Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende tucatinib i kombination med trastuzumab og capecitabin til behandling af lokalt fremskreden inoperabel eller metastatisk HER2+ brystkræft efter progression på to HER2-rettede behandlinger

Vers. 2.0

Bilagsoversigt

1. Ansøgers endelige ansøgning
2. Forhandlingsnotat fra Amgros vedr. tucatinib – vers. 1.1 – 23.03.2022
3. Ansøgers notat til Rådet – 08.03.2022
4. Forhandlingsnotat fra Amgros vedr. tucatinib – vers. 2.0 – 25.10.2023

Application for the assessment of tucatinib in combination with trastuzumab and capecitabine for the treatment of patients with advanced unresectable or metastatic HER2-positive breast cancer after at least two prior anti-HER2-based regimens

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1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	Tucatinib
Generic name	TUKYSA®
Marketing authorization holder in Denmark	Seagen B.V. Evert van de Beekstraat 1, -104 1118CL Schiphol The Netherlands
ATC code	L01EH03
Pharmacotherapeutic group	Tyrosine kinase inhibitor (TKI)
Active substance(s)	Tucatinib
Pharmaceutical form(s)	Tablet
Mechanism of action	Tucatinib is an oral TKI that is highly selective for the tyrosine kinase domain of the HER2 receptor with minimal inhibition of EGFR.
Dosage regimen	300 mg twice daily
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Tucatinib in combination with trastuzumab and capecitabine for the treatment of patients with advanced unresectable or metastatic HER2-positive breast cancer after at least two prior anti-HER2 treatment regimens
Other approved therapeutic indications	-
Will dispensing be restricted to hospitals?	Yes (BEGR)
Combination therapy and/or co-medication	Tucatinib in combination with capecitabine and trastuzumab
Packaging – types, sizes/number of units, and concentrations	Oral, 50 and 150 mg film-coated tablets.

Overview of the pharmaceutical	
Orphan drug designation	No

2. Abbreviations

Abbreviation / term	Definition
BICR	Blinded independent central review
BM	Brain metastases
CBR	Clinical benefit rate
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
cORR	Confirmed objective response rate
CR	Complete response
CT	Computed tomography
DMC	Danish Medicine's council
DOR	Duration of response
ECOG	Eastern cooperative oncology group
ED	Emergency department
GP	General practitioner
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Health resource use
HSUV	Health state utility values
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
LOS	Length of stay
LYG	Life years gained
MBC	Metastatic breast cancer
MRI	Magnetic Resonance Imaging
ORR	Overall response rate
OS	Overall survival
OWSA	One way sensitivity analysis
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PFSbrain	Progression free survival in patients with brain metastases
PR	Partial response
QALY	Quality-adjusted life years
QoL	Quality of life
RECIST	Response evaluation criteria in Solid Tumors
T-DM1	Trastuzumab-emtasine conjugate
TRASCAP	Trastuzumab capecitabine
TUC	Tucatinib
VAS	Visual analogue scale
VAT	Value added tax

3. Tables and Figures

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4. Summary

4.1 Breast cancer

Human epidermal growth factor receptor 2 positive (HER+) metastatic breast cancer (MBC) is a biologically aggressive form of breast cancer (BC) that is likely to progress, remains difficult to treat, and is associated with a poor prognosis. In 2019, 5,105 women and 54 men were diagnosed with breast cancer in Denmark. There is no way to access the total incidence and prevalence of *metastatic* breast cancer (MBC) patients in Denmark as the nationwide cancer register does not capture recurrence of breast cancer and most patients with MBC have a recurrence with metastases after an earlier local diagnosis. Yearly, approximately 200 patients suffer from HER2-positive, unresectable locally advanced or metastatic breast cancer who failed at least one treatment. Approximately 56% of incident patients with MBC reach third-line systemic treatment.

In contrast to patients diagnosed with early breast cancer where cure is possible, MBC, is considered incurable and treatment is palliative. Treatment goals include reducing metastatic burden, slowing tumour growth, and delaying metastatic progression. However, as patients are living longer with metastatic disease, emphasis on maintaining health-related quality of life is increasingly important.

4.2 Tucatinib

Tucatinib (TUKYSA®) is a new therapy for the treatment of HER2-positive (HER+) metastatic breast cancer (MBC). It is indicated in combination with trastuzumab and capecitabine (tucatinib combination) 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.

Tucatinib is an orally bioavailable, reversible, small molecule tyrosine kinase inhibitor (TKI) that is highly specific to HER2. In vitro, tucatinib inhibits phosphorylation of the tyrosine kinase domain of the HER2 receptor, resulting in inhibition of downstream cell signaling and cell proliferation, and induces death in HER2-driven tumor cells.

Tucatinib received a positive opinion by the EMA CHMP on the 10th of December 2020 and received market authorization in the European Union on the 11th of February 2021.

The recommended dose is 300 mg tucatinib (two 150 mg tablets) taken twice daily continuously in combination with trastuzumab (6 mg per kg of body weight intravenously once every 21 days, with an initial loading dose of 8 mg per kg) and capecitabine (1000 mg per m^2 of body-surface area orally twice daily on days 1 to 14 of each 21-day cycle).

4.3 Clinical documentation for tucatinib

The efficacy of tucatinib was demonstrated in the clinical trial HER2CLIMB, the first and only randomized, double-blind, placebo-controlled, active-comparator global trial of HER2-positive MBC to include patients both with and without brain metastases. The trial included 612 patients with HER2-positive MBC who were previously treated with trastuzumab, pertuzumab, and trastuzumab-emtasine (T-DM1). The primary endpoint was progression-free survival, key secondary endpoints were overall survival, confirmed objective response rate and duration of response. The results demonstrated a reduced risk of progression or death compared to placebo, both in patients with and without brain metastasis. 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). 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).

Further, tucatinib demonstrated a manageable safety profile with low rates of discontinuation due to adverse events. The addition of tucatinib to trastuzumab and capecitabine did not lead to any clinical meaningful differences in health-related quality of life compared to placebo in combination with tucatinib and trastuzumab as measured by the EQ-5D-5L instrument.

4.4 Health economic analysis

The most relevant comparator to the tucatinib combination in Denmark is trastuzumab in combination with capecitabine (TRASCAP). The base case analysis of the cost-utility analysis reflects this, comparing tucatinib in combination with trastuzumab and capecitabine with trastuzumab and capecitabine in a Danish setting from an extended health service perspective. The analysis was performed using a life-time time horizon and costs and benefits were discounted with 3.5%.

The cost-utility analysis predicted that the tucatinib combination was more effective and more costly compared to the combination of trastuzumab and capecitabine with an incremental cost-effectiveness ratio (ICER) of DKK 887,621.

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

In Europe and North America, an estimated one in eight women will develop breast cancer during their lifetime [1]. Breast cancer is responsible for 15% of all cancer deaths in women and is the leading cause of cancer-related mortality in women in 103 of 185 countries [2]. In 2019, 5,105 women and 54 men were diagnosed with breast cancer in Denmark. The corresponding age-standardized incidence rate was 148.9 per 100,000 inhabitants for women and 1.6 for men [3]. Among women, the most frequent age groups at diagnosis were between 45 and 59 years (28%) and between 60 and 74 years (37%). The estimated prevalence was 72,193 of which 78% were aged 60 years (43% 60 – 74 years) or older (35% 75+ years) [3].

5.1.1 Metastatic breast cancer

In MBC, cancer cells break away from where they first formed (primary cancer), travel through the blood or lymph system, and form new tumours (metastatic tumours) in other parts of the body. The metastatic cancer cells have features similar to the primary tumour, and are unlike the cells in the place where the metastatic tumor is found [4]. MBC is either identified at first BC diagnosis (*de novo*) or recurs in those originally diagnosed with early BC. Approximately 20-25% of patients experience a relapse after diagnosis with early BC [5] and approximately 75% of MBC is due to early BC that has progressed to distant disease [6-9].

Clinical outcomes of patients with MBC are dependent on tumour biology, extent, and localization of metastasis [10]. For patients with BC, common sites of metastasis include the bone, brain, liver, and lungs [11, 12]. Symptoms of MBC can vary depending on where the cancer has spread [4, 13]:

- Bone metastases: severe, progressive pain; fractures
- Brain metastases: persistent, severe headaches or pressure to the head; visual disturbances; seizures; vomiting/nausea; and cognitive, functional, and behavioral changes
- Liver metastases: jaundice; itchy skin or rash; high liver enzymes; abdominal pain; loss of appetite; nausea/vomiting
- Lung metastases: chronic cough; inability to take a full breath; chest pain; nonspecific symptoms including weight loss, fatigue, poor appetite

In contrast to the early BC setting in which patients can be cured, treatment in the metastatic setting focuses on palliation [14], with goals of reducing metastatic burden, slowing tumour growth, and delaying metastatic progression. However, as patients are living longer with metastatic disease, emphasis on maintaining health related quality of life (HRQoL) is increasingly important. The median survival for these patients is approximately two years, but longer in the younger patient population where 15-25% of the patients still live after five years and some even live 10 years or more with good quality of life .

5.1.2 Human epidermal growth factor receptor 2 positive breast cancer

Human epidermal growth factor receptor 2 (HER2) status, alongside with the hormone receptor status, of the breast cancer is informative regarding the pathology of the disease, prognosis and available treatment alternatives. HER2 is a protein that normally is expressed at low levels in healthy breast tissue. An overproduction of HER2 leads to increased division and growth of cells. Approximately 15% – 20% of breast cancer tumors show an overexpression of HER2 [15].

HER2-positive breast cancer is often characterized by an aggressive tumor with rapid growth associated with higher risk of relapse and death in absence of adequate treatment. Patients with HER2-positive breast cancer are also more prone to develop brain metastasis (often multiple) compared to other sub-types of breast cancer. Distant metastasis in patients with HER2-positive breast cancer is rather evenly found in skeleton, lung, liver, soft tissue and the brain [16].

Systemic therapies, such as monoclonal antibodies, are effective in treating early breast cancer, however, they have limited activity in the brain. This may have led to a change in the pattern of metastatic occurrence in patients with HER2-positive MBC [17, 18] as the brain is increasingly becoming the first site of metastasis [17, 19], and patients are presenting with a higher number of brain metastases at diagnosis [20]. HER2-positive MBC is frequently associated with metastases to the brain [21, 22], and up to 50% of patients will develop brain metastases throughout the course of HER2-positive MBC [23-26]. In addition, among MBC patients with brain metastases, up to 40% are asymptomatic and are diagnosed based only on imaging exams [27-29]. Because routine brain imaging is not recommended for these patients [30, 31], brain metastases often remain undiagnosed, and thus the prevalence of brain metastases in patients with HER2-positive MBC is likely underestimated in the literature.

Patients who develop brain metastases have an even greater burden of disease because they have a worse prognosis, and the symptomatic patients also suffer from neurological symptoms leading to further deteriorations in HRQoL, and incur higher treatment costs [26, 32-34]. Despite treatment, survival after the development of brain metastases in patients with HER2-positive MBC is poor, with a 1-year survival of 50% and a 3-year survival of only 16% [35], and death most frequently (61% to 70%) due to progression of brain metastases [36, 37]. Development of brain metastases is a devastating diagnosis and patients experience lower HRQoL compared with patients with metastases at other sites due to pain, potentially life-threatening seizures, activity limitations, and cognitive decline associated with both the disease and its treatment [26, 38, 39].

5.1.3 Prognosis

The 5-year survival rate for BC is relatively high, however, it decreases dramatically by stage at diagnosis [40, 41]. Despite treatment advances, 5-year survival among patients with HER2-positive MBC is less than 50%.

Among HER2-positive patients with *de novo* MBC diagnosed between 1998 and 2009, treatment with trastuzumab (targeted therapy) led to improvements in 1- and 5-year relative survival[1] compared with those who did not receive trastuzumab [42]. However, the survival benefit observed with HER2-directed therapy decreases over time and 5-year overall survival (OS) is low for treated and untreated patients.

5.1.4 Incidence

According to a Danish clinical expert approximately 200 patients are diagnosed with HER2-positive MBC annually in Denmark of which 55% reach third-line systemic treatment [43]. The estimated incidence for HER2-positive MBC is given in Table 1. The estimated patient population eligible for treatment with the tucatinib combination is given in Table 2. Only the incidence is presented as only incidence patients will be treated.

Table 1. Incidence in the past 5 years

Year	2017	2018	2019	2020	2021
Incidence in Denmark	200	200	200	200	200

Table 2. Estimated number of patients eligible for treatment

Year	2021	2022	2023	2024	2025
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	111	111	111	111	111

Source: [43]

5.1.5 Patient populations relevant for this application

The relevant patient population for the health economic analysis of tucatinib are patients with advanced unresectable or metastatic HER2-positive breast cancer who have received two prior anti-HER2-based regimens. The median age at breast cancer diagnosis was 62 years in Denmark during 2010 – 2012 [44]. However, it is believed that HER2-positive breast cancer is more common among younger patients [45, 46]. This assumption was also made in the assessment of T-DM1 (Kadcyla®). The DMC accepted a starting age of 49 years for patients with advanced HER2-positive MBC [47]. According to clinical expert opinion the mean age of patients with HER2-positive breast cancer at diagnosis (first line treatment) in Denmark is 58 years. Patients in HER2CLIMB had a mean age of 54 years, which is the implicit age used in the health economic analysis [48].

For the estimation of treatment doses in the health economic analysis, the mean body surface and weight from the pivotal trial HER2CLIMB were assumed to be representative for Denmark. This assumption was validated by a Danish clinical expert [43]. The mean body surface was assumed to be 1.8 m^2 and the body weight was assumed to be 69.5 kg.

[1] Relative survival is the ratio between the observed survival rate in the patient group and the expected survival rate of a comparable group from the general population of the same age and sex, free of the disease of interest.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Danish guidelines recommend the combination of trastuzumab, pertuzumab and vinorelbine as first-line treatment for HER2-positive breast cancer [49]. If the patient does not tolerate chemotherapy, trastuzumab as monotherapy is recommended. In case of disease progression after the first-line of treatment, T-DM1 is recommended as second-line treatment. If patients have not received adjuvant chemotherapy they may be eligible for the combination of docetaxel with trastuzumab [49].

Recommended third- or consecutive treatment lines may include any of the following options: docetaxel with trastuzumab, capecitabine with trastuzumab or lapatinib, paclitaxel/gemcitabine/eribulin/cyclophosphamide, methotrexate and 5-flourouracil (CMF)/lapatinib with trastuzumab, T-DM1, or epirubicin [49].

. In case of brain metastases, treatment with capecitabine combined with trastuzumab or lapatinib is recommended.

Table 3. Overview of treatment guidelines for HER2-positive breast cancer in Denmark

	Prior adjuvant chemo therapy	No prior adjuvant chemo therapy
First line treatment	Vinorelbine + trastuzumab + pertuzumab	
Second line treatment	T-DM1	T-DM1 (or docetaxel + trastuzumab)
Following second line treatment	Docetaxel + trastuzumab	
	Capecitabine + trastuzumab (or lapatinib)	
	Paclitaxel + trastuzumab	
	Gemcitabin + trastuzumab	
	CMF + trastuzumab	
	Eribulin + trastuzumab	
	Epirubicin	
	Trastuzumab + lapatinib	
	T-DM1	

5.2.2 Choice of comparator(s)

The Danish treatment guidelines do not specify a specific preferred treatment after the use of second-line T-DM1 [50]. Considering the population of HER2CLIMB, where 100% had prior treatment with T-DM1 in the metastatic setting, it is believed that the tucatinib combination will replace treatment with TRASCAP alone for patients that have failed second-line treatment with T-DM1. This assumption was validated by a Danish clinical expert [43].

5.2.3 Description of the comparator(s)

The comparator is the combination of trastuzumab (L01XC03) and capecitabine (L01XC03). Capecitabine is an oral (tablet) chemotherapeutic agent, that is enzymatically converted to fluorouracil (antimetabolite) in the tumor, where it inhibits DNA synthesis and slows growth of tumor tissue. Trastuzumab is a monoclonal antibody that interferes with the HER2/neu receptor administrated as an infusion. Treatment should continue until disease progression or unacceptable toxicity. Capecitabine is given 1000 mg/m^2 orally twice daily on days

1-14 of each 21-day cycle and trastuzumab, 8 mg/kg intravenously (IV) on day 1 of cycle 1, followed by 6 mg/kg on day 1 of each 21-day cycle. Cardiac assessments should be performed every three months (trastuzumab).

See Table 4 and Table 5 for available packaging.

Table 4. Packaging – Trastuzumab

Brand name	Form	Strength (mg)	Pack size	Company
Herceptin	IV	600	1	Roche
Herceptin	IV	150	1	Roche
Ontruzant	IV	420	1	MSD
Trazimera	IV	150	1	Pfizer
Trazimera	IV	420	1	Pfizer

Source: [51]

Table 5. Packaging - Capecitabine

Brand name	Form	Strength (mg)	Pack size	Company
Capecitabine Stada	tablet	150	60	PharmaCoDane
Capecitabine Stada	tablet	500	120	PharmaCoDane
Capecitabine Accord	tablet	150	60	Accord
Capecitabine Accord	tablet	500	120	Accord
Capecitabine Orion	tablet	500	120	Orion Pharma

Source: [51]

5.3 The intervention

Tucatinib 300 mg taken orally twice daily together with 1000 mg/m² capecitabine orally twice daily on days 1 to 14 of each 21-day cycle and 8 mg/kg trastuzumab intravenously on the first day of the treatment cycle followed by 6 mg/kg of each 21-day cycle. For patients with severe hepatic impairment, the recommended dosage is 200mg orally twice daily. The treatment is administered until disease progression or intolerable toxicity. Cardiac assessments should be performed every three months (trastuzumab).

With the introduction of tucatinib in Denmark the clinical practice is assumed to change. For second-line treatment, the recommended first-choice is trastuzumab-emtansine conjugate (T-DM1). Alternative and later line treatments are trastuzumab in combination with chemotherapies (not previously used), and trastuzumab in combination with lapatinib. A specific preferred third-line treatment is not given in the Danish guidelines. Possible treatments in third line are alternative second-line treatments (trastuzumab or lapatinib in combination with oral capecitabine, or other chemotherapies). Based on the indication and the population in the pivotal trial HER2CLIMB [52], Danish clinical expertise believes that tucatinib would most likely be placed as preferred third-line treatment following the treatment with TDM-1 [43].

6. Literature search and identification and selection of relevant studies

The analysis is based on a head-to-head comparison. Tucatinib is a novel treatment and no other studies are expected to provide valuable information regarding effect and safety comparing tucatinib in combination with TRASCAP and TRASCAP only in the relevant patient population.

HER2CLIMB was identified as the only relevant study for this assessment and no systematic literature review is necessary in order to identify other trials with tucatinib.

