53 years with progressive, HER2+ locally advanced or MBC previously treated with a minimum of anthracycline, taxane, and	Expected QALY gain: 0.12 Utilities Stable disease: 0.70 (range, 0.50-0.80) Respond to therapy: 0.84 (range, 0.57-0.93) Disease progression: 0.50 (range, 0.45-0.72)	Average total cost per patient; LAP+CAP: $66,499 CAP alone: $46,869	ICER: $166,113/ QALY gained. (95% CLs ranged from $158,000 to $215,000/ QALY)

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		studies	TRAS			
Sequencing strategies						
Diaby et al. (93) (Mexico) Sequence 1 1st line THP: 2nd line: T-DM1 3rd line: CAP+LAP (THP → T-DM1 → CAP/LAP). Sequence 2 (PER, no T-DM1) 1st line: THP 2nd line: TRAS+LAP 3rd line: TRAS+CAP (THP → TRAS/LAP → TRAS/CAP) Sequence 3 (T-DM1, no PER) 1st line: TRAS+doc 2nd line: T-DM1 3rd line: TRAS+LAP (TRAS/doc → T-DM1 → TRAS/LAP Sequence 4 (no T-DM1 or PER).	2017	CEA and CUA, Markov model using four perspective with a time horizon of a lifetime. Cycle length: weekly Health states: pre-progression or PF 1st line, PF 2nd line, PF 3rd line, and death Sources: cost data were obtained from official publications from Mexican health care institutions. Utility weights obtained from published literature	Newly diagnosed with HER2+ MBC	IMSS & ISSSTE, QALY 4th sequence: 1.407 1st sequence: 1.808 3rd sequence: 1.275 2nd sequence: 1.780 SP, QALY 4th sequence: 1.407 1st sequence: 1.808 3rd sequence: 1.275 2nd sequence: 1.780 Private, QALY 4th sequence: 1.407 1st sequence: 1.808 3rd sequence: 1.275 2nd sequence: 1.780	IMSS & ISSSTE, cost 4th sequence: $48,558 1st sequence: $154,179 3rd sequence: $52,087 2nd sequence: $148,625 SP, cost 4th sequence: $46,296 1st sequence: $151,291 3rd sequence: $50,037 2nd sequence: $145,782 Private, cost 4th sequence: $82,986 1st sequence: $196,715 3rd sequence: $77,386 2nd sequence: $196,221	IMSS & ISSSTE, ICER 4th sequence: Ref 1st sequence: $263,113.955 3rd sequence: $-26,736.680 2nd sequence: $267,671.722 SP, ICER 4th sequence: Ref 1st sequence: $261,552.476 3rd sequence: $-28,340.541 2nd sequence: $266,115.45 Private, ICER 4th sequence: $42,423.933 1st sequence: $223,699.075 3rd sequence: Ref 2nd sequence: $234,921.801

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Diaby et al. (94)(US) 1st sequence: 1L THP, 2L T-DM1, 3L LAP+CAP 2nd sequence: 1L THP, 2L TRAS+LAP, 3L TRAS+CAP; 3rd sequence: 1L TH, 2L T-DM1, 3L TRAS+LAP; 4th sequence 1L TH, 2L TRAS+LAP, 3L TRAS+CAP	2016	CEA, Markov model Health states: PFS 1st to 3rd lines and death with a time horizon of a lifetime. Sources: costs identified according to the US CMS perspective and measured based on medical resources us ed. Costs associated with AEs captured from published literature. Lloyd et al. (2006) study used for utility values. Similar sources used for coefficients of AEs	HER2+ MBC	1st sequence: 1.81 2nd sequence: 1.81 3rd sequence: 1.78 4th sequence: 1.41	1st sequence (US $): 335,231.35 2nd sequence: 333,797.20 3rd sequence: 149,250.19 4th sequence: 175,240.69	1st sequence (US$): 348,630.87 2nd sequence: 364,883.82 3rd sequence: Ref 4th sequence: 197,012.54

1L, first line; 2L, second line; 3L, third line; AE, adverse event; ANA, anastrozole; BC, breast cancer; BIM, budget-impact model; CAP, capecitabine; CEA, cost-effectiveness analysis; CI, confidence interval; CL, confidence limit; CMA, cost-minimisation analysis; CMS, Centeris for Medicare & Medicaid Services; CUA, cost-utility analysis; DOC, docetaxel; EBC, early breast cancer; ECOG, Eastern Cooperative Oncology Group; EGP, economic guidance panel; ERG, evidence review group; HER2, human epidermal growth factor receptor 2; HER2+, HER2 positive; HR, hazard ratio; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; IHC, immunohistochemical; IHC3, immunohistochemical score 3+; IMSS, Mexican Institute of Social Security; ISH, in situ hybridization; ISSSTE, *Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado*; ITT, intention to treat; IV, intravenous; JDMC, JDMC, Inc.; LAP, lapatinib; LET, letrozole; LY, life-year; MBC, metastatic breast cancer; NA, not applicable; NICE, National Institute for Health and Care Excellence; NR, not reported;; PER, pertuzumab; PF, progression free; PFS, progression-free survival; Pub, publication; QALY, quality-adjusted life-year; RCT, randomised controlled trial; SC, subcutaneous; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results; SMC, Scottish Medicine Consortium; SP, Seguro Popular; T-DM1, trastuzumab emtansine; TH, DOC + TRAS; THP, DOC + TRAS + PER; TRAS, trastuzumab; UK, United Kingdom; US, United States.

[a] Including data sources, if available.

[b] For example, an HTA submission.

[c] Including a description of severity; line of treatment (or number of previous treatments); comorbidities; and the author's definition of population, age, sample size, etc.

[d] Results include total expected costs and QALYs for each intervention, incremental costs and QALYs, and ICERs (where reported).

[e] Including HTA recommendations, if available.

B.3.2 Economic analysis

Relevant cost-effectiveness studies identified in the economic analysis were used to inform the development of the cost-effectiveness model for tucatinib with trastuzumab and capecitabine (jointly referred to as “tucatinib combination”). All three T-DM1 technology appraisals NICE (TA458) (52), Scottish Medicines Consortium (SMC 990) (82) and Canadian Agency for Drugs and Technologies in Health (CADTH IS14) (89) used a partitioned survival analysis model structure for the analysis. Additionally, in the literature the Uechi study (Table 16) explored the cost-effectiveness of pertuzumab and used a partitioned survival analysis structure (80). As such, the three-state partitioned survival model structure (progression-free, progressed disease and death) was used in the economic analysis of the tucatinib combination and is described in further detail in Section B.3.2.

A variety of model time horizons were used in previous studies, ranging from one year to a lifetime. A lifetime horizon was the most common (n=7) (81-83, 87, 92, 94) (93). The economic analysis of the tucatinib combination utilises a time horizon of 20 years as 99.9% of patients in HER2CLIMB had died at 10 years (15). As third-line HER2+ MBC patients are unlikely to survive to 20 years, it is sufficiently long enough to adequately capture both costs and health benefits in the base-case economic analysis. For sensitivity analyses, a longer time horizon of 30 years was explored as a scenario in Section B.3.8. A range of cycle lengths used in the cost-effectiveness studies identified by the economic SLR, ranging from 1 week to 6 months. A weekly cycle length was chosen for the economic analysis of the tucatinib combination, consistent with the Diaby et al. (2017) (93) and Durkee et al. (2016) (81) studies with justification provided in Section B.3.3.

B.3.2.1 Patient population

Aligned with the NICE final scope, the base-case patient population for this analysis includes adults with HER2+ MBC who have received two or more prior anti-HER2 regimens (55). This population reflects the ITT population of the HER2CLIMB clinical trial and is consistent with that described in the MHRA SmPC. Patients in HER2CLIMB were treatment experienced, having received two or more prior anti-

HER2 regimens including trastuzumab, pertuzumab, and T-DM1. Baseline demographics and clinical characteristics for patients enrolled in HER2CLIMB are available in Table 4 in Section B.2.3.3.

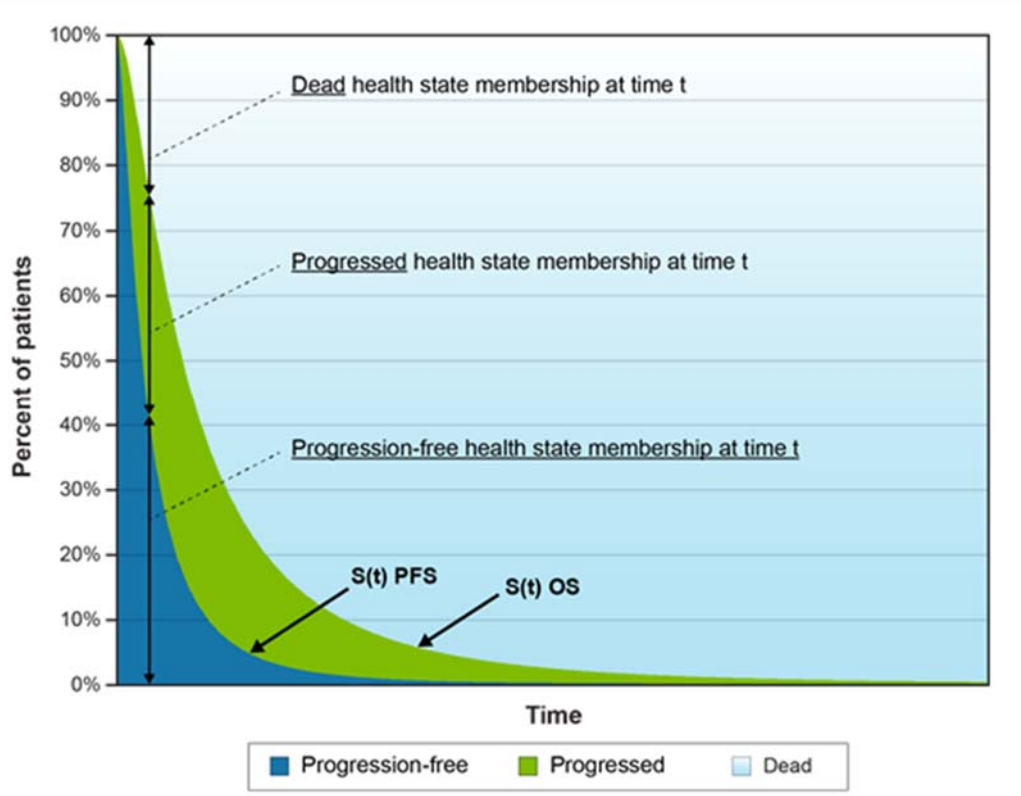
HER2CLIMB was unique among large, randomised trials in that it included patients with active brain metastases (previously untreated or treated, progressing brain metastases) who have historically been excluded from clinical trials (15). It is the first randomised, double-blind trial in HER2+ MBC to enrol a large proportion of patients with brain metastases at baseline (48%), with approximately 60% of these patients having active (untreated or progressing) brain lesions (95). Because it included patients with brain metastases, HER2CLIMB is more representative of the patient population treated in real-world clinical practice.

Patients with HER2+ MBC with brain metastases were included in the NICE final scope as a subgroup (55). As stated in the decision problem (Table 1 in B.1.1), the brain metastases subgroup will not be explored in cost-effectiveness analyses due to a lack of appropriate evidence for comparators including eribulin, capecitabine, and vinorelbine. Although HER2CLIMB included patients with stable and active brain metastases, prior clinical trials excluded patients with brain metastases, particularly those with active or progressing brain lesions. Due to the uniqueness of HER2CLIMB with respect to the inclusion of patients with brain metastases, the evidence does not allow for a methodologically robust subgroup analysis in patients with brain metastases.

B.3.3 Model structure

The model structure used a partitioned survival model analysis developed in Microsoft® Excel. A visual representation of the partitioned survival model structure is indicated in Figure 22 (96). The modelled health states were progression-free, progressed, and dead. In the model, patients begin in the progression-free state and initiate either the tucatinib combination or the comparators. Patients can remain progression-free for a time, experience disease progression, or progress to death. Once patients progress, they can receive subsequent lines of anticancer therapy and supportive care.

Figure 22: Partitioned survival model structure



OS, overall survival; PFS, progression-free survival
Note: The data in the figure are fictitious and used for illustrative purposes only. S(t) PFS is the survival function describing the probability that a patient remains in the progression-free health state beyond a specific time point (t) from model entry. S(t) OS is the survival function describing the probability that a patient survives in the progression-free or the progressed health states beyond a specific time point (t) from model entry. Membership in the progressed health state is determined by subtracting the progression-free state membership from the dead state membership. The analysis was based on the results of the HER2CLIMB trial, which assessed the efficacy and the safety of tucatinib + trastuzumab + capecitabine compared with trastuzumab + capecitabine. An indirect treatment comparison was used to determine the efficacy of external comparators. A partitioned survival model was used to assess the cost-utility of tucatinib + trastuzumab + capecitabine versus these comparators.

Justification for the partitioned survival analysis structure was based on deriving state membership for the model health states from OS and PFS survival curves from the HER2CLIMB trial, including for variation in the risk of progression and death over time (15). Secondly, the model assumption of HER2+ MBC is progressive and captures the expected patient pathway from treatment initiation to death. This reflects the expected clinically important differences in costs and outcomes among patients receiving alternative systemic therapies for HER2+ MBC. The design of the model was informed by a combination of the economic SLR as well as previous NICE Oncology appraisals, which all presented a partitioned survival model structure (97-99). In each of these appraisals, the NICE Committee concluded that the

partitioned survival model structure was appropriate for decision making (97-99). As such, the partitioned survival analysis structure was the most suitable choice for HER+ MBC. As stated in Section B.3.2, the model cycle length of 1 week was applied to provide precision in monitoring the number of patients in each health state over time. In addition, this 1 week cycle length accounts for the different administrations of each treatment during a 21 day cycle: tucatinib (oral) is taken continuously, trastuzumab (IV) once, and capecitabine (oral) daily for two weeks then one week off. As the cycle length is short in comparison to the model time horizon, no half-cycle correction was applied to the model (100).

B.3.3.1 Health states

In the tucatinib economic model, patients begin in the progression-free state and initiate either the tucatinib combination or a comparator combination treatment as shown in Table 17. Patients can remain progression-free for a time, and go on to experience disease progression, or die. Once patients progress, they can receive subsequent lines of anticancer therapy.

Table 17: Model health states

Health State	Description

Progression-free	• Period of treatment with tucatinib + trastuzumab + capecitabine or comparator
	• Adverse events associated with tucatinib + trastuzumab + capecitabine or comparator
	• HRQoL reflects the average for patients
	  o During treatment, including the impact of adverse events
	  o After treatment but before disease progression
	• Costs of treatment with tucatinib + trastuzumab + capecitabine or comparator regimens: drugs, supportive drugs, administration, and monitoring
	• Costs of managing adverse events associated with tucatinib + trastuzumab + capecitabine or comparator

Progressed	• Costs of subsequent systemic anticancer therapy o Patients no longer receive tucatinib or comparator after progression • HRQoL reflects the average for patients from first progression until death • Costs of treatment with subsequent systemic treatment regimens: drugs, administration, and monitoring
Dead	Dead

HRQoL, health-related quality of life

A comparison of the key features of the tucatinib economic model with previous HTAs in HER2+ and HER2- MBC is summarised in Table 18. A more detailed overview of the main features of the tucatinib economic model are presented in Table 19.

Table 18: Features of the economic analysis based on previous NICE technology appraisals

	Previous appraisals[a]				Current appraisal	
Factor	**TA458(52)**	**TA563 (97)**	**TA639 (99)**	**TA619 (98)**	**Chosen values**	**Justification**
Time horizon	Base case:10 years	Base case: Lifetime horizon 35 years	Base case: 15 years	Base case: Lifetime horizon maximum of 40 years	Base case: 20 years	This time frame captures the lifetime of patients by using a variety of methods for extrapolation of OS beyond the follow-up period of the HER2CLIMB trial (4). Though more than 99.9% of patients had died at 10 years, a 20 year time horizon was chosen. This is also a conservative time horizon when compared to, TA639 (99) and TA563 (97).
Treatment waning effect	Not applicable	Not applicable	No waning	Not applicable	Not applicable	Not applicable
Source of utilities	NR	EQ-5D data were collected as part of the MONARCH 3 trial and TA496 using Lloyd 2006 (101) (company submission)	EQ-5D-5L mapped to EQ-5D-3L from IMpassion 130 literature (company submission)	Utility values for pre-progressed health state derived from PALOMA-3 EQ-5D data. Post-progression health states, utility values estimated based on the Lloyd et al 2006 (company submission)	HRQoL data for progression-free and progressed health states were collected in the HER2CLIMB trial using EQ-5D-5L then subsequently mapped to the EQ-5D-3L.	HRQoL data from HER2CLIMB using the EQ-5D-5L. The questionnaire was included in a protocol amendment (version 7) and data are available for subsequent patients. Baseline demographics and characteristics of patients who completed the EQ-5D

	Previous appraisals[a]				Current appraisal	
Factor	**TA458(52)**	**TA563 (97)**	**TA639 (99)**	**TA619 (98)**	**Chosen values**	**Justification**
						are consistent with those of the full ITT population. A further mapping of the EQ-5D-5L to EQ-5D-3L was conducted using the van Hout et al. (2012) method (102) aligned with NICE reference case (103)
Source of costs	NR	NHS reference costs (2016-17); PSSRU (2017)	NHS reference costs PSSRU BNF/eMIMS Published literature Expert opinion	Drug acquisition, wastage (eMIT; BNF), monitoring, administration, adverse events, miscellaneous (NHS Reference Costs 2017/18; PSSRU 2018).	BNF costs 2021, NHS Reference Costs 2018/2019, eMIT PSSRU 2020	Sources of costs and resource use are consistent with patients who have third-line HER2+ MBC, costs were obtained from UK national resources to reflect the UK NHS/PSSRU perspective. The NHS reference costs and PSSRU sources are consistent with previous NICE TAs and as per NICE reference case (103).

BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information tool; EQ-5D, EuroQoL 5-Dimensions; EQ-5D-3L, EuroQoL 5-Dimensions 3-Levels; EQ-5D-5L, EuroQoL 5-Dimensions 5-Levels HER2, Human epidermal growth factor receptor 2; HRQoL, health-related quality of life; ITT, intent to treat; MBC, metastatic breast cancer; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; NR, not reported; QALYs, quality adjusted life years; OS, overall survival; PSS, Personal social services; PSSRU, Personal social services research unit; TA, technology assessment; UK, United Kingdom

[a] Search of previous NICE TAs included both HER2+ MBC appraisals identified as well as relevant HER2- MBC appraisals

Table 19: Features of the economic analysis

Factor	Model Features	Justification
Perspectives	Health care payer (NHS and PSSRU)	The analysis was conducted from the perspective of the NHS, and PSS, in line with current NICE guidelines (103). The analysis excluded patients' out-of-pocket expenses and lost productivity derived costs.
Cost-year	2020 (NHS Reference costs), 2020 (PSSRU), 2021, eMIT 2021 and BNF, 2021	The cost-year for the analysis was 2020 based on the most up-to-date NHS Reference costs available. Costs quoted for other cost-years were inflated to the model cost-year using the Hospital and Community Health Services index (8, 104).
Discount rates	Costs: 3.5% Outcomes: 3.5%	NICE reference case.
Time horizon	20 years	Please refer to Table 18
Cycle length	7 days (no half-cycle correction applied)	Cycle length chosen to track the number of patients in each health state over time in the early years of the model as well as to account for differing administration of the treatments in the tucatinib combination. As the cycle length is short in comparison to the model time horizon, no half-cycle correction was applied in this model (100).
Populations	All-comers (external comparisons)	All-comers population is consistent in HER2CLIMB within-trial and for external comparisons
Comparators	HER2CLIMB: trastuzumab + capecitabine NMA: eribulin, vinorelbine and capecitabine	As indicated in B.2.9 HER2CLIMB and the SLR outputs provided no direct head-to-head evidence with the tucatinib combination versus the single-agent chemotherapy agents included as relevant comparators in this submission (eribulin, capecitabine and vinorelbine)
Survival analysis[b]	Flexible Weibull (2 knots) (PFS) Weibull (OS)	Please refer to Section B.3.3.4.
NMA (external comparators)[c]	Hazard ratio fixed effects model (PFS and OS) Hazard ratio random effects model (PFS and OS) Fractional polynomial fixed effects model (PFS and OS) Fractional polynomial random effects model (PFS and OS)	As stated in (Section B.2.9) The comparators of interest included in the SLR reflect the comparators considered in the decision problem addressed in this submission, however no direct head-to-head evidence exists with the tucatinib combination versus the single-agent chemotherapy agents included as relevant comparators in this submission (eribulin, capecitabine and vinorelbine). All relevant studies included in the NMA met the proportional hazards assumption for both PFS and OS, therefore HR NMAs were conducted. As some trials in the network violated the proportional hazards assumption, fractional polynomial analyses were conducted, and the results were compared to the HR analyses. Results were consistent for all comparisons relevant to the current decision

Factor	Model Features	Justification
		problem. Please refer to Section B.2.9 and the decision problem in Table 1.
Treatment duration[d]	TTD survival extrapolations (HER2CLIMB only) flexible Weibull (2 knots) TTD estimation using the exponential function for external comparators	Please refer to Section B.3.3.5
Source of utilities[e,f]	**Base case – tucatinib** Treatment-specific values (HER2CLIMB only) EQ-5D-3L (15, 105) **Base case – eribulin** Combination of Crott and Briggs (2010) (106) and Lloyd et al. (2006) (101) **Sensitivity analyses – tucatinib** Treatment-specific values (HER2CLIMB only) EQ-5D-5L (15) **Sensitivity analyses** - vinorelbine NICE TA423 (2016) (47) **Sensitivity analyses -** capecitabine NICE TA423 (2016) (47)	Please refer to Table 18 and Table 24.
Source of costs	BNF 2021, 2019/2020 NHS Reference Costs, eMIT (8)	Please refer to Table 18

EQ-5D-3L, EuroQoL 5-Dimensions 3-Levels; HR, hazard ratio; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PSS, Personal and Social Services; PSSRU, Personal social services research unit; SLR, systematic literature review; T-DM1, trastuzumab emtansine; TTD, time-to-treatment discontinuation; UK, United Kingdom.

[a] This model setting is used in the base-case analysis for all treatment comparisons.

[b] Survival models used in the base-case analysis for the within-trial comparison (tucatinib + trastuzumab + capecitabine vs trastuzumab + capecitabine): PFS = flexible Weibull (2 knots); OS = Weibull.
[c] This NMA model is used in the base-case analysis for all indirect treatment comparisons with external comparators.
[d] TTD survival extrapolations are used as the base-case assumption. The flexible Weibull (2 knots) survival model is used for tucatinib + trastuzumab + capecitabine and trastuzumab + capecitabine. TTD is estimated for external comparators using the exponential function.
[e] Treatment-specific health-state utility values are used in the base-case analysis for the within-trial comparison (tucatinib + trastuzumab + capecitabine vs trastuzumab + capecitabine).
[f] Treatment-dependent health-state utility values (calculated from (101)) are used in the base-case analysis for all comparisons with external comparators.

B.3.3.2 Clinical experts

In the scope for this appraisal, NICE identified three single-agent chemotherapies, eribulin, capecitabine, and vinorelbine, as comparators for the tucatinib combination in the third-line setting. Seagen also recently commissioned an advisory board with seven expert clinicians who provided insights on the treatment pathway for HER2+ MBC in England. The clinical experts agreed that these three single-agent treatments are currently used in England in this setting (as further described in Section B.2). Clinicians also confirmed [redacted] demonstrating that the three relevant comparators of eribulin, capecitabine and vinorelbine are [redacted]. In extensive advisory board discussions, the physicians agreed that capecitabine is typically used in combination with trastuzumab. As such, the clinicians agreed that eribulin is the most plausible standard of care as it is used as a single agent and it is the only treatment approved by NICE for use in the third-line setting (NICE TA423) (47). However, the consensus of the advisory board was that a significant unmet need exists for new and efficacious treatments in this setting (16). Based on this advice, eribulin is the base-case in the evidence submission and economic model, with additional analyses conducted against capecitabine and vinorelbine for completeness.

B.3.3.3 Key clinical studies

As stated in Section B.2.6, HER2CLIMB is the key clinical study for the tucatinib combination (see Section B.2.3 and Figure 3 for the study design). As indicated in Section B.2.3.2, the primary endpoint in HER2CLIMB assessed the effect of the tucatinib combination versus the placebo combination on PFS according to RECIST 1.1 (4). The primary analysis of PFS concluded that treatment with the tucatinib combination was superior to the placebo combination as indicated by a 46% reduction in the risk of disease progression or death (HR=0.54; 95% CI 0.42, 0.71; p<0.001). The key secondary endpoints for the trial are also described in Section B.2.6 and included OS, PFS in patients with brain metastases ($PFS_{brain\ metastases}$), and ORR (4). Additional secondary endpoints included duration of response, clinical benefit rate (CBR), and HRQoL (4). As mentioned in Section B.2.6.2, HER2CLIMB results showed OS was significantly prolonged in

patients who received the tucatinib combination compared with patients who received the placebo combination, with a 34% reduction in the risk of death (HR=0.66; 95% CI 0.50, 0.88; p=0.005). In Section B.2.6.3, Figure 6, a 52% reduction in the risk of disease progression or death was seen with the tucatinib combination compared with the placebo combination (15).

B.3.3.4 Survival Analyses

Survival analyses were performed to determine survival curves for the tucatinib combination and control arms for the OS and PFS endpoints. A wide range of survival models were fitted to data from the HER2CLIMB trial alone and in conjunction with external data for MBC and the general population. External data for MBC were identified from targeted literature searches for studies that presented longer-term Kaplan-Meier data than the HER2CLIMB trial presented in Table 1 of Appendix L. Of these 12 studies, the data reported by Kaufman et al. (2015) was selected as the most suitable for extrapolation of the HER2CLIMB trial for the following: the proportion of patients alive at 3 years was similar to HER2CLIMB, the shape of the survival curves provided a similar visual fit, the trial had the largest sample size (n=1,102) and the longer follow-up compared with HER2CLIMB allowed it to be used to confirm the extrapolation of the HER2CLIMB data over a longer period (57). A time acceleration adjustment was performed to the PFS and OS data from the Kaufman et al. study was conducted to match the placebo arm of HER2CLIMB more closely, which is described in detail in the Appendix L. Survival models fitted to PFS and OS data included parametric models, flexible spline-based models, and hybrid models. The following sets of functions were fitted:

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

To determine the most appropriate survival functions, the recommended methods from the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 was used to assess the model fit and validation of the extrapolation methods as

indicated in the summary below (107). Full methodology and results of the survival analyses are detailed in Appendix L.

- Testing of −log(−log(survival)) plot and significance to assess the proportional hazards assumptions for OS and PFS Appendix L in Figure 13 and Figure 40, respectively
- Estimation of smoothed hazard rates to investigate how the hazard rates and ratios change over time for OS and PFS. Further detail is described in Appendix L in Figure 15 and Figure 16 for OS and Figure 42 for PFS
- Graphic comparison of the predicted curve from a given parametric function to the Kaplan-Meier curve from patient data
- Internal validity using Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness-of-fit tests and visual inspection
- The extrapolated portion of the survival curves were validated using the external data by Kaufman et al. (2015) (57) and further validated by UK clinical experts via an advisory board (16)

Multiple survival models were fitted to the HER2CLIMB trial data alone for PFS and OS, with further methodology over the range of curves fitted described further in Appendix L. This produced a good fit to the trial data with plausible extrapolations that did not exceed the predicted survival from the models fitted to the external data from the Kaufman et al. study. Therefore, only survival models fitted to the HER2CLIMB trial data alone were included in the cost-effectiveness model as these represented the simplest approach. As indicated in Appendix L, more complex survival models incorporating external data did not result to substantially different outcomes.

B.3.3.4.1 Progression-free survival

The survival models fitted to the HER2CLIMB PFS data and the long-term extrapolations are presented in Appendix L, representing the mean survival estimates for the extrapolated models (calculated as the area under the curve between 0 and 100 years). Of the 21 models fitted, 7 provided a good fit with the trial data and produced extrapolations that did not exceed those from the models fitted to the Kaufman et al. (2015) (57) data and general population data (108) and are

summarised in Table 20. The fit to RCT column represents how well the models fitted to the external data (57). The plausibility of the curves was determined where the estimate did not exceed the predicted survival from the models fitted to the external data.

Table 20: Predicted mean PFS times for best-fitting models to HER2CLIMB (in months)

	Placebo Combination			Tucatinib Combination			Difference, Months				
Model	**Mean**	**Lower CrI**	**Upper CrI**	**Mean**	**Lower CrI**	**Upper CrI**	**Mean**	**Lower CrI**	**Upper CrI**	**Fit to RCT**	**Clinically Plausible**
Stratified log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Good	Yes
Stratified log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Good	Yes
Stratified generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Good	Yes
Flexible Weibull (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Good	Yes
Flexible Weibull (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Good**	**Yes**
Stratified flexible Weibull (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Good	Yes
Hybrid exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Good	Yes

PFS, progression-free survival; RCT, randomised clinical trial

As indicated in Table 20, the differences in the point estimates for the mean survival from these models for the tucatinib combination versus placebo + trastuzumab + capecitabine indicated a small range as evidenced by [redacted] to [redacted] months. The flexible Weibull 2-knots was chosen as the final model for PFS in the base-case (in bold with mean survival difference of [redacted] months), as it was in line with the results from the models that directly used external data (4).

B.3.3.4.2 Overall survival

The survival models fitted to the HER2CLIMB OS data and the long-term extrapolations are presented in Appendix L, representing the mean survival estimates for the extrapolated models (calculated as the area under the curve between 0 and 100 years). Of the 21 models fitted, 13 models provided a good fit with HER2CLIMB and produced extrapolations that did not exceed those from the models fitted to the (57) and general population data are summarised in Table 21.

Table 21: Predicted mean OS times for best-fitting models to HER2CLIMB (in months)

Model	Placebo Combination			Tucatinib Combination			Difference, Months			Fit to RCT	Clinically Plausible
	Mean	Lower CrI	Upper CrI	Mean	Lower CrI	Upper CrI	Mean	Lower CrI	Upper CrI		
Weibull	**19.9**	**16.9**	**23.1**	**26.0**	**22.6**	**29.9**	**6.2**	**1.3**	**10.7**	**Good**	**Yes**
Stratified Weibull	[redacted]						8.0	[redacted]		Good	Yes
Gompertz	20.7	16.8	29.4	27.4	22.3	39.9	4.8	1.4	8.9	Good	Yes
Stratified Gompertz	[redacted]						5.9	[redacted]		Good	Yes
Gamma	[redacted]						6.4	[redacted]		Good	Yes
Stratified gamma	[redacted]						8.8	[redacted]		Good	Yes
Generalised gamma	[redacted]						6.2	[redacted]		Good	Yes
Stratified generalised gamma	[redacted]						6.5	[redacted]		Good	Yes
Flexible Weibull (1 knot)	[redacted]						6.2	[redacted]		Good	Yes
Flexible Weibull (2 knots)	[redacted]						7.2	[redacted]		Good	Yes
Stratified flexible Weibull (1 knot)	[redacted]						7.1	[redacted]		Good	Yes
Stratified flexible Weibull (2 knots)	[redacted]						6.8	[redacted]		Good	Yes
Hybrid exponential	[redacted]						7.7	[redacted]		Good	Yes

OS, overall survival; RCT, randomised clinical trial

The 13 best-fitting plausible models for OS gave predictions between [redacted] and [redacted] months. Of these, the Weibull was chosen as the final model for OS in the base-case (as indicated in bold with a mean survival difference of 6.2 months) based on AIC and BIC goodness-of-fit tests (107). However, the AIC and BIC were not able to differentiate between the non-stratified and stratified Weibull models and as such this was combined with visual inspection and external validation through the advisory board with clinicians based in England as described in Section B.2.13.2 (16). The consensus among the advisory board was that both the Weibull and stratified generalised gamma OS respectively, were the most appropriate model for OS (16). In summary, based on a combination of AIC/BIC, visual inspection and external validation using the Kaufman et al. (2015) data (57) and the consensus from the advisory board (16), the Weibull was assumed for the base-case for OS. The stratified generalised gamma for OS the was subsequently explored in the sensitivity analysis in Section B.3.8 scenario 1 to assess the impact on the ICER.

B.3.3.5 Treatment duration

The flexible Weibull (2 knots) was selected for the base-case, in part, as it was aligned with the PFS survival model from HER2CLIMB. As disease progression is the primary reason for treatment discontinuation, the anticipated time-to-treatment discontinuation (TTD) curve follows a [redacted]. No TTD data were available for eribulin, vinorelbine and capecitabine; TTD is estimated using the exponential function for these treatments based on the treatment exposure reported in clinical trials. The methodology is fully described in Appendix L. The justification for using the exponential function was to provide a more valid comparison with the TTD survival analysis available for the tucatinib combination and was in line with the assumption that eribulin, vinorelbine and capecitabine followed the shape of the exponential function. To incorporate the exponential TTD curve for external comparators as a parameter in the model, treatment duration values were identified from the studies included in the NMA, which is described in Appendix D.

B.3.3.6 Transition probabilities

Transition probabilities were not used in the model as the model structure assumed a partitioned survival analysis model structure as stated in Section B.3.3. As such, the transition matrix would not be applicable as the survival was derived directly from the KM curve from HER2CLIMB.

B.3.3.7 Transition probabilities treatment effect

As stated in Section B.3.3.2, state membership was derived directly from the OS and PFS survival curves from the HER2CLIMB trial. As indicated in Section B.2.9, the treatment effects are expressed as HRs from the Bayesian FE model in the NMA using the lapatinib plus capecitabine anchoring. As such, transition probabilities changing over time would not be applicable as these are already factored in using the HRs.

B.3.3.8 Clinical experts

The economic analysis did not include consultations with clinicians for the development of the clinical parameters or the approximation of the clinical parameters.

B.3.4 Measurement and valuation of health effects

B.3.4.1 HRQoL data from HER2CLIMB

HRQoL data for the progression-free and progressed health states were collected in HER2CLIMB, using the EQ-5D-5L preference-based health-state utility questionnaire. As stated in Section B.2.6.9, HRQoL assessment was added to HER2CLIMB in protocol version 7 resulting in a subset of patients with baseline HRQoL data (n=217 in the tucatinib-combination group and n=112 in the placebo-combination group) (64), including [redacted] patients from UK centres ([redacted] in the tucatinib combination group and [redacted] in the placebo combination group). However, baseline patient characteristics were consistent between the full study population (ITT-OS, as defined in Table 3) and those who had baseline HRQoL data.

Patients completed an HRQoL assessment every two treatment cycles until cycle 12, then subsequently every three cycles (4) of which each cycle is 21 days. In addition, a post-treatment assessment occurred approximately 30 days after the end of study treatment. HRQoL was analysed by treatment group for all randomised patients in the ITT population who consented after the EQ-5D-5L was added to HER2CLIMB.

B.3.4.2 Mapping

In addition, the EQ-5D-5L utilities from HER2CLIMB data were mapped to EQ-5D-3L in alignment with the NICE reference case (103). The utility index scores were mapped using the EuroQol data set of cross-walked values for each of the possible EQ-5D-5L response sets with UK preference weighting using the van Hout et al. (2012) method (102, 109). This method was chosen as it is a validated mapping method by NICE for reference case analyses (102, 109). Given NICE's position on the EQ-5D-5L as having greater sensitivity over the EQ-5D-3L (109), the treatment-specific utilities using the EQ-5D-5L from HER2CLIMB was included in the sensitivity

analyses in Section B.3.8. Detailed methodology for the cross-walk can be found in the Seagen data on file (2020) (105) and the mapped EQ-5D-3L treatment-specific health-state utility weights are summarised in **Error! Reference source not found.**.

B.3.4.3 Health-related quality-of-life studies

An economic SLR was conducted using a single search strategy to identify HRQoL studies for unresectable, locally advanced or metastatic HER2+ breast cancer with or without brain metastases with progression after previous treatment. The original search was conducted on 11 December 2019 with an ongoing SLR expected to be completed on 7 May 2021, with no changes in the scope. One search strategy was devised to identify cost-effectiveness, utility, HRQoL and cost and resource use studies. The PICO principle described in the York CRD guidance was used to develop the review question below, which guided the search for HRQoL studies. For more details on the search strategies, the inclusion/exclusion criteria, and HRQoL results please see Appendices G and H, respectively. The review question evaluated in the SLR was:

- To identify and summarise utility data for unresectable, HER2+ locally advanced or metastatic breast cancer with or without brain metastases

Using this search strategy, 11 studies were found to be eligible for data extraction. Hagiwara et al. (2018) was the only primary utility study comparing the EQ-5D index of adjuvant trastuzumab monotherapy with trastuzumab plus chemotherapy in a RCT, societal preferences of the general population in Japan (110). The adjusted mean EQ-5D-3L index scores from enrolment to 36 months of follow-up ranged from 0.80 to 0.85 in a cohort of patients receiving trastuzumab monotherapy, and from 0.77 to 0.81 in a cohort receiving trastuzumab plus chemotherapy (110). However, as the study was based in Japan, the utilities were not generalisable to the UK population and as such, could not be used in the cost-effectiveness analysis (103).

The majority of the extracted studies were economic evaluations that included utility data used as input parameters for the economic model. Utility values across various combinations of health states and adverse events in patients with MBC were derived for use in the economic model. From the 10 economic evaluations, the most widely

used source in the models was Lloyd et al. (2006) (101), a preference-based study estimating utilities at distinct stages of MBC in the general population. The application of Lloyd et al. (2006) was consistent in NICE TAs, as this featured in the Evidence Review Group's (ERG) preferred approach for eribulin in TA423. As indicated in Table 18, Lloyd et al. (2006) was also used in TA563 (abemaciclib with aromatase inhibitor) (97) and TA619 (palbociclib with fulvestrant) (111) for HER- locally advanced or MBC. The final utilities for eribulin are described at length in B.3.4.10. For the purpose of the tucatinib cost-effectiveness analysis, the Lloyd et al. (2006) study was not appropriate for the economic analysis since treatment-specific utilities were collected in the HER2CLIMB trial (15). In addition, the HER2+ MBC treatment landscape has evolved since 2006 to include additional anti-HER2 therapies (pertuzumab and T-DM1) in earlier lines of therapy, thereby improving the prognosis, and likely the HRQoL of first- and second-line HER2+ MBC patients.

B.3.4.4 Adverse reactions

Adverse reaction data from HER2CLIMB is available in Section B.2.10 and were assumed to be captured in the utility weights for the tucatinib combination. In addition, it is assumed that utility decrements due to adverse reactions were captured in utility weights for eribulin and capecitabine taken from NICE TA423 (47). As the economic analysis assumes treatment-specific health-state utility values capture utility associated with AEs; when these values are selected, utility decrements are not applied in the model to avoid double-counting.

B.3.4.5 Patient experience

The goals of reducing metastatic burden among MBC is to slow tumour growth and delay metastatic progression. However, as patients are living longer with metastatic disease, there is an emphasis on maintaining HRQoL in the progression-free health state. As indicated in Section B.2.13.1, patients in HER2CLIMB maintained HRQoL during the course of the study whilst on the tucatinib combination and had their risk of disease progression or death reduced by 46%.

B.3.4.6 HRQoL over time

As stated in Section B.2.6.9, no clinically meaningful declines were observed in HER2CLIMB and the VAS scores indicated similar results for the tucatinib combination compared with the placebo combination. Once patients move to progressed disease, HRQoL is expected to diminish before transitioning to death. The HER2CLIMB EQ-5D-5L data and mapped EQ-5D-3L utilities for the overall population are described in further detail below.

B.3.4.6.1 Overall population EQ-5D-5L

The utility values reported for each health state using the EQ-5D-5L for the overall population is summarised in Table 22. In the progression-free state, utility values increased with subsequent treatment cycles in the tucatinib arm and decreased with subsequent cycles for the placebo arm, with the exception of the utility value in cycle 7+ (0.810) for the placebo arm, which was slightly higher than the value reported for cycle 5 to 6 (0.808). Utility values were higher for placebo than tucatinib in cycle 1 to 2 and the post-progression state, equal in cycle 3 to 4, and higher for tucatinib than placebo in cycle 5 to 6 and cycle 7+.

Table 22: Mean EQ-5D-5L scores for the overall population

Health State	Tucatinib Combination	Placebo Combination	Source
Progression-free, cycle 1 to 2	0.823	0.845	HER2CLIMB (15)
Progression-free, cycle 3 to 4	0.835	0.835	
Progression-free, cycle 5 to 6	0.859	0.808	
Progression-free, cycle 7+	0.872	0.810	
Progressed[a]	0.738	0.778	
Dead	0	0	

EQ-5D-5L, EuroQoL 5 Dimensions 5-Levels

[a] This was captured at the 30 day follow up visit.

B.3.4.6.2 Overall population EQ-5D-3L

The mapped EQ-5D-3L values produced lower values when compared with the EQ-5D-5L in the overall population. The utility values are reported for each health state

by treatment arm for the overall population (Table 23). In the progression-free state, utility values increased with subsequent treatment cycles for the tucatinib combination and decreased with subsequent cycles for the placebo combination, with the exception of the utility value in cycle 7+ (0.748) for the placebo combination, which was slightly higher than the value reported for cycle 5 to 6 (0.741). Utility values were slightly higher for the placebo combination than the tucatinib combination in cycle 1 to 2, cycle 3 to 4, and the post-progression state and higher for the tucatinib combination than the placebo combination in cycle 5 to 6 and cycle 7+. The HRQoL in the progressed state is captured during the 30-day follow-up.

Table 23: Mean EQ-5D-3L scores overall population

Health State	Tucatinib Combination	Placebo Combination	Source
Progression-free, cycle 1 to 2	0.748	0.770	HER2CLIMB (15)
Progression-free, cycle 3 to 4	0.763	0.765	
Progression-free, cycle 5 to 6	0.792	0.741	
Progression-free, cycle 7+	0.807	0.748	
Progressed[a]	0.653	0.698	
Dead	0	0	

EQ-5D-3L, EuroQoL 5 Dimensions 3-Levels

[a] This was captured at the 30 day follow up visit.

B.3.4.7 Baseline HRQoL

Utility values for all health states were based on the EQ-5D-5L from HER2CLIMB at baseline and incorporated in the economic analysis then mapped to the EQ-5D-3L. Therefore, the baseline health state utility values (HSUVs) were from HER2CLIMB and did not differ from what was included in the model.

B.3.4.8 Adjustment of health state utility values

None of the health state utilities for the tucatinib combination were adjusted for the purpose of the economic analysis. As stated in section, eribulin was not explored in the HER2CLIMB trial. As such, the treatment-specific HSUVs for eribulin were incorporated using the NICE Committee's decision in eribulin TA423. In TA423, the

company initially incorporated the mapping algorithm published by Crott and Briggs (2010) (106) for progression-free, progressed and death health states, which were considered implausible by the ERG in part because they were for locally advanced and not metastatic disease (47). The ERG's preferred approach was to include utilities by Lloyd et al. (2006), while the NICE Committee's preferred approach was to assume the values for progressed disease as somewhere between the two (47). Based on the Committee's decision in the final appraisal determination (FAD) in TA423, the average of the Crott and Briggs (2010) (106) and Lloyd et al. (2006) (101) utilities were applied for eribulin for progressed in addition to the progression-free states (47).

B.3.4.9 Excluded health effects found in the literature or clinical trials

Health effects, such as productivity loss among patients and carers, were excluded from the economic analysis. Though in Section B.3.4.2 and in Appendix H, the Hagiwara et al. (2018) study explored the societal impact of HER+ MBC on patients. Any health effects associated with societal impact was excluded in the model, as this is not a requirement for NICE. For the utility decrements due to adverse reactions for the tucatinib combination and the external comparators please see Section B.3.3.4.

B.3.4.10 HRQoL data included in the cost-effectiveness analysis

The treatment-specific health-state utility weights were used in the base-case analysis from HER2CLIMB. The treatment-specific health-state utility weights mapped to the EQ-5D-3L were selected for the base-case analyses of the tucatinib combination versus eribulin and are summarised below in Table 24.

Table 24: Mapped treatment-specific utilities from (HER2CLIMB) and eribulin

	Tucatinib Combination	Eribulin		
Health state	Tucatinib + Trastuzumab + Capecitabine EQ-5D-3L (15, 102, 105)	Crott and Briggs (2010) (106)	Lloyd et al. (2006)(101)	Chosen final values (average of Crott & Briggs and Lloyd et al. (2006) (47, 101, 106)
Progression-free, cycles 1–2	0.748	0.780	0.786	0.783
Progression-free, cycles 3–4	0.763	0.780	0.786	0.783

Progression-free, cycles 5–6	0.792	0.780	0.786	0.783
Progression-free, cycles 7+	0.807	0.780	0.786	0.783
Progressed	0.653[a]	0.705	0.538	0.622
Dead	0	0	0	0

EQ-5D-3L, EuroQoL 5 Dimensions 3-Levels
[a] This was captured at the 30 day follow up visit for the tucatinib combination only.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An economic SLR was conducted to identify existing studies that reported direct and indirect costs and resource use by health state for patients with locally advanced or metastatic HER+ breast cancer. The original search was conducted on 11 December 2019 with an ongoing SLR expected to be completed on 7 May 2021, with no changes in the scope. One search strategy was devised to identify cost-effectiveness, HRQoL and cost and resource use studies. The PICO principle described in the CRD guidance was used to develop the review question below, which guided the search for costs and resource studies only. For more details on the search strategies, the inclusion/exclusion criteria, and costs and resource use results please see Appendices G and I, respectively. The review question to evaluate costs and resource use in the SLR was:

- To identify and summarise resource-use and cost (direct and indirect) data for unresectable, locally advanced or metastatic HER2+ breast cancer with or without brain metastases with progression after previous treatment

Of the four HER+ MBC studies identified in the economic SLR, two were from the US, one provided data for Spain and one for Canada. Non-UK studies have limited suitability for this economic analysis. Only one study provided limited disaggregated costs (Reyes et al. 2017) (112); however, unit cost or resource use estimates were not available. Piwko et al. 2015 (113) provided detailed costs for adverse effects that are suitable for economic analysis from a Canadian perspective. The other two studies – Goertz et al. 2018 (114) and Colomer et al. 2017 (115) – only reported total

cost of care, which did not inform the microcosting approach of the UK NHS system. For further details of the studies please see Appendices G and I.

Based on the paucity of cost and resource studies for HER2+ MBC studies from the UK in the literature, a search of previous NICE TAs for HER2- MBC was used to identify the cost and resource use parameters as identified in Table 18. Cost and resource sources were based on PSSRU, NHS reference costs, and BNF aligned with the NICE reference case (103).

B.3.5.1 Intervention and comparators' costs and resource use

The tucatinib combination and eribulin are provided in secondary care. There is no additional infrastructure required to administer care within this setting. All aspects can be adopted within the current skillset of the nurses and general practitioners (GPs) and does not require additional visits to a healthcare professional and resources beyond the standard follow-up. As a result, only treatment administration and acquisition costs were applied to fully represent the costs of treatment itself for both interventions.

B.3.5.1.1 Tucatinib acquisition cost

The cost for a 150-mg pack of 84 tablets of tucatinib at Patient Access Scheme (PAS) price is [redacted] and the 50-mg pack of 88 tablets is [redacted]. The cost for a 150-mg pack of 84 tablets of tucatinib at list price is [redacted] and the 50-mg pack of 88 tablets is [redacted]. As stated in Section B.2.3.2, Table 2 and aligned with the MHRA SmPC, the recommended dosing for the tucatinib combination is:

- Tucatinib 300 mg taken orally twice daily continuously until progression
- Capecitabine 1000 mg/m^2 orally twice daily on days 1–14 of each 21-day cycle, mean body surface area (BSA) 1.8 m^2
- Trastuzumab loading dose of 8 mg/kg IV infusion followed by 6 mg/kg once every 21 days, mean weight 69.5 kg

Treatment with tucatinib should be continued until disease progression or unacceptable toxicity. Dose modifications for adverse reactions or toxicities

suspected to be caused by the tucatinib dose are also provided based on the SmPC (116):

- Recommended starting dose: 300 mg twice daily
- First dose reduction: 250 mg twice daily
- Second dose reduction: 200 mg twice daily
- Third dose reduction: 150 mg twice daily

For the first and second dose reduction, the 50 mg dose would be relevant for the NHS, as patients can adhere to the SmPC's guidelines (116). The unit costs per pack for the tucatinib combination and comparators are summarised below in Table 25.

Table 25: Tucatinib combination unit cost

Treatment	Pack price	Source
Tucatinib (150 mg x 84 tablets)	[redacted] (PAS price) [redacted] (list price)	Seagen Tucatinib anticipated list price (at the time of submission, the price has been submitted to DoH, but is not yet listed)
Tucatinib (50 mg)	[redacted](PAS price) [redacted] (list price)	Seagen (at the time of submission, the price has been submitted to the DoH, but is not yet listed)
Capecitabine (500 mg x 120 tablets)	£25.02	eMIT. Pharmex data for the period 01/01/20 - 31/12/20, for Pharmex products shown as generic in the period 01/07/20 - 31/12/20 2021 (8)
Trastuzumab IV per 150 mg vial (cycle 1)	£36.67	BNF, Trastuzumab – medicinal forms 2021 (7) and model-assumed discount
Trastuzumab IV per 150 mg vial (cycle 2 +)		BNF, Trastuzumab – medicinal forms 2021 (7)

BNF, British National Formulary; DoH, Department of Health; eMIT, drugs and pharmaceutical electronic market information tool; IV, intravenous; PAS, Patient Access Scheme

B.3.5.1.2 Comparator unit costs

The unit price and price per cycle for the tucatinib comparators are calculated in Table 26Table 27. For the comparators, the unit costs for eribulin were sourced using BNF (2021) and drugs and pharmaceutical electronic market information tool (eMIT) (2021).

Table 26: Comparator unit costs

Treatment	Pack price	Planned dose per 21-day cycle (mg)	Source
Eribulin	£361.00	6	BNF, 2021 (117)
Vinorelbine	£157.69	135	eMIT, 2021 (DHA225) (8)
Capecitabine	£25.02	63,000	eMIT, 2021 (DHA225) (8)

BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information tool

B.3.5.1.3 Administration costs

Drug administration costs have been included in the model (Table 27). The cost of administering tucatinib was modelled as a one-off cost of £195.44 for oral chemotherapy treatment, based on NHS Reference Costs and the Healthcare Reference Group code of SB11Z (118). As capecitabine is also an orally administered chemotherapy, an additional administration cost was not included when given alongside tucatinib; capecitabine is given at each clinical visit so administration cost is captured by the administration costs for trastuzumab in the tucatinib combination. Trastuzumab is administered intravenously and therefore has a higher cost of £241.06, which is incurred once for each 21-day cycle (118). The same drug administration costs were assumed for eribulin and vinorelbine, based on the method of administration (infusion). For capecitabine monotherapy, the oral administration cost is applied in each model cycle instead of as a one-off cost. This was based on the UK clinical expert advice that patients must go to hospital to collect capecitabine for each treatment cycle.

Table 27: Drug administration costs

Treatment	Drug administration cost per patient per cycle	Source
Tucatinib	£195.44 (one-off)	NHS Improvement, 2019 (118)
Capecitabine	£195.44 (one-off)	NHS Improvement, 2019 (118)
Trastuzumab IV (cycle 1)	£241.06	NHS Improvement, 2019 (118)
Trastuzumab IV (cycle 2)		
Eribulin	£241.06	NHS Improvement, 2019 (118)
Vinorelbine	£241.06	NHS Improvement, 2019 (118)
Capecitabine	£195.44	NHS Improvement, 2019 (118)

IV, intravenous; NHS, National Health Service

B.3.5.1.4 Investigational treatments

In the base-case analysis, drug acquisition and administration costs are applied in each model cycle to the proportion of patients who remain on treatment determined using the TTD survival extrapolations aligned with Section B.3.3.5. The total costs are distributed equally in each model cycle over the selected treatment duration to account for discounting.

Pre-progression costs

For the pre-progression costs, this is calculated using the planned dose per 21-day cycle with the relative dose intensity informed by the HER2CLIMB trial (Table 28). The mean doses of capecitabine and trastuzumab were calculated using a mean BSA of (1.80 m^2) and mean body weight (69.5 kg) from the HER2CLIMB trial. Dose adjustments were made in the HER2CLIMB trial with the proportion of planned doses received to reflect the real cost of treatment. The treatment costs include the tucatinib PAS price, as well as an assumption of a [redacted]% discount to the list price for biosimilar trastuzumab, as utilised in TA509 (53). The relative dose intensity of the comparators was informed by dose reductions utilised in clinical trials. The dose intensity for eribulin was 83% in the Yuan et al. (2019) study (56). The relative dose intensity of vinorelbine was 66% in Yuan et al. (2019) (56), while capecitabine used relative dose intensity of 78.8% was based on the NALA trial from the Saura et al. (2020) (119) study.

Table 28: Pre-progression treatment costs

Treatment Regimen	Pack price/ BNF [redacted]	Planned dose per 21-day cycle (mg)	Relative dose intensity	Drug acquisition cost per patient per 21-day cycle	Source
Tucatinib Combination					
Tucatinib (150 mg x 84 tablets)	[redacted]	12,600	88.5%	[redacted]	Seagen and HER2CLIMB trial (4)
Capecitabine (500 mg x 120 tablets)	£25.02	50,400	[redacted]	[redacted]	HER2CLIMB trial (Seagen 2019) eMIT (8)
Trastuzumab IV per 150mg	[redacted]	556	[redacted]	[redacted]	BNF, Trastuzumab – medicinal forms 2021 (7)[a]

Treatment Regimen	Pack price/ BNF [redacted]	Planned dose per 21-day cycle (mg)	Relative dose intensity	Drug acquisition cost per patient per 21-day cycle	Source
vial (cycle 1)					
Trastuzumab IV per 150 mg vial (cycle 2 +)		417	[redacted]	[redacted]	BNF, Trastuzumab – medicinal forms 2021 (7)[b]
Comparator					
Eribulin	£361.00	6	83%	£1,716.06	Yuan et al., 2019 (119) and BNF, 2021 (117)
Vinorelbine	£157.69	135	66%	£28.10	Yuan et al., 2019 (119) and eMIT, 2021(8)
Capecitabine	£25.02	63,000	78.8%	£20.70	Von Minckwitz et al., 2009. (65) Assumed relative dose intensity, Saura et al., 2020 (119) and eMIT, 2021 (8)

BNF, British National Formulary; eMIT, drugs and pharmaceutical electronic market information tool; IV, intravenous
a Assumed all patients received intended dose in first cycle.
b Assumed all trastuzumab relative dose intensity equals capecitabine.

Post-progression costs

Costs associated with post-progression anticancer treatments were included in the model for patients who enter the progressed health state. In **Error! Reference source not found.**, the cost per 21-day cycle estimated using the drug acquisition costs from the BNF (2021) (7) and eMIT (2021) (8) as summarised in Table 25 and Table 26. The dose and treatment duration for each drug were taken from HER2CLIMB trial for tucatinib (15), the NALA trial, which compared neratinib + capecitabine with lapatinib + capecitabine (119), PHEREXA, which compared trastuzumab + capecitabine with pertuzumab + trastuzumab + capecitabine (120) and the EMILIA trial for trastuzumab emtansine (121).

Table 29: Post-progression costs list price

Treatment	List price per 21-day cycle[a]	Treatment duration (months)	Source
Trastuzumab IV, 150 mg vial[b]	£101.93	[redacted]	BNF (2021) (7) and HER2CLIMB trial (4)
Lapatinib, 250 mg, pack 84 tablets	£1,206.45	[redacted]	BNF (2021) (122) and Saura et al. (2019) (119)
Neratinib, 40 mg, pack 180 tablets	£3,150.00	[redacted]	BNF (2021) (123) and Saura et al. (2019) (119)
Pertuzumab, 420 mg/14 ml vial	£2,395.00	[redacted]	BNF (2021) (124) and Urruticoechea

			et al. 2017 (120)
T-DM1, 100 mg vial	£4,105.81	[redacted]	BNF (2021) (125) and Verma et al., 2012

[a] Administration cost per cycle is not captured in the total drug cost per patient.
[b] Cost per cycle price for trastuzumab may be subject to an agreed discount.

The post-progression treatments and the percentages of patients receiving them were obtained from the HER2CLIMB trial (4). As no data could be identified for eribulin, vinorelbine, capecitabine; a weighted average of the values for both treatment arms in the HER2CLIMB trial was assumed as summarised in **Error! Not a valid bookmark self-reference.**Table 37: . There is no standard of care for this line of therapy and UK clinical experts advised that there is a heterogenous use of treatments in clinical practice (16).

Table 30: Proportion of patients receiving post-progression costs anticancer treatments

Drug	Tucatinib Combination	External Comparators (Eribulin, vinorelbine, capecitabine)
Trastuzumab	[redacted]	[redacted]
Pertuzumab	[redacted]	[redacted]
T-DM1	[redacted]	[redacted]
Lapatinib	[redacted]	[redacted]
Neratinib	[redacted]	[redacted]

T-DM1, trastuzumab emtansine

The model includes the cost of the supportive antidiarrheal medication loperamide, taken from the BNF (126). The dosage of loperamide is 6 mg per day, which results in a cost of £0.09 per patient per day. This cost is applied for a mean treatment duration of [redacted] days for patients receiving tucatinib + trastuzumab + capecitabine and [redacted] days for patients receiving trastuzumab + capecitabine, as calculated from HER2CLIMB (4). The calculation is based on the proportion of patients who received antidiarrheal medication in each treatment arm of the trial. As no data were identified for the duration of supportive antidiarrheal medication for eribulin, vinorelbine and capecitabine, the dosage of loperamide and mean treatment duration was assumed equal to trastuzumab + capecitabine (4).

B.3.5.2 Health state costs

Resource use assumptions for progression-free and progressed disease and dead are summarised in Table 31. The progression-free and progressed disease health states were based on NICE TA458 as this was the most recent and relevant HER+ MBC NICE TA (52). The cost inputs were sourced using NHS reference costs (118) and PSSRU costs (104) and aggregated for the progression-free and progressed health state. For the dead health state, a one-time end-of-life care cost of £12,540 was applied, based on the NICE TA458 and inflated to the current cost-year.

Table 31: Health state costs

Cost item	Frequency per month	Unit cost	Cost per patient per month	Reference
Progression-free health state				
Specialist nurse	1	£68.98	£68.98	NICE (TA458) (52) and NHS improvement (118)
Community nurse	2	£39.68	£79.36	NICE (TA458) (52) and PSSRU (2020) (104)
GP	1	£39.23	£39.23	NICE (TA458) (52) and PSSRU (2020) (104)
Total			187.57	Calculated
Progressed health state				
Specialist nurse	1	£68.98	£68.98	NICE (TA458) (52) and NHS improvement (118)
Community nurse	2	£39.68	£79.36	NICE (TA458) (52) and PSSRU (2020) (104)
GP	1	£39.23	£39.23	NICE (TA458) (52) and PSSRU (2020) (104)
Total			£187.57	Calculated
Dead health state			£12,540	NICE (TA458) (52) and PSSRU (2020) (104)

GP, general practitioner; NICE, National Institute for Health and Care Excellence; PSSRU, Personal social services research unit

B.3.5.3 Adverse reaction unit costs and resource use

Costs associated with Grade 3 and 4 TEAEs that occurred in ≥2% of patients in HER2CLIMB were incorporated in the economic analysis. The unit costs for the management of these events were identified from previous NICE technology appraisals and updated to current cost-year using NHS reference costs (118).

Adverse event costs for each treatment arm were calculated as the sum product of each AE and the proportion of AEs observed in the trial. This calculated an average cost per patient are summarised in Table 32.