6.1 For completeness, and in order to identify utilities and potential studies that could be used as external validation of projected outcomes for the health economic analysis, a literature review was conducted and included in Appendix A.List of relevant studies

The most relevant study for the health technology assessment is the pivotal trial HER2CLIMB (Table 6) [52]. For more information regarding the pivotal trial see section 7. For more detailed information see Appendix B Main characteristics of included studies.

Table 6. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Murthy, R. K., et al. (2020). "Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer." N Engl J Med 382(7): 597-609.	HER2CLIMB	NCT02614794	Start date: January 28, 2016 Primary completion date: September 4, 2019 Estimated study completion date: May 31, 2022

7. Efficacy and safety

7.1 Efficacy and safety of tucatinib in combination with capecitabine and trastuzumab compared to capecitabine combined with trastuzumab for patients with advanced unresectable or metastatic HER2-positive breast cancer after at least two prior anti-HER2-based regimens

7.1.1 Relevant studies

For the health economic assessment of tucatinib in combination with capecitabine and trastuzumab the pivotal trial (marketing authorization study), HER2CLIMB, represents the most relevant study.

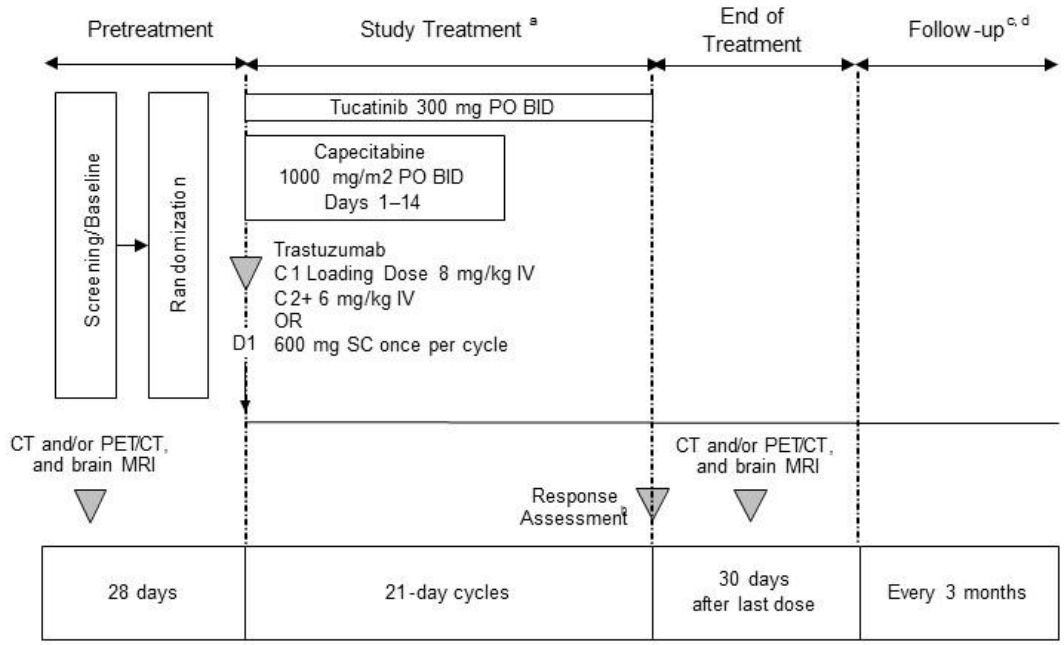
The primary endpoint was PFS (defined as time from randomization to documented disease progression, as assessed by blinded independent central review (BICR), or death from any cause [whichever occurred first]) in the first 480 patients randomized (i.e., primary endpoint population). Secondary (alpha-controlled) endpoints in the total population included OS (intent-to-treat [ITT]-OS), defined as time from randomization to death from any cause; PFS in patients with brain metastases (PFSbrain metastases); confirmed objective response rate (cORR), defined as the proportion of patients with measurable disease at baseline who had confirmed complete response (CR) or partial response (PR) as assessed by BICR; and safety. Exploratory analyses by investigator assessment were performed to evaluate the intracranial efficacy of the tucatinib combination in patients with brain metastases as an overall subpopulation as well as by the status of their brain lesions (stable or active).

Subgroup analyses of progression-free survival was done. Subgroups were prespecified according to age (≥ 65 yr/ <65 yr), race (white/nonwhite), hormone-receptor status (positive/negative for ER, PR or both), baseline

brain metastasis (yes/no), Eastern Cooperative Oncology Group (ECOG) performance status score (0/1), and geographic region (North America/Rest of the world). The results for the subgroup analysis were consistent with the results for the ITT population. Table 56 shows an overview of HER2CLIMB.

Patients were randomized 2:1 to receive either tucatinib or placebo in combination with trastuzumab and capecitabine. Figure 1 shows the study design for HER2CLIMB. Patients were stratified by known history of treated or untreated brain metastases[2] (yes or no), ECOG performance status (0 or 1), and geographic region (US and Canada or rest of world). Contrast-enhanced spiral computed tomography (CT), positron emission tomography (PET)/CT, and/or contrast-enhanced magnetic 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.

Figure 1. Schematic of Study Design for HER2CLIMB



BID, twice daily; CNS, central nervous system; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; PET, positron emission tomography; PD, progressive disease; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors; 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: [53]

The patient characteristics from the trial are presented in Table 57. In the comparison of the tucatinib combination with the placebo combination, possible effect modifiers and prognostic factors, e.g., age, stage at diagnosis, HR-status, presence of brain metastases, and locale of other metastases were balanced between the

[2] In the literature, the terminology central nervous system (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, randomized, controlled trial of this size has included patients with active brain metastases.

two arms. An overview of patient characteristics at baseline is presented in: Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

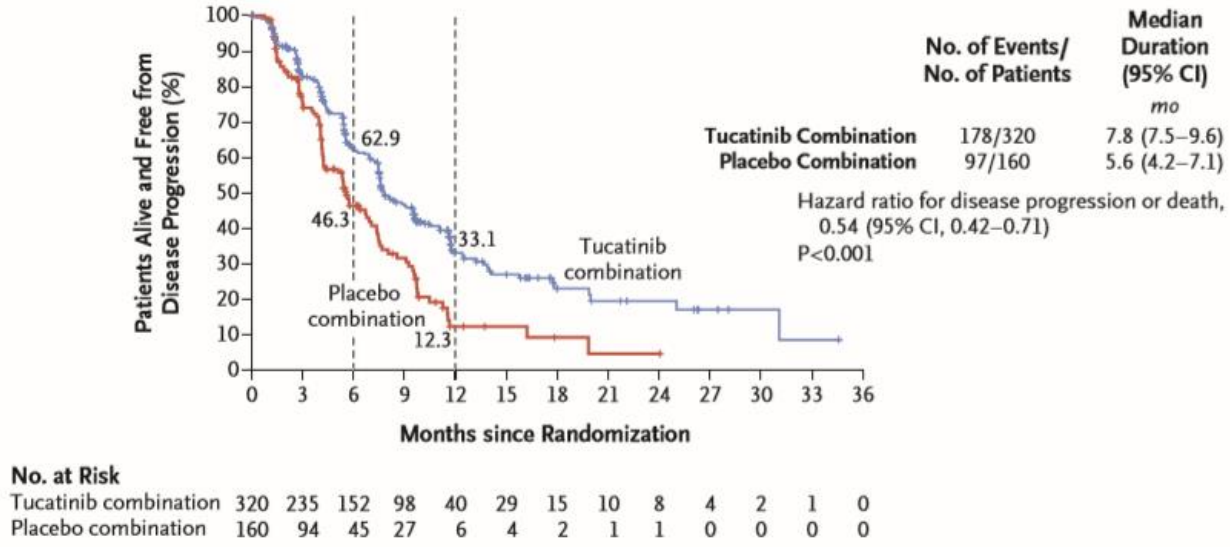
The detailed results of HER2CLIMB is presented below.

7.1.2 Efficacy and safety – HER2CLIMB

7.1.2.1.1 Progression-free survival

As of the September 4, 2019 data cut-off date, 275 of the first 480 randomized 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 2). 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 [52].

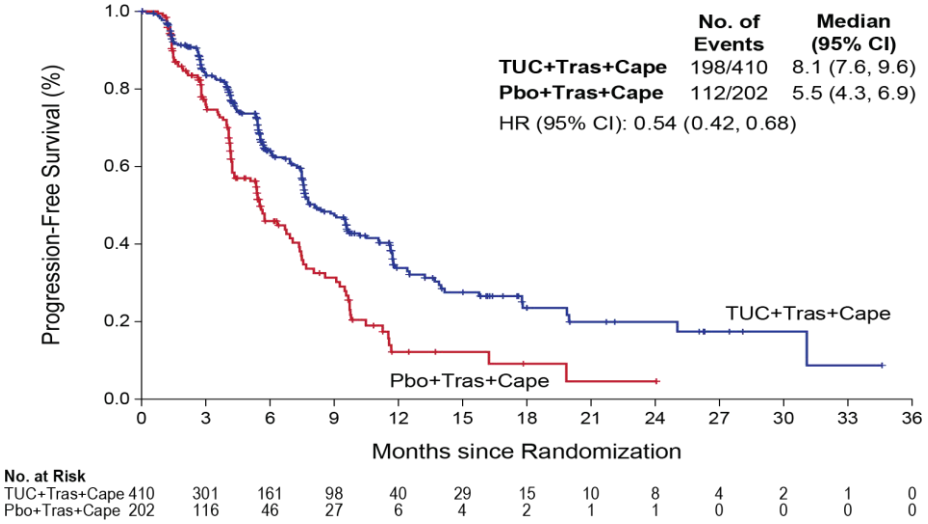
Figure 2. Kaplan-Meier Estimate of Progression-Free Survival per BICR (Primary Endpoint Population)



BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; No, number
Source: [52]

In the primary endpoint population, results of the PFS by investigator analysis were consistent with the primary efficacy endpoint (PFS by 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] (see Figure 3).

Figure 3. Kaplan-Meier Estimate of Progression-Free Survival by BICR (Total Study Population; ITT-OS)



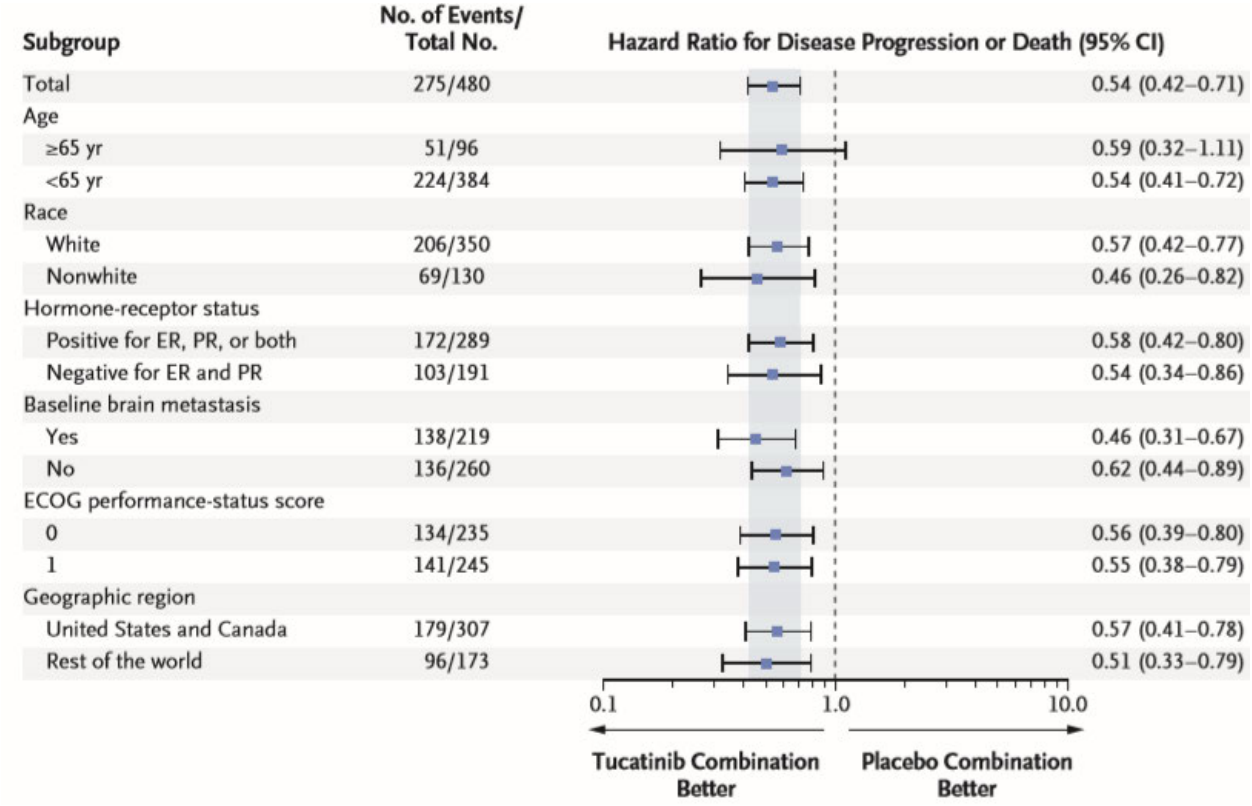
BICR, blinded independent central review; Cape, capecitabine; CI, confidence interval; HR, hazard ratio; ITT, intent to treat; No, number; OS, overall survival; Pbo, placebo; Tras, trastuzumab; TUC, tucatinib

Source: [54]

7.1.2.1.2 Progression-Free Survival Key Subgroup Analyses

A forest plot of the primary analysis of PFS by selected baseline characteristics and prespecified subgroups is presented in Figure 4. The results of these analyses were consistent with the overall study result in the primary endpoint population.

Figure 4. Progression-Free Survival per BICR by Subgroups (Primary Endpoint Population)



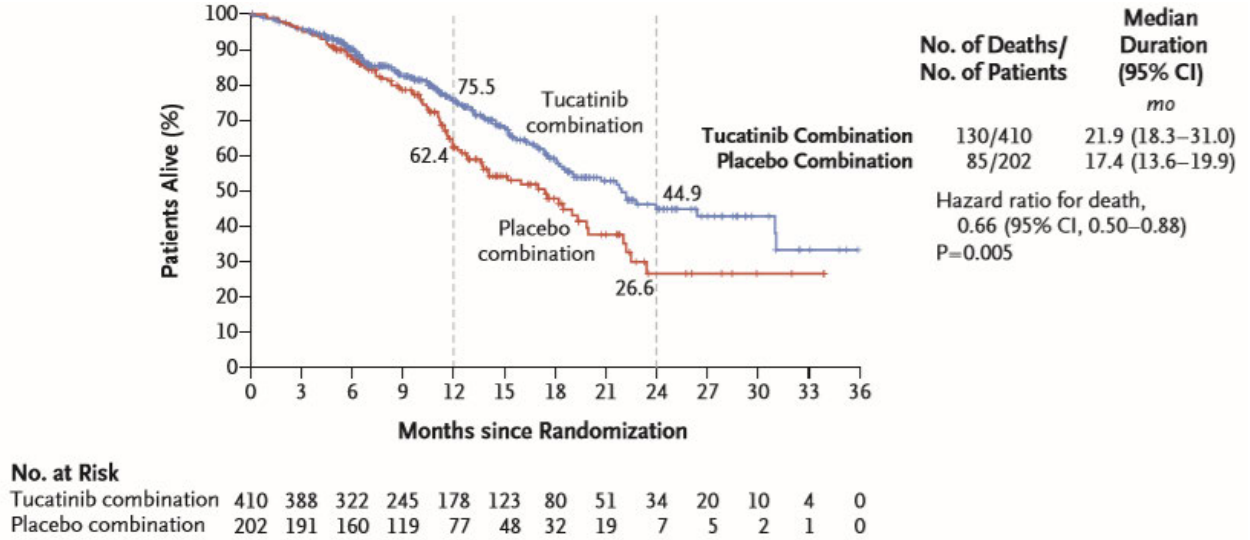
BICR, blinded independent central review; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; No, number; PR, progesterone receptor; yr, year

Source: [52]

7.1.2.1.3 Overall survival

In the ITT-OS population, 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) (see 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.

Figure 5. Kaplan-Meier Estimate of Overall Survival per BICR (Total Study Population; ITT-OS)

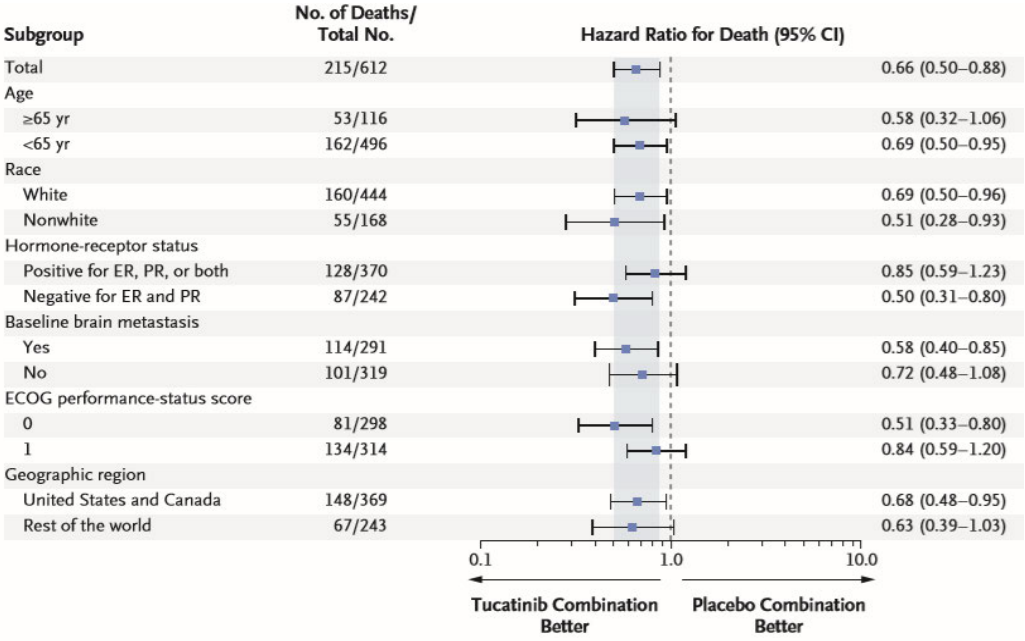


BICR, blinded independent central review; CI, confidence interval; ITT, intent to treat; mo, months; No, number; OS, overall survival
Source: [52]

7.1.2.1.4 Overall survival key subgroup analyses

A forest plot of OS by selected baseline characteristics and subgroups is presented in Figure 6. The analysis of OS by selected prespecified subgroups (age ≥65 or <65 years, race, hormone receptor status, baseline brain metastases, ECOG status and geographic region) show results that were consistent with the overall total study population (ITT-OS).

Figure 6. Overall Survival per BICR by Subgroups (ITT-OS Population)



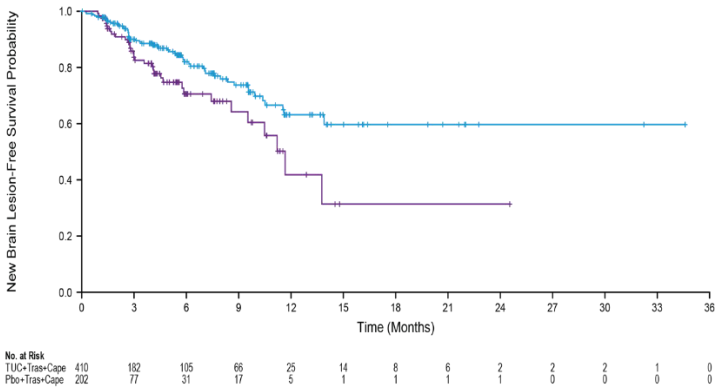
BICR, blinded independent central review; CI, confidence interval; ER, estrogen receptor; ECOG, Eastern Cooperative Oncology Group; ITT, intent to treat; OS, overall survival; PR, progesterone receptor; yr, year

Source: [52]

7.1.2.1.5 Time to new brain lesions (or progression of a previous lesion) or death (post-hoc analysis)

In a post-hoc analysis the time to new brain lesions (or the progression of an existing brain lesion) or death were explored in the ITT-OS population of HER2CLIMB [55, 56]. For patients without brain metastases at baseline this was the time to a first lesion, while for patients with brain metastases this represented a progression of a lesion or the development of new lesion. The tucatinib combination was found to be associated with a 48% reduction in the risk of progression in the brain during the study time (HR=0.52, 95% CI [0.33, 0.82], see Figure 7). The median new brain lesion free survival for the tucatinib combination arm was not reached (NR, 95% CI [13.9, -]) and estimated to 11.7 months for the placebo combination (95% CI [9.5, -]).

Figure 7. Time to new brain lesion-free survival: time from randomization to new, or a progression of a lesion in the brain or death by investigator assessment



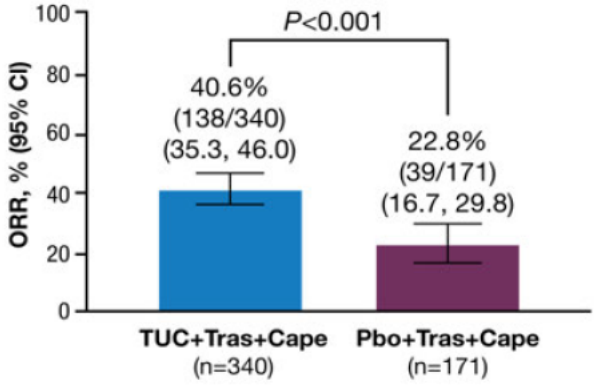
Source: [55, 56]

Patients that progress due to brain metastases are assumed to have different resource use and quality of life compared to patients that progress due to other reasons. This assumption was based on discussion with a Danish clinical expert [43]. The Kaplan-Meier estimate was directly used in the cost-effectiveness analysis to identify patients that progress due to a new, or a progression of an existing lesion in the brain.

7.1.2.1.6 Objective Response Rate

In the total study population, almost twice as many patients responded to the tucatinib combination compared to the placebo combination, as measured by confirmed objective response rate (ORR) (see Figure 8). Table 7 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 PR and fewer had progressive disease compared with the placebo-combination group. Table 8 shows the best overall response achieved among 511 patients with measurable disease at baseline by investigator assessment. Both assessments, by BICR and by investigator analysis, were consistent.

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: [52]

Table 7. Confirmed objective response per BICR in patients with measurable disease (total study population; ITT-OS)

	Tucatinib Combination (N=340)	Placebo Combination (N=171)	Relative risk	Confidence Interval (95%) Lower	Upper
Objective response, n (%)	138 (40.6)	39 (22.8)	1.78	1.31	2.41
95% CI[c]	35.3, 46.0	16.7, 29.8			
Stratified CMH p-value[d]		<0.001			
Best confirmed overall response [a], n (%)					
Complete response	3 (0.9)	2 (1.2)	0.75	0.13	4.47
Partial response	135 (39.7)	37 (21.6)	1.84	1.34	2.51
Stable disease	155 (45.6)	100 (58.5)	0.78	0.66	0.93
Progressive disease	27 (7.9)	24 (14.0)	0.57	0.34	0.95
Not evaluable	0	1 (0.6)			
Not available[b]	20 (5.9)	7 (4.1)	1.44	0.62	3.33

BICR, blinded independent central review; BM, brain metastases; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ECOG, Eastern Cooperative Oncology Group; ITT, intent to treat; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; US, United States

[a] Confirmed best overall response assessed per RECIST 1.1.

[b] Patients with no post-baseline response assessment.

[c] Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934).

[d] 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 randomization.

Source: [54]

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

	Tucatinib Combination (N=357)	Placebo-Combination (N=173)	Relative risk	Confidence Interval (95%)	
				Lower	Upper
Objective response, n (%)	146 (40.9)	37 (21.4)	1.91	1.40	2.61
95% CI[a]	(35.8, 46.2)	(15.5, 28.3)			
Stratified CMH p-value[b]	0.00001				
Best confirmed overall response[c], n (%)					
Complete response	8 (2.2)	2 (1.2)	1.94	0.42	9.03
Partial response	138 (38.7)	35 (20.2)	1.91	1.38	2.64
Stable disease	151 (42.3)	96 (55.5)	0.76	0.64	0.91
Progressive disease	39 (10.9)	33 (19.1)	0.57	0.37	0.88
Not evaluable	0	1 (0.6)			
Not available[d]	21 (5.9)	6 (3.5)	1.70	0.70	4.13

BM, brain metastases; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ECOG, Eastern Cooperative Oncology Group; ITT, intent to treat; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; 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 randomization.

[c] Confirmed best overall response assessed per RECIST 1.1.

[d] Patients with no post-baseline response assessment.

Source: [54]

7.1.2.1.7 Clinical Benefit Rate

The clinical benefit rate (CBR) was defined as achieving stable disease (SD) or non-CR/non-PD for ≥6 months (i.e., no documented PD or death within 6 months from date of randomization) or a best overall response of CR or PR as determined by BICR review using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. In the total study population (ITT-OS), the CBR 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) and the CBR per investigator was 58.0% (95% CI [53.1, 62.9]) for the tucatinib-combination group compared with 37.6% (95% CI [30.9, 44.7]) for the placebo-combination group (stratified Cochran-Mantel-Haenszel p<0.00001) (Table 9) [53].

Table 9. Clinical benefit rate (ITT-OS population)

	Tucatinib combination (N=410)	Placebo combination (N=202)	Relative risk	Confidence Interval (95%)	
				Lower	Upper
CBR per BICR	59.8% (95% CI [54.8, 64.5])	38.1% (95% CI [31.4, 45.2])	1.57	1.29	1.90
CBR per investigator	58.0% (95% CI [53.1, 62.9])	37.6% (95% CI [30.9, 44.7])	1.54	1.27	1.88

CBR, Clinical benefit rate; ICR, blinded independent central review

7.1.2.1.8 Duration of Response

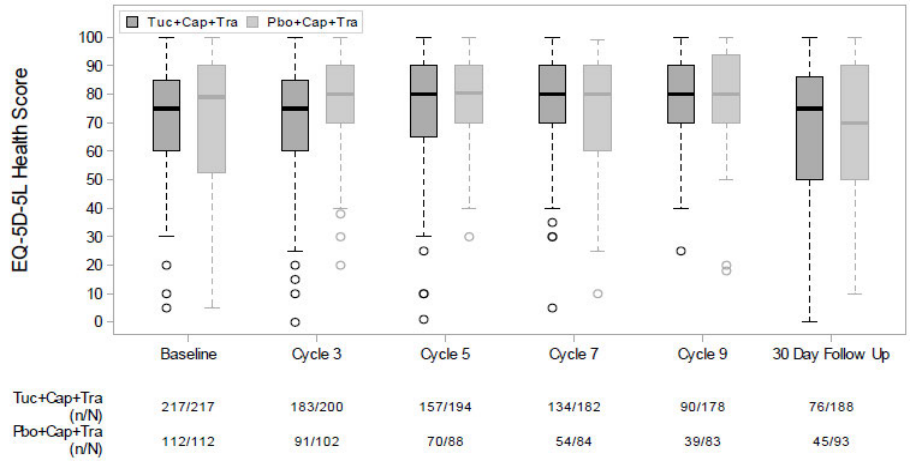
Duration of response (DOR) was defined as the time from the first objective response (CR or PR that is subsequently confirmed) to documented disease progression per RECIST 1.1 or death from any cause, whichever occurs first. The median DOR for patients with measurable disease at baseline per BICR was 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 [53]. The median DOR for patients with measurable disease at baseline per investigator was 6.9 months (95% CI [6.2, 8.3]) for the tucatinib-combination group and 6.9 months (95% CI [4.2, 8.9]) for the placebo-combination group.

7.1.2.1.9 Patient-Reported Outcomes/EQ-5D-5L

HRQoL was evaluated in the ITT-OS population using the EuroQoL 5 Dimensions (EQ-5D-5L), which consists of the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The questionnaire was implemented in protocol amendment 7 and, consequently, only a subset of patients has baseline HRQoL data (217 in the tucatinib-combination group and 112 in the placebo-combination group).

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 [53]. The mean EQ-5D-5L VAS score was similar between treatment arms and stable throughout the trial, suggesting maintenance of HRQoL in both arms (Table 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 9. EQ-5D-5L Visual Analog Scale Score Over the Course of Treatment (Full Study Population; ITT-OS[a])



Cap, capecitabine; EQ-5D-5L, EuroQol 5 dimensions; HRQoL, health-related quality of life; ITT-OS, intent to treat overall survival population; Tra, trastuzumab; Tuc, tucatinib

[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=330, 217 in the tucatinib-combination group and 224 in the placebo-combination group) than in the full ITT-OS.

Baseline was defined as most 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: [57]

7.1.2.1.10 Safety

In the primary endpoint population, patients had a longer median treatment exposure to tucatinib (7.3 months) compared with placebo (4.4 months) (Table 10) [52]. 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.

Table 10. Duration of tucatinib and placebo exposure in HER2CLIMB

	Primary Endpoint 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 (SD)	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
Min, Max	< 0.1, 35.1	< 0.1, 24.0	< 0.1, 35.1	< 0.1, 24.0
Number of treatment cycles[a] initiated				
Mean (SD)	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
Min, Max	1, 51	1, 35	1, 51	1, 35
Median relative dose intensity[b] (%)	NR	NR	93.6	97.0

NR, not reported; SD, standard deviation
[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: [53]

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. 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 11).

Table 11. Discontinuation of study drug due to adverse events (safety analysis population)

	Tucatinib-Combination (N=404)	Placebo Combination (N=197)	Relative risk	Confidence Interval (95%) Lower	Upper
Patients who discontinued any study treatment due to TEAE	45 (11.1)	19 (9.6)	1.15	0.69	1.92
Patients who discontinued tucatinib/placebo	23 (5.7)	6 (3.0)	1.87	0.77	4.52
Patients who discontinued capecitabine	41 (10.1)	18 (9.1)	1.11	0.66	1.88
Patients who discontinued trastuzumab	18 (4.5)	5 (2.5)	1.76	0.66	4.66
Patients with TEAEs resulting in tucatinib/placebo dose modification	220 (54.5)	81 (41.1)	1.32	1.10	1.60
Dose withheld	216 (53.5)	80 (40.6)	1.32	1.09	1.59
Dose reduced	84 (20.8)	21 (10.7)	1.95	1.25	3.05
Patients with TEAEs resulting in capecitabine dose modification	313 (77.5)	122 (61.9)	1.25	1.11	1.41
Dose withheld	276 (68.3)	113 (57.4)	1.19	1.04	1.37
Dose reduced	243 (60.1)	77 (39.1)	1.54	1.27	1.86
Patients with TEAEs resulting in trastuzumab dose modification[a]	104 (25.7)	38 (19.3)	1.33	0.96	1.86
Dose withheld[b]	104 (25.7)	38 (19.3)	1.33	0.96	1.86

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: [52, 53]

7.1.2.1.11 Treatment-Emergent Adverse Events

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 12). Rates of any, Grade ≥3, or serious treatment-emergent adverse events (TEAE) were balanced between treatment arms.

Table 12. Summary of treatment-emergent adverse events (safety analysis population)

Adverse Event	Tucatinib Combination (N=404) n (%)	Placebo Combination (N=197) n (%)	Relative risk	Confidence Interval (95%) Lower	Upper
Any TEAE[a]	401 (99.3)	191 (97.0)	1.02	1.00	1.02
Grade ≥3 TEAE	223 (55.2)	96 (48.7)	1.13	0.96	1.34
Any TE serious adverse events	104 (25.7)	53 (26.9)	0.96	0.72	1.27
TEAE leading to death	8 (2.0)	6 (3.0)	0.65	0.23	1.85

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: [52, 53]

The most common adverse events observed in patients in the tucatinib-combination group were diarrhea, hand-foot syndrome, nausea, fatigue, and vomiting (Table 13). Most adverse events were Grade 1 and 2 in severity.

Table 13. Most common (≥20% in the tucatinib combination) adverse events (safety analysis population)

Preferred Term	Incidence Rate, n (%)				Relative risk	Confidence Interval (95%)		Relative risk	Confidence Interval (95%)	
	Tucatinib Combination (N=404)		Placebo Combination (N=197)			Lower	Upper		Lower	Upper
	Any AE	Grade ≥3	Any AE	Grade ≥3		Any AE			Grade ≥3	
Diarrhea	327 (80.9)	52 (12.9)	105 (53.3)	17 (8.6)	1.52	1.32	1.75	1.49	0.89	2.51
Hand-foot/PPE syndrome	256 (63.4)	53 (13.1)	104 (52.8)	18 (9.1)	1.20	1.03	1.40	1.44	0.86	2.38
Nausea	236 (58.4)	15 (3.7)	86 (43.7)	6 (3.0)	1.34	1.12	1.60	1.22	0.48	3.09
Fatigue	182 (45.0)	19 (4.7)	85 (43.1)	8 (4.1)	1.04	0.86	1.27	1.16	0.52	2.60
Vomiting	145 (35.9)	12 (3.0)	50 (25.4)	7 (3.6)	1.41	1.08	1.86	0.84	0.33	2.09
Stomatitis	103 (25.5)	10 (2.5)	28 (14.2)	1 (0.5)	1.79	1.22	2.63	4.88	0.63	37.83
Decreased appetite	100 (24.8)	2 (0.5)	39 (19.8)	0	1.25	0.90	1.74	NA	NA	NA
Headache	87 (21.5)	2 (0.5)	40 (20.3)	3 (1.5)	1.06	0.76	1.48	0.33	0.05	1.93
AST increased	86 (21.3)	18 (4.5)	22 (11.2)	1 (0.5)	1.91	1.23	2.95	8.78	1.18	65.28
ALT increased	81 (20.0)	22 (5.4)	13 (6.6)	1 (0.5)	3.04	1.73	5.32	10.73	1.46	79.01

AE, adverse event; ALT, alanine transaminase AST, aspartate transaminase; PPE, palmar-plantar erythrodysesthesia
Source: [52]

7.1.2.1.12 Efficacy studies – Documentation for the comparator's clinical efficacy

See section 7.1.

7.1.2.1.13 Ongoing studies for the intervention

See Table 14 for ongoing studies of the tucatinib.

Table 14. Ongoing trials

Ongoing trials								
Study name	***NCT identifier***	***Study design***	***Study population***	***Intervention***	***Comparator***	***Study start date***	***Estimated completion date***	***Expected date of publication***
Tucatinib, Palbociclib and Letrozole in Metastatic Hormone Receptor Positive and HER2-positive Breast Cancer	*NCT03054363*	*Phase IB/II, Open-label, Single Arm Study*	*Patients with Hormone Receptor Positive and HER2-positive Metastatic Breast Cancer*	Tucatinib in Combination with Palbociclib and Letrozole	-	November 27, 2017	March 31, 2023 (March 18, 2022 primary completion date)	
TOPAZ: Tucatinib in COmbination With Pembrolizumab And TrastuZumab in Patients With HER2-Positive Breast Cancer Brain Metastases	NCT04512261	*Phase IB/II, Open-label, Single Arm Study*	Patients with HER2-Positive Breast Cancer Brain Metastases	Tucatinib + Pembrolizumab + Trastuzumab	-	January 1, 2021	July 1, 2023	
Tucatinib, Trastuzumab, and Capecitabine for the Treatment of HER2-positive LMD	NCT03501979	*Phase II, Open-label, Single Arm Study*	Patients with HER2 positive breast cancer with leptomeningeal metastases	Tucatinib + Trastuzumab + Capecitabine	-	March 6, 2019	September 2023 (September 2022 primary completion date)	
A Study of Tucatinib Plus Trastuzumab Deruxtecan in HER2-positive Breast Cancer (HER2CLIMB-04)	NCT04539938	*Phase II, Open-label, Single Arm Study*	Patients with With Previously Treated Unresectable Locally-Advanced or Metastatic HER2-positive Breast Cancer	Tucatinib + trastuzumab deruxtecan	-	December 1, 2020	October 2025 (October 2022 primary completion date)	
A Study of Tucatinib vs.	NCT03975647	Randomized, Double-	Patients With	Tucatinib + T-	Placebo + T-	October 2, 2019	April 30, 2024	

Placebo in Combination With Ado-trastuzumab Emtansine (T-DM1) for Patients With Advanced or Metastatic HER2-positive Breast Cancer		blind, Phase 3 Study	Unresectable Locally-advanced or Metastatic HER2-positive Breast Cancer	DM1	DM1		
A Phase 1b/2 Study of T-DXd Combinations in HER2-positive Metastatic Breast Cancer (DB-07)	NCT04538742	*Phase IB/II, Open-label, Single Arm Study*	HER2-positive Metastatic Breast Cancer	Trastuzumab deruxtecan, Durvalumab, Paclitaxel, Pertuzumab, Tucatinib	-	December 28, 2020	April 30, 2025

7.1.3 Comparative analyses of efficacy and safety

Not applicable – the comparative efficacy is based on the HER2CLIMB study presented above.