Table 32: Adverse reaction costs used in the economic model

Adverse reaction	Cost per event	References	Reference in submission
Hand-foot syndrome	£1,614.00	NHS Improvement (118) and TA423 (47)	Section B.3.4.4 (page 105)
Diarrhoea	£432.62	NHS Improvement (118) TA496 (127)	Section B.3.4.4 (page 105)
Alanine aminotransferase increased	£499.01	NHS Improvement (118) and TA621 (128)	Section B.3.4.4 (page 105)
Fatigue	£475.29	NHS Improvement (118) and TA496 (127)	Section B.3.4.4 (page 105)
Aspartate aminotransferase increased	£499.01	NHS Improvement (118) and TA621 (128)	Section B.3.4.4 (page 105)
Anaemia	£475.29	NHS Improvement (118) and TA423 (47)	Section B.3.4.4 (page 105)
Nausea	£579.31	NHS Improvement (118) and TA496 (127)	Section B.3.4.4 (page 105)
Neutropenia	£194.00	NHS Improvement (118) and TA579 (111)	Section B.3.4.4 (page 105)
Vomiting	£579.31	NHS Improvement (118) and TA496 (127)	Section B.3.4.4 (page 105)
Hypokalaemia	£475.29	NHS Improvement (118) and TA496	Section B.3.4.4 (page 105)
Mucosal inflammation	£432.62	NHS Improvement (118)	Section B.3.4.4 (page 105)
Thrombocytopenia	£3,091.92	NHS Improvement (118)	Section B.3.4.4 (page 105)
Stomatitis	£443.09	NHS Improvement (118) and TA579 (111)	Section B.3.4.4 (page 105)

NHS, National Health Service

B.3.5.4 Miscellaneous unit costs and resource use

No miscellaneous unit costs and resource use was used in the economic analysis.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 B.3.6.1 Summary of base-case analysis inputs

The base-case analysis inputs assumed in the model are summarised below in Table 33:

Table 33: Base-case assumptions included in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Analysis settings			
Time horizon	20 years	Fixed	Section B.3.3.1Table 18
Discount rate: costs	3.5%	Fixed	Section B.3.3.1
Discount rate: outcomes	3.5%	Fixed	Section B.3.3.1Table 19
Patient characteristics			
Mean starting age	54 years	SE = 0.44 (normal)	Section B.2.3.3
Mean BSA	1.8 m^2	SE = 0.18 (normal)	Section B.2.3.3
Mean body weight	69.5 kg	SE = 6.95 (normal)	Section B.2.3.3
NMA model (indirect comparisons)			
PFS NMA model	Hazard ratio fixed effects	Multivariate normal	Section B.3.3.4
OS NMA model	Hazard ratio fixed effects	Multivariate normal	Section B.3.3.4
Treatment duration: investigational treatments			
Tucatinib combination	TTD: Flexible Weibull (2 knots)	Multivariate normal	Section B.3.3.5
External comparators	TTD	Multivariate normal	Section B.3.3.5
Treatment duration: post-progression treatments			
Trastuzumab	[redacted] months	SE = 0.31 (normal)	Section B.3.5.1.4
Pertuzumab	[redacted] months	SE = 1.03 (normal)	Section B.3.5.1.4
T-DM1	[redacted] months	SE = 0.96 (normal)	Section B.3.5.1.4
Lapatinib	[redacted] months	SE = 0.44 (normal)	Section B.3.5.1.4
Neratinib	[redacted] months	SE = 0.57 (normal)	Section B.3.5.1.4
Anti-diarrhoeal medication (loperamide)			
Tucatinib combination	[redacted] days	SE = 2.16 (normal)	Section B.3.5.1.4
Trastuzumab + capecitabine	[redacted] days	SE = 0.58 (normal)	Section B.3.5.1.4
Lapatinib + capecitabine	[redacted] days	SE = 2.16 (normal)	Section B.3.5.1.4
Neratinib + capecitabine	[redacted] days	SE = 4.57 (normal)	Section B.3.5.1.4
Pertuzumab + trastuzumab +	[redacted] days	SE = 2.16 (normal)	Section B.3.5.1.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
capecitabine			
T-DM1	[redacted] days	SE = 0.58 (normal)	Section B.3.5.1.4
Capecitabine	[redacted] days	SE = 0.58 (normal)	Section B.3.5.1.4
Relative dose intensity: tucatinib combination			
Tucatinib	88.5%	SE = 0.01 (Beta)	Section B.3.5.1.4
Capecitabine	[redacted]	SE = 0.01 (Beta)	Section B.3.5.1.4
Trastuzumab (cycle 1)	[redacted]	Fixed	Section B.3.5.1.4
Trastuzumab (cycle 2+)	[redacted]	SE = 0.01 (Beta)	Section B.3.5.1.4
Adverse events incidence: tucatinib combination			
Hand-foot syndrome	13.1%	α = 53, β = 351 (beta)	Section B.3.4.4
Diarrhoea	12.9%	α = 52, β = 352 (beta)	Section B.3.4.4
Alanine aminotransferase increased	5.4%	α = 22, β = 382 (beta)	Section B.3.4.4
Fatigue	4.7%	α = 19, β = 385 (beta)	Section B.3.4.4
Aspartate aminotransferase increased	4.5%	α = 18, β = 386 (beta)	Section B.3.4.4
Anaemia	3.7%	α = 15, β = 389 (beta)	Section B.3.4.4
Nausea	3.7%	α = 15, β = 389 (beta)	Section B.3.4.4
Neutropenia	0.0%	α = 0, β = 404 (beta)	Section B.3.4.4
Vomiting	3.0%	α = 12, β = 392 (beta)	Section B.3.4.4
Hypokalaemia	0.0%	α = 0, β = 404 (beta)	Section B.3.4.4
Mucosal inflammation	0.0%	α = 0, β = 404 (beta)	Section B.3.4.4
Stomatitis	2.5%	α = 10, β = 394 (beta)	Section B.3.4.4
Adverse events incidence: trastuzumab + capecitabine			
Hand-foot syndrome	9.1%	α = 18, β = 179 (beta)	Section B.3.4.4
Diarrhoea	8.6%	α = 17, β = 180 (beta)	Section B.3.4.4
Alanine aminotransferase increased	0.0%	α = 0, β = 197 (beta)	Section B.3.4.4
Fatigue	4.1%	α = 8, β = 189	Section B.3.4.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
		(beta)	
Aspartate aminotransferase increased	0.0%	α = 0, β = 197 (beta)	Section B.3.4.4
Anaemia	2.5%	α = 5, β = 192 (beta)	Section B.3.4.4
Nausea	3.0%	α = 6, β = 191 (beta)	Section B.3.4.4
Neutropenia	0.0%	α = 0, β = 197 (beta)	Section B.3.4.4
Vomiting	0.0%	α = 0, β = 197 (beta)	Section B.3.4.4
Hypokalaemia	0.0%	α = 0, β = 197 (beta)	Section B.3.4.4
Mucosal inflammation	0.0%	α = 0, β = 197 (beta)	Section B.3.4.4
Stomatitis	0.0%	α = 0, β = 197 (beta)	Section B.3.4.4
Health-state utilities: treatment-specific (tucatinib combination) EQ-5D-3L			
Progression-free, cycle 1-2	0.748	α = 16.9, β = 3.6 (beta)	Section B.3.4.6.2
Progression-free, cycle 3-4	0.763	α = 15.7, β = 3.1 (beta)	Section B.3.4.6.2
Progression-free, cycle 5-6	0.792	α = 13.2, β = 2.2 (beta)	Section B.3.4.6.2
Progression-free, cycle 7+	0.807	α = 11.9, β = 1.8 (beta)	Section B.3.4.6.2
Progressed	0.653	α = 25.5, β = 9.0 (beta)	Section B.3.4.6.2
Dead	0.000	Fixed	Section B.3.4.6.2
Health-state utilities: treatment-specific (eribulin)			
Progression-free, cycle 1-2	0.783	α = 20.92, β = 5.80 (beta)	Section B.3.4.6.2
Progression-free, cycle 3-4	0.783	α = 20.92, β = 5.80 (beta)	Section B.3.4.6.2
Progression-free, cycle 5-6	0.783	α = 20.92, β = 5.80 (beta)	Section B.3.4.6.2
Progression-free, cycle 7+	0.783	α = 20.92, β = 5.80 (beta)	Section B.3.4.6.2
Progressed	0.622	α = 37.18, β = 22.59(beta)	Section B.3.4.6.2
Dead	0.000	Fixed	Section B.3.4.6.2
Adverse-event utility decrements			
Hand-foot syndrome	0.100	α = 89, β = 810 (beta)	Section B.3.4.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Diarrhoea	0.088	α = 90.2, β = 945.16 (beta)	Section B.3.4.4
Alanine aminotransferase increase	0.088	α = 90.2, β = 945.16 (beta)	Section B.3.4.4
Fatigue	0.099	α = 89.1, β = 820 (beta)	Section B.3.4.4
Aspartate aminotransferase increase	0.099	α = 89.1, β = 820 (beta)	Section B.3.4.4
Anaemia	0.120	α = 87, β = 645.33 (beta)	Section B.3.4.4
Nausea	0.088	α = 90.2, β = 945.16 (beta)	Section B.3.4.4
Neutropenia	0.066	α = 92.4, β = 1,321.8 (beta)	Section B.3.4.4
Vomiting	0.088	α = 91.1, β = 944.2 (beta)	Section B.3.4.4
Hypokalaemia	0.099	α = 90.0, β = 819.8 (beta)	Section B.3.4.4
Mucosal inflammation	0.088	α = 91.1, β = 944.2 (beta)	Section B.3.4.4
Thrombocytopenia	0.066	α = 93.3, β = 1,320.8 (beta)	Section B.3.4.4
Stomatitis	0.132	α = 86.7, β = 570.58 (beta)	Section B.3.4.4
Health-state costs per month			
Progression-free	£187.58	SD = 1.88 (gamma)	Section B.3.5.2
Progressed	£187.58	SD = 1.88 (gamma)	Section B.3.5.2
Dead	£12,540	SD = 125.40 (gamma)	Section B.3.5.2
Adverse-event unit costs			
Hand-foot syndrome	£1,614	SD = 161.4 (gamma)	Section B.3.5.3
Diarrhoea	£432.62	SD = 43.26(gamma)	Section B.3.5.3
Alanine aminotransferase increased	£499.01	SD = 49.90 (gamma)	Section B.3.5.3
Fatigue	£475.29	SD = 47.52 (gamma)	Section B.3.5.3
Aspartate	£499.01	SD =	Section B.3.5.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
aminotransferase increased		49.90 (gamma)	
Anaemia	£475.29	SD = 47.52 (gamma)	Section B.3.5.3
Nausea	£579.31	SD = 57.93 (gamma)	Section B.3.5.3
Neutropenia	£194	SD = 47.52 (gamma)	Section B.3.5.3
Vomiting	£579.31	SD = 57.93 (gamma)	Section B.3.5.3
Hypokalaemia	£475.29	SD = 47.52 (gamma)	Section B.3.5.3
Mucosal inflammation	£432.62	SD = 43.26 (gamma)	Section B.3.5.3
Thrombocytopenia	£3,091.92	SD = 309.19 (gamma)	Section B.3.5.3
Stomatitis	£443.09	SD = 44.31 (gamma)	Section B.3.5.3
Drug costs			
Tucatinib (150 mg x 84)	[redacted]	Fixed	Section B.3.5.1.1
Capecitabine (500 mg x 120)	£25.02	Fixed	Section B.3.5.1.1
Trastuzumab (150 mg)	£366.65	Fixed	Section B.3.5.1.1
Eribulin	£361.00	Fixed	Section B.3.5.1.2
Vinorelbine	£157.69	Fixed	Section B.3.5.1.2
Capecitabine	£25.02	Fixed	Section B.3.5.1.2
Post-progression treatment: following tucatinib combination			
Trastuzumab	[redacted]	α = 141, β = 151 (beta)	Section B.3.5.1.4
Lapatinib	[redacted]	α = 37, β = 255 (beta)	Section B.3.5.1.4
Neratinib	[redacted]	α = 11, β = 281 (beta)	Section B.3.5.1.4
Pertuzumab	[redacted]	α = 11, β = 281 (beta)	Section B.3.5.1.4
T-DM1	[redacted]	α = 5, β = 287 (beta)	Section B.3.5.1.4
Post-progression treatment: following external comparators			
Trastuzumab	[redacted]	α = 238, β = 229 (beta)	Section B.3.5.1.4
Lapatinib	[redacted]	α = 69, β = 398 (beta)	Section B.3.5.1.4
Neratinib	[redacted]	α = 22, β = 445 (beta)	Section B.3.5.1.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Pertuzumab	[redacted]	α = 21, β = 446 (beta)	Section B.3.5.1.4
T-DM1	[redacted]	α = 10, β = 457 (beta)	Section B.3.5.1.4
Drug administration costs			
Tucatinib	£195.44 (one-off)	Fixed	Section B.3.5.1.3
Capecitabine	£195.44 (one-off)	Fixed	Section B.3.5.1.3
Trastuzumab	£241.06	Fixed	Section B.3.5.1.3
Vinorelbine	£241.06	Fixed	Section B.3.5.1.3
Capecitabine	£195.44	Fixed	Section B.3.5.1.3

BSA, body surface area; EQ-5D-3L, EuroQoL 5 Dimensions 3-Levels; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; SD, standard deviation; SE, standard error; T-DM1, trastuzumab emtansine; TTD, time-to-treatment discontinuation.

B.3.6.2 Assumptions

Table 34: Base-case assumptions included in the economic model including justifications

Parameter	Assumption/Limitation	Comment
Pre-progression treatment duration	The proportion of patients remaining on treatment over time for external comparator treatments was estimated using the exponential function.	TTD data were not available for external comparators. TTD was estimated for external comparators using the exponential function. The methodology used available treatment duration data for the external comparators. TTD is prevented from crossing PFS in the model to avoid implausible estimates.
Post-progression treatment duration	The duration of post-progression treatments was taken from key clinical trials for those treatments.	No treatment duration data specifically for post-progression treatments were available from the HER2CLIMB trial or identified in the literature. Data taken from the key trials for the included treatments may overestimate the treatment duration because patients who progress may experience worse outcomes.
Post-progression treatments	For external comparators, it was assumed that the proportion of patients receiving different post-progression treatments is equal to the overall population in the	No data reporting the proportion of patients who receive different treatments following progression after receiving external comparators was identified. The proportions taken from the

Parameter	Assumption/Limitation	Comment
	HER2CLIMB trial.	HER2CLIMB trial for the overall population may not accurately reflect treatment pathways. However, there is no standard of care and heterogenous use of treatments in this setting; the HER2CLIMB data were considered the best available.
Supportive therapy treatment duration	Assumptions were made about the duration of supportive loperamide for external comparators.	No data were identified for external comparators. The duration for patients receiving capecitabine monotherapy, eribulin, or vinorelbine was assumed to be equal for that of trastuzumab + capecitabine.
NMA model	The HR fixed effects NMA model is used in the base-case for indirect treatment comparisons.	There were some signs of non-proportionality in the evidence network, suggesting that the proportional hazards assumption may not hold. The proportional hazards assumption is not an issue for fractional polynomial NMA models, which are included in the cost-effectiveness model.
Health-state utility weights	Treatment-specific utility values are used for indirect comparisons with eribulin, capecitabine and vinorelbine.	EQ-5D data were captured in the HER2CLIMB trial for trastuzumab. Treatment-specific health-state utility weights were identified from the eribulin TA423 appraisal. No treatment-specific estimates were identified for vinorelbine; these were assumed to be the same as capecitabine monotherapy as both are monotherapy treatments most frequently used in combination with trastuzumab.
Utility decrements	Utility decrements were sourced from published literature.	Disutilities for AEs were not directly reported in the HER2CLIMB trial. However, the impact of AEs should be captured by the treatment-specific health-state utility weights.
Health-state costs	It is assumed that the costs for patients in the progression-free and progressed health states are the same.	Direct health care costs associated with each model health state were based on resource utilisation estimates and costs from TA458 (52).
Adverse events	It is assumed that all AE costs and utility decrements are applied as a one-off cost in the first cycle of the model.	Data reporting the timing of adverse events were not available in the HER2CLIMB trial. The majority of treatment-related AEs

Parameter	Assumption/Limitation	Comment
		are expected to occur within the first year of treatment; applying AE costs and utility decrements in the first model cycle is expected to have little impact on the results (e.g., due to discounting in subsequent model years).

B.3.7 Base-case results

In the model base-case, model results are presented in Table 35. Using a 20-year time horizon, the incremental total life-years gained (LYG) with the tucatinib combination versus eribulin was [redacted] years. When the PAS price is used in the model the incremental costs of [redacted] resulted in an ICER of £46,756 versus eribulin.

Table 35: Base-case results: tucatinib combination versus eribulin – PAS price

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LY)	ICER (£/QALY)
Tucatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,756

ICER, incremental cost-effectiveness ratio; LY, life-year; PAS, Patient Access Scheme; QALY, quality-adjusted life-year

The list price results are summarised in Table 36. The incremental costs of [redacted] and incremental QALYs of [redacted] resulted in an ICER of [redacted] versus eribulin.

Table 36: Base case results: tucatinib combination versus eribulin – List price

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LY)	ICER (£/QALY)
Tucatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year

B.3.8 Sensitivity analysis

B.3.9 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was undertaken to explore the uncertainty of all model parameters and their associated impact on cost-effectiveness results. One thousand iterations were used to ensure convergence. Total costs, LYs and QALYs were recorded for each iteration and averaged.

The PSA results for the comparison of the tucatinib combination to eribulin using the PAS price are presented in Table 37 and show the PSA results are in line with the deterministic results. The PSA cost per LYG was [redacted] compared to the deterministic result of [redacted]. Similarly, the cost per QALY gained was [redacted] compared to the base-case deterministic result of £46,756.

Table 37: Probabilistic sensitivity analysis results: tucatinib combination versus eribulin – PAS price

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LY)	ICER (£/QALY)
Tucatinib Combination	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LY, life-year; PAS, Patient Access Scheme; QALY, quality-adjusted life-year

The PSA results for the comparison of the tucatinib combination to eribulin using the list price are presented in Table 38 and show that the PSA results are in line with the deterministic results. The PSA cost per LYG was [redacted] compared to the deterministic result of [redacted] Similarly, the cost per QALY gained was [redacted] compared to the base-case deterministic result of [redacted]

Table 38: Probabilistic sensitivity analysis results: tucatinib combination versus eribulin – list price

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LY)	ICER (£/QALY)
Tucatinib Combination	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year

Figure 23**Error! Reference source not found.** and **Error! Reference source not found.** represent the scatter plots of the incremental costs and QALYs from the PSA results of the tucatinib combination versus eribulin, based on 1,000 iterations for the PAS price and list price, respectively. The tucatinib combination is associated with a clear clinical benefit over eribulin with only 5 simulations showing a clinical benefit for eribulin. Figure 26 and Figure 25 show the cost-effectiveness acceptability curve for the tucatinib combination versus eribulin for the PAS price and list price, respectively. At a willingness to pay threshold of £50,000, the probability of cost-effectiveness for the tucatinib combination is [redacted]% for the PAS price and [redacted]% at list price.

Figure 23: Cost-effectiveness plane – tucatinib combination versus eribulin – PAS price

QALY, quality-adjusted life-year; PAS, Patient Access Scheme; PSA, probability sensitivity analysis

Figure 24: Cost-effectiveness plane – tucatinib combination versus eribulin – list price

QALY, quality-adjusted life-year; PSA, probability sensitivity analysis

Figure 25: Cost-effectiveness acceptability curve – tucatinib combination versus eribulin – PAS price

QALY, quality-adjusted life-year; PAS, Patient Access Scheme

Figure 26: Cost-effectiveness acceptability curve – tucatinib combination versus eribulin – list price

QALY, quality-adjusted life-year

B.3.9.1 Deterministic sensitivity analysis

A one-way sensitivity analysis (OWSA) was performed to investigate key drivers of the cost-effectiveness model. Each input parameter was set to its respective upper or lower bound and the deterministic results for the model recorded. The upper and lower bounds around the mean value for each input parameter were varied by ±10%.

Tornado diagrams for the tucatinib combination versus eribulin are presented in Figure 27 and

Figure 28. The OWSA highlighted that the relative dose intensity for the tucatinib combination, and the progressed utility for both the tucatinib combination and eribulin had the greatest impact on the cost-effectiveness results

Figure 27: Tornado diagram – tucatinib combination versus eribulin - PAS price

BSA, body surface area; Cap, capecitabine; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; Tras, trastuzumab; Tuc, tucatinib

Figure 28: Tornado diagram – tucatinib combination versus eribulin – list price

BSA, body surface area; Cap, capecitabine; ICER, incremental cost-effectiveness ratio; Tras, trastuzumab; Tuc, tucatinib

B.3.9.2 Scenario analysis

The list of scenarios explored in the model are provided in Table 39 and results are shown in Table 40 (PAS price) and Table 41 (list price). For the PAS price, scenarios presented where eribulin was the comparator (scenarios 1-6) [redacted], the choice of survival curve extrapolation from the advisory board, (the stratified generalised gamma for PFS and OS for stratified Weibull) and inputs related to the NMA [redacted] Comparisons to vinorelbine and capecitabine resulted in [redacted]. A blended ICER was estimated with [redacted]% of patients treated with capecitabine monotherapy, [redacted]% with vinorelbine and the remaining [redacted]% with eribulin. In this scenario the ICER was [redacted].

Table 39: Scenario analyses explored in the model

No	Parameter	Scenario	Base case
1	PFS curve OS curve	[redacted]	PFS - Flexible Weibull (2 knots) OS - Weibull
2	Tucatinib combination utilities	EQ-5D-5L	EQ-5D-3L
3	NMA random effects	PFS - HR random effects OS - HR random effects	PFS - HR fixed effects OS - HR fixed effects
4	NMA random effects	PFS - Fractional polynomial random effects OS - Fractional polynomial random effects	PFS - HR fixed effects OS - HR fixed effects
5	NMA random effects	PFS - Fractional polynomial fixed effects OS - Fractional polynomial fixed effects	PFS - HR fixed effects OS - HR fixed effects
6	Treatment duration	Restricted mean treatment exposure	TTD survival analysis
7	Comparator	Vinorelbine	Eribulin
8	Comparator	Capecitabine	Eribulin
9	Blended ICER	Capecitabine – [redacted]% Eribulin – [redacted]% Vinorelbine – [redacted]%	Eribulin

EQ-5D-3L, EuroQoL 5 Dimensions 3-Levels; EQ-5D-5L, EuroQoL 5 Dimensions 5-Levels; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; No, number; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation

Table 40: Scenario analyses results – PAS price

No	Scenario	ICER
Base case		£46,756
1	Survival curves: PFS [redacted] OS [redacted]	[redacted]
2	Tucatinib combination utilities: EQ-5D-5L	[redacted]
3	NMA random effects: PFS - HR random effects OS - HR random effects	[redacted]
4	NMA random effects: PFS - Fractional polynomial random effects OS - Fractional polynomial random effects	[redacted]
5	NMA random effects: PFS - Fractional polynomial fixed effects OS - Fractional polynomial fixed effects	[redacted]
6	Treatment duration:	[redacted]

No	Scenario	ICER
	Restricted mean treatment exposure	
7	Comparator: Vinorelbine	[redacted]
8	Comparator: Capecitabine	[redacted]
9	Blended ICER: Capecitabine – [redacted]% Eribulin – [redacted]% Vinorelbine – [redacted]%	[redacted]

EQ-5D-5L, EuroQoL 5 Dimensions 5-Levels; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; No, number; OS, overall survival; PAS, Patient Access Scheme; PFS, progression-free survival

Table 41: Scenario analyses results – list price

No	Scenario	ICER
Base case		[redacted]
1	Survival curves: PFS [redacted] OS [redacted]	[redacted]
2	Tucatinib combination utilities: EQ-5D-5L	[redacted]
3	NMA random effects: PFS - HR random effects OS HR random effects	[redacted]
4	NMA random effects: PFS - Fractional polynomial random effects OS - Fractional polynomial random effects	[redacted]
5	NMA random effects: PFS - Fractional polynomial fixed effects OS - Fractional polynomial fixed effects	[redacted]
6	Treatment duration: Restricted mean treatment exposure	[redacted]
7	Comparator: Vinorelbine	[redacted]
8	Comparator: Capecitabine	[redacted]
9	Blended ICER: Capecitabine – [redacted]% Eribulin – [redacted]% Vinorelbine – [redacted]%	[redacted]

EQ-5D-5L, EuroQoL 5 Dimensions 5-Levels; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; No, number; OS, overall survival; PFS, progression-free survival

B.3.10 Subgroup analysis

The brain metastases subgroup could not be explored in the cost-effectiveness analysis. As stated in Section B.1-Table 1, the brain metastases subgroup was not available for eribulin, vinorelbine or capecitabine, as this population was excluded from their trials. Due to the absence of data on the brain metastases subgroup for

eribulin, vinorelbine and capecitabine, an objective and evidence-based comparison cannot be conducted by way of an NMA and economic evaluation.

B.3.11 Validation

The inputs contributing to the cost-effectiveness, namely the survival curves for PFS and OS, were validated by an advisory board as described in Section B.3.3.8.

B.3.12 Interpretation and conclusions of economic evidence

HER2+ status is associated with an increased risk of brain metastases over the course of the disease compared with HER2-negative breast cancer (71). However, until now, most systemic therapies have limited ability to penetrate the blood-brain barrier and therefore, have variable levels of activity in the brain. The design of HER2CLIMB is also unprecedented compared with trials of other treatments for HER2+ MBC. HER2CLIMB is the first randomised, double-blind trial to enrol a large (48%) proportion of patients with brain metastases at baseline, with approximately 60% of these patients having active or progressing brain metastases (24). Despite brain metastases being a common clinical problem in HER2+ MBC, patients with active brain metastases are typically excluded from clinical trials of other systemic treatments, due to their historically poor prognosis. This is also true for the eribulin, vinorelbine and capecitabine clinical trials. The tucatinib combination is the first regimen to offer clinically meaningful efficacy both systemically and in the brain, which is particularly important for patients with HER2+ MBC who are at risk to develop brain metastases over the course of the disease.

However, the benefit of the tucatinib combination in the subgroup of patients with brain metastases was not able to be included in cost-effectiveness analyses because the available evidence does not allow an indirect comparison with other treatments. Indirect comparisons with other agents are not possible because prior clinical trials excluded patients with brain metastases, particularly those with active lesions.

The value of the tucatinib combination is driven by the clinically meaningful and statistically significant improvements in PFS and OS among HER2+ MBC patients

with high unmet need, including patients with brain metastases. This increase in survival is achieved while maintaining HRQoL.

The base-case deterministic analysis in the UK showed adding tucatinib to trastuzumab and capecitabine is cost-effective compared with trastuzumab plus capecitabine alone. Over a 20-year time horizon, patients receiving the tucatinib combination accrued an incremental increase of [redacted] QALYs and [redacted] LYG compared to eribulin with a resulting ICER of [redacted] per QALY and [redacted] per LYG at the list price for Tucatinib. The analysis with the PAS price reduced the cost per QALY to £46,756, at a willingness to pay threshold of £50,000 the probability of being cost-effective at the PAS price was [redacted]%.

Scenario analyses show that with the PAS price, the tucatinib combination versus the single-agent chemotherapies of capecitabine and vinorelbine were above the £50,000 willingness to pay threshold with an ICER of [redacted] and [redacted]. The blended ICER scenario for likely utilisation of the three comparators resulted in an ICER of [redacted]. The model was sensitive to the relative dose intensity of tucatinib and progressed utility values for both treatment and comparators.

The tucatinib combination is a cost-effective treatment option for patients with HER2+ MBC who have already received two anti-HER2 regimens; however, its value is beyond these types of value measurements as further treatment options are limited and their prognosis is very poor. A cost-effectiveness model alone does not capture all of the elements that establish value beyond LYs and QALYs gained, such as disease burden, unmet need, and the value of hope to patients with HER2+ MBC. Improving OS, including in patients with brain metastases, while maintaining HRQoL clearly demonstrates the value of the tucatinib combination for HER2+ MBC patients. Giving eligible patients access to the tucatinib combination represents a step-change in the management of HER2+ MBC in the third-line setting in England.

B.4 References

1. Segovia-Mendoza M, Gonzalez-Gonzalez ME, Barrera D, Diaz L, Garcia-Becerra R. Efficacy and mechanism of action of the tyrosine kinase inhibitors gefitinib, lapatinib and neratinib in the treatment of HER2-positive breast cancer: preclinical and clinical evidence. Am J Cancer Res. 2015;5(9):2531-61.
2. Moulder S, Baetz T, Borges V. ARRY-380, a selective HER2 inhibitor: From drug design to clinical evaluation. Molecular Cancer Therapeutics. 2011;10:Abstract A143.
3. Moulder SL, Borges VF, Baetz T, McSpadden T, Fernetich G, Murthy RK, et al. Phase I Study of ONT-380, a HER2 Inhibitor, in Patients with HER2(+)-Advanced Solid Tumors, with an Expansion Cohort in HER2(+) Metastatic Breast Cancer (MBC). Clin Cancer Res. 2017;23(14):3529-36.
4. Seagen Inc. HER2CLIMB Clinical Study Report. 2019.
5. Herceptin® (trastuzumab). Summary of Product Characteristics – Herceptin 150mg Powder for concentrate for solution for infusion 2020 [updated 20 August. Available from: www.medicines.org.uk/emc/product/3856/smpc/print.
6. Capecitabine. Summary of Product Characteristics – capecitabine 500 mg film-coated tablets 2021 [updated 08 March 2021. Available from: www.medicines.org.uk/emc/product/11498/smpc.
7. BNF. Trastuzumab – medicinal forms 2021 [Available from: https://bnf.nice.org.uk/medicinal-forms/trastuzumab.html.
8. eMIT. Drugs and pharmaceutical electronic market information tool (eMIT) – DHA225 2021 [updated 11 March. Available from: www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.
9. NCI. Cancer Stat Facts: Female Breast Cancer Subtypes (SEER 2010–2016) 2020 [Available from: https://seer.cancer.gov/statfacts/html/breast-subtypes.html.
10. pCODR. pan-Canadian Oncology Drug Review – Lapatinib (Tykerb) with letrozole for Metastatic Breast Cancer – Final Clinical Guidance Report pERC Meeting: April 18, 2013; Reconsideration Meeting: June 20, 2013. 2013:1-60.
11. Cacho-Diaz B, Spinola-Marono H, Arrieta VA, Granados-Garcia M, Wegman-Ostrosky T, Mendoza-Olivas LG, et al. Diagnosis of brain metastases in breast cancer patients resulting from neurological symptoms. Clin Neurol Neurosurg. 2018;173:61-4.
12. Muller V, Nabieva N, Haberle L, Taran FA, Hartkopf AD, Volz B, et al. Impact of disease progression on health-related quality of life in patients with metastatic breast cancer in the PRAEGNANT breast cancer registry. Breast. 2018;37:154-60.
13. Walker MS, Hasan M, Yim YM, Yu E, Stepanski EJ, Schwartzberg LS. Retrospective study of the effect of disease progression on patient reported outcomes in HER-2 negative metastatic breast cancer patients. Health Qual Life Outcomes. 2011;9:46.

14. Reyes C, Engel-Nitz NM, DaCosta Byfield S, Ravelo A, Ogale S, Bancroft T, et al. Cost of Disease Progression in Patients with Metastatic Breast, Lung, and Colorectal Cancer. Oncologist. 2019;24(9):1209-18.
15. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2020;382(7):597-609.
16. Seagen Inc. Data on file – Tucatinib UK advisory board meeting (virtual meeting, March 2021). 2021.
17. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol. 2004;22(17):3608-17.
18. Witzel I, Laakmann E, Weide R, Neunhoffer T, Park-Simon TJ, Schmidt M, et al. Treatment and outcomes of patients in the Brain Metastases in Breast Cancer Network Registry. Eur J Cancer. 2018;102:1-9.
19. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
20. Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States. Cancer Epidemiol Biomarkers Prev. 2017;26(6):809-15.
21. Malmgren JA, Mayer M, Atwood MK, Kaplan HG. Differential presentation and survival of de novo and recurrent metastatic breast cancer over time: 1990-2010. Breast Cancer Res Treat. 2018;167(2):579-90.
22. Perol D, Robain M, Arveux P, Mathoulin-Pelissier S, Chamorey E, Asselain B, et al. The ongoing French metastatic breast cancer (MBC) cohort: the example-based methodology of the Epidemiological Strategy and Medical Economics (ESME). BMJ Open. 2019;9(2):e023568.
23. Lobbezoo DJ, van Kampen RJ, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ, et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? Br J Cancer. 2015;112(9):1445-51.
24. Ignatov A, Eggemann H, Burger E, Ignatov T. Patterns of breast cancer relapse in accordance to biological subtype. J Cancer Res Clin Oncol. 2018;144(7):1347-55.
25. Gabos Z, Sinha R, Hanson J, Chauhan N, Hugh J, Mackey JR, et al. Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breast cancer. J Clin Oncol. 2006;24(36):5658-63.
26. NCRAS NCRaAS. Stage breakdown by CCG 2016. London: Public Health England 2016 [Available from: www.ncin.org.uk/view?rid=3604.
27. Macmillan Cancer Support. Receptors for HER2 2018 [Available from: www.macmillan.org.uk/cancer-information-and-support/breast-cancer/receptors-for-breast-cancer.

28. Olson EM, Najita JS, Sohl J, Arnaout A, Burstein HJ, Winer EP, et al. Clinical outcomes and treatment practice patterns of patients with HER2-positive metastatic breast cancer in the post-trastuzumab era. Breast. 2013;22(4):525-31.
29. Pestalozzi BC, Holmes E, de Azambuja E, Metzger-Filho O, Hogge L, Scullion M, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). Lancet Oncol. 2013;14(3):P244-8.
30. Jacot W. Poster display session: Breast cancer - early stage, locally advanced & metastatic, CNS tumours, Developmental therapeutics, Genitourinary tumours - prostate & non-prostate, Palliative care, Psycho-oncology, Public health policy, Sarcoma, Supportive care. Annals of Oncology. 2018;29:viii90-viii121.
31. Darlix A, Louvel G, Fraisse J, Jacot W, Brain E, Debled M, et al. Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a large multicentre real-life cohort. Br J Cancer. 2019;121(12):991-1000.
32. Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, et al. Metastatic behavior of breast cancer subtypes. J Clin Oncol. 2010;28(20):3271-7.
33. Leyland-Jones B. Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. J Clin Oncol. 2009;27(31):5278-86.
34. Lin NU, Gaspar LE, Soffietti R. Breast Cancer in the Central Nervous System: Multidisciplinary Considerations and Management. Am Soc Clin Oncol Educ Book. 2017;37:45-56.
35. Extra JM, Antoine EC, Vincent-Salomon A, Delozier T, Kerbrat P, Bethune-Volters A, et al. Efficacy of trastuzumab in routine clinical practice and after progression for metastatic breast cancer patients: the observational Hermine study. Oncologist. 2010;15(8):799-809.
36. Lin NU, Amiri-Kordestani L, Palmieri D, Liewehr DJ, Steeg PS. CNS metastases in breast cancer: old challenge, new frontiers. Clin Cancer Res. 2013;19(23):6404-18.
37. Swain SM, Baselga J, Miles D, Im YH, Quah C, Lee LF, et al. Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA. Ann Oncol. 2014;25(6):1116-21.
38. Tsukada Y, Fouad A, Pickren JW, Lane WW. Central nervous system metastasis from breast carcinoma. Autopsy study. Cancer. 1983;52(12):2349-54.
39. Breast Cancer Now. Facts and statistics 2021 [Available from: https://breastcancernow.org/about-us/media/facts-statistics.

40. Cancer Research UK. Breast cancer incidence (invasive) statistics 2017 [updated 5 March 2020. Available from: www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Zero
41. Cancer Research UK. Breast cancer mortality statistics 2021 [updated 29 January. Available from: www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/mortality#heading-Zero.
42. McClelland SI, Holland KJ, Griggs JJ. Quality of life and metastatic breast cancer: the role of body image, disease site, and time since diagnosis. Qual Life Res. 2015;24(12):2939-43.
43. NICE. NICE Pathways – managing advanced breast cancer 2020 [updated 07 October 2020. Available from: https://pathways.nice.org.uk/pathways/advanced-breast-cancer/managing-advanced-breast-cancer.
44. Enhertu® (trastuzumab deruxtecan). Summary of Product Characteristics – Enhertu 100 mg powder for concentrate for solution for infusion (Daiichi Sankyo UK Limited) 2021 [updated 21 March. Available from: www.medicines.org.uk/emc/product/12135#gref.
45. NICE. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697] – in development [GID-TA10582], expected publication date: 19 May 2021 2021 [
46. NICE. Advanced breast cancer: diagnosis and treatment – clinical guidance [CG81] (last updated 16 August 2017) 2009 [Available from: www.nice.org.uk/guidance/cg81.
47. NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens – technology appraisal guidance [TA423] 2016 [updated 21 December. Available from: www.nice.org.uk/guidance/TA423.
48. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, Andre F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)(dagger). Ann Oncol. 2020.
49. NCCN. Clinical practice guidelines in oncology (NCCN Guidelines®). Breast Cancer. Version 6.2020 2020 [updated September 8. Available from: www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
50. Chacón López-Muñiz JI, de la Cruz Merino L, Gavila Gregori J, Martinez Duenas E, Oliveira M, Segui Palmer MA, et al. SEOM clinical guidelines in advanced and recurrent breast cancer (2018). Clin Transl Oncol. 2019;21(1):31-45.
51. Giordano SH, Temin S, Chandarlapaty S, Crews JR, Esteva FJ, Kirshner JJ, et al. Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018;36(26):2736-40.

52. NICE. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane – technology appraisal guidance [TA458] 2017 [updated 20 November. Available from: www.nice.org.uk/guidance/TA458.
53. NICE. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer – technology appraisal guidance [TA509] 2018 [updated 07 March. Available from: www.nice.org.uk/guidance/ta509.
54. NICE. Guidance on the use of trastuzumab for the treatment of advanced breast cancer – technology appraisal guidance [TA34] 2002 [updated 15 March. Available from: www.nice.org.uk/guidance/TA34.
55. NICE. Tucatinib with trastuzumab and capecitabine for treating HER2-positive unresectable locally advanced or metastatic breast cancer after 2 or more antiHER2 therapies [ID3828] – final scope 2021 [updated 12 February. Available from: www.nice.org.uk/guidance/indevelopment/gid-ta10708.
56. Yuan P, Hu X, Sun T, Li W, Zhang Q, Cui S, et al. Eribulin mesilate versus vinorelbine in women with locally recurrent or metastatic breast cancer: A randomised clinical trial. Eur J Cancer. 2019;112:57-65.
57. Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015;33(6):594-601.
58. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377(9769):914-23.
59. Lin NU, Borges V, Anders C, Murthy RK, Paplomata E, Hamilton E, et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. J Clin Oncol. 2020;38(23):2610-9.
60. Lin NC, Murthy RK, Anders CK, Borges VF, Hurvitz SA, Loi S, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with previously treated HER2+ metastatic breast cancer with brain metastases (HER2CLIMB). J Clin Oncol. 2020;38(15_suppl):1005.
61. Seagen Inc. Data on file – HER2CLIMB History and Milestones. 2020.
62. A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer (HER2CLIMB) [Internet]. [cited February 2021]. Available from: https://ClinicalTrials.gov/show/NCT02614794.
63. Bachelot T, Lin NU, Murthy RK, Hurvitz SA, Borges V, Oliveira M, et al. 293P - Impact of tucatinib on progression free survival in patients with HER2+ metastatic breast cancer and stable or active brain metastases. Annals of Oncology. 2020;31:S348-S95.

64. Mueller V, Paplomata E, Hamilton EP, Zelnak A, Fehrenbacher L, Jakobsen EH, et al. A2750 – Impact of tucatinib on health-related quality of life (HRQoL) in patients with HER2+ metastatic breast cancer (MBC) with and without brain metastases (BM). Annals of Oncology. 2020;31(suppl_4):S348-S95.
65. von Minckwitz G, du Bois A, Schmidt M, Maass N, Cufer T, de Jongh FE, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol. 2009;27(12):1999-2006.
66. Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat. 2008;112(3):533-43.
67. Pivot X, Manikhas A, Zurawski B, Chmielowska E, Karaszewska B, Allerton R, et al. CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2015;33(14):1564-73.
68. Takano T, Tsurutani J, Takahashi M, Yamanaka T, Sakai K, Ito Y, et al. A randomized phase II trial of trastuzumab plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxanes: WJOG6110B/ELTOP. Breast. 2018;40:67-75.
69. Wardley A, Mueller V, Paplomata E, Crouzet L, Iqbal N, Aithal S, et al. Poster PD13-04 – Impact of Tucatinib on Health-Related Quality of Life in Patients with HER2+ Metastatic Breast Cancer with Brain Metastases. San Antonio Breast Cancer Symposium® December 8–11. 2020.
70. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page WJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane 2021 [Available from: www.training.cochrane.org/handbook.
71. Musolino A, Ciccolallo L, Panebianco M, Fontana E, Zanoni D, Bozzetti C, et al. Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer registry study. Cancer. 2011;117(9):1837-46.
72. Gao C, Wang F, Suki D, Strom E, Li J, Sawaya R, et al. Effects of systemic therapy and local therapy on outcomes of 873 breast cancer patients with metastatic breast cancer to brain: MD Anderson Cancer Center experience. Int J Cancer. 2021;148(4):961-70.
73. Pasquier D, Darlix A, Louvel G, Fraisse J, Jacot W, Brain E, et al. Treatment and outcomes in patients with central nervous system metastases from breast cancer in the real-life ESME MBC cohort. Eur J Cancer. 2020;125:22-30.
74. Maurer C, Tulpin L, Moreau M, Dumitrescu C, de Azambuja E, Paesmans M, et al. Risk factors for the development of brain metastases in patients with HER2-positive breast cancer. ESMO Open. 2018;3(6):e000440.

75. Halaven® (eribulin). Summary of Product Characteristics – Halaven 0.44 mg/ml solution for injection 2021 [updated 10 March 2021. Available from: www.medicines.org.uk/emc/product/4517/smpc#gref.
76. Kulukian A, Lee P, Taylor J, Rosler R, de Vries P, Watson D, et al. Preclinical Activity of HER2-Selective Tyrosine Kinase Inhibitor Tucatinib as a Single Agent or in Combination with Trastuzumab or Docetaxel in Solid Tumor Models. Mol Cancer Ther. 2020;19(4):976-87.
77. Pestalozzi BC, Francis P, Quinaux E, Dolci S, Azambuja E, Gelber RD, et al. Is risk of central nervous system (CNS) relapse related to adjuvant taxane treatment in node-positive breast cancer? Results of the CNS substudy in the intergroup Phase III BIG 02-98 Trial. Ann Oncol. 2008;19(11):1837-41.
78. Bendell JC, Domchek SM, Burstein HJ, Harris L, Younger J, Kuter I, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer. 2003;97(12):2972-7.
79. Hurvitz SA, O'Shaughnessy J, Mason G, Yardley DA, Jahanzeb M, Brufsky A, et al. Central Nervous System Metastasis in Patients with HER2-Positive Metastatic Breast Cancer: Patient Characteristics, Treatment, and Survival from SystHERs. Clin Cancer Res. 2019;25(8):2433-41.
80. Uechi S, Moriwaki K. Preliminary analysis of the cost-effectiveness of pertuzumab in patients with Her2-positive breast cancer in Japan. Value Health. 2018;21.
81. Durkee BY, Qian Y, Pollom EL, King MT, Dudley SA, Shaffer JL, et al. Cost-Effectiveness of Pertuzumab in Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2016;34(9):902-9.
82. Scottish Medicines Consortium (SMC). Following a resubmission assessed under the orphan equivalent and end of life process: trastuzumab emtansine (Kadcyla®) is accepted for use within NHS Scotland [990/14] 2017 [updated 10 March. Available from: www.scottishmedicines.org.uk/medicines-advice/trastuzumab-emtansine-kadcyla-resubmission-99014/.
83. Le QA, Bae YH, Kang JH. Cost-effectiveness analysis of trastuzumab emtansine (T-DM1) in human epidermal growth factor receptor 2 (HER2): positive advanced breast cancer. Breast Cancer Res Treat. 2016;159(3):565-73.
84. CADTH (Canadian Agency for Drugs and Technologies in Health). Pan-Canadian Oncology Drug Review final economic guidance report – trastuzumab emtansine (Kadcyla) metastatic breast cancer 2014 [updated 19 September. Available from: www.cadth.ca/sites/default/files/pcodr/pcodr-kadcyla-mbc-fn-egr.pdf.
85. Poquet-Jornet JE, Carrera Hueso J, Crespo C, Cuesta-Grueso C, Ramón Barrios MA, Gasent-Blesa JM, et al. Budget impact analysis with use of subcutaneous trastuzumab. Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe; November 2018; Barcelona, Spain2018.

86. Scottish Medicines Consortium (SMC). Following a full submission: trastuzumab 600mg/5mL solution for injection (Herceptin®) is accepted for restricted use within NHS Scotland [928/13] 2013 [updated 6 December. Available from: www.scottishmedicines.org.uk/medicines-advice/trastuzumab-herceptin-fullsubmission-92813/.
87. Matter-Walstra KW, Dedes KJ, Schwenkglenks M, Brauchli P, Szucs TD, Pestalozzi BC. Trastuzumab beyond progression: a cost-utility analysis. Ann Oncol. 2010;21(11):2161-8.
88. Garrison LP, Jr., Veenstra DL. The economic value of innovative treatments over the product life cycle: the case of targeted trastuzumab therapy for breast cancer. Value Health. 2009;12(8):1118-23.
89. CADTH (Canadian Agency for Drugs and Technologies in Health). Pan-Canadian Oncology Drug Review final economic guidance report – lapatinib (Tykerb) with letrozole for metastatic breast cancer 2013 [updated 5 July. Available from: www.cadth.ca/sites/default/files/pcodr/pcodr-tykerb-mbc-fn-egr.pdf.
90. Ballali S, Chiffi D, Trojniak MP, Gregori D, Agreement E-VRP. Evaluating Trastuzumab and Lapatinib's Economic Impact in the Treatment of Metastatic Breast Cancer in Veneto Region Cohort. The Open Pharmacology Journal. 2013;7:17-25.
91. Machado M, Einarson TR. Lapatinib in patients with metastatic breast cancer following initial treatment with trastuzumab: an economic analysis from the Brazilian public health care perspective. Breast Cancer (Dove Med Press). 2012;4:173-82.
92. Le QA, Hay JW. Cost-effectiveness analysis of lapatinib in HER-2-positive advanced breast cancer. Cancer. 2009;115(3):489-98.
93. Diaby V, Ali AA, Williams KJ, Ezendu K, Soto-Perez-de-Celis E, Chavarri-Guerra Y, et al. Economic evaluation of sequencing strategies in HER2-positive metastatic breast cancer in Mexico: a contrast between public and private payer perspectives. Breast Cancer Res Treat. 2017;166(3):951-63.
94. Diaby V, Adunlin G, Ali AA, Zeichner SB, de Lima Lopes G, Kohn CG, et al. Cost-effectiveness analysis of 1st through 3rd line sequential targeted therapy in HER2-positive metastatic breast cancer in the United States. Breast Cancer Res Treat. 2016;160(1):187-96.
95. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer – supplementary appendix. N Engl J Med. 2020;382(7):597-609.
96. Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU Technical Support Document 19. Partitioned survival analysis for decision modelling in health care: a critical review 2017 [Available from: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf.
97. NICE. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Technology appraisal guidance [TA563] 2019 [updated 27 February. Available from: www.nice.org.uk/guidance/TA563.

98. NICE. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. Technology appraisal guidance [TA619] 2020 [updated 15 January. Available from: www.nice.org.uk/guidance/TA619.
99. NICE. Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cance. Technology appraisal guidance [TA639] 2020 [updated 01 July. Available from: www.nice.org.uk/guidance/TA639.
100. Nemeth BVA. The role of half-cycle correction in the models used for health technology assessment. Value Health. 2013;6(7):592-3.
101. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683-90.
102. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.
103. NICE. Guide to the methods of technology appraisal – processes and methods 2013 [Available from: www.nice.org.uk/process/pmg9.
104. PSSRU. Unit costs of health and social care 2019. Personal Social Services Research Unit. 2020.
105. Seagen Inc. Data on file – Health Utility Scores for Patients with HER2+ Metastatic Breast Cancer (MBC) with and without Brain Metastases from the HER2CLIMB Trial. 2020.
106. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. Eur J Health Econ. 2010;11(4):427-34.
107. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for
economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011 2013 [updated March. Available from: http://nicedsu.org.uk/technical-support-documents/survival-analysis-tsd/.
108. ONS. National life tables: UK. Office for National Statistics 2019 [Available from: www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.
109. NICE. Position statement on use of the EQ-5D-5L value set for England (updated October 2019) 2019 [Available from: www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l.
110. Hagiwara Y, Taira N, Saito T, Baba S, Kobayashi K, Kawahara T. The EQ-5D index of elderly patients with HER2-positive breast cancer: results from the randomized N-SAS BC 07 trial for adjuvant trastuzumab with and without chemotherapy. Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); Asia Pacific; September 2018. Tokyo, Japan.2018.
111. NICE. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [TA579] 2019 [Available from: www.nice.org.uk/guidance/ta579.

112. Reyes C, Engel-Nitz N, Goertz H, Fung A, Dacosta Byfield S. What is the cost of treating HER2 metastatic disease? [abstract]. J Manag Care Spec Pharm. 2017;23:S27-S8.
113. Piwko C, Prady C, Yunger S, Pollex E, Moser A. Safety Profile and Costs of Related Adverse Events of Trastuzumab Emtansine for the Treatment of HER2-Positive Locally Advanced or Metastatic Breast Cancer Compared to Capecitabine Plus Lapatinib from the Perspective of the Canadian Health-Care System. Clin Drug Investig. 2015;35(8):487-93.
114. Goertz H, Sheinson D, Wu N. Relationship of healthcare costs and disease progression in patients with HER2+ breast cancer [abstract]. J Clin Oncol. 2018;36.
115. Colomer R, Ciruelos E, De La Haba J, Martin M, De Salas-Cansado M, Munoz-Molina B. Estimating costs of relapsing HER2+ breast cancer in Spain [abstract]. Cancer Res. 2017;77:P3-15-P3-2-05.
116. TUKYSA® (tucatinib). Summary of product characteristics. 2021.
117. BNF. Eribulin – medicinal forms 2021 [Available from: https://bnf.nice.org.uk/medicinal-forms/eribulin.html.
118. NHS. 2018/19 National Cost Collection data (NHS Improvement) 2019 [Available from: www.england.nhs.uk/national-cost-collection/#ncc1819
119. Saura C, Oliveira M, Feng YH, Dai MS, Chen SW, Hurvitz SA, et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With >/= 2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol. 2020;38(27):3138-49.
120. Urruticoechea A, Rizwanullah M, Im SA, Ruiz ACS, Lang I, Tomasello G, et al. Randomized Phase III Trial of Trastuzumab Plus Capecitabine With or Without Pertuzumab in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Who Experienced Disease Progression During or After Trastuzumab-Based Therapy. J Clin Oncol. 2017;35(26):3030-8.
121. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91.
122. BNF. Lapatinib – medicinal forms 2021 [Available from: https://bnf.nice.org.uk/medicinal-forms/lapatinib.html.
123. BNF. Neratinib – medicinal forms 2021 [Available from: https://bnf.nice.org.uk/medicinal-forms/neratinib.html.
124. BNF. Pertuzumab – medicinal forms 2021 [Available from: https://bnf.nice.org.uk/medicinal-forms/pertuzumab.html.
125. BNF. Trastuzumab emtansine – medicinal forms 2021 [Available from: https://bnf.nice.org.uk/medicinal-forms/trastuzumab-emtansine.html.
126. BNF. Loperamide – medicinal forms 2021 [Available from: https://bnf.nice.org.uk/medicinal-forms/loperamide-hydrochloride.html.

127. NICE. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer – technology appraisal guidance [TA496] 2017 [updated 20 December. Available from: www.nice.org.uk/guidance/ta496.
128. NICE. Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer – technology appraisal guidance [TA621] 2020 [updated 22 January. Available from: www.nice.org.uk/guidance/ta621.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Responses to clarification questions

May 2021

File name	Version	Contains confidential information	Date
ID3828 Tucatinib - responses to clarification letter [redacted]	1	Yes	24 May 2021

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

HER2CLIMB study

A1. PRIORITY QUESTION. The Clinical Study Report (CSR, dated 7 Nov 2019) provided with the reference pack of the company submission does not include any tables, figures (section 15) or appendices (section 16). Please provide the tables and figures for section 15, and the following appendices:

- 16.1 Study Information
- 16.1.1 Protocol Amendment (version 10)
- 16.1.7 Randomization Scheme and Codes
- 16.1.9 Statistical Analysis Plan
- 16.1.11 Publications Based on the Study.

COMPANY RESPONSE: Please find each document with the information outlined in the bullet points above as Addendums A1a to A1g, as follows:

- Addendum A1a: CSR appendices, including the study Information, randomisation scheme and codes, statistical analysis plan and publications based on the study

- Addendum A1b: Protocol Amendment (version 10) – please also find the final protocol amendment (version 11) as Addendum A1c and the summary of differences in Addendum A1d for completeness

A2. Company submission (CS), section B.2.6.9. Please provide the EQ-5D-5L index data at baseline and at the longest point of follow-up for each treatment arm, and any comparative statistical analyses. Please provide similar data for the brain metastases subgroup.

COMPANY RESPONSE: Please find the tables below with the EQ-5D-5L data in the in the intent-to-treat (ITT) population (Table A2a) and in patients with brain metastases (Table A2b). For completeness, the EQ-5D-3L data in the ITT population and in patients with brain metastases are also provided (Table A2c and Table A2d, respectively).

Table A2a: EQ-5D-5L index scores in the in the ITT population

	Tuc+Cap+Tra (N=410)	Pbo+Cap+Tra (N=202)
Baseline		
n	213	112
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	-0.010, 1.000	0.087, 1.000
Cycle 3		
n	175	89
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.275, 1.000	0.270, 1.000
Cycle 5		
n	152	71
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.087, 1.000	0.239, 1.000
Cycle 7		
n	130	54

	Tuc+Cap+Tra (N=410)	Pbo+Cap+Tra (N=202)
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.280, 1.000	0.255, 1.000
Cycle 9		
n	86	38
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.444, 1.000	-0.007, 1.000
30 Day Follow Up		
n	72	42
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	-0.285, 1.000	0.218, 1.000

CI, confidence interval; EQ-5D-5L, EuroQoL 5 Dimensions 5-Levels; ITT, intent-to-treat; Max, maximum; Min, minimum; Pbo+Cap+Tra, placebo + capecitabine + trastuzumab; SD, standard deviation; Tuc+Cap+Tra, tucatinib + capecitabine + trastuzumab

Baseline is defined as most recent non missing assessment on or before first dose date.
Cycles where the number of subjects in each arm reaches >=20% of initial cohort size are presented.
Snapshot date: 14OCT2019, data cutoff date: 04SEP2019.
Source: O:\Projects\Tucatinib\ONT380-206\hta_1900\v01\outputs\tlfs\pgms\t-uk-pro-indxs.sas Output: t-uk-pro-indxs5l-itts.rtf (19MAY21:14:07) Data: adsl, adpro

Table A2b: EQ-5D-5L index scores in the in patients with brain metastases

	Tuc+Cap+Tra (N=198)	Pbo+Cap+Tra (N=93)
Baseline		
n	104	57
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.334, 1.000	0.171, 1.000
Cycle 3		
n	84	43
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.275, 1.000	0.276, 1.000

	Tuc+Cap+Tra (N=198)	Pbo+Cap+Tra (N=93)
Cycle 5		
n	76	33
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.149, 1.000	0.492, 1.000
Cycle 7		
n	68	27
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.280, 1.000	0.364, 1.000
Cycle 9		
n	46	14
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.520, 1.000	0.332, 1.000
30 Day Follow Up		
n	29	21
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	-0.285, 1.000	0.218, 1.000

CI, confidence interval; EQ-5D-5L, EuroQoL 5 Dimensions 5-Levels; Max, maximum; Min, minimum; Pbo+Cap+Tra, placebo + capecitabine + trastuzumab; SD, standard deviation; Tuc+Cap+Tra, tucatinib + capecitabine + trastuzumab

Baseline is defined as most recent non missing assessment on or before first dose date.

Cycles where the number of subjects in each arm reaches >=20% of initial cohort size are presented.

Snapshot date: 14OCT2019, data cutoff date: 04SEP2019.

Source: O:\Projects\Tucatinib\ONT380-206\hta_1900\v01\outputs\tlfs\pgms\t-uk-pro-indxs.sas Output: t-uk-pro-indxs5l-bmitts.rtf (19MAY21:14:07) Data: adsl, adpro

Table A2c: EQ-5D-3L index scores in the in the ITT population

	Tuc+Cap+Tra (N=410)	Pbo+Cap+Tra (N=202)
Baseline		
n	213	112
Mean (SD)	[redacted]	[redacted]

95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	-0.151, 1.000	0.028, 1.000
Cycle 3		
n	175	89
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.122, 1.000	-0.071, 1.000
Cycle 5		
n	152	71
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	-0.107, 1.000	-0.062, 1.000
Cycle 7		
n	130	54
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.017, 1.000	-0.065, 1.000
Cycle 9		
n	86	38
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.235, 1.000	-0.187, 1.000
30 Day Follow Up		
n	72	42
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	-0.594, 1.000	0.028, 1.000

CI, confidence interval; EQ-5D-3L, EuroQoL 5 Dimensions 3-Levels; ITT, intent-to-treat; Max, maximum; Min, minimum; Pbo+Cap+Tra, placebo + capecitabine + trastuzumab; SD, standard deviation; Tuc+Cap+Tra, tucatinib + capecitabine + trastuzumab

Baseline is defined as most recent non missing assessment on or before first dose date.

Cycles where the number of subjects in each arm reaches >=20% of initial cohort size are presented.

Index score is calculated based on UK value set (mapping the EQ-5D-5L to EQ-5D-3L).

Snapshot date: 14OCT2019, data cutoff date: 04SEP2019.

Source: O:\Projects\Tucatinib\ONT380-206\hta_1900\v01\outputs\tlfs\pgms\t-uk-pro-indxs.sas Output: t-uk-pro-indxs3l-itts.rtf (19MAY21:14:07) Data: adsl, adpro

Table A2d: EQ-5D-3L index scores in the in patients with brain metastases

	Tuc+Cap+Tra (N=198)	Pbo+Cap+Tra (N=93)
Baseline		
n	104	57
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.157, 1.000	0.028, 1.000
Cycle 3		
n	84	43
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.136, 1.000	-0.071, 1.000
Cycle 5		
n	76	33
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.066, 1.000	0.316, 1.000
Cycle 7		
n	68	27
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	0.084, 1.000	0.281, 1.000
Cycle 9		
n	46	14
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

	Tuc+Cap+Tra (N=198)	Pbo+Cap+Tra (N=93)
Median	[redacted]	[redacted]
Min, Max	0.404, 1.000	0.249, 1.000
30 Day Follow Up		
n	29	21
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	-0.594, 1.000	0.028, 1.000

CI, confidence interval; EQ-5D-3L, EuroQoL 5 Dimensions 3-Levels; Max, maximum; Min, minimum; Pbo+Cap+Tra, placebo + capecitabine + trastuzumab; SD, standard deviation; Tuc+Cap+Tra, tucatinib + capecitabine + trastuzumab

Baseline is defined as most recent non missing assessment on or before first dose date.

Cycles where the number of subjects in each arm reaches >=20% of initial cohort size are presented.

Index score is calculated based on UK value set (mapping the EQ-5D-5L to EQ-5D-3L).

Snapshot date: 14OCT2019, data cutoff date: 04SEP2019.

Source: O:\Projects\Tucatinib\ONT380-206\hta_1900\v01\outputs\tlfs\pgms\t-uk-pro-indxs.sas Output: t-uk-pro-indxs3l-bmitts.rtf (19MAY21:14:07) Data: adsl, adpro

Network meta-analysis (NMA)

A3. CS, section B.2.9. The company submission states that "The results presented here are aligned with the decision problem of this appraisal and although the conducted NMA included treatments and combination treatments that are not licensed in the UK in the subpopulation of interest in this appraisal (Table 9), this submission only reports on comparisons of the tucatinib combination versus either eribulin, capecitabine or vinorelbine as monotherapy in patients with HER2+ MBC". There are 7 "relevant" trials (Table 9) and a further 5 trials considered not relevant to the decision problem (that is, EMELIA, SOPHIA, PHEREXA, NALA, NCT00777101). Please confirm whether these 5 trials do not provide additional connectivity between relevant treatments in the network. Please clarify the rationale for the inclusion of these 5 studies in the network.

COMPANY RESPONSE: The NMA performed was intended to inform submissions in multiple markets including the UK. We confirm that the five trials mentioned provide no additional connectivity for the comparators of interest for the UK (capecitabine, eribulin and vinorelbine) and therefore are not relevant to the NICE decision problem. We also note that the five trials correspond to five terminal nodes in the network and therefore will not influence the relative effect estimates of the

comparisons of interest to NICE. These five trials were included in the network because the presented NMA was developed for all global markets, where the agents assessed in those trials were relevant. Given that the inclusion or exclusion of these trials had no bearing on the comparators of interest for NICE, and that a single NMA to inform multiple decision problems (where appropriate and feasible) was more efficient and would appeal to a wider audience from a publication perspective, a combined NMA was deemed both acceptable and appropriate.

In summary, inclusion of these five trials in the network did not impact the treatments (i.e., eribulin, vinorelbine, and capecitabine) included in the current decision problem.

A4a. PRIORITY QUESTION. CS, sections B.2.9.2.1 and B.2.9.2.2 and Appendix D. Please clarify which outcome data was used in the hazard ratio (HR) NMA for the outcomes of progression free survival (PFS) and overall survival (OS). It is unclear from Table 18 (Appendix D) which studies have been used as some studies report more than one HR per outcome.

COMPANY RESPONSE: Table A4a summarises the OS and PFS HR data used in the HR NMA.

Table A4a: OS and PFS HR data utilised in NMA

Study Name	Treatments	OS HR (95% CI)	PFS HR (95% CI)	Population	Notes
HER2CLIMB	Tucatinib + capecitabine + trastuzumab	0.662 (0.501-0.875)	0.535 (0.42-0.682)	ITT	The PFS HR for HER2CLIMB is for the primary endpoint analysis population (i.e., the first 480 randomised subjects in the ITT population). The PFS HR used in the NMA includes all randomised subjects in the ITT population to be consistent with other trials included in the NMA (Seagen, HER2CLIMB Clinical Study Report, 2019).
	Placebo + capecitabine + trastuzumab	Ref	Ref		
WJOG6110B/ELTOP	Lapatinib + capecitabine	0.58 (0.26-1.31)	0.81 (0.55-1.21)	ITT	
	Trastuzumab + capecitabine	Ref	Ref		
GBG 26/BIG 3-05	Trastuzumab + capecitabine	NA	0.685 (0.482-0.974)[a]	ITT	The OS HR for GBG 26/BIG 3-05 is unadjusted for treatment switching. Trials with a crossover design were only included in the OS HR NMA if they reported an OS HR that was adjusted using the RPSFTM method. We could not identify OS HR data that was adjusted for treatment switching using the RPSFTM method; hence, this trial was excluded from the OS HR NMA.
	Capecitabine		Ref		
CEREBEL	Lapatinib + capecitabine	1.18 (0.76-1.183)	1.13 (0.85-1.5)	Subgroup (patients with prior trastuzumab)	
	Trastuzumab + capecitabine	Ref	Ref		
EGF100151	Lapatinib + capecitabine	0.775 (0.532-1.128)	0.55 (0.41-0.74)	ITT	The OS HR for EGF100151 unadjusted for treatment switching. The OS HR used in the NMA is adjusted for treatment switching using the RPSFTM method (Latimer, 2012).
	Capecitabine	Ref	Ref		
Study 301	Eribulin	0.965 (0.688-1.355)	1.356 (0.93-1.98)	Subgroup (patients with HER2+ status)	The OS HR for Study 301 corresponds to the published data from this trial and is rounded to two decimal places. The OS HR used in the NMA is rounded to three decimal places and was reported in a press release from Eisai (Eisai News Release, 2012).
	Capecitabine	Ref	Ref		
NCT02225470	Eribulin	1.03 (0.8-1.31)	0.94 (0.6-1.48)	▪ ITT for OS	
	Vinorelbine	Ref	Ref		

				▪ Subgroup for PFS (patients with HER2+ status)	
EMILIA	T-DM1	0.693 (0.577-0.848)	0.65 (0.549-0.771)	ITT	
	Lapatinib + capecitabine	Ref	Ref		
NALA	Neratinib + capecitabine	0.881 (0.723-1.073)	0.762 (0.626-0.926)	ITT	
	Lapatinib + capecitabine	Ref	Ref		
NCT00777101	Neratinib	1.25 (0.83-1.86)	1.19 (0.89-1.6)	ITT	NCT02225470 did not report an OS HR for a subgroup of patients with HER2+ status. However, to facilitate a comparison between tucatinib and vinorelbine (which is a comparator of interest for NICE), the OS HR data for the ITT population was used as a proxy in the HR NMA.
	Lapatinib + capecitabine	Ref	Ref		
PHEREXA	Pertuzumab + trastuzumab + capecitabine	0.76 (0.6-0.98)	0.82 (0.65-1.02)	ITT	
	Trastuzumab + capecitabine	Ref	Ref		
SOPHIA	Margetuximab + capecitabine	1 (0.63-1.59)	0.773 (0.473-1.262)	Subgroup (patients who received capecitabine as investigator's choice of chemotherapy)	
	Trastuzumab + capecitabine	Ref	Ref		

CI, confidence interval; HER2+, human epidermal growth factor receptor 2-positive; HR, hazard ratio; ITT, intention-to-treat; NA, not applicable; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PFS, progression-free survival; OS, overall survival; Ref, reference; T-DM1, trastuzumab emtansine

[a] HR for time-to-progression was used as a proxy for the PFS HR.

Trials highlighted in grey are not of interest to the NICE decision problem and their data were not presented in Table 18 (Appendix D) of the submission document. However, they were included in the HR NMA for the reasons stated in response to question A3.

The other trials are of interest to the NICE decision problem and their data match the data shown in Table 18 with a few exceptions, as noted in table A4a. Those exceptions arose when statisticians quality-checked the data extracted in the SLR to ensure that the most appropriate data were used in the NMA for each trial given variations in study designs and the reporting of endpoints.

References – copy of references not previously provided in this submission are attached to this response document:

- Seagen Inc. HER2CLIMB Clinical Study Report. 2019.
- Latimer NR. The role of treatment crossover adjustment methods in the context of economic evaluation. PhD thesis, University of Sheffield. 2012. Available at: http://etheses.whiterose.ac.uk/3720/1/Thesis_Final_with_corrections.pdf (last accessed 19 May 2021).
- Eisai News Release. Phase III study (Study 301) results of anticancer agent Halaven® versus capecitabine in locally advanced or metastatic breast cancer presented at 2012 SABCS. 2012. Available at: www.eisai.com/news/news201281.html (last accessed 19 May 2021).

A4b. PRIORITY QUESTION. CS, section B.2.9.1.2, Figure 15 and Appendix D, Table 18. There seems to be some inconsistencies in the data reported in the OS network plot in Figure 15 (Document B) and Table 18 (Appendix D) and . In Figure 15, the NCT02225470 study is included although no HR is reported in Table 18. Conversely, the GBG study is excluded from Figure 15 although a HR for this study is reported in Table 18. Please clarify.

The OS HR for the CEREBEL study is reported in Table 18 as 1.18 (95% CI of 0.760, 1.183). Please clarify whether these figures are correct.

COMPANY RESPONSE: NCT02225470 reports only OS in a mixed population (ITT: HER2+ and HER2- patients) and reported no HER2+ subgroup data. Despite the absence of HER2+ subgroup data for the OS data of this trial, the option to include the ITT data as a proxy was preferred to the exclusion of the trial given that vinorelbine was part of the NICE decision problem (consequently its presence in

Figure 15 is correct). The exclusion from Table 18 (Appendix D) of the OS HR was due to the absence of HER2+ subgroup data for this endpoint (see response to A4a).

The **GBG study** incorporated a crossover-design; however, the OS data was not adjusted to account for treatment switching. A targeted search of the literature was conducted to identify adjusted data, but none could be found. Consequently, this study was excluded from the OS NMA even though unadjusted data was reported. This is explained in the Appendix D (page 87) of the tucatinib submission, as follows: '*To address the bias caused by treatment switching, results that had been adjusted for treatment switching using the RPSFTM method were included in the NMA for these studies only. Therefore, the OS data for GBG 26 were excluded from the NMA*.'

The **OS HR for the CEREBEL study** is reported correctly in Table 18, as mentioned in the question. The OS HR between lapatinib + capecitabine and trastuzumab + capecitabine in the subgroup of patients who received prior trastuzumab (n=167) is shown in the supplementary appendix of Pivot et al. 2015, which has now been provided alongside the present document (reference pack folder). These data correspond to the subgroup of the CEREBEL trial that excludes patients who were naïve to anti-HER2 therapies as reported by Pivot et al. (2015) in the supplementary materials. The ITT population of this trial comprises (~40%) patients who were naïve to HER2-targeted regimens, so it could not be included in its entirety.

The population of interest according to the NICE scope was patients with HER2+, unresectable locally advanced or metastatic breast cancer who have had 2 or more prior anti-HER2 therapies. Due to the absence of evidence in this population to form a viable network, the NMA inclusion criteria were relaxed to include data for patients who had received 1 or more prior anti-HER2 therapies or where subgroup data were reported in this population (e.g., CEREBEL).

A5. CS, sections B.2.9.2.1 and B.2.9.2.2. Please report the NMA HR random effects results for the Bayesian and frequentist analyses for OS and PFS.

COMPANY RESPONSE: Please find the requested results of the Bayesian and frequentist analyses, respectively, for OS (Figure A5a and Figure A5b) and PFS (Figure A5c and Figure A5d).

Additionally, sections 6.2.1 and 6.2.2 of the NMA report briefly compare the random effects and fixed effects results for PFS and OS, respectively. These sections also describe the rationale behind the choice of the fixed effects results as the primary results for the respective outcomes.

Figure A5a: OS HR, Bayesian random effects NMA, pairwise treat comparisons [AIC]

CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; T-DM1, trastuzumab emtansine
Values are HR and 95% CrIs for the intervention listed on the vertical axis versus the intervention listed on the horizontal axis. In total, 11 treatments were included in the network and allowed the comparison between the treatments of interest for this appraisal, namely the tucatinib combination versus monotherapy with either eribulin, capecitabine or vinorelbine.

Figure A5b: OS HR, frequentist random effects NMA, pairwise treatment comparisons [AIC]

CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; T-DM1, trastuzumab emtansine
Values are HR and 95% CrIs for the intervention listed on the vertical axis versus the intervention listed on the horizontal axis.
In total, 11 treatments were included in the network and allowed the comparison between the treatments of interest for this appraisal, namely the tucatinib combination versus monotherapy with either eribulin, capecitabine or vinorelbine.

Figure A5c: PFS HR, Bayesian random effects NMA, pairwise treat comparisons [AIC]

CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; T-DM1, trastuzumab emtansine
Values are HR and 95% CrIs for the intervention listed on the vertical axis versus the intervention listed on the horizontal axis. If the cell is not coloured, then there is no statistical significance (threshold p value: 0.05). Where the treatment listed on the left side of the table was significantly better compared with treatments on the horizontal axes of the table, the results are coloured yellow to red, and where treatments on the bottom of the table were significantly worse versus those on the left, the results are coloured blue. The darker the shading of the colour in the cell, the larger the relative difference.
In total, 11 treatments were included in the network and allowed the comparison between the treatments of interest for this appraisal, namely the tucatinib combination versus monotherapy with either eribulin, capecitabine or vinorelbine.

Figure A5d: PFS HR, frequentist random effects NMA, pairwise treatment comparisons [AIC]

CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; T-DM1, trastuzumab emtansine
Values are HR and 95% CrIs for the intervention listed on the vertical axis versus the intervention listed on the horizontal axis. If the cell is not coloured, then there is no statistical significance (threshold p value: 0.05). Where the treatment listed on the left side of the table was significantly better compared with treatments on the horizontal axes of the table, the results are coloured yellow to red, and where treatments on the bottom of the table were significantly worse versus those on the left, the results are coloured blue. The darker the shading of the colour in the cell, the larger the relative difference.
In total, 11 treatments were included in the network and allowed the comparison between the treatments of interest for this appraisal, namely the tucatinib combination versus monotherapy with either eribulin, capecitabine or vinorelbine.

A6. PRIORITY QUESTION. CS, section B.2.9.2.1. The company submission states that: "[redacted]". Please clarify:

a. which Bayesian RE results were [redacted] with the trial data.
b. whether the frequentist RE results were also [redacted].
c. whether this [redacted] is retained when only the 6/7 key trials are included in the NMA.

COMPANY RESPONSE:

a. Data from the NALA trial suggested that neratinib plus capecitabine had a significantly greater PFS than lapatinib plus capecitabine with a HR (95% CI) of 0.762 (0.626-0.926). However, this treatment comparison [redacted] based on the Bayesian RE results ([redacted]). Notably, this treatment comparison was [redacted] on the Bayesian FE results ([redacted]).

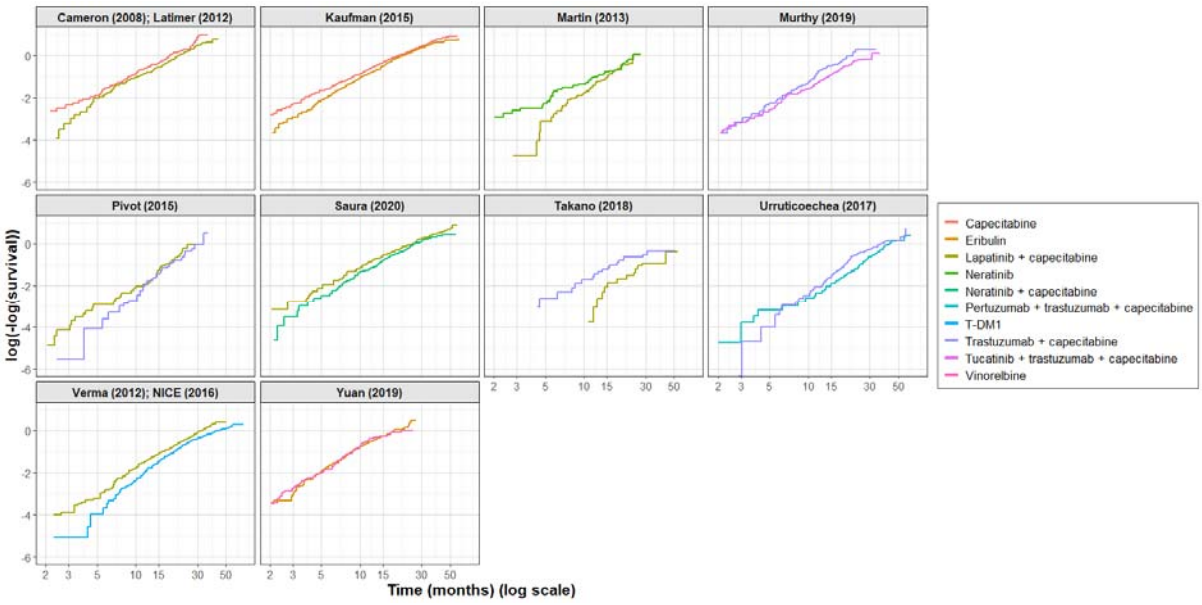
b. There were [redacted] between the frequentist RE results and head-to-head trial data in terms of significant treatment effects.

c. When only the key trials relevant to the NICE decision problem are considered, the results of the Bayesian RE results are [redacted] with the head-to-head trial results from HER2CLIMB. In HER2CLIMB the tucatinib combination demonstrated significantly better PFS and OS than the comparator arm, which is [redacted]. Given this key [redacted], as well as the [redacted], the [redacted] reflect the significant treatment benefit of tucatinib over eribulin, vinorelbine, and capecitabine.

A7. CS, section B.2.9.1.6. Please clarify why Pivot et al (2015) is missing from the OS loglog plot in Figure 17. Please provide Schoenfeld residuals plots to test for proportionality.

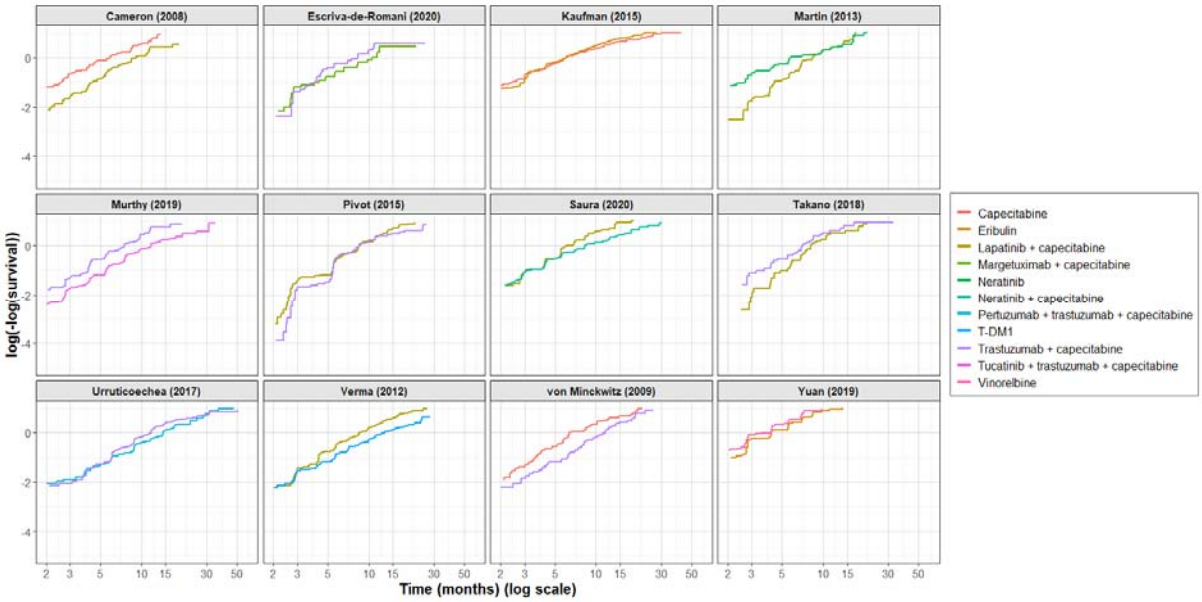
COMPANY RESPONSE: The Pivot study should have been provided in the figure and the log(-log) plots for all studies are shown in Figure A7a for OS, including Pivot et al (2015), and, for reference, in Figure A7b for PFS.

Figure A7a: Log(-log(survival) plot for OS



T-DM1, trastuzumab emtansine

Figure A7b: Log(-log(survival) plot for PFS



PFS, progression-free survival; T-DM1, trastuzumab emtansine
Note: Escriva-de-Romani et al. (2020) is a secondary reference of the SOPHIA trial that reported a KM curve and number at risk table for PFS in the subgroup of patients that received capecitabine as the chemotherapy of investigator's choice.

We tested for the proportional hazard assumption using log(-log(Survival)) plots and significance tests. We used the cox.zph function in Therneau's survival package in

R. We used the default transform option (transform = 'km'), which is supposed to be less sensitive to censoring patterns (Therneau et al. 2000). The results from the assessment of proportionality for OS and PFS are discussed in Section 6.1 of the NMA report.

Reference: Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer; 2000.

A8. CS, section B.2.9. Please provide the reconstructed OS and PFS data as formatted for use with the fractional polynomial (FP) code. Please also provide the initial values used with the code.

COMPANY RESPONSE: The formatted data are provided in the following files attached to this response document as addendum files:

- Addendum A8a: OS.FP.data.update.csv
- Addendum A8b: PFS.FP.data.update.csv

Time intervals = 1 month

A9. CS, section B.2.9. Please clarify whether the reconstructed OS and PFS data were validated against the original study data. If so, please provide details of this validation.

COMPANY RESPONSE: The reconstructed OS and PFS data were validated against the original study data. The results of this validation are shown in Table F-1, Appendix F and Table G-1, Appendix G of the NMA report for PFS and OS, respectively. The full NMA report is provided as Addendum A9a and its appendices as Addendum A9b.

A10. CS, section B.2.9.3. Please present time-varying hazard ratio plots and tabulated time-varying hazard ratios for each of the FP models fitted for OS and PFS.

COMPANY RESPONSE:

The charts showing hazard ratios varying with time are provided in the following PowerPoint slide decks with the results from the FP NMAs, which have been attached to this response document as addendum files A10a and A10b:

- Addendum A10a – overall survival: Fractional polynomial NMA OS Updated Results 12 Feb 2021.pptx

  Here is a selection of the charts of hazard ratios varying with time by treatment:

  - Bayesian FE NMA with anchoring – slide 60
  - Bayesian FE NMA with anchoring and HR NMA applied to reference from FP NMA – slide 83
  - Bayesian RE NMA with anchoring – slide 101
  - Bayesian RE NMA with anchoring and HR NMA applied to reference from FP NMA – slide 126

- Addendum A10b – progression-free survival: Fractional polynomial NMA PFS Updated Results 12 Feb 2021.pptx

  Here is a selection of the charts of hazard ratios varying with time by treatment:

  - Bayesian FE NMA without anchoring – slide 60
  - Bayesian FE NMA with anchoring – slide 64
  - Bayesian FE NMA with anchoring and HR NMA applied to reference from FP NMA - slide 87
  - Bayesian RE NMA with anchoring – slide 112
  - Bayesian RE NMA with anchoring and HR NMA applied to reference from FP NMA – slide 135

These charts were generated programmatically, but accompanying tables of the underlying data were not saved and so are not provided. The charts present predicted values with 95% credible intervals for 1 month intervals with a follow-up of 10 years i.e. present 360 values per treatment per model and were therefore only

presented in chart form. In addition to the NMA report, these slide decks provide all available information on the results from the FP analyses.

A11. CS, section B.2.9.3. Please present the model fit statistics (deviance information criterion) for all FP models and provide the rationale for the company's preferred FP model fit chosen to inform survival estimates in the economic model.

COMPANY RESPONSE: All model fit statistics (figures, tables and accompanying explanatory text for model selection) for PFS and OS are provided in Appendix F and G of the NMA report respectively.

A12. **CS, section B.2.9.1.3.** Please clarify whether NCT02225470 and Study 301 are the only studies in the NMA to include HER2- patients.

COMPANY RESPONSE: Yes. These are the only studies to include HER2- patients.

A13. CS, section B.2.9.1.3. Please elaborate on any evidence or clinical opinion/consensus about potential treatment effect modifiers in patients with HER2+ metastatic breast cancer. Please discuss how the distribution of any such effect modifiers in the included studies might potentially influence (that is, bias) the results of the NMA.

COMPANY RESPONSE: The following Table A13 identifies prognostic and treatment effect modifiers within HER2+ metastatic breast cancer. Overall, our NMA was holistically representative of most factors.

Table A13: Prognostic and treatment effect modifiers within HER2+ metastatic breast cancer

Factor	Prognostic factor or treatment effect modifier	Comparator studies in which factor is reported
Prior treatment with pertuzumab (yes/no)	• Treatment effect modifier	• HER2CLIMB • ELTOP
Prior treatment with trastuzumab (yes/no)	• Treatment effect modifier	• HER2CLIMB • NCT02225470 • GBG 26 • EGF 100151 • CEREBEL • ELTOP
Number of lines of prior therapy (<3, ≥3)	• Treatment effect modifier	• HER2CLIMB • Study 301 • NCT02225470

		• GBG 26 • EGF 100151 • CEREBEL • ELTOP
Hormone receptor status (positive/negative)	• Prognostic factor	• HER2CLIMB • Study 301 • NCT02225470 • GBG 26 • EGF 100151 • CEREBEL • ELTOP
HER2 status	• Prognostic factor	Note that all studies included were HER2+ or their subgroups. • HER2CLIMB • Study 301 (subgroup only) • NCT02225470 (subgroup only) • GBG 26 • EGF 100151 • CEREBEL • ELTOP
Presence of visceral disease (yes/no)	• Prognostic factor	• Study 301 • EGF 100151 • CEREBEL
Age	• Prognostic factor	• HER2CLIMB • Study 301 • NCT02225470 • GBG 26 • EGF 100151 • CEREBEL • ELTOP
ECOG-PS (0/1+)	• Prognostic factor	• HER2CLIMB • Study 301 • NCT02225470 • EGF 100151 • CEREBEL • ELTOP
Brain metastases (yes/no)	• Treatment effect modifier	• HER2CLIMB • GBG 26 • EGF 100151 • CEREBEL • ELTOP
Prior endocrine therapy (yes/no)	• Prognostic factor	• NCT02225470

ECOG-PS, Eastern Cooperative Oncology Group performance status; HER2+, human epidermal growth factor receptor 2-positive; T-DM1, trastuzumab emtansine

Patient and disease characteristics, as well as number and type of prior treatments, at baseline may modify the effect of subsequent treatments in HER2+ metastatic breast cancer as presented in Table A13. Although these factors were generally consistent among the trials included in the NMA, the two trials assessing eribulin included patients who have previously received chemotherapy only instead of prior exposure to anti-HER regimens.

Also, most of the trials included in the NMA involved patients who were less heavily treated than those in HER2CLIMB, and many did not include patients previously treated with standard agents in the metastatic setting such as pertuzumab, which was not approved at the time the studies were conducted. Additionally, 48% of patients enrolled in HER2CLIMB had brain metastases at baseline, including patients with active brain metastases, whereas other studies included minimal numbers of patients with brain metastases, and limited these to patients with stable and treated brain metastases. The bias that may be introduced with the different patient populations may understate the relative benefit of the tucatinib combination.

A14. PRIORITY QUESTION. CS, sections B.2.9.3.1 and B2.9.3.2. The company submission states "[redacted]". Please clarify what these "[redacted]" were. In addition, the company submission states "[redacted]" Please clarify how the OS FP is "[redacted]" with the HR analysis.

COMPANY RESPONSE: When comparing results from the Bayesian FE HR NMA and the Bayesian FE fractional polynomial NMA with HR tapering for PFS (Figure 6 and Figure F-27, Appendix F of the NMA report, respectively), the following two [redacted] were noted (however we acknowledge that these comparisons are not relevant to the NICE decision problem):

- The comparison of neratinib with eribulin was [redacted] in the HR NMA (HR [95% credible interval {CrI}] = [redacted]; *P*=[redacted])

but was [redacted] in the fractional polynomial NMA (difference in mean PFS [95% CrI] = [redacted] months [redacted]; *P*=[redacted]).

- The comparison of neratinib with vinorelbine was [redacted] in the HR NMA (HR [95% CrI] = [redacted] [redacted]; *P*=[redacted]) but was [redacted] in the fractional polynomial NMA (difference in mean PFS [95% CrI] = [redacted] months [redacted]; *P*=[redacted]).

When comparing results from the Bayesian FE HR NMA and the Bayesian FE fractional polynomial NMA with HR tapering for OS (Figure 11 and Figure G-31, Appendix G of the NMA report, respectively), 11 [redacted] were noted, which are not listed here for simplicity.

Given that there were more [redacted] between the Bayesian FE HR NMA and Bayesian FE fractional polynomial NMA with HR tapering for OS than for PFS, we concluded that "the results of the Bayesian FE fractional polynomial NMA were [redacted] with the corresponding HR NMA for the OS analysis than observed for the PFS analysis."

A15. Appendix D, page 87. Appendix D states "A targeted search was conducted after the initial SLR using the term [redacted] in studies where [redacted] to have occurred." Please provide further details on:

a. the sources that were searched.
b. the results that were found (for example, number of published estimates, range of adjustment methods used).
c. how the [redacted] used in the NMA were selected from any other available estimates identified from the search.

COMPANY RESPONSE: The targeted review performed was an informal review that comprised several iterative searches with no record kept of all the searches performed and all the results found (Section 5.3 of the NMA report describes the search that identified the most consistently reported type of adjusted data). Internet searches were conducted that included PubMed and Google Scholar, which only included "[redacted]" and the trial number used as search terms. This identified a small number of results which included Nick Latimer's PhD thesis and a few HTA

submission documents to NICE. [redacted] charts were found for two of the three trials with a [redacted] design (i.e., EGF100151 and EMILIA). Data for the iterative parameter estimation and IPCW methods were also identified but only for EGF100151. No adjusted data were identified for GBG 26. We considered [redacted] to the be the most appropriate method for an NMA for three reasons:

1. The same assumption is used in all studies i.e., constant treatment effect with line of treatment.

2. Kaplan-Meier estimates for the counterfactual data produced by [redacted] are typically presented for this method, which can be re-constructed and used in survival NMAs.

3. [redacted] is typically more commonly reported in publications compared to other treatment switching methods.

In contrast to [redacted], IPCW and two-stage methods rely on covariates and are therefore sensitive to the choice of covariates and how the covariates are modelled. Different covariates are likely to be selected for different studies, which makes it difficult to know how comparable results will be. In addition, the results from IPCW and two-stage methods are typically only presented as adjusted hazard ratios. This means they are not applicable to survival NMAs that model re-constructed patient-level data and so their use with NMAs is more restrictive. For this study, [redacted] was the most frequently presented method to adjust for treatment switching. For all these reasons, only [redacted] data were used in the NMAs.

A16. Appendix D. Please clarify whether any attempts were made to locate survival estimates for the 3 trials with patient switching included in the NMA, using other available valid methods (for example, the two-stage method, IPCW, etc). If these adjusted survival estimates are available, please consider including them in the NMA to provide alternative results to the those based on the [redacted] estimates.

COMPANY RESPONSE: We were not able to locate survival estimates for EGF100151, GBG 26, and EMILIA and therefore did not perform the corresponding RE NMAs because there is insufficient information to accurately estimate the heterogeneity parameter for the Bayesian model due to the absence of closed loops

in the OS network and limited duplicate comparisons. This could result in the over-estimation of the error of all pairwise comparisons in the Bayesian RE OS model (see Figure E-22, Appendix E of the NMA report).

A17. CS, section B2.9.2.2. and Appendix B. Instead of excluding the GBG 26/BIG 3-05 study from the OS NMA, please conduct a sensitivity analysis in which the unadjusted OS HR from this study is included.

COMPANY RESPONSE: Table A17 below summarises the available OS HR data from the GBG 26 study.

Table A17: Summary of Available Overall Survival Hazard Ratio Data From the GBG 26 Study

Description of OS data	OS HR (95% CI)	Source(s)
HR for ITT population; unadjusted for treatment switching (initial data cut with a median follow-up of 15.6 months)	0.763 (0.477-1.220)	von Minckwitz et al. (2009)
HR for ITT population; unadjusted for treatment switching (final data cut with a median follow-up of 20.7 months)	0.94 (0.65-1.35)	von Minckwitz et al. (2011); Paracha et al. (2020)
HR for patients without crossover at third-line treatment (56% of patients in the ITT population)	0.70 (NR)	von Minckwitz et al. (2011)

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not reported; OS, overall survival

The second row (highlighted in grey) is the data that we used in the sensitivity analysis. This data cut for OS matches the data used in the NMA reported by Paracha et al. (2020). Since the highlighted row represents the most up-to-date published unadjusted data for the ITT population, we used this data in the sensitivity analysis.

The results of the sensitivity analysis for the OS HR NMA, including the unadjusted OS HR data for GBG 26, are provided in the following PowerPoint files as addendum documents:

- Addendum A17a-OS ITT **FE** Results_UK_With GBG 26.pptx
- Addendum A17b-OS ITT **RE** Results_UK_With GBG 26.pptx

References – copy of references not previously provided in this submission are attached to this response document**:**

- von Minckwitz G, Du Bois A, Schmidt M, Maass N, Cufer T, De Jongh FE, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: A German Breast Group 26/Breast International Group 03-05 study. J Clin Oncol. 2009;27(12):1999-2006.
- von Minckwitz G, Schwedler K, Schmidt M, Barinoff J, Mudhenke C, Cufer T, et al. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. Eur J Cancer. 2011;47: 2273-81.
- Paracha N, Reyes A, Diéras V, Krop I, Pivot X, Urruticoechea A. Evaluating the clinical effectiveness and safety of various HER2-targeted regimens after prior taxane/trastuzumab in patients with previously treated, unresectable, or metastatic HER2-positive breast cancer: a systematic review and network meta-analysis. Breast Cancer Res Treat. 2020 Apr;180(3):597-609.

Section B: Clarification on cost-effectiveness data

Utilities

B1. PRIORITY QUESTION. Seagen Data on File. In Table 8 (Summary Table of Mean EQ-5D-3L Index Scores for Overall Population) of the Seagen 2020 report on the analysis of utility data from the HER2CLIMB trial (CS, reference 105), the row labels for statistics in column 1 (n, mean, median, min and max) do not correspond with the values reported in columns 2 and 3. Please clarify and if appropriate, provide a corrected table, including a measure of variance (standard error or confidence interval) in addition to the other statistics.

COMPANY RESPONSE: Please find the corrected values in the tables in Addendum B1.

B2. PRIORITY QUESTION. CS, section B.3.4.10. The company's base case economic analysis uses mapped EQ-5D-3L utility estimates for the tucatinib combination based on simple means of HER2CLIMB data by study arm and by time of assessment (treatment cycles 3, 5, 7, 9 and 30-days follow up). The decisions to use separate estimates by treatment arm and by treatment cycle are not supported by the descriptive analyses presented in the company submission (CS, section

B.2.6.9, Figure 11), the Seagen 2020 report or the Mueller et al. 2020 ESMO congress slides.

Please conduct an appropriate statistical analysis of the mapped EQ-5D-3L utility data from the HER2CLIMB trial to estimate pre- and post-progression utilities. This analysis should adjust for individuals' baseline utility and take account of repeated measures.

COMPANY RESPONSE: Analysis of a repeated measures model controlling for baseline utility is ongoing and will be provide by 28 May 2021. Seagen apologizes for the delay in providing these results and will provide them as soon as possible.

B3. PRIORITY QUESTION. CS, section B.3.4.8 and Excel model. Please explain how the utilities for the comparators eribulin, capecitabine and vinorelbine in the model were derived. The Evidence Review Group (ERG) notes that the model values for eribulin (0.783 pre-progression and 0.622 post-progression) are an average of the 'Crott and Briggs' and 'Lloyd et al' values as reported in Table 24 (Document B). However, these values differ from the corresponding company-preferred (Crott and Briggs) and ERG-preferred (Lloyd et al.) utilities as used in TA423 (see slide 16 of the Committee cost-effectiveness slides for TA423). In addition, the pre- and post-progression utilities for the chemotherapy comparators in the current model (0.691 and 0.651 respectively) are not reported in the company submission. In the Excel model, the company cites 'NICE 2016' as the source for the capecitabine/vinorelbine utilities, but the ERG notes that these values differ from those used in the Treatment of Physician's Choice (TPC) comparator in TA423.

COMPANY RESPONSE:

The capecitabine utilities of 0.783 and 0.651 for tumour response and progression were taken directly from TA423 Committee Papers in Table 50 of the submission and utilized in the model. The eribulin utilities were calculated as described in the TA423 FAD by averaging the mapped utilities using the company's utility estimates in Table 50 of 0.780 and 0.705 using the mapping algorithm by Crott and Briggs (2010) and 0.786 and 0.538 from Lloyd et al. (2006) for progression-free and progressed health states. The utilities in the submitted model for eribulin were 0.783 and 0.622 for progression-free and progressed health states respectively.

However, Seagen had not understood that the eribulin and TPC utilities presented in Slide 16 of the Committee cost-effectiveness slides represent the utilities utilised by NICE and the ERG in the assessment of TA423, and agree with the ERG recommendation that these utility values are the most appropriate to include in this submission. Therefore, the model was updated to include the eribulin and TPC (for capecitabine and vinorelbine) utilities from Committee slide 16 and the updated results are presented below in Table B3a and base case and scenario ICER results summarised in Table B3b.

Table B1a: Utilities summary from company submission and proposed ERG utilities

Tucatinib submission						
Health state	**Eribulin**				**Capecitabine and vinorelbine**	
	TA423	**Lloyd et al. (2006)**	**Utilities in submitted model**	**Source**	**Value**	**Source**
Progression-free	0.780	0.786	0.783	TA423 Committee Papers, manufacturer's submission Table 50 and Lloyd et al. (2006)	0.783	TA423 Committee Papers Table 50
Progressed	0.705	0.538	0.622	TA423 Committee Papers Table 50 and Lloyd et al. (2006)	0.651	TA423 Committee Papers Table 50
ERG recommendations based on TA423 1st Committee slides						
Health state	**ERG**		**Company**		**Utilities in updated final tucatinib model per ERG recommendation**	
	Eribulin	**TPC[a]**	**Eribulin**	**TPC[a]**	**Eribulin**	**TPC[a]**
Progression-free	0.706	0.701	0.706	0.701	0.706	0.701
Progressed	0.496	0.496	0.679	0.679	0.496	0.496

ERG, Evidence Review Group; TPC, treatment of physician's choice

[a] TPC denotes capecitabine and in this submission, vinorelbine.

Table B3b: base case and scenario analyses results – PAS price

No	Scenario	ICER (new)	ICER (old)
Base case		£38,206	£46,756
1	[redacted]	[redacted]	[redacted]
2	Tucatinib combination utilities: EQ-5D-5L	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	Treatment duration: Restricted mean treatment exposure	[redacted]	[redacted]
7	Comparator: Vinorelbine	[redacted]	[redacted]
8	Comparator: Capecitabine	[redacted]	[redacted]
9	Blended ICER: Capecitabine – [redacted]% Eribulin – [redacted] % Vinorelbine – [redacted]%	[redacted]	[redacted]

EQ-5L-5D, EuroQoL 5 Dimensions 5-Levels; HR, hazard ratio; ICER, incremental cost effectiveness ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

Time to treatment discontinuation

B4. CS, section B.3.3.5 and Appendix L. The company submission states that the methods for estimating time to treatment discontinuation for the HER2CLIMB study arms and for other external comparators are described in Appendix L. However, there is no mention of the approach used in Appendix L. Please explain the methods for fitting survival curves to the HER2CLIMB data and justify the distribution that was used in the company's base case (flexible Weibull with 2 knots).

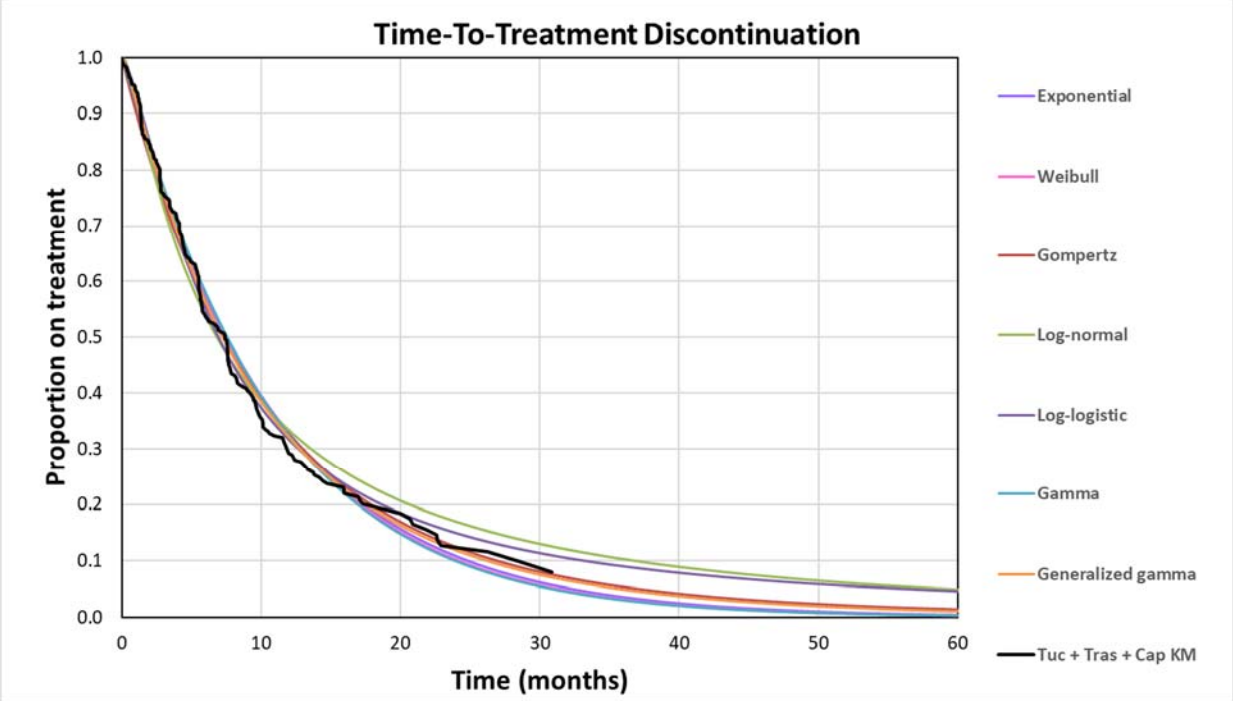
COMPANY RESPONSE: A range of parametric and flexible spline-based survival models were fitted to time-to-treatment discontinuation (TTD) data from HER2CLIMB for each treatment arm and extrapolated beyond the trial time horizon. The TTD analyses were not summarised in Appendix L; we have provided the requested information in this response.

Figure B4a presents extrapolations for the standard parametric models fitted to the HER2CLIMB TTD data for tucatinib + trastuzumab + capecitabine. The log-logistic and log-normal models did not give a good visual fit.

Figure B4b presents extrapolations for the flexible spline-based models fitted to the HER2CLIMB TTD data for tucatinib + trastuzumab + capecitabine. All models gave a good visual fit with the Kaplan-Meier estimates.

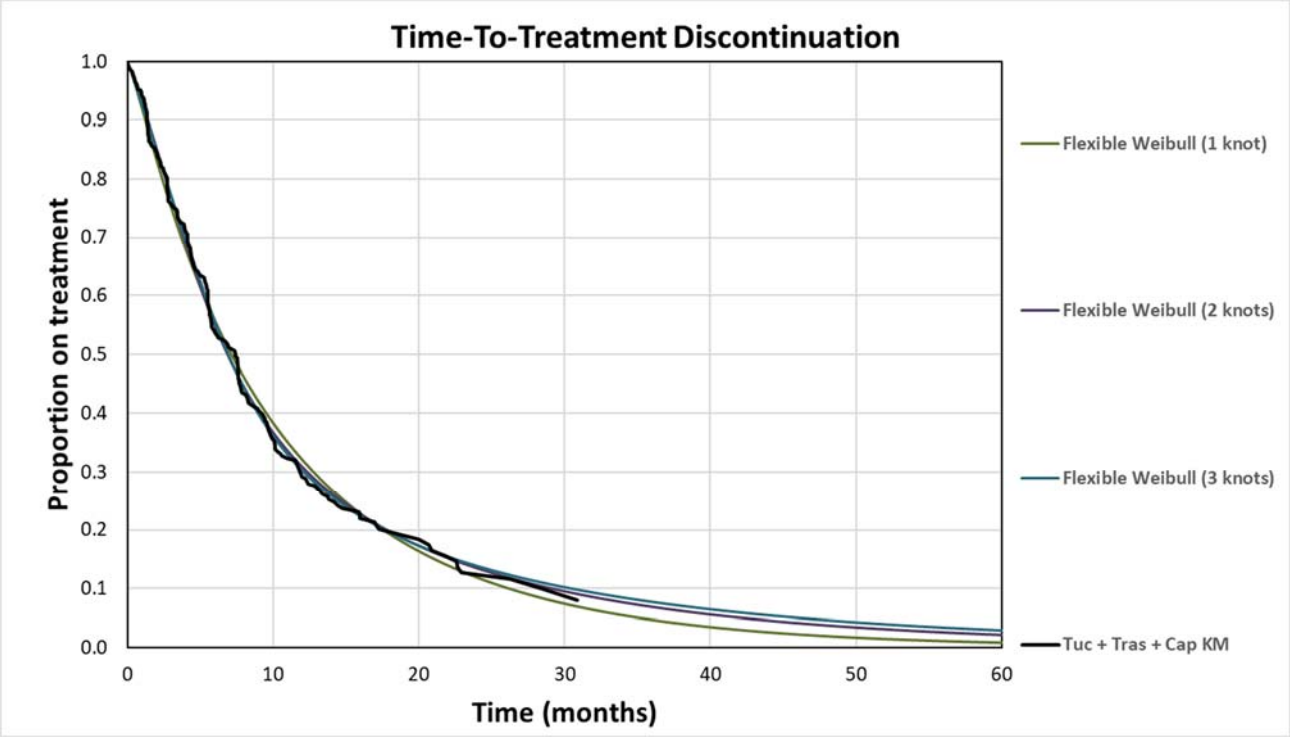
Table B4c presents the model fit statistics (AIC and BIC) from all models fitted to the HER2CLIMB TTD data for tucatinib + trastuzumab + capecitabine.

Figure B4a: Standard Parametric Models Fitted to the HER2CLIMB TTD Data: Tucatinib + Trastuzumab + Capecitabine



Tuc + Tras + Cap KM, tucatinib + trastuzumab + capecitabine Kaplan-Meier; TTD, time-to-treatment discontinuation

Figure B4b: Flexible Spline Models Fitted to the HER2CLIMB TTD Data: Tucatinib + Trastuzumab + Capecitabine



Tuc + Tras + Cap KM, tucatinib + trastuzumab + capecitabine Kaplan-Meier; TTD, time-to-treatment discontinuation

Figure B4c: Model Fit Statistics for the Models Fitted to the HER2CLIMB TTD: Tucatinib + Trastuzumab + Capecitabine

Model	AIC	BIC
Exponential	1933.90	1937.90
Weibull	1935.52	1943.52
Gompertz	1934.50	1942.50
Log-normal	1949.87	1957.87
Log-logistic	1929.06	1937.06
Gamma	1934.72	1942.72
Generalised gamma	1932.30	1942.72
Flexible Weibull (1 knot)	1933.22	1939.22
Flexible Weibull (2 knots)	1930.12	1934.13
Flexible Weibull (3 knots)	1930.96	1932.96

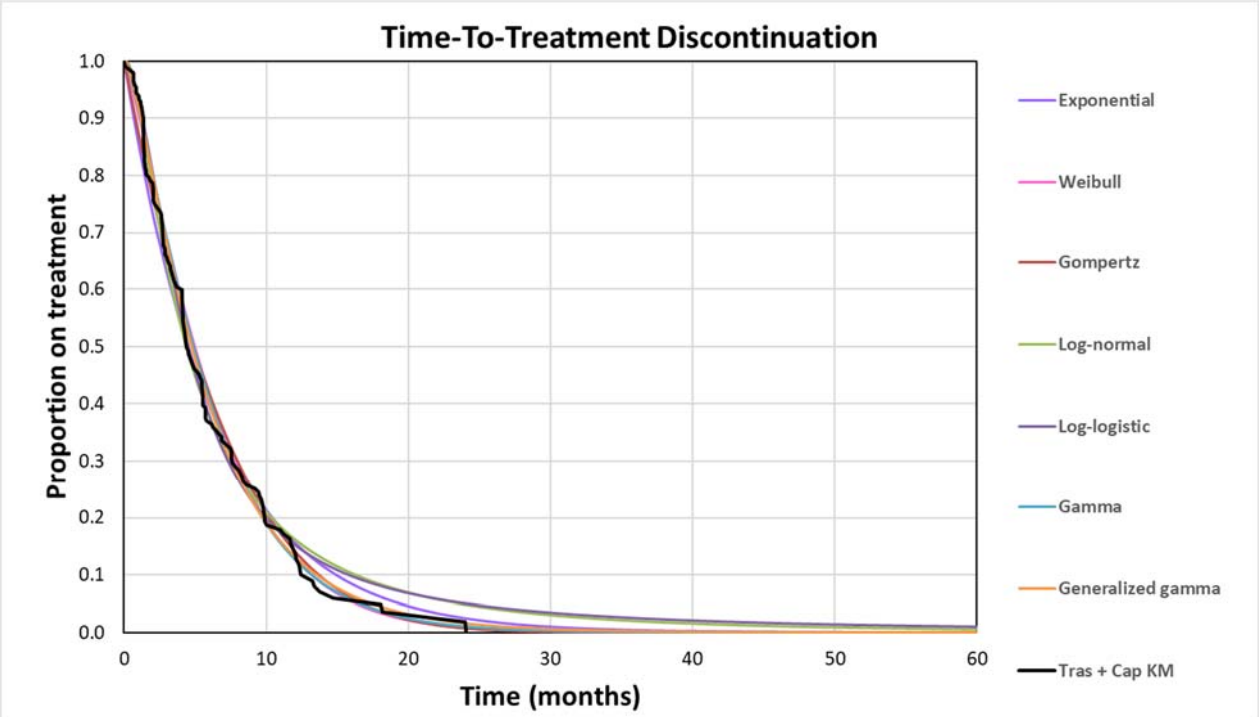
AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time-to-treatment discontinuation

Figure B4d presents extrapolations for the standard parametric models fitted to the HER2CLIMB TTD data for trastuzumab + capecitabine. The log-logistic and log-normal models did not give a good visual fit with the Kaplan-Meier estimates.

Figure B4e presents extrapolations for the flexible spline-based models fitted to the HER2CLIMB TTD data for trastuzumab + capecitabine. All models gave a good visual fit with the Kaplan-Meier estimates.

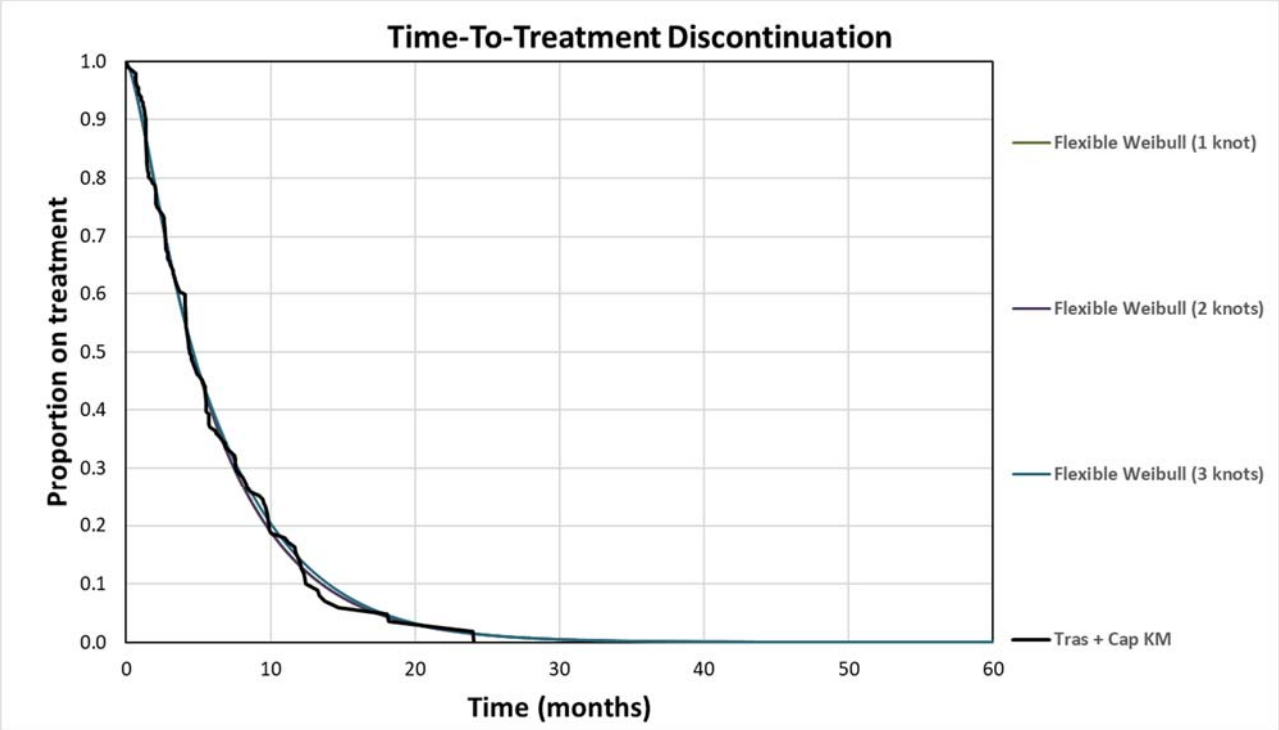
Figure B4f presents the model fit statistics (AIC and BIC) from all models fitted to the HER2CLIMB TTD data for trastuzumab + capecitabine.

Figure B4d: Standard Parametric Models Fitted to the HER2CLIMB TTD Data: Trastuzumab + Capecitabine



Tras + Cap KM, trastuzumab + capecitabine Kaplan-Meier; TTD, time-to-treatment discontinuation

Figure B4e: Flexible Spline Models Fitted to the HER2CLIMB TTD Data: Trastuzumab + Capecitabine



Tras + Cap KM, trastuzumab + capecitabine Kaplan-Meier; TTD, time-to-treatment discontinuation

Figure B4f: Model Fit Statistics for the Models Fitted to the HER2CLIMB TTD: Trastuzumab + Capecitabine

Model	AIC	BIC
Exponential	976.45	979.73
Weibull	967.90	974.46
Gompertz	974.37	980.92
Log-normal	978.29	984.85
Log-logistic	970.74	977.29
Gamma	965.96	972.52
Generalised gamma	967.09	972.52
Flexible Weibull (1 knot)	966.86	971.42
Flexible Weibull (2 knots)	968.84	971.41
Flexible Weibull (3 knots)	970.53	971.10

AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time-to-treatment discontinuation

The base case survival models were selected based on assessment of fit statistics and visual fit to the trial data. The log-normal and log-logistic models were ruled out because they did not give a good visual fit with the Kaplan-Meier estimates. Based

on the Burnham and Anderson rule of thumb, a model with AIC and BIC difference less than 4 with respect to the lowest AIC and BIC values was considered appropriate. Moreover, disease progression is the primary reason for treatment discontinuation; therefore, TTD is expected to follow a similar shape to the PFS curve. The flexible Weibull (2 knots) model was selected for both arms because a) it had amongst the lowest model fit statistics and met the Burnham and Anderson rule of thumb criterion, and b) to align with the most likely PFS survival model recommended in the HER2CLIMB survival analysis report (presented in Appendix L of the company submission).

TTD for external comparators

No TTD data were available for the external comparators. TTD for external comparators, utilising median treatment duration values, was estimated using the exponential function to provide a more valid comparison with the TTD survival analysis available for tucatinib combination therapy.

Reference: Burnham K, Anderson D. Model selection and multimodel inference: a practical information-theoretic approach; 2004.

External data sources for survival extrapolations

B5. Appendix L. Section 5.1 refers to a manual search conducted to identify external data sources for the survival extrapolations. Please explain how these searches were conducted and justify why a systematic search strategy was not used.

COMPANY RESPONSE: A clinical SLR was conducted to identify survival data from RCTs in patients with HER2+, unresectable locally advanced or metastatic breast cancer who have had one or more prior anti-HER2 therapies. This SLR served to identify data to inform the NMA, and long-term RCT evidence that could inform survival extrapolation beyond the HER2CLIMB follow up. A further targeted review was also conducted to identify long-term observational data that might also be suitable to inform the extrapolation. However, ultimately, the data considered most appropriate was from an RCT identified by the SLR (Kaufman et al., 2015). The process by which suitable external data was identified and selected is described in Section 5 of the survival analysis report.

B6. Appendix L. Please provide demographic and prognostic information as presented in Table 4 for the other external data sources listed in Table 1.

COMPANY RESPONSE: The demographic and prognostic information for all external data sources listed in Table 1 are provided in a table in Addendum B6-Study and Sample Size_for B6.docx.

Searches conducted for economic modelling

B7. CS, sections B.3.1, B.3.4.3 and B.3.5. The company submission states that the economic search was conducted on 11/12/2019 and that an updated SLR is expected on 7 May 2021. Please provide the results of the updated searches.

COMPANY RESPONSE: The results of the updated searches are provided in Addendum B7-0305299_eSLR update_Final Report_12 May_clean.docx.

Section C: Textual clarification and additional points

C1. CS, section B.2.5, Table 7. In the quality assessment of HER2CLIMB, in response to the question 'Were the care providers, participants and outcome assessors blind to treatment allocation?', the company submission states 'Yes – the first part of the study was carried out blindly…'. Please clarify what is meant by 'the first part of the study.

COMPANY RESPONSE: The first part of HER2CLIMB means the period from enrolment to primary study readout, when patients were blinded for the treatment they were randomly assigned to receive. As shown in HER2CLIMB protocol version 11 and the summary of differences between version 10 and 11 (Addendum A1c and Addendum A1d), after the primary readout of the trial, the protocol was amended to allow patients to either continue receiving (tucatinib arm) or switch to the tucatinib combination (placebo arm). This open-label extension period is still ongoing.

C2. CS, section B.2.5, Table 7 and Appendix D, Figure 11. In the quality assessment of HER2CLIMB, in response to the question 'Were there any unexpected imbalances in dropouts between groups?', the company submission states 'No – balanced, low rates of dropouts were observed in both treatment arms: 23/404 (5.7%) patients discontinued tucatinib and 6/197 (3.0%) patients discontinued

placebo'. Please clarify what these numbers refer to as they do not tally with the CONSORT diagram in Figure 11 (Appendix D).

COMPANY RESPONSE: The values mentioned in the question are the rates of adverse events leading to discontinuation whilst the CONSORT diagram shows total rates of discontinuation due to any reason in the tucatinib arm (286/410, 70%) and placebo arm (170/202, 84%).

C3. CS, section B.3.6.1, Table 33. In the economic model, the company uses the mean body weight (69.5kg) and body surface area (1.80m^2) for cost calculations. These figures are referred to as relating to the HER2CLIMB study population, but they are not referenced in section B.3.3.1, the Murthy 2020 paper or the CSR provided with the submission. Please provide the source for these figures.

COMPANY RESPONSE: The mean body weight and body surface area values were sourced from a separate analysis of HER2CLIMB data and are provided in Addendum C3-t-base-vs_BSA and weight.rtf.

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Breast Cancer Now
3. Job title or position	Policy Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Care and Breast Cancer Now merged on 1 April 2019 to create one charity – Breast Cancer Now. From research to care, our charity has people affected by breast cancer at its heart – providing support for today and hope for the future. United, we'll have the ability to carry out even more world-class research, provide even more life-changing support and campaign even more effectively for better services and care. All of our funding comes from the public and our partners.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	In the last 12 months, Breast Cancer Now has received the following funding from manufacturers listed in the appraisal matrix. Please note, Breast Cancer Now does not receive any pharmaceutical funding for our Policy, Evidence and Influencing work. Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs. <u>Company</u> Seagen: at the time of writing this submission, we have submitted a grant proposal to Seagen and are awaiting an update. <u>Possible comparator companies</u> Roche – March 2020, £44,121, grant towards our Living with Secondary Breast Cancer Service - May 2020, £25,000, grant towards out Helpline

If so, please state the name of manufacturer, amount, and purpose of funding.	- November 2020, £41,555, grant towards our online Living With Secondary Breast Cancer Service Pfizer – May 2020, £10,000 grant towards our helpline - November 2020, £40,9000 grant towards our personalised support programme
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we utilise our various networks of those affected by breast cancer to gather information about patient experience.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Secondary (also known as advanced, metastatic or stage 4) breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones or liver. There is no cure for secondary breast cancer. Treatment aims to control and slow the spread of the cancer, relieve any symptoms, and maintain health, wellbeing and a good quality of life for as long as possible. A patient can be diagnosed initially with secondary breast cancer (de novo), or they can develop it months or years after treatment for their primary breast cancer has ended.

	Some breast cancer cells have a higher than normal level of a protein called HER2 on their surface, which stimulates them to grow. This is known as HER2 positive breast cancer. Around one in five invasive breast cancers are HER2 positive. Being diagnosed with secondary breast cancer is extremely difficult to come to terms with both for patients and their family and friends. Everyone's experience of being diagnosed and living with secondary breast cancer is different. Many people will feel overwhelmed, upset and shocked or anxious, as well as angry and alone. The uncertainty of living with secondary breast cancer can be the hardest part for many people, with people telling us it has fundamentally changed their perspective on life and they feel they are living on borrowed time. These common feelings can have a huge impact on people's mental health. A diagnosis of secondary breast cancer can also affect people's relationship with those closest to them which can be particularly difficult to cope with. People living with secondary breast cancer have told us: "How confused and scared I am all the time; even when I'm happy it's always there in the back of your mind". "It is scary. I am permanently scared about my future and what my family will have to deal with without me". As well as the huge emotional toll of living with secondary breast cancer, patients often have to cope with numerous practical concerns, such as managing their day to day activities, which may include working, household and parental responsibilities as well as travelling to and from hospital appointments. People living with secondary breast cancer have shared the following: "It totally and completely affects your life after diagnosis. Endless doctors' appointments can begin to wear you down in no time at all".

	"My treatment goes on for as long as it works and this is my life now. Constant 'scanxiety', endless hospital appointments and the struggle with day to-day living that others either don't see or understand". The symptoms of secondary breast cancer can vary depending on where the cancer has spread to. For example, if it has spread to the bones the main symptoms can include pain in the bones or bone fractures. If breast cancer has spread to the lungs, someone may experience symptoms such as breathlessness or continuous pain and tightness in the chest. For people who have secondary breast cancer in the brain, symptoms may include seizures, nausea and vomiting, pain and fatigue which can have a significant toll on people's physical and emotional wellbeing. Also all breast cancer treatments can cause some side effects and although everyone reacts differently to drugs, for those people who experience more side effects than others, it can cause a significant impact on their day to day lives and health and wellbeing. Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients when considering their treatment decisions.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Although in recent years there has been the welcome introduction of new HER2 targeted therapies in the first and second line setting for patients with HER2 positive secondary breast cancer, at the time of writing this submission (March 2021), there are currently no targeted treatments recommended for use after 2 or more prior lines of treatment. This can be incredibly agonising for those who have already progressed beyond these treatment options. The exact treatment for patients who have already received 2 or more anti-HER2 therapies may differ. Eribulin is an option which may be considered as it is recommended by NICE for treating patients with secondary breast cancer after 2 or more chemotherapy regimens. Other chemotherapies may also be considered, including capecitabine or vinorelbine. Patients we have spoken to currently receiving Kadcyla, have told us that they fear progressing on Kadcyla as the next option is chemotherapy alone rather than

	targeted treatments and they are concerned about some of the symptoms they may experience with these chemotherapies. Clinical experts have also suggested the efficacy of chemotherapy alone is limited in this setting. Trastuzumab deruxtecan is currently being assessed for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies which we expect a decision on shortly. This could significantly change the landscape of treatment for patients who progress on Kadcyla.
8. Is there an unmet need for patients with this condition?	Yes, there is an urgent need for new and clinically-effective treatments for pre-treated patients who progress on current treatments. There have been welcome treatment developments for HER2 positive secondary breast cancer including pertuzumab in combination with trastuzumab and docetaxel as a first line treatment and trastuzumab emtansine in the second line setting. However, at the time of writing this submission (March 2021) there remains a lack of targeted treatment options for third and later lines when these initial treatments stop working. There is also a significant unmet need in the treatment options for patients whose breast cancer has spread to the brain.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	We consider this treatment to be an innovative oral tyrosine kinase inhibitor that could provide a very important new treatment option to pre-treated HER2 positive secondary breast cancer patients. The HER2CLIMB study demonstrated an improvement in progression free survival (PFS) with this triple treatment combination providing a median PFS of 7.8 months compared to 5.6 months for trastuzumab with capecitabine. We know patients value this extra time, as delaying disease progression means more quality time to spend with their relatives and friends. Importantly, data at this stage also suggests there could be an improvement in overall survival with this triple treatment combination extending survival by on average by 4.5 months versus trastuzumab and capecitabine. Maintaining a high quality of life for as long as possible is currently the best outcome for this patient group

	as secondary breast cancer remains incurable. The above outcomes can also have a positive impact on patients' emotional wellbeing and mental health, as it may mean that a patient can continue doing the activities they enjoy and leading a more or less normal daily life. For example, for some people it is important to be able to continue working which the patient quote below highlights. Another important outcome is bringing some comfort to patients their relatives and friends. This in turn could help to reduce any stress the patient is experiencing as a result of worrying about any burden placed on their friends and family. When breast cancer spreads to the brain, it is incredibly hard to treat. New treatments such as tucatinib (in combination with trastuzumab and capecitabine) which may benefit a group of patients with brain metastases are desperately needed. Results at this stage suggest the median duration of PFS for this subgroup of patients is 7.6 months versus the placebo arm of 5.4 months. In terms of other advantages of this treatment - two components of this triple combination (tucatinib and capecitabine) are tablets which patients can take independently at home which makes it very convenient. With patients then needing to travel to hospital to receive the trastuzumab every 3 weeks (either subcutaneously or intravenously). A patient who has received this treatment combination told us: "I was diagnosed with secondary breast cancer in April 2017 with spread to my lymph nodes and lungs. I was treated with Herceptin, Pertuzumab and docetaxel for 6 months before I had a pericardial effusion and had to switch to Kadcyla for a year, but after spread to my brain in October 2018 and targeted gamma knife radiotherapy to the brain I was running out of targeted treatment lines. This was when I was lucky enough to get accepted on the HER2 climb trial of capecitabine, herceptin and tucatinib in January 2019. 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." The patient also told us;

	"The treatment is quick. Every 3 weeks, minimal side effects, can take tablets at home. It has shrunk all my tumours to barely measurable after 6 weeks and I have remained stable for the past 2 years. Prior to this, other treatments did not work for me for very long (6-9 months) and this is the longest I have been on the same treatment - it has 100% prolonged my life where other treatment failed. I have been on this treatment since January 2019. I am able to lead a normal life, I work part time, I do get tired occasionally. I can't run now due to feet issues from capecitabine. But compared to iv treatment where I am usually house bound, have no energy, can't work - this treatment not only has prolonged life it has allowed me to live as normal a life as possible."
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	This treatment is associated with some increased side effects compared to trastuzumab with capecitabine alone. In the HER2CLIMB trial, the most common side effects experienced by patients taking the triple combination included diarrhoea, hand-foot syndrome, nausea, fatigue and vomiting. Every treatment for breast cancer has some side effects and each patient's situation will be different, with side effects affecting some patients more than others. Patients' willingness to take treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice with the support of their clinician regarding treatment options. The administration method of a particular treatment can also be important to patients. Whilst some components of this treatment combination are taken orally at home, patients would also need to attend hospital for trastuzumab to be administered. However, for many patients, any inconvenience caused by needing to attend hospital for the trastuzumab cycles will be outweighed by the benefits this treatment can bring. A patient with experience of this treatment combination told us:

	"I have found the side effects to be minimal. To start with had stomach issues for first few cycles but now to totally manageable and I don't take any other medication to counter act any side effects. Also have issues with feet and hands but this is from capecitabine (and I just moisturise twice daily and have had one dose reduction in the 2 years when feet got really bad). Otherwise no major disadvantages that I can think of. Tucatinib has to be kept in fridge but that is only an issue if going away somewhere."
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is particularly welcoming to see a treatment which could benefit patients with brain metastases as mentioned previously in this submission.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.

Other issues	
13. Are there any other issues that you would like the committee to consider?	Not at this stage.
14. Which treatments are used at the third line setting for people with HER2-positive unresectable locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies in the NHS?	The exact treatment for patients who have already received 2 or more anti-HER2 therapies may differ. At the time of writing this submission (March 2021) the following treatments may be given: eribulin is an option which may be considered as it is recommended by NICE for treating patients with secondary breast cancer after 2 or more chemotherapy regimens. Other chemotherapies may also be considered, including capecitabine or vinorelbine. In some areas, patients may receive trastuzumab with capecitabine in the third line setting. Trastuzumab is not licensed with chemotherapy for use as a later line treatment for patients who have progressed on earlier treatments such as trastuzumab emtansine (Kadcyla). However, off-label prescribing of trastuzumab may happen in some circumstances, so access to this treatment is variable. As set out in a recent paper (T.Robinson, C.Palmieri, J.P Braybrooke, Trastuzumab beyond progression in advanced HER2 positive breast cancer: UK practice now and in the future, Clinical Oncology), of the centres that responded to the research, just over 50% of centres were prescribing trastuzumab beyond progression. Furthermore, a new targeted treatment, trastuzumab deruxtecan, is also in the final stages of being assessed by NICE for treating HER2 positive unresectable or secondary breast cancer after 2 or more anti-HER2 therapies. We expect a decision will have been announced by the time of this committee meeting which could result in a significant change in the landscape for third line treatments.
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission:	

- A diagnosis of incurable secondary breast cancer can cause considerable anxiety and fear for patients and their loved ones, impacting on all aspects of their lives. The uncertainty can be the hardest part for many people.
- There is a significant unmet need for later line treatments for secondary breast cancer. This treatment could add to the options available for patients with this type of breast cancer which is incurable.
- Tucatinib in combination with trastuzumab and capecitabine would be a significant new treatment option for patients with brain metastases and has shown promising benefits.
- There are some increased side effects with this treatment combination, however, a patient with experience of this treatment finds them to be minimal and the treatment enables her to carry on having a normal life. It would be important that the risks and benefits were discussed with the patient and patients may see that the benefits outweigh the potential of side effects.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NCRI-ACP-RCP-RCR

3. Job title or position	Interim RCP registrar
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NCRI-ACP-RCP-RCR
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.) 7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Background Approximately 15–20% of breast cancers are human epidermal growth factor receptor-positive (HER2-positive), which is associated with worse survival outcomes as compared to oestrogen receptor (ER) positive, HER2-negative breast cancer. Specifically, metastatic breast cancer refers to breast cancer which has spread beyond the breast and nearby lymph nodes to other organs in the body; and unresectable locally advanced means that the cancer cannot be treated by surgery. Current treatments for advanced breast cancer aim to relieve symptoms, prevent progression, prolong survival and maintain a good quality of life with few adverse events. Targeting of the HER2 receptor with the humanized monoclonal antibody trastuzumab inhibits breast cancer cell proliferation, survival and angiogenesis. The gain in progression-free survival (PFS) and overall survival (OS) with trastuzumab-based regimens have profoundly changed the natural history of advanced HER2-positive breast cancer, with median survival in metastatic disease now reported in excess of 57 months. Decision making in HER2-positive unresectable or metastatic breast cancer depends on 1) whether the patient has received trastuzumab previously; and 2) time elapsed since the last dose of trastuzumab. NICE technology appraisal guidance (509) recommends patients with HER2-positive unresectable or metastatic breast cancer

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	who have not had previous anti-HER2 treatment or chemotherapy for their metastatic disease are candidates for first-line treatment with a taxane, trastuzumab and pertuzumab (humanized monoclonal antibody against subdomain II of the extracellular domain of HER2, the blockade of which inhibits the most potent heterodimer HER2/HER3). The results of the PERUSE clinical trial suggested that paclitaxel is no less effective than docetaxel, and that it may be less toxic. NICE technology appraisal guidance (34) recommends trastuzumab with paclitaxel as an option for people with tumours expressing HER2 who have not received chemotherapy for metastatic breast cancer and in whom anthracycline is not appropriate. For patients who have progressed while on (neo)adjuvant trastuzumab or less than 6 months after its use or, alternatively, who progressed after receiving it first-line for advanced HER2-positive breast cancer, NICE technology appraisal guidance (458) recommends trastuzumab emtansine (TDM-1). There is no current recognized standard of care third-line therapy option for HER2-positive advanced breast cancer. Patients with HER2-positive advanced breast cancer, including those with brain metastases, need therapies that improve clinical outcomes and have unmet medical need. A number of new agents have recently emerged in this setting. Such agents include tucatinib, trastuzumab deruxtecan, and neratinib.
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care? 10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be	As discussed above, there is no uniformly accepted standard of care after THP and T-DM1. After progression on T-DM1, patients have several therapeutic options, but none have shown an overall survival (OS) benefit. NICE clinical guideline (CG81) recommends that patients may receive treatment with non-targeted chemotherapies such as capecitabine or vinorelbine. NICE technology appraisal guidance 423 recommends eribulin for locally advanced or metastatic breast cancer after 2 or more lines of chemotherapy regimens. In addition, lapatinib is a HER2 targeted treatment which in combination with capecitabine or trastuzumab is also licensed for use at this point in the treatment pathway, although this is not funded through NICE and is therefore not available for NHS patients. <u>The technology</u> Tucatinib is a novel oral TKI that is highly selective for the kinase domain of HER2 with little inhibitory effect on EGFR, with activity in heavily pre-treated HER2-positive MBC. It is given orally. Combining tucatinib with trastuzumab has demonstrated increased apoptosis of HER2-expressing breast cancer cells in vitro and antitumor activity in mouse models compared with either drug alone. Tucatinib with trastuzumab and capecitabine does not currently have marketing authorisation in the UK for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies. Tucatinib has been studied in a randomised controlled trial, HER2CLIMB. In the HER2CLIMB study, 612 patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1 were randomized in a 2:1 ratio to receive either tucatinib (300 mg orally twice daily continuously) or placebo, in combination with trastuzumab and capecitabine (1,000mg/m^2 Days 1–14 of a 21-day cycle). Tucatinib in combination with trastuzumab and capecitabine improved median PFS (7.8 m vs 5.6 m; 33.1% vs 12.3% had not progressed at 1 year, HR 0.54, 95% CI, 0.42–0.71, p < 0.001) and median OS (21.9 m vs 17.4 m; 44.9% vs 26.6% alive at 2 years, HR 0.66; 95% CI, 0.50 to 0.88; P = 0.005) in comparison with trastuzumab, capecitabine and placebo. The triplet regimen reached a response rate of 40.6% in a population exposed to a median of three previous lines of treatment. The most common side effects associated with tucatinib were diarrhea, oral mucositis, hand-foot syndrome, nausea, fatigue and vomiting. Grade 3 or more events (55.2% v 48.7%) and grade 3 transaminases elevations were more common in the tucatinib combination arm. Tucatinib was discontinued more often than placebo (5.7% vs 3%) and capecitabine was dis- continued more often in the tucatinib arm (9.8% vs 9.1%). Based on these results, on 17th April 2020 the FDA approved tucatinib in combination with trastuzumab and capecitabine for the treatment of patients with advanced

used? (For example, primary or secondary care, specialist clinics.) • What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) 11. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care? 12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting. This allows clinicians to potentially utilize this approach early on for patients with CNS progression or rapid relapse following use of trastuzumab, pertuzumab, and T-DM1 in the curative intent setting. **HER2-positive advanced breast cancer with brain metastases** The incidence of brain metastasis is clinically significant in advanced HER2-positive breast cancer with approximately 50% of patients developing brain metastasis. Median survival after brain metastasis is 25–27 months. Despite brain metastases being so common in this breast cancer subtype, these patients have historically been excluded from trials. Progressive CNS disease with controlled systemic disease is also a frequent scenario; and though little data are available, these patients receive local treatment and continue the same systemic regimen, whenever possible. Though monoclonal antibodies, such as trastuzumab or TDM-1 have shown to have some activity in the CNS, TKIs are likely to have be superior as they are more likely to penetrate the blood-brain barrier than antibodies and have demonstrated activity against CNS metastasis in a number of studies. It is important to note, however, that lapatinib failed to prevent CNS relapses in CEREBEL (a phase III, randomized, open-label study of lapatinib plus capecitabine versus trastuzumab plus capecitabine in patients with HER2-Positive metastatic breast cancer). Furthermore, in the tucatinib arm, 40.6% of patients experienced an objective response in the brain, vs 22.8% in the placebo arm ($p < 0.001$). These data match the previous 6.7 m PFS and 42% objective response for brain metastases with this triplet seen in a phase Ib trial. HER2CLIMB is the pivotal study for this clinically relevant scenario in that it included 48% of patients with brain metastasis; this included 19% with treated and stable brain metastases and 28% with active brain metastases (treated and progressing or untreated lesions). Importantly, among patients with brain metastases, PFS was 24.9% at 1 year with tucatinib compared with 0% with placebo (7.6months vs 5.4months; HR 0.48, 95%CI 0.34–0.69). In patients with previously untreated brain metastasis, median OS was 20.7 vs 11.6 months, HR 0.49, 95% CI 0.30-0.80, p= 0.004. Time between first and second brain progression suggests that tucatinib could delay brain progression (median time to progression 7.6 vs 3.1 months, HR 0.33, 95% CI 0.13-0.85, p= 0.02)

	These data are compelling in favouring tucatinib as the TKI of choice given the OS benefit, but it is noteworthy that Grade ≥3 adverse events occurred in 55.2% of patients on the HER2CLIMB trial. Additionally, whilst this data on tucatinib is provocative, foregoing local treatment (such as resection or stereotactic radiosurgery (SRS) for a systemic strategy upfront cannot be considered standard of care until a formal comparison of both strategies is made in a prospective trial. Conversely, for patients who are not candidates for further local therapy, a TKI-based regimen especially with tucatinib triple therapy is a reasonable approach. FDA approval for tucatinib is the first approval which specifies patients with brain metastases in their indication statement. This is appropriate for a number of reasons: 1) patients with brain metastases accounted for almost half of the study population; HER2CLIMB applied expanded brain metastases eligibility criteria including patients with progressive or untreated lesions; PFS brain metastasis endpoint showed benefit in this subgroup; and OS benefit consistent with the overall ITT population was demonstrated for patients with brain metastases. Although tucatinib is the only agent to report an OS benefit in this setting, there are other newer agents that have emerged as possible competitors, namely trastuzumab deruxtecan, Margetuximab and neratinib: 1: Trastuzumab-deruxtecan (DS-8201): DS-8201 showed a response rate of 60.9% in heavily pre-treated HER2-positive population (with a median of 6 previous lines for metastatic disease) and a median PFS of 16.4 months. 86.2% of treated patients were alive at 12 months. 2. Neratinib. Neratinib + capecitabine improved PFS (5.6 m vs 5.5 m; HR 0.76, 95%CI 0.63–0.93) in comparison with lapatinib plus capecitabine in the NALA trial. In a landmark analysis showed, PFS curves began to separate with 6-month PFS rates of 47% versus 38% and 1-year rates of 29% versus 15%. The coprimary endpoint of OS was not met (21 months vs 18.7 months; HR 0.88, 95%CI 0.72–1.07). The FDA granted approval for the neratinib and capecitabine combination in March 2020 for patients previously exposed to at least 2 previous lines of anti-HER2 therapy. 3. Margetuximab. In the SOPHIA trial, margetuximab with chemotherapy versus trastuzumab and chemotherapy in a population previously treated with standard first and second line therapies, demonstrated a PFS improvement (5.8 months vs 4.9 months; HR 0.76, 95%CI 0.59–0.98), but no OS gain (21.6 months vs 19.2 months; HR 0.89, 95%CI 0.69–1.13). FDA approval is awaited.