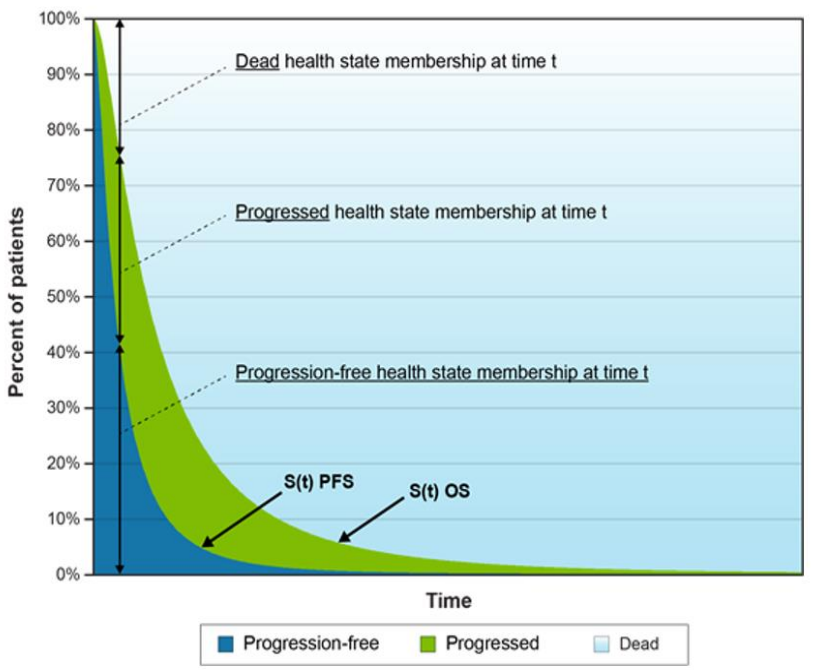
8. Health economic analysis

For the health economic analysis of tucatinib, a cost-utility analysis was performed, comparing the tucatinib combination with the combination of capecitabine and trastuzumab. The outcomes of analysis were incremental cost per QALY and LY gained.
Both the quality of life and life span are of interest as HER2-positive breast cancer in the metastatic setting is associated with relatively short survival. Hence, additional lifetime spent with the best possible health-related quality of life was considered as relevant.
The base-case analysis includes both direct treatment and healthcare utilization costs. Direct non-medical and indirect costs encompass travel costs and productivity loss which are included in the sensitivity analysis.

8.1 Model

A partitioned survival model was used in this cost-effectiveness analysis; a visual representation of the model structure is presented in Figure 10: Model structure. Partitioned survival models are commonly used in oncology modeling. In the current model, patients begin in the progression-free state and initiate either tucatinib plus capecitabine and trastuzumab or a comparator treatment. Patients can remain progression-free for a time, experience disease progression (not related to brain metastases), disease progression due to brain metastases, or die. Once patients progress, they can receive subsequent lines of anticancer therapy and supportive care.

Figure 10: 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 model structure captures the expected patient pathway from treatment initiation to death and reflects differences in costs and outcomes among patients receiving alternative systemic therapies for pretreated HER2-positive locally advanced or mBC. The model structure allows for variation in the risk of progression and death over time, which is observed in PFS and OS data for patients. The model cycle length of one week was chosen to provide precision in the tracking of the number of patients in each health state over time in the early years of the model. As the cycle length is short in comparison to the model time horizon, no half-cycle correction is applied in this model [58].

Costs and health-related utilities are allocated to each health state and multiplied by the number of patients in each health state to calculate weighted costs and QALYs per cycle.
Treatment costs included costs of drug acquisition, administration, and monitoring. Costs and disutilities associated with adverse events (AEs) were estimated per episode and were applied once at the beginning of the simulation, based on the proportion of patients in each treatment arm who experience each AE.
The time horizon for the base case was selected to be 20 years. Considering the prognosis of patients included in the analysis it is assumed that this time horizon reflects the lifespan and a longer time frame would not translate into additional information regarding differences in the treatment effect, costs or other outcomes.

A discount rate of 3.5% was applied based on the socio-economic discount rate from the Ministry of Finance [59].
The global model was validated internally, externally and a cross validation was conducted. To ensure it reflects Danish clinical practice, a clinical expert was consulted to ensure that the clinical pathway and disease complexity, as well as important differences in costs and outcomes between treatments, were accurately captured by the model.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

The input data used for the base case was mainly derived from the pivotal trial HER2CLIMB and literature. Where needed, data was extrapolated based on goodness-fit statistics and clinical plausibility. A summary of included clinical inputs is presented in Table 15.

Table 15. Estimates applied in the health economic model

Variable	Value	Source
Patient characteristics		
Mean starting age	54 years	HER2CLIMB
Mean body surface area	1.8 m^2	
Mean body weight	69.5 kg	
Survival analysis		
PFS survival model	Lognormal	HER2CLIMB, best fit
OS survival model	Log-logistic	
Treatment duration		
Tucatinib combination	TTD: Extended mean	HER2CLIMB
TRASCAP	TTD: Extended mean	
Treatment duration: post-progression treatments		
Trastuzumab	5.70 months	HER2CLIMB
Lapatinib	6.35 months	[60]
Vinorelbine	8.66 months	[61]
Eribulin	4.50 months	[62]
Letrozole	20.34 months	[63]
Treatment duration: antidiarrheals (loperamide)		
Tucatinib combination	21.63 days	HER2CLIMB
TRASCAP	5.80 days	
Relative dose intensity: tucatinib + trastuzumab + capecitabine		
Tucatinib	88.5%	HER2CLIMB
Capecitabine	73.9%	
Trastuzumab	73.9%	
Relative dose intensity: trastuzumab + capecitabine		
Capecitabine	79.0%	HER2CLIMB
Trastuzumab	79.0%	
Adverse events – tucatinib combination		
Hand-foot syndrome	13.1%	HER2CLIMB
Diarrhoea	12.9%	
Alanine aminotransferase increased	5.4%	
Fatigue	4.7%	
Aspartate aminotransferase increased	4.5%	
Anaemia	3.7%	
Nausea	3.7%	
Vomiting	3.0%	
Stomatitis	2.5%	
Adverse events – TRASCAP		
Hand-foot syndrome	9.1%	HER2CLIMB

Diarrhoea	8.6%	
Fatigue	4.1%	
Anaemia	2.5%	
Nausea	3.0%	
Vomiting	3.6%	
Quality of life (EQ-5D-5L)		HER2CLIMB
Progression free	0.844	
Progression	0.773	
Disutility due to brain metasteses (EQ-5D-3L)	-0.151	
Post progression treatment		
Trastuzumab	70.0%	[64]
Lapatinib	15.0%	
Vinorelbine	35%	
Eribulin	20%	
Pertuzumab	5%	

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The pivotal trial assessing the tucatinib combination (HER2CLIMB) included patients with HER2-positive breast cancer with or without brain metastases aged 18 years or older. The HER2 status was determined based on immunohistochemical analysis, *in situ* hybridization, or fluorescence in situ hybridization and confirmed at a central location. All patients had prior treatment with trastuzumab, pertuzumab, and T-DM1 as well as an ECOG performance-status score of 0 or 1. Median age at treatment initiation was 54 years (mean age: 60 years). Mean body weight was 69.5 kg and mean body surface was 1.8 m^2. The patient population in the health economic analysis submitted reflects the patient population in HER2CLIMB. Model inputs related to patient characteristics are body weight and body surface.

Baseline characteristics of participants in HER2CLIMB are assumed to be representative for Denmark. The assumption was validated by a Danish clinical expert [43]. Table 16 shows the characteristics of the patient population used in the model compared to Danish clinical practice. The estimated body weight of 75 kg in clinical practice was tested in scenario analyses.

Table 16. Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
Age at treatment start	54 [52]	54	60 [43]
Body weight (kg)	69.5 [53]	69.5	75 [43]
Body surface (m2)	1.8 [53]	1.8	1.8 [43]

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice (as defined in section 2.2):
The ability to achieve a sustained meaningful response to treatment in patients with HER2-positive MBC declines as the disease progresses [65, 66]. As a result, most patients cycle through multiple lines of systemic therapy (including re-challenge with different trastuzumab-based regimens) to palliate HER2-positive MBC [67, 68]. Currently available systemic treatments also have limited impact on brain metastases due to limited penetration of the blood-brain barrier [69, 70]. The tucatinib combination is indicated for the treatment of unresectable advanced or metastatic HER2-positive breast cancer who have received two prior anti-HER2-based regimens. It is currently not introduced or used in Denmark.

Intervention in the clinical documentation submitted:
The key clinical documentation in this health economic assessment is the pivotal trial HER2CLIMB. See section 7 for details and results of HER2CLIMB and section on patient population above.

Intervention as in the health economic analysis submitted:
Inputs used in the cost-effectiveness analysis are primarily informed by the clinical trial HER2CLIMB and clinical literature in combination with clinical expertise [52, 64, 71-73]. In the model treatments were administered according to treatment cycles of 21 days. Tucatinib (300 mg) was administered orally twice daily. Capecitabine (1000 mg/m^2) was administered orally twice daily on days 1-14 of each treatment cycle. Trastuzumab was administered (8 mg loading dose, 6 mg maintenance dose) the 1st day of each treatment cycle. Posology of the intervention are based on HER2CLIMB [52] and available dosing recommendations for tucatinib, trastuzumab [72], and capecitabine.
To estimate the treatment duration of tucatinib as well as associated drug acquisition and administration costs the use the extended mean of the treatment exposure from HER2CLIMB was used. Time to treatment discontinued was defined as discontinuing either tucatinib or placebo, or trastuzumab and capecitabine.

Table 17. Intervention

Intervention	Clinical documentation [52]	Used in the model [52]	Expected Danish clinical practice [43]
Posology	Drug: tucatinib 300 mg orally twice daily	Drug: tucatinib 300 mg orally twice daily	Drug: tucatinib 300 mg orally twice daily
	Drug: capecitabine 1000 mg/m^2 orally twice daily on days 1-14 of each 21-day cycle	Drug: capecitabine 1000 mg/m2 orally twice daily on days 1-14 of each 21-day cycle	Drug: capecitabine 1000 mg/m2 orally twice daily on days 1-14 of each 21-day cycle
	Drug: trastuzumab 8 mg/kg intravenously (IV) (or subcutaneous) on day 1 of cycle 1, followed by 6 mg/kg on day 1 of each 21-day cycle.	Drug: trastuzumab 8 mg/kg intravenously (IV) on day 1 of Cycle 1, followed by 6 mg/kg on day 1 of each 21-day cycle.	Drug: trastuzumab 8 mg/kg intravenously (IV)/subcutaneously /SC) on day 1 of Cycle 1, followed by 6 mg/kg on day 1 of each 21-day cycle.
Length of treatment	7.6 months	TTD based on the extended mean of TTD in HER2CLIMB.	Treatment until disease progression or intolerable side effects, in line with results seen in HER2CLIMB (TTD).

Intervention	Clinical documentation [52]	Used in the model [52]	Expected Danish clinical practice [43]
The pharmaceutical's position in the Danish clinical practice	3rd line HER2-directed treatment	3rd line HER2-directed treatment	3rd line HER2-directed treatment

8.2.2.3 Comparators

In Denmark, the recommended second-line treatment for patients with HER2-positive breast cancer is T-DM1. Third-line may comprise trastuzumab in combination with orally administered chemotherapies such as trastuzumab in combination with capecitabine, is a likely combination [49]. This information has been validated by a Danish clinical expert [43].

The most relevant comparator for the tucatinib combination in Denmark is the combination of trastuzumab and capecitabine alone. According to Danish treatment guidelines, this combination represents a viable HER2-directed treatment following the treatment with T-DM1 [43].

In the model the comparators capecitabine (1000 mg/m^2) was administered orally twice daily on days 1-14 of each treatment cycle and trastuzumab was administered (8 mg loading dose, 6 mg maintenance dose) the 1st day of each treatment cycle [52]. A summary of the comparator characteristics is shown in Table 18.

Table 18. Comparator

Comparator	Clinical documentation [52]	Used in the model [52]	Expected Danish clinical practice [43]
Posology	Drug: capecitabine 1000 mg/m^2 orally twice daily on days 1-14 of each 21-day cycle Drug: trastuzumab 8 mg/kg intravenously (IV) on day 1 of cycle 1, followed by 6 mg/kg on day 1 of each 21-day cycle [52].	Drug: capecitabine 1000 mg/m2 orally twice daily on days 1-14 of each 21-day cycle Drug: trastuzumab 8 mg/kg intravenously (IV) on day 1 of Cycle 1, followed by 6 mg/kg on day 1 of each 21-day cycle.	Drug: capecitabine 1000 mg/m2 orally twice daily on days 1-14 of each 21-day cycle Drug: trastuzumab 8 mg/kg intravenously (IV) on day 1 of Cycle 1, followed by 6 mg/kg on day 1 of each 21-day cycle.
Length of treatment	4.4 months (range, <0.1 -24 months)	TTD	TTD
The comparator's position in Danish clinical practice	3rd line treatment	3rd line treatment	3rd line treatment

8.2.2.4 Relative efficacy outcomes

Relative efficacy outcomes used to compare the tucatinib combination with the combination of trastuzumab and capecitabine was PFS and OS and time to new brain lesion or death. See section 7.1.2.1.1 and 7.1.2.1.3 for results in PFS and OS, respectively. See section 7.1.2.1.5 for time to new brain lesion or death. All relative efficacy outcomes were sourced from the pivotal trial HER2CLIMB [52].

The Danish treatment guidelines for metastatic/advanced breast cancer aim to ensure optimal treatment. Survival is used as indicator for efficacy [43]. Together with safety and tolerability, efficacy represents a relevant factor regarding treatment decisions in Denmark. Both PFS and OS as well as safety and quality of life were main endpoints in the HER2CLIMB trial [52] and are applied in the health economic analysis for tucatinib. Hence, it is believed that the clinical data derived from the pivotal trial for tucatinib is relevant for Danish clinical practice.

A partitioned survival model was used to analyze the cost-effectiveness of the tucatinib combination in Denmark. The model was directly based on key outcomes of the HER2CLIMB pivotal trial, which directly represents treatment goals for Denmark: Progression free survival, quality of life, and overall survival. Table 19 shows the summary of described value, Table 20 shows the summary of value regarding relevance.
The values in the model represent the extrapolated survival and consequently differ from the observed survival. However, extrapolations were based on the observed survival in HER2CLIMB and are assumed to be representative for Danish clinical practice [74]. For more information regarding the survival extrapolation see section 8.3.

Table 19. Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint: **Progression free survival (PFS)**	7.8 months (median) for intervention group, 5.6 months for the placebo group	Tucatinib combination 8.7 months vs. TRASCAP 5.3
Secondary endpoint: **Overall-survival (OS)**	21.9 months (median) for the intervention group, 17.4 months for the placebo group	Tucatinib combination 23.2 months vs. TRASCAP 16.6
Time to new (or progression of brain lesion)	The median new brain lesion free survival for the tucatinib combination arm was not reached (NR, 95% CI [13.9, -]) and estimated to 11.7 months for the placebo combination (95% CI [9.5, -])	The Kaplan-Meier estimate for HER2CLIMB was used directly in the model.

Table 20. Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study: **Progression-free survival**	Defined as the time from randomization to documented disease progression or death from any cause, whichever occurs first. Determined by blinded independent central review (BICR).	PFS represents a relevant outcome measure with regards to treatments for HER2-positive breast cancer. Based on PFS, treatments may be prioritized over others.	Relevant.

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Secondary endpoints: Overall survival	Defined as time from randomization to death from any cause.	OS represents a relevant outcome measure with regards to treatments for HER2-positive breast cancer. Based on OS, treatments may be prioritized over others.	Relevant.
Time to new (or progression of brain lesion)	Defined as time from randomization to the development of a new or the progression of a previous brain lesion or death.	Brain metastases is a common manifestation of MBC in clinical practice	Relevant.

8.2.2.5 Adverse reaction outcomes

Safety was one of the secondary outcomes in the HER2CLIMB trial. Adverse events included amongst others diarrhea, fatigue, stomatitis, and vomiting. The frequency differed across patients and between the treatment options [52].

In the assessment, grade 3+ treatment-emergent adverse events occurring in at least 2% of patients were included for both tucatinib and the comparator (Table 21). The incidence of adverse events was derived from the HER2CLIMB trial..

Table 21. Adverse reaction outcomes

Adverse reaction outcome	Tucatinib combination	TRASCAP
Hand-foot syndrome	13.1%	9.1%
Diarrhea	12.9%	8.6%
Alanine aminotransferase increase	5.4%	0.0%*
Fatigue	4.7%	4.1%
Aspartate aminotransferase increase	4.5%	0.0%*
Anemia	3.7%	2.5%
Nausea	3.7%	3.0%
Vomiting	3.0%	3.6%
Stomatitis	2.5%	0.0%*
Source:	Murthy et al. (2020) [52]	Murthy et al. (2020) [52]

* the frequencies where one arm had a frequency above 2% but the other didn't, the frequency in the other arm has been set to 0% to align to the approach taken in the model.
TRASCAP: Trastuzumab and capecitabine

8.3 Extrapolation of relative efficacy

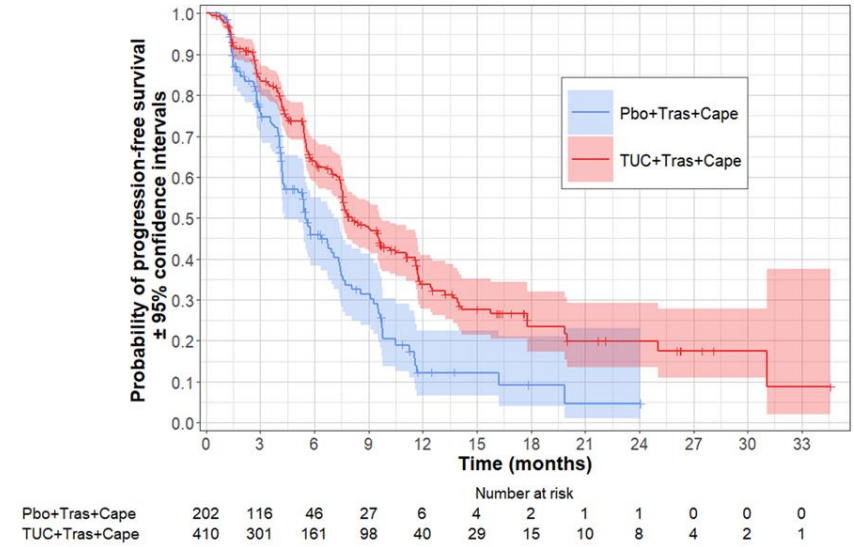
8.3.1 Time to event data

The inputs regarding effectiveness for the tucatinib combination and TRASCAP were sourced from the pivotal trial HER2CLIMB (see section 7). The two main inputs regarding effectiveness used in the model and economic analysis were PFS and OS. The ITT population from the HER2CLIMB trial was used to conduct the survival analyses for PFS and OS.