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The tucatinib combination will provide a new standard of care with potential for OS benefit even after progression in the second line setting for metastatic breast cancer. Having an established standard of care for the third line setting will make decision making much easier for oncologists and patients. The triple therapy is easy to administer and monitoring required is already part of clinical follow up pathways in this setting; e.g. routine clinical follow up , blood tests and mid treatment response imaging.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Imaging after every 3-4 cycles of therapy is part of standard of care monitoring and will continue to be part of this treatment pathway

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? 16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, this technology can be considered to be innovative in its potential to make a significant and substantial impact on health-related benefits. The tucatinib label specifies that patients should have received one or more prior HER2-based regimens in the metastatic setting which reflects the HER2CLIMB population. The protocol required previous trastuzumab, pertuzumab, and T-DM1 but did not specify the setting (early or metastatic) and did not stipulate a number for prior lines of therapy. The approved indication for tucatinib does not list prior therapies by name to allow for flexibility and ensure continued access if the treatment landscape for HER2-positive MBC changes in the future.
• Is the technology a 'step-change' in the management of the condition?	Yes

• Does the use of the technology address any particular unmet need of the patient population?	Yes. The treatment after 1st (trastuzumab, herceptin and taxane) and 2nd (TDM1) line therapy is suboptimal compared with the use of the tucatinib combination as described above, particularly in those patients with brain involvement.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The gastrointestinal tract and liver were major target organs of toxicity in rat and monkey repeat-dose toxicology studies. This is consistent with the adverse event profile in human clinical trials. Tucatinib can cause fetal harm when given to pregnant women and may also impair fertility in males and females based on animal findings. In the bacterial reverse mutation assay, tucatinib was not mutagenic and was not clastogenic in the in vitro chromosome aberration test or the in vivo mouse bone marrow micronucleus assay. On the basis of drug–drug interaction studies, patients are recommended to avoid concomitant use of strong CYP2C8 inhibitors with tucatinib; the recommended dose for tucatinib is 100 mg twice daily if concomitant use of a strong CYP2C8 inhibitor is unavoidable. The most common adverse event in HER2CLIMB was diarrhoea with 81% of patients on the tucatinib arm, compared with 53% of patients on the control arm. Diarrhoea is a toxicity associated with both tucatinib and capecitabine. 12% of patients on the tucatinib arm developed grade 3 diarrhoea, and 0.5% of patients had grade 4 diarrhoea. The 2 patients who developed grade 4 diarrhoea had sequelae such as dehydration, hypotension, and acute kidney injury, and ultimately died. There was no requirement for antidiarrheal prophylaxis, but 66% of patients on the tucatinib arm used an anti-diarrheal at some point on study. Hepatoxicity was a safety signal of concern throughout the tucatinib development program with a pattern of predominantly mild-to- moderate transaminase elevation. There were no cases of tucatinib-associated liver failure or hepatotoxicity leading to death in the safety database. The tucatinib USPI lists hepatotoxicity under Warnings and Precautions and recommends monitoring liver tests at baseline and every 3 weeks and as clinically indicated, with prompt dose modification if needed. Diarrhoea, hepatotoxicity, and embryo-fetal toxicity are labelled as Warnings and Precautions. The tucatinib label includes recommendations for dose monitoring and modification. These toxicities are manageable with careful oversight.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Important outcomes were measured: PFS, PFS of subgroup of patients with presence or history of brain metastasis at baseline, ORR in patients with measurable disease, OS and safety profiles.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials	NA

but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA423]?	
21. How do data on real-world experience compare with the trial data?	Currently not available for tucatinib.
Equality	
22a. Are there any potential equality issues that should be	This drug combination is available in other countries, and therefore UK patients are disadvantaged

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23. Which treatments are used at the third line setting for people with HER2-positive unresectable locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies in the NHS?	NICE clinical guideline (CG81) recommends that patients may receive treatment with non-targeted chemotherapies such as capecitabine or vinorelbine. NICE technology appraisal guidance 423 recommends eribulin for locally advanced or metastatic breast cancer after 2 or more lines of chemotherapy regimens. In addition, lapatinib is a HER2 targeted treatment which in combination with capecitabine or trastuzumab is also licensed for use at this point in the treatment pathway (but is not available for NHS patients).
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- After T-DM1, there are a variety of treatment options, but none have shown an OS benefit in the post-T-DM1 setting.
- Tucatinib with trastuzumab and capecitabine is the first treatment combination to demonstrate an improvement in median OS in the post-T-DM1 setting.
- Tucatinib is specifically labelled to indicate benefit in patients with brain metastases.
- Tucatinib in combination with trastuzumab and capecitabine has an acceptable safety profile for the intended population

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NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England and Improvement**

3. Job title or position	**Clinical Chair of the Chemotherapy Clinical Reference Group**
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? **X**☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? **X**☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? **X**☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England is an executive non departmental public body of the DHSC overseeing the budget, planning, delivery and day to day operation of NHS commissioning.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no CDF approved treatments for third or further line Her2 positive metastatic breast cancer. There is NICE guidance for the management of advanced breast cancer (CG81) which does not include Her2 targeted treatments beyond second line. It recommends chemotherapy without a Her2 targeted element such as Eribulin.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	As there are no funded third or further line Her2 targeted treatment for Her2 positive metastatic breast cancer there is variation across England as to the treatment patients receive. Most patients (if fit enough) will receive SACT without a targeted drug, others would be treated in a clinic trial if available and others still might receive a Her2 targeted drug if the provider organisation agrees to fund this or the patient co-funds.
8. What impact would the technology have on the current pathway of care?	Many patients survive for years with Her2 positive metastatic breast cancer and are still very fit at the point when they become third or greater line. It will allow patients to remain as symptom free as possible with good quality of life and have longer survival.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Tucatinib is not currently available outside of clinical trials

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Currently very few patients have Her2 targeted treatment beyond second line so there will be a need for more echocardiography resource if tucatinib is approved.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care oncology clinics although could explore community shared care delivery for patients once established on it.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Similar treatments already being used in oncology clinics so very little extra required.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	Will be the same as other patients – regular CT monitoring for ongoing response. RECIST criteria should be used as in most solid tumours.

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	I do not know
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	See answer to 7. This treatment might improve equality if approved.
12b. Consider whether these issues are different from issues with current care and why.	

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- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England and Improvement**

3. Job title or position	**National Programme of Care lead commissioner- cancer ;**
4. Are you (please tick all that apply):	**X**☒ commissioning services for a CCG or NHS England in general? **X**☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England is an executive non departmental public body of the DHSC overseeing the budget, planning, delivery and day to day operation of NHS commissioning.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
Current treatment of the condition in the NHS	

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The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Tucatinib is not currently available outside of clinical trials

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• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	Will be the same as other patients – regular CT monitoring for ongoing response. RECIST criteria should be used as in most solid tumours.

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	Unknown
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	See answer to 7. This treatment might improve equality if approved.
12b. Consider whether these issues are different from issues with current care and why.	

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

ERRATUM

Post factual accuracy check version with corrections

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Declared competing interests of the authors and advisors

The authors and clinical advisor declare no competing interests

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

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Contributions of authors

David Scott critically appraised the clinical effectiveness systematic review and network meta-analysis, and drafted the report; Lorna Hazell critically appraised the clinical effectiveness systematic review and network meta-analysis, and drafted the report; Jill Colquitt critically appraised the clinical effectiveness systematic review and drafted the report; Neelam Kalita critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Jo Lord critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted

the report; Emma Loveman critically appraised the clinical effectiveness systematic review and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Academic in confidence
BICR	Blinded Independent Central Review
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
DSU	Decision Support Unit
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
ERG	Evidence Review Group
HER2	Human epidermal growth factor receptor 2
HER2-	Human epidermal growth factor receptor 2-negative
HER2+	Human epidermal growth factor receptor 2-positive
HER2CLIMB	A Study of Tucatinib vs Placebo in Combination with Capecitabine & Trastuzumab in Patients with Advanced HER2+ Breast Cancer
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient level data
ITT	Intent to treat
ITC	Indirect treatment comparison
LFT	Liver function tests

mITT	Modified intent to treat
MRI	Magnetic resonance imaging
NHS	National Health Service
NMA	Network meta-analysis
NICE	National Institute for Health and Care Excellence
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal social services research unit
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Relative risk/risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
T-DM1	Trastuzumab emtansine
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1 Summary of key issues

Issue number	Summary of issue	Report sections
1	The results of the indirect comparison between tucatinib in combination with trastuzumab and capecitabine and comparator treatments are uncertain due to clinical heterogeneity across the trials included in the network meta-analysis. The ERG uses a random effects model rather than the fixed-effect model favoured by the company. We also correct a HR typographical error in one of the trials included in the NMA Pivot et al (2015).	3.3 and 3.4
2	Lack of justification for the company's survival extrapolation model (based on the fractional polynomial NMA Weibull model for a reference arm), adjusted for indirect comparators with the HR NMA. The ERG proposes use of survival curves directly fitted to the HER2CLIMB trial.	4.2.6
3	Cost-effectiveness analysis may not reflect the prevalence of brain metastases in the clinical population. We suggest an exploratory analysis with baseline survival adjusted for the proportion of patients with brain metastases.	4.2.6
4	There is a lack of justification for the use of different health state utilities for the tucatinib combination and comparators. The analysis of EQ-5D data from the HER2CLIMB trial is an appropriate source for estimation of utilities, but the analysis is poorly reported, and potentially subject to bias from missing data.	4.2.9

1.2 Overview of key model outcomes

Table 2 reports the company's revised base case results. These estimates are based on PAS discount for tucatinib and an assumed discount for trastuzumab, and other drugs at list price. The company's model results were most sensitive to relative dose intensity for the tucatinib combination, and health state utilities for progressed health.

Table 2 Company's revised base case, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs Tuc + tras + cap vs. comparators	ICERs fully incremental Excluding Tras + cap	ICERs fully incremental Including Tras + cap
Capecitabine	[redacted]	[redacted]	[redacted]	-	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	-	[redacted]
Eribulin	[redacted]	[redacted]	£37,483	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-	[redacted]	[redacted]

Source: Clarification response Table B2c (tucatinib combination and eribulin), other results produced by the ERG
[a] PAS discount for tucatinib and assumed discount for trastuzumab, other drugs at list price
Ext dom, extendedly dominated; ICER, incremental cost-effectiveness ratio; Tras + cap, trastuzumab with capecitabine; Tuc + tras + cap, tucatinib with trastuzumab and capecitabine.

1.3 The decision problem: summary of the ERG's key issues

The ERG identified no key issues relating to the decision problem in general. Aspects of the decision problem where there is uncertainty (e.g. subgroup of patients with brain metastases) are covered by key issues for clinical and cost effectiveness.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 1 Uncertain indirect comparison results due to study heterogeneity

Report section	3.3 and 3.4
Description of issue and why the ERG has identified it as important	The results of the network meta-analysis (NMA) which provides an indirect comparison of the tucatinib combination versus the comparators relevant to the scope of the appraisal (eribulin monotherapy, capecitabine monotherapy and vinorelbine monotherapy), are uncertain. The primary cause of uncertainty is heterogeneity between studies included in the NMA in terms of the proportion of patients with brain metastases, a likely effect modifier. The HER2CLIMB trial includes patients with and without brain metastases. The comparator trials, in contrast, include

	few or no patients with brain metastases. This creates an uneven distribution of patients with brain metastases across the trials, and there is likely to be bias in the results, though the direction and magnitude of this bias is unclear. The company's choice of a fixed-effect NMA model is inappropriate given this heterogeneity.
What alternative approach has the ERG suggested?	In the context of this heterogeneity, we suggest that a random-effects NMA model is more appropriate than a fixed-effect model. The ERG revised the company's random-effect NMA to correct for a reporting error in the paper by Pivot et al. (section 3.6.1). We use the corrected NMA random-effect HRs in the ERG preferred cost-effectiveness analysis (section 6.4). The ERG also conducted an exploratory NMA scenario analysis using data for the subgroup of patients without brain metastases from the HER2CLIMB trial (3.6.3). This reduces heterogeneity between the studies included in the evidence network and produced HRs that are less favourable for the tucatinib combination in patients with brain metastases than for the whole trial population. The results of this subgroup analysis are subject to limitations, and we did not include them in additional ERG cost-effectiveness analysis.
What is the expected effect on the cost-effectiveness estimates?	The use of random-effect NMA with Pivot correction increased the ICERs for the tucatinib combination. The implications of our exploratory NMA analysis for patients without brain metastases is unclear. It suggests that heterogeneity over the proportion of patients with brain metastases is likely to affect cost-effectiveness. All else being equal, the higher HRs for patients without brain metastases would give higher ICERs. However, it is not possible to conduct a subgroup analysis for people with brain metastases, due to the lack of evidence for the indirect comparators. It is also likely that other model parameters will differ for people with/without brain metastases (see Issue 3).
What additional evidence or analyses might help to resolve this key issue?	The lack of clinical effectiveness evidence for the comparator treatments in the subgroup of patients with brain metastases is difficult to resolve without further evidence. We request that the company revise their random-effect NMA analysis to correct for the reporting error for the Pivot et al. study. The NMA outputs should be included in their economic model.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 2 Survival extrapolations

Report section	4.2.6
Description of issue and why the ERG has identified it as important	For their base case, the company obtain OS and PFS extrapolations by applying relative effects from the NMA ([redacted]) to fractional polynomial OS and PFS survival curves for a reference treatment (lapatinib plus capecitabine). The resulting modelled OS estimates are substantially more favourable than those observed in the HER2CLIMB study. This may be due to the population in this trial, which included more patients with brain metastases than other trials in the NMA (which included few or no patients with brain metastases). The company did not explore the impact of alternative functional forms for PFS and OS in their scenario analysis. Although a scenario with alternative survival models is reported (CS Table 39), QALY estimates from this scenario did not differ from those in the base case analysis (see section 6.2). This is not surprising as the model only includes one fractional polynomial function for OS and one for PFS.
What alternative approach has the ERG suggested?	The ERG has used the 'within trial' approach, which was coded in the company's model but not used, to estimate OS and PFS curves fitted to the HER2CLIMB trial data and then adjusted for indirect comparators with HRs from the NMA (section 6.3.1). We explored the impact of alternative survival models for OS and PFS.
What is the expected effect on the cost-effectiveness estimates?	The 'within-trial' analysis produced PFS and OS curves that are reflective of outcomes in the pivotal HER2CLIMB trial. This reduced survival and QALY estimates for all treatments, and also incremental differences between them. Hence ICERs were significantly higher than with the company's NMA based modelling approach. There is residual uncertainty because several models for OS had a good fit to the trial data and appeared plausible but gave a range of ICER results.
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion on the plausibility of the survival extrapolations and whether the company's NMA-based survival estimates or ERG's within-trial estimates are more reflective of the population in clinical practice.

Issue 3 Subgroup analysis

Report section	4.2.3
Description of issue and why the ERG has identified it as important	The HER2CLIMB trial included patients with presence or a history of brain metastases: nearly 50% of the total study population (CS Table 6). The NICE scope requested subgroup analysis for patients with brain metastases if the evidence allowed. The company did not attempt to model cost-effectiveness for this subgroup, on the basis that there is a lack of clinical evidence in this group for the scope comparators. The ERG acknowledges this lack, but we note that the economic model nevertheless relies on estimates of relative effectiveness derived from NMA comparisons across these heterogeneous studies. The ERG within-trial analysis has also demonstrated that the ICERs are sensitive to the absolute levels of survival for a reference comparator, as well as to relative treatment effects from the NMA. It is unclear whether the HER2CLIMB trial (which included a high proportion of patients with brain metastases) or other trials in the NMA (with few or no patients with brain metastases) provide a more realistic reflection of clinical practice.
What alternative approach has the ERG suggested?	Modelling a 'real-world' baseline for the survival extrapolations, based on a relevant, reliable cohort or a weighted average for HER2CLIMB patients with and without brain metastases. In the absence of subgroup-specific estimates of relative effects, NMA results could be used to model results for the direct comparators, as in the current model.
What is the expected effect on the cost-effectiveness estimates?	This is uncertain. We anticipate that the survival predictions would be less favourable than with the company's NMA-based model. But if the proportion of patients with brain metastases in practice is lower than that in HER2CLIMB, the results should be more favourable than with the ERG's within-trial analysis.
What additional evidence or analyses might help to resolve this key issue?	An exploratory analysis with a modelled reference arm that is representative of the population in clinical practice.

Issue 4 Health state utilities

Report section	4.2.9
Description of issue and why the ERG has identified it as important	The company conducted a revised analysis of the HER2CLIMB utility data as a response to clarification question B2 for which they used a repeated measures model with adjustment for baseline values. Whilst this approach is preferable to the approach in the original base case, there are concerns about the method of analysis and lack of detail in

	reporting. We note the potential for bias due to missing data, particularly at the post-treatment follow-up. The company's revised base case includes the post-progression utility of 0.496 from Lloyd et al.[1] However, the TA423 committee concluded that the most plausible post-progression utility lies between the Lloyd et al. estimate and an estimate of 0.679 (Crott and Briggs mapping of the Study 301 trial data).[2 3] In TA423 the same post-progression utility was used across treatments. By comparison, the post-progression utility for the tucatinib combination in the company's revised base case (0.698) is much higher than that assumed for eribulin, capecitabine and vinorelbine (0.496). This difference is not based on comparative evidence and seems implausible. It is not clear why such a large difference should persist after progression and treatment discontinuation. The clinical plausibility of the difference in pre-progression utility for the tucatinib combination (0.762) and comparators (0.706 for eribulin and 0.701 for capecitabine and vinorelbine) is questionable. This may well relate to differences in the trial populations (HER2CLIMB versus Study 301)[3 4] or valuation methods (crosswalk EQ-5D versus Crott and Briggs mapping), rather than to differences in treatment-related quality of life. Clinical advice to the ERG is that the adverse effects and quality of life will be similar across these treatments.
What alternative approach has the ERG suggested?	We suggest that the same utilities should be used for all treatments in the pre- and post-progression health states. We prefer the HER2CLIMB utilities, as these are derived from EQ-5D data in a relevant trial population, using NICE-recommended methods. An alternative that provides continuity between proposals for the same indication would be to use estimates from TA423.
What is the expected effect on the cost-effectiveness estimates?	ERG scenario analysis shows that the model is sensitive to the assumption of equal pre-progression utility and/or equal post-progression utilities between treatments (Table 35 and Table 39). ICERs were similar with estimates from the HER2CLIMB trial or TA423.
What additional evidence or analyses might help to resolve this key issue?	Further evidence and expert opinion on the plausibility of differences between treatments in health-related quality experienced before progression and after progression. Further information on the methods analysis of HER2CLIMB EQ-5D data and how missing data was handled.

1.6 Other key issues: summary of the ERG's view

The ERG does not have any other key issues to discuss.

1.7 Summary of ERG's preferred assumptions and resulting ICER

Based on the ERG critique of the company's (revised) cost effectiveness model, we have identified six key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

- **Within-trial analysis:** We use the OS and PFS fitted to HER2CLIMB trial data for the tucatinib combination and trastuzumab + capecitabine (see section 4.2.6).
- **Relative effects for other comparators** from the HR NMA with random effects and the ERG correction for the Pivot upper confidence limit (section 3.6).
- **Health state utilities** from HER2CLIMB EQ-5D analysis applied to all treatments (section 4.2.9.2).
- ERG scenario for the use of **subsequent treatments** (section 4.2.10.2)
- **Adjustment of utilities** for age
- Costs for **drug wastage**.

The cumulative effect of ERG preferred assumptions to the company's (revised) base case is shown in Table 3 .

Table 3 Cumulative change from company base case to ERG's preferred model assumptions

Treatment	Cost [a]	QALYs	Pairwise ICERs	Change to pairwise ICERs
Revised company base case				
Capecitabine	[redacted]	[redacted]	[redacted]	
Vinorelbine	[redacted]	[redacted]	[redacted]	
Tras + cap	[redacted]	[redacted]	[redacted]	
Eribulin	[redacted]	[redacted]	£37,483	
Tuc + tras + cap	[redacted]	[redacted]		
+ Within-trial analysis (PFS and OS, with HR NMA fixed effect)				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		
+ HR NMA random effects with ERG Pivot correction				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		
+ HER2CLIMB utilities (0.762 pre-progression, 0.698 post-progression)				

Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		
+ Age-adjustment for utilities				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		
+ ERG subsequent treatment scenario (50% tras, 20% cap/vin: [redacted] per person)				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		
+ Include costs for drug wastage (ERG preferred analysis)				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		

The ERG conducted a range of scenario analyses on our preferred base case model. These are presented in Table 39 of this report.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Seagen on the clinical effectiveness and cost effectiveness of tucatinib (TUKYSA®) with trastuzumab and capecitabine for treating HER2-positive unresectable locally advanced or metastatic breast cancer after two or more anti-HER2 therapies. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the evidence review group (ERG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 7th May 2021. A response from the company via NICE was received by the ERG on 25th May 2021 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on HER2-positive locally advanced or metastatic breast cancer

The CS (Section B1.3) provides a brief overview of the condition, describing the course of the disease; global and national epidemiology; and the impact on health-related quality of life (HRQoL) and survival. The CS highlights the significant impact of metastases to the brain, stating that this affects up to 50% of people over the course of the disease. In contrast, the ERG notes that a recent meta-analysis of epidemiological studies[5] estimated the proportion of people with HER2+ breast cancer with brain metastases to be lower, at 31%. Similarly, the ERG's expert clinical advisor estimates that around a third of patients with HER2+ metastatic disease develop brain metastases.

The CS states that the brain acts as a "sanctuary site" for HER2+ disease due to the inability of current drug treatments to penetrate the blood-brain barrier. Survival after the occurrence of brain metastases in HER2+ disease is poor: 1-year survival of 50% and 3-year survival of 16%. As will become apparent in subsequent sections of this report, brain metastasis is a disease characteristic of significant importance in the clinical effectiveness and cost-effectiveness evidence submitted.

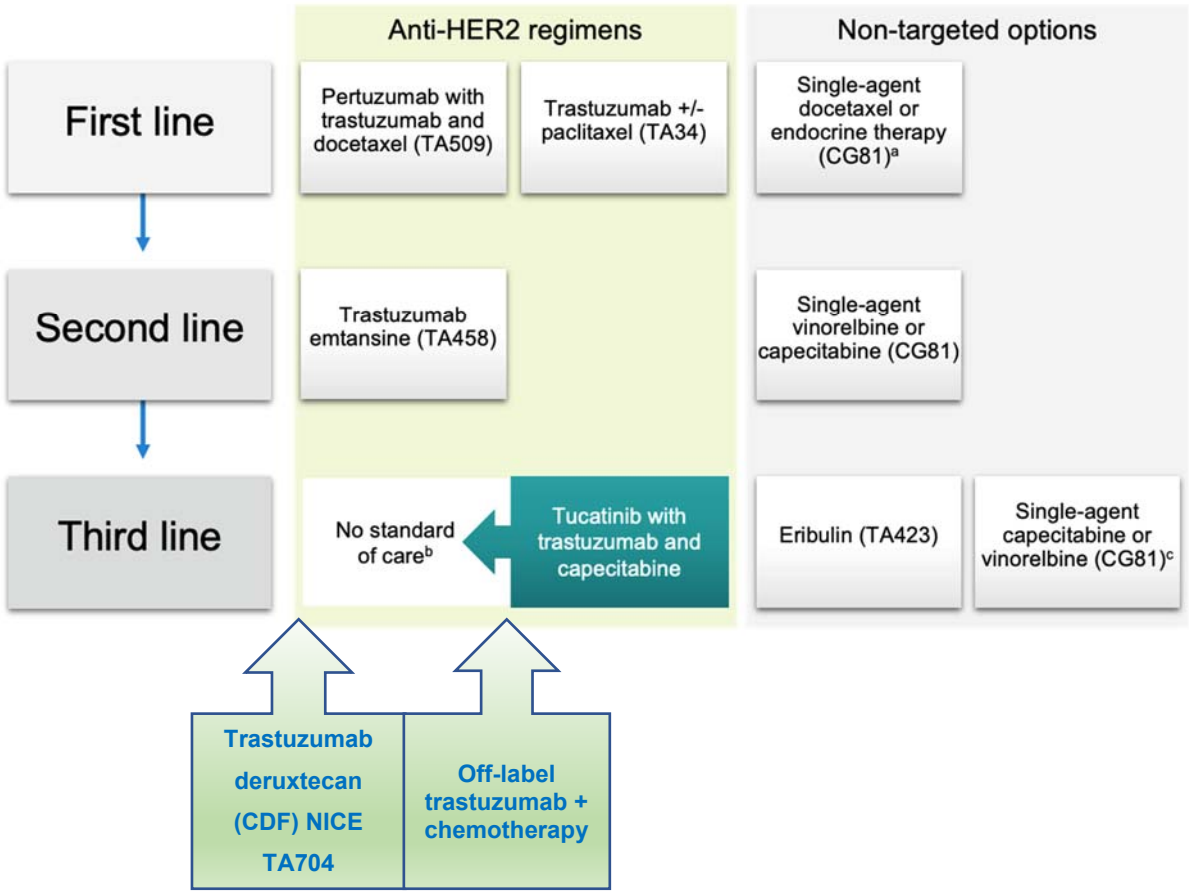
2.2.2 Background information on tucatinib

The CS describes the mechanism of action of tucatinib, an oral tyrosine kinase inhibitor (TKI), and that of two other drugs it is used in combination with: trastuzumab (a recombinant

humanised IgG1 monoclonal antibody) and capecitabine (an anti-metabolite chemotherapy). Tucatinib is an orally bioavailable, reversible small molecule TKI that is highly specific to HER2, and therefore defined as a targeted treatment. Tucatinib received its UK regulatory approval on 22 February 2021 and is 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 two prior anti-HER2 treatment regimens.

2.2.3 The position of tucatinib in the treatment pathway

Figure 1 is the company's depiction (with minor adaptation by the ERG) of the current treatment pathway for locally advanced and metastatic HER2 positive breast cancer, and the proposed third line positioning of tucatinib in combination with trastuzumab and capecitabine.



Source: adapted by the ERG from CS Figure 1

CDF – Cancer Drugs Fund

Figure 1 Current treatment pathway in HER2+ metastatic breast cancer in England and proposed positioning of tucatinib

As patients progress through successive lines of therapy they may receive anti-HER2 regimens and/or non-targeted treatments (e.g. chemotherapies or endocrine therapy for those patients whose tumours express hormone receptors).

The CS suggests that there is no standard of care for patients progressing to third line therapy, as no anti-HER2 regimens are currently recommended. However, the CS also mentions that eribulin (a non-targeted chemotherapy) "is the most plausible standard of care" (CS page 19) as it is the only NICE recommended treatment at third line (see NICE TA423). The ERG notes that NICE clinical guideline (CG81) recommends that patients may receive treatment with non-targeted chemotherapies such as capecitabine or vinorelbine. The ERG's expert clinical advisor points out that NICE guidance on eribulin is for metastatic breast cancer irrespective of HER2 status (+/-) and that capecitabine, vinorelbine and eribulin as single agents are equally appropriate third line treatment options. Our expert advisor also notes that single agent chemotherapy in combination with trastuzumab is used (off label) at third line, and that hormone therapy may also be used at third line in people with hormone receptor positive disease (though most hormone therapy tends to be given earlier in the pathway).

Since the CS was written, NICE has published guidance on an anti-HER2 regimen for use at third line: Trastuzumab deruxtecan is recommended for use within the Cancer Drugs Fund (CDF) as an option for treating HER2-positive unresectable or metastatic breast cancer in adults after 2 or more anti-HER2 therapies (NICE TA704). After a period of further data collection based on the use of trastuzumab deruxtecan in the NHS, and availability of data from trials currently in progress, NICE will review whether this treatment is cost-effective and can be recommended for routine commissioning in the NHS. Thus, standard care may potentially include this treatment in due course.

The company argues that there is unmet need for an efficacious third line therapy that can target brain metastases. They cite the inability of systemic treatments (e.g. single agent chemotherapies) to treat brain metastases effectively and the potential for greater clinical benefit with targeted treatment in the third line setting. The ERG's expert clinical advisor agreed this is a significant unmet need and noted that trastuzumab deruxtecan is not expected to target brain metastases because it is unlikely to cross the blood-brain barrier.

Finally, the ERG's clinical expert commented that the treatment pathway does not reflect the fact many patients will have received prior adjuvant treatment for their primary tumour. Thus, only a minority will present to secondary care with de novo metastases. In this respect the requirement to have received at least two prior anti-HER2 treatment regimens before receiving tucatinib could be interpreted as including anti-HER2 adjuvant treatments.

ERG conclusion

The ERG considers that tucatinib is appropriately positioned as a third line treatment of metastatic disease given the lack of available targeted anti-HER2 treatments for patients whose disease has progressed in this setting. Expert clinical advice to the ERG is that trastuzumab (used off label) in combination with chemotherapy (e.g. capecitabine) is used at third line. This is not, however, included as a comparator in the NICE scope or the decision problem.

2.3 Critique of the company's definition of the decision problem

Table 4 compares the company's decision problem to the final scope for this appraisal issued by NICE. The ERG concludes that the decision problem adheres to the NICE scope, with the following exceptions:

- **Population**. The population is not restricted to people with unresectable locally advanced or metastatic breast cancer. This widens the population to also include people whose tumours are resectable, and potentially the effects of tucatinib may not necessarily be the same for them as they are for people with unresectable tumours.
- **Comparators.** The base case economic analyses includes only one of the three comparators – eribulin. The other two comparators (capecitabine and vinorelbine) are included in additional analyses "for completeness". The company regards the three comparators to be similar in efficacy and safety based on clinical advice. Expert clinical advice to the ERG suggests there is variation in clinical practice at third line. For example, some clinicians may continue trastuzumab treatment with the addition of a single agent chemotherapy (e.g. capecitabine), whilst others may use single agent capecitabine. We discuss the appropriateness of the company's approach in our critique of cost effectiveness, in section 4 of this report.
- **Subgroups.** Cost effectiveness is not estimated for the subgroup of people with brain metastases. Although the HER2CLIMB trial included patients with brain metastases, this is atypical in breast cancer treatment clinical trials. Trials of the comparator drugs tended to exclude patients with unstable brain metastases. The

company was therefore unable to conduct an indirect treatment comparison to inform this cost-effectiveness analysis. We discuss this in sections 3.3 and 3.4 of this report.

Table 4 Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
Population	People with HER2-positive unresectable locally advanced or metastatic breast cancer who have had 2 or more prior anti-HER2 therapies	As per scope, except not restricted to people with unresectable cancer.	Company state this is because tucatinib's licence indication does not mention the term unresectable.	Expert clinical advice to the ERG is that resection is an option for a small number of patients and surgery would not be expected to be curative.
Intervention	Tucatinib with trastuzumab and capecitabine	As per scope	N/A	Decision problem matches the NICE scope
Comparators	• Eribulin • Capecitabine • Vinorelbine	Only eribulin is included in the base case economic analyses. Capecitabine and vinorelbine are included in additional analyses.	Expert clinical advice to the company is that eribulin is the most plausible standard of care as it is used as a single agent and is the only treatment approved by NICE for use in the third-line setting.	Expert clinical advice to the ERG is that there is variation in practice and other treatments may be given.
Outcomes	The outcome measures to be considered include: • progression-free survival	As per scope	N/A	Decision problem matches the NICE scope

	• overall survival • response rate • duration of response • adverse effects of treatment • health-related quality of life			
Subgroups	People with brain metastases (where evidence allows)	People with untreated and previously treated brain metastases	Clinical effectiveness evidence is presented for this subgroup, but not cost effectiveness estimates, due to the lack of available evidence for potential comparators including a similar subgroup of patients.	Decision problem does not completely match the NICE scope The ERG concurs that evidence for this subgroup in comparator trials is lacking (see sections 4.2.3 and 4.2.6)

Source: Adapted from CS Table 1

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Evidence for the clinical effectiveness of tucatinib was identified from a single broad systematic literature review (SLR); the full methods of which are reported in CS Appendix D and summary points referred to in CS section B.2.1. This SLR also identified studies for the indirect comparisons between the treatments identified in the decision problem (referred to in CS section B.2.9.1.1). The ERG provides a critique of the methods and processes of the SLR in Table 5. We have no concerns that the search strategy or study eligibility assessments may have missed potentially eligible studies. The CS summarises the included studies appropriately and the ERG assessment of the risk of bias generally concurs with that of the CS. For the NMA, additional study eligibility criteria were applied. The ERG has no concerns with the final selection of studies, although notes that five peripheral studies were included in the NMA. The ERG has no concerns over the conduct of the NMA analysis.

Table 5 ERG appraisal of systematic review methods

Systematic review components and processes	ERG response (Yes, No, Unclear)	Comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	PICOD framework used. Different criteria for titles and abstracts as full text review but minimal differences (CS Appendix D, Tables 10 and 11).
Were appropriate sources of literature searched?	Yes	The sources searched were comprehensive. The date of the last search was November 2020.
What time period did the searches span and was this appropriate?	Yes	All years were searched (CS Appendix D page 4)
Were appropriate search terms used and combined correctly?	Yes	Search terms were appropriate and combined correctly, the RCT search strings were somewhat sparse and not translated consistently across the databases, however, the ERG has no concerns about this.

Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	• Two stage approach, slightly different criteria between the two stages of review but reasonable and with criteria that were relevant to the decision problem. • The company included systematic reviews at the titles and abstract review stage and checked reference lists of 'robust systematic reviews' (CS Appendix D page 4) but no further detail was provided and it is unclear if any references were identified from these systematic reviews. • The ERG has checked the excluded studies lists in CS Appendix D (Tables 13 and 14) and exclusions appear appropriate based on the information provided. • The ERG has also cross-checked studies identified in a recent NMA [6] to validate the company's approach; no additional references were identified. • Studies assessed as meeting the PICOD criteria were then assessed on additional eligibility criteria for inclusion in the NMA. (CS Appendix Table 15). The ERG has no concerns with the final study selection for the NMA.
Were study selection criteria applied by two or more reviewers independently?	Yes	Both screening and full text assessment were undertaken by two independent reviewers, CS Appendix D, Page 23.
Was data extraction performed by two or more reviewers independently?	No	Data extraction was undertaken by one reviewer (CS Appendix D Page 24)
Was a risk of bias assessment or a quality assessment of the included	Yes	NICE criteria for RCTs (CS Appendix D1.3) and ERG assessment generally concurs

studies undertaken? If so, which tool was used?		
Was risk of bias assessment (or other study assessment) conducted by two or more reviewers independently?	Unclear	Unclear if single reviewer or double reviewer (CS Appendix D1.3)
Is sufficient detail on the individual studies presented?	Yes	CS describes trial methodology, outcomes and results of the pivotal trial in Sections B.2.2-2.6 and summarises the comparator trials in CS Section B.2.9.1.3 and CS Appendix D.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	The CS NMA analysis was well-conducted and appropriate studies were included. The ERG preferred the random effects NMA, discussed in Section 3.2.4.

NMA – Network meta-analysis; PICOD – population, intervention, comparator(s), outcome(s) and study design(s)

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The key source of clinical effectiveness evidence in the CS is the HER2CLIMB trial, a company-sponsored Phase II randomised, double-blind controlled trial of tucatinib in combination with trastuzumab and capecitabine versus placebo in combination with trastuzumab and capecitabine for unresectable locally advanced or metastatic HER2+ breast cancer. Although the trial was originally designed as a Phase II trial, the company states that the eventual sample size attained, and the conduct of the trial, made it consistent with the standards of a Phase III trial. HER2CLIMB is currently ongoing in an open-label extension where the placebo group can switch to tucatinib combination treatment. The CS does not appear to specify the trial's completion date, but the National Clinical Trial record on clinicaltrials.gov states this will be 31st May 2022.[7]

3.2.1.1 Study characteristics

The HERCLIMB2 trial was conducted in 15 countries, with 10 centres in the UK. The trial was initiated with 180 participants, but sample size was increased on two occasions to improve statistical robustness (see section 3.2.4 for details). The original study protocol was also amended after the first sample size increase to include European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) for subsequently enrolled participants. The history and timelines of HER2CLIMB can be seen in CS Figure 2.

The population of HER2CLIMB is people with unresectable locally advanced or metastatic HER2+ breast carcinoma previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1). The ERG's clinical expert notes that these treatments are standard practice in the UK. Key inclusion and exclusion criteria are summarised in CS Table 4. Of note, participants with brain metastases were eligible, including those with active (treated progressing or untreated) or treated stable brain metastases. Clinical trials in this setting generally exclude patients with brain metastases or include only those with stable brain metastases. People were excluded if they had previously received the following treatments in the metastatic setting: capecitabine, lapatinib within 12 months (except if lapatinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity), neratinib, afatinib or other investigational HER2/ epidermal growth factor receptor or HER2 tyrosine kinase inhibitor.

Eligible participants were randomised in a 2:1 ratio to one of the following arms:

Tucatinib combination

- Tucatinib: 300 mg orally twice daily continuously during treatment period
- Trastuzumab: 8 mg/kg intravenous loading dose then 6 mg/kg (or 600 mg subcutaneous injection) once every 21 days
- Capecitabine: 1000 mg/m^2 orally twice daily days 1–14 of each 21-day cycle

Placebo combination

- Placebo orally twice daily continuously during treatment period
- Trastuzumab: 8 mg/kg intravenous loading dose then 6 mg/kg (or 600 mg subcutaneous injection) once every 21 days
- Capecitabine: 1000 mg/m^2 orally twice daily days 1–14 of each 21-day cycle

Treatments continued until unacceptable toxicity, disease progression, withdrawal of consent or study closure.

The key features of HER2CLIMB are summarised in Table 6.

Table 6 Summary of HER2CLIMB trial characteristics

Trial characteristic	Description
Study design	Phase II randomised, double-blind, controlled clinical trial (originally registered as Phase II but amended to be consistent with Phase III)
Number and location of centres	155 sites across 15 countries: US, Canada, Austria, Belgium, Czechia, Denmark, France, Germany, Italy, Portugal, Spain, Switzerland, Israel, Australia and UK (10 sites; [redacted] patients)
Study population	Unresectable locally advanced or metastatic HER2+ breast carcinoma previously treated with trastuzumab, pertuzumab and T-DM1
Intervention	Tucatinib in combination with trastuzumab and capecitabine (Primary endpoint population n=320) (Total population n=410)
Comparator	Placebo in combination with trastuzumab and capecitabine (Primary endpoint population n=160) (Total population n=202)
Primary outcome	PFS in the primary endpoint population (n=480)
Key secondary outcomes	PFS in all randomised patients with brain metastases (n=291) Overall survival in total population (n=612) ORR in total population (n=612)
Randomisation stratification factors	Known history of treated or untreated brain metastases (yes or no), ECOG performance status (0 or 1) geographic region (US, Canada or rest of world).
Status	Ongoing (open-label extension)
Latest available data	4th September 2019 Median follow-up 14.0 months (total population)
Pre-specified sub-groups	• Age (≥65 or <65 years) • Race (white or non-white) • Hormone receptor status (HmR+ or HmR-) • Baseline brain metastases (yes or no) • ECOG performance-status score (0 or 1) • Geographic region (US and Canada or rest of world)
Source: CS section B.2.3.1, CS Table 3 and 4.	

ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PFS progression-free survival T-DM1, trastuzumab emtansine.

3.2.1.2 Patients' baseline characteristics

Baseline characteristics in HER2CLIMB are summarised in Table 7 below. The arms are generally well balanced for both the primary endpoint population and the total study population, although the ERG notes there is a slight imbalance in the proportion of white participants and those with liver metastases in the primary endpoint population, both of which are slightly higher in the placebo-combination arm. People with liver metastases generally have a worse prognosis than those without, but the extent this may affect treatment outcomes in the trial arms is unclear. A subgroup analysis was not undertaken for presence/absence of liver metastases.

[redacted] The ERG's clinical expert notes that very few patients have locally advanced disease at third-line treatment. These patients have biologically distinct disease which has a propensity not to metastasise and which has a better response to treatment compared to distant (particularly visceral) metastases. Around 63% of participants had Stage 0 to III disease at initial diagnosis and would have already received treatment for their primary tumour, although details of types of treatment were not provided. The proportion with stage IV disease at initial diagnosis (36%) is high compared with UK practice, where around 10-15% present with stage IV disease (estimated by the ERG's clinical expert). Some of the participants were extensively pre-treated, with up to 17 prior lines of therapy (median 4 lines), and up to 14 lines of prior therapy in the metastatic setting (median 3 lines).

The proportion of patients with brain metastases was 45.6% in the primary endpoint population and 47.5% in the total study population. The ERG clinical expert considers that this is higher than expected in UK clinical practice, possibly due to study screening identifying asymptomatic cases or to the trial attracting participants with active brain metastases. Approximately 60% of the brain metastases were active (i.e. either treated and progressing or untreated).

Table 7 Baseline characteristics in HER2CLIMB

	Primary endpoint population (N=480)		Total study population (N=612)	
Variable, no. (%) if not otherwise stated	**Tucatinib combination (n=320)**	**Placebo combination (n=160)**	**Tucatinib combination (n=410)**	**Placebo combination (n=202)**
Female sex	317 (99.1)	158 (98.8)	407 (99.3)	200 (99.0)
Age				
<65 years	252 (78.8)	132 (82.5)	328 (80.0)	168 (83.2)
≥65 years	68 (21.3)	28 (17.5)	82 (20.0)	34 (16.8)
Median – years	54.0	54.	55.0	54.0
Race				
Asian	17 (5.3)	3 (1.9)	18 (4.4)	5 (2.5)
Black/African American	30 (9.4)	13 (8.1)	41 (10.0)	14 (6.9)
White	225 (70.3)	125 (78.1)	287 (70.0)	157 (77.7)
Unknown/other	48 (15.0)	19 (11.9)	64 (15.6)	26 (12.9)
Region				
US/Canada	204 (63.8)	103 (64.4)	246 (60.0)	123 (60.9)
Rest of world	116 (36.3)	57 (35.6)	164 (40.0)	79 (39.1)
Hormone receptor status				
ER and/or PgR-positive	190 (59.4)	99 (61.9)	243 (59.3)	127 (62.9)
ER and PgR-negative	126 (39.4)	61 (38.1)	161 (39.3)	75 (37.1)
Other	4 (1.3)	0	6 (1.5)	0
ECOG performance status				
0	159 (49.7)	76 (47.5)	204 (49.8)	94 (46.5)
1	161 (50.3)	84 (52.5)	206 (50.2)	108 (53.5)
Disease status at study entry				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV at initial diagnosis	108 (33.8)	67 (41.9)	143 (34.9)	77 (38.1)
Presence or history of brain metastases	148 (46.3)	71 (44.4)	198 (48.3)	93 (46.0)
Previously treated stable	Not reported	Not reported	80 (40.4)	37 (39.8)
Previously treated progressing	Not reported	Not reported	74 (37.4) [a]	34 (36.6) [a]
Untreated	Not reported	Not reported	44 (22.2) [a]	22 (23.7) [a]
Location of other metastases				
Lung	160 (50.0)	82 (51.3)	200 (48.8)	100 (49.5)
Liver	108 (33.8)	64 (40.0)	137 (33.4)	78 (38.6)
Bone	178 (55.6)	85 (53.1)	223 (54.4)	111 (55.0)
Prior lines of therapy, median (range)	4.0 (2, 14)	4.0 (2,17)	4.0 (2, 14)	4.0 (2,17)

	Primary endpoint population (N=480)		Total study population (N=612)	
Variable, no. (%) if not otherwise stated	**Tucatinib combination (n=320)**	**Placebo combination (n=160)**	**Tucatinib combination (n=410)**	**Placebo combination (n=202)**
Prior lines of therapy in the metastatic setting, median (range)	3.0 (1, 14)	3.0 (1, 13)	3.0 (1, 14)	3.0 (1, 13)
Prior therapies				
Trastuzumab	320 (100)	160 (100)	410 (100)	202 (100)
Pertuzumab	320 (100)	159 (99.4)	409 (99.8)	201 (99.5)
T-DM1	320 (100)	160 (100)	410 (100)	202 (100)
Lapatinib	22 (6.9)	10 (6.2)	24 (5.9)	10 (5.0)

Source: CS Table 6, CS Appendix E Table 1

ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; ITT, intent to treat; no, number; OS, overall survival; PgR, progesterone receptor; T-DM1, trastuzumab emtansine; US, United States

[a] Previously treated progressing and Untreated rows are transposed in CS Table 6. [b] CSR Table 4 and Table 8.

3.2.1.3 Ongoing studies

No additional ongoing studies are reported in the CS. The ERG is not aware of any relevant ongoing studies.

ERG conclusion on included studies

The ERG considers the population of the HER2CLIMB trial to be generally representative of the target population with unresectable locally advanced or metastatic HER2+ breast cancer previously treated with two or more anti-HER2 therapies. We note, however, that the trial participants have experienced more previous lines of therapy than typical in UK practice. Furthermore, the proportion of patients with brain metastases included in the trial appears to be higher than in clinical practice. The comparator trial arm (which includes trastuzumab and capecitabine in combination) is not licensed for use at third line and is not included as a comparator treatment in the NICE scope for this appraisal.

3.2.2 Risk of bias assessment

The company assessed the quality of HER2CLIMB using criteria recommended by NICE. This is presented in CS Table 7 and CS Appendix D; the company's comments on quality

assessment differ slightly between these sources, but the overall judgements are the same. A comparison of the company's and the ERG's assessment of HERCLIMB2 can be seen in 9.1. The ERG generally agrees with the company's assessment, although we note the following minor points:

- There is a slight imbalance in the proportion of white participants and those with liver metastases, both of which are slightly higher in the placebo-combination arm. The implications of this are unclear.
- There were no unexpected imbalances in dropouts between groups. A higher proportion discontinued treatment in the placebo-combination arm (86.3%) than in the tucatinib-combination arm (70.8%), mostly due to progressive disease in the placebo-combination arm (68% vs 50%) (CS Appendix D Figure 11). Discontinuations due to adverse events were higher with tucatinib (5.7% vs 3.0%).
- The protocol [8] lists duration of response (DOR) and clinical benefit rate (CBR) determined by the investigator as well as blinded independent central review (BICR) as secondary endpoints, however only BICR-determined DOR and CBR are reported in the CS. Investigator results are reported on the National Clinical Trial record [7] (although there is a discrepancy between the BICR DOR reported on the trial record and that reported in the CS and CSR).

Overall, the ERG considers there is a low risk of bias in HER2CLIMB.

3.2.3 Outcomes assessment

The efficacy and safety outcome measures included in the HER2CLIMB trial are reported in CS Section 2.3 and CS Table 4. These are standard outcomes used in trials of cancer drugs and their definitions appear appropriate. An overview of all the outcomes and ERG comments is provided in Appendix 9.2.

The key outcomes were assessed by blinded independent central review (BICR) using RECIST (Response Evaluation Criteria in Solid Tumours) criteria version 1.1. In the protocol, the CSR and the National Clinical Trial record [7] secondary outcomes as determined by the investigator assessments were also provided. Investigator assessments were included predominantly to ensure treatment decisions could be made in a timely manner.

The trial's primary outcome was PFS in the 'primary endpoint population' (see Section 3.2.4 of this report for further detail on the trial's statistical analysis populations). Secondary outcomes were classed as being 'key' or 'other'. The key secondary outcomes included

overall survival (OS) and the objective response rate (ORR) in the total population, and PFS in patients with baseline brain metastases at baseline. The latter outcome was included in response to promising results from an early phase I dose-escalation trial of tucatinib, trastuzumab and capecitabine in people with brain metastases.[9] Outcomes were assessed every six weeks in the initial 24 weeks and then once every nine weeks until disease progression, initiation of a new therapy, withdrawal of consent, or study closure (CS Figure 3).

The patient-reported outcome of health-related quality of life (HRQoL) was measured using the EQ-5D-5L in a subset of the total population following a protocol amendment (see Section 3.2.5). As such, the outcomes from the EQ-5D should be considered as exploratory. The CS reports baseline and endpoint data for the EQ-5D descriptive system and the EQ-5D Visual analogue scale (VAS) but not for the EQ-5D index scores, however, these were provided in response to clarification question A2 (see Section 3.2.5.4).

The outcomes that inform the economic model are PFS, OS, adverse events and HRQoL (CS Table 4).

ERG conclusion on outcomes assessment

Overall, the outcome measures included in the HER2CLIMB trial are appropriate for a cancer treatment trial and the ERG has no concerns over their definition or measurement.

3.2.4 Statistical methods in the HER2CLIMB trial

The CS presented only summary descriptions of the statistical analyses of the HER2CLIMB trial, however, the trial publication [4 8] includes the trial protocol and the statistical analysis plan (SAP) which have been checked by the ERG.

The original sample size (n=180) was increased prior to unblinding or knowledge of the trial results on two occasions (CS B.2.3.1). The first increase, to n=480, was necessary for the upgrade of the trial's status from phase 2 to phase 3 to support the tucatinib licensing registration. This was undertaken at approximately 12 months and the n=480 became the primary endpoint population. The second increase, to a target of n=600, was to improve power for the key secondary endpoint of PFS in patients with brain metastases (described in

CS B.2.4) and was undertaken at approximately 3 years. The ERG does not have any concerns with the sample size or the power analysis.

The primary analysis of PFS was conducted for the first 480 participants recruited. The CS says (CS B.2.3.1) this was to avoid potential bias from early progression in the overall population owing to the short follow-up of some participants. Additional analyses sets were as described in Table 8. The statistical approach for the primary outcome and key secondary outcomes is described in Appendix 9.2, the ERG has taken information from CS B.2.4 and the HER2CLIMB trial publication, protocol and SAP. [8] Multiplicity was controlled using a group sequential procedure described in Appendix 9.2. The additional secondary outcomes were not subject to type 1 error control and are deemed as exploratory. The handling of missing data, sensitivity analyses and analysis of pre-specified subgroups were described in the trial protocol / SAP and are summarised in Appendix 9.2. The ERG does not have any significant concerns with the analysis plan or the statistical analyses.

Table 8 HER2CLIMB analysis populations

Analysis population	Definition	Analyses
Primary endpoint population	First 480 patients randomised	Primary endpoint of PFS per BICR
ITT-OS	Total study population (N=612)	Secondary endpoints of OS and confirmed ORR
ITT-PFS brain metastases	All randomised patients with brain metastases (N=291)	Secondary endpoint of PFS per BICR in brain metastases subgroup
Safety	All randomised who received at least 1 dose of study treatment (N=601)	Safety analyses
Source: CS Table 5		

BICR, blinded independent central review; BM, brain metastases; ITT, intent to treat; OS, overall survival, ORR, objective response rate; PFS, progression-free survival.

3.2.5 Efficacy results of the intervention studies

The CS presents results from the HER2CLIMB trial up to 4th September 2019. The ERG assumes this is the final analysis for the trial as no further planned analyses are mentioned in the CS.

In this section we focus on the clinical effectiveness outcomes from the trial that inform the economic model, as follows:

- PFS (primary endpoint); assessed in the first 480 randomised patients, the ITT-PFS population
- OS (key secondary endpoint); assessed in the total trial population (n=612), the ITT-OS population
- HRQoL (exploratory endpoint) assessed in a subset of patients (n=331) from the total trial population. The subset was used because baseline data collection for HRQol measures did not start until part way through the trial following a protocol amendment.

The HER2CLIMB trial was also designed to assess the effect of the tucatinib combination on PFS in patients with brain metastases; a subgroup relevant to the NICE scope for this appraisal. Thus, PFS was assessed as a key secondary endpoint in a subset of the total trial population with active or stable brain metastases at baseline, the 'ITT-PFS brain metastases' population (N=291). We summarise the results from this analysis below along with results from an exploratory analysis of PFS in patients without brain metastases.

The outcome measures ORR and DOR do not inform the economic model but are listed in the NICE scope and are summarised briefly in this section. Additional outcomes which do not inform the economic model (clinical benefit rate and time to new brain lesions or death). are not reproduced here but can be found in CS sections B.2.6.6 and B.2.6.8. In addition, exploratory analyses were conducted within the ITT-PFS brain metastases population (central nervous system PFS, intracranial objective response rate, overall survival, duration of response and HrQoL) and are presented in CS Appendix E.

Safety data, including adverse events and treatment exposure, are summarised in section 3.2.5.6.

3.2.5.1 Progression-free survival

Primary endpoint population

The primary endpoint in the HER2CLIMB trial was PFS measured by BICR according to RECIST 1.1. criteria in the primary endpoint population (ITT-PFS, n=480). A statistically significant reduction in the risk of progression or death was observed for the tucatinib-combination group compared to the placebo-combination group with a hazard ratio (HR) of 0.54 (95% CI: 0.42, 0.71; p<0.0012) and a 2 month increase in median PFS (Figure 2). Results were similar when PFS was measured by investigator assessment ([redacted]) in this study population (CSR section 11.1.4.1).

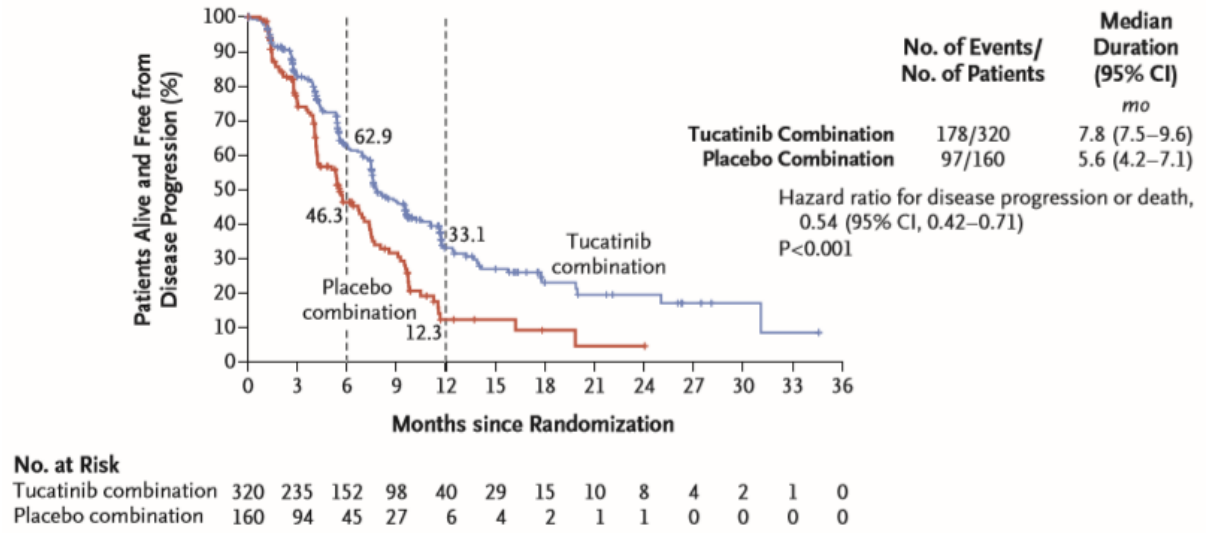


Figure 2 Kaplan-Meier estimate of PFS per BICR (primary endpoint population)

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; No, number
Source: CS Figure 4

Total population

In the total study population (ITT-OS, n=612), PFS with BICR results were comparable with those in the primary endpoint population with a HR of 0.54 (95% CI: 0.42, 0.68; CS section B.2.6.1).

3.2.5.2 Overall survival

A statistically significant reduction in the risk of death (key secondary endpoint) was observed for the tucatinib-combination group compared to the placebo-combination group in the total study population with a HR of 0.66 (95% CI 0.50, 0.88; p=0.005) and a 4.5 month improvement in OS (Figure 2).

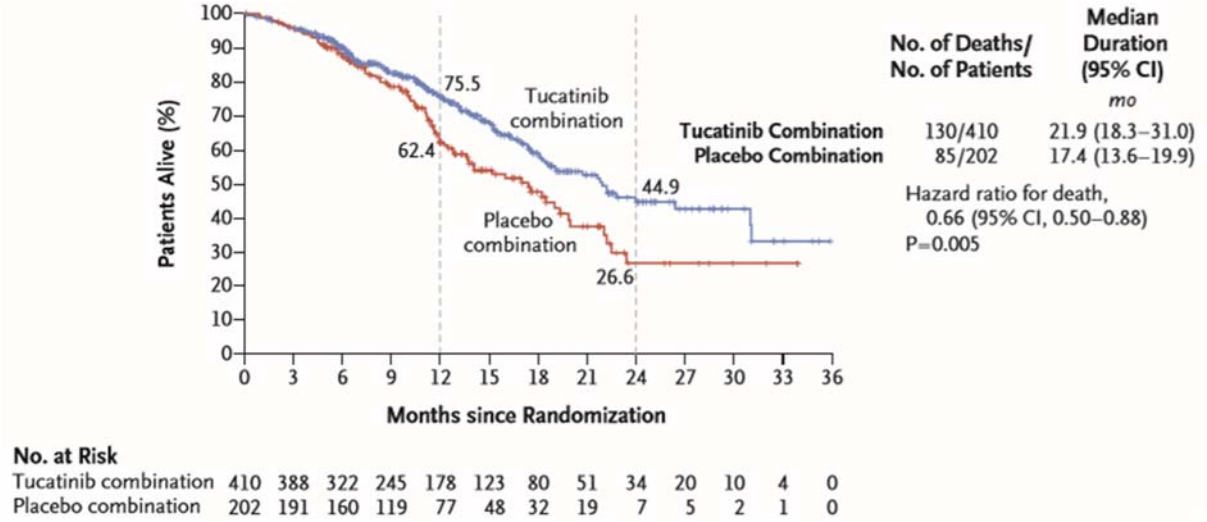


Figure 3 Kaplan-Meier estimate of OS per BICR (total study population; ITT-OS)

BICR, blinded independent central review; CI, confidence interval; mo, months; ITT, intent to treat; No, number; OS, overall survival; source: CS Figure 5

3.2.5.3 Objective response rate and duration of response

A higher proportion of patients had an objective response in the tucatinib-combination group compared to the placebo-combination group (46.0% vs 22.8%, p<0.00008; Table 9) in patients with measurable disease by BICR at baseline (n=511). Median DOR was longer in the tucatinib-combination group compared to placebo-combination group (median 8.3 vs 6.3 months) but the 95% confidence intervals overlapped suggesting no evidence of a difference between groups. (Table 9).

Table 9 Confirmed objective response per BICR and duration of response in patients with measurable disease at baseline

Outcome	Tucatinib combination (N=340)	Placebo combination (N=171)	p-value
Objective response, n (%)	138 (40.6)	39 (22.8)	<0.00008
95% CI	35.3, 46.0	16.7, 29.8	
Median duration of response (months)	8.3[a]	6.3[a]	Not reported[b]
95% CI	6.2, 9.7	5.8, 8.9	
Source: CS Table 8 and CS section B.2.6.7			

[a] in patients with a confirmed response
[b] nominal only

3.2.5.4 HRQoL outcomes

Baseline EQ-5D-5L data were available for a subset of the trial's total population (217 patients in the tucatinib-combination group and 112 patients in the placebo-combination group) as collection of baseline HRQoL data was only introduced after the start of the trial following a protocol amendment. The CS states that the baseline characteristics were similar between those patients with and without available baseline HRQoL data but does not present these data.

The CS presents graphical EQ-5D-5L VAS and subscale data only (CS Figures 10 and 11). The company additionally provided EQ-5D-5L index scores in response to clarification question A2 for the total population and for the subgroup of patient with brain metastases (Table 10). No comparative statistical analysis is provided (exploratory only). In the total population, [redacted]. In the subgroup of patients with brain metastases, [redacted]. The ERG clinical expert noted that these are meaningful changes with index scores rising to closer to population norms.

In both trial populations [redacted].

Similarly, the proportion of patients with moderate, severe or extreme problems were generally higher than baseline at the post-treatment 30 day follow up point, particularly in the tucatinib combination arm (CS Figure 11).

Table 10 EQ-5D-5L index scores in the total population and subgroup of patients with brain metastases

Time point	Total population		Patients with brain metastases	
	Tucatinib-combination	Placebo-combination	Tucatinib-combination	Placebo-combination
Baseline				
n	213	112	104	57
Mean (SD)	0.817 (0.158)	0.807 (0.190)	[redacted]	[redacted]
95% CI	0.796, 0.839	0.771, 0.842	[redacted]	[redacted]
Median	0.838	0.859	[redacted]	[redacted]
Cycle 3				
n	175	89	84	43
Mean (SD)	0.823 (0.164)	0.845 (0.155)	[redacted]	[redacted]
95% CI	0.799, 0.848	0.812, 0.878	[redacted]	[redacted]

Median	0.859	0.887	[redacted]	[redacted]
Cycle 5				
n	152	71	76	33
Mean (SD)	0.835 (0.185)	0.835 (0.157)	[redacted]	[redacted]
95% CI	0.806, 0.865	0.798, 0.872	[redacted]	[redacted]
Median	0.887	0.859	[redacted]	[redacted]
Cycle 7				
n	130	54	68	27
Mean (SD)	0.859 (0.143)	0.808 (0.188)	[redacted]	[redacted]
95% CI	0.834, 0.884	0.757, 0.860	[redacted]	[redacted]
Median	0.89	0.859	[redacted]	[redacted]
Cycle 9				
n	86	38	46	14
Mean (SD)	0.872 (0.129)	0.810 (0.246)	[redacted]	[redacted]
95% CI	0.845, 0.900	0.729, 0.891	[redacted]	[redacted]
Median	0.904	0.869	[redacted]	[redacted]
30 Day Follow Up				
n	72	42	29	21
Mean (SD)	0.738 (0.287)	0.778 (0.207)	[redacted]	[redacted]
95% CI	0.670, 0.805	0.713, 0.842	[redacted]	[redacted]
Median	0.835	0.835	[redacted]	[redacted]
Source: Clarification response Tables A2a and A2b; table drawn by ERG				

SD: standard deviation; CI: confidence interval

The ERG notes that only 50.6% and 47.0% of patients with baseline data and remaining in the study completed the EQ-5D-5L survey at the end of cycle 9 in the tucatinib- and placebo-combination groups respectively (CS Figure 10). Thus, data beyond cycle 9 are likely to be less reliable due to increased attrition. The CS does not describe any methods to impute missing HRQoL data. Section 4.2.9.1 of this report describes how the index scores from HER2CLIMB are used in the economic model.

3.2.5.5 Subgroup analyses

Results for PFS per BICR in patients with and without brain metastases

The CS reports results from the total population separately for patients with brain metastases (PFS brain metastases population) at baseline (key secondary endpoint, CS section B.2.6.3) and for patients without brain metastases (prespecified exploratory endpoint, CS section B.2.6.4). A statistically significant improvement in PFS was observed in patients with brain metastases in the tucatinib-combination group compared to the placebo-combination group Table 11. An improvement in PFS was also observed in patients without brain metastases (exploratory only; nominal p value<0.001). The effect size was

slightly greater in the subgroup of patients with brain metastases (52% reduction in progression or death) versus those without brain metastases (43% reduction), however, a formal comparison between these two groups was not intended or performed.

Table 11 PFS by BICR in patients with and without brain metastases

Outcome	With brain metastases[a] (key secondary endpoint)		Without brain metastases[a] (exploratory endpoint)	
	Tucatinib - combination (n=198)	Placebo-combination (n=93)	Tucatinib-combination (n=211)	Placebo-combination (n=108)
No. of PFS events (%)	106 (53.5)	51 (54.8)	91 (43.1)	60 (55.6)
Median PFS (95% CI)	7.6 (6.2, 9.5)	5.4 (4.1, 5.7)	9.6 (7.6, 12.4)	6.8 (4.3, 9.3)
HR (95% CI)	0.48 (0.34, 0.69)		0.57 (0.41, 0.80)	
p-value	p<0.001		Nominal p<0.001	
Table drawn by ERG. Source: CS sections B.2.6.3 and B.2.6.4				

[a] [redacted]

Results for PFS per BICR and OS for pre-specified subgroups

The effects of the tucatinib combination on PFS by BICR in the primary endpoint population and OS in the total population across pre-specified subgroups were generally consistent with the overall treatment effect for these outcomes (CS Figures 12 and 13). The 95% confidence intervals crossed the line of no effect indicating no evidence of a difference in PFS/OS between treatment arms for some subgroups . Slight differences in point estimates were observed for some subgroups, however, these should be interpreted with caution as these analyses were exploratory and no formal tests for interaction were performed.

3.2.5.6 Safety outcomes

3.2.5.6.1 Treatment exposure

Treatment exposure was assessed in all randomised patients who received at least one dose of study treatment in the primary endpoint safety population (n=474) and in the total safety population (n=601). The median duration of exposure for the tucatinib-combination group was 7.3 months and 4.4 months for the placebo-combination group in the primary endpoint safety population (CS Table 11).

In the total safety population, the median duration of treatment was 5.8 months for the tucatinib component of the intervention combination (5.7 months for capecitabine, 6.0 months for trastuzumab) and 4.4 months for the placebo component of the control combination (4.4 months for capecitabine, 4.6 months for trastuzumab).