8.3.1.1 Progression free survival

As of the September 4, 2019 data cutoff date for HER2CLIMB 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 [52]. The median PFS in patients receiving tucatinib was 7.8 months (95% CI: 7.5 -9.6) compared to 5.6 months (95% CI: 4.2 -7.1) for patients receiving placebo (Figure 11).

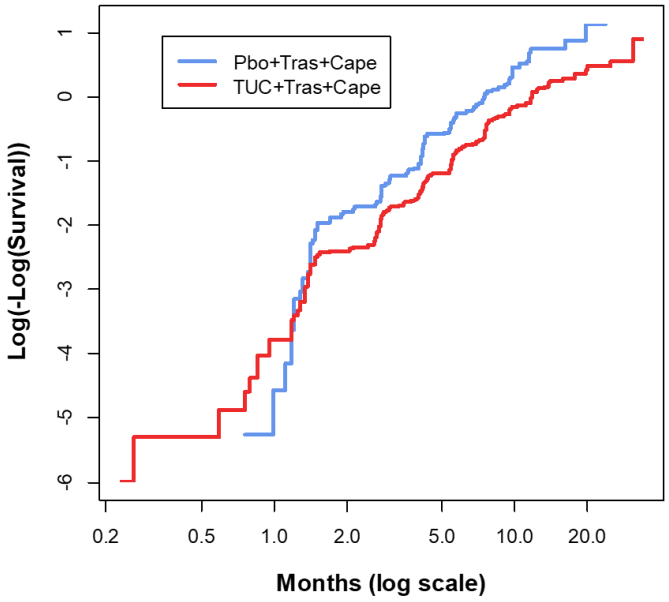
Figure 11. Kaplan-Meier estimates for progression free survival from HER2CLIMB.



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

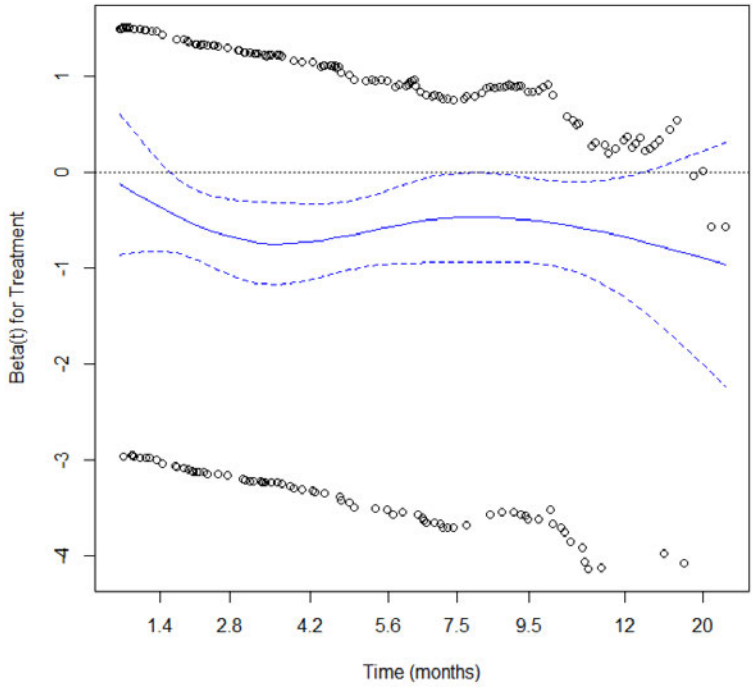
Although the PFS data from the HER2CLIMB trial was reasonably mature (56% and 61%, for the tucatinib combination and placebo, respectively [52]), it still required extrapolation to estimate the unrestricted mean difference in PFS needed for the economic analysis. To investigate if proportional hazards (PHs) or accelerated failure time factors (AFTs) may be used in the survival analysis the log-cumulative hazard was plotted (Figure 12).

Figure 12. Log cumulative hazard plot for PFS HER2CLIMB.



The two arms of the PFS in HER2CLIMB cross, indicating non-proportional hazards. The proportionality of hazards were further graphically explored with Shoenfeld residuals (Figure 13).

Figure 13. Schoenfeld residuals as a function of time in HER2CLIMB, progression free survival



The residuals showed variation with time, indication of non-proportionality for treatment effect. However, a formal test failed to reject a zero slope for the (linier) dependence of the residuals with time (Chi-squared = 0.275, degrees of freedom = 1; p = 0.60).

As the PH assumption is uncertain, survival distributions allowing for different hazards (e.g., different scale and shape) were fitted to the data and a constant treatment effect was thus not assumed in the projections. It is important to note that the PH assumption is not rejected as the estimators for the shape parameters of the fitted distributions are not restricted to be different. The standard survival distributions were used, the

exponential, Weibull, Gompertz, log-logistic, lognormal, and generalised gamma. The distributions fitted to PFS with corresponding AIC and BIC are presented in Table 22.

Table 22. Fit statistics for fitted survival distributions to PFS from HER2CLIMB, base case distribution in italics

Distribution	AIC			BIC			Mean PFS tucatinib combination	Mean PFS TRASCAP	Difference PFS
	Tucatinib combination*	TRASCAP†	Total‡	Tucatinib combination*	TRASCAP†	Total‡			
Exponential	30.6	99.6	130.2	34.6	102.9	137.7	13.6	8.3	5.3
Weibull	16.6	77.8	94.4	24.6	84.4	109.4	11.5	6.9	4.6
Lognormal	*5.6*	*66.5*	*72.1*	*13.7*	*73.1*	*87.1*	*15.5*	*7.7*	*7.7*
Log-logistic	2.9	70.4	73.3	10.9	77.0	88.2	16.4	8.4	8.0
Gompertz	30.7	94.0	124.7	38.7	100.6	139.6	12.2	7.3	5.0
Generalised gamma	6.1	68.5	74.5	18.1	78.4	97.0	13.5	7.9	5.5

TRASCAP: Trastuzumab and capecitabine. *1400 was subtracted from the AIC/BIC for ease of interpretation, †600 was subtracted from the AIC/BIC for ease of interpretation, ‡2000 was subtracted from the AIC/BIC for ease of interpretation.

Models typically associated with the PH assumption, Gompertz and Weibull, together with the exponential model demonstrated the worst statistical fit (highest AIC and BIC, Table 22). Both the Gompertz and the Weibull predict an increasing difference in progression rate between the tucatinib combination and TRASCAP with time (see Figure 14 and Figure 15).

Figure 14. Projection of the Gompertz progression rate (hazard)

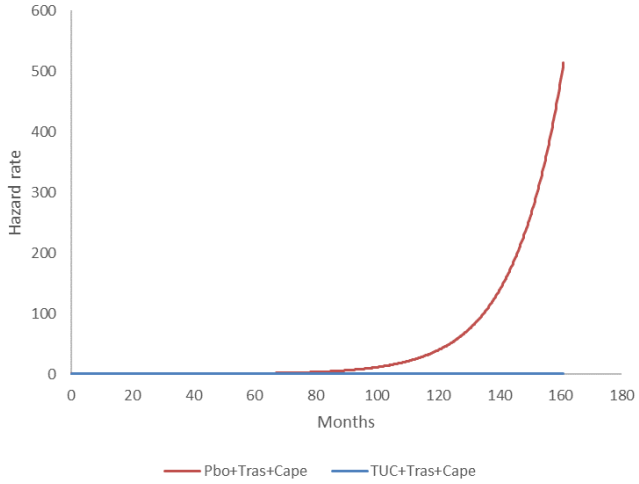
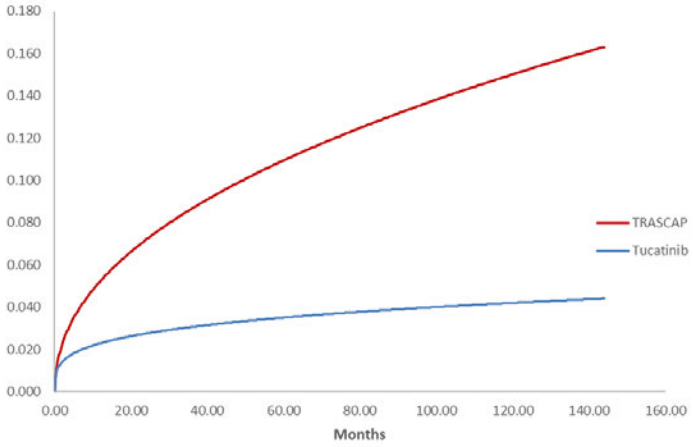
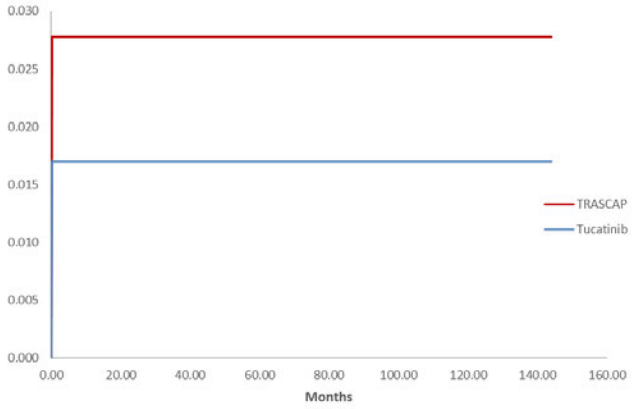


Figure 15. Projection of the Weibull progression rate (hazard)



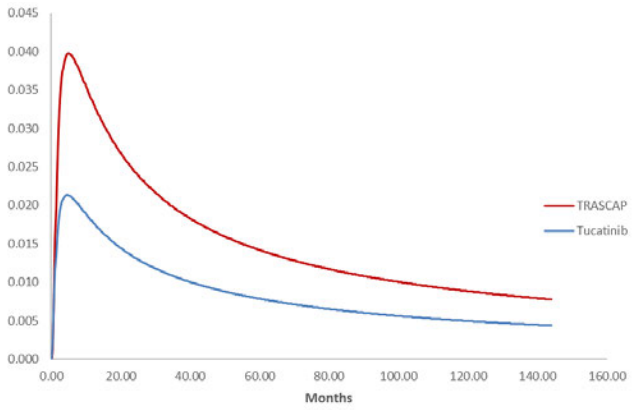
The exponential model predicts a constant difference (Figure 16). These distributions (Gompertz, Weibull and the exponential model) predict less plausible differences in mean survival compared with the difference seen in the restricted mean observed in HER2CLIMB (approximately 5.2 months).

Figure 16. Projection of the exponential progression rate (hazard)



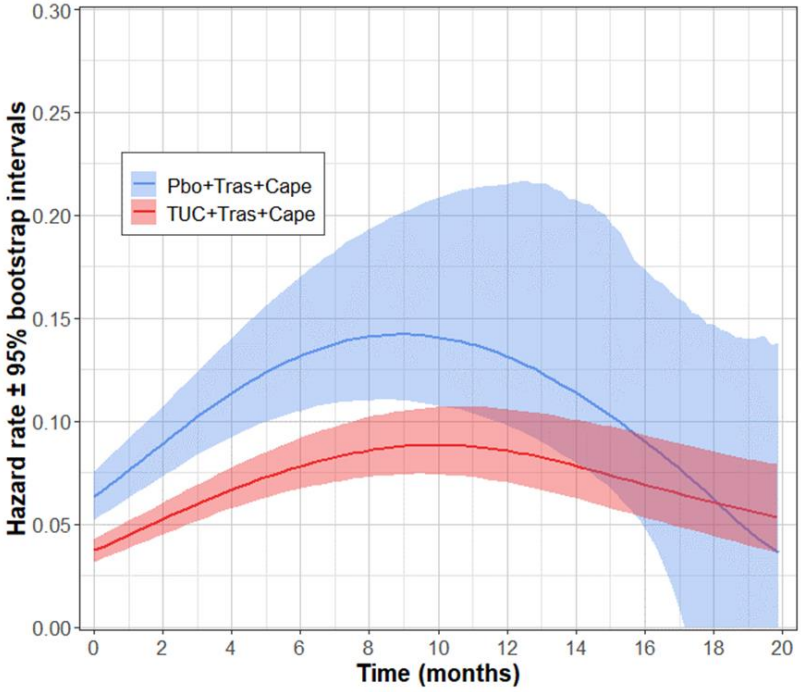
The most clinically plausible situation is believed to be a difference in progression rates during the trial with a *converging progression risk with time*. Based on external clinical input the most clinically plausible difference in progression rates would demonstrate convergence over time in progression rates between study arms as the effect of therapy wears out [43]. This is also consistent with what is observed in HER2CLIMB (smoothed hazard rate is presented in Figure 18). The progression rates in HER2CLIMB are both unimodal – the hazards show an increase during the first 10 months, followed by a decrease and convergence of rates past 16 months. This non-monotonic increase/decrease of the hazard may be modelled using the standard survival distributions: generalised gamma, log-logistic or lognormal. The lognormal had the overall best fit of the three while demonstrating a clinically plausible development of the hazard (Figure 17) and was thus selected for the base case.

Figure 17. Projection of the lognormal progression rate (hazard)



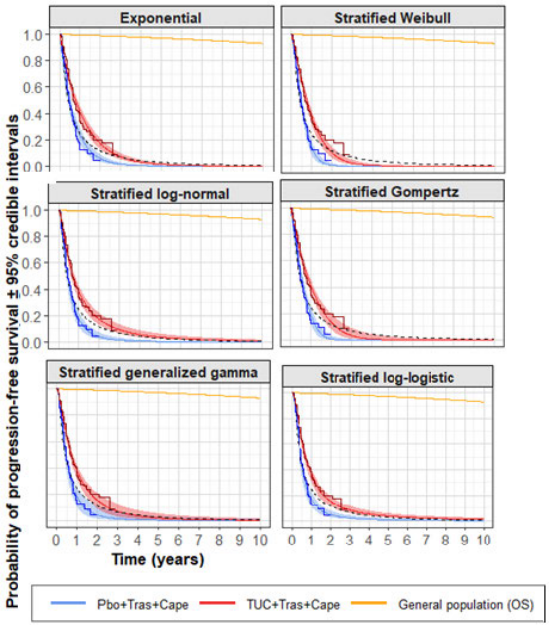
The log-logistic distribution offers a plausible alternative while generalised gamma clearly underestimates the mean difference in survival as the extended mean is close to the restricted mean seen in HER2CLIMB (approximately 5.2 months).

Figure 18. Smoothed hazard PFS from HER2CLIMB



An overlay of the different distributions with the Kaplan-Meier (KM)-estimate for the two arms in HER2CLIMB is presented in Figure 19. The lognormal distribution show clinically plausible survival extrapolations over ten years for both arms.

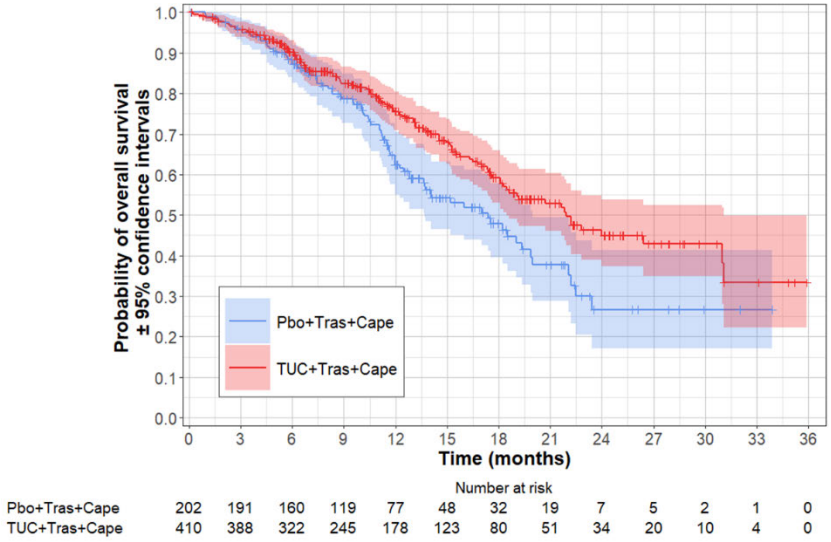
Figure 19. Extrapolation of survival distributions, PFS HER2CLIMB



8.3.1.2 Overall survival

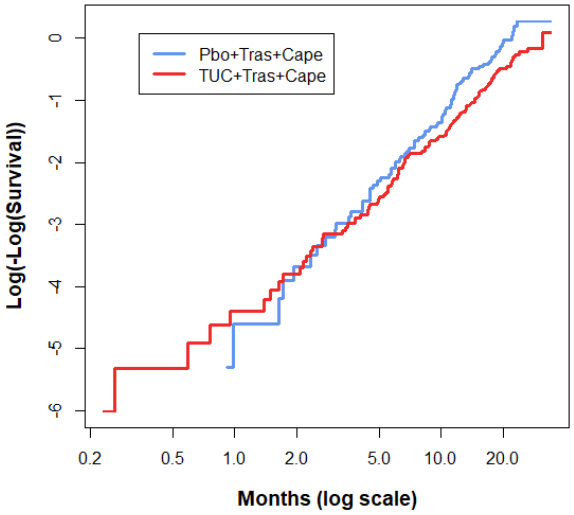
The OS from HER2CLIMB is presented in Figure 20. The tucatinib combination extended median OS by 4.5 months over the placebo-combination group, in patients receiving tucatinib the median OS was 21.9 months (95% CI: 18.3 - 31.0) compared to 17.4 months (95% CI: 13.6 - 19.9) for patients receiving TRASCAP.

Figure 20. Kaplan-Meier estimates for overall survival from HER2CLIMB.



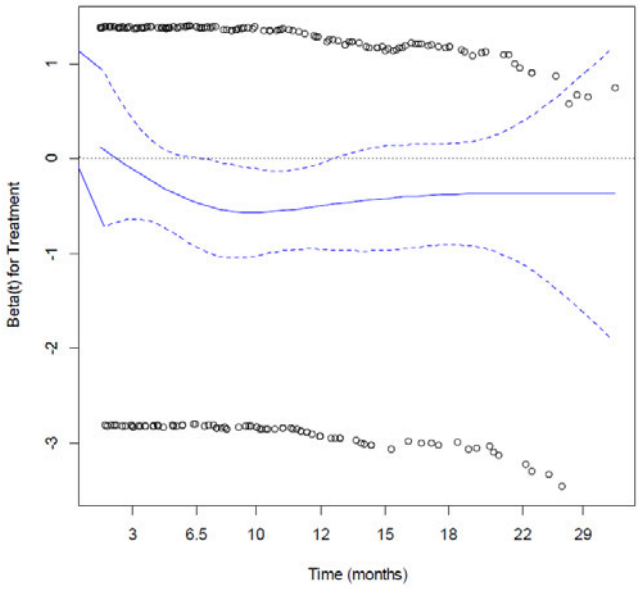
The same approach to the survival analysis was used for OS as for PFS. The log-cumulative hazard plot is presented in Figure 21 and reveals crossing curves and thus separate distributions were fitted.