In the total population (n=612), 118 (28.8%) patients in the tucatinib-combination group and 27 (13.4%) patients in the placebo-combination group were still receiving treatment at the data cut off.

3.2.5.6.2 Treatment emergent adverse events

Adverse events were assessed in all randomised patients who received at least one dose of study treatment (n=601). Treatment emergent adverse events (TEAEs) were defined as events that were new or worsened on or after receiving the first dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab) and up to 30 days after the last dose of study treatment. Rates of TEAEs, serious TEAEs and discontinuations due to TEAEs were comparable between trial arms (Table 12). A slightly higher proportion of patients experienced ≥Grade 3 severity TEAEs in the tucatinib-combination group (55.2%) compared to the placebo-combination group (48.7%).

CS Table 12 provides additional detail regarding dose modifications due to adverse events including doses withheld and dose reductions. Rates of dose modifications were generally higher for tucatinib (54.5%), capecitabine (77.5%) and trastuzumab (25.7%) in the tucatinib-combination group compared to the respective components of the placebo-combination group (41.1%, 61.9% and 19.3%).

Table 12 Summary of TEAEs (safety analysis population)

Adverse event, n (%)	**Tucatinib-combination (N=404)**	**Placebo-combination (N=197)**
Any TEAE	401 (99.3)	191 (97.0)
TEAE leading to discontinuation of:		
Any study treatment	45 (11.1)	19 (9.6)
Tucatinib/placebo	23 (5.7)	6 (3.0)
Capecitabine	41 (10.1)	18 (9.1)
Trastuzumab	18 (4.5)	5 (2.5)
Grade ≥3 TEAE	223 (55.2)	96 (48.7)

Adverse event, n (%)	Tucatinib-combination (N=404)	Placebo-combination (N=197)
Any TE serious adverse events	104 (25.7)	53 (26.9)
TEAE leading to death	8 (2.0)	6 (3.0)
Table drawn by ERG. Source: CS Tables 12 and 13		

TE, treatment-emergent; TEAE, treatment-emergent adverse event

The most frequently reported TEAEs in patients in the tucatinib-combination group were diarrhoea, hand-foot syndrome, nausea, fatigue and vomiting (Table 13). Most of these events were of Grade 1 or 2 severity.

Table 13 Most common (≥20% in the tucatinib-combination) adverse events (safety analysis population)

	Tucatinib-combination (N=404)		Placebo-combination (N=197)	
Adverse event	Any (N, %)	Grade ≥3 (N, %)	Any (N, %)	Grade ≥3 (N, %)
Diarrhoea	327 (80.9)	52 (12.9)	105 (53.3)	17 (8.6)
Hand-foot/PPE syndrome	256 (63.4)	53 (13.1)	104 (52.8)	18 (9.1)
Nausea	236 (58.4)	15 (3.7)	86 (43.7)	6 (3.0)
Fatigue	182 (45.0)	19 (4.7)	85 (43.1)	8 (4.1)
Vomiting	145 (35.9)	12 (3.0)	50 (25.4)	7 (3.6)
Stomatitis	103 (25.5)	10 (2.5)	28 (14.2)	1 (0.5)
Decreased appetite	100 (24.8)	2 (0.5)	39 (19.8)	0
Headache	87 (21.5)	2 (0.5)	40 (20.3)	3 (1.5)
AST increased	86 (21.3)	18 (4.5)	22 (11.2)	1 (0.5)
ALT increased	81 (20.0)	22 (5.4)	13 (6.6)	1 (0.5)
Source: CS Table 14 AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; PPE, palmar-plantar erythrodysesthesia				

3.2.5.6.3 Adverse events of special interest

CS Appendix F, Table 1 describes the frequencies of prespecified adverse events of special interest including diarrhoea, elevations in liver enzymes, elevations in serum creatinine, cerebral oedema and left ventricular dysfunction. Events of diarrhoea and elevations in liver enzymes were more commonly reported in the tucatinib-combination group, however, most events were <Grade 3 severity, were managed with supportive care and/or dose

modification and ≤1% of patients discontinued treatment due to these events. Elevations in serum creatinine were also more common in the tucatinib-combination group but were reversible and no patients discontinued therapy due to these events. Left ventricular systolic dysfunction leading to dose modification or discontinuation and cerebral oedema events were infrequent (≤2% of patients) with no cerebral oedema events reported in the tucatinib-combination group.

3.2.5.6.4 Use of adverse event data in the economic model

The frequencies of grade 3/4 severity TEAEs reported in ≥2% of patients in the HER2CLIMB trial are used in the company's base case economic model to calculate costs and health resources. Trial-derived utilities are assumed to capture utility loss due to adverse events (CS B.3.4.4). Further details on the sources of adverse event data for the company's chosen comparators are described in Section 4.2.8.

3.2.6 Pairwise meta-analysis of intervention studies

As only one clinical trial of tucatinib was reported in the CS, a pairwise meta-analysis of clinical effectiveness studies was not possible.

3.3 Critique of studies included in the network meta-analysis (NMA)

3.3.1 Rationale for indirect comparisons

The HER2CLIMB trial provides a direct comparison between tucatinib in combination with trastuzumab and capecitabine versus trastuzumab and capecitabine (plus placebo). The control arm of the pivotal HER2CLIMB trial is not, however, a relevant comparator in the NICE scope for this appraisal and the decision problem. The NICE scope states eribulin, capecitabine or vinorelbine as relevant comparators at third-line treatment of patients with HER2+ locally advanced or metastatic breast cancer. Therefore, in the absence of direct head-to-head comparisons the company conducted a network meta-analysis (NMA) to provide indirect comparisons between tucatinib and these treatments. Hazard ratios for PFS and OS analyses from these indirect comparisons directly inform estimates of clinical effectiveness used in the economic model.

3.3.2 Identification, selection and feasibility assessment of studies for NMA

The company's SLR of clinical effectiveness studies (section 3.1 above) was used to inform HTA reimbursement submissions across multiple national markets including England (clarification response A2). The SLR therefore includes a broader range of treatments than

those currently licensed for use in the UK for locally advanced or metastatic HER2+ breast cancer.

The SLR identified [redacted] of which [redacted] were included in the evidence network. Reasons for exclusion of studies from the NMA are listed in CS Appendix D Table 14.

[redacted] however, in response to an ERG query, the company clarified that these five studies do not provide additional connectivity for the comparators relevant to the decision problem and due to their positioning as "terminal" nodes in the evidence network. Therefore, they do not influence the relative effect estimates of the relevant intervention and comparator treatments in the NMA (i.e. the tucatinib combination; eribulin; vinorelbine; and capecitabine) (clarification response A3). The ERG is satisfied that these five studies do not affect comparisons relevant to the decision problem. Thus, the NMA includes seven "relevant" trials (HER2CLIMB, CEREBEL, ELTOP, GBG26, EGF100151, Study 301, NCT02225470) that provide direct or indirect comparisons of interest. Henceforth, we have therefore confined our review to these seven studies (Figure 4).

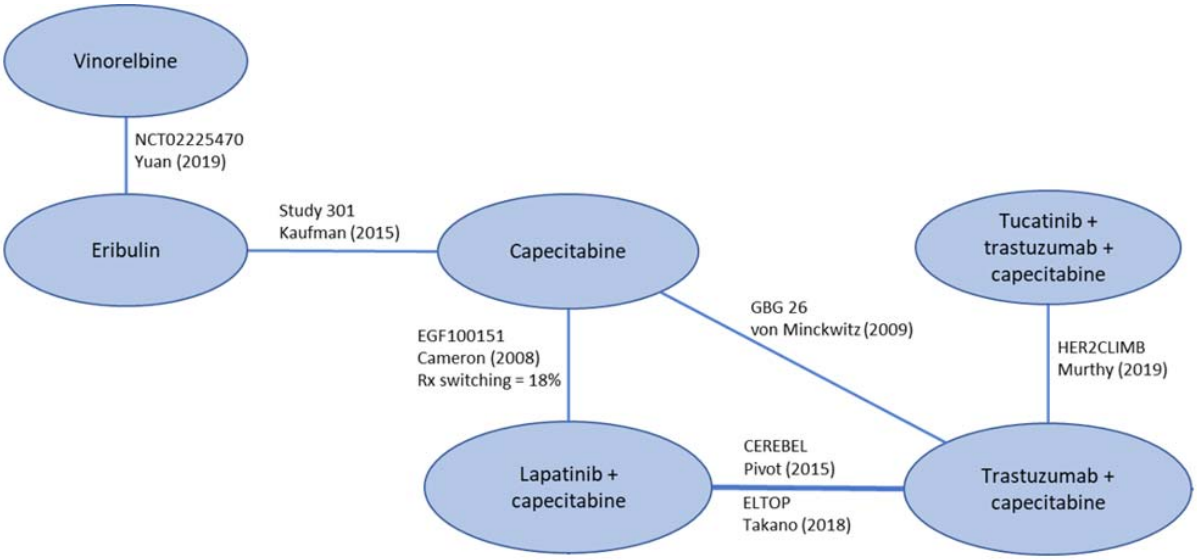


Figure 4 Company evidence network with seven studies relevant to the decision problem

Adapted from CS Figure 14

All seven studies were included in the NMA for the PFS outcome and six of the seven studies were included in the NMA for the OS outcome (Table 14). The GBG 26 study was excluded by the company from the NMA for OS [redacted]. At the

ERG's request the company reported a scenario analysis which retained the GBG 26 study using the unadjusted OS HR (clarification response A17). (see section 3.4.1)

Table 14 Studies contributing to NMA for PFS and OS outcomes

Study identifier	PFS	OS
HER2CLIMB[4]	Yes	Yes
ELTOP[10]	Yes	Yes
CEREBEL[11]	Yes	Yes
GBG 26[12]	Yes	No
EGF100151[13]	Yes	Yes
Study 301[3]	Yes	Yes
NCT02225470[14]	Yes	Yes

The primary objective of the SLR was to identify studies in the population of patients with progression after previous treatment with at least two prior anti-HER2 regimens or at least two prior chemotherapy treatments before eribulin therapy in HER2+ patients.

[redacted] to include studies in patients who had received one or more prior anti-HER2 regimens (or one or more chemotherapies prior to eribulin). The ERG considers this approach reasonable given the lack of available trials. This applied to two of the seven studies (EGF100151 and CEREBEL) but the trial publications do not report the actual numbers of prior lines of therapy used by patients in these trials so it is unclear whether these differ substantially from the other trials in the network. The ERG note that this may introduce heterogeneity in the NMA but the impact is uncertain.

A subgroup analysis for patients with brain metastases was not included in the CS. Whilst the HER2CLIMB trial permitted inclusion of participants with active brain metastases, such participants were not generally eligible for inclusion in trials of the comparator treatments. The ERG agrees there is insufficient data are available to perform an NMA subgroup analysis by brain metastases status. Although it was not feasible to conduct a subgroup analysis for patients with brain metastases, the ERG present an exploratory scenario analysis using the HRs from the subgroup of patients without metastases from HER2CLIMB (see section 3.6).

Finally, the ERG's clinical expert considered that the HER2CLIMB trial direct evidence is available for the subgroup of people with brain metastases for a comparison between the

tucatinib combination versus trastuzumab plus capecitabine. As mentioned earlier (section 2.2.3), in practice, trastuzumab plus capecitabine is given to some patients at third line, even though it is not licensed for this indication. However, to reiterate, trastuzumab plus capecitabine is not included as a comparator in the NICE scope for this appraisal.

3.3.3 Assessment of heterogeneity

3.3.3.1 Clinical heterogeneity

The company proposed several prognostic factors in HER2+ metastatic breast cancer (clarification response Table A13) including age, hormone receptor status, presence of visceral disease, ECOG performance score and prior endocrine therapy. Prior treatment with pertuzumab or trastuzumab, the number of previous lines of therapy and presence of brain metastases were identified as potential treatment effect modifiers. The ERG's clinical expert considers the company's proposed effect modifiers to be reasonable, but he also noted that hormone receptor status and presence of visceral disease could be effect modifiers as well as prognostic factors.

Baseline characteristics of the seven studies included in the NMA are compared in CS Table 10 and Appendix D Table 17. The ERG considered several potential sources of heterogeneity include:

- **Brain metastases.** Almost half of patients in HER2CLIMB trial had brain metastases at baseline, including active brain metastases. In the other studies, patients with brain metastases were either excluded altogether, or were included if brain metastases were stable, or represented a smaller proportion of the trial population. The company states that any bias introduced by these differences in trial populations may understate the relative benefit of tucatinib (clarification response A13). This would assume that patients with brain metastases are less likely to benefit from treatment. However, in the HER2CLIMB trial, the OS and PFS HRs for the subgroup of patients with brain metastases were numerically but not statistically significantly more favourable for the tucatinib combination than for those patients without brain metastases (see section 3.2.5.5). It is unclear if this observation is unique to the HER2CLIMB trial or whether this would apply to other treatment comparisons. The ERG clinical expert noted that such patients generally have a much worse prognosis and only rarely respond to chemotherapy alone or in combination with targeted treatments (trastuzumab or lapatinib). The ERG considers that the direction and magnitude of any bias in the NMA is uncertain because it is unclear whether patients with brain metastases are more or less likely to benefit from the tucatinib-combination

or any other treatment than patients without brain metastases. Our NMA scenario analysis (section 3.6) excluding the subgroup of patients with brain metastases from HER2CLIMB resulted in slightly less favourable survival estimates for the tucatinib combination.

- **Previous lines of treatment.** Two studies (EGF100151 and CEREBEL) included patients with one or more prior lines of therapy while most other studies included patients with two or more prior lines of therapy. Time since diagnosis was shorter in the latter study. The CS does not report the number of lines of prior therapy per trial, but mentions that patients in the HER2CLIMB trial were more heavily pre-treated than in the other studies included in the NMA and that many of the studies in the NMA did not include patients previously treated with agents such as pertuzumab as this drug was not approved at the time the studies were conducted (clarification response A13).
- **Previous exposure to anti-HER2 treatment**. The two eribulin studies (Study 301 and NCT02225470) included patients who had previously received chemotherapy only.

  [redacted]

  (Appendix D Table 17).
- **Mixed HER2 status**. Study 301 and NCT02225470 included a mixture of HER2 positive and negative patients while the other studies included HER2 positive patients only. Only the HER2 positive subgroup data were used in the NMA except for the OS outcome in the NCT02225470 trial where only data for the mixed population were available. The ERG notes that only a fifth of patients in this study were HER2+.
- **Performance status**. The proportion of patients with ECOG score of 1 varied from 28% to 98% across the seven studies. Although ECOG score is a likely prognostic factor, it is unclear whether this is also an effect modifier.
- **Race**. Most studies included mainly Caucasian patients, but two studies included only Chinese and Japanese patients respectively (NCT02225470 and ELTOP). It is unclear whether treatment effect may vary by race or ethnicity.

Other potential sources of heterogeneity may have arisen from differences in study methodology:

[redacted] 3.4.1 [redacted]

[redacted]

The company considers that the main source of heterogeneity in the network is differences in prior exposure to specific anti-HER2 therapies. However, they did not consider methods such as covariate adjustment to account for this to be appropriate. The ERG agrees as the number of studies available would likely preclude reliable covariate adjustment. The company state that there was no evidence of high heterogeneity and did not therefore consider it appropriate to exclude studies from the NMA e.g. in sensitivity analyses. The ERG considers this decision appropriate since exclusion of studies such as ELTOP and CEREBEL would remove the closed loop within the network and potentially weaken the NMA. The company did attempt to evaluate heterogeneity by using a random effects model in their NMA scenario analyses. We critique this further in Section 3.4.2.

3.3.3.2 Statistical heterogeneity

CS section B.2.9.1.4 reports an I^2 value of 30.6%, suggesting a moderate level of statistical heterogeneity in the overall network, although Cochran's Q test for heterogeneity was not significant at the 5% level (p=0.237). It is not clear which outcome (PFS or OS) this value refers to and limited details are provided in the CS on the method used to calculate heterogeneity statistics for the overall network. Outcome-specific heterogeneity parameters are reported as follows:

[redacted]).

ERG conclusion on heterogeneity

The ERG considers the differences between trials in the percentage of patients with active brain metastases to be an important potential source of heterogeneity. The HER2CLIMB trial may over-represent these patients while the comparator trials under-represent them. The magnitude and direction of any bias is uncertain, and thus it remains unclear whether the treatment effect from the NMA adequately represents that in a typical UK population.

3.3.4 Similarity of treatment effects between direct and indirect evidence

There was one closed loop for the PFS evidence network comprising three treatments (from four trials): capecitabine, lapatinib plus capecitabine, and trastuzumab plus capecitabine. Node-splitting analysis found no statistically significant inconsistency ($p>0.05$) between the direct and indirect evidence in this loop (CS section B.2.9.1.4), however, the exact p value is not provided in the CS. The company compared the treatment effects within individual pair-wise comparisons for the two trials (ELTOP and CEREBEL) in this loop that compared lapatinib plus capecitabine with trastuzumab plus capecitabine. Point estimates for PFS and OS from these two trials were in opposing directions and although Cochran's Q test did not provide strong evidence of statistical heterogeneity between these two trials for PFS (p[redacted]), some evidence of statistical heterogeneity was evident for OS ([redacted]; assuming a 10% significance level).

[redacted].

3.3.5 Risk of bias assessment for studies included in the NMA

The company assessed the risk of bias for all seven studies included in the NMA using criteria recommended by NICE (CS Appendix D, Tables 22 to 28). This assessment included an appraisal of the method of randomisation, allocation concealment, balance in baseline study characteristics across trial arms and selective reporting of results. The ERG independently appraised the studies using the NICE criteria and our judgements generally concur with those in the CS. We regard these trials as being generally at a low risk of bias, with the main exception being high risk of detection and performance bias due to lack of blinding in most studies

ERG conclusion on the studies included in the NMA

The company have selected appropriate studies for inclusion in the NMA and the ERG is not aware of any other eligible studies missing. The HER2CLIMB trial and comparator trials in the NMA were generally considered to be at low risk of bias. The ERG has concerns regarding evidence of clinical heterogeneity in the NMA which likely arise from differences in patient characteristics between the trials. In particular, the trials vary considerably in the proportion of patients with active brain metastases. It is unclear, however, whether patients with active brain metastases are more likely to benefit from treatment with tucatinib than those without brain metastases, or with stable brain metastases, and therefore whether relative effect

estimates are biased. The company views the differences between trials in the number of previous treatments patients had received as the main source of heterogeneity. However, the company has not formally addressed these concerns using sensitivity analyses or covariate adjustment methods. The ERG considers this to be appropriate given the limited number of studies in the network. Thus, at present, the clinical effectiveness of the tucatinib combination versus the decision problem comparators is uncertain due to unexplained heterogeneity in the NMA.

3.4 Critique of the network meta-analysis (NMA) statistical methods

3.4.1 Trial data inputs to the NMA

The ERG inspected the OS and PFS data values from the seven trials included in the NMA (CS Appendix D Table 18), and note the following issues:

- In some studies, more than one HR is reported per outcome measure, but it is not explicit which HR was used in the NMA model.
- One study (study NCT02225470) was included in the OS network (CS Figure 15) but no HR for OS was reported in CS Appendix D Table 18.
- Conversely, a HR for OS is reported for the GBG 26 trial but this study was excluded from CS Figure 15.

The company resolved the above issues in response to a clarification question by the ERG (clarification response A4a). However, there was one remaining issue with the data which the company did not resolve; the ERG noted the OS HR for the CEREBEL study is reported as 1.18 (95% CI of 0.760, 1.183) in the CS. The company confirmed this was the correct figure, taken from the supplement to the Pivot et al (2015) journal paper[11] (clarification response A4b). However, to the ERG the upper bound CI does not seem plausible and we suggest the correct value should be 1.83.

[redacted] Hence, the ERG contacted the principal author of the trial manuscript to request clarification. Professor Xavier Pivot subsequently confirmed that 1.83 is the correct value and that the published paper contained a typographical error (personal communication, 16/06/21). An updated figure from Professor Pivot is provided in Appendix 9.3. We use the correct value in the ERG's additional NMA analyses, presented below in section 3.6.

All seven studies provided data for the PFS outcome measure, however, only six studies were included in the OS analysis [redacted]. At the ERG's request the company reported a scenario analysis which retained the GBG 26 study using the unadjusted OS HR (clarification response A17). This analysis resulted in HRs which were less favourable than those obtained in the base case for the tucatinib combination compared to eribulin, capecitabine and vinorelbine in fixed effect and random effects models.

3.4.2 Statistical methods used in the NMA

The company conducted NMA using two contrasting approaches:

1. A **Bayesian hazard ratio (HR) NMA** reporting results for both fixed effect and random effects models. This approach assumes proportional hazards between treatments, and the relative treatment effect is represented by a constant HR.
2. A **fractional polynomial NMA** to account for potential violation of the proportional hazards assumption in some of the included trials. The fractional polynomial analysis generates results which reflect the time course of the log-hazard function and the relative treatment effect is represented by a time-varying HR.

As will be explained, the ERG considers that the proportional hazards assumption cannot necessarily be rejected and therefore we consider the HR NMA is suitable for the decision problem. We focus on the HR NMA approach in the following sub-sections, and provide a brief appraisal of the fractional polynomial NMA in Appendix 9.4.

[redacted]. This approach is in line with a recent published NMA by Paracha et al (2020),,[6] although Paracha et al (2020) used slightly different informative priors from an earlier version of the Turner paper.[16] Paracha et al (2020) favoured random effects to account for between-study heterogeneity.

The company validated the Bayesian HR NMA by repeating the analysis using frequentist methods (CS Figures 19 & 21). It was found that the two methods provided consistent results. The deviance information criterion (DIC) was reported for the Bayesian models to compare relative model fit (CS sections B.2.9.2.1 & B.2.9.2.2). Random effects results were not provided in the CS but were reported in response to an ERG clarification question (A5).

Meta-regression to address heterogeneity was precluded due to the limited number of available studies.

3.4.2.1 Proportional hazards assessment

An examination of log (-log) plots appears to show some potential violation of the proportional hazards assumption (clarification response A7; NMA report sections 6.1.1 and 6.1.2). The ERG asked the company to provide Schoenfeld residuals plots to inform an assessment of proportional hazards (clarification question A7), however these were not provided. ([redacted]).

[redacted]

The ERG concludes that there is insufficient evidence to reject the proportional hazards assumption and therefore the HR NMA is acceptable to estimate relative treatment effects for the tucatinib combination and comparators in this appraisal.

3.4.2.2 External validation

The random effects results of the company's HR NMA were generally consistent with those of the recently published NMA by Paracha et al (2020). (N.B. Paracha et al reported a smaller of network of studies, excluding HER2CLIMB, NCT02225470, and Study 301 but including GBG 26, EGF100151, ELTOP, and CEREBEL). Outcomes for OS and PFS comparing capecitabine, lapatinib + capecitabine, and trastuzumab + capecitabine (i.e., the comparisons common to both NMAs) were similar apart from the OS for capecitabine versus trastuzumab + capecitabine. However, results are similar when compared to the company's scenario analysis including the GBG 26 trial (clarification response A17). The ERG is satisfied with the external validity of the results, albeit we note that both the company and Paracha et al used the OS HR with the typographical error in the upper bound of the CI from Pivot et al [11].

Computer programming code was provided by the company for all NMA models including fractional polynomials (CS Appendix D, Figures 2-8). The trial data input values for the HR NMA provided in CS Appendix D, Tables 18 & 19 are superseded by Table A4a clarification question response). Reconstructed IPD data for use in the fractional polynomial model were provided in clarification response A8. The IPD data formatted to use in with the

JAGS/WinBUGS code were requested by the ERG but was not provided, nor were the initial values used with the code (clarification question A8). The ERG found no issues with the code and are satisfied the analysis is appropriate.

3.4.2.3 Choice between random effects and fixed-effect model

The company used a fixed-effect model for both OS and PFS due to random effects results showing "inconsistencies" in terms of statistically significant results compared with the trial data (sections B.2.9.2.1 & B.2.9.2.2, clarification response A6). Whilst the respective trials reported statistically significant differences between treatments, the random effects NMA model did not. Of note, in the HER2CLIMB trial the tucatinib combination arm showed a statistically significant OS benefit over the control arm ([redacted] which was not observed in the Bayesian random effects results ([redacted]; Clarification responses Figure A5a).

[redacted] (CS Appendix D, pages 83-84). [redacted]

Whilst the Bayesian HR NMA fixed-effect model was used as the base case, the company's scenario analyses investigated the Bayesian HR NMA random effects model, and fixed-effect and random effects fractional polynomials.

In contrast to the company, the ERG favours use of the random effects model with an informative prior; this avoids the over-estimate of uncertainty from using a vague prior in a network with few studies per comparison, and the underestimate of uncertainty from using a fixed-effect model due to between-study heterogeneity.

3.4.3 Summary of ERG critique of the NMA

- The company performed NMA based on a comprehensive SLR of clinical effectiveness studies. The ERG has no concerns that relevant studies are missing from the SLR and hence the NMA.
- Two contrasting approaches were used: a Bayesian constant hazards NMA, based on the assumption of proportional hazards between treatment comparisons; and a fractional polynomial NMA with time-varying hazards, based on the assumption that the proportional hazards assumption may not hold in all studies. The ERG's view is

there is insufficient evidence to reject the proportional hazards assumption, and the Bayesian HR NMA is more appropriate than the fractional polynomial NMA.

- Potential violations of proportional hazards are most likely to affect studies in the wider evidence network, rather than the seven trials directly relevant to the decision problem. Hence, the HR NMA is acceptable as a source of comparative evidence in this appraisal.
- The company chose the fixed effect model for their NMA base case. As discussed earlier in section 3.3.3, we have concerns about the unexplained heterogeneity in the evidence network with regard to likely effect modifying specific patient characteristics at baseline which are likely to be effect modifying (e.g. presence of active brain metastases, and number of previous treatment lines received). A heterogeneous evidence network is incompatible with the assumption of a fixed-effect model (i.e. that all trial effect estimates are estimating the same underlying intervention effect). We therefore consider a random effects model is more appropriate in this instance as it takes into account heterogeneity, though it does not remove it.
- The upper bound of the CI containing the OS HR in the journal publication of the trial by Pivot et al (2015) contains a confirmed typographical error. Hence, the narrow CI used by the company gives this study a disproportionately higher weight in the company's base case fixed-effect HR NMA. The ERG has corrected this error in our NMA analysis (section 3.6).

3.5 Results of the indirect comparison

In the fixed effect analysis (company base case), the [redacted] (Table 15). In the random effects (company scenario), [redacted] (Table 16).

Table 15 Company Bayesian HR NMA - fixed effect results (base case)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Source: reproduced from CS p45, document B

Table 16 Company Bayesian HR NMA – random effects results (scenario)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

Source: Reproduced from Figures A5a, A5c clarification responses

3.6 Additional work on clinical effectiveness undertaken by the ERG

The ERG conducted the following additional analyses based on the company's NMA:

1. Correction of the Pivot et al (2015) study upper bound CI in the OS HR NMA analysis (ERG "base case")
2. Use of an alternative informative prior for PFS (random effects only)
3. Use of the HRs from the subgroup of patients without brain metastases in the HER2CLIMB trial.

The ERG used the same number of burn-in and iterations as the company for the fixed effect and random effects models. Both models were thinned, although on inspection of autocorrelation plots we considered less thinning of consecutive samples was required (we thinned observations by a factor of 10 in the fixed effect, and 50 in random effects).

3.6.1 Correction of the Pivot et al (2015) study upper bound CI for OS

As noted above, the company used the incorrect upper CI bound for the OS HR [1.18 (95% CI 0.76, 1.183)] reported by Pivot et al (2015). We use the corrected upper bound [1.18 (95% CI 0.76, 1.83)]. As stated above, a narrower CI gives relatively more weight to the study in a fixed effect meta-analysis (the company base case). Table 17 shows the impact of using the corrected figure: in the fixed-effect NMA, the tucatinib combination is no longer statistically significantly better than eribulin and vinorelbine. The ERG prefers the random effects due to heterogeneity between studies as noted above.

Table 17 ERG Bayesian HR NMA – OS scenarios (corrected Pivot et al HR)

Tucatinib combination versus	Fixed effect OS HR (95% CrI)	Random effects OS HR (95% CrI)
Eribulin	0.53 (0.26, 1.06)	0.55 (0.17, 2.05)
Capecitabine	0.51 (0.28, 0.94)	0.53 (0.19, 1.63)
Vinorelbine	0.55 (0.26, 1.14)	0.57 (0.15, 2.42)

[redacted]

3.6.2 Use of an alternative informative prior for PFS (random effects only)

The company chose the "Cause-specific mortality/major morbidity event/composite" outcome from Turner 2015[15] to define the informative prior for PFS [Lognormal (μ=-3.95, σ=1.79^2)] where μ and σ are the mean and standard deviation on the log scale. Previous NICE appraisals have used an alternative category "Internal/external structure-related outcomes" [Lognormal (μ=-2.94, σ=1.79^2)] to represent PFS (e.g. NICE TA492, TA584). The ERG thus considered this alternative informative prior as a scenario for random effects PFS. Results were similar compared to the company model with a slightly wider 95% credible interval (Table 18).

Table 18 ERG Bayesian HR NMA – random effects results (alternative informative PFS prior)

Tucatinib combination versus	PFS HR (95% CrI)
Eribulin	0.25 (0.08, 0.77)
Capecitabine	0.34 (0.14, 0.82)
Vinorelbine	0.23 (0.06, 0.91)

CrI, credible interval

3.6.3 Subgroup analysis of patients without brain metastases in the HER2CLIMB trial

We conducted a scenario using the HRs from the subgroup of patients without brain metastases from the HER2CLIMB trial. The HR for PFS in patients without brain metastases is provided in CS B.2.6.4 (0.57, 95% CI 0.41, 0.80) and the HR for OS is provided in CS B.2.7.2 (0.72, 95% CI 0.48, 1.08). A caveat to this analysis is that some of the comparator studies reported small proportions of patients with brain metastases at baseline, but they did not report outcomes separately by brain metastases status. A further caveat is that PFS in patients without brain metastases in HER2CLIMB is an exploratory endpoint with nominal statistical significance testing. Table 19 shows there is no change in statistical significance in this subgroup but the HRs are less favourable for the tucatinib combination versus comparators than those based on the whole trial population. This is to be expected as patients in HER2CLIMB with brain metastases had numerically (but not

statistically) better PFS HRs than patients without brain metastases (see section 3.6.3 of this report).

Table 19 ERG Bayesian HR NMA – Random effects scenarios (HRs from HER2CLIMB in patients without brain metastases)

Tucatinib combination versus	OS HR (95% CrI)	PFS HR (95% CrI)
Eribulin	0.60 (0.17, 2.36)	0.26 (0.11, 0.66)
Capecitabine	0.58 (0.20, 1.91)	0.36 (0.17, 0.73)
Vinorelbine	0.62 (0.15, 2.80)	0.25 (0.08, 0.75)

Note: the OS analysis includes the Pivot et al correction

Although the NCT02225470 trial comprises a mixed HER2+/- population, we did not deem it necessary to conduct a scenario analysis excluding this study. NCT02225470 is peripheral to the network in that it only serves to connect vinorelbine to the network via eribulin (Figure 4). Hence, its omission would only serve to remove the indirect comparison with vinorelbine and would not impact any of the other treatment effects.

4 COST EFFECTIVENESS

4.1 ERG critique of the company's review of cost-effectiveness evidence

The company conducted a combined systematic literature search to identify published economic evaluations, utilities and resource use or cost data for locally advanced unresectable, or metastatic HER2+ breast cancer with progression after previous treatment. The search reported in CS section B.3.1 and Appendix G was conducted in November 2018, and updated in March 2021, as reported in an addendum submitted with the company's response to clarification questions.[18] The reporting of the search strategies and results was clear. Results are presented in CS section B.3.1 and CS Appendix G for economic evaluations; CS section B.3.4.3 and Appendix H for the review of utilities; and CS section B.3.5 and Appendix I for the review of resource use and cost data. The clarification addendum summarises results from the original and updated reviews.

Sixteen economic evaluations were included in the original review and an additional five in the update. None these evaluations address the current decision problem. One recent abstract reported a US cost-utility analysis comparing trastuzumab deruxtecan with tucatinib combination treatment (Vondeling et al. 2020), and another abstract reported a US budget

impact analysis comparing neratinib, lapatinib and tucatinib combination therapies (Anderson et al. 2020).[19 20]

The search identified four UK evaluations of other treatments for the population of interest, including: the NICE (TA458) and Scottish Medicines Consortium (SMC) appraisals of T-DM1; and the SMC cost comparison of intravenous and subcutaneous trastuzumab.[21-23]The company use TA458 to inform decisions about the economic evaluation (CS B.3.3.1 Table 18) and health state costs (CS B.3.5.2). It is not clear why the NICE appraisal of eribulin (TA423)[24] is not included in the company's review of economic evaluations. However, it is referred to as a source of information in relation to their economic evaluation (CS B.3.3.1 Table 18), utilities (CS B.3.4), and the cost of adverse events (B.3.5.3).

ERG conclusion

The company's search strategy and eligibility criteria for their review of cost-effectiveness studies are appropriate. The search did not identify any economic evaluations that directly address the decision problem.

4.2 ERG summary and critique of the company's economic evaluation

4.2.1 NICE reference case checklist

The ERG assessed the company's economic evaluation against NICE Reference Case requirements as shown in Table 20.

Table 20 NICE reference case

Issue	Reference case	ERG comment
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company only reported pairwise comparisons, but their model includes a 'multiway analysis' function that facilitates full incremental analysis.

Issue	Reference case	ERG comment
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. The base case model has a time horizon of 20 years (from 54 to 74 years of age). The company state that they explored a time horizon of 30 years (CS B.3.2), but this is not reported, and the model is limited to a maximum of 20 years. This is not an important omission, given survival predictions for the population of interest (modelled 10-year survival is less than 1%).
Synthesis of evidence on health effects	Based on systematic review	Yes. The company use results from their systematic review and NMA to model survival outcomes (CS B.2.9 & B.3.3.4).
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes. The model estimates QALYs. Utilities for the tucatinib combination is derived from HER2CLIMB EQ-5D-5L data. Utilities for comparators are based on values used in NICE TA423[24] (CS section B.3.4.10).
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes. HER2CLIMB EQ-5D-5L data are valued using the van Hout crosswalk algorithm with the UK value set (CS section B.3.4.1 to B.3.4.2).[25] Comparator utilities from TA423 are derived from a mapping to UK EQ-5D-3L values and direct elicitation from a UK general population sample.[1 2]

Issue	Reference case	ERG comment
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company describe the structure and key features of their model in CS section B.3.3. Assumptions are summarised in CS Tables 17-19 and 33; and parameters in CS sections B.3.3 to 3.5, with an overview in CS Table 33. The model uses a partitioned survival structure, with a cycle length of 1 week and 20-year time horizon. No half-cycle correction was incorporated due to the short cycle length. Costs and QALYs are discounted at 3.5% per year. The model consists of three 'partitioned survival' health states, as illustrated in Figure 5:

- *Progression-free (PF):* the proportion of patients alive and progression-free (PFS)
- *Progressed disease (PD):* the proportion of patients alive (OS) minus the proportion of patients alive and progression-free (PFS)
- *Death:* calculated as one minus the proportion of patients alive (OS)

Patients enter the model in the progression-free state and can experience disease progression or death. While in the progressed disease state, patients receive subsequent lines of anticancer therapy and supportive care.

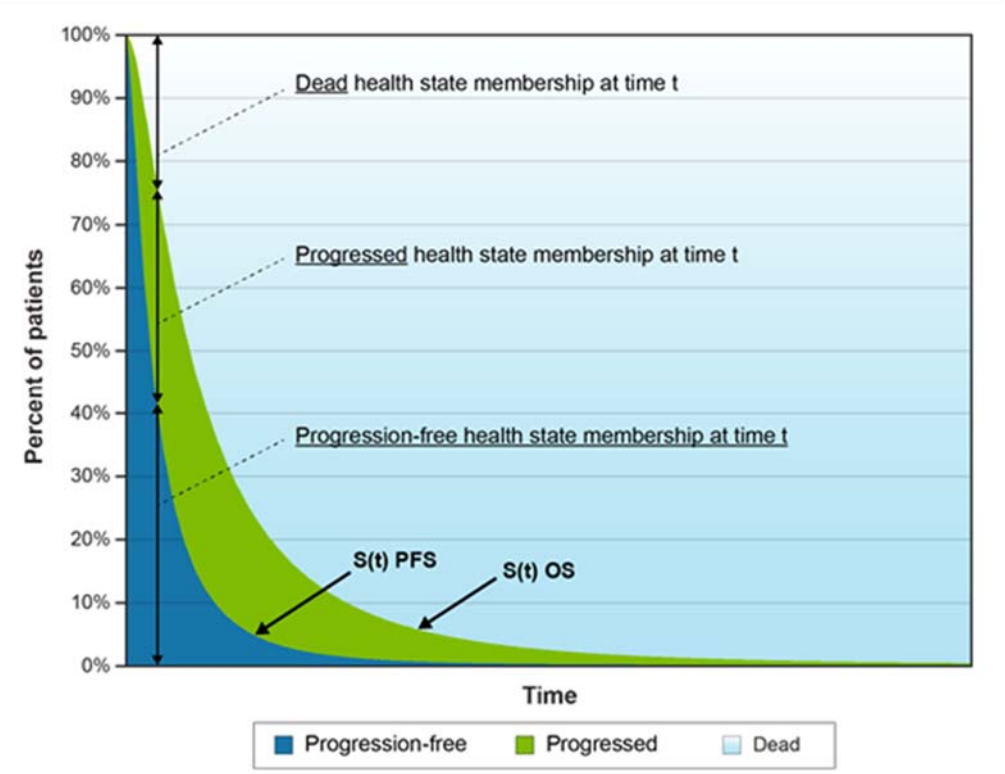


Figure 5 Partitioned survival model structure
Source: reproduced from CS Figure 22

ERG conclusion

The model structure is appropriate and accurately implemented. We agree with the partitioned survival approach.

4.2.3 Population

The company model a population of adults with HER2+ metastatic breast cancer who have received two or more prior anti-HER2 regimens (CS section B.3.2.1). Baseline characteristics of the modelled cohort are based on those of patients in HER2CLIMB: mean age 54 years; mean body surface area 1.8 m^2; mean body weight 69.5 kgs (CS Table 33).

The HER2CLIMB trial included patients with presence or a history brain of metastases: nearly 50% of the total study population (CS Table 6). The NICE scope requested subgroup analysis for patients with brain metastases if the evidence allows. The company did not attempt to model cost-effectiveness for this subgroup, on the basis that there is a lack of clinical evidence for the scope comparators in this subgroup. See 3.3.3 above for a discussion of this and other differences in patient characteristics between HER2CLIMB and other trials included in the NMA.

ERG conclusions

- The modelled population is consistent with the licensed indication for the tucatinib combination and that specified in the NICE scope.
- It is not clear whether the HER2CLIMB trial (which included a high proportion of patients with brain metastases) or other trials in the NMA (which largely excluded patients with brain metastases) provide a more realistic reflection of the target population in routine practice. This heterogeneity has implications for survival modelling because OS and PFS extrapolations anchored by curves fitted to the HER2CLIMB data differ from those based on fractional polynomial curves estimated from the NMA (see section 4.2.6).
- Modelling cost-effectiveness for the subgroup of patients with brain metastases is problematic, due to the lack of evidence for the comparators in this subgroup. However, omitting this subgroup analysis does not negate the need for estimates of relative treatment effectiveness across this heterogeneous evidence base.

4.2.4 Interventions and comparators

The company describe the intervention and comparators in their decision problem in CS section B.1.2. The submitted model includes the tucatinib combination and scope comparators (eribulin, capecitabine and vinorelbine). It also includes trastuzumab with capecitabine, which can be used as a reference arm to link survival extrapolations for the tucatinib combination with those for comparators in the network of clinical evidence. The company focus on the comparison with eribulin in their economic analysis (CS B.3.7 to B.3.9). They report scenarios with pairwise ICERs for the tucatinib combination compared with capecitabine and with vinorelbine (CS Tables 40 and 41), but do not explore the sensitivity of these results, or report a full incremental analysis.

We note that trastuzumab + capecitabine is not licensed or recommended by NICE for the population of interest and was not included in the NICE scope. Expert advice to the ERG is that clinical practice varies, and that some NHS centres do use trastuzumab with capecitabine at third line. It is not clear if this constitutes routine practice, or therefore whether it should be included as a comparator in the economic analysis.

ERG conclusion

The company only report pairwise cost-effectiveness estimates, rather than a full incremental analysis as recommended by NICE. In ERG analysis, we present full incremental results for the tucatinib combination against all of the scope comparators

(see sections 6.3 and 6.4). We also report incremental results including trastuzumab + capecitabine, as this is used in some NHS centres.

4.2.5 Perspective, time horizon and discounting

The company uses a 20-year time horizon and take the perspective of the NHS and PSS in England. Both costs and outcomes (life years and QALYs) are discounted at 3.5%, in line with the NICE guidance.

4.2.6 Survival analyses

The company uses data from the HER2CLIMB study as well as the NMA to produce long term extrapolations of PFS and OS (CS B.3.3.4). Three main sets of survival parameters are included in the model and are discussed below:

1. OS and PFS curves fitted to HER2CLIMB data
2. OS and PFS curves estimated from the fractional polynomial NMA
3. Relative treatment effects from the hazard ratio NMA

4.2.6.1 OS and PFS curves fitted to HER2CLIMB data

Survival curves fitted to HER2CLIMB data for the tucatinib combination and trastuzumab + capecitabine. The company report analysis with 23 survival models fitted to individual patient data from the trial, including:

- Conventional parametric distributions (exponential, Weibull, log-normal, log-logistic, gamma and generalised gamma)
- Flexible spline models (Weibull 1, 2 and 3 knot)
- Stratified versions of parametric and flexible spline models, equivalent to fitting separate models by treatment arm
- Hybrid models combining Kaplan-Meier estimates for an initial period with exponential, Weibull, log-normal or log-logistic extrapolations

Details of how these curves were fitted and the approach used to select the company's base case and scenario models are described in CS B.3.3.4 and Appendix L. See sections 4.2.6.4 and 4.2.6.5 below for ERG commentary on the trial-based OS and PFS extrapolations respectively.

CS Appendix L also reports survival curves fitted to HER2CLIMB data but constrained to give long-term projections that are consistent with an external data source (Kaufman et al. 2015).[3] However, the company chose not to include the survival models with external data in

the economic model, as they considered that the curves based on HER2CLIMB data alone had a good fit and gave plausible extrapolations (see CS Section B.3.3.4).

4.2.6.2 OS and PFS curves estimated from the fractional polynomial NMA

Survival curves are also available for the tucatinib combination, the comparators and other treatments in the network from fixed and random effects fractional polynomial NMA models. The economic model only includes parameter sets for the company's preferred fractional polynomial models: P1=0 (Weibull) for OS and P1=-2 and P2=-0.5 for PFS. The model uses 6,000 draws from the fractional polynomial posterior distributions for the probabilistic analysis and the means of these parameter sets for deterministic analysis.

4.2.6.3 Relative treatment effects from the hazard ratio NMA

The economic model also includes relative treatment effects from the Bayesian HR NMA, fixed and random effect models (see section 3.4 and section 3.5 above). With an assumption of proportional hazards, the HR estimates can be applied to trial-based or fractional polynomial survival curves for a reference treatment to obtain curves for the other comparators. The economic model uses 6,000 correlated sets of HR NMA estimates for probabilistic analysis, and the mean of these parameter sets for deterministic analysis. We note that these means are similar, but not identical to the HR NMA results reported in the CS (section 3.5).

The company's base case uses input parameters described above for OS and PFS. Relative effects from the NMA ([redacted]) are applied to fractional polynomial survival curves for a reference treatment. The company chose lapatinib plus capecitabine as the reference, as it is the most used treatment in the NMA (described in Document B Section CS B.2.9.1.7). Figure 6 below shows the modelled OS and PFS curves for the company's base case, alongside HER2CLIMB KM data.

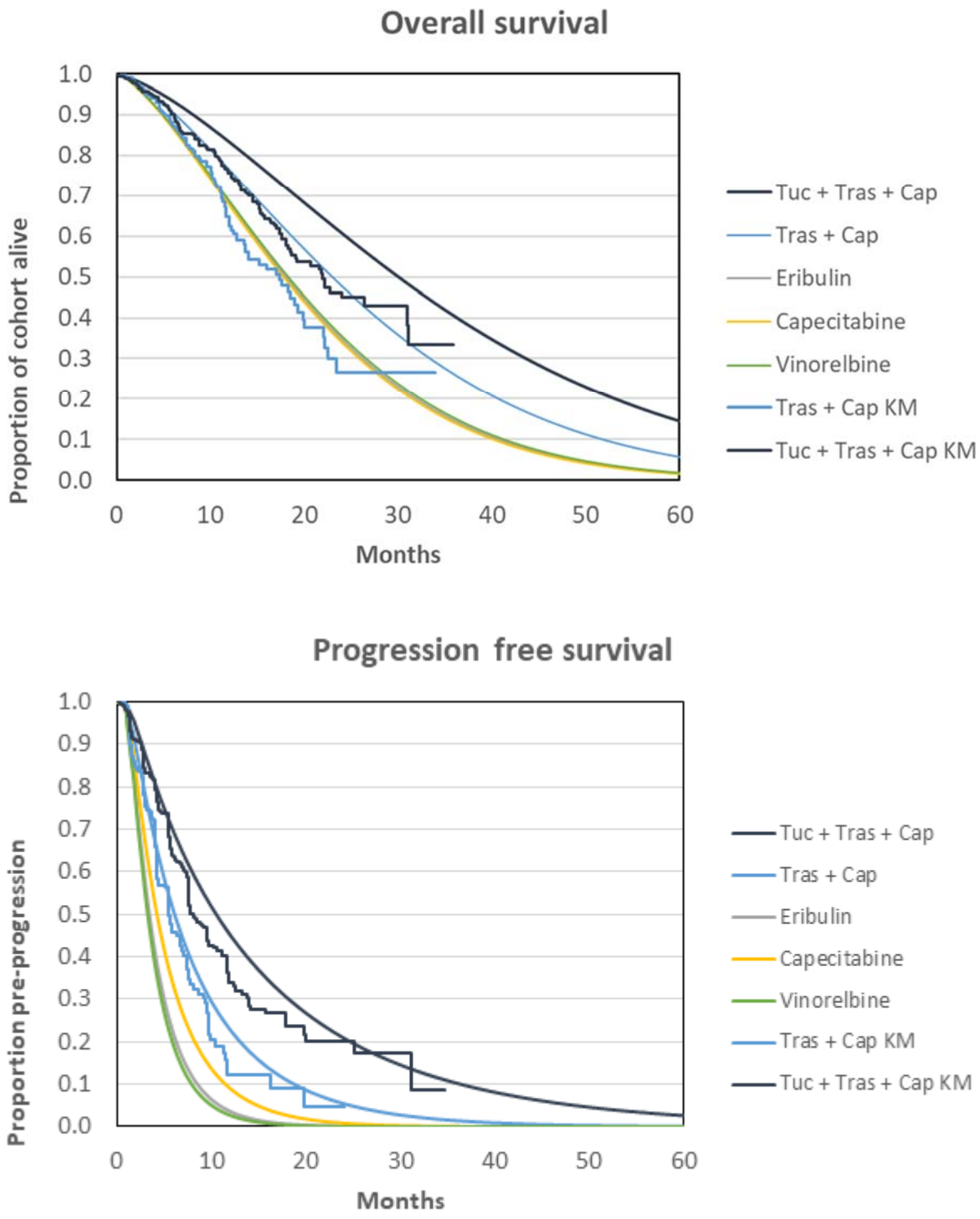


Figure 6 Survival curves from base case model with HER2CLIMB KM data

Source: Obtained from the company's model by the ERG

The company's base case extrapolations for the tucatinib combination have a poor fit to the HER2CLIMB trial data. In particular, modelled OS is much better than that observed in the trial. This is possibly due to differences between the HER2CLIMB population and that of

other trials in the evidence network (section 3.3.3). Nearly half of the patients in HER2CLIMB had brain metastases and one would expect poorer outcomes for this group. The difference in survival expectations between the data sources is potentially important for the economic model because even with a constant HR between treatments, the QALY gain will be greater if absolute survival is higher.

This leads to the question of which data source is more reflective of routine practice. The proportion of patients with brain metastases in HER2CLIMB may be higher than expected, but the zero or very low proportion in the other trials is certainly not representative. We therefore suggest that the survival curves fitted to HER2CLIMB data provide a more valid foundation for the economic analysis than the NMA fractional polynomials. However, it is important to acknowledge that a 'within-trial' model anchored by survival curves fitted to HER2CLIMB data may underestimate survival (and hence QALYs) if patients with a poor prognosis are over-represented in this trial.

ERG conclusions

- The company's base case survival estimates are substantially more favourable than those observed in the HER2CLIMB study. This may be due to the population in this trial, which included more patients with brain metastases than other trials in the NMA (which included few or no patients with brain metastases). This raises a question of which trials are more reflective of routine practice.
- The company's submission does not explore uncertainty over to the choice of reference survival curves for their base case (OS and PFS curves for lapatinib + capecitabine from the fractional polynomial NMA).The model includes an option to use 'within-trial' curves fitted to HER2CLIMB tucatinib and placebo combinations, which are adjusted for indirect comparators with relative effects from the NMA. However, this model was not used in company scenario analysis and was not functioning in the submitted model (see section 6.1).
- In addition, the company did not test the impact of alternative functional forms for PFS and OS in their model. Although a scenario with alternative survival models is reported (CS Table 39), QALY estimates from this scenario do not differ from those in the base case analysis (see section 5.2.2). This is not surprising as the model only includes one fractional polynomial function for OS and one for PFS.
- In ERG analysis, we explore the 'within trial' approach to survival modelling and test alternative scenarios for the PFS and OS survival functions fitted to HER2CLIMB data, and adjusted for comparators with HRs from the NMA (sections 6.3 and 6.4).

In the following sections, we summarise the company's approach to fitting OS and PFS survival functions to HER2CLIMB trial data and consider the choice of curves for ERG scenario analyses.

4.2.6.4 Overall survival for within-trial analysis

The company outline their approach to modelling OS with individual patient data from the HER2CLIMB trial in CS section B.3.3.4, with further details in CS Appendix L. The approach in the Appendix is thorough and consistent with methodological advice from the NICE Decision Support Unit.[26] It also makes use of techniques for flexible curve fitting and integration of longer-term external data to improve the plausibility of extrapolations.

The validity of the proportional hazards assumption between the HER2CLIMB arms is discussed in section 9.2 of CS Appendix L. Log-(log) survival and Schoenfeld residual plots are shown in CS Appendix L Figures 13 and 14, respectively. The log-(log) survival curves [redacted]. Plots of smoothed hazards (CS Appendix L Figure 15) show [redacted]. The rates were [redacted]. The smoothed hazard ratio plot (CS Appendix L Figure 16) [redacted].

The fit and plausibility of the 23 models fitted to HER2CLIMB OS data is discussed in CS Appendix L section 9.3. For convenience, we reproduce illustrations of the fitted models in Figure 7, Figure 8 and Figure 9 below (CS Appendix L Figures 17, 19 and 22 respectively) and a summary of the predicted means in Table 21 (CS Appendix L Table 9).

The company selected 13 models that they considered to have both a good fit to the trial data and plausible extrapolations (CS Document B Table 21). Out of these 13 models, the company chose the Weibull for use in the base case cost-effectiveness analysis. They justify this based on AIC/BIC statistics, visual inspection, external validation against the Kaufman et al. study (2015)[3] and the views of an external advisory board. Although the company state that they conducted a scenario analysis with [redacted] (CS B.3.3.4.2), it appears that this scenario actually used a [redacted] (CS Table 39).

Table 12 in CS Appendix L contains recommendations for the 'most likely', 'optimistic' and 'pessimistic' models based on the difference in mean survival between treatment arms. These were selected from the shortlist of models judged to have a good fit and plausible extrapolations. For OS fitted to HER2CLIMB data alone, this suggested:

- Most likely: Weibull, gamma (difference in mean survival 6.2, 6.4 months)
- Optimistic: Stratified Weibull, stratified gamma (mean difference 8.0, 8.8 months)
- Pessimistic: Gompertz (mean difference 4.8 months)

We note that the company's model does not constrain the mortality rate to be no less than that of people of the same age in the general population. However, given the poor survival of the modelled population, this is not expected to produce unrealistic predictions.

ERG conclusions

- The company's analysis of survival data from the HER2CLIMB trial follows methodological guidance and is thorough and well-reported. [redacted].
- A range of curves had a good visual fit to the trial data and produced plausible extrapolations (mean survival in the control arm of between [redacted] months)
- We agree with the company's choice of Weibull for their base case and consider that the stratified Weibull and Gompertz extrapolations provide an appropriate range of optimistic and pessimistic predictions of the mean difference in survival between the arms (8.8 and 4.8 months respectively). We use these distributions in ERG sensitivity analysis (see Table 31).

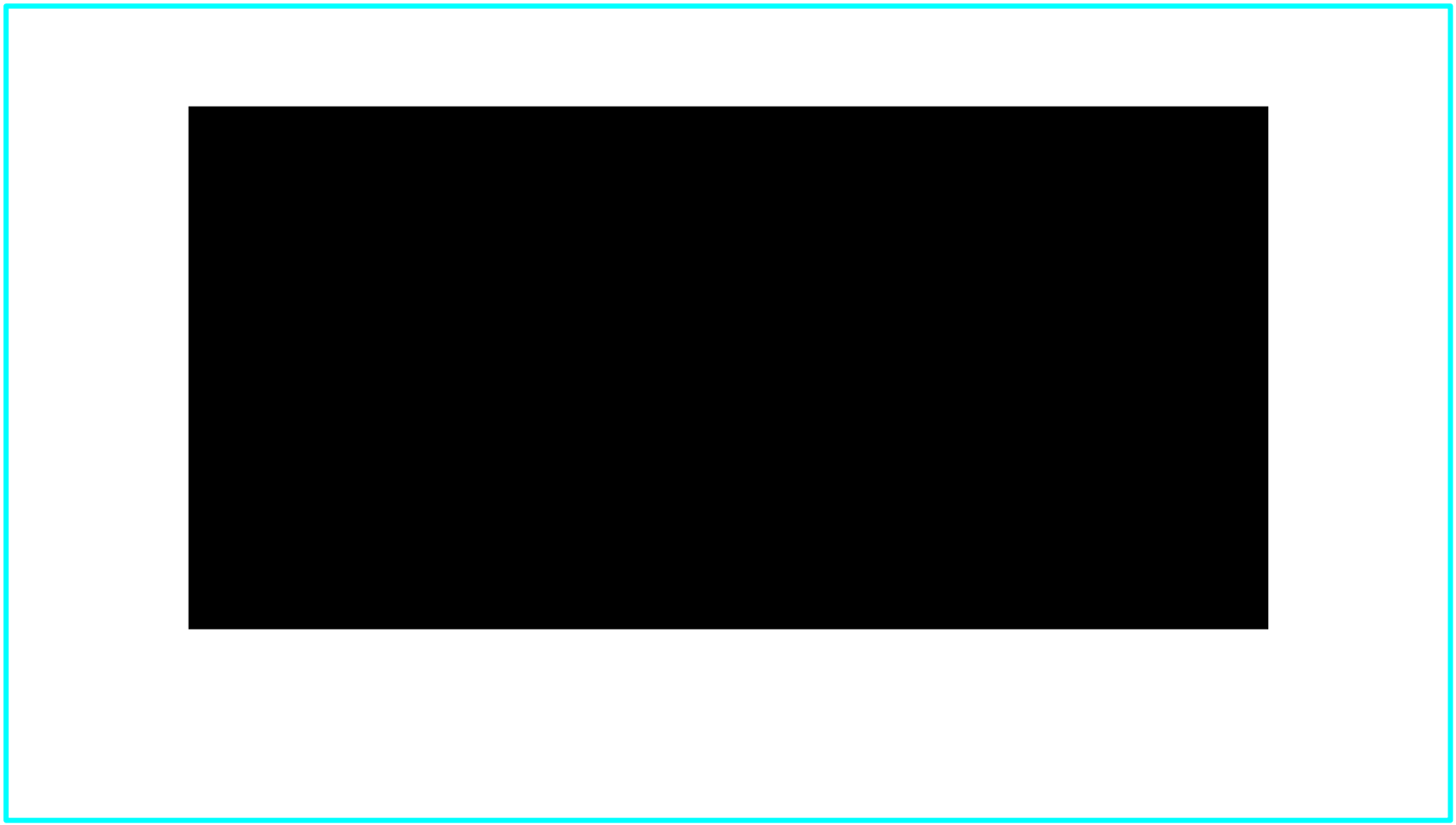


Figure 7 Standard parametric models fitted to the HER2CLIMB trial data: OS [redacted]

Source: Reproduced from CS Appendix L Figure 17

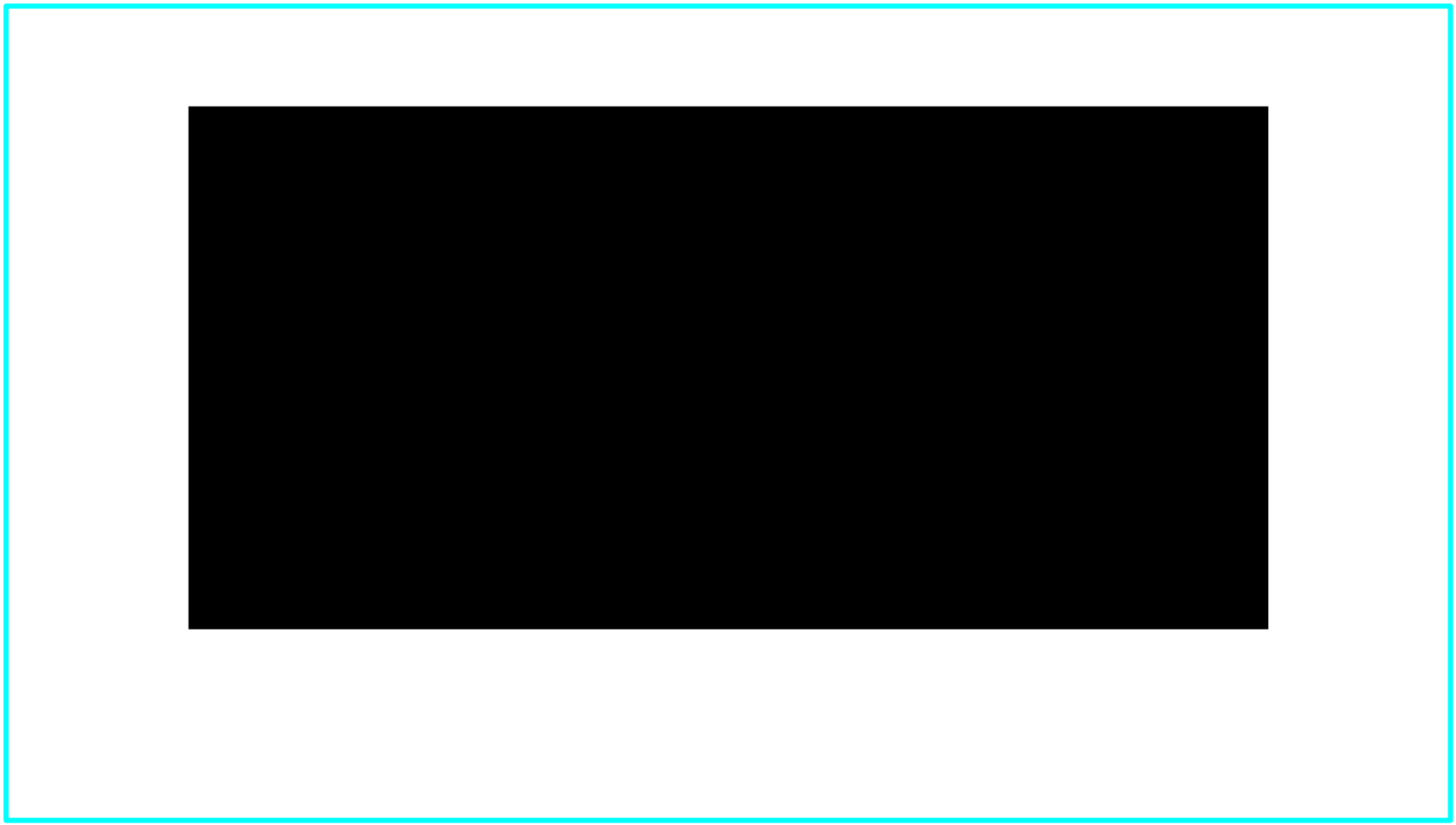


Figure 8 Flexible Spline-based models fitted to the HER2CLIMB trial data: OS [redacted]

Source: Reproduced from CS Appendix L Figure 18

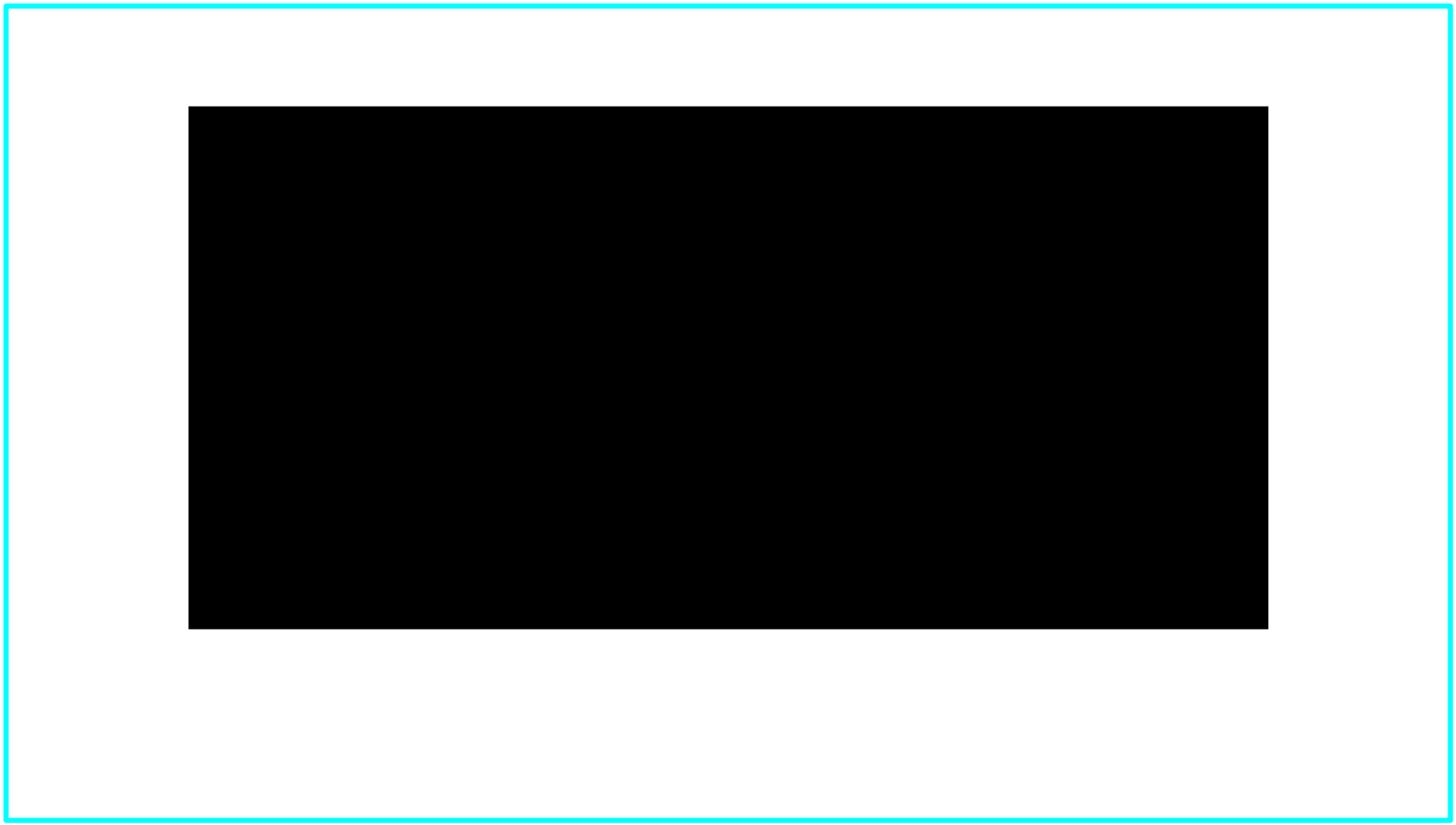


Figure 9 Hybrid survival models fitted to the HER2CLIMB trial data: OS [redacted]

Source: Reproduced from CS Appendix L Figure 22

Table 21 Predicted mean OS times in months for models fitted to the HER2CLIMB data

	Pbo+Tras+Cape			TUC+Tras+Cape			Difference, Months				
Model	Mean	Lower CrI	Upper CrI	Mean	Lower CrI	Upper CrI	Mean	Lower CrI	Upper CrI	Fit to RCT	Plausible
Exponential	[redacted]									Poor	Yes
Weibull	19.9	16.9	23.1	26.0	22.6	6.2	6.2	1.3	10.7	Good	Yes
Stratified Weibull	[redacted]					8.0				Good	Yes
Gompertz	20.7	16.8	29.4	27.4	22.3	4.8	4.8	1.4	8.9	Good	Yes
Stratified Gompertz	[redacted]					5.9				Good	Yes
Log-normal	[redacted]									Poor	No
Stratified log-normal	[redacted]									Poor	No
Log-logistic	[redacted]									Good	No
Stratified log-logistic	[redacted]									Good	No
Gamma	[redacted]					6.4				Good	Yes
Stratified gamma	[redacted]					8.8				Good	Yes
Generalized gamma	[redacted]					6.2				Good	Yes
Stratified generalized gamma	[redacted]					6.5				Good	Yes
Flexible Weibull (1 knot)	[redacted]					6.2				Good	Yes
Flexible Weibull (2 knots)	[redacted]					7.2				Good	Yes
Flexible Weibull (3 knots)	[redacted]									Good	No
Stratified flexible Weibull (1 knot)	[redacted]					7.1				Good	Yes
Stratified flexible Weibull (2 knots)	[redacted]					6.8				Good	Yes
Stratified flexible Weibull (3 knots)	[redacted]									Good	No
Hybrid exponential	[redacted]					7.7				Good	Yes
Hybrid Weibull	[redacted]									Good	No
Hybrid log-normal	[redacted]									Good	No
Hybrid log-logistic	[redacted]									Good	No

Source: Reproduced from CS Appendix L Table 9

Green shading indicates models that the company considered to provide both a good fit to RCT data and plausible extrapolations. Red indicates that the company considered that the model did not meet both of these criteria.