Figure 21. Log-cumulative hazard function for OS, HER2CLIMB



As for PFS, the time-dependence of the hazard ratio was further graphically explored with Schoenfeld residuals (Figure 22).

Figure 22. Schoenfeld residuals as a function of time in HER2CLIMB, overall survival



The smoothed residuals showed variation with time. A formal statistical test of the (linear) dependence of the Shoenfeld residuals failed to reject the null hypothesis (Chi-squared = 0.286, degrees of freedom = 1; p = 0.5929) indicating that there is not strong evidence against proportional hazards. The situation was similar to the analysis of PFS and separate survival models were fitted to the two arms of the trial - the PH assumption is thus not rejected as the estimators for the shape parameters of the fitted distributions are not restricted to be different.

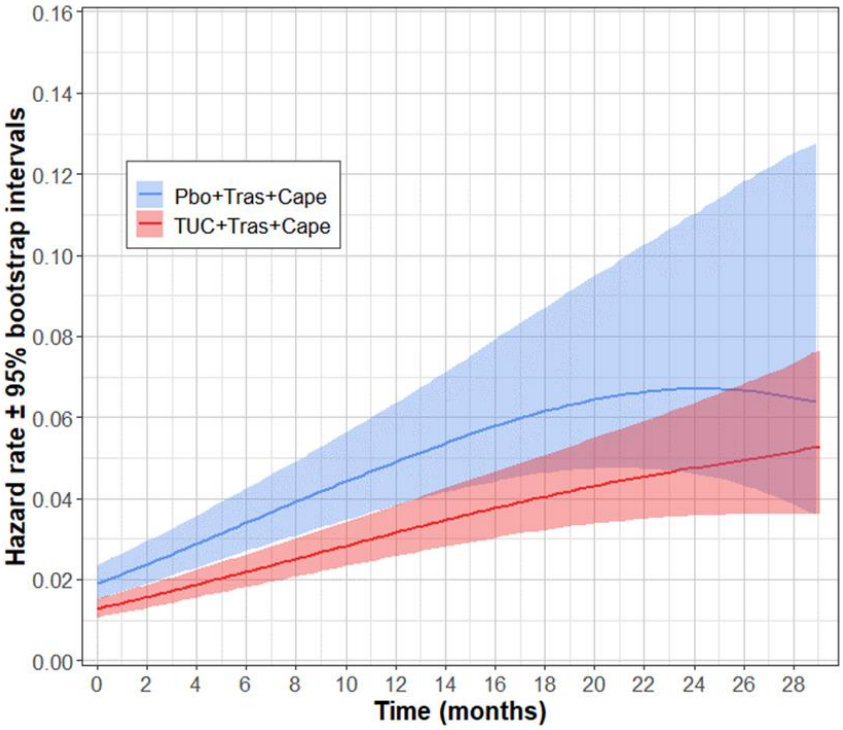
Table 23. Fit statistics for fitted survival distributions to OS from HER2CLIMB, base case distribution in italics

Distribution	AIC			BIC			Mean OS tucatinib combination	Mean OS TRASCAP	Difference OS
	Tucatinib combination*	TRASCAP†	Total‡	Tucatinib combination*	TRASCAP†	Total‡			
Exponential	109.9	32.8	42.7	113.9	36.1	49.5	38.4	26.9	11.2
Weibull	94.9	12.4	7.0	102.6	19.1	20.5	27.1	19.1	8.0
Log-normal	107.7	14.7	22.3	115.7	21.3	35.8	55.0	27.1	28.2
Log-logistic	*95.7*	*11.0*	*6.6*	*103.7*	*17.6*	*20.1*	*46.7*	*26.7*	*20.0*
Gompertz	99.7	21.6	21.3	107.7	28.2	34.7	24.3	18.3	5.9
Generalised gamma	96.5	13.3	9.9	108.6	23.2	30.1	27.4	20.7	6.5

TRASCAP: Trastuzumab and capecitabine. *1100 was subtracted from the AIC/BIC for ease of interpretation, †700 was subtracted from the AIC/BIC for ease of interpretation, ‡1900 was subtracted from the AIC/BIC for ease of interpretation.

Gompertz, lognormal, and exponential demonstrated the worst fit to the data from HER2CLIMB. Weibull and log-logistic show the lowest AIC and BIC but predicted very different survival estimates. The smoothed hazard is presented in Figure 23.

Figure 23. Smoothed hazard OS from HER2CLIMB.



The smoothed hazard for OS, the mortality rate, for TRASCAP show a similar shape as the hazard for PFS (unimodal with convergence of hazards over time). The TRASCAP data is more mature (42% versus 32% for TRASCAP and the tucatinib combination, respectively). The shape of the hazard for TRASCAP is clinically plausible, as frail patients will fail (die) early, and with disease specific survival reaching a maximum to then decrease as patients overcome the critical phase of the disease. The different shape seen for the tucatinib arm of HER2CLIMB is assumed to be a consequence of less events (less mature data) as only events inform the shape of the hazard and there is no reason to assume a different shape for the tucatinib arm compared to the TRASCAP arm.

Further, it is clinically plausible that the hazard for OS follows the approximate shape of the PFS, as mortality in breast cancer would be expected to be closely linked to the progression of the tumors(s). In the base case a distribution that predicts a similar shape for both arms of the model was selected.

The Weibull, log-logistic and generalized gamma were associated with the best statistical fit. Comparing the clinical plausibility of extrapolations, the log-logistic model demonstrates a plausible development consistent with HER2CLIMB, with a unimodal shape and most importantly a converging risk between the two arms with time – i.e., the difference in mortality between the two arms seen in the trial converges with time. The log-logistic and the lognormal distributions show this behavior and as the log-logistic had the best fit to the data in HER2CLIMB it was selected for the base case.

The generalized gamma predicts different shapes for the two arms in analysis, with an increased mortality in the tucatinib compared to TRASCAP which is not consistent with the clinical data. The Weibull distribution predicts an increasing difference between the two arms of the trial. The projections of the distributions are presented in Figure 24, Figure 25, and Figure 26.

Figure 24. Extrapolation of the log-logistic distribution for mortality rate (hazard)

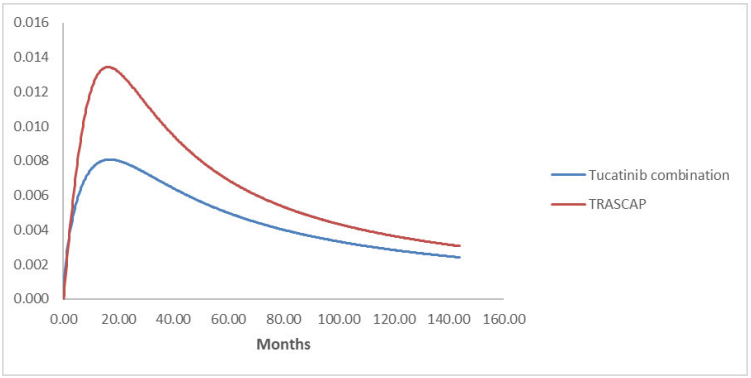


Figure 25. Extrapolation of the Weibull distribution for mortality rate (hazard)

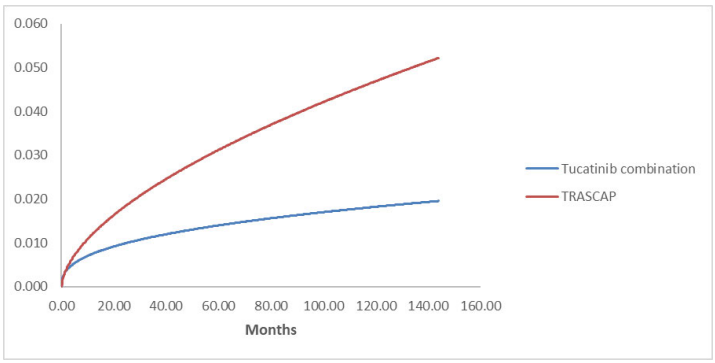
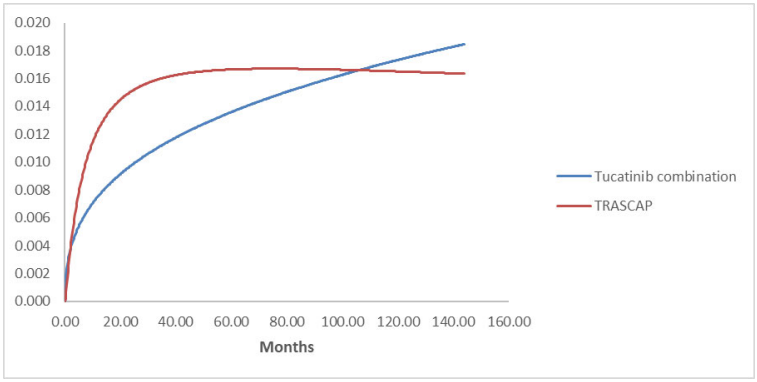
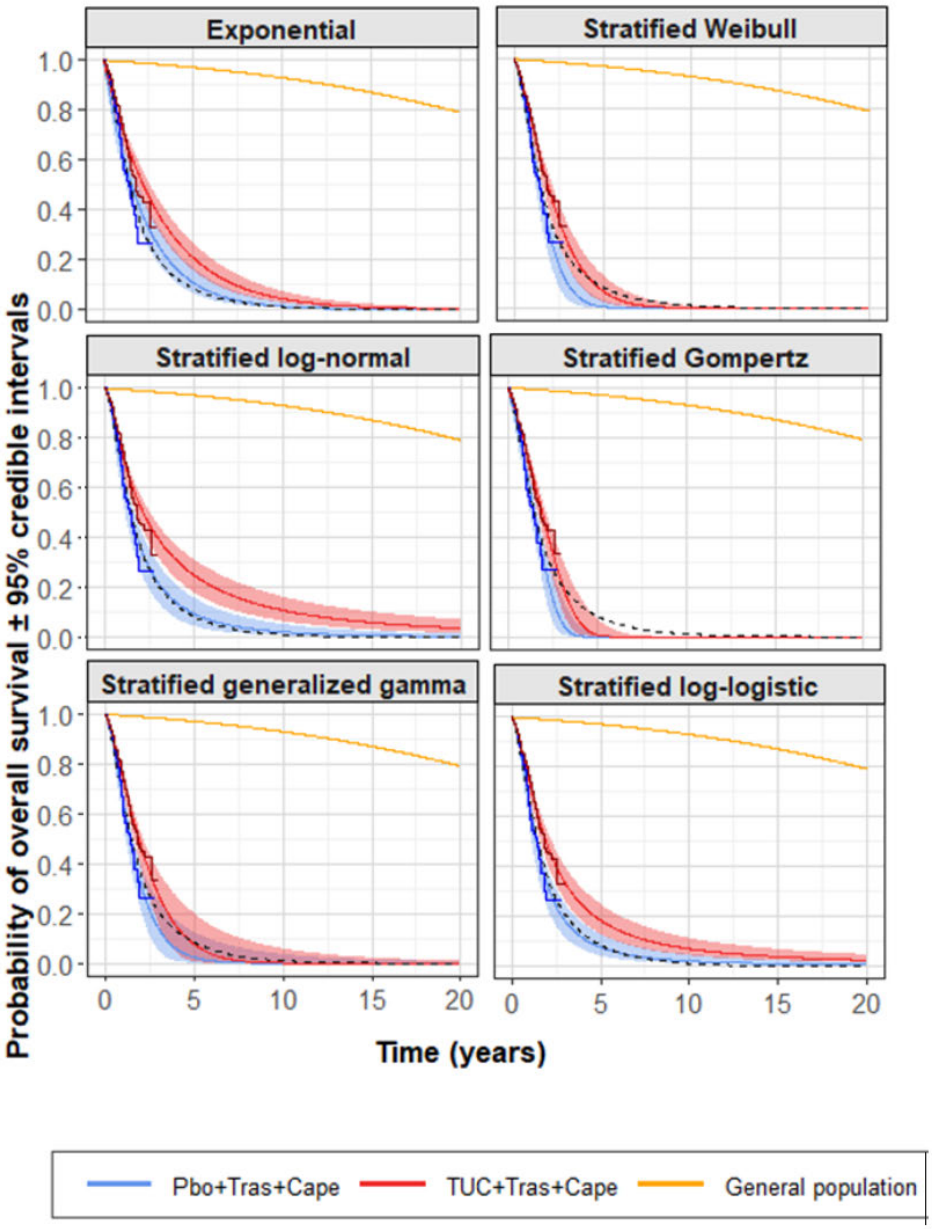


Figure 26. Projection of the genarlised gamma distribution for mortality rate (hazard)



The clinical plausibility of the extrapolation of survival was validated in discussions with clinical experts [43, 64]. The Gompertz and exponential was completely discarded as the statistical fit was poor and the shapes and development of the hazards with time were clinically implausible. Long-term extrapolations for the different survival distributions on survival probability are presented in Figure 27. It is more difficult to assess clinical plausibility based on the survival curves, but visual inspection shows that log-logistic is a good fit to the data from HER2CLIMB. Low proportions of survivors are predicted beyond 15 years, which is to be expected in this patient population [43].

Figure 27. Extrapolation of survival distributions, OS HER2CLIMB



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

8.3.1.3 Validation of extrapolations from HER2CLIMB

No suitable studies were identified in a systematic literature review (details in Appendix A) that could validate the extrapolation of time to event data from HER2CLIMB. The review revealed three studies that potentially could include traszumab + capecitabine treated HER2+ patients after 2 anti HER2 therapies; The MonarcHER trial, the SOPHIA trail and the TH3RESA trial [75-78]. The MonarcHER [78] trial included 79 patients treated with trastuzumab plus standard-of-care or single-agent chemotherapy of physician's choice. As the trial had 19 months follow-up and only included PFS and as it was not reported how many patients were indeed treated with trastuzumab + capecitabine, the trial was excluded as potential external validation for the survival projections for HER2CLIMB. The SOPHIA [77] trial included in the comparator arm 270 patients treated with trastuzumab and physicians choice of chemotherapy. Median follow up was 15.8 months and of the 270 patients only 72 were treated with trastuzumab + capecitabine. A KM curve for this sub-population was not published. As median follow up was not longer than in HER2CLIMB and as no KM curve for the trastuzumab + capecitabine patients was published, the

SOPHIA trial was excluded as potential external validation for the survival projections for HER2CLIMB. The TH3RESA trial [75, 76] included 154 patients randomized to a combination with HER2-directed therapy + physicians choice of chemotherapy after progression on trastuzumab and lapatinib. The follow up was for the primary analysis 6.5 months for the comparator arm. A later and final OS update with median follow up in the comparator arm of 15.8 months was published in 2017 [76]. At the time of this final OS update 47% of patients in the physicians choice arm had crossed over to the intervention therapy. As median follow up was not longer than in HER2CLIMB and as 47% of patients had crossed over, the TH3RESA trial was excluded as potential external validation for the survival projections for HER2CLIMB.

8.3.1.4 Treatment duration

Treatment duration for the tucatinib combination and TRASCAP was taken from HER2CLIMB to best capture resource use of drug. The KM-estimate was close to complete and the extended mean was used in the base case analysis, the cut-point for the exponential extension of the KM-estimate was 20 months. As a scenario analysis, treatment during PFS was tested. Treatment duration as used in the analysis is presented in Figure 28.

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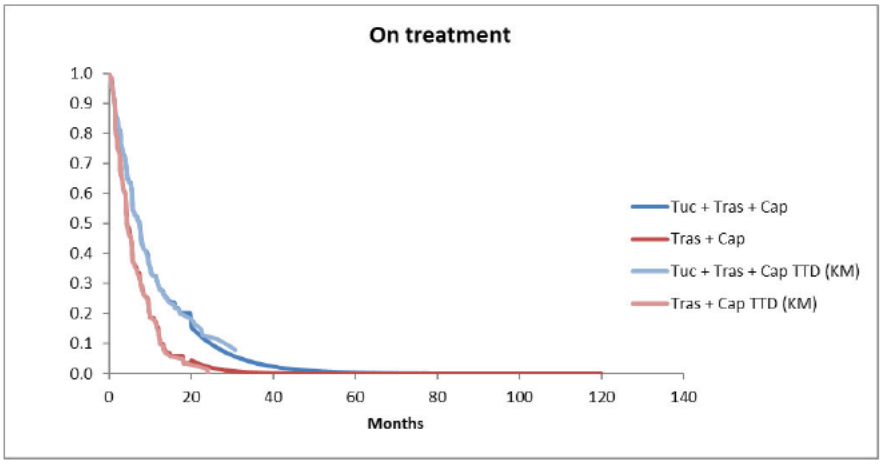
Figure 28. Treatment duration of the tucatinib combination and TRASCAP in HER2CLIMB



8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

Of the 612 patients, EQ-5D-5L data were available for 331, of which 218 patients (66%) had received tucatinib and 113 patients (34%) had received placebo. The EQ-5D-5L was added in an amendment to the original protocol and thus was not available to patient that were enrolled prior to the time of the amendment. Patient demographic and disease characteristics at baseline were well balanced between the treatment groups in the overall HER2CLIMB trial. Characteristics were also similar between the total trial population and subset with available EQ-5D data with no notable between-group differences in baseline characteristics (see Table 24). The proportion of patients with EQ-5D-5L measures missing at baseline and at each timepoint for both treatment arms is presented in Table 25.

Table 24. Baseline characteristics for the total study population and subset with available EQ-5D Data

		Total Study Population		HRQoL Sub population		Missing HRQoL Subopulation	
		Tucatinib combination (n=410)	TRASCAP (n=202)	Tucatinib combination (n=218)	TRASCAP (n=113)	Tucatinib combination (n=192)	TRASCAP (n=89)
Age (years), median (range)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV at initial diagnosis, n (%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology, n (%)	ER and/or PR positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ER and PR negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior lines of therapy, median (range)	Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Metastatic setting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Presence/history of brain metastases		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: [53]

Table 25. Completion of EQ-5D by visit for the overall population

	Tucatinib combination N=410	TRASCAP N=202
Timepoint	Completed at baseline [redacted]	Completed at baseline [redacted]
Cycle 3	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]
30-day follow-up (progressed)	[redacted]	[redacted]

Source: [53]

Numerator is # of patients who completed the EQ-5D survey in that cycle. Denominator is # of patients who completed the baseline survey and were still on treatment.