4.2.6.5 Progression-free survival for within-trial analysis

Evidence related to proportional hazards between the HER2CLIMB arms for PFS is shown in CS Appendix L section 10.2. The log-(log(survival)) plots [redacted] and the Schoenfeld test [redacted] (CS Appendix L Figures 40 and 41). Smoothed hazard rates (CS Appendix L Figure 42) indicate that [redacted]. The hazard ratio was [redacted] (CS Appendix L Figure 43).

The company fitted 23 PFS models to the HER2CLIMB data. See

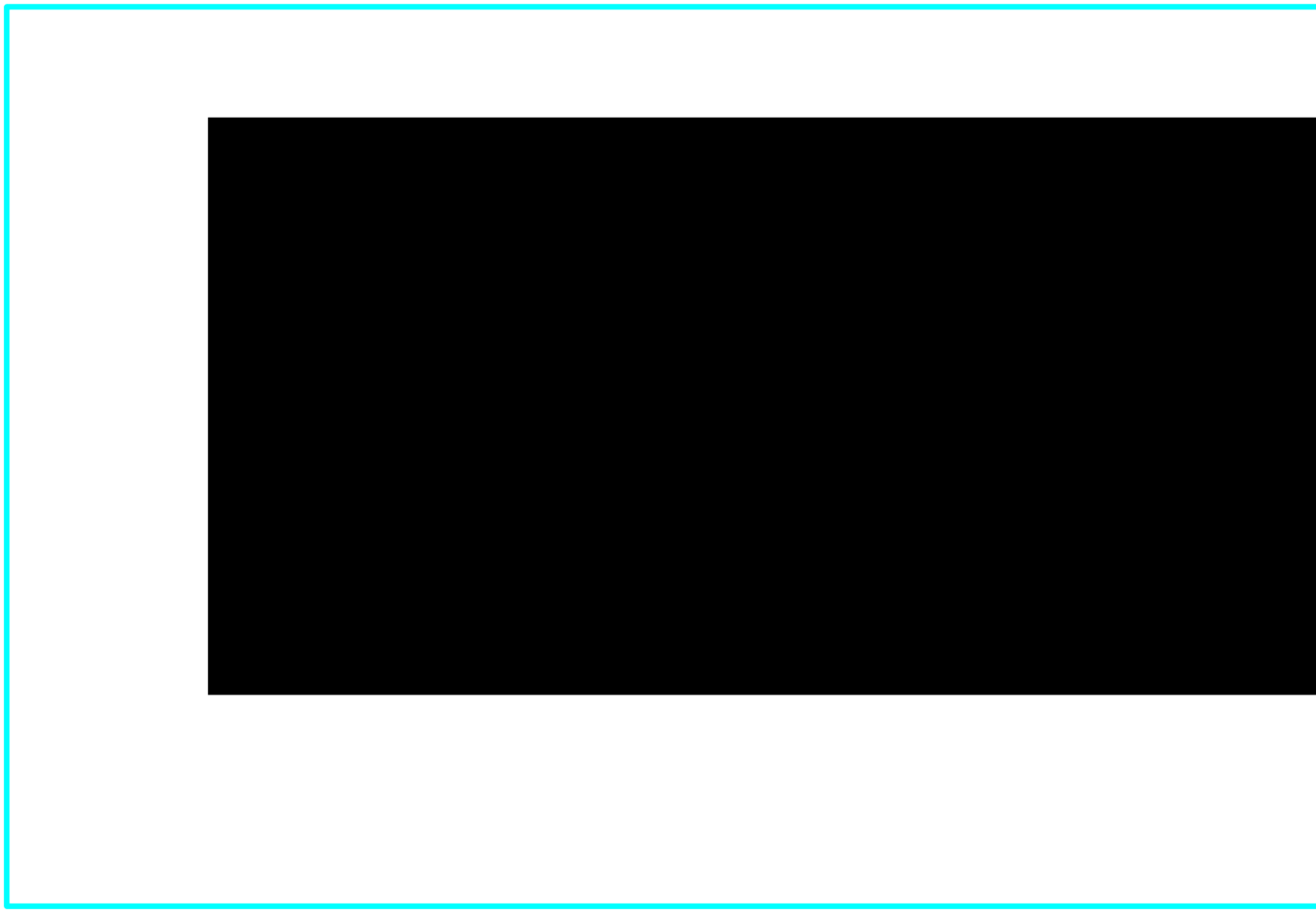


Figure **10**, Figure 11 and Figure 12 (reproduced from CS Appendix L Figures 44, 46 and 49) and summary of the predicted mean OS times Table 22 (reproduced from CS Appendix L Table 15). The company concluded that seven models have a good fit to trial data and produced plausible extrapolations (CS B.3.3.4.1 and Table 20). These gave predictions of mean PFS between [redacted] months. They selected the flexible Weibull with 2 knots for the base case analysis, as it was in line with results from the models with the selected external

data (Kaufman et al. 2015).[3] The company conducted a scenario analysis with the [redacted].

Table 12 in CS Appendix L concludes that the 'most likely', 'optimistic' and 'pessimistic' models from the shortlist with good fit and plausible extrapolations were:

- Most likely: [redacted]
- Optimistic: [redacted]
- Pessimistic: [redacted]

ERG conclusions

- [redacted].
- A range of curves had a good visual fit to the trial data and produced plausible extrapolations (mean PFS in the control arm from [redacted] months)
- For the ERG base case, we use the flexible Weibull 2 knots PFS curve. We include the stratified generalized gamma and stratified log-normal in scenario analyses (mean difference in PFS [redacted] months).

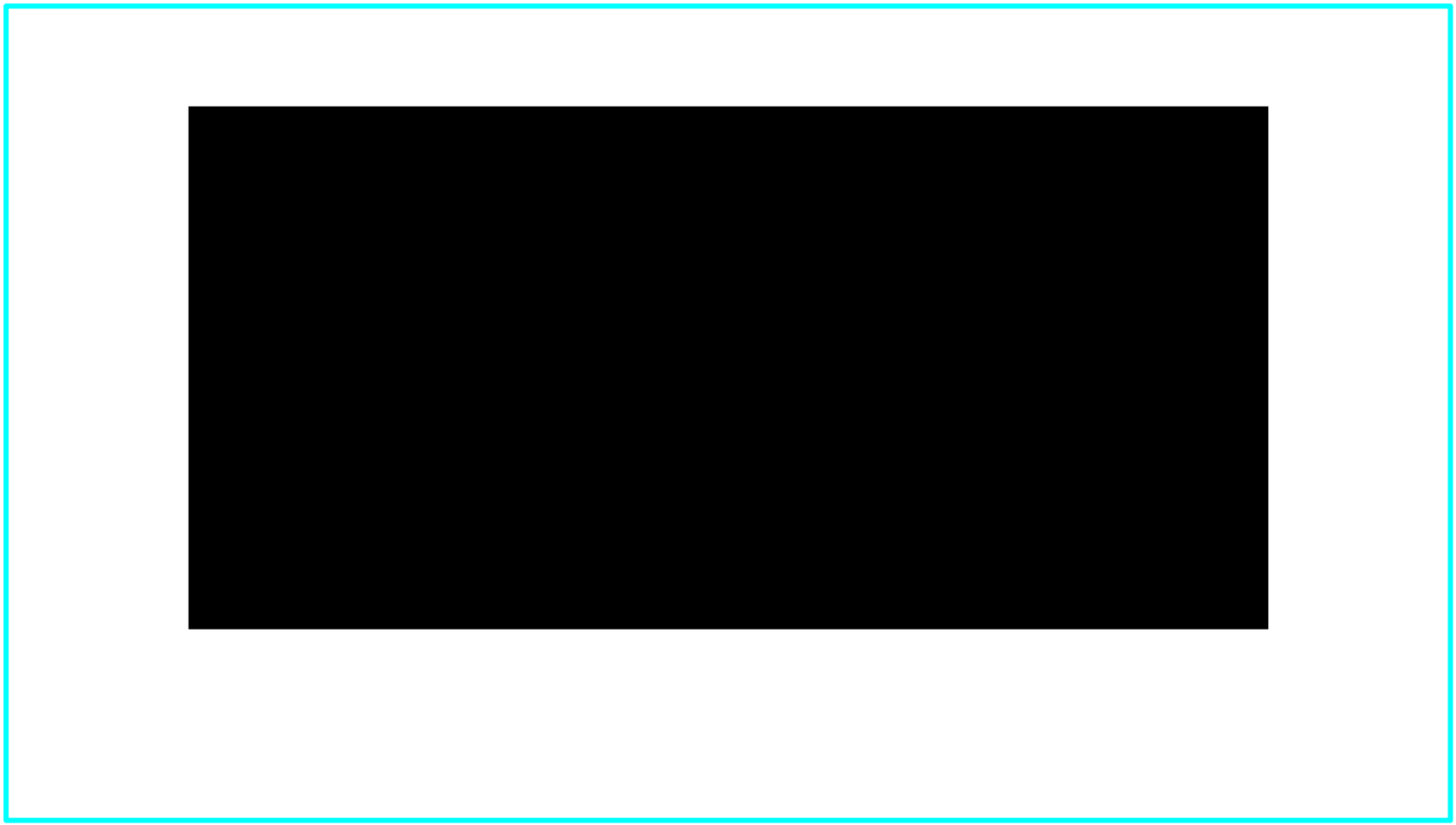


Figure 10 Standard parametric models fitted to the HER2CLIMB trial data: PFS [redacted]

Source: reproduced from CS Appendix L Figure 44

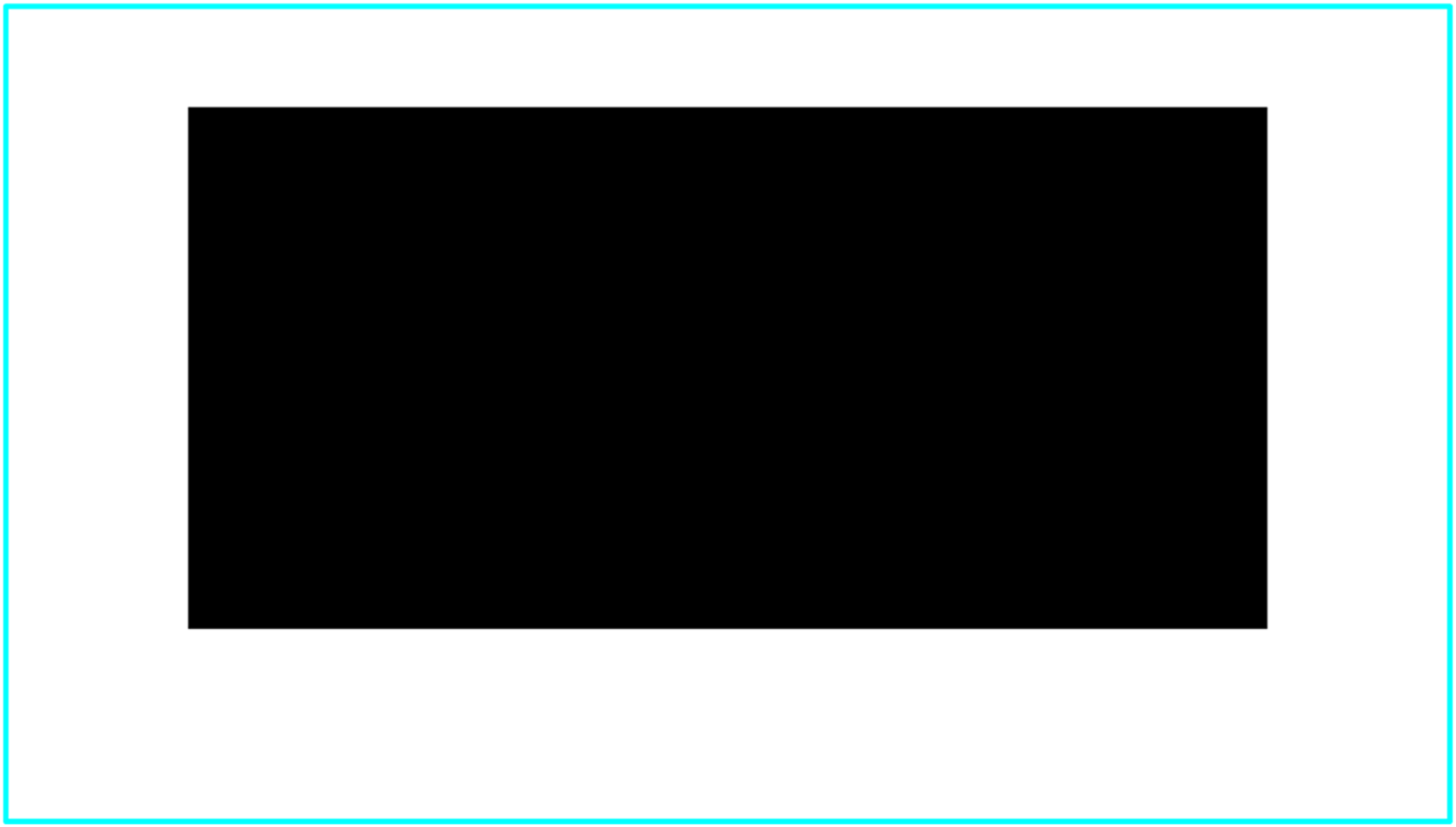


Figure 11 Flexible spline based fitted to the HER2CLIMB trial data: PFS [redacted]

Source: reproduced from CS Appendix L Figure 46

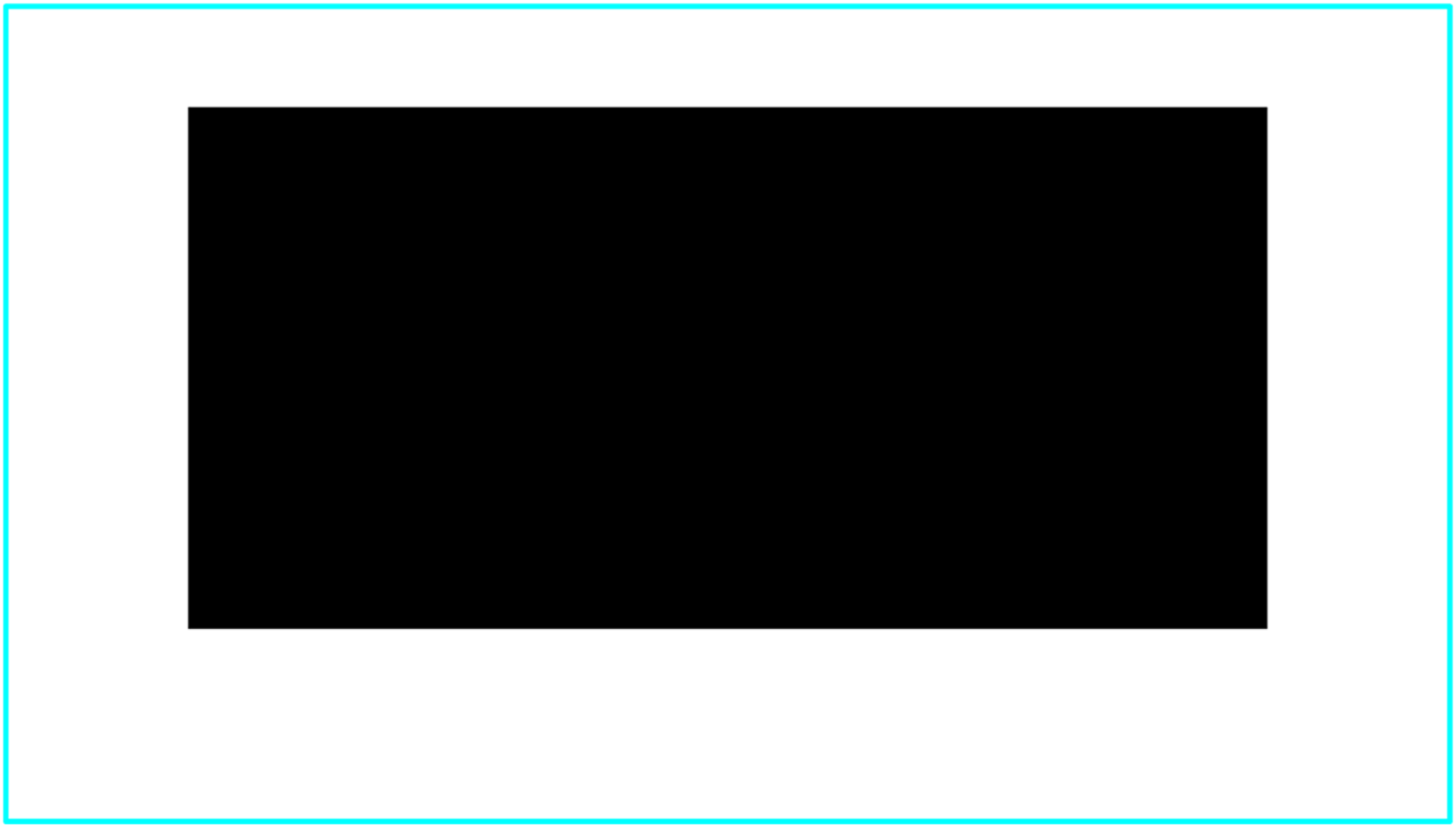


Figure 12 Hybrid survival models fitted to the HER2CLIMB trial data: PFS [redacted]

Source: reproduced from CS Appendix L Figure 49

Table 22 Predicted mean PFS times in months for models fitted to the HER2CLIMB data

	Pbo+Tras+Cape			TUC+Tras+Cape			Difference, Months				
Model	Mean	Lower CrI	Upper CrI	Mean	Lower CrI	Upper CrI	Mean	Lower CrI	Upper CrI	Fit to RCT	Plausible
Exponential	[redacted]									Poor	Yes
Weibull	[redacted]									Poor	Yes
Stratified Weibull	[redacted]									Poor	Yes
Gompertz	[redacted]									Poor	Yes
Stratified Gompertz	[redacted]									Poor	Yes
Log-normal	[redacted]									Poor	Yes
Stratified log-normal	[redacted]									Good	Yes
Log-logistic	[redacted]									Poor	Yes
Stratified log-logistic	[redacted]									Good	Yes
Gamma	[redacted]									Poor	Yes
Stratified gamma	[redacted]									Poor	Yes
Generalized gamma	[redacted]									Poor	Yes
Stratified generalized gamma	[redacted]									Good	Yes
Flexible Weibull (1 knot)	[redacted]									Good	Yes
Flexible Weibull (2 knots)	[redacted]									Good	Yes
Flexible Weibull (3 knots)	[redacted]									Good	No
Stratified flexible Weibull (1 knot)	[redacted]									Good	Yes
Stratified flexible Weibull (2 knots)	[redacted]									Good	No
Stratified flexible Weibull (3 knots)	[redacted]									Good	No
Hybrid exponential	[redacted]									Good	Yes
Hybrid Weibull	[redacted]									Good	No
Hybrid log-normal	[redacted]									Good	No
Hybrid log-logistic	[redacted]									Good	No

Source: Reproduced from CS Appendix L Table 15

Green shading indicates models that the company considered to provide both a good fit to RCT data and plausible extrapolations. Red indicates that the company considered that the model did not meet both of these criteria

4.2.6.6 Waning of treatment effects (HR tapering)

CS Appendix L also explores scenarios using external data and hazard ratio tapering, to reflect the waning of OS and PFS treatment effects after trial follow up. The NMA fractional polynomial data in the model includes estimated times to HR=1: approximately 4 years from the start of treatment for PFS and 6 years for OS. The model includes a function to gradually reduce HRs to 1 between maximum trial follow up and these timepoints. This was not used in the company submission. We report the effect of HR tapering in ERG scenario analysis (see section 6.4 below).

4.2.7 Treatment duration

The company used data from the HER2CLIMB trial to estimate time to treatment discontinuation (TTD) for the tucatinib combination and trastuzumab with capecitabine (CS B.3.3.5 and clarification response B4). A range of parametric and flexible spline models were fitted to the TTD data. All of the models gave a good visual fit to the trial data, except for the log-logistic and log-normal which overestimated treatment continuation towards the end of the trial. The Flexible Weibull with 2 knots was chosen for the base case analysis, as it has the best model fit statistics and aligns with the base case PFS model. We agree that it is reasonable to assume that TTD follows a similar shape to PFS because progression is the primary reason for treatment discontinuation.

TTD data were not available for eribulin, capecitabine and vinorelbine. For the base case, the company assumed constant hazards (exponential model), based on median treatment durations for clinical studies in the NMA (CS B.3.3.7). These sources are not reported in the CS or clarification response, but the model (sheet External_TTD) uses estimated mean treatment durations of:

- 5.61 months for eribulin (Kaufman et al. 2015 and Yuan et al. 2019)[3 14]
- 5.67 months for capecitabine (von Minckwitz et al. 2009 and Kaufman et al. 2015)[3 12]
- 3.98 months for vinorelbine (Yuan et al. 2003)[14]

The model also includes options to assume that TTD is equal to PFS or to limit treatment duration to the median times reported for clinical studies.[12 14 27] The company report results for a scenario with treatment duration restricted to mean exposure (CS Table 39). They do not report the results of assuming that TTD is equal to PFS, but we do in ERG scenario analysis (Table 36 below).

ERG conclusion

- We agree with the use of HER2CLIMB trial data to model treatment duration for the tucatinib combination and for trastuzumab with capecitabine. We also agree with the company's rationale for choosing the same survival function for TTD as for PFS (flexible Weibull with 2 knots). This has a good fit to the trial data and appears plausible (clarification response Figures B4a- B4f).
- The company's approach to modelling treatment duration for the external comparators is also reasonable. This assumes a constant rate of discontinuation, estimated from median treatment durations in clinical studies included in the NMA.
- We report results for a scenario with TTD assumed equal to PFS for all comparators in ERG analysis (see section 6.3 below). This is likely to overestimate treatment duration (and hence costs) for all treatments, as some patients are likely to stop treatment for reasons other than progression.
- The company's scenario in which treatment duration is limited to the median reported from clinical trials is likely to underestimate treatment costs. This will favour the tucatinib combination, which has the highest treatment cost and duration.

4.2.8 Adverse events

The company base case includes costs for treating grade 3 and 4 treatment-emergent adverse events (TEAEs) that occurred in at least 2% of patients for any of the treatment arms in the clinical studies (CS B.3.5.3). The references cited for TEAE incidences in the model are Murthy et al. (2020) for the HER2CLIMB treatments; von Minckwitz 2009 for capecitabine; and Yuan et al. for eribulin and vinorelbine.[4 12 14] Sources for the treatment costs for TEAEs are listed in CS Table 32.

The company assumes that the utility impacts of adverse events are captured in the health state utility weights (CS B.3.4.4). However, the model does include parameters for TEAE disutilities and durations, and QALY losses associated with TEAEs can be included in the model (CS Table 33). This has a negligible impact on cost effectiveness results.

We note that there are some discrepancies between TEAE incidence parameters in the model compared with CS Table 33 and cited sources: e.g. Murthy et al. cite an incidence of 2.5% for anaemia in the trastuzumab + capecitabine control arm but the model uses 0%;

and CS Table 33 cites a 0% incidence of vomiting in this control arm, compared with 3.6% in the model and Murthy at al.[4] These differences do not impact on cost-effectiveness results.

ERG conclusions

The company's approach to modelling adverse events is reasonable. The base case model includes estimated costs for treating adverse events and although the disutilities are not included, they can be added in a scenario analysis. We found some inconsistencies between adverse event incidences in the model and values reported in the CS and the cited sources. This does not impact on cost effectiveness results.

4.2.9 Health related quality of life

The company explain their approach to estimation of utilities in CS section B.2.4 and in their responses to clarification questions B1, B2 and B3. Table 23 below summarises the health state utilities used in the company's original base case economic model and their revised base case after clarification.

Table 23 Utility values in the company's original and revised base case analyses

Treatment	Health state (treatment cycle)	Original base case	Revised base case	Sources
Tucatinib combination	Progression free (1-2)	0.748	0.762	HER2CLIMB EQ-5D (CS Table 23 and clarification response B2)
	Progression free (3-4)	0.763		
	Progression free (5-6)	0.792		
	Progression free (7+)	0.807		
	Post progression	0.653	0.698	
Trastuzumab + capecitabine	Progression free (1-2)	0.770	0.762	
	Progression free (3-4)	0.765		
	Progression free (5-6)	0.741		
	Progression free (7+)	0.748		
	Post progression	0.698	0.698	
Eribulin	Progression free	0.783	0.706	TA423 (CS Table 24 and clarification response B3)
	Post progression	0.622	0.496	
Capecitabine	Progression free	0.691	0.701	
	Post progression	0.651	0.496	
Vinorelbine	Progression free	0.691	0.701	
	Post progression	0.651	0.496	

4.2.9.1 Health state utilities from HER2CLIMB

Utilities for the tucatinib combination intervention were obtained from HER2CLIMB EQ-5D-5L data, mapped to the EQ-5D-3L UK 'social tariff' value set using the crosswalk

procedure.[25] The company also report results for a scenario with an EQ-5D-5L value set, but we do not discuss this further as it does not follow the NICE recommended approach.[28]

The original base case uses simple means by HER2CLIMB study arm, as assessed at treatment cycle 3, 5, 7 and 9 to model pre-progression utility in cycles 1-2, 3-4, 5-6 and 7+ respectively (Clarification response Addendum B1). Post-progression utilities are based on data from the 30-day post-treatment assessment. As explained in CS B.2.6.9 and B.3.4.1, the EQ-5D-5L assessments were introduced as a protocol amendment and so only conducted for a subset of patients: 217/410 (53%) in the tucatinib combination arm and 112/202 (55%) in the placebo combination arm. The company argue that patient characteristics for this subset are reflective of those for the whole study population (see section 3.2.5.4 above).

In response to clarification question B2, the company revised their base case utilities for the tucatinib combination and trastuzumab + capecitabine based on a repeated measures analysis of the HER2CLIMB data with baseline utility as a covariate. Utility estimates differed between 'on treatment' and 'off treatment' assessments: 0.762 (95% CI: 0.744-0.781) and 0.698 (95% CI: 0.668- 0.728) respectively. However, other details of the analysis are not reported. In particular, there is no mention of tests for a difference in utility between the study arms or for a trend in utility over pre-progression treatment cycles. There is also no discussion of missing data or how this was handled, which is potentially important given the high proportion of missing data at later assessments. At treatment cycle 3, utility scores were available for 175 out of 213 patients with a baseline score (82%) in the tucatinib arm, and 89 out of 112 patients (79%) in the placebo arm. By treatment cycle 9, completion rates fell to 86/213 (40%) in the tucatinib arm and 38/ 112 (34%) in the placebo arm. And at 30 days post-treatment, scores were available for 72/213 (34%) in the tucatinib arm and 42/112 (38%) in the placebo arm.

4.2.9.2 Health state utilities for comparators

The company report results from their systematic literature review of utilities (CS B.3.4.3 and Appendix H; and Addendum for the updated search). They state that this did not identify any relevant 'primary' utility studies, but that a direct elicitation study by Lloyd et al. (2006)[1] was commonly used in economic evaluations, including the NICE appraisal of eribulin (TA423).[24] Lloyd et al. used a direct preference-based approach (standard gamble) to elicit utilities for different stages of breast cancer from a UK general population sample (n=100).

In TA423, the company (Eisai) estimated utilities by applying a mapping algorithm (Crott and Briggs 2010)[2] to health-related quality of life data (QLQ-C30) from a trial of eribulin compared with capecitabine (Study 301).[3] The ERG in TA423 (LRiG) accepted the company estimates for pre-progression utility (0.706 for eribulin and 0.701 for capecitabine) but argued that the estimate for progressed disease (0.679) was not plausible. The ERG preferred the Lloyd et al. estimate for progressed disease (0.496).[1] The NICE committee in TA423 concluded that the most plausible utility value for progressed disease was likely to be somewhere between the company and ERG estimates.

In the current submission, the company based their utility estimates for the comparators eribulin, capecitabine and vinorelbine on the values reported in TA423 (see Table 23 above). However, they used the wrong values for the Crott and Briggs estimates (taken from Table 50, rather than Table 57, in the Eisai company submission for TA423). This error was corrected in response to clarification question B3.

In their original submission, the company also argued that it would be appropriate to take an average of the TA423 company and ERG utility estimates, to reflect the committee's conclusion that the most plausible value lies between these estimates (CS B.3.4.8). However, the revised company base case only uses the TA423 ERG (Lloyd et al) estimate for progressed disease, rather than taking a mean of the Crott and Briggs and Lloyd et al. values.

4.2.9.3 Adverse event disutilities

The company assumes that utility loss due to treatment-related adverse events is captured in the utility weight for the tucatinib combination, as estimated from HER2CLIMB EQ-5D data (CS B.3.4.4). Similarly, they assume that utility loss due to adverse events are captured in the utility weights for eribulin and capecitabine from TA423. The model includes an option to include QALY loss associated with adverse events, although this was not applied in the company base case or scenario analyses. We found that this has a very negligible effect on the QALY results (see section 6.3).

ERG conclusions

- We agree with the use of pre-progression utilities from the HER2CLIMB for the trial (EQ-5D UK crosswalk values).[25] This is consistent with NICE preferred methods and relevant to the population and intervention in the decision problem.[29 30] In revised analysis of the HER2CLIMB utility data, the company use a repeated measures model with adjustment for baseline values (clarification

response B2): 0.765 for pre-progression and 0.698 for post-progression for the tucatinib combination. This is preferable to the approach in the original base case, though we have concerns about the lack of detail in reporting and potential for bias due to missing data, particularly at the post-treatment follow-up.

- The company use utility estimates for eribulin, capecitabine and vinorelbine from the NICE appraisal TA423.[24] The revised base case includes pre-progression utilities of 0.706 for eribulin and 0.701 for capecitabine and vinorelbine; and the post-progression utility of 0.496 from Lloyd et al.[1] However, the TA423 committee concluded that the most plausible post-progression utility lies somewhere between the Lloyd et al. estimate and an estimate of 0.679 (Crott and Briggs mapping of the Study 301 trial data).[2 3] For ERG scenario analysis, we use a mean of these values for post-progression utility (0.588).
- We also note that in TA423 the same post-progression utility was used across treatments. By comparison, the post-progression utility for the tucatinib combination in the company's revised base case (0.698) is much higher than that assumed for eribulin, capecitabine and vinorelbine (0.496). This difference is not based on comparative evidence and seems implausible. It is not clear why such a large difference should persist after progression and treatment discontinuation. For ERG analysis, we therefore use the same post-progression utility for the tucatinib combination and comparators.
- We further question the clinical plausibility of the difference in pre-progression utility for the tucatinib combination (0.762) and comparators (0.706 for eribulin and 0.701 for capecitabine and vinorelbine). This may well relate to differences in the trial populations (HER2CLIMB versus Study 301)[3 4] or valuation methods (crosswalk EQ-5D versus Crott and Briggs mapping),[2 25] rather than to differences in treatment-related quality of life. And clinical advice to the ERG is that adverse effects and quality of life will be similar across these treatments. We therefore test the effect of assuming the same pre-progression utility across treatments.
- The company assume that the impact of adverse effects on utility is captured in the trial-based utility estimates. This is reasonable and there is no evidence of a difference in the incidence or severity of adverse events between treatments. Furthermore, we note that the using the model option to include disutilities for adverse events has a minimal effect on results.
- The company's model does not include adjustment for the expected decline in utility with age. We have added this for ERG analysis, based on the relationship

between EQ-5D values and age estimated from Health Survey for England data (Ara and Brazier 2010).[31]

4.2.10 Resources and costs

The economic model includes costs for drug acquisition and administration for the tucatinib combination, comparators and subsequent treatments; follow-up and care; and treatment of adverse effects (CS Document B section B.3.5). The CS reported that a systematic literature review was conducted to identify costs and resource use (Appendices G and I, and clarification response Addendum).

4.2.10.1 Drug acquisition and administration costs

Drug acquisition costs for the tucatinib combination and comparators are summarised in CS Document B Tables 25 and 26; and drug administration costs are summarised in CS Document B Table 27. The dosing regimen for the tucatinib combination is based on the MHRA SmPC (CS Document B section B.3.5.1.1).

Total drug acquisition costs per 21-day treatment cycle are summarised in CS Table 28. These include adjustment for relative dose intensity, based on the HER2CLIMB trial for the tucatinib combination and trastuzumab + capecitabine and Yuan et al. (2019)[14] for eribulin and vinorelbine. The source of the relative dose intensity for capecitabine monotherapy (78.8%) is not clear. In CS Table this is attributed to the NALA study (Saura et al. 2020).[32] However, the online appendix (Table A3) in the Saura et al. paper quotes a relative dose intensity for capecitabine of 93% in the neratinib + capecitabine arm and 86% in the lapatinib + capecitabine arm (89% pooled across the arms). This causes a small increase in the estimated cost of capecitabine, but the impact on cost-effectiveness results is negligible.

The model includes wastage estimates for intravenous trastuzumab and T-DM1, but the company does not include these estimates in base case analysis or a scenario.

4.2.10.2 Subsequent treatment costs

Costs for post-progression anticancer treatments were estimated for patients entering the progressed state (CS Table 29). Drug acquisition costs were obtained from the BNF 2021[33] and eMIT 2021[34], and the dose and treatment duration for the drugs were based on related trials: HER2CLIMB, NALA, PHEREXA and EMILIA.[4 32 35 36]

The company use data from the HER2CLIMB trial to estimate use of subsequent treatments (Table 24 below). For the comparator drugs (that is, eribulin, capecitabine and vinorelbine) a weighted average for the HER2CLIMB treatment arms is used. These assumptions are not reflective of current clinical practice in England because pertuzumab, T-DM1, lapatinib and neratinib are not funded for fourth-line treatment of HER2+ metastatic breast cancer. We understand that after progression, about half of this patient group would receive trastuzumab with capecitabine and that others who receive further treatment would have chemotherapy alone (e.g. capecitabine or vinorelbine). We conduct an exploratory ERG scenario analysis based on these estimates, and assuming that 30% of patients would not receive further anticancer therapy (ERG scenario in Table 24).

Table 24 Proportion of patients receiving post-progression anticancer treatments

Subsequent treatment	Tucatinib Combination	Trastuzumab + capecitabine	Eribulin, vinorelbine, capecitabine	ERG scenario (all treatments)
Trastuzumab	[redacted]	[redacted]	[redacted]	
Pertuzumab	[redacted]	[redacted]	[redacted]	
T-DM1	[redacted]	[redacted]	[redacted]	
Lapatinib	[redacted]	[redacted]	[redacted]	
Neratinib	[redacted]	[redacted]	[redacted]	
Tras + cap				50.0%
Capecitabine				10.0%
Vinorelbine				10.0%
No treatment	[redacted]	[redacted]	[redacted]	30.0%

Source: adapted by ERG from CS Table 30.
T-DM1, trastuzumab emtansine; Tras + cap, trastuzumab with capecitabine

4.2.10.3 Health state costs

Resource use and costs for the pre- and post-progression health states and for end of life care are summarised in CS Document B Table 31. Assumptions about the frequency of consultations were taken from TA458[21], with unit costs from the NHS National Cost Collection 2018/19 and PSSRU 2020.[37 38] End of life care costs were based on TA458, updated for inflation.

4.2.10.4 Adverse events costs

Adverse events costs used in the economic model are summarised in CS Document B Table 32. The company included costs associated with Grade 3 and 4 treatment-emergent adverse events that occurred in at least 2% of patients in HER2CLIMB. They used previous NICE appraisals (TA423, TA496, TA621, TA579) to inform the cost estimates.

The company also included the cost of the supportive antidiarrheal medication-loperamide. Data from HER2CLIMB was used for the proportion of patients receiving loperamide in the tucatinib combination and trastuzumab + capecitabine arms. For the eribulin, capecitabine and vinorelbine comparators, the company assumed that the dose of loperamide and mean treatment duration were the same as for trastuzumab + capecitabine.

ERG conclusions

The company's estimates of resource use and costs are generally appropriate. In ERG analysis, we include drug wastage costs, and an alternative scenario for the cost of subsequent treatments (see section 6.3).

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company report their deterministic base case results in CS Document B Table 35. This and all other cost-effectiveness results in this report are conducted with a Patient Access Scheme (PAS) price discount for tucatinib and an assumed price discount for trastuzumab, with all other comparator and subsequent treatments at list price. We present results with all available PAS/CMU price discounts in a confidential addendum to this report. In their response to clarification question B2, the company provided results for a revised base case, which includes changes to the utility estimates from the analysis of HER2CLIMB EQ-5D data and values used in TA423 (see Table 25 below).

Table 25 Company's base case cost-effectiveness results, deterministic (PAS price for tucatinib and assumed discount for trastuzumab, all other drugs at list price)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Tucatinib combination	[redacted]	[redacted]	-	-	-
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	37,483

Source: Reproduced from company's response to clarification question B2 Table B2c

The company did not provide incremental analyses including all the other comparators. We report full incremental analysis for the company's base case in section 6.

5.2 Company's sensitivity analysis

5.2.1 Deterministic sensitivity analysis

The company report results from their one-way, deterministic sensitivity analysis in the tornado plot in CS Document B Figure 27. The variations for most input parameters were based on simple assumed percentages rather than empirical evidence. This applies to discount rates, mean age, body weight, body surface area, dose intensity, post progression rates, treatment costs, AEs and utilities. The company did not include any parameters for survival models in their deterministic sensitivity analyses. Their sensitivity analysis results indicated that relative dose intensity for the tucatinib combination, and health state utilities have the largest impact on the cost-effectiveness results.

The company did not update their one-way, deterministic sensitivity analysis alongside their updated cost-effectiveness results that was provided as response to their clarification response to question B2. We found similar results to those for the original base case.

5.2.2 Scenario analysis

The company reported nine scenario analyses (CS Document Table 39). They updated their results in their clarification response. We present results including the PAS price for tucatinib and an assumed discount for trastuzumab, and all other drugs at list price in Table 26 (reproduced from CS Document B Table 40 and company's response to clarification question B2 Table B2d).

Table 26 Scenario analyses explored in the model

No	Scenario	ICER (original)	ICER (updated)
Base case		£46,756	£37,483
1	[redacted]	[redacted]	[redacted]
2	Tucatinib combination utilities: EQ-5D-5L	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	Treatment duration: Restricted mean treatment exposure	[redacted]	[redacted]
7	Comparator: Vinorelbine	[redacted]	[redacted]
8	Comparator: Capecitabine	[redacted]	[redacted]
9	Blended ICER: [redacted]	[redacted]	[redacted]

With the PAS for tucatinib and assumed price reduction for trastuzumab (and list prices for other drugs), scenarios for the revised base case give ICERs ranging between [redacted]. The [redacted]. In both these scenarios, the [redacted].

[redacted].

We report additional ERG scenario analyses in section 6.3 below.

5.2.3 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA), with input parameter distributions as reported in CS Document B, Table 33. The company's probabilistic base case results for their original base case (PAS price for tucatinib, assumed discount for trastuzumab and list price for other drugs) are reported in CS Document B Table 37. The cost-effectiveness scatter plot and acceptability curve (PAS price for tucatinib and trastuzumab, list price for others) are shown in CS Document B Figures 23 and 25. The company did not update their probabilistic sensitivity analysis for their revised base case produced in response to clarification question B2. However, the ERG confirms that the probabilistic results are similar to the deterministic results: ICER for the tucatinib combination compared with eribulin £35,452 per QALY gained compared with £37,483.

ERG conclusions

- The company's deterministic and probabilistic sensitivity analyses do not provide an accurate reflection of parametric uncertainty because the variance assumed for many of the input parameters is not based on the available evidence.
- The company presented very limited scenario analyses and did not explore uncertainty related to different survival models fitted to OS and PFS.

5.3 Model validation

The company approach to validation is described in CS section B.3.11. This included assessment of clinical plausibility of PFS and OS extrapolations by an advisory board. They did not provide any information on model quality control, internal validity (i.e. comparing the model results with outputs from the HER2CLIMB trial) or external validity (i.e. comparison of the model results with external data.

The ERG conducted a series of quality checks of the company model. This included: checking that the input parameters in the model matched the values cited in the CS and in the original sources; and validating the results of the scenario and sensitivity analyses as reported by the company. We also conducted a series of 'white box' and 'black box' checks

to validate the model. We spotted a few inconsistencies between parameters in the model and values reported in the CS; these have been described in our critique above.

5.3.1 Internal validation

For internal validation, the ERG have provided a comparison of the modelled survival estimated with the observed data from the HER2CLIMB, produced in Figure 6 within section 4.2.6 of this document. The model OS estimates in the company's base case are not comparable with those in the HER2CLIMB trial, the model survival estimates are consistently higher than in the trial. We present a comparison of the survival estimates in Table 27 below.

Table 27 Comparison of survival predictions from the model and HER2CLIMB

Timepoint	Tucatinib combination		Trastuzumab + capecitabine	
	Model	HER2CLIMB	Model	HER2CLIMB
Overall Survival				
1-year	[redacted]	[redacted]	[redacted]	[redacted]
2-years	[redacted]	[redacted]	[redacted]	[redacted]
3-years	[redacted]	[redacted]	[redacted]	[redacted]
Progression Free Survival				
1-year	[redacted]	[redacted]	[redacted]	[redacted]
2-years	[redacted]	[redacted]	[redacted]	[redacted]
3-years	[redacted]	[redacted]	[redacted]	[redacted]

5.3.2 External validation

The company report a targeted search to identify studies that presented long-term survival data for metastatic breast cancer. Further details are in CS Appendix L. Of the 12 studies identified, only HER2CLIMB provided survival data for the tucatinib combination (612 patients for a duration of 3 years).[4] Two studies had follow up >10 years; 4 studies had follow up over 5 years but <10 years; and 6 studies were considered to provide a good match to the HER2CLIMB data. The study by Urruticoechea et al. (2017) included a trastuzumab + capecitabine control arm with five years of follow up.[35] This was a peripheral study in the company's NMA network that did not contribute to the indirect comparisons of interest for this appraisal. Figure 13 shows the modelled OS curve for tras + cap from the company's base case analysis, alongside their 'trial based' OS curve (fitted to HER2CLIMB trial data) and the KM data for the HER2CLIMB and Urruticoechea control arms. This shows the difference in OS estimates from these two trials, possibly due to differences in the patient populations (e.g. prevalence of brain metastases). It also shows the difference in OS extrapolations derived from the HER2CLIMB trial data alone, compared with the company's

base case modelling approach (fractional polynomial curve for the reference lapatinib + capecitabine, adjusted for with NMA HRs).

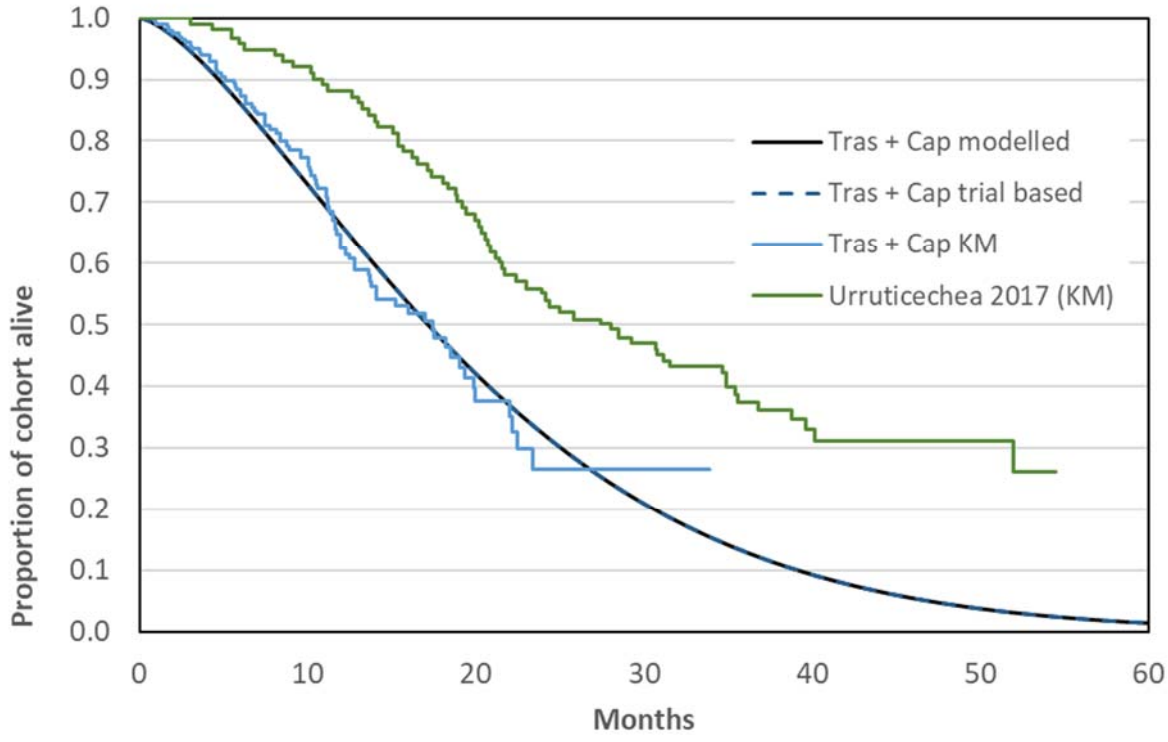


Figure 13 OS trastuzumab + capecitabine: modelled extrapolations and KM data

6 ERG'S ADDITIONAL ANALYSES

6.1 Corrections to the company's base case

The ERG did not identify any errors that affected the company's base case analysis. However, we did make some edits to the model to run the company's revised base case and to enable additional scenario analysis. These changes are described in Table 28.

Table 28 ERG changes to the company model

Issue	Change made	Location in model
Control sheet	Addition of new sheet to apply company and ERG scenario analysis a view summary of fully incremental results	'ERG' sheet. Note that ERG changes to the model are highlighted in green.
Utilities for HER2CLIMB arms	Added pooled estimates from RRMM analysis (clarification response Addendum B2)	'Default Data' sheet, rows 213 to 218. Controls on 'Utilities' and 'ERG' sheets.
Utilities for comparators	Added correct values for ERG and company analysis in TA423 as agreed in company response to clarification question B3	'Default Data' sheet, rows 219 to 229. Controls on 'Utilities' and 'ERG' sheets.
Utility age multipliers	Utility multiplier used to adjust utilities in Markov sheets as the cohort ages within the model. Adjustment based on Ara and Brazier 2010 formula for the general population.[31]	Coefficients for the Ara and Brazier formula added to 'Utilities' sheet. Controls on 'Utilities' and 'ERG' sheets. Edits to columns G, H, AD, AF, AI and AJ on 'Calc_Int' and 'Calc_Comp6' to 'Calc_Comp8' sheets.
Within-trial analysis	Extended direct trial survival estimates to end of 20-year time horizon (rows 1041 to 1062). This enables multiway comparison for within-trial analysis	CB1041 to MQ1062 on 'RCT Survival_PFS' and 'RCT Survival_OS' sheets
Gompertz extrapolations	#Num! error due to estimation of hazard from survival estimates below Excel smallest number	Error trap added to Survival Curves D7 and rows G and K
Taper for OS HR NMA	Corrected 'Time to HR=1' for the OS HR NMA - converted from years to months, as on for PFS HR NMA and FP sheets.	'Bayesian NMA HR Models_OS' BX3
Subsequent treatment	Included 'no subsequent treatment' as class in Dirichlet distribution for PSA. Does not change deterministic results	'Country-Specific Data' rows 128 to 165
Tucatinib discount	For clarity only, same method as for calculation of PAS discount for tucatinib for other drugs.	'Country-Specific Data' K47-L47

6.2 Company revised base case and scenarios

We show results for the company's base case and scenarios in Table 29 and Table 30 respectively. For the revised base case analysis, the company reports the pairwise ICER for the tucatinib combination compared with eribulin, £37,483 per QALY gained. In the full incremental analyses for scope comparators, eribulin is dominated and vinorelbine is subject to extended dominance, so the ICER for the tucatinib combination is [redacted] per QALY compared with capecitabine. If trastuzumab + capecitabine is also included, this is the correct incremental comparator for the tucatinib combination (ICER [redacted]).

Table 29 Company's revised base case, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs Tuc + tras + cap vs. comparators	ICERs fully incremental	
				Excluding Tras + cap	Including Tras + cap
Capecitabine	[redacted]	[redacted]	[redacted]	-	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	-	[redacted]
Eribulin	[redacted]	[redacted]	£37,483	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-	[redacted]	[redacted]

Source: Clarification response Table B2c (tucatinib combination and eribulin), other results produced by the ERG
[a] PAS discount for tucatinib and assumed discount for trastuzumab, other drugs at list price
Ext dom, extendedly dominated; ICER, incremental cost-effectiveness ratio; Tras + cap, trastuzumab with capecitabine; Tuc + tras + cap, tucatinib with trastuzumab and capecitabine.

We note that in the company's scenario with alternative survival curves [redacted], the QALYs do not change. This is because the company base case uses a curve from the FP NMA for a reference treatment (lapatinib + capecitabine), which is adjusted for other comparators using hazard ratios from the NMA. The model only actually includes one FP model for PFS and one for OS. Thus, it is not possible to do scenario analysis on the choice of survival curves for extrapolation in this version of the model. The change in cost for the tucatinib combination arm in this scenario is misleading. This is caused by the method for estimation of TTD. This is derived from fitted curves to HER2CLIMB data, with constraints that TTD cannot exceed PFS, and that PFS cannot exceed OS. Hence, in this scenario the trial-based survival models for PFS and OS change, which has an indirect effect on TTD.

Table 30 Company's scenario analyses on revised base case, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs
Revised company base case			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	£37,483
Tuc + tras + cap	[redacted]	[redacted]	-
Survival curves ([redacted])			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
NMA (PFS and OS [redacted])			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
NMA (PFS and OS [redacted])			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
NMA (PFS and OS [redacted])			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Treatment duration (restricted mean exposure)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-

6.3 ERG scenarios applied to the company's base case

6.3.1 Within-trial analysis and survival extrapolations

Table 31 shows the effect of applying a 'within-trial' method for the survival extrapolations for the HER2CLIMB arms to the company's revised base case. This has the effect of reducing

QALYs across all treatments, and also reducing incremental QALYs and hence increasing the ICERs. Changes to the fitted OS survival model (stratified Weibull and Gompertz) have moderate impact on the ICERs.

Table 31 ERG additional scenarios for OS extrapolations, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs
Revised company base case			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	£37,483
Tuc + tras + cap	[redacted]	[redacted]	-
Within-trial analysis – OS Weibull			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Within-trial analysis – OS stratified Weibull			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Within-trial analysis – OS Gompertz			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-

Table 32 shows results for the within-trial survival analyses with changes to extrapolations for PFS. Alternative survival models for PFS have a small impact on the ICER estimates.

Table 32 ERG additional scenarios for PFS extrapolations, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs
Revised company base case			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	£37,483
Tuc + tras + cap	[redacted]	[redacted]	-
Within-trial analysis – PFS flexible Weibull 2 knots			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Within-trial analysis – PFS stratified generalised gamma			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Within-trial analysis - PFS stratified log-normal			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-

6.3.2 Indirect treatment effects

Changes to the NMA model used in the within-trial analysis are shown in Table 33. The ERG's random effects NMA with correction to the Pivot upper confidence limit (see section 3.6 above) reduces the differences in QALYs between the tucatinib combination and indirect comparators, hence increasing these pairwise ICERs.

Table 33 ERG additional scenarios for NMA analyses, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs
Revised company base case			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	£37,483
Tuc + tras + cap	[redacted]	[redacted]	-
Within-trial analysis – HR NMA fixed effect (PFS and OS)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Within-trial analysis – HR NMA random effects (PFS and OS)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Within-trial analysis – HR NMA random effects with ERG Pivot correction			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-

6.3.3 Waning of treatment effects

The model includes a scenario to taper HR values from the end of maximum follow up, to a defined timepoint when the HR=1. The default time to HR=1 in the model for OS is 72 months from the start of treatment. This causes a moderate increase in the ICERs. We also tested the impact of reducing the time to HR=1 for OS to 48 months, which causes a further increase in the ICERs. For PFS, the default time to HR=1 is 48 months. This has very little impact on QALYs but reduces costs, hence ICERs are lower with PFS tapering.

Table 34 ERG additional scenarios for tapering of treatment effects, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs
Revised company base case			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	£37,483
Tuc + tras + cap	[redacted]	[redacted]	-
Tapering of OS HRs from end of trial follow-up to HR=1 at 72 months			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Tapering of OS HRs from end of trial follow-up to HR=1 at 48 months			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Tapering of PFS HRs from end of trial follow-up to HR=1 at 48 months			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-

6.3.4 Utility scenarios

The model is sensitive to changes to assumptions about the health state utilities (Table 35). Reducing the difference in utility values between the HER2CLIMB arms and external comparators increases the ICERs for tucatinib compared with capecitabine, vinorelbine and eribulin. The effects of including utility loss due to adverse events and or adjusting for age have little impact on the ICERs.

Table 35 ERG additional scenarios for utilities, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs
Revised company base case			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	£37,483
Tuc + tras + cap	[redacted]	[redacted]	-
Pre-progression utility 0.706 for tucatinib and Tras + Cap (TA423 eribulin value)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Post-progression utility 0.588 for all treatments (mean of TA423 estimates)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
HER2CLIMB utilities for all treatments (0.762 pre-progression, 0.698 post-progression)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-

Include AE disutilities			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Age adjustment for utilities			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-

6.3.5 Resource use and cost scenarios

Finally, we consider scenarios related to resource use and costs (Table 36). Assuming that treatment duration is equal to PFS increases costs for all treatments, but proportionately more for the tucatinib combination, hence increasing ICERs. The ERG scenario for subsequent treatment use does not have a big impact, except for trastuzumab + capecitabine (because the company's base case assumed higher use of some expensive anti-cancer drugs in this arm, based on HER2CLIMB data). Including drug wastage costs has little impact on overall costs or ICERs.

Table 36 ERG additional scenarios for resource use and costs, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs Tuc + tras + cap vs. comparators
Revised company base case			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-

Treatment duration based on PFS (all treatments)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Include costs for drug wastage			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
ERG subsequent treatment scenario (50% tras, 20% cap/vin: [redacted] per person)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-

6.4 ERG preferred analysis and scenarios

ERG preferred assumptions are:

- Within-trial analysis: OS and PFS fitted to HER2CLIMB trial data for the tucatinib combination and trastuzumab + capecitabine (see section 4.2.6 above).
- Relative effects for other comparators from the HR NMA with random effects and the ERG correction for the Pivot upper confidence limit (3.6).
- Health state utilities from HER2CLIMB EQ-5D analysis applied to all treatments (4.2.9.2).
- ERG scenario for the use of subsequent treatments (4.2.10.2)
- Adjustment of utilities for age
- Costs for drug wastage.

The cumulative effect of ERG preferred assumptions to the company's base case is shown in Table 37.

Table 37 Cumulative change from company base case to ERG base, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs	Change to pairwise ICERs
Revised company base case				
Capecitabine	[redacted]	[redacted]	[redacted]	
Vinorelbine	[redacted]	[redacted]	[redacted]	
Tras + cap	[redacted]	[redacted]	[redacted]	
Eribulin	[redacted]	[redacted]	£37,483	
Tuc + tras + cap	[redacted]	[redacted]		
+ Within-trial analysis (PFS and OS, with HR NMA fixed effect)				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		
+ HR NMA random effects with ERG Pivot correction				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		
+ HER2CLIMB utilities (0.762 pre-progression, 0.698 post-progression)				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		
+ Age-adjustment for utilities				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		
+ ERG subsequent treatment scenario (50% tras, 20% cap/vin: [redacted] per person)				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		
+ Include costs for drug wastage (ERG preferred analysis)				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]		

Full incremental results from the ERG preferred analysis are shown in Table 38. Alternative scenarios applied to the ERG base case are shown in Table 39.

Table 38 ERG preferred analysis, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs Tuc + tras + cap vs. comparators	ICERs fully incremental Excluding Tras + cap	ICERs fully incremental Including Tras + cap
Capecitabine	[redacted]	[redacted]	[redacted]	-	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]	-	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-	[redacted]	[redacted]

Source: Clarification response Table B2c (tucatinib combination and eribulin), other results produced by the ERG
[a] PAS discount for tucatinib and assumed discount for trastuzumab, other drugs at list price
Ext dom, extendedly dominated; ICER, incremental cost-effectiveness ratio; Tras + cap, trastuzumab with capecitabine; Tuc + tras + cap, tucatinib with trastuzumab and capecitabine.

Table 39 ERG preferred analysis and scenarios, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs
ERG preferred analysis			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
OS stratified Weibull			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
OS Gompertz			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-

NMA HR fixed effect (no Pivot correction)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Utilities from TA423 (pre-progression 0.706/701; post-progression 0.588)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Treatment duration equal to PFS (all treatments)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Treatment duration restricted mean treatment exposure			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-
Subsequent treatment (trial-based)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Tras + cap	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tuc + tras + cap	[redacted]	[redacted]	-

Figure 14 shows the survival curves from this model, alongside HER2CLIMB KM plots. This shows that the within-trial analysis in the ERG preferred model gives a better fit to the results from the pivotal trial than the company's NMA based approach (Figure 6 above).

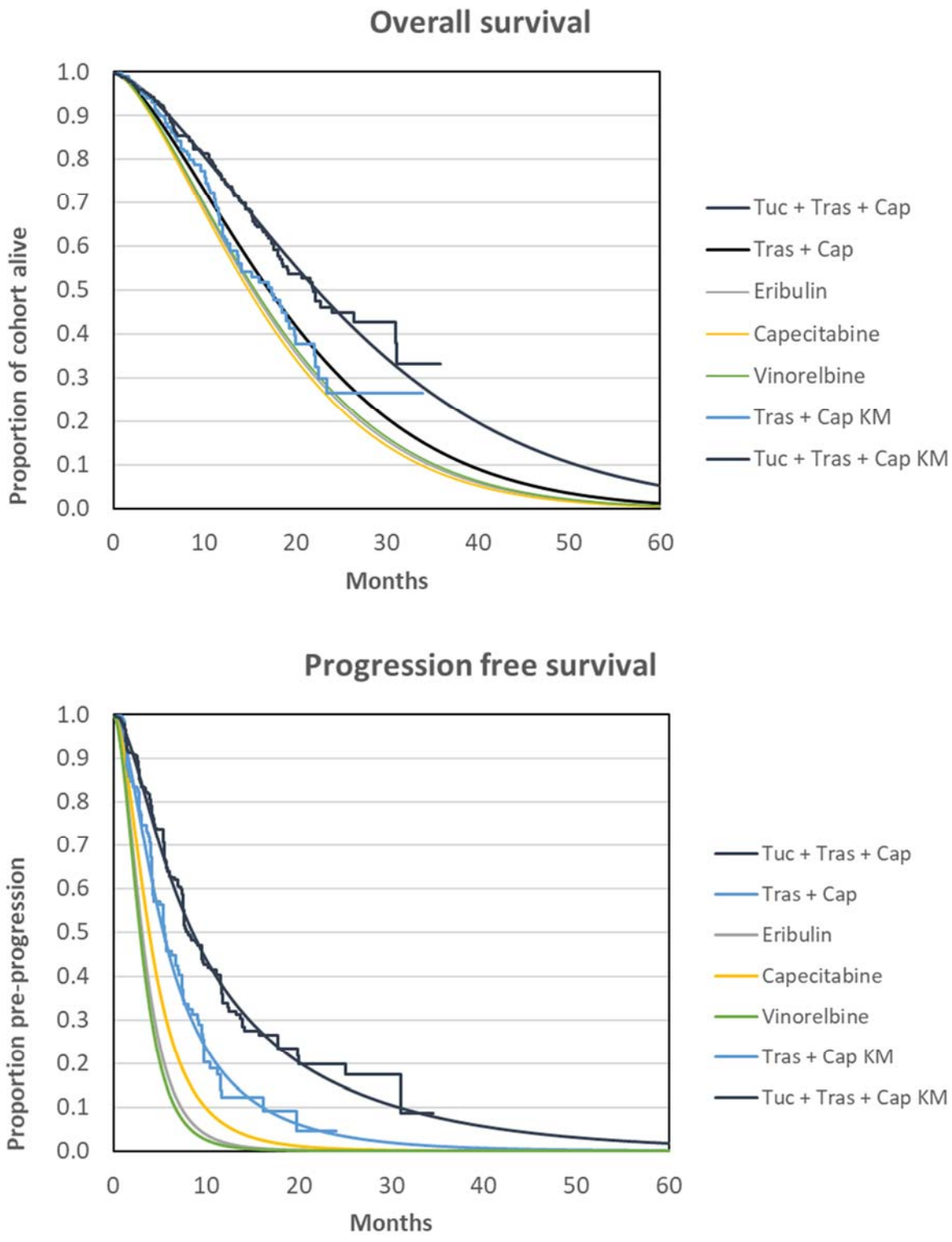


Figure 14 Survival curves from ERG preferred model, with KM data from HER2CLIMB

Source: Obtained from the company's model by the ERG

7 END OF LIFE

The company consider that the tucatinib combination meets NICE end of life criteria for patients with HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies (CS Table 15). They state that clinical experts in England agreed with their argument that the life expectancy at third line treatment is less than 24 months and the gain in life extension with the tucatinib combination is expected to be greater than 3 months. Furthermore, they state that their argument aligns with previous NICE appraisals for second line and third-line treatment in metastatic setting.

In Table 40, we summarise and critique the company's evidence in support of their case for end of life criteria applying to patients with HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies.

Table 40 Summary and critique of the CS case for meeting end of life criteria

Criterion	Data available	ERG comment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The median OS achieved with the single-agent chemotherapy currently available in the third-line setting (eribulin) is less than 16 months	Median OS with eribulin ranged from 13.1 to 15.9 months in three clinical trials including patients with HER2+ and HER2-negative (HER2-) metastatic breast cancer. We agree with the company's assertion.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The median OS difference between the tucatinib combination and the placebo combination in HER2CLIMB exceeds 3 months (21.9 versus 17.4 months)	For the tucatinib combination, the mean undiscounted life years based on the company's (revised) model is 2.91 years and that on the ERG's modelled base case is 2.19 years. Tucatinib combination extended life by greater than 3 months in both the ERG and the company's (revised) base case models.

In Table 41 below, we present a comparison of the undiscounted life years of the treatments in comparison for the company's (revised) base case and the ERG base case. We note that tucatinib combination extended life by greater than 3 months compared to the comparators in both the cases.

Table 41 Comparison of the undiscounted life years

Treatment	Undiscounted life years			
	Company's revised base case	Difference (Tucatinib vs comparator)	ERG base case	Difference (Tucatinib vs comparator)
Capecitabine	1.72	1.19	1.45	0.74
Vinorelbine	1.77	1.14	1.51	0.68
Tras + cap	2.22	0.69	1.68	0.51
Eribulin	1.74	1.17	1.49	0.70
Tuc + tras + cap	2.91		2.19	

ERG conclusion

We agree with the company that tucatinib combination meets both the end of life criteria.

8 References

1. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. Br J Cancer 2006;95(6):683-90. doi: 10.1038/sj.bjc.6603326 [published Online First: 2006/09/13]

2. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. Eur J Health Econ 2010;11(4):427-34. doi: 10.1007/s10198-010-0233-7 [published Online First: 2010/05/18]

3. Kaufman PA, Awada A, Twelves C, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2015;33(6):594-601. doi: 10.1200/JCO.2013.52.4892 [published Online First: 2015/01/22]

4. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med 2020;382(7):597-609. doi: 10.1056/NEJMoa1914609 [published Online First: 2019/12/12]

5. Kuksis M, Gao Y, Tran W, et al. The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis. Neuro-Oncology 2020;23(6):894-904. doi: 10.1093/neuonc/noaa285

6. Paracha N, Reyes A, Dieras V, et al. Evaluating the clinical effectiveness and safety of various HER2-targeted regimens after prior taxane/trastuzumab in patients with previously treated, unresectable, or metastatic HER2-positive breast cancer: a systematic review and network meta-analysis. Breast Cancer Res Treat 2020;180(3):597-609. doi: 10.1007/s10549-020-05577-7 [published Online First: 2020/02/27]

7. ClinicalTrials.gov. A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer (HER2CLIMB).

8. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer – supplementary appendix. N Engl J Med 2020;382(7):597-609. doi: 10.1056/NEJMoa1914609 [published Online First: 2019/12/12]

9. Murthy R, Borges VF, Conlin A, et al. Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study. Lancet Oncol 2018;19(7):880-88. doi: 10.1016/S1470-2045(18)30256-0 [published Online First: 2018/05/29]

10. Takano T, Tsurutani J, Takahashi M, et al. A randomized phase II trial of trastuzumab plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxanes: WJOG6110B/ELTOP. Breast 2018;40:67-75. doi: 10.1016/j.breast.2018.04.010 [published Online First: 2018/04/27]

11. Pivot X, Manikhas A, Zurawski B, et al. CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol 2015;33(14):1564-73. doi: 10.1200/JCO.2014.57.1794 [published Online First: 2015/01/22]

12. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol 2009;27(12):1999-2006. doi: 10.1200/JCO.2008.19.6618 [published Online First: 2009/03/18]

13. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat 2008;112(3):533-43. doi: 10.1007/s10549-007-9885-0 [published Online First: 2008/01/12]

14. Yuan P, Hu X, Sun T, et al. Eribulin mesilate versus vinorelbine in women with locally recurrent or metastatic breast cancer: A randomised clinical trial. Eur J Cancer 2019;112:57-65. doi: 10.1016/j.ejca.2019.02.002 [published Online First: 2019/04/01]

15. Turner RM, Jackson D, Wei Y, et al. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med 2015;34(6):984-98. doi: 10.1002/sim.6381 [published Online First: 2014/12/06]

16. Turner RM, Davey J, Clarke MJ, et al. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol 2012;41(3):818-27. doi: 10.1093/ije/dys041 [published Online First: 2012/03/31]

17. Therneau TM GP. Modeling survival data: extending the Cox model. . New York: Springer 2000.

18. RTI Health Solutions. Update of economic systematic literature review to support tucatinib in metastatic breast cancer, 2021.

19. Anderson SA, Carrico J, Brodtkorb T-H, et al. Abstract PS10-45: Budget impact of introducing neratinib for third-line treatment of HER2+ metastatic breast cancer in the United States: AACR, 2021.

20. Vondeling G, Palaka E, Livings C, et al. PCN69 Cost-Effectiveness Analysis of NOVEL Therapies for HER2+ Metastatic Breast Cancer:[FAM-] Trastuzumab Deruxtecan Versus Tucatinib Trastuzumab and Capecitabine Combination. Value in Health 2020;23:S433-S34.

21. NICE. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane – technology appraisal guidance [TA458] 2017 [updated 20 November. Available from: www.nice.org.uk/guidance/TA458 accessed March 2021.

22. Scottish Medicines Consortium (SMC). Following a full submission: trastuzumab 600mg/5mL solution for injection (Herceptin®) is accepted for restricted use within NHS Scotland [928/13] 2013 [updated 6 December. Available from: www.scottishmedicines.org.uk/medicines-advice/trastuzumab-herceptin-fullsubmission-92813/ accessed April 2021.

23. Scottish Medicines Consortium (SMC). Following a resubmission assessed under the orphan equivalent and end of life process: trastuzumab emtansine (Kadcyla®) is accepted for use within NHS Scotland [990/14] 2017 [updated 10 March. Available from: www.scottishmedicines.org.uk/medicines-advice/trastuzumab-emtansine-kadcyla-resubmission-99014/ accessed April 2021.

24. NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens – technology appraisal guidance [TA423] 2016 [updated 21 December. Available from: www.nice.org.uk/guidance/TA423 accessed April 2021.

25. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15(5):708-15. doi: 10.1016/j.jval.2012.02.008 [published Online First: 2012/08/08]

26. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for

economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011 2013 [updated March. Available from: http://nicedsu.org.uk/technical-support-documents/survival-analysis-tsd/ accessed April 2021.

27. Seagen Inc. HER2CLIMB Clinical Study Report, 2019.

28. NICE. Position statement on use of the EQ-5D-5L value set for England, 2019.

29. NICE. Guide to the methods of technology appraisal – processes and methods 2013 [Available from: www.nice.org.uk/process/pmg9 accessed April 2021.

30. NICE. Position statement on use of the EQ-5D-5L value set for England (updated October 2019) 2019 [Available from: www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l accessed April 2021.

31. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13(5):509-18. doi: 10.1111/j.1524-4733.2010.00700.x [published Online First: 2010/03/17]

32. Saura C, Oliveira M, Feng YH, et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With >/= 2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol 2020;38(27):3138-49. doi: 10.1200/JCO.20.00147 [published Online First: 2020/07/18]

33. BNF. British National Formulary, 2021.

34. eMIT. Drugs and pharmaceutical electronic market information tool (eMIT) – DHA225 2021 [updated 11 March. Available from: www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit accessed April 2021.

35. Urruticoechea A, Rizwanullah M, Im SA, et al. Randomized Phase III Trial of Trastuzumab Plus Capecitabine With or Without Pertuzumab in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Who Experienced Disease Progression During or After Trastuzumab-Based Therapy. J Clin Oncol 2017;35(26):3030-38. doi: 10.1200/JCO.2016.70.6267 [published Online First: 2017/04/25]

36. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367(19):1783-91. doi: 10.1056/NEJMoa1209124 [published Online First: 2012/10/02]

37. NHS. 2018/19 National Cost Collection data (NHS Improvement) 2019 [Available from: www.england.nhs.uk/national-cost-collection/#ncc1819 accessed April 2021.

38. PSSRU. Unit costs of health and social care 2019. Personal Social Services Research Unit. 2020

9 Appendices

9.1 Company and ERG risk of bias assessment of HER2CLIMB

Assessment criteria	Company judgement		ERG judgement
Was randomisation carried out appropriately?	Yes	Yes – patients were randomised in a 2:1 ratio using a dynamic hierarchical randomisation scheme to receive tucatinib or placebo in combination with capecitabine and trastuzumab	Agree: low risk of bias
Was the concealment of treatment allocation adequate?	Yes	Yes – adequate blind allocation was achieved with the applied randomisation scheme	Agree: low risk of bias
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes – baseline patient characteristics were balanced between the treatment arms	Agree: low risk of bias We note a slight imbalance in the proportion of white participants and those with liver metastases, both of which are slightly higher in the placebo arm. The implications of this are unclear.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes – the first part of the study was carried out blindly for the investigator, study centre personnel, clinical research organisation staff and sponsor personnel (except for prespecified Safety personnel)	Agree: low risk of bias[a]
Were there any unexpected imbalances in dropouts between groups?	No	No – balanced, low rates of dropouts were observed in both treatment arms: 23/404 (5.7%) patients discontinued tucatinib and 6/197 (3.0%) patients discontinued placebo	Agree: low risk of bias[b] We note a higher proportion discontinued placebo (86.3%) than tucatinib (70.8%), more commonly due to progressive disease in the placebo arm (68% vs 50%). Discontinuations due to adverse events were higher with tucatinib (5.7% vs 3.0%)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No – all predefined endpoints were reported	Agree: low risk of bias We note DOR and CBR determined by the investigator as well as BICR are listed in the protocol as secondary endpoints, only BICR is reported in the CS.

			Investigator results are reported on clinical trials register.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes – the primary endpoint was assessed in the first 480 enrolled patients (primary endpoint population), and patients without outcomes for PFS and OS were censored and those with missing data considered non-responders for ORR and CBR outcomes	Agree: low risk of bias EQ-5D was completed by a subset of the population.

Source CS Table 7 and CS Appendix D Table 22. [a] 'the first part of the study' refers to the phase prior to the open label extension (clarification response C1). [b] the rates in the company response are rates of adverse events leading to discontinuation (clarification response C2).

9.2 Summary of HER2CLIMB trial outcomes and statistical procedures

Trial outcomes

Outcome type	**Outcome measures** (CS Table 4)	**Outcome definitions**	**ERG comments**
Primary endpoint	PFS	Disease response and progression were evaluated in accordance with RECIST criteria version 1.1 by Blinded Independent Central Review (BICR)	Assessed in the 'primary endpoint population' (see discussion Section 3.2.1.1). Defined in the Clinical Study Report (CSR) as the time from randomisation to documented disease progression or death from any cause. Details of the BICR were not reported.
Secondary endpoints (pre-specified alpha-controlled see Section 3.2.4)	-PFS in people with brain metastases at baseline -OS -Confirmed objective response rate (ORR)		-Assessed in a subgroup of the total population -In the total population OS defined in the CSR (time from randomisation to death from any cause) -Confirmed ORR defined as the best overall response in those with measurable disease at baseline. No ERG concerns
Other secondary endpoints	-PFS -Duration of response (DOR) and clinical	-By investigator assessment -By BICR	-Assessed in the total population -In the CSR and trial protocol DOR and CBR determined by investigator assessment were also secondary endpoints.

	benefit rate (CBR)		DOR defined as the time from the first objective response to documented disease progression or death from any cause. CBR defined as those achieving stable disease (SD) or non-complete response (CR)/non-progressive disease (PD) for at least 6 months or a best overall response of confirmed CR or confirmed partial response (PR). Additional secondary / exploratory outcomes reported were time to brain progression by BICR (CS B.2.6.8)
Patient reported outcomes	HRQoL by EQ-5D-5L (CS 2.6.9)	Following a protocol amendment, subgroup of total sample	The CS reports baseline and endpoint data for the EQ-5D descriptive system and the EQ-5D VAS. The trial protocol states that the treatment and placebo group index value changes will be summarised and that responses on the descriptive system will be converted to EQ-5D Index scores using a valuation set as recommended by EuroQol. However, no index scores were provided in the CS but were provided in response to clarification question A2. As described in CS 2.6.9 the inclusion of HRQoL as an outcome was made at protocol amendment seven and consequently only a subset of the total population (tucatinib n=217; placebo n=112) had data.
Safety endpoints	-Adverse events -Clinical laboratory assessments; vital signs and other relevant safety variables -Frequency of dose modifications of tucatinib, capecitabine and trastuzumab	-Modifications could include dose holding, dose reductions and discontinuations	Matches CSR and protocol No ERG concerns

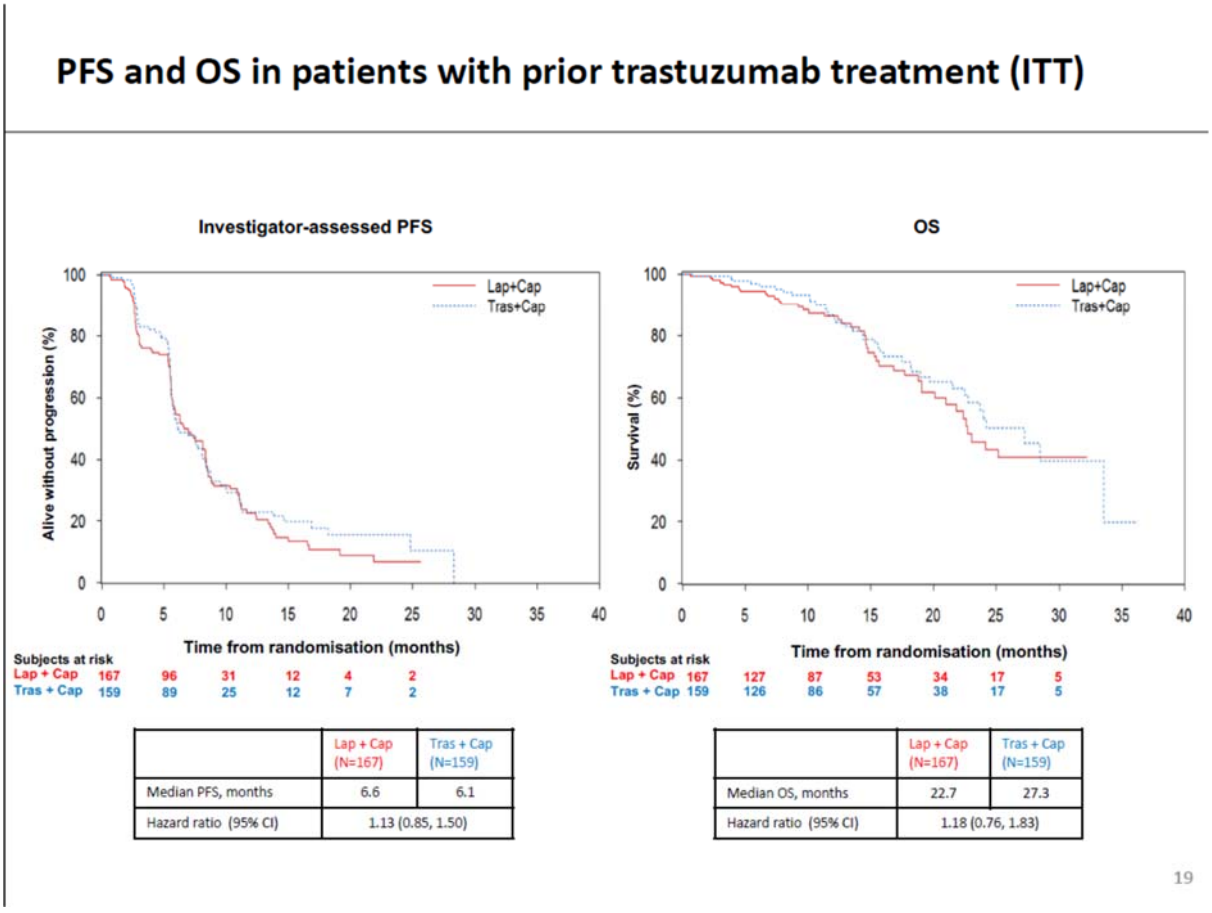
Summary of trial statistical procedures

	ERG comments
Sample size calculation	Reported in CS Section B. 2.3.1 and B.2.4, with further detail in the trial protocol / statistical analysis plan and the CSR. The ERG has no concerns over the sample size calculation; the trial was large and appeared adequately powered for the reported outcomes.

Statistical approach for each outcome	Detail as reported in CS Section B.2.4 unless otherwise stated. - PFS in the primary endpoint evaluation set used a stratified, log-rank test controlling for the randomisation stratification factors after 275 PFS events (aim was for 288 events). Unstratified log-rank tests and the stratified and unstratified Wilcoxon tests were also reported in the trial publication to be undertaken as supportive measures. - With the primary endpoint PFS analysis being statistically significant, the alpha controlled key secondary outcomes of OS (total population) and PFS (brain metastases subgroup) were parallel tested (changed from hierarchical testing at protocol amendment 8 to allow for the importance of OS) at significance levels (alpha) initially set at 0.02 and 0.03, respectively, in an interim analysis. To control for multiplicity of outcomes and analyses (interim and final), the risk of a type I error was controlled using the group sequential Holm variable procedure (if only one of the two key secondary outcomes were statistical significant, the unused alpha could be passed to the other outcome [from the trial protocol / SAP]) with the Lan–DeMets alpha-spending function with an O'Brien–Fleming boundary (where the total number and timing of the interim analyses does not need to be specified in advance and how much of the alpha is 'spent' each time an analysis is undertaken is defined). In the interim analysis of PFS brain metastases and OS the 2-sided alpha's were 0.008 and 0.0074 respectively (CS page 32) and no further analysis is planned. The trial arms were compared using the same statistical approaches described above (taken from the trial publication). - With OS and PFS brain metastases being statistically significant, ORR was tested at a two-sided alpha level of 0.05 using a stratified Cochran–Mantel–Haenszel test. - PFS and OS curves were estimated with Kaplan-Meier methodology and stratified Cox proportional-hazards models to estimate hazard ratios (HRs) and 95% CI were undertaken. CS Figures 16 and 17 (Section B.2.9.1.6) provide log hazard plots for PFS and OS respectively as evidence that the proportional hazards assumption holds. -A re-randomisation procedure (with 10,000 alternative subject randomisations) was used to generate p-values for the primary endpoint and key secondary endpoint analyses to reflect the dynamic hierarchical allocation scheme (Table 5, ref SAP) - The additional secondary and exploratory outcomes were not subject to type 1 error control
Handling of missing data for each outcome	Participants without disease progression or death outcomes as appropriate for PFS and OS were censored at the time of the last assessment or the date of randomisation if there was no post baseline information (described in the trial protocol / SAP). Participants with missing data for ORR and CBR were considered non-responders / not having clinical benefit (described in the trial protocol / SAP). The CS do not provide any details of how missing EQ-5D data were handled.
Sensitivity analysis for statistical analyses	In the trial SAP (CS ref 15 Murthy 2020) Section 5.2.1.2 discusses potential sensitivity analyses which may be undertaken for the primary PFS endpoint, including in the case of a non-proportional hazard or stratification errors, and for missing disease response assessments and new anti-cancer therapy before disease progression or death. These were not discussed in the CS. The CSR reports that the latter two sensitivity analyses were undertaken

	and that results were [redacted] The proportional hazards assumption held and therefore sensitivity analyses were not required.
Prespecified subgroups	Pre-planned subgroups were reported in CS Table 4 (Age (≥65 or <65 years); Race (white or non-white); Hormone receptor status (HmR+ or HmR-); Baseline brain metastases (yes or no); ECOG performance-status score (0 or 1); Geographic region (US and Canada or rest of world)). The CS does not describe the statistical analyses for these subgroups but the trial protocol / SAP reports that the subgroup analyses used conventional stratified log rank statistical methods and stratified Cox proportional hazards regression models.

9.3 Corrected hazard ratio confidence interval for Pivot et al (2015)[11]



Personal communication, Professor Xavier Pivot, 16/06/21

9.4 ERG critique of the fractional polynomial NMA

As mentioned in section 3.4 of this report, the company conducted an NMA using fractional polynomial methodology, as an alternative to the HR NMA, to account for potential violation in proportional hazards. The ERG does not consider there is sufficient evidence to reject the proportional hazards assumption, and we therefore consider the HR NMA is appropriate for this appraisal. For this reason we do not discuss the fractional polynomial NMA in detail in this report. For completeness we provide a brief appraisal of the fractional polynomial NMA below.

The ERG considers the fractional polynomial analysis well conducted in terms of:

- [redacted] (CS Appendix D, page 94)
- [redacted] In general, the fractional polynomial NMA results were consistent with those of the HR NMA; where inconsistencies were noted, these were "not relevant to the NICE decision problem" (clarification response A14).
- As the company point out, there is no current methodology for the use of informative priors with the fractional polynomial model, hence a random effects model would likely overestimate uncertainty.
  [redacted].

However, the ERG also had a number of concerns:

- The choice of the preferred fractional polynomial models is somewhat opaque and the ERG cannot confirm the most suitable model were selected for PFS and OS in each case.
- [redacted]

[redacted]

Time-varying hazard ratio plots (as requested in clarification question A10) were only presented for the company's chosen best fit models, as detailed above. If these plots were provided for other fractional polynomial models the ERG could have investigated whether the shape of the hazards over time were clinically plausible.

- Furthermore, only the base case fractional polynomial models were available for use in the economic model so the impact of other fractional polynomial models, some of which may present a similar fit, is uncertain.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 5 July 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Deviation from final scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 11 and subsequent parts of the report, treatment with trastuzumab + capecitabine is included as a comparator. In particular, this comparison is included in section 6 of the report including section 6.4, the ERG's preferred analyses and scenarios. Evidence relating to a comparison with trastuzumab + capecitabine is not relevant to this appraisal since this combination is not included in NICE's final scope. Such evidence cannot have any bearing on the assessment of incremental cost-effectiveness for tucatinib and should not therefore be reported by the ERG.	Please remove trastuzumab + capecitabine as a comparator – and specifically please remove this comparator from all results tables presented in the document throughout the ERG report	Trastuzumab + capecitabine is not included in the final scope and all results relating to this comparator are irrelevant to the decision problem. Their inclusion in the ERG's preferred analyses tables is potentially misleading. We suggest that it would be appropriate to remove this comparator from all results tables in section 6.4 for the final ERG report post-FAC.	**This is not a factual inaccuracy, no change made.** We explain our rationale for reporting results for trastuzumab + capecitabine in the cost-effectiveness analysis in section 4.2.4 of the ERG report. We are clear that trastuzumab + capecitabine is not included in the NICE scope and do not refer to it as a comparator. Incremental results are reported both with and without trastuzumab + capecitabine.

Issue 2 Clarity of treatment pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 20, Figure 1 – Enhertu® (trastuzumab deruxtecan) is included in the treatment pathway schematic	Please remove this treatment from diagram and the reference to trastuzumab deruxtecan.	Trastuzumab deruxtecan is out of scope of the decision problem. It is not available through routine commissioning but is funded through the Cancer Drugs Fund (CDF) until further data are available. Based on section 4 of the	**Not a factual inaccuracy – no change made.** We do not imply that trastuzumab deruxtecan is an established treatment in the care pathway. We mention it only for information and context, to

		NICE Position Statement: consideration of products recommended for use in the CDF as comparators, or in a treatment sequence, in the appraisal of a new cancer product, Enhertu should not be considered as a potential standard-of-care option and included in the treatment pathway.	illustrate that NICE is appraising other treatments at third line. Figure 1 clearly shows it is a CDF treatment and gives the NICE TA number for reference. The accompanying text clearly states it is not in routine use currently, but that NICE will review their guidance following further data collection. Trastuzumab deruxtecan is not included as a comparator in any of the ERG's analyses.

Issue 3 Patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 21, the ERG may have mischaracterised the use of 'unresectable' in the decision problem and indication statement to state that the population has widened.	Please delete: • This widens the population to also include people whose tumours are resectable, and potentially the effects of tucatinib may not necessarily be the same for them as they are for people with unresectable tumours. However, expert clinical advice to the ERG is that there is a small number of patients with isolated cerebral metastases that are resectable, and these patients may receive non-curative-intent surgery. Thus, the impact of tucatinib on mortality would be unlikely to differ according to resection status.	The term 'unresectable' refers to the site of the primary tumour in the breast. Unresectable in this context of the indication statement and decision problem does not relate to surgical resection of a brain metastasis, or any other site of metastasis.	We have removed the sentence beginning "However, expert clinical advice…" and the subsequent sentence "Thus, the impact…" to avoid confusion (page 21).

Issue 4 Assumption of relative benefit

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 47, the ERG states incorrectly an assumption that patients with brain metastases are more likely to benefit from treatment.	Can the ERG clarify if they are referring to absolute or relative treatment effect?	Whilst the PFS and OS HRs for the brain metastases subgroup were numerically more favourable than for those patients without brain metastases, patients with brain metastases have a poorer prognosis than those without, and the median PFS and OS were numerically longer for patients without brain metastases than those with brain metastases. If the HER2CLIMB trial had excluded patients with brain metastases, rather than including patients with brain metastases, it may have extended the overall PFS and OS. The indirect comparison of the results to other trials may therefore understate the relative benefit of tucatinib since other clinical trials excluded most patients with brain metastases.	Thank you for your explanation. We have corrected the following sentence: "This would assume that patients with brain metastases are ~~more~~ less likely to benefit from treatment". Based on this assumption we would expect to see more favourable estimates for tucatinib from the NMA if these patients were excluded. Clinical advice suggests that brain metastases patients would not generally respond well to existing treatments. However, evidence (albeit weak evidence) from HER2CLIMB suggests a potentially greater relative benefit for tucatinib in this subgroup. If patients with brain metastases were excluded from HER2CLIMB then absolute PFS and OS would be expected to increase (based on brain metastases patients having a worse prognosis). But it is unclear how this would influence the relative tucatinib

			treatment effect in the NMA. We tested this scenario and found that excluding the subgroup of patients with brain metastases resulted in *less* favourable HRs in the NMA. Our conclusion, therefore, is that the direction and magnitude of bias in the NMA from the uneven distribution of brain metastases patients across trials, is uncertain. We have made some edits to the text on page 47/48 to explain the above with greater clarity.

Issue 5 Upper bound CI of the Pivot study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 51, the ERG cites an unpublished, personal communication as a source to revise the CIs used NMA. These values were not published, and therefore not available for Seagen's assessment. Neither Professor Pivot nor the Journal of Clinical Oncology have issued a correction to the paper published in 2015.	The company submission relied upon the peer reviewed, published values.	The HRs and CIs utilised in both the HR and fractional polynomial NMAs utilised the data presented in peer reviewed publications identified by the SLR. There was a typographical error in the NMA report, Appendix G, Table G-1 that lists the upper bound CI as 1.83, however, the published CI of 1.183 was the value used in all modelling undertaken by Seagen.	Noted, but there is no factual inaccuracy as regards the ERG report. The ERG's observation was that the upper bound of the CI lacked face validity and was likely to be an error, hence why we contacted the author for clarification. The company were at liberty to do the same when they included the study in their NMA. The author was unaware of the

			typographical error and a journal correction will no doubt be forthcoming.

Issue 6 Source of utility estimates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 83, the ERG cites the source of the utility estimates used in the revised base case as TA423 without specifying a document/section.	Please change from: However, the revised company base case only uses the TA423 ERG (Lloyd et al) estimate for progressed disease, rather than taking a mean of the Crott and Briggs and Lloyd et al. values. To: However, the revised company base case uses an estimate for progressed disease as referenced in slide 16 of TA423 ERG (Lloyd et al.), rather than taking a mean of the Crott and Briggs and Lloyd et al. values.	As agreed in the response clarification meeting with NICE and the ERG, the utilities used for eribulin, capecitabine, and vinorelbine in the revised base case were sourced from slide 16 of the Committee cost-effectiveness slides for TA423.	**This is not a factual inaccuracy – no change made.** It is clear from the preceding paragraph in our report that the company had corrected the Crott and Briggs estimates in response to the clarification question B3 (and we cite the correct source for the values used in TA423). The final paragraph in this section refers to a different question: whether or not an average of the Lloyd et al. and Crott and Briggs values should be used.

Issue 7 Wording

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 12, the ERG mentions patients ‘with’ brain metastases when referring to a section describing results in patients	Please revise from: The ERG also conducted an exploratory NMA scenario analysis using data for the subgroup of patients without brain metastases from the	Section 3.6.3 describes exploratory analysis in patients without brain metastases	We have corrected this to say ‘without’ (page 12)

'without' brain metastases.	HER2CLIMB trial (3.6.3). This reduces heterogeneity between the studies included in the evidence network and produced HRs that are less favourable for the tucatinib combination in patients with brain metastases than for the whole trial population. To: The ERG also conducted an exploratory NMA scenario analysis using data for the subgroup of patients without brain metastases from the HER2CLIMB trial (3.6.3). This reduces heterogeneity between the studies included in the evidence network and produced HRs that are less favourable for the tucatinib combination in patients without brain metastases than for the whole trial population.		
On page 89, the ERG summarises the original ICERs and updated ICERs based on the ERG clarification and questions without providing the necessary context.	Please change from: The company reported nine scenario analyses (CS Document Table 39). They updated their results in their clarification response. To: Based on the recommended post-progression utilities in the ERG report for TA423, the company updated the results in their clarification response.	Minor amendment for clarity	**This is not a factual inaccuracy – no change made.**
On page 102 in the ERG's preferred analysis and scenarios summary, health state utilities are incorrectly referenced.	Please change from: health state utilities from HER2CLIMB EQ-5D analysis applied to all treatments (4.2.9.2). to:	Minor amendment for clarity	**This is not a factual inaccuracy- no change made.** As is clear in Table 37, we use the HER2CLIMB utility results in the ERG preferred analysis. The rationale for this is

	health state utilities from NICE FAD TA423 applied to all comparators.		explained in the ERG conclusions to section 4.2.9.

Issue 8 Grammar

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 19, Section 2.2.2 – preposition misuse	Suggest replacing 'in' with 'on' before date '22 February 2021'	Minor amendment for correctness	Corrected
On page 32, Section 2.2.1.3 – unnecessary article in sentence	Suggest removing unnecessary 'the' in the following sentence: 'The comparator trial arm (which includes trastuzumab and capecitabine in combination) is not licensed for use at third line and is not included as a comparator treatment in the NICE ~~the~~ scope for this appraisal.'	Minor amendment for correctness	Corrected
On page 54, Section 3.4.2.3 – typographical error	Suggest replacing 'an' with 'a' before word 'network'	Minor amendment for correctness	Corrected
On page 57, Section 3.6.2 – typographical error	Suggest replacing '…standard deviaTurntion…' with '…standard deviation…'	Minor amendment for correctness	Corrected
On page 88, the ERG stated: 'Their sensitivity analysis results indicated that relative dose intensity for the tucatinib combination, and health state utilities for the have the largest impact on the cost-effectiveness	Suggested amendment: 'Their sensitivity analysis results indicated that relative dose intensity for the tucatinib combination, and health state utilities had the largest impact on the cost-effectiveness results.'	Minor amendment for consistency	Corrected

results.'			

Issue 9 Cross-reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 10, Section 1 – broken cross-reference to section in the document	Suggest re-inserting correct cross-reference in 'Sections 1.3 to ~~0~~'	Minor amendment for correctness	Corrected

Issue 10 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 30, paragraph 2 – typographical error	Please replace "noes" should be "notes"	Minor amendment for correctness	Corrected
On page 34, Section 3.2.3 – unnecessary bracket in sentence	Suggest removing unnecessary bracket in the following sentence: 'The latter outcome was included in response to promising results from an early phase I dose-escalation trial of tucatinib, trastuzumab and capecitabine in people with brain metastases~~)~~.[9]'	Minor amendment for correctness	Corrected
On page 42, Section 3.2.5.6.2 first paragraph – typographical error	Please replace 'patents' with 'patients'	Minor amendment for correctness	Corrected
On page 46, Table 14, typographical error in study name	Please replace 'Study 201' with 'Study 301'	Minor amendment for correctness	Corrected

Issue 11 Accuracy and clarity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 44, second paragraph, text may imply a low rate of cerebral oedema in the tucatinib arm.	Suggest adding clause 'with no cerebral oedema events reported in the tucatinib-combination group' to the end of the following sentence: 'Left ventricular systolic dysfunction leading to dose modification or discontinuation and cerebral oedema events were infrequent (≤2% of patients).'	Minor amendment for clarity	Updated as suggested.

Issue 12 Spelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 91, the ERG made the following spelling error: Urritecechea	Suggested correction: Urruticoechea	Minor amendment for consistency	Corrected.

ACIC marking check

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
[ID3828] Tucatinib final ERG report SD 240621 [ACIC].docx, page 48 – missing academic-in-confidence highlight on underlined information	Please highlight the whole sentence in yellow, including part underlined only: [redacted] [redacted] rank preserving structural failure	[redacted]	Corrected

	time model [redacted]	[redacted]	

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **12 August 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Seagen Inc.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertain indirect comparison results due to study heterogeneity	**YES**	**Seagen considers the direction of the bias within the random effects (RE) network meta-analysis (NMA) to be against tucatinib.** The ERG states that "The HER2CLIMB trial includes patients with and without brain metastases. The comparator trials, in contrast, include few or no patients with brain metastases. This creates an uneven distribution of patients with brain metastases across the trials, and there is likely to be bias in the results, though the direction and magnitude of this bias is unclear." Company Response: • Seagen agrees that the inclusion of patients with brain metastases (BM), who are typically excluded from clinical trials, creates a bias in the network. • Historically, clinical trials have excluded patients with BM due to concerns regarding adverse events and fear of poorer results, despite these patients representing up to 50% of patients treated at this line of therapy in clinical practice (1-3). The HER2CLIMB trial is one of the first pivotal trials to recruit BM patients, including those with active BM, in this setting. • BM are associated with significant morbidity and mortality. o Patients with BM have a poor prognosis and more complications than patients without BM.

		• Evidence from trials of trastuzumab+capecitabine within the network that exclude patients with BM demonstrate the bias against HER2CLIMB: o In the CEREBEL (Pivot et al) trial (4), the median overall survival (OS) for the trastuzumab+capecitabine arm was 27.3 months (95% confidence interval [CI]: 23.7 to not reached), while in HER2CLIMB the median OS for the trastuzumab+capecitabine arm was 17.4 months (95% CI: 13.6, 19.9) in the intent-to-treat (ITT) population and 12.0 months (95% CI: 11.2 to 15.5) in patients with BM. o The median PFS in CEREBEL for the trastuzumab+capecitabine arm was 8.1 months (95% CI: 6.1 to 8.9), while in HER2CLIMB the median PFS for the trastuzumab+capecitabine arm was 5.6 months (95% CI: 5.2 to 7.1) for the ITT and 5.4 month (95% CI: 4.1 to 5.7) for the BM patients. o The lack of overlapping OS CIs for the ITT population clearly demonstrates the disadvantage to HER2CLIMB when comparing to other trials. o The lower progression-free survival (PFS) and OS in HER2CLIMB versus CEREBEL and lack of overlapping CIs between the BM patients in HER2CLIMB and the CEREBEL, which excluded patients with BM, demonstrate that BM patients have poorer outcomes when treated with the same therapy as patients without BM. • In addition, Seagen sought clinical feedback from six clinical experts at centres across England, which further confirmed that the bias is against HER2CLIMB when comparing to trials that excluded patients with BM (see Appendix A for the physician survey outputs). • The tucatinib regimen is disadvantaged due to the uniqueness of HER2CLIMB, which was designed to generate evidence generalisable to real-world clinical practice, including patients treated in England.
Key issue 1: Uncertain indirect comparison results due to study heterogeneity	**YES**	**Seagen considers that methodological issues exist with the RE model. Although Seagen still considers the fixed effects model to be the most appropriate, the Fractional Polynomial (FP) remains the next best choice of model for the analysis** The ERG states that: • The primary cause of uncertainty is heterogeneity between studies included in the network meta-analysis (NMA) in terms of the proportion of patients with BM, a likely effect modifier. • In the context of this heterogeneity, the ERG suggests that a random-effects NMA model is more appropriate than a fixed-effect model.

		Company Response: • Seagen acknowledges that HER2CLIMB included patients with BM, who are typically excluded from clinical trials. While the inclusion of patients with BM makes the evidence from HER2CLIMB generalisable to clinical practice, it is challenging to compare with the evidence from trials that included a different patient population. • Seagen agrees that BM is a prognostic modifier for all treatments. • A formal interaction test demonstrated that BM are not a treatment modifier for the tucatinib regimen but are a treatment modifier for the comparators. • This treatment modification is demonstrated by the evidence presented in Sabatier et al. (2021) (5) that patients with BM have poorer outcomes than those without BM when treated with eribulin. While no similar studies have been identified for capecitabine or vinorelbine monotherapy, the mode of action of these treatments makes it similarly unlikely that they have benefit in BM patients. • Clinical feedback from six experts at centres across England (physician survey in Appendix A) further supports that single agent chemotherapies are unlikely to have a treatment benefit for BM. • While the random-effects model accounts for heterogeneity among the trials, there is evidence of convergence issues with that model, e.g., tall spikes in the iterative trace plots, auto-regression plots still deviating from 0 in subsequent iterations and the Gelman-Rubin statistics. Also, it is clear that the RE model predicts a higher degree of uncertainty that renders the results less consistent with head-to-head trial results. This is particularly the case for OS and is likely due to an absence of closed loops and limited duplicate comparisons in the network. • Although Seagen recognises the general principle that the RE model is more suitable for networks characterised by heterogeneity, for the OS network in particular, this model is not suitable for the reasons stated above, as well as being inconsistent with head-to-head trial data. • Given this, Seagen also conducted the FP NMA, which models hazards over time rather than relying on a single hazard ratio (HR) to describe the relative effect over the entire follow-up period. • The preferred FP model was selected utilising the method described by Wiksten (2020) (6), which involves fitting all models in a frequentist setting using generalized linear models with a binomial distribution and complementary log-log function to give the equivalent Bayesian FP models. The efficiency with which models can then be compared is an advantage over traditional comparison of Deviance Information Criterion (DIC) from models fit in Bayesian software (e.g., JAGS or OpenBUGS), as a much larger range of models can be explored. Different basis functions for time were used to enable standard parametric models, FP models, and spline-based models to be fitted. Instead of DIC, AIC and BIC values are used to compare the fit of the models. Given the agreement

between AIC and BIC in choosing best fitting models, and theoretical similarity between AIC and DIC, it is unlikely model selection would differ substantially by DIC over AIC or BIC.

- While a Weibull proportional hazard model gave a slightly better fit compared to a stratified Weibull model in terms of Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC), it did not fit the study by Martin (2013) well (7). It is also worth noting that the proportional hazard Weibull did not give as a good fit statistics compared to other first-order fractional polynomial models such as P1= -1. However, when Seagen ran first-order models with P1 <1, this overfitted the earlier part of the curve which resulted in some simulations having infinite HRs for neratinib. Consequently, the stratified Weibull model was deemed to provide the best balance between fit to the trial data and plausible estimation of survival beyond the trial.
- For OS, the best fitting second order FP with p1= 0 and p2= 1 had an AIC of 3116.1 and BIC of 3390.6; best fitting first order FP with p1= -1 had AIC 3203.5 and BIC 3386.5; in comparison the proportional hazard with Weibull baseline had AIC 3263.2 and BIC 3402.9, as presented in the Addendum A9b (Figures G-4–G-20) of the company's responses to the ERG clarification letter. For PFS, the best fitting second order FP with p1= -1 and p2= -0.5 had an AIC of 3212.1 and BIC of 3518.8; best fitting first order FP with p1= -2 had AIC 3547.4 and BIC 3751.9; in comparison the proportional hazard with Weibull baseline had AIC 4051.6 and BIC 4209.6, as presented in the Addendum A9b (Figures F-5–F-15) of the company's responses to the ERG clarification letter. This substantially poorer comparative fit of the proportional hazards with Weibull baseline hazards model gives a global test of proportional hazards (rather than study/local tests of Schoenfeld residuals) and strengthens the case for FP models.
- The results with the FP NMA when applied to the base case (revised after clarification responses) are presented below:

Comparator Treatment	Cost	QALYs	Pairwise ICERs
Company base case (post clarification responses)			
Eribulin	[redacted]	[redacted]	£37,483
FP NMA Fixed Effects			
Eribulin	[redacted]	[redacted]	[redacted]
FP NMA Random Effects			
Eribulin	[redacted]	[redacted]	[redacted]

- The FP data formatted as requested by the ERG is provided in Appendix B.

Key issue 2: Survival extrapolations	**YES**	**Seagen believes that the comparator survival curves produced using the ERG's approach do not appropriately reflect the expected outcomes from a population representative of the real world, including patients with BM. Application of the FP NMA more appropriately reflects the absolute survival benefit from tucatinib in this population**
		
		The ERG proposes to estimate OS and PFS curves using survival curves directly fitted to the HER2CLIMB trial data and adjusting for indirect comparators with HRs from the RE NMA.
		
		Company response:
		
		• Utilisation of the ERG suggested method does not appropriately adjust inclusion of the harder to treat, real-world, population included H2C trial as evidenced by:
		  • Applying the method proposed by the ERG results in survival curves that are similar to those seen in the clinical trials of the comparators, all of which excluded patients with BM.
		  • Approximately 50% of the patients in HER2CLIMB had BM at baseline. As discussed above, inclusion of this real-world population in the trial creates bias against tucatinib as these patients have poorer outcomes than patients without BM.
		  • Applying the ERG's method overestimates the benefit of the comparator treatments and fails to reflect the differences in outcomes that will be seen in real world clinical practice, and hence the differences in life years gained (LYG) and QALYs between tucatinib and the comparators.
		• While Seagen maintains that its base case model using the fixed effects NMA most accurately reflects the true differences in LYG and QALYs, we believe that application of the FP NMA leads to more realistic predictions than the ERG's preferred random effects NMA.
		• Seagen acknowledges that the modelled FP curves are more favourable than those seen in HER2CLIMB, which is a result of the FP analysis representing an average of the evidence of the trials within the network.
		• Given the differences in the patient population in the trials in the network, the differences between the treatments seen in the FP curves most likely represent the differences in outcomes that will be seen in real-world clinical practice.

Key issue 3: Subgroup analysis	**YES**	**Seagen believes that the HER2CLIMB population is generalisable to the patients who will be treated with tucatinib in clinical practice in England. Therefore, no subgroup analyses are required, and no external data sources are required to provide an alternative baseline survival curve to which results of the NMA are applied** The ERG states: • It is unclear whether the HER2CLIMB trial (which included a high proportion of patients with BM) or other trials in the NMA (with few or no patients with BM) provide a more realistic reflection of clinical practice. • In the absence of subgroup-specific estimates of relative effects, NMA results could be used to model results for the direct comparators, as in the current model. Company response: • While identifying the proportion of HER2+ MBC patients with BM is challenging due to the lack of proactive screening for BM, the literature, including a UK study conducted in patients who progressed on trastuzumab emtansine (T-DM1), suggests that approximately 50% of third-line (3L) HER2+ MBC patients have BM (8-13). • There is limited evidence of the efficacy of single-agent chemotherapies in patients who have BM; however, a recent study (5) demonstrated that MBC patients with BM have shorter PFS and OS when treated with eribulin in clinical practice than was shown in a clinical trial of eribulin. • In addition, the comments from the UK professional organisation submission (NCRI-ACP-RCP-RCR) as well as clinical input received in the physician survey suggest that approximately 50% of 3L HER2+ MBC patients have BM, and that single agent chemotherapy is likely less effective in those patients compared to patients without BM. • Taken together, the overall population from HER2CLIMB resembles that of clinical practice since many 3L HER2+ MBC patients may have undiagnosed BM and could benefit from a targeted, efficacious option in this setting.

Key issue 4: Utilities	**YES**	**Seagen believes that the significant treatment benefit and limited toxicity of the tucatinib regimen provides better quality of life than single-agent chemotherapies for HER2+ MBC patients, leading to higher utility scores in both the pre- and post-progression health states** The ERG states: • We suggest that the same utilities should be used for all treatments in the pre- and post-progression health states. We prefer the HER2CLIMB utilities, as these are derived from EQ-5D data in a relevant trial population, using NICE-recommended methods Company response: • There are two aspects of treatment that support difference in quality of life: efficacy and toxicity. • In the pre-progression state, more effective treatments are associated with better quality of life than less effective treatments and therefore higher utility scores. o Clinical input received in the physician survey indicates that patients who respond to treatment have a better quality of life while on treatment, which has also been demonstrated in literature (14). o The objective response rate (ORR) in HER2CLIMB was 40.6%, as opposed to the ORR of 11.5% demonstrated by eribulin in its pivotal trial (15). The best tumour response assessment conducted as part of the NMA showed that tucatinib was significantly favoured over eribulin, vinorelbine, and capecitabine. o Previous MBC NICE appraisals of eribulin (TA423) (16) and Palbociclib (TA619) (17) utilised different pre-progression utilities for the different treatment arms due to differences in treatment response rates. In TA423, eribulin had higher utilities compared to other single agent chemotherapies, including vinorelbine and capecitabine, suggesting that the poorer efficacy of those treatments contributes to lower utility scores. o Clinical input (Appendix A) indicated that symptomatic toxicity has a negative impact on quality of life. o Toxicity associated with eribulin includes peripheral neuropathy, hematologic toxicity that can lead to infection and septic shock, and fatal febrile neutropenia, all of which could contribute to lower utility scores and peripheral neuropathy can be chronic and continue after treatment discontinuation (Appendix A). o In TA423 eribulin had higher utilities compared to other single agent chemotherapies, including vinorelbine and capecitabine, demonstrating that the poorer efficacy and safety of those treatments led to lower utility scores.

- After disease progression, the quality-of-life benefits associated with disease response, particularly the central nervous system (CNS) response demonstrated by tucatinib (18), could continue.
    - In addition, peripheral neuropathy can continue after treatment discontinuation/disease progression and continue to have a negative impact on quality of life.
- Three scenarios assessing post-progression utilities are provided below. In all scenarios the pre-progression utility for the tucatinib arm comes from HER2CLIMB (0.76) and TA 423 for eribulin (0.706):
    - Tucatinib arm enters the post progression state with the post-progression utility value captured in HER2CLIMB (0.698) and tapers to the same post-progression utility as eribulin (0.496) over the course of 1 year.
    - Different -pre-progression utilities are used for the two arms and both use the HER2CLIMB post-progression utility (0.698)
    - Different -pre-progression utilities are used for the two arms and both use the TA423 post-progression utility (0.496)
- Scenarios utilising different utility scores are presented below:

Comparator Treatment	Cost	QALYs	Pairwise ICERs	Change to Pairwise ICER
Company base case (post-clarification responses)				
Eribulin	[redacted]	[redacted]	£37,483	
Tapering tucatinib post-progression utility score over one year				
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Different pre-progression utilities for tucatinib (0.762) and eribulin and (0.706); same post-progression (0.698)				
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Different pre-progression utilities for tucatinib (0.762) and eribulin and (0.706); same post-progression (0.496)				
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g., at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
• **Issue 1:** Uncertain indirect comparison results due to study heterogeneity	• Section 3.6.1	• YES	• The HR NMA results were updated to reflect the correction recommended by the ERG and presented at ESMO 2012 (19) and are presented in the slide decks Appendix C (FE model) and Appendix D (RE model) submitted alongside the current form.
• Additional issue 1: **Wastage**	• ERG preferred analysis	• NO	• The ERG proposed including wastage in the model. Company response: • Tucatinib and capecitabine are both oral therapies available in multiple pill doses. In previous NICE appraisals of oral MBC treatments, i.e., TA619, 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.

• Additional issue 4: **Utilities**	• Section 3.2.5.4	• NO	• The ERG notes that the Company Submission does not describe imputation of missing data. Company response: • No imputation of missing data from the EQ-5D was used. Data was assumed missing at random.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
• **Issue 1:** Uncertain indirect comparison results due to study heterogeneity	• The NMA in Seagen's submission included evidence from peer reviewed publication, however the ERG noted a typo in one of the studies.	• The HR NMA fixed effected results were updated to reflect the correction recommended by the ERG and presented at ESMO 2012 (19).	<table><tr><th>Comparator Treatment</th><th>Cost</th><th>QALYs</th><th>Pairwise ICERs</th></tr><tr><td colspan="4">Company base case (post clarification responses)</td></tr><tr><td>Eribulin</td><td>[redacted]</td><td>[redacted]</td><td>£37,483</td></tr><tr><td colspan="4">New base case</td></tr><tr><td>Eribulin</td><td>[redacted]</td><td>[redacted]</td><td>£42,760</td></tr></table>

References

1. Lin NU, Amiri-Kordestani L, Palmieri D, Liewehr DJ, Steeg PS. CNS metastases in breast cancer: old challenge, new frontiers. Clin Cancer Res. 2013;19(23):6404-18.
2. Food and Drug Administration (FDA). Cancer Clinical Trial Eligibility Criteria: Brain Metastases – Guidance for Industry. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-brain-metastases (last accessed August 2021). 2020.
3. Kim ES, Bruinooge SS, Roberts S, Ison G, Lin NU, Gore L, et al. Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. J Clin Oncol. 2017;35(33):3737-44.
4. Pivot X, Manikhas A, Zurawski B, Chmielowska E, Karaszewska B, Allerton R, et al. CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2015;33(14):1564-73.
5. Sabatier R, Martin J, Vicier C, Guerin M, Monneur A, Provansal M, et al. Eribulin Efficacy on Brain Metastases in Heavily Pretreated Patients with Metastatic Breast Cancer. J Clin Med. 2021;10(6).
6. Wiksten A, Hawkins N, Piepho HP, Gsteiger S. Nonproportional Hazards in Network Meta-Analysis: Efficient Strategies for Model Building and Analysis. Value Health. 2020;23(7):918-27.
7. Martin M, Bonneterre J, Geyer CE, Jr., Ito Y, Ro J, Lang I, et al. A phase two randomised trial of neratinib monotherapy versus lapatinib plus capecitabine combination therapy in patients with HER2+ advanced breast cancer. Eur J Cancer. 2013;49(18):3763-72.
8. Darlix A, Louvel G, Fraisse J, Jacot W, Brain E, Debled M, et al. Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a large multicentre real-life cohort. Br J Cancer. 2019;121(12):991-1000.
9. Pestalozzi BC, Francis P, Quinaux E, Dolci S, Azambuja E, Gelber RD, et al. Is risk of central nervous system (CNS) relapse related to adjuvant taxane treatment in node-positive breast cancer? Results of the CNS substudy in the intergroup Phase III BIG 02-98 Trial. Ann Oncol. 2008;19(11):1837-41.
10. Bendell JC, Domchek SM, Burstein HJ, Harris L, Younger J, Kuter I, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer. 2003;97(12):2972-7.

11. Okines A, Irfan T, Khabra K, Smith I, O'Brien M, Parton M, et al. Development and responses of brain metastases during treatment with trastuzumab emtansine (T-DM1) for HER2 positive advanced breast cancer: A single institution experience. Breast J. 2018;24(3):253-9.
12. Clayton AJ, Danson S, Jolly S, Ryder WD, Burt PA, Stewart AL, et al. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. Br J Cancer. 2004;91(4):639-43.
13. Lai R, Dang CT, Malkin MG, Abrey LE. The risk of central nervous system metastases after trastuzumab therapy in patients with breast carcinoma. Cancer. 2004;101(4):810-6.
14. Ou SI, Socinski MA, Gadgeel S, Gandhi L, West H, Chiappori AA, et al. Patient-reported outcomes in a phase II, North American study of alectinib in patients with ALK-positive, crizotinib-resistant, non-small cell lung cancer. ESMO Open. 2018;3(5):e000364.
15. Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015;33(6):594-601.
16. NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens – technology appraisal guidance [TA423] – committee papers 2016 [updated 21 December. Available from: www.nice.org.uk/guidance/TA423.
17. NICE. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. Technology appraisal guidance [TA619] – committee papers 2020 [updated 15 January. Available from: www.nice.org.uk/guidance/TA619.
18. Lin NU, Borges V, Anders C, Murthy RK, Paplomata E, Hamilton E, et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. J Clin Oncol. 2020;38(23):2610-9.
19. Pivot X, Semiglazov V, Żurawski B, Allerton R, Fabi A, Ciruelos E, et al. LBA11 – Cerebel (EGF111438): An Open Label Randomized Phase III Study Comparing the Incidence of CNS Metastases in Patients (PTS) with HER2+ Metastatic Breast Cancer (MBC), Treated with Lapatinib Plus Capecitabine (LC) Versus Trastuzumab Plus Capecitabine (TC). Annals of Oncology. 2012;23:IXE5.

NICE National Institute for Health and Care Excellence

Appendix A – clinical survey sent to six clinical experts and their responses

Following the Technical Engagement Meeting (part of the NICE process) for Tucatinib, between the Evidence Review Group (ERG), NICE and Seagen on July the 22nd, we are collecting further insights on the clinical relevance and plausibility related to the below listed questions. We would be grateful for your answers to the questions based on your clinical experience in the treatment of HER2-positive metastatic breast cancer.
The answers of the survey from you and your colleagues will be sent to NICE and the ERG as part of our response to the ERG report for tucatinib.

Clinical input on the plausibility and likely source of bias in the indirect comparison of Tucatinib and single agent chemotherapy.

Clinical expert #1

	Clinical Plausibility: What does your clinical experience tell you			
	Patients with BM would have little or no response to single agent chemo	Patients with BM may respond to single agent chemo, however the benefit would be significantly lower than patients without BM	Outcomes for patients with BM would be similar to patients without BM	Patients with BM will have better outcomes than patients without BM
How would 3L HER2+ MBC patients with brain metastases (BM) treated with single agent chemotherapy (eg. eribulin) respond to treatment compared to patients without BM treated with single agent chemo:		Hard to say as brain metastases are rarely treated with single agent chemotherapy and it would depend on other sites of disease and whether or not they were symptomatic from those		No
Any additional comments:	Patients with brain mets are likely to get some degree of benefit for any extracranial disease but brain metastases themselves are less likely to respond to single agent chemo			

Clinical Plausibility: What does your clinical experience tell you

	Differences in trial design will likely disadvantage tucatinib in the indirect treatment comparison with single agent chemotherapy	Differences in trial design likely do not affect the indirect comparisons between tucatinib and single agent chemotherapy	Differences in trial design will likely be an advantage for tucatinib in the indirect comparison to single agent chemotherapy
How do the differences in clinical trial populations likely affect an indirect comparison of clinical outcomes (PFS and OS) between tucatinib and single agent chemotherapy? ~50% of the patients included in the HER2CLIMB trial had brain metastases. Typically trials conducted in HER2+ MBC, including those in the indirect treatment comparison, exclude most patients with brain metastases.		Difficult to interpret and compare data between trials in this way. Given that the responses were similar in patients with and without brain metastases it is unlikely to have made a significant impact	
Any additional comments			

Clinical Plausibility: What does your clinical experience tell you

	Symptomatic toxicities had a negative impact on a patient's QoL	Symptomatic toxicities have no impact on a patient's QoL	Symptomatic toxicities improves a patient's QoL
Do symptomatic toxicities (eg peripheral neuropathy) impact a patient's QoL?	Yes		
Any additional comments	Some toxicities are more manageable than others and can be modified more easily with supportive medications, for example diarrhoea in the case of Tucatinib which is generally mild. Neuropathy can have a major impact and be quite disabling		

	Clinical Plausibility: What does your clinical experience tell you	
	Peripheral neuropathy associated with single agent chemotherapy **continues** after a patient discontinues treatment	Peripheral neuropathy associated with single agent chemotherapy **stops** after a patient discontinues treatment
Can peripheral neuropathy associated with single agent chemotherapy continue after a patient discontinues treatment?	Yes, it can last for many months and sometimes be permanent	
Any additional comments		

Clinical expert #2

	Clinical Plausibility: What does your clinical experience tell you			
	Patients with BM would have little or no response to single agent chemo	Patients with BM may respond to single agent chemo, however the benefit would be significantly lower than patients without BM	Outcomes for patients with BM would be similar to patients without BM	Patients with BM will have better outcomes than patients without BM
How would 3L HER2+ MBC patients with brain metastases (BM) treated with single agent chemotherapy (eg. eribulin) respond to treatment compared to patients without BM treated with single agent chemo:		Probably this answer – i.e. they may respond outside the brain, but little evidence of response in brain therefore if they progress in brain their benefit will be less		
Any additional comments:				

Clinical Plausibility: What does your clinical experience tell you

	Differences in trial design will likely disadvantage tucatinib in the indirect treatment comparison with single agent chemotherapy	Differences in trial design likely do not affect the indirect comparisons between tucatinib and single agent chemotherapy	Differences in trial design will likely be an advantage for tucatinib in the indirect comparison to single agent chemotherapy
How do the differences in clinical trial populations likely affect an indirect comparison of clinical outcomes (PFS and OS) between tucatinib and single agent chemotherapy? ~50% of the patients included in the HER2CLIMB trial had brain metastases. Typically trials conducted in HER2+ MBC, including those in the indirect treatment comparison, exclude most patients with brain metastases.	Yes – because you'd expect the brain mets population to have a worse prognosis		
Any additional comments			

Clinical input on plausibility of different utility values in pre- and post-progression.

	Clinical Plausibility: What does your clinical experience tell you		
	A patient who responds to treatment has worse QoL than a patient who does not respond	A patient who responds to treatment will likely have same QoL as a patient who does not respond to treatment	A patient who responds to treatment has a better QoL than a patient who does not respond
How does response to treatment affect quality of life (QoL) of a HER2+ MBC patient?		If a patient progresses in the lung but is asymptomatic, then if the lung mets shrink it won't affect QoL	Usually QoL is the same or better depending on the degree of response and whether the pt was symptomatic from their mets – e.g.: if the mets were causing pain and they shrink on therapy, pain will reduce.
Any additional comments			

	Clinical Plausibility: What does your clinical experience tell you		
	Symptomatic toxicities had a negative impact on a patient's QoL	Symptomatic toxicities have no impact on a patient's QoL	Symptomatic toxicities improves a patient's QoL
Do symptomatic toxicities (eg peripheral neuropathy) impact a patient's QoL?	Yes, but it depends on the symptom and the degree of the toxicity		
Any additional comments			

	Clinical Plausibility: What does your clinical experience tell you	
	Peripheral neuropathy associated with single agent chemotherapy **continues** after a patient discontinues treatment	Peripheral neuropathy associated with single agent chemotherapy **stops** after a patient discontinues treatment
Can peripheral neuropathy associated with single agent chemotherapy continue after a patient discontinues treatment?	Yes, often pts have residual neuropathy after treatment	This can also happen
Any additional comments		

Clinical expert #3

Clinical Plausibility: What does your clinical experience tell you

	Patients with BM would have little or no response to single agent chemo	Patients with BM may respond to single agent chemo, however the benefit would be significantly lower than patients without BM	Outcomes for patients with BM would be similar to patients without BM	Patients with BM will have better outcomes than patients without BM
How would 3L HER2+ MBC patients with brain metastases (BM) treated with single agent chemotherapy (eg. eribulin) respond to treatment compared to patients without BM treated with single agent chemo:		x		
Any additional comments:	Data on single agent CT for BM is predominantly ph 2 and efficacy limited.			

Clinical Plausibility: What does your clinical experience tell you

	Differences in trial design will likely disadvantage tucatinib in the indirect treatment comparison with single agent chemotherapy	Differences in trial design likely do not affect the indirect comparisons between tucatinib and single agent chemotherapy	Differences in trial design will likely be an advantage for tucatinib in the indirect comparison to single agent chemotherapy
How do the differences in clinical trial populations likely affect an indirect comparison of clinical outcomes (PFS and OS) between tucatinib and single agent chemotherapy? ~50% of the patients included in the HER2CLIMB trial had brain metastases. Typically trials conducted in HER2+ MBC, including those in the indirect treatment comparison, exclude most patients with brain metastases.	x		
Any additional comments			

Clinical input on plausibility of different utility values in pre- and post-progression.

	Clinical Plausibility: What does your clinical experience tell you		
	A patient who responds to treatment has worse QoL than a patient who does not respond	A patient who responds to treatment will likely have same QoL as a patient who does not respond to treatment	A patient who responds to treatment has a better QoL than a patient who does not respond
How does response to treatment affect quality of life (QoL) of a HER2+ MBC patient?			x
Any additional comments			

	Clinical Plausibility: What does your clinical experience tell you		
	Symptomatic toxicities had a negative impact on a patient's QoL	Symptomatic toxicities have no impact on a patient's QoL	Symptomatic toxicities improves a patient's QoL
Do symptomatic toxicities (eg peripheral neuropathy) impact a patient's QoL?	x		
Any additional comments			

	Clinical Plausibility: What does your clinical experience tell you	
	Peripheral neuropathy associated with single agent chemotherapy **continues** after a patient discontinues treatment	Peripheral neuropathy associated with single agent chemotherapy **stops** after a patient discontinues treatment
Can peripheral neuropathy associated with single agent chemotherapy continue after a patient discontinues treatment?	x	
Any additional comments		

Clinical expert #4

Clinical Plausibility: What does your clinical experience tell you

	Patients with BM would have little or no response to single agent chemo	Patients with BM may respond to single agent chemo, however the benefit would be significantly lower than patients without BM	Outcomes for patients with BM would be similar to patients without BM	Patients with BM will have better outcomes than patients without BM
How would 3L HER2+ MBC patients with brain metastases (BM) treated with single agent chemotherapy (eg. eribulin) respond to treatment compared to patients without BM treated with single agent chemo:		yes		
Any additional comments:	Patients with her2+ disease and brain mets do better (ms 1yr) than triple neg (ms 3 months). However they have a worse outcome than pts without brain mets. A few do well if suitable for surgery/srs but still best without brain mets. Response outside brain not effected by brain mets. Response in brain not great			

Clinical Plausibility: What does your clinical experience tell you

	Differences in trial design will likely disadvantage tucatinib in the indirect treatment comparison with single agent chemotherapy	Differences in trial design likely do not affect the indirect comparisons between tucatinib and single agent chemotherapy	Differences in trial design will likely be an advantage for tucatinib in the indirect comparison to single agent chemotherapy
How do the differences in clinical trial populations likely affect an indirect comparison of clinical outcomes (PFS and OS) between tucatinib and single agent chemotherapy? ~50% of the patients included in the HER2CLIMB trial had brain metastases. Typically trials conducted in HER2+ MBC, including those in the indirect treatment comparison, exclude most patients with brain metastases.	yes		
Any additional comments	If population is better prognostic group then they look like they do better. Her2climb has worse prognosis therefore pfs/os worse. However odds ratio in trial will not be effected		

Clinical input on plausibility of different utility values in pre- and post-progression.

	Clinical Plausibility: What does your clinical experience tell you		
	A patient who responds to treatment has worse QoL than a patient who does not respond	A patient who responds to treatment will likely have same QoL as a patient who does not respond to treatment	A patient who responds to treatment has a better QoL than a patient who does not respond
How does response to treatment affect quality of life (QoL) of a HER2+ MBC patient?			yes
Any additional comments	If patients has symptoms of cancer and it shrinks enough to alleviate symptoms, as long as not replaced by worse symptoms of toxicity		

	Clinical Plausibility: What does your clinical experience tell you		
	Symptomatic toxicities had a negative impact on a patient's QoL	Symptomatic toxicities have no impact on a patient's QoL	Symptomatic toxicities improves a patient's QoL
Do symptomatic toxicities (eg peripheral neuropathy) impact a patient's QoL?	yes		
Any additional comments	obviously		

	Clinical Plausibility: What does your clinical experience tell you	
	Peripheral neuropathy associated with single agent chemotherapy **continues** after a patient discontinues treatment	Peripheral neuropathy associated with single agent chemotherapy **stops** after a patient discontinues treatment
Can peripheral neuropathy associated with single agent chemotherapy continue after a patient discontinues treatment?	yes	
Any additional comments	Often cumulative. They will have had taxanes at least once and Kadcyla. If beyond third line other agents too	

Clinical expert #5

	Clinical Plausibility: What does your clinical experience tell you			
	Patients with BM would have little or no response to single agent chemo	Patients with BM may respond to single agent chemo, however the benefit would be significantly lower than patients without BM	Outcomes for patients with BM would be similar to patients without BM	Patients with BM will have better outcomes than patients without BM
How would 3L HER2+ MBC patients with brain metastases (BM) treated with single agent chemotherapy (eg. eribulin) respond to treatment compared to patients without BM treated with single agent chemo:		agree		
Any additional comments:				

Clinical Plausibility: What does your clinical experience tell you

	Differences in trial design will likely disadvantage tucatinib in the indirect treatment comparison with single agent chemotherapy	Differences in trial design likely do not affect the indirect comparisons between tucatinib and single agent chemotherapy	Differences in trial design will likely be an advantage for tucatinib in the indirect comparison to single agent chemotherapy
How do the differences in clinical trial populations likely affect an indirect comparison of clinical outcomes (PFS and OS) between tucatinib and single agent chemotherapy? ~50% of the patients included in the HER2CLIMB trial had brain metastases. Typically trials conducted in HER2+ MBC, including those in the indirect treatment comparison, exclude most patients with brain metastases.	agree		
Any additional comments			

Clinical input on plausibility of different utility values in pre- and post-progression.

	Clinical Plausibility: What does your clinical experience tell you		
	A patient who responds to treatment has worse QoL than a patient who does not respond	A patient who responds to treatment will likely have same QoL as a patient who does not respond to treatment	A patient who responds to treatment has a better QoL than a patient who does not respond
How does response to treatment affect quality of life (QoL) of a HER2+ MBC patient?			agree
Any additional comments			

	Clinical Plausibility: What does your clinical experience tell you		
	Symptomatic toxicities had a negative impact on a patient's QoL	Symptomatic toxicities have no impact on a patient's QoL	Symptomatic toxicities improves a patient's QoL
Do symptomatic toxicities (eg peripheral neuropathy) impact a patient's QoL?	Agree but only if they cannot be managed and improved by supportive medication		
Any additional comments			

	Clinical Plausibility: What does your clinical experience tell you	
	Peripheral neuropathy associated with single agent chemotherapy **continues** after a patient discontinues treatment	Peripheral neuropathy associated with single agent chemotherapy **stops** after a patient discontinues treatment
Can peripheral neuropathy associated with single agent chemotherapy continue after a patient discontinues treatment?	Agree but rare	
Any additional comments		

Clinical expert #6

	Clinical Plausibility: What does your clinical experience tell you			
	Patients with BM would have little or no response to single agent chemo	Patients with BM may respond to single agent chemo, however the benefit would be significantly lower than patients without BM	Outcomes for patients with BM would be similar to patients without BM	Patients with BM will have better outcomes than patients without BM
How would 3L HER2+ MBC patients with brain metastases (BM) treated with single agent chemotherapy (eg. eribulin) respond to treatment compared to patients without BM treated with single agent chemo:		X		
Any additional comments:	Sites outside of the brain would probably respond similarly but as unable to have meaningful clinical effect on BM those with BM will do worse as this aspect often dominates the prognosis			

Clinical Plausibility: What does your clinical experience tell you

	Differences in trial design will likely disadvantage tucatinib in the indirect treatment comparison with single agent chemotherapy	Differences in trial design likely do not affect the indirect comparisons between tucatinib and single agent chemotherapy	Differences in trial design will likely be an advantage for tucatinib in the indirect comparison to single agent chemotherapy
How do the differences in clinical trial populations likely affect an indirect comparison of clinical outcomes (PFS and OS) between tucatinib and single agent chemotherapy? ~50% of the patients included in the HER2CLIMB trial had brain metastases. Typically trials conducted in HER2+ MBC, including those in the indirect treatment comparison, exclude most patients with brain metastases.	x		
Any additional comments			

Clinical input on plausibility of different utility values in pre- and post-progression.

Clinical Plausibility: What does your clinical experience tell you

	A patient who responds to treatment has worse QoL than a patient who does not respond	A patient who responds to treatment will likely have same QoL as a patient who does not respond to treatment	A patient who responds to treatment has a better QoL than a patient who does not respond
How does response to treatment affect quality of life (QoL) of a HER2+ MBC patient?			x
Any additional comments	Majority of clinical trial data shows stability to improvement. QOL is inextricably linked to response and improved depression and mood scores		

Clinical Plausibility: What does your clinical experience tell you

	Symptomatic toxicities had a negative impact on a patient's QoL	Symptomatic toxicities have no impact on a patient's QoL	Symptomatic toxicities improves a patient's QoL
Do symptomatic toxicities (eg peripheral neuropathy) impact a patient's QoL?	x	x	
Any additional comments	These side effects have to be quite significant to overcome the positive effects of improved response.		