The EQ-5D index score was calculated using specific weights for Denmark according to the recommendations by the Danish Medicines Council [79]. The effect of AEs on HRQoL is assumed to be included in the HRQoL measures from HER2CLIMB. A repeated measure model was used to estimate the EQ-5D-5L index score per health state (Table 26)

Table 26. QALY-weights from HER2CLIMB

Health State	Tucatinib	TRASCAP	Instrument	Tariff (value set) used
	Value	**Value**		
Progression-free	[redacted]	[redacted]	EQ-5D-5L	DK tariff
Progressed[a]	[redacted]	[redacted]	EQ-5D-5L	DK tariff
Dead	0	0		

Source: [53]

[a] Calculated from the 30-day post-treatment assessment. Source: HER2CLIMB analysis. TRASCAP: Trastuzumab and capecitabine

8.4.1.1 Missing data

Because the majority of EQ-5D was missing due to a protocol-driven change in collection rather than driven by patient adherence or follow-up, data were assumed to be missing completely at random for the base-case analysis. No imputation of missing data was done, unless a patient died, in which case zero was imputed. Further, if any of the 5 items within the EQ-5D-5L were missing, the utility score was recorded as missing without imputation. Ambiguous values (e.g., two boxes are ticked for a single dimension) were treated as missing values. Patient characteristics for patients with missing EQ-5D-5L data were similar to patients with available data (see Table 24)

8.4.1.2 Disutility due to brain metastases

The disutility due to progression due to brain metastases were sourced from HER2CLIMB, see Table 27. The additional disutility associated with progression due to brain metastases was calculated as the mean difference between progression due to other reasons than brain metastases and progression due to brain metastases. The EQ-5D index score was calculated using specific weights for Denmark.

Table 27. Disutility associated with progression due to brain metastases

	Mean	SE
Disutility due to progression due to brain metastases	[redacted]	[redacted]

Source: [53]

SE: Standard error

8.4.2 Health state utility values used in the health economic model

In the base case analysis, the EQ-5D values from the pivotal clinical trial HER2CLIMB was used. These values represent the best quality of life (QoL) estimates for the relevant patient group. The QoL values from HER2CLIMB also captures the QoL estimates for the most relevant comparator in Denmark, trastuzumab in combination with capecitabine. Further, QoL estimates directly from the trial also capture any disutility associated with adverse events, removing uncertainty associated with sourcing this disutility from other sources. In "Table 15. Quality of Life: Patients With ≥ 2 Prior Anti-HER2 Regimens" page 65 in Appendix A, all quality of life data extracted from the included studies are shown. It is noted that the MonarcHER [78] and NALA [60] trials included the cancer specific measure EORTC QLQ-C30. The utility values for HER2CLIMB seems in line with findings from other studies. Further "Table 24. Quality of Life" page 115 in Appendix A includes all quality of life data extracted for HER2+ patients after one or more anti-HER2 therapies and confirms that utility values for HER2CLIMB are in line with findings from earlier studies.

A disutility associated with brain metastases was added to patients that progress due to progression of, or the development of a new lesion in the brain. The disutility is presented in Table 27.

8.5 Resource use and costs

Healthcare utilization and resource use were estimated and linked costs were included in the health economic model. Table 28 - Table 31 present drug acquisition costs of the intervention, the comparator and post-progression treatments, respectively. For the analysis, the pharmacy purchasing price (wholesale price) was used.

Table 34 presents administration costs for intravenous infusion, subcutaneous injection and oral administration. Healthcare utilization frequencies for routine care as well as monitoring and associated costs are presented in Table 35 - Table 39. Table 40 shows the costs linked to the management of adverse events. Additionally, end-of-life costs were included to reflect increased resource use towards the end of life (Table 41).

According to the societal perspective of the health economic analysis indirect and non-healthcare direct costs were included. These include travel costs and time spent due to treatment for both patients and caregivers and are presented in Table 42 and Table 43.

Table 28. Tucatinib unit cost in Denmark

Drug	Strength (mg)	Pack size	Pack price (DKK) - PPP	Pack price (DKK) - PSP
Tucatinib	150	84	45,930.8	49,435
	50	88	16,039.33	17,271.78

PPP: Pharmacy purchasing price, PSP: Pharmacy selling price

Table 29. Trastuzumab and capecitabine unit costs in Denmark

Drug	Strength (mg)	Pack size	Pack price (DKK)		Source
			PPP	PSP	
Trastuzumab (IV)	600	1	11,114	14,966	Medicinpriser.dk*
Capecitabine	500	120	250	353	Medicinpriser.dk*

PPP: Pharmacy purchasing price, PSP: Pharmacy selling price Relative dose intensity (RDI) as seen in HER2CLIMB was used in calculating drug use in the model. The RDI is presented in **Table 30**..*Accessed March 2021

Table 30. Relative dose intensity

Treatment	Relative dose intensity	Source
Tucatinib	88.5%	[52]
Capecitabine – Tucatinib arm	73.9%	[52]
Trastuzumab IV (cycle 1) – Tucatinib arm	100%	[52]/Assumed the same as for capecitabine
Trastuzumab IV (cycle 2+) – Tucatinib arm	73,9%	[52]/Assumed the same as for capecitabine
Capecitabine – Tucatinib arm	79%	[52]
Trastuzumab IV (cycle 1) – Tucatinib arm	100%	[52]/Assumed the same as for capecitabine
Trastuzumab IV (cycle 2+) – Tucatinib arm	79%	[52]/Assumed the same as for capecitabine

Post progression treatments were based on feedback from a Danish clinical expert with experience of treating the relevant patient population in Denmark [43]. The total sums to more than 100% as patients receive combination treatment, e.g. 70% receive trastuzumab in combination with either eribulin (50% of tratuzumab treated patients – 35% of total patients) or vinorelbine (50% of tratuzumab treated patients – 35% of total patients), 15% of total patients receive lapatinib and 4% of total patients receive pertuzumab.

Table 31. Systemic treatments post-progression

Treatment/Drug	Dose (mg)	Total dose (mg)	Doses per cycle	Proportion receiving treatment, tucatinib combination [43]	Proportion receiving treatment, TRASCAP [43]	Treatment duration (months)
Trastuzumab (IV)	6.0	417	1	70%	70%	5.7 [52]
Lapatinib	1250	1250	21	15%	15%	4.4 [80]
Vinorelbine	80	144	3	35%	35%	8.7 [61]
Eribulin	1.4	2.214	2	35%	35%	4.5 [81]
Pertuzumab	420	420	1	4%	4%	10.3 [82]

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Additionally, antidiarrheals are administered for both treatment groups (Table 32 and Table 33).

Table 32. Loperamide cost in Denmark

Drug	Strength (mg)	Pack size	Pack price (DKK) PPP	PSP
Loperamide	2	100	218.40	310.55

PPP: Pharmacy purchasing price, PSP: Pharmacy selling price

Table 33. Antidiarrheal treatment

Treatment/Drug	Dose (mg)	Total dose (mg)	Doses per cycle	Proportion receiving treatment	Treatment duration (days)
Tucatinib combination	6.0	6.0	21	100% [52]	21.63 [52]
TRASCAP	6.0	6.0	21	100% [52]	5.8 [52]

TRASCAP: Trastuzumab and capecitabine

Table 34. Cost of administration

Resource	Unit cost (DKK)	Source
IV administration	712*	[83, 84]

IV: Intravenous,* inflated to 2021 (Inflation rate: 1.003 [85])

Intravenous administration

The cost of an intravenous administration was assumed with be DKK 709.83 per administration. The cost was based on the use of time for a physician and nurse per IV administration following the first administration. For the administration and following observation time, it was assumed that a physician is involved for 30 minutes and a nurse is involved for 10 minutes [84]. For a physician an hourly cost of DKK 1,316 (Overlæger) was assumed, for a nurse (Sygeplejersker) DKK 554 [83]. The cost was then inflated to 2021 [85].

Table 35. Monthly healthcare utilization frequencies for routine care

Item	Health states		
	Progression free	**Progressed disea**	Progressed disease with brain metastases
Oncologist	0.5	0.5	0.8
Specialist nurse	1.4	1.4	1.4
Community nurse	0.1	0.1	0.1
GP	0.0	0.1	0.0

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Table 36. Monthly healthcare utilization frequencies radiation therapy

Item		Health states		
		Progression free	**Progressed disease**	Progressed disease with brain metastases
Radiation	Stereotactic radiation*	0	0	0.08
	Whole brain radiation*	0	0	0.08

*It was assumed that 50% of the patients receive stereotactic radiation and 50% whole brain radiation.

Table 37. Health care utilization inputs for routine care

Item	Unit cost (DKK)	Comment	Reference
Oncologist	1,320	Besøg hos onkolog/ Overlæger (1 hour)*	[83]
Specialist nurse	555.8	Sygeplejersker (1 hour)*	[83]
Community nurse	555.8	Sygeplejersker (1 hour)*	[83]
General practitioner	1,320	Overlæger (1 hour)*	[83]
Radiation for brain metastases	10,090	Stereotaksi (50%), Stråleplanlægning, kompleks, med strålebehandling, 1-2 fraktioner (ekskl. stereotaksi) (50%)	[86]

* inflated to 2021 (Inflation rate: 1.003 [85])

Oncologist visit

For all three health states, oncologist visits were included based on the assumption that the relevant patient population attends follow-up visits within specialized both in a progression-free and progressed health state. The cost applied in the model represents the cost per one oncologist visit and was derived from the unit cost document published by the DMC (DKK 1316, inflated to 2021 – Inflation rate: 1.003 [85]) [83].

Specialist nurse visit

For all three health states, specialist nurse visits were included based on the assumption that the relevant patient population attends follow-up visits within specialized care both in a progression-free and progressed health state. The cost per visit reflects the cost of one nurse visit (one hour). The unit cost was estimated (Sygeplejersker) to be DKK 555.8 based on the unit cost document published by the DMC (DKK 554, inflated to 2021 – Inflation rate: 1.003 [85]) [83].

Community nurse visit

The cost of a community nurse visit was assumed to be the same as a specialist nurse visit.

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General practitioner visit

For all three health states, general practitioner (GP) visits were included based on the assumption that the relevant patient population receives follow-up visits within primary care both in a progression-free and progressed health state. The applied cost reflects the cost of one GP visit (one hour). The unit cost was derived from the unit cost document published by the DMC (DKK 1316, inflated to 2021 – Inflation rate: 1.003 [85]) [83].

Radiation therapy

For patients who progressed due to brain metastases, radiation therapy including whole and stereotactic brain radiation was applied. To derive a unit cost it was assumed that 50% of these patients would receive whole brain irradiation and 50% would receive stereotactic brain radiation. The cost was applied once a year. The unit cost was estimated to be the average of DKK 13,764 (DRG code: 27MP12 Stråleplanlægning, kompleks, med strålebehandling, 1-2 fraktioner (ekskl. stereotaksi)) and DKK 5,383 based on the Danish DRG list or 2021 (DRG code: 27MP10 Stereotaksi) [3].

Table 38. Monthly healthcare utilization frequencies for monitoring

Item	Health states		
	Progression free	**Progressed disea**	Progressed disease with brain metastases
Liver function test	1	1	1
Echocardiogram	0.5	0.5	0.5
CT scan	0.5	0.5	0.5

Table 39. Health care utilization inputs for monitoring care utilization inputs for monitoring

Resource item	Unit cost (DKK)	Comment	Reference
Liver function test	230	ALAT, ALB, ASAT, BASP, GGT	[87]*
Echocardiogram	1,823	DRG 2021: 05PR05 Kardiologisk undersøgelse, udvidet.Kardiologisk undersøgelse, udvidet	[86]
CT scan	1,835	DRG 2021: 30PR07 CT-scanning,CT-scanning, ukompliceret, el. Osteodensitometri	[86]

***Accessed in March 2021**

Liver function test

For all three health states, liver function tests were included based on the assumption that the relevant patient population is monitored frequently in connection with treatment both in a progression-free and progressed health state. The cost per test reflects the cost of one sample

and respective analyses. The unit cost was estimated to be DKK 230 (ALAT DKK 28 + ALB DKK 28 + ASAT DKK 28 + BASP DKK 28 + GGT DKK 118) [87].

Echocardiogram

For all three health states, ECHO scan were included based on the requirement for cardiac monitoring linked to the treatment of HER2-positive breast cancer. The cost per scan was based on the Danish DRG list for 2021 and represents a cardiological examination (DRG code: 05PR05 Kardiologisk undersøgelse, udvidet) [86]. The applied unit cost was estimated to be DKK 1,823.

CT scan

CT scans were included for all patients based on the assumption that patients are monitored frequently. The cost per scan was based on the Danish DRG list for 2021 (DRG code: 30PR07 CT-scanning, ukompliceret, el. osteodensitometri) [86]. The unit cost was estimated to be DKK 1,835.

The management of adverse events was included in the model for grade 3+ treatment-emergent adverse events occurring in at least 2% of patients for both tucatinib and the comparator. Table 40 shows the included adverse events as well as the assumed unit costs for each event. In the model, each adverse event is assumed to last 21 days.

Table 40. Health care utilization inputs for the management of adverse events

Input	Cost (DKK)	Comment/assumption	Reference
Hand-foot syndrome	13,366	DRG 2021:21MA07 Andre skader, forgiftning og toksiske virkninger	[86]
Diarrhea	22,115	DRG 2021: 06MA10 Betændelse i spiserør, mave og tarm m.v., pat. mindst 18 år, m. kompl. bidiag.	[86]
Alanine aminotransferase increased	13,366	DRG 2021 21MA07 Andre skader, forgiftning og toksiske virkninger	[86]
Fatigue	3,987	DRG 2021:23MA03 Symptomer og fund, u. kompl. bidiag.	[86]
Aspartate aminotransferase increased	13,366	DRG 2021:21MA07 Andre skader, forgiftning og toksiske virkninger	[86]
Anemia	69,514	DRG 2021:16MP06 Mangelanæmier	[86]
Nausea	5,130	DRG 2021:06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år,u. kompl. bidiag.	[86]
Vomiting	22,115	DRG 2021:06MA10 Betændelse i spiserør, mave og tarm m.v., pat. mindst 18 år, m. kompl. bidiag.	[86]
Stomatitis	1,186	DRG 2021:03MA09 Andre sygdomme i øre, næse, mund og hals	[86]

Hand-foot-syndrome

The cost of management of the hand-foot syndrome was applied for every occurrence. The management was assumed to include the treatment toxicities. A total sum of DKK 13,366 was assumed based on the Danish DRG list (21MA07 Andre skader, forgiftning og toksiske virkninger) [86].

Diarrhea

The cost of management of diarrhea was applied for every occurrence. The management was assumed to be the same as the management of inflammation of the esophagus, stomach and

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intestines (complicated). The cost of DKK 22,115 was derived for the Danish DRG list (06MA10 Betændelse i spiserør, mave og tarm m.v., pat. mindst 18 år, m. kompl. bidiag) [86].

Alanine aminotransferase increased

The cost of management of increased alanine aminotransferase was applied for every occurrence. The cost of DKK 13,366 linked to toxicities and other damages was assumed to be representative for the management of increased ALT. The cost was derived for the Danish DRG list (21MA07 Andre skader, forgiftning og toksiske virkninger) [86].

Aspartate aminotransferase increased

The cost of management of increased aspartate aminotransferase was assumed to be the same as increased alanine aminotransferase and was applied for every occurrence.

Fatigue

The cost of management of fatigue was applied for every occurrence. The cost of DKK 3987 was derived the Danish DRG list (23MA03 Symptomer og fund, u. kompl. bidiag) [86].

Anemia

The cost of management of anemia was applied for every occurrence. The management of anemia was derived from the Danish DRG list (16MP06 Mangelanæmier) [86]. A cost of DKK 69,514 applied.

Nausea

The cost of management of nausea was applied for every occurrence. The cost of DKK 5130 was derived from the Danish DRG list (06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år,u. kompl. bidiag.) [86].

Vomiting

The cost of management of vomiting was applied for every time the event occurs. The cost of DKK 22,115 was based on the Danish DRG list (06MA10 Betændelse i spiserør, mave og tarm m.v., pat. mindst 18 år, m. kompl. bidiag.) [86].

Stomatitis

The cost of management of stomatitis was applied for every time the event occurs. The cost of DKK 1,186 was derived from the Danish DRG list (03MA09 Andre sygdomme i øre, næse, mund og hals) [86].

A one-off cost is applied at the transition to the death health state to represent the cost of palliative care. No other costs are associated with the death health state. The end of life cost or 'Terminal care cost' is presented in Table 41. The cost was derived from a previous decision document published by Amgros and inflated to 2021 [88].

Table 41. End of life costs

Unit cost (DKK)	Source
68,888.61*	[88]

* inflated to 2021 (Inflation rate: 1.003 [85])

For the analysis, an extended health service perspective was applied including time spent due to treatment and transportation cost. For one hour of time a value of DKK 180 was assumed [83]. Table 42 shows the estimated use of time and linked indirect cost for routine care. Table 43

shows the proportion of productivity losses applied for patients and caregivers. It was assumed that the productivity loss applies to 100% of the patients regardless of health state. For caregivers, 50% spent time due to the patient's treatment in the progression-free health state and 100% for patients with progressed disease. The indirect costs are applied for each cycle and are presented as part of the health state costs.

Table 42. Overview of applied indirect costs for routine care

Resource item	Assumed time use	Cost per visit (DKK)	Reference
Oncologist	4 h	721*	[83]
Specialist nurse	4 h	721*	[83]
Nurse	4 h	721*	[83]
GP	4 h	721*	[83]
Transportation costs per visit	-	101*	[83]

* inflated to 2021 (Inflation rate: 1.003 [85])

Table 43. Proportion of time spent due to treatment for patients and caregiver

Population	Proportion of time spent due to treatment			Source
	Progression free	Progressed disease	Progressed disease with brain metastases	
Patients	100%	100%	100%	[74]
Caregiver	100%	100%	100%	[74]

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8.6 Results

8.6.1 Base case overview

An overview of the base case is presented in Table 44.

Table 44 Base case overview

Setting	Value/choice
Comparator	Trastuzumab combined with capecitabine (TRASCAP)
Type of model	Partitioned survival model
Time horizon	20 years (life time)
Treatment line	3rd line
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in HER2CLIMB [52]. Danish population weights were used to estimate health-state utility values
Included costs	Pharmaceutical costs Healthcare utilization costs Costs of adverse events Indirect costs
Dosage of pharmaceutical	Based on body weight and body surface area
Average time on treatment	Intervention: Extended mean Comparator: Extended mean
Parametric function for PFS	Intervention: Log-normal Comparator: Log-normal
Parametric function for OS	Intervention: Log-logistic Comparator: Log-logistic

Base case resultsTable 45 presents total costs, life-years gained, QALYs, and incremental costs per QALY for the tucatinib combination versus TRASCAP. Compared with TRASCAP, the tucatinib combination generated 0.85 incremental QALYs and 1.01 incremental life-years gained, and the tucatinib-treated cohort had higher total lifetime costs. The ICER was DKK 887,621 per QALY gained.