	Clinical Plausibility: What does your clinical experience tell you	
	Peripheral neuropathy associated with single agent chemotherapy **continues** after a patient discontinues treatment	Peripheral neuropathy associated with single agent chemotherapy **stops** after a patient discontinues treatment
Can peripheral neuropathy associated with single agent chemotherapy continue after a patient discontinues treatment?	x	
Any additional comments	Taxanes are supposed to be reversible but can linger for many years and then when add another tubulin agent reactivates meaning this tox runs and runs	

Appendix B – interaction test

Covariate	P-value from OS analysis
Brain metastases	[redacted]
Region	[redacted]
Eastern Cooperative Oncology Group (ECOG)	[redacted]
Age	[redacted]
Race	[redacted]
Hormone Receptor Status	[redacted]

Please find the full analyses for PFS and OS in Appendix E and Appendix F, respectively, submitted alongside the current form.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **12 August 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies and current treatment options	
About you	
1. Your name	**Dr Alicia Okines**
2. Name of organisation	**The Royal Marsden NHS Foundation Trust**
3. Job title or position	**Consultant medical oncologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with HER2-positive locally advanced or metastatic breast cancer? ☒ a specialist in the clinical evidence base for HER2-positive locally advanced or metastatic breast cancer or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for HER2-positive locally advanced or metastatic breast cancer	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop disease progression and spread, control symptoms and extend life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Improved response rate At least 2-3 months improvement in median progression-free and overall survival

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in HER2-positive locally advanced or metastatic breast cancer, after 2 prior HER2-targeted therapies?	Yes, this is an area of significant unmet need. Although Trastuzumab deruxtecan(T-DXd) has just been approved by the CDF and is an effective treatment, it has not yet been proven to have a survival benefit. Furthermore, it is not anticipated to cross the blood-brain barrier, so patients with unstable brain metastases do not currently have a good treatment option. Capecitabine/tucatinib/trastuzumab provides a well-tolerated 3rd line option which is a particularly important option for patients with brain metastases. Patients without brain metastases would also benefit from having an additional line of effective and well-tolerated HER2 targeted therapy with a proven survival benefit.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Until recently, NICE approved options comprised single agent chemotherapy (usually capecitabine then eribulin) which give only a short duration of disease control at best. T-DXd has now been approved by the CDF based on the high response rate and progression-free survival reported in the phase 2 DESTINY-BREAST-01 trial.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESMO clinical practice guidelines 2020
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	In the 3rd line setting, most patients outside the UK would continue to receive trastuzumab with all lines of chemotherapy. NICE has not recommended trastuzumab beyond progression, therefore in the UK, there is variable access to this. Where available outside the UK, T-DM1 is now followed by tucatinib/trastuzumab/capecitabine then T-DXd, then chemotherapy plus trastuzumab.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	The availability of the technology would allow its use in the 3rd line setting, prior to T-DXd for most patients, although due to the higher response rate with T-DXd, preference would be given to using that before the technology for patients with impending visceral crisis/very symptomatic extra-cranial disease but no active/untreated brain metastases.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not currently used in the NHS. It will be used in place of capecitabine (plus trastuzumab where available) in the NHS
• How does healthcare resource use differ between the technology and current care?	The addition of a second oral medication to capecitabine will not affect healthcare resource. As trastuzumab is available as a subcutaneous injection which can be delivered in outpatients, or self-administered by patients at home, this will not affect healthcare resources at the centres currently unable to prescribe trastuzumab beyond progression.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care only
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None

13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the prolonged progression-free and overall survival seen in the trial were clinically meaningful benefits
• Do you expect the technology to increase length of life more than current care?	Yes, this is clear from the HER2-Climb trial results
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, because the treatment does not worsen QoL through side-effects (additional side effects were minimal) but prolongs disease control, which prolongs good QoL
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any	No different to current care, no additional monitoring required other than regular (6-monthly) echocardiograms for centres who weren't previously able to give trastuzumab with capecitabine.

practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Prolonged control of brain disease will reduce/delay the need for stereotactic brain radiotherapy and whole brain radiotherapy
18. Do you consider the technology to be innovative in its potential to make a significant and	Yes. This is an important drug combination to control brain metastases for patients with HER2 positive breast cancer in addition to being an effective therapy for patients without brain metastases.

substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes, patients with brain metastases have a particular unmet need
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Tucatinib adds little toxicity to capecitabine. Because patients are on the combination longer (as it works better), there was an increased rate of diarrhoea and hand-foot syndrome reported, which, when corrected for treatment exposure, was minimal (Okines et al., ASCO 2020 poster). Both side effects are easily managed with supportive medications and/or dose reductions. The increased rate of transaminitis (raised AST/ALT) is asymptomatic and does not impact on QoL. Controlling cancer for longer improves the duration of good QoL for patients
Sources of evidence	

20. Do the clinical trials on the technology reflect current UK clinical practice?	No, because trastuzumab is not NICE approved beyond progression, so is only available to around 50% of patients in the UK (from a previous poll by UKBCG)
• If not, how could the results be extrapolated to the UK setting?	Comparison with other studies of capecitabine, eribulin and vinorelbine monotherapy
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS and overall survival; yes these were measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found	No

by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA704]?	Updated survival results presented at ASCO 2021
23. How do data on real-world experience compare with the trial data?	I am not aware of any real-world data for the technology as yet However, the trial population is representative of a real-world population, therefore I would anticipate little difference
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Indirect comparison results between tucatinib in combination with trastuzumab and capecitabine and comparator treatments are uncertain due to clinical heterogeneity across the trials included in the network meta-analysis.	In clinical practice, we see very poor progression-free (usually 3-4 months) and overall survival beyond second-line if anti-HER2 targeted therapies are unavailable. Whilst none of the comparator studies allowed patients with active brain metastases to be included (therefore selecting a better prognosis population) and none of the studies were conducted solely in HER2 positive breast cancer, the outcomes reported in the monotherapy trials are similar (if anything slightly better due to exclusion of poor prognosis patients with active brain metastases) to that expected in clinical practice.

Key issue 2: Company's modelling of progression-free and overall survival for tucatinib (in combination) and comparator treatments is not robust.	
Key issue 3: Cost-effectiveness analysis may not reflect the prevalence of brain metastases in NHS clinical practice.	I disagree. In my own practice, I apply for compassionate access to neratinib to use in combination with capecitabine for patients who have progressed after 2 lines of anti-HER2 therapy. This has similar efficacy to the technology (allowing for cross-trial comparison) but significantly more side effects (See Saura et al., J Clin Oncol 2020 NALA trial). We presented our experience of 29 patients at ESMO Breast 2019 (Shepherd S et al.), of whom 14/29 (48%) had brain metastases. We have a manuscript in preparation for the updated analysis of 73 patients of whom 39 (53%) had brain metastases. I have published our experience of brain metastases and T-DM1 (Okines et al., The Breast Journal 2017). Amongst 55 patients starting second-line T-DM1, 16 (29%) had brain metastases at the outset and a further 7 (total 42%) developed symptomatic brain metastases during T-DM1. This is without any screening for brain metastases. An updated analysis of our T-DM1 experience (Battisti et al., Cancer Treatment and Research Communications 2020) reports brain metastases in 49/134 patients (38.3%) commencing T-DM1, which would be expected to increase by the end of treatment (although we did not specifically look at brain progression in that manuscript).
Key issue 4: Company uses different health state utilities for	In my clinical experience, patients' QoL is at its greatest when their cancer is controlled. The technology controls HER2 positive advanced breast cancer for longer than any of the comparators without adding significant toxicity.

the tucatinib combination and comparators.	
Additional key issue: Inclusion of trastuzumab + capecitabine as a comparator in the ERG analysis.	Whilst the most robust comparator is of course trastuzumab and capecitabine as that was the standard arm in the clinical trial, this is not a treatment that is available to all patients in the NHS. As such, it should not be used as a comparator unless trastuzumab beyond progression becomes available to all NHS patients.
Are there any important issues that have been missed in ERG report?	No
Additional technical team questions	
The HER2CLIMB trial included patients with and without brain metastases. The comparator trials, in contrast, included few or no patients with brain metastases. Do you think this may impact on results of indirect comparison between	Yes, the population of patients included in the comparator studies will have a better prognosis by not including those with brain metastases. Therefore overall survival results from the comparator studies will be better than would be expected if applied to the HER2CLIMB population.

tucatinib (in combination) and its comparators? If so, how?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies have brain metastases in NHS clinical practice?	As above, by the 3rd line setting, approximately 50% of my patients with metastatic HER2-positive breast cancer have brain metastases. This is reflective of UK clinical practice.
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would be expected to be alive at 1, 2 and 5 years from the start of next-line therapy, in current NHS practice? How would this differ	In my practice, through the use of neratinib, the 1-year OS we reported was 59% (Shepherd et al., 2019 ESMO Breast poster). In the (unpublished) updated results, 1-year OS is 58%, 2-year OS is 30.2%. I would anticipate 5 year OS to be <5% but do not have these data. Without HER2 targeted agents, I would expect 1-year OS to be <50%, 2-year OS <20% and 5-year OS to be 0. The rates would be lower after 3 or more HER2 targeted therapies, but I do not have these data.

after failure after 3 or more prior anti-HER2 therapies?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would be expected to be alive at 1, 2 and 5 years from the start of next-line tucatinib (in combination) therapy? How would this differ after failure after 3 or more prior anti-HER2 therapies?	As per the HER2Climb trial, 1 year OS was 75% and 2-year OS was 51% (Curigliano et al., ASCO 2021) in patients who received a median of 3 prior lines of therapy. We do not yet have data at 5 years, but would expect the rate to be <20%. The rates could be reasonably expected to be slightly higher after fewer prior lines of therapy (2 or more HER2 targeted therapies than 3), but no sub-group analysis was performed on the number of prior lines and the number of prior lines of HER2 targeted therapies was not specifically reported but all patients had received prior pertuzumab and T-DM1 ie 2 lines.
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would you expect to be progression free at 1, 2 and 5 years from the start of next-	If treated with standard chemotherapy without HER2 targeting, I would expect the 1-year PFS to be <10% as per the EMBRACE trial of eribulin. 2-year and 5-year PFS were not reported but would likely be <5% and 0% respectively in my clinical experience. This would differ minimally after 3 prior lines of HER2-targeted therapy in my opinion.

line therapy, in current NHS practice? How would this differ after failure after 3 or more prior anti-HER2 therapies?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would you expect to be progression free at 1, 2 and 5 years from the start of next-line tucatinib (in combination) therapy? How would this differ after failure after 3 or more prior anti-HER2 therapies?	In the updated results of the HER2Climb trial, 1 year PFS was 29% and 2-year PFS was <20%. 5-year PFS has not yet been reported, but will be <20%. The results might be slightly better in those who have received 2 rather than 3 prior lines of HER2 targeted therapy, but these data are not available.
Would you expect patients' health-related quality of life before progression to be higher for tucatinib (in combination) compared to	Yes, this is a better tolerated regimen than vinorelbine or eribulin. Prior to progression, HR-QoL would be similar on capecitabine to the technology combination.

eribulin, capecitabine and vinorelbine?	
Would you expect patients' health-related quality of life after progression to be higher for tucatinib (in combination) compared to eribulin, capecitabine and vinorelbine?	After disease progression, HR QoL is likely to be similar amongst these groups.
Which treatments are currently used in NHS clinical practice after failure of 2 or more anti-HER2 therapies?	Capecitabine Eribulin Vinorelbine

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- The technology is an effective and well-tolerated treatment for patients with HER2-positive advanced breast cancer who have progressed after 2 lines of prior HER2 targeted therapy
- The technology addresses an unmet need, especially for patients with brain metastases for whom there is no effective systemic therapy available to NHS patients at present

- Brain metastases affect approximately 50% of women with HER2 positive advanced breast cancer and cause significant morbidity and mortality. Having an effective treatment for women with brain metastases and one which could, due to known CNS penetration, delay the onset of brain metastases in others is vital
- Single agent chemotherapy is not a very effective treatment for patients with HER2 positive advanced breast cancer, so outcomes are poor without sustaining HER2 targeting
- The technology represents an important advance in this disease and should be made available to NHS patients with HER2 positive advanced breast cancer with and without brain metastases

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

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- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **12 August 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies and current treatment options	
About you	
1. Your name	**SHEEBA IRSHAD**
2. Name of organisation	**NCRI/ACP**
3. Job title or position	**CONSULTANT MEDICAL ONCOLOGY AT GUY'S & ST THOMAS' NHS TRUST**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with HER2-positive locally advanced or metastatic breast cancer? ☐ a specialist in the clinical evidence base for HER2-positive locally advanced or metastatic breast cancer or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
The aim of treatment for HER2-positive locally advanced or metastatic breast cancer	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
9. What do you consider a clinically significant treatment	

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in HER2-positive locally advanced or metastatic breast cancer, after 2 prior HER2-targeted therapies?	
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful	

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA704]?	

23. How do data on real-world experience compare with the trial data?	
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	
24b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Indirect comparison results between tucatinib in combination with trastuzumab and capecitabine and comparator treatments are uncertain due to clinical heterogeneity across the trials included in the network meta-analysis.	HER2CLIMB included 48% of patients with brain metastasis; this included 19% with treated and stable brain metastases and 28% with active brain metastases (treated and progressing or untreated lesions). Many of the comparator trials excluded patients with brain metastases. Although, in the SOPHIA trial that compared margetuximab to trastuzumab, both in combination with chemotherapy (investigator's choice: capecitabine, eribulin, gemcitabine, or vinorelbine); patients with brain metastases were eligible if the metastases were treated and stable. No brain metastasis specific endpoints have been reported so far for SOPHIA; therefore, it remains unknown whether margetuximab is effective in BM for HER2-positive breast cancer. The incidence of brain metastasis is clinically significant in advanced HER2-positive breast cancer with approximately 50% of patients developing brain metastasis at the time of disease progression post second line of therapy. HER2CLIMB therefore represents a pivotal study for this clinically relevant scenario for patients seen in the NHS. In many ways, the inclusion of a large group of high-risk patient population within the HER2CLIMB trial, if anything would disadvantage the tucatinib combination vs its comparators. It is also noteworthy that German guidelines have already been updated (February 202), to include tucatinib, trastuzumab, and capecitabine as the treatment regimen of choice after the failure of T-DM1 in the second line.

Key issue 2: Company's modelling of progression-free and overall survival for tucatinib (in combination) and comparator treatments is not robust.	There is a lack of large trials assessing the efficacy of sequential administration, due to the nature of the historical simultaneous development of drugs within the anti-HER2 drug development pipeline. However, updated results from the HER2CLIMB trial presented at ASCO 2021 help provide some guidance here. At the time of data cut-off in February 2021, 35 patients taking tucatinib and 1 patient taking placebo were still on their respective treatments, while the others had completed treatment. Of the placebo patients, 26 (12.9%) had crossed over to the other arm, with the first crossover being in February 2020. Nine patients who crossed over remain on tucatinib. The median overall study follow-up was 29.6 months, including 15.6 months since the primary analysis. The median OS was 24.7 months in the tucatinib arm compared with 19.2 months in the placebo arm (95% confidence interval 0.59–0.90, P = .004). The OS benefit with tucatinib was consistent across prespecified patient subgroups. Sensitivity analyses accounting for crossover patients also revealed similar OS benefits. The benefit in PFS was similarly maintained with longer follow-up, at 7.6 months in the tucatinib arm versus 4.9 months in the placebo arm (hazard ratio 0.57, P < .00001).
Key issue 3: Cost-effectiveness analysis may not reflect the prevalence of brain metastases in NHS clinical practice.	Whilst many studies confirm the prevalence of brain metastases in HER2+ breast cancers to be in the range of 30%, but given the lack of routine screening, it is estimated that 20% to 40% of MBC patients have asymptomatic brain metastases that remain undetected and untreated. It is generally well accepted that up to 50% of $HER2^+$ MBC patients will develop brain metastases throughout the course of disease and therefore HER2CLIMB within the third line setting is very representative of the patient population seen in clinical practice in England.
Key issue 4: Company uses different health state utilities for the tucatinib combination and comparators.	Maintaining QoL in pts with MBC who progress through different lines of therapy is an important outcome in clinical trials. Within the HER2CLIMB study, the reported health related quality of life was presented at EMSO in 2020. Assessment of quality of life was made using the EQ-5D-5L which includes a EQ visual analog scales and descriptive system of 5 health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. QoL in patients treated with tucatinib combination was maintained throughout the treatment period which was longer compared to patients not receiving tucatinib. Specifically, the safety profile of tucatinib is good. Many of the investigators involved in the HER2CLIMB trial could not discern between patients on the placebo and those on the experimental drug. The most common adverse event in HER2CLIMB was diarrhoea. Diarrhoea is a toxicity associated with both tucatinib

	and capecitabine. The management is quite simple. Trial reported a low rate of treatment discontinuation due to adverse events: 7% in the tucatinib arm and approximately 4% in the placebo arm. It is noteworthy point that whilst it is difficult to separate out disease progression related effects on QOL vs effects from toxicity; what is well know is that if the disease is well controlled, QOL improves.
Additional key issue: Inclusion of trastuzumab + capecitabine as a comparator in the ERG analysis.	Trastuzumab and capecitabine in the third line setting is not available for NHS patients. Patients may receive treatment with non-targeted chemotherapies such as capecitabine or vinorelbine or eribulin following progression. In addition, lapatinib is a HER2 targeted treatment which in combination with capecitabine or trastuzumab is also licensed for use at this point in the treatment pathway, although this is not funded through NICE and is therefore not available for NHS patients.
Are there any important issues that have been missed in ERG report?	NA
Additional technical team questions	
The HER2CLIMB trial included patients with and without brain metastases. The comparator trials, in contrast, included few or no patients with brain metastases. Do you think this may impact on results of indirect comparison between	Please see my answer to “key issue 1” and key issue 3. In short, HER2CLIMB represents a pivotal study within the third line setting as it is very representative of the patient population seen in clinical practice in England.

tucatinib (in combination) and its comparators? If so, how?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies have brain metastases in NHS clinical practice?	Please see my answer to “key issue 3”.
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would be expected to be alive at 1, 2 and 5 years from the start of next-line therapy, in current NHS practice? How would this differ	Please see my answer to “key issue 2”.

after failure after 3 or more prior anti-HER2 therapies?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would be expected to be alive at 1, 2 and 5 years from the start of next-line tucatinib (in combination) therapy? How would this differ after failure after 3 or more prior anti-HER2 therapies?	Please see my answer to “key issue 2”.
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would you expect to be progression free at 1, 2 and 5 years from the start of next-	Please see my answer to “key issue 2”.

line therapy, in current NHS practice? How would this differ after failure after 3 or more prior anti-HER2 therapies?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would you expect to be progression free at 1, 2 and 5 years from the start of next-line tucatinib (in combination) therapy? How would this differ after failure after 3 or more prior anti-HER2 therapies?	Please see my answer to “key issue 2”.
Would you expect patients’ health-related quality of life before progression to be higher for tucatinib (in combination) compared to	Please see my answer to “key issue 4”.

eribulin, capecitabine and vinorelbine?	
Would you expect patients' health-related quality of life after progression to be higher for tucatinib (in combination) compared to eribulin, capecitabine and vinorelbine?	Please see my answer to "key issue 4".
Which treatments are currently used in NHS clinical practice after failure of 2 or more anti-HER2 therapies?	Please see my answer to "additional key issue"

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- After T-DM1, there are a variety of treatment options, but none have shown an OS benefit in the post-T-DM1 setting.
- Tucatinib with trastuzumab and capecitabine is the first treatment combination to demonstrate an improvement in median OS in the post-T-DM1 setting.

- Tucatinib is specifically labelled to indicate benefit in patients with brain metastases; which represent a large proportion of HER2+ metastatic breast cancer patients at this point in the patient pathway.
- Tucatinib in combination with trastuzumab and capecitabine has an acceptable safety profile for the intended population

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **12 August 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with treating HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies and current treatment options	
About you	
1.Your name	**Vicki McGinn**
2. Are you (please tick all that apply):	**x**☐ a patient with HER2-positive locally advanced or metastatic breast cancer? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with HER2-positive locally advanced or metastatic breast cancer? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Breast Cancer Now
4. Has your nominating organisation provided a submission? Please tick all options that apply. They will provide a separate response	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement

	☐ I agree with it and **will be** completing X I am submitting my response and they will submit a separate response
5. How did you gather the information included in your statement? (please tick all that apply)	**X**☐ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: **X**☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with HER2-positive locally advanced or metastatic breast cancer? If you are a carer (for someone with HER2-positive locally advanced or metastatic breast cancer) please share your experience of caring for them.	I was diagnosed with HER2 positive secondary breast cancer in May 2017 (aged 39), 3 years after my primary diagnosis. It had spread to my left ancillary nodes, both lungs and sternum. Initially it was hard to come to terms with my diagnosis and the fact that there was no cure. I felt like I had a death sentence hanging over my head. I also dreaded having to go back on chemotherapy again as this made me extremely ill last time resulting in being admitted to hospital with neutropenic sepsis, I was unable to work and was reliant on family for round the clock care. This was hard for me having previously led an independent fulfilling life. The thought of always being on some sort of treatment with limited quality of life and the uncertainty of what the future held had a huge impact on my mental and financial health. There was also the emotional impact it had on my friends and family. Many felt that as I had got through treatment once and got the all clear I could do it again, not

	understanding there is no cure and my treatment would never end. It put pressure and emotional stress on family members and I was reliant on them for care and support and it was distressing for them seeing me so ill. My first year of treatment was tough. I started treatment with docetaxol, herceptin & perjeta for 6 months which managed to shrink the sternum metastasis, however my quality of life was non-existent on this regime, I could not work, needed constant care and I ended up hospitalised with infections and I then had fluid around the heart and a pericardial effusion so my treatment was changed to Kadcyla. The mets continued to grow albeit slowly, so despite progression I remained on Kadcyla for a year as there was no alternative third line of targeted approved treatment. This was a very scary time as I felt like I was running out of options and far too quickly. I found out the cancer had spread to the brain, so on top of this I lost my independence with not being able to drive. It really did feel like this was the end as at the same time my lung and ancillary mets had started to grow more rapidly. Luckily, I found out I was eligible for the HER2CLIMB trial at the Royal Marsden. I started the trial in January 2019. As the trial was blinded I was not sure if I was on Tucatinib or the placebo, however within 6 weeks all of my mets started to shrink. The ancillary tumours completely resolved and I only have a few tiny lung mets remaining that are too small to measure on a CT scan. I have had no progression or reoccurrence in the brain metastasis which has enabled me to resume driving again which has a positive impact on my mental well-being and independence. When the trial was unblinded I found out I had been on Tucatinib from the start. The results of the trial were so much more than I could have hoped for and these drugs worked when other treatments didn't work for very long for me. I went from having minimal options other than an intravenous chemotherapy, to finding a drug that worked and is still working over 2 and half years later with no evidence of active disease.

	The treatment not only works very effectively and has helped me to keep the cancer at bay it has enabled me to have a very good quality of life. I am able to enjoy a normal and fulfilling life. I am able to work again and my job provides a purpose to my life. I get to undertake leisure and social activities to the full. I have rediscovered my zest for life and I no longer feel like I am a cancer patient, I do not feel ill and I am now able to look to the future whereas in the past the future outlook was bleak and I didn't expect to still be alive. This has a beneficial impact on my mental wellbeing as well as also having a positive impact on my friends and family who no longer have to provide daily care and support as they have in the past on chemotherapy. I have seen too many young women die of this disease and this drug offers the opportunity to extend life but also offers a good quality of life. This drug has helped to extend my life and no price can be put on the memories I have made and the additional time I have had with my family.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for HER2-positive locally advanced or metastatic breast cancer on the NHS?	I do not feel like there are enough options available for secondary breast cancer patients especially targeted treatments and specifically for treating brain metastasis. Also the lines of treatment are very restrictive – when I was taken off herceptin & perjeta I was not aware that I could not return to these drugs at some point in the future, as they are only authorised for first line. These drugs were working for me but other health complications from the chemotherapy (docetaxel) meant I was taken off these.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Patients should be given more freedom of choice to find the drugs that work for them and not necessarily restricted by set lines of treatments. Targeted treatments appear to be more effective in treating HER2 positive than chemotherapy alone so should be available to be used in conjunction with chemotherapy on any line of treatment.
8. If there are disadvantages for patients of **current NHS treatments** for HER2-positive locally advanced or metastatic breast cancer (for example how tucatinib with trastuzumab and capecitabine is given or taken, side effects of treatment etc) please describe these	Most current treatments involve an IV chemotherapy which has significant side effects, weakened immune system and leads to a poor quality of life, inability to continue working and loss of independence as there is a greater need for care and support at home. This can have significant impact on the financial and emotional wellbeing on patients. Chemotherapy can often lead to hair loss which can be very distressing to patients and can affect self-confidence and mental wellbeing. IV Chemotherapy has to be administered in a hospital which takes longer than injection/tablets and can cause issues with veins and cannulation. No current HER2 targeted drug treatments that are aimed at brain metastasis. Also targeted treatment for HER2 like Herceptin, Kadcyla and perjeta are not available in third line setting alongside chemotherapy.
Advantages of this treatment	
9a. If there are advantages of tucatinib with trastuzumab and capecitabine over current treatments on the NHS, please describe these. For example, the impact on your Quality of Life, your	9a) The treatment is quick as I only need to have the subcut herceptin injection in clinic every 3 weeks as the tucatinib and capecitabine can be taken at home as in tablet form.

ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does tucatinib with trastuzumab and capecitabine help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	There are minimal side effects from the treatment and I find the drugs very manageable. I had stomach issues initially for the first few cycles but now I don't take any other medication to counter act any side effects. No hair loss so self-esteem is maintained. I am in no pain. I have a good quality of life and am able to work, able to look after myself and undertake social and leisure activities with my friends and family. This would not have been possible with an IV chemotherapy regime where I could not work, had no quality and life and was reliant on family members for care and support. The treatment is highly effective and has worked for the longest amount of time than any previous drug regime I have been on, not only shrinking the metastasis but then keeping the cancer at bay for the past 2 and half years (and hopefully this will continue for even longer). It has extended my life. 9b) I think most important advantage is the effectiveness of the drug for extending the life of patients whilst maintaining a good quality of life with minimal side effects. 9c) The combination of tucatinib with trastuzumab and capecitabine addresses most of the disadvantages of current treatment options available. It is quick and does not require IV infusion as it is possible to have the herceptin as sub cut and remainder is tablets. Less side effects than IV chemotherapy, leading to less care/support, able to work and have a good quality of life. My immune system is better leading to less infections/other illnesses. No hair loss on trial regime v IV chemotherapy.

	Worked more effectively and for longer than previous current treatments for me. Effective on brain metastasis. Also allows for HER2 targeted Herceptin to be used in conjunction with other drugs.
Disadvantages of this treatment	
10. If there are disadvantages of tucatinib with trastuzumab and capecitabine over current treatments on the NHS please describe these? For example, are there any risks with tucatinib with trastuzumab and capecitabine? If you are concerned about any potential side effects you have heard about, please describe them and explain why.	The only disadvantages are:- - tucatinib has to be stored in the fridge which is only an issue when planning holidays or trips away. - Capecitabine can cause issues with feet but this can usually be dealt with specialised daily moisturisers.
Patient population	
11. Are there any groups of patients who might benefit more from tucatinib with trastuzumab and capecitabine or any who may benefit less? If so, please describe them and explain why.	Patients with brain metastasis. Also those that have suffered with complications or significant side effects from other chemotherapy regimes as this combination has less side effects and offers a better quality of life.

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering HER2-positive locally advanced or metastatic breast cancer and tucatinib with trastuzumab and capecitabine? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	Tucatinib has been authorised by the European Commission, Australia and FDA (USA) and therefore UK residents are disadvantaged in their HER 2 cancer treatment options compared to other countries.

More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

Key issue 1: Indirect comparison results between tucatinib in combination with trastuzumab and capecitabine and comparator treatments are uncertain due to clinical heterogeneity across the trials included in the network meta-analysis.	
Key issue 2: Company's modelling of progression-free and overall survival for tucatinib (in combination) and comparator treatments is not robust.	
Key issue 3: Cost-effectiveness analysis may not reflect the prevalence of brain	

metastases in NHS clinical practice.	
Key issue 4: Company uses different health state utilities for the tucatinib combination and comparators.	
Additional key issue: Inclusion of trastuzumab + capecitabine as a comparator in the ERG analysis.	
Are there any important issues that have been missed in ERG report?	
Additional technical team questions	
The HER2CLIMB trial included patients with and without brain metastases. The comparator trials, in contrast, included few	Survival rates for people with brain metastasis is generally shorter than those without.

or no patients with brain metastases. Do you think this may impact on results of indirect comparison between tucatinib (in combination) and its comparators? If so, how?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies have brain metastases in NHS clinical practice?	From my own point of view with HER2 I always knew that the likelihood of progression to the brain was high (from other peers in support groups, oncology team and general reading of HER2 prognosis). I developed brain metastasis during my 2nd line treatment.
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would be expected to be alive at 1, 2 and 5 years from the start of next-line	

therapy, in current NHS practice? How would this differ after failure after 3 or more prior anti-HER2 therapies?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would be expected to be alive at 1, 2 and 5 years from the start of next-line tucatinib (in combination) therapy? How would this differ after failure after 3 or more prior anti-HER2 therapies?	From my own point of view I have already survived 2 year and 7 months since starting the trial and am stable/ no evidence of active disease and hope this will continue for the foreseeable future. My first line of treatment lasted 6 months before progression and second line I had small progression for the whole year I was on Kadcyla so the trial is the first treatment that has worked for me for any period of time
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would you expect to	

be progression free at 1, 2 and 5 years from the start of next-line therapy, in current NHS practice? How would this differ after failure after 3 or more prior anti-HER2 therapies?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would you expect to be progression free at 1, 2 and 5 years from the start of next-line tucatinib (in combination) therapy? How would this differ after failure after 3 or more prior anti-HER2 therapies?	
Would you expect patients' health-related quality of life before progression to be	My quality of life from when I started the trial to now has improved significantly. I have a full and fulfilling life, I am able to return to work and undertake leisure and social activities to the full. I don't need care and support from friends and family that I have required round the clock care on previous treatments/chemotherapy. The side effects of treatment are minimal. It has also improved the quality

higher for tucatinib (in combination) compared to eribulin, capecitabine and vinorelbine?	of life of my family as they need to provide less support and have less emotional worry.
Would you expect patients' health-related quality of life after progression to be higher for tucatinib (in combination) compared to eribulin, capecitabine and vinorelbine?	
Which treatments are currently used in NHS clinical practice after failure of 2 or more anti-HER2 therapies?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Tucatinib is a highly effective drug and the combination used in the HER2 climb trial had made me NEAD, in the brain and other parts. It is still working to keep me stable and is the most effective treatment I have had since my diagnosis.

- There are minimal side effects to the treatment.
- I am able to have a good quality of life and no longer need support and care of family
- It has improved my physical and mental health as well as the emotional stress on my family as I am now living a normal fulfilled life
- This drug has extended my life and it can benefit so many more people living with HER2 breast cancer. I believe I would not still be here without this drug combination.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **12 August 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with treating HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies and current treatment options	
About you	
1.Your name	**Holly Heath**
2. Are you (please tick all that apply):	☐ a patient with HER2-positive locally advanced or metastatic breast cancer? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with HER2-positive locally advanced or metastatic breast cancer? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Breast Cancer Now
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement

	☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with HER2-positive locally advanced or metastatic breast cancer? If you are a carer (for someone with HER2-positive locally advanced or metastatic breast cancer) please share your experience of caring for them.	

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for HER2-positive locally advanced or metastatic breast cancer on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of **current NHS treatments** for HER2-positive locally advanced or metastatic breast cancer (for example how tucatinib with trastuzumab and capecitabine is given or taken, side effects of treatment etc) please describe these	
Advantages of this treatment	
9a. If there are advantages of tucatinib with trastuzumab and capecitabine over current treatments on the NHS, please describe these. For example, the impact on your Quality of Life, your	

ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does tucatinib with trastuzumab and capecitabine help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of tucatinib with trastuzumab and capecitabine over current treatments on the NHS please describe these? For example, are there any risks with tucatinib with trastuzumab and capecitabine? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	

Patient population	
11. Are there any groups of patients who might benefit more from tucatinib with trastuzumab and capecitabine or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering HER2-positive locally advanced or metastatic breast cancer and tucatinib with trastuzumab and capecitabine? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and	

civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Indirect comparison results between tucatinib in combination with trastuzumab and capecitabine and comparator treatments are uncertain due to clinical heterogeneity across the trials included in the network meta-analysis.	
Key issue 2: Company's modelling of progression-free and overall survival for tucatinib (in combination) and comparator treatments is not robust.	

Key issue 3: Cost-effectiveness analysis may not reflect the prevalence of brain metastases in NHS clinical practice.	
Key issue 4: Company uses different health state utilities for the tucatinib combination and comparators.	
Additional key issue: Inclusion of trastuzumab + capecitabine as a comparator in the ERG analysis.	Trastuzumab is not licensed with chemotherapy for use as a later line treatment for patients who have progressed on earlier treatments such as trastuzumab emtansine (Kadcyla). However, off-label prescribing of trastuzumab may happen in some circumstances across the NHS in England, so access to this treatment is currently variable for patients. As set out in a recent paper (T.Robinson, C.Palmieri, J.P Braybrooke, Tratuzumab beyond progression in advanced HER2 positive breast cancer: UK practice now and in the future, Clinical Oncology), of the NHS centres that responded to the research, just over 50% (51.6%) centres were prescribing trastuzumab beyond progression. Also to note, in the recent NICE appraisal of trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies, trastuzumab in combination with capecitabine was not considered a comparator as it is not routinely available on the NHS.

Are there any important issues that have been missed in ERG report?	
Additional technical team questions	
The HER2CLIMB trial included patients with and without brain metastases. The comparator trials, in contrast, included few or no patients with brain metastases. Do you think this may impact on results of indirect comparison between tucatinib (in combination) and its comparators? If so, how?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 therapies have brain	

metastases in NHS clinical practice?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would be expected to be alive at 1, 2 and 5 years from the start of next-line therapy, in current NHS practice? How would this differ after failure after 3 or more prior anti-HER2 therapies?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would be expected to be alive at 1, 2 and 5 years from the start of next-line	

tucatinib (in combination) therapy? How would this differ after failure after 3 or more prior anti-HER2 therapies?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would you expect to be progression free at 1, 2 and 5 years from the start of next-line therapy, in current NHS practice? How would this differ after failure after 3 or more prior anti-HER2 therapies?	
What proportion of people with HER2-positive locally advanced or metastatic breast cancer after 2 prior anti-HER2 therapies would you expect to	

be progression free at 1, 2 and 5 years from the start of next-line tucatinib (in combination) therapy? How would this differ after failure after 3 or more prior anti-HER2 therapies?	
Would you expect patients' health-related quality of life before progression to be higher for tucatinib (in combination) compared to eribulin, capecitabine and vinorelbine?	We consider this treatment to be an innovative oral tyrosine kinase inhibitor that could provide a very important new treatment option to pre-treated HER2 positive secondary breast cancer patients. Maintaining a high quality of life for as long as possible is currently a crucial outcome for this patient group as secondary breast cancer remains incurable. A patient who is currently receiving this treatment through the clinical trial told us: "My quality of life from when I started the trial to now has improved significantly. I have a full and fulfilling life, I am able to return to work and undertake leisure and social activities to the full. I don't need care and support from friends and family that I have required round the clock care on previous treatments/chemotherapy. The side effects of treatment are minimal. It has also improved the quality of life of my family as they need to provide less support and have less emotional worry." "The treatment is quick. Every 3 weeks, minimal side effects, can take tablets at home. It has shrunk all my tumours to barely measurable after 6 weeks and I have remained stable for the past 2 years. Prior to this, other treatments did not work for me for very long (6-9 months) and this is the longest I have been on the same treatment - it has 100% prolonged my life where other treatment failed. I have been on this treatment since January 2019.

	I am able to lead a normal life, I work part time, I do get tired occasionally. I can't run now due to feet issues from capecitabine. But compared to iv treatment where I am usually house bound, have no energy, can't work - this treatment not only has prolonged life it has allowed me to live as normal a life as possible." "I have found the side effects to be minimal. To start with had stomach issues for first few cycles but now to totally manageable and I don't take any other medication to counter act any side effects. Also have issues with feet and hands but this is from capecitabine (and I just moisturise twice daily and have had one dose reduction in the 2 years when feet got really bad).
Would you expect patients' health-related quality of life after progression to be higher for tucatinib (in combination) compared to eribulin, capecitabine and vinorelbine?	
Which treatments are currently used in NHS clinical practice after failure of 2 or more anti-HER2 therapies?	Following a NICE recommendation in May 2021 for use on the CDF, trastuzumab deruxtecan is now available for patients after 2 or more prior anti-HER2 therapies. Prior to this the exact treatment for patients who have already received 2 or more anti HER2 therapies may differ. As set out in our response to the scoping consultation, for the population being considered in this appraisal, eribulin is an appropriate comparator as it is recommended by NICE for treating secondary breast cancer after 2 or more chemotherapy regimens.

	It is also correct for NICE to have included other chemotherapies such as capecitabine or vinorelbine as comparators for this treatment.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- As per our original patient organisation submission.
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **12 August 2021.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche Products Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Indirect comparison results between tucatinib in combination with trastuzumab and capecitabine and comparator treatments are uncertain due to clinical heterogeneity across the trials included in the network meta-analysis.	**NO**	No comment.
Key issue 2: Company's modelling of progression-free and overall survival for tucatinib (in combination) and comparator treatments is not robust.	**NO**	No comment.
Key issue 3: Cost-effectiveness analysis may not reflect the prevalence of brain metastases in NHS clinical practice.	**NO**	No comment
Key issue 4: Company uses different health state utilities for the	**NO**	No comment

tucatinib combination and comparators.		
Additional key issue: Inclusion of trastuzumab + capecitabine as a comparator in the ERG analysis.	**NO**	No comment

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

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

Evidence Review Group's summary and critique of the company's response to technical engagement

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	David Alexander Scott, Principal Research Fellow, SHTAC Lorna Hazell, Senior Research Assistant, SHTAC Neelam Kalita, Senior Research Fellow, SHTAC Joanne Lord, Director, SHTAC Jonathan Shepherd, Principal Research Fellow.
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Date completed	25th August 2021

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[redacted]

LIST OF ABBREVIATIONS

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

1. Introduction

This document is the Evidence Review Group's (ERG) summary and critique of the response by the company, Seagen, to the key issues for technical engagement proposed in the ERG report for this appraisal (submitted to NICE on 23rd June 2021). The ERG received the company's response on 13th August 2021.

The company's technical engagement response form contains the following information:

- A written response to each of the four key issues, three of which include new evidence and/or analyses (see Table 1), albeit to a limited extent.
- New base case cost effectiveness estimates based on a correction made to one of the studies included in the network meta-analysis (NMA).
- Cost effectiveness results informed by a fractional polynomial NMA "applied to the base case (revised after clarification responses)"
- Scenarios utilising different utility scores

In this report we present a brief critique of the company's response to each of the four issues for technical engagement (Section 2). We also verify the company's updated cost effectiveness results against the latest version of their economic model (Section 3).

Table 1 Summary of key issues for technical engagement

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
1	The results of the indirect comparison between tucatinib in combination with trastuzumab and capecitabine and comparator treatments are uncertain due to clinical heterogeneity across the trials included in the network meta-analysis.	Yes, new analyses
2	Lack of justification for the company's survival extrapolation model	No[a]
3	Cost-effectiveness analysis may not reflect the prevalence of brain metastases in the clinical population.	Yes, new information
4	There is a lack of justification for the use of different health state utilities for the tucatinib combination and comparators.	Yes, new analyses

[a] NB. The company stated 'Yes' for this issue.

2. Critique of the company's response to key issues for technical engagement

2.1 Issue 1 – Uncertain indirect comparison results due to study heterogeneity

2.1.1 Summary of the issue

The results of the NMA, which provides an indirect comparison of the tucatinib combination versus eribulin, capecitabine and vinorelbine monotherapies, are uncertain due to heterogeneity between the trials in certain prognostic factors and effect modifiers. The ERG used a random effects NMA model as this is more appropriate in the presence of heterogeneity than a fixed-effect model. In contrast, the company used the fixed-effect model in their original base case. (N.B. this NMA assumes proportional hazards in the included trials' effect estimates. We refer to this as the 'constant hazard NMA'. The company submission also included an NMA approach which does not require proportional hazards – the fractional polynomial based NMA – see below).

At technical engagement we invited the company to apply random effects in their base case in place of the fixed-effect model, and to update the constant hazards NMA with a corrected

confidence interval for the OS HR estimate in one of the included trials (N.B. the ERG had identified a numerical typographical error in the journal publication of the trial by Pivot et al. When we corrected this value in our analysis the incremental cost effectiveness ratio (ICER) for tucatinib increased).

2.1.2 Critique of the company's response

In their response to technical engagement the company has not adopted the ERG's recommended approach. Instead the company:

- Maintains a preference for the fixed-effect constant hazards NMA model to inform their base case cost-effectiveness analysis. The updated base case ICER for tucatinib versus eribulin (using the corrected HR from the Pivot et al trial) increases from £37,483 to £42,760 per QALY (tucatinib PAS price).
- Dismiss using the ERG-favoured constant hazards random effects model because of "methodological issues" (see below).
- Select the fractional polynomial NMA approach as "the next best choice of model for the analysis" (page 4).
- Present cost effectiveness estimates for tucatinib versus eribulin based on the fractional polynomial NMA. These ICERs are [redacted] than the company's original and updated base case estimates ([redacted] and [redacted] per QALY for fixed-effect and random effects fractional polynomial NMA models respectively; tucatinib PAS price) (see section 3 below for a tabulation of original and updated ICERs).

The ERG notes that these fractional polynomial NMA results were presented in the company's submission. The relative treatment effect estimates from the fractional polynomial NMA informed cost effectiveness scenario analyses (scenarios 4 and 5) in the submission. Apart from correcting the HR estimate from the Pivot et al study in the constant hazards NMA, the company have made no other changes to the NMA.

We reiterate our view, as expressed in the ERG report, that there is insufficient evidence to reject the proportional hazards assumption in the evidence network. Thus, we remain in favour of the constant hazards HR NMA to inform the base case over the fractional polynomial NMA. We also remain in favour of the random effects constant hazards NMA model, given the presence of heterogeneity across the studies.

We make the following comments on relevant aspects of the company's response:

The robustness of the fractional polynomial NMA survival estimates is not sufficiently investigated

- The company has provided cost-effectiveness estimates based on the best-fitting fractional polynomial NMA, without any alternative such models for comparison. The ERG expected (and indeed had requested) cost effectiveness scenarios based on a wide range of plausible fractional polynomial models. Our experience from previous fractional polynomial NMAs is that the shape of time-varying hazards curves may vary widely between different model functional forms, depending on the characteristics of the available evidence. It is important to demonstrate the full extent of variation in the NMA estimates and to investigate the impact on cost effectiveness. The absence of alternative estimates undermines the company's assertion that the fractional polynomial based NMA approach is the next best available evidence.

The stated limitations of the random effects constant hazard NMA do not negate the imperative to assume random effects in a heterogeneous evidence base

- The company cites convergence issues in the random effects model as one of the factors influencing their preference for the fractional polynomial NMA. The ERG considers these convergence issues as relatively minor, and that these can often be resolved with technical adjustments such as "thinning" of the Bayesian posterior sampling (allowing the model to be run with fewer samples and thus reducing the likelihood of autocorrelation between samples, in turn reducing the risk of Monte Carlo error). We posit that some of the company's convergence issues may be exacerbated by inclusion of peripheral studies in the network which are not relevant to this decision problem.
- The company notes "it is clear that the RE model predicts a higher degree of uncertainty that renders the results less consistent with head-to-head trial results" (page 5). Our view is that this is to be expected, as random effects predicts more uncertainty due to heterogeneity present in the network.

2.2 Issue 2 – Lack of justification for the company's survival extrapolation model

2.2.1 Summary of the issue

In their base case, the company estimate OS and PFS curves for the tucatinib combination and comparators by applying relative effects (constant HRs from the fixed-effect NMA) to survival curves for a reference treatment (lapatinib plus capecitabine), fitted to KM data in the fractional polynomial NMA. This entails two choices, both of which impact the cost-effectiveness results: how the absolute survival curves are modelled for a reference

treatment; and how relative differences in survival between treatments are estimated. The company confounds these two issues in their response.

2.2.2 Critique of the company's response

The company acknowledges that the modelled fractional polynomial survival curves are more favourable than the survival estimates observed in the HER2CLIMB trial. This is attributed to the pooling of heterogeneous evidence from the network of trials. However, they do not address this as a source of bias or correct for it in their revised base case analysis. Figure 1 and Figure 2 below demonstrate that modelled overall survival estimates from the company's base case and their fixed-effect fractional polynomial NMA scenario are substantially more favourable for the tucatinib combination and control arm than observed survival in the HER2CLIMB trial (as shown in the KM curves). This is also true for the constant HR random effects NMA model and the fractional polynomial random effects NMA model, and also for the PFS outcome.

By contrast, Figure 3 shows modelled OS from the ERG's preferred analysis alongside the HER2CLIMB trial KM. We used the within-trial method coded in the company's model: with survival curves for a reference treatment (trastuzumab + capecitabine) fitted to HER2CLIMB control arm data, then adjusted for the relative effects of other treatments with the constant HR NMA. We believe that this approach has several advantages over the company's base case or fractional polynomial scenarios:

- The OS and PFS extrapolations have better face validity than the company's base case or FP scenarios.
- The within-trial results are more generalisable to real world outcomes if, as the company argues, the population in the HER2CLIMB trial is more representative of patients seen in routine practice (including patients with brain metastases) than other trials in the evidence network.
- We have shown the impact of alternative survival functions for the within-trial estimates of OS and PFS in ERG scenario analysis (ERG report Tables 30 and 31). However, the company has not presented scenario analysis to test the impact of alternative fractional polynomial functional forms on the ICER. It is therefore unclear how much uncertainty is associated with this choice.

The within-trial approach does rely on the assumption of proportional hazards for OS and PFS, but so does the company's base case (which also uses a constant HR NMA). As

mentioned in the ERG report (sections 3.4.2.1, 4.2.6.4 and 4.2.6.5), and mentioned above, the ERG considers that proportional hazards assumption cannot necessarily be rejected.

In conclusion, the company's response does not address the issue raised by the ERG.

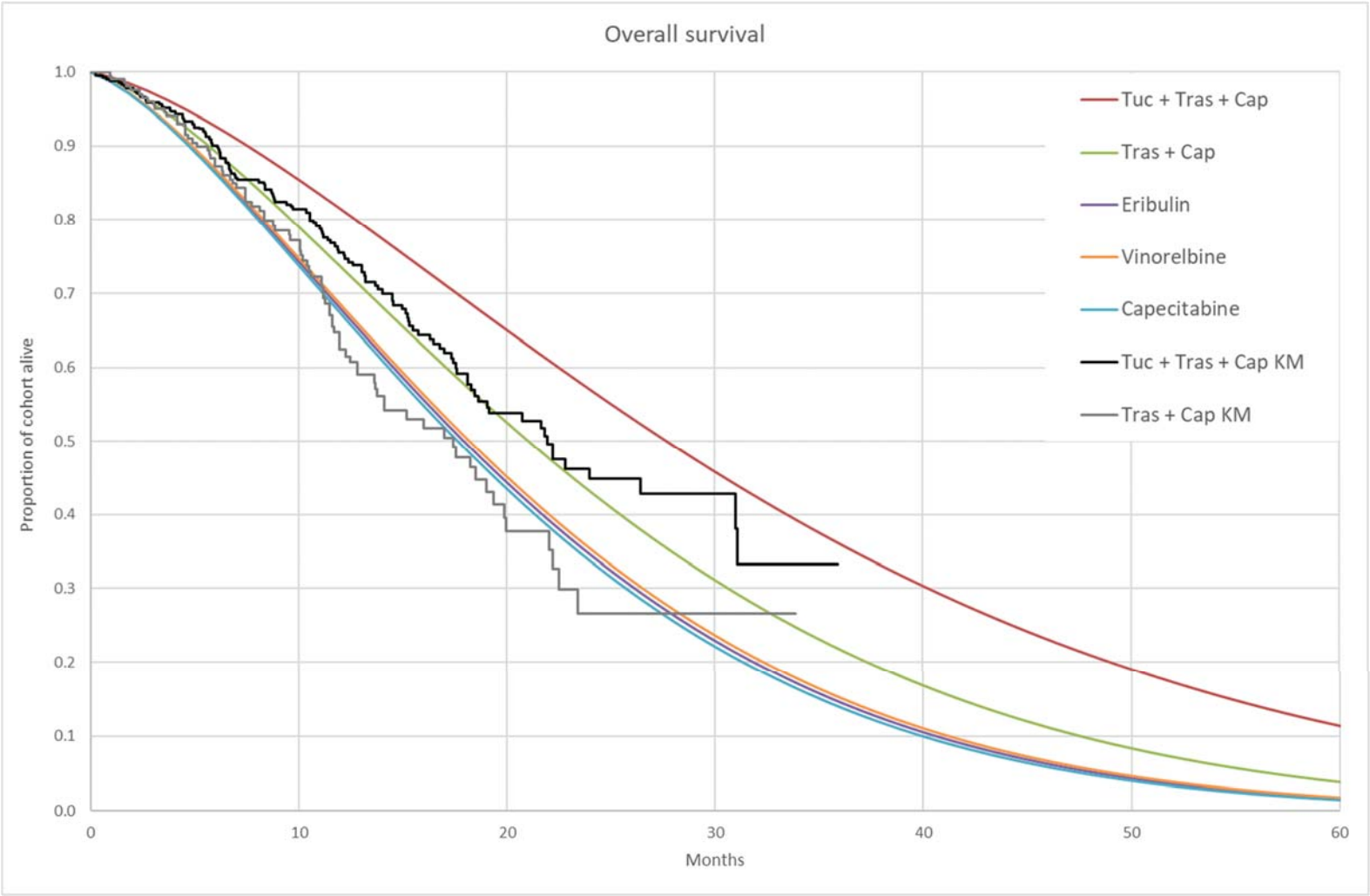

Figure 1 Modelled OS and HER2CLIMB KM: fractional polynomial curves for reference treatment (lapatinib + capecitabine) with relative effects from constant hazard ratio fixed-effect NMA (company base case)

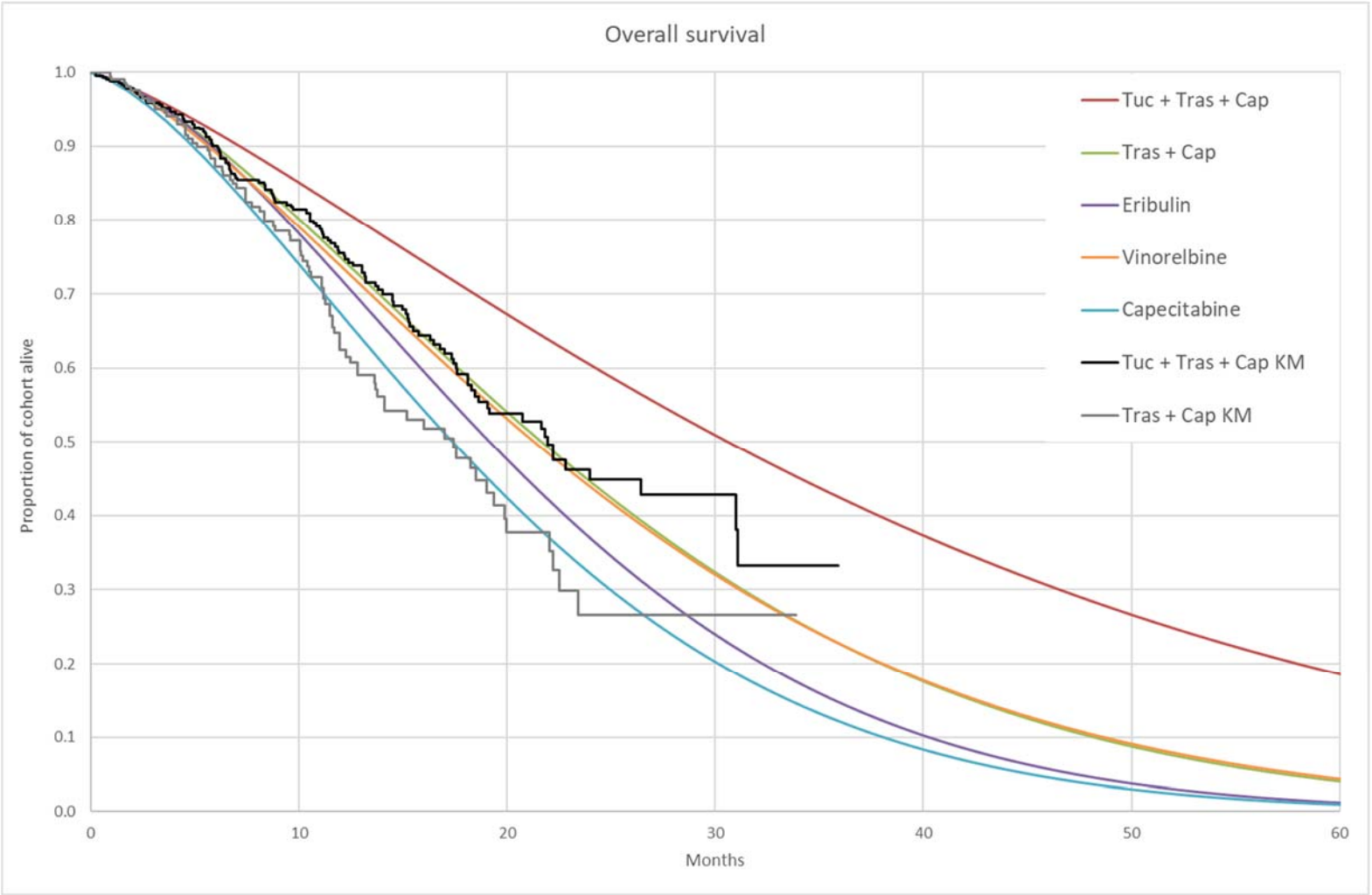

Figure 2 Modelled OS and HER2CLIMB KM: fractional polynomial curves for reference treatment with relative effects from the fractional polynomial NMA (company FP NMA fixed-effect scenario)

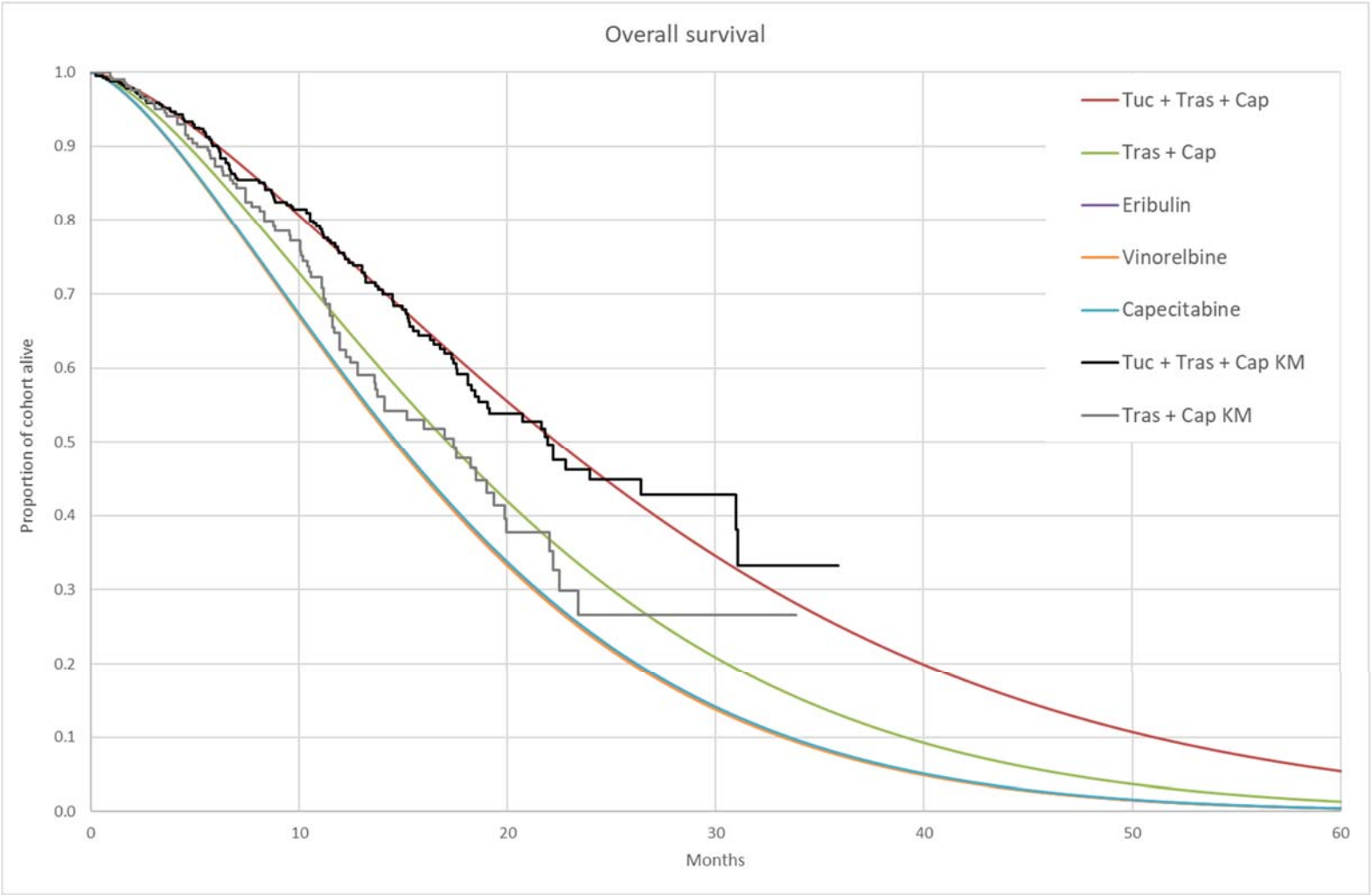

Figure 3 Modelled OS and HER2CLIMB KM: fitted curve for trial control arm (trastuzumab + capecitabine) with relative effects from constant hazard ratio fixed-effect NMA (ERG preferred analysis)

2.3 Issue 3 – Lack of subgroup analyses for patients with brain metastases

2.3.1 Summary of the issue

The NICE scope requested subgroup analysis for patients with brain metastases if the evidence allowed. Almost 50% of the participants in the HER2CLIMB trial had brain metastases at baseline, but this proportion was much lower across the comparator treatment trials. We acknowledge the company's argument that the lack of clinical effectiveness evidence for patients with brain metastases impedes an indirect comparison in this sub population. As an alternative, the ERG proposed an exploratory analysis with a modelled reference arm representative of the population in clinical practice.

2.3.2 Critique of the company's response

The company are of the opinion that the overall population from HER2CLIMB sufficiently represents the patient population seen in clinical practice, and therefore "No subgroup analyses are required, and no external data sources are required to provide an alternative baseline survival curve to which results of the NMA are applied".

We note the evidence cited by the company in support of this assertion and the clinical expert opinion provided, all of which suggests that in practice approximately 50% of third-line HER2+ metastatic breast cancer patients would develop brain metastases. Equally, we note the lower estimate of 31% reported in a recent meta-analysis of epidemiological studies (cited in the ERG report, section 2.2.1), and that this lower estimate matched the ERG's clinical expert's experience.

If the true proportion of patients with brain metastases is nearer to 50% then this adds support to the ERG's 'within-trial' approach to modelling survival rather than the company's fractional polynomial-based methods (Key issue 2). The within-trial approach yields modelled survival curves for the tucatinib combination and trastuzumab + capecitabine link to the indirect comparators that are a much better fit to the HER2CLIMB trial data, and hence are more reflective of the real-world clinical population than the averaged results across the network of evidence from the fractional polynomial NMA.

In conclusion, the modelled survival predictions are uncertain due to the occurrence of heterogeneity in the NMA, affecting the relative effect estimates applied to the survival curves. Further clinical opinion could help establish the degree to which HER2CLIMB trial participants are reflective of the typical patient population in clinical practice.

2.4 Issue 4 – Lack of justification for using different health state utilities for tucatinib combination and comparators.

2.4.1 Summary of the issue

We acknowledge the arguments and clinical opinion cited on the relationship between quality of life and treatment response. Clinical advice to the ERG was that adverse effects and quality of life would be broadly similar across these treatments.

It is difficult to quantify the magnitude of any differences in quality of life between treatments in the absence of comparative evidence. The differences in pre-progression utility estimates for the tucatinib combination and comparators may well relate to differences in the trial populations (HER2CLIMB versus Study 301) or valuation methods (crosswalk EQ-5D versus Crott and Briggs mapping), rather than to genuine differences in treatment-related quality of life.

There is uncertainty over the health state utilities from HER2CLIMB data, because of the methods of analysis. The company has not provided evidence a difference in utility between the study arms or a trend in utility over pre-progression treatment cycles. They have confirmed that they did not use imputation for missing EQ-5D data: assuming that such data was missing at random. This is potentially important given the high proportion of missing data at later assessments. It is good practice to use appropriate imputation methods for missing data, which was not available in this instance. We discussed this in section 4.2.9.1 of the ERG report.

With respect to post-progression utilities, the NICE guidelines recommend the use of the same utility values across treatment arms. This approach was adopted in NICE TA423 (Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens). Furthermore, the difference in the post-progression utility for the tucatinib combination in the company's revised base case compared to that for eribulin, capecitabine and vinorelbine (the value for tucatinib is much higher than that assumed for the comparators) is not based on comparative evidence. We still consider this implausible, and question why such a large difference should persist after progression and treatment discontinuation.

2.4.2 Critique of the company's response

In their response, the company present three alternative scenarios for utility. The first of these, assumes that after progression, the utility for the tucatinib combination tapers to the same post-progression utility as eribulin over one year. The rationale for this and why it should only apply to the tucatinib combination is not clear. However, the second and third scenarios, are reasonable alternatives, as they use best-available evidence for pre-progression utility for tucatinib (based on EQ-5D data from HER2CLIMB), accepted estimates from TA423 for pre-progression utility for comparators and the same post-progression utility for all treatments. We presented a similar scenario in Table 35 of the ERG report, with a post-progression utility of 0.588 (the mean of estimates from the TA423 company 0.679 and ERG 0.496). We consider this a plausible alternative scenario.

3. Updated cost-effectiveness results - ERG summary and critique

The ERG checked the revised base case and scenario results reported in the company's response to technical engagement. We compared the results against the original and updated versions of the model submitted by the company, as well the ERG version of the model used for additional scenario analyses. We revised the latter by pasting 6,000 samples of HR estimates from company's revised HR NMA analysis with the Pivot correction into the '*Bayesian NMA HR Models_PFS*' and '*Bayesian NMA HR Models_OS*' sheets. This slightly different results to the previous version of the ERG model, which used over-rides for the mean HR estimates (rounded to two decimal places) from the ERG's replication of the HR NMA random effects model with the Pivot et al correction.

3.1 Company's revised base case cost-effectiveness results

We compare results for the company's previous base case and their revised base case with the Pivot trial correction in Table 2 below. This shows results for all comparators, including capecitabine and vinorelbine as well as eribulin, produced from the ERG version of the model. There is an error in the cost and QALYs results for eribulin as presented in the company's response to technical engagement (they report the same cost and QALYs for the original and revised base case). The results in the table below are consistent with those from the company's revised model and the revised ERG version used of the model.

Table 2 Company's revised base case, deterministic

Treatment	Cost [a]	QALYs	ICERS (£ per QALY gained)	
			Pairwise	Incremental
Original company base case				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	£37,483	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]
Revised company base case post technical engagement				
Capecitabine	[redacted]	[redacted]	[redacted]	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	£42,760	[redacted]
Tucatinib combination	[redacted]	[redacted]	-	[redacted]

Source: Results produced by the ERG
[a] PAS discount for tucatinib and assumed discount for trastuzumab other drugs at list price

3.3 ERG preferred model assumptions

We have not changed our preferred assumptions. Table 3 below shows the cumulative effect of adding ERG assumptions to the company's revised base case. The results are a little different to those in the equivalent table in the ERG report (Table 37) because of the different method of adding the Pivot et al trial correction.

Table 3 Change from revised company base case to ERG analysis, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs	Change to pairwise ICERs
Revised company base case				
Capecitabine	[redacted]	[redacted]	[redacted]	
Vinorelbine	[redacted]	[redacted]	[redacted]	
Eribulin	[redacted]	[redacted]	£42,760	
Tucatinib	[redacted]	[redacted]	-	
+ Within-trial analysis (PFS and OS, with HR NMA fixed effect with Pivot correction)				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-	
+ Random effects NMA (HR NMA random effect with Pivot correction)				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-	
+ HER2CLIMB utilities ([redacted] pre-progression, [redacted] post-progression, all treatments)				

Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-	
+ Age-adjustment for utilities				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-	
+ ERG subsequent treatment scenario (50% tras, 20% cap/vin: [redacted] per person)				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-	
+ Include costs for drug wastage - ERG preferred analysis				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-	

The assumption of equal utilities for all treatments in the pre-progression ([redacted]) and post-progression ([redacted]) health states, based on HER2CLIMB EQ-5D data, causes a large increase in the pairwise ICERs for all comparators. The change to the within-trial method for extrapolating survival estimates also causes a large increase in the pairwise ICERs. The ERG scenario for use of subsequent treatments and the adjustment of utilities for age have a moderate impact. The use of random effects rather than fixed-effect for the HR constant hazards NMA has different impacts for different comparators, but the overall impact on the ICERs is limited. Including the company's drug wastage estimates (for trastuzumab) has very little impact.

3.4 Scenario analyses conducted on the ERG's preferred analysis

Table 4 shows the results of alternative scenarios applied to the ERG base case.

Table 4 ERG preferred analysis and scenarios, deterministic

Treatment	Cost [a]	QALYs	Pairwise ICERs
ERG preferred analysis			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-
OS stratified Weibull			
Capecitabine	[redacted]	[redacted]	[redacted]

Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-
OS Gompertz			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-
Fractional polynomial NMA fixed-effect			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-
Fractional polynomial NMA random effects			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-
Utilities pre-progression 0.706 tucatinib and eribulin, 701 other comparators; post-progression 0.588 for all treatments			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-
Utilities pre-progression 0.762 tucatinib, eribulin 706, other comparators 701; post-progression 0.588 for all treatments			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-
Treatment duration equal to PFS (all treatments)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-
Treatment duration restricted mean treatment exposure			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-
Subsequent treatment (trial-based)			
Capecitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]
Tucatinib	[redacted]	[redacted]	-