Table 45. Base case results

	Tucatinib combination (DKK)	TRASCAP (DKK)	Incremental (DKK)	ICER (DKK)
Total cost	1,230,634	479,242	751,392	
LYs	3.01	2.00	1.01	744,398
QALYs	2.40	1.55	0.85	886,942

TRASCAP: trastuzumab and capecitabine, LYs: Life years, QALYs: Quality-adjusted life years

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Table 46. Time pre- and post-progression (years per patient, undiscounted)

Health state	Tucatinib combination (Years)	TRASCAP (Years)	Incremental (Years)
Progression-free	1.30	0.66	0.64
Progressed w.o. Brain Metastases	1.98	1.21	0.76
Progressed w. Brain Metastases	0.10	0.26	-0.17
Total	3.37	2.14	1.24

TRASCAP: trastuzumab and capecitabine

Table 47 presents a breakdown of costs by category. The incremental cost of DKK 751,392 for the tucatinib combination versus TRASCAP was predominantly due to additional drug acquisition costs.

Table 47. Summary of Costs (Discounted)

	Tucatinib combination	TRASCAP	Incremental
Cost of study treatments (kr)			
Tucatinib	625,387		625,387
Trastuzumab	122,253	81,253	41,000
Capecitabine	2,388	1,577	811
Drug administration	10,728	6,536	4,192
Total	**760,756**	**89,366**	**671,390**
PFS - disease management and monitoring			
Direct costs - healthcare resource use	**52,077**	**27,422**	**24,655**
Other costs			
Direct costs - transportation costs	5,988	3,153	2,835
Indirect costs - healthcare resource use	43,404	22,855	20,549
Total other costs	**49,391**	**26,008**	**23,383**
Total PFS costs	**101,469**	**53,431**	**48,038**
Progression - disease management and monitoring w BM			
Direct costs - healthcare resource use	**5,436**	**14,660**	**-9,225**
Other costs			

Direct costs - transportation costs	509	1,373	-864
Indirect costs - healthcare resource use	4,043	10,905	-6,862
Total other costs	**4,552**	**12,278**	-7,726
Total	**9,988**	**26,938**	**-16,950**
Progression - disease management and monitoring wo BM			
Direct costs - healthcare resource use	**72,412**	**47,129**	**25,282**
Other costs			
Direct costs - transportation costs	8,223	5,352	2,871
Indirect costs - healthcare resource use	61,036	39,725	21,310
Total other costs	**69,259**	**45,077**	**24,182**
Total	**141,670**	**92,206**	**49,464**
Total PPS costs	**151,658**	**119,145**	**32,514**
Death	**62,091**	**65,154**	**-3,063**
Total health state costs	**315,218**	**237,729**	**77,489**
Post progression treatments	144,950	147,876	-2,926
Antidiarrheals	142	38	104
Adverse events	9,568	4,234	5,335
Total costs	**1,230,634**	**479,242**	**751,392**

TRASCAP: Trastuzumab and capecitabine

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8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

A one-way deterministic sensitivity analysis (OWSA) was conducted. Where upper and lower 95% confidence intervals were not available, input values were varied by 20% for both lower and upper bound. shows the results of the OWSA including the 25 values which had the largest impact on the ICER when being varied. The tornado diagram in Figure 29 shows the ten most sensitive values. The relative dose intensity for tucatinib had the largest impact on the ICER followed by the relative dose intensity for trastuzumab.

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Table 48. Results of deterministic sensitivity analysis

Parameter	Lower Bound	Upper Bound	ICER Difference
Tuc + Tras + Cap - Tucatinib Relative dose intensity	(147,641)	147,641	295,282
Tuc + Tras + Cap - Trastuzumab IV (cycle 2+) Relative dose intensity	(25,415)	25,415	50,830
Tras + Cap - Trastuzumab IV (cycle 2+) Relative dose intensity	15,926	(15,926)	(31,853)
Post-progression % - Trastuzumab IV - Tras + Cap	10,440	(10,440)	(20,880)
Post-progression % - Trastuzumab IV - Tuc + Tras + Cap	(10,233)	10,233	20,467
Mean Body weight (Kg)	(9,428)	9,428	18,855
Post-progression % - Vinorelbine cycle 2+ - Tras + Cap	8,434	(8,434)	16,868)
Post-progression % - Vinorelbine cycle 2+ - Tuc + Tras + Cap	(8,267)	8,267	16,534
Post-progression % - Eribulin - Tras + Cap	7,005	(7,005)	(14,010)
Post-progression % - Eribulin - Tuc + Tras + Cap	(6,866)	6,866	13,733
Health State Costs - Progressed (Direct)	(5,969)	5,969	11,937
Health State Costs - Progression-free (Direct)	(5,821)	5,821	11,641
Health State Costs - Progressed (Other)	(5,709)	5,709	11,418
Health State Costs - Progression-free (Other)	(5,520)	5,520	11,041
Utility - Utility decrement BM	5,287	(5,225)	(10,511)
Tras + Cap - Trastuzumab IV (cycle 1) Relative dose intensity	3,256	(3,256)	(6,512)
Post-progression % - Trastuzumab IV cycle 1 - Tras + Cap	3,244	(3,244)	(6,489)
Tuc + Tras + Cap - Trastuzumab IV (cycle 1) Relative dose intensity	(3,240)	3,240	6,480
Post-progression % - Trastuzumab IV cycle 1 - Tuc + Tras + Cap	(3,180)	3,180	6,360
Post-progression % - Pertuzumab (cycle 2+) - Tras + Cap	2,511	(2,511)	(5,021)

Post-progression % - Pertuzumab (cycle 2+) - Tuc + Tras + Cap	(2,461)	2,461	4,922
Post-progression % - Lapatinib - Tras + Cap	2,370	(2,370)	(4,740)
Post-progression % - Lapatinib - Tuc + Tras + Cap	(2,323)	2,323	4,646
Health State Costs - Progressed w. BM (Direct)	2,178	(2,178)	(4,355)
Health State Costs - Progressed w. BM (Other)	1,824	(1,824)	(3,648)

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Figure 29. Tornado diagram for one-way sensitivity analysis

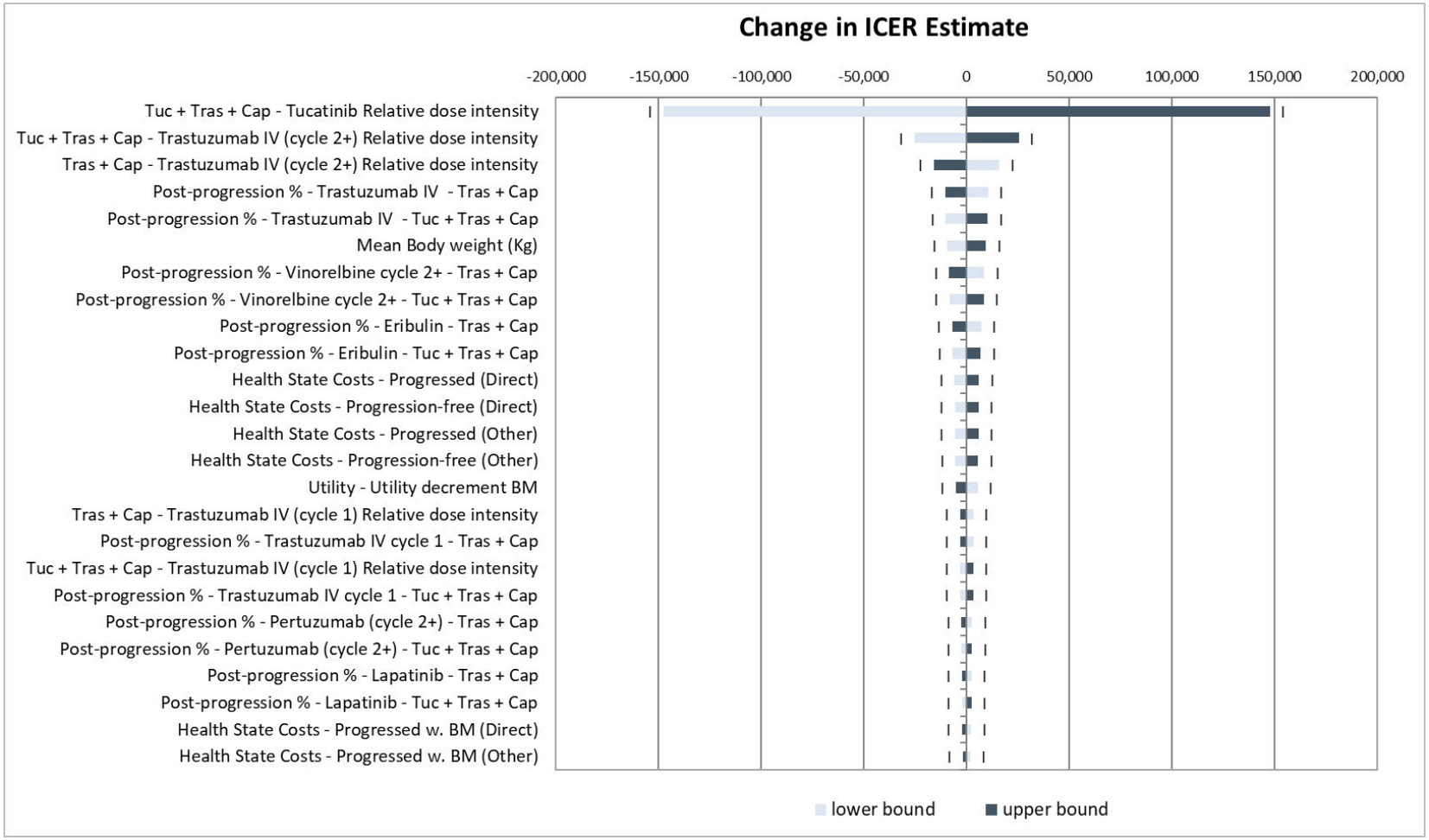


Table 49 shows the exploration of the ICER in relation to different discounts applied to the pack price of tucatinib. With a discount of 100% the ICER is DKK 135,041 Tucatinib does not dominate since it is administered in combination with trastuzumab and capecitabine and combined with longer survival as well as longer treatment duration, patients in the tucatinib arm accumulate higher cost over time.

Table 49. Results of exploration of the ICER in relation to the drug pack price

Discount for pack price	ICER – Base case (no discount)	ICER – With applied Discount	Difference
10%	886,942	813,122	-73,821
20%		739,301	-147,641
30%		665,481	-221,462
40%		591,660	-295,282
50%		517,839	-369,103
60%		444,019	-442,924
70%		370,198	-516,744
80%		296,378	-590,565
90%		222,557	-664,385
100%		148,736	-738,206

In Table 50 below the results of the scenario analyses are presented.

Table 50. Scenario analyses

Scenario	Base case	Base case ICER (DKK)	ICER (Scenario) (DKK)
Treatment dependent health state utilities (mean values)	Treatment independent	886,942	932,371
Progression due to brain metastases switched off (progression due to any cause)	On		917,904
Disutility due to brain metastases turned off	On		914,023
Payer perspective	Restricted societal		839,916
Time horizon 5 years	20 years		1,472,179
Time horizon 10 years	20 years		1,045,498
Time horizon 15 years	20 years		934,866
Treatment duration: Restricted mean	Extended mean		650,860
Treatment duration: PFS	Extended mean		1,230,345
PFS distribution: Log-logistic	Lognormal		890,432
OS distribution: Lognormal	Log-logisitic		668,697
Discount trastuzumab 80%	0%		849,232
Discount rate – Effect: 0%	3.5%		730,949
Discount rate – Effect: 5%			954,648

Discount rate – Costs: 0%	3.5%	929,094
Discount rate – Costs: 5%		871,896
Body weight: 75 kg	69.5 kg	890,673
Age adjusted utilities	No	887,182

8.7.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analyses (PSA) were conducted to establish the impact of parameter uncertainty. A total of 1,000 iterations were run. An overview of all assumptions regarding the PSA is presented in Appendix J Probabilistic sensitivity analyses.

Figure 30 presents the cost-effectiveness plane, which showed that all 1,000 iterations were in the North-East quadrant.

Figure 30. Cost-effectiveness plane

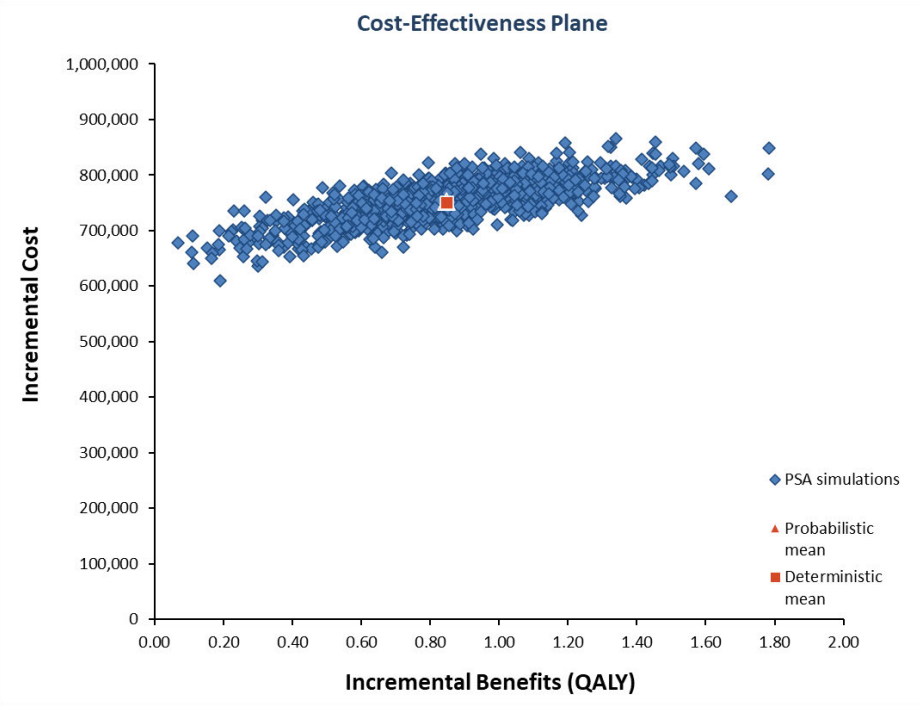
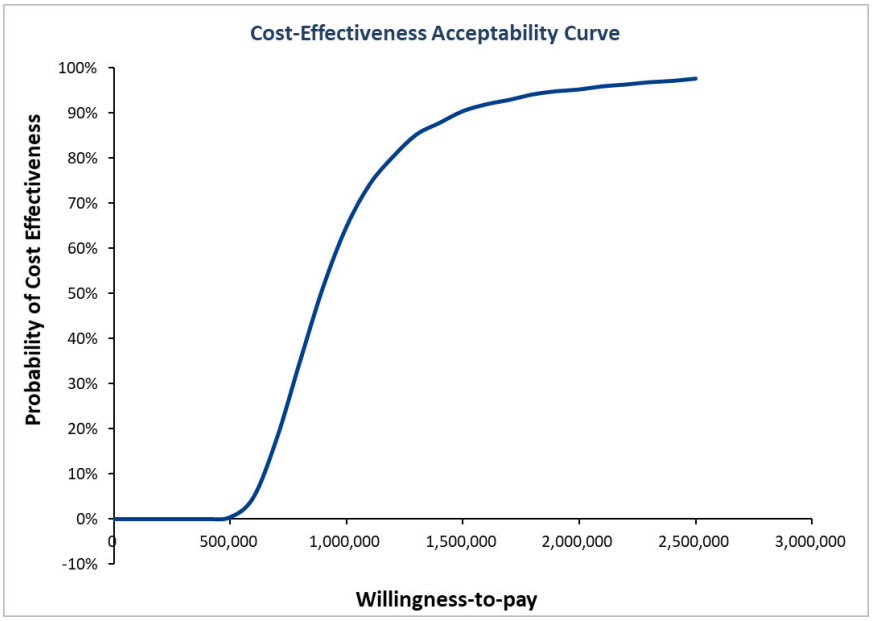


Figure 31 presents the cost-effectiveness acceptability curve (CEAC). The CEAC showed that the tucatinib combination had a 50% probability of being cost-effective at a willingness-to-pay of DKK 900,000.

Figure 31. Cost-effectiveness acceptability curve



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9. Budget impact analysis

The budget impact of tucatinib is presented below in Table 51 - Table 55. Prices are pharmacy purchasing price (PPP/AIP). All costs relevant to the regions have been included: drug costs (Table 28-Table 33), the administration of drugs (Table 33), adverse events (Table 40), death (Table 41), disease management and monitoring (Table 35-Table 39). Per patient costs from the first five years of the cost-effectiveness analysis was used on inform the budget impact analysis. The calculation was employs an open cohort with patients entering each year.

Number of patients

See section 5.1.4 for the estimate of patient numbers. The uptake of tucatinib in Denmark is estimated to start at 50% and to increase by 5% per year to reach 70% year 5. The analysis assumes that no new HER2-positive targeted therapy enters the Danish market in third line during the time period.

Table 51. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Tucatinib combination	55	61	67	72	78
Trastuzumab + capecitabine	55	50	44	39	33

Table 52. Number of patients expected to be treated in the next five-year period - if the pharmaceutical is NOT introduced.

	Year 1	Year 2	Year 3	Year 4	Year 5
Tucatinib combination	0	0	0	0	0
Trastuzumab + capecitabine	111	111	111	111	111

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Table 53. Costs if The Danish Medicines Council recommends the new pharmaceutical as a possible standard treatment for the indication being applied for.

Costs category	Year 1		Year 2		Year 3		Year 4		Year 5	
	Tucatinib combination	TRASCAP	Tucatinib combination	TRASCAP	Tucatinib combination	TRASCAP	Tucatinib combination	TRASCAP	Tucatinib combination	TRASCAP
Tucatinib	23,777,428	-	33,833,209	-	39,515,989	-	43,751,704	-	47,510,366.98	-
Trastuzumab	4,711,699	4,032,858	6,638,991	4,026,503	7,736,954	3,665,113	8,560,484	3,226,803	9,293,542.49	2,776,399.43
Capecitabine	90,778	77,917	129,169	78,116	150,865	71,168	167,037	62,671	181,386.43	53,930.96
Administration	403,910	321,561	578,810	323,705	677,100	295,169	750,040	259,986	814,623.32	223,758.41
Antidiarrheals	7,855	2,106	8,641	1,895	9,426	1,684	10,212	1,474	10,997.43	1,263.31
Post prog. drugs	5,066,480	6,891,185	7,323,584	7,255,761	8,670,199	6,676,799	9,730,337	5,923,538	10,676,356.88	5,123,874.35
Adverse events	530,477	234,712	583,525	211,241	636,573	187,770	689,620	164,298	742,668.12	140,827.28
Death	978,206	1,382,804	2,040,330	2,449,303	2,825,585	2,735,054	3,435,731	2,680,665	3,950,907.38	2,479,704.77
Disease management and monitoring	2,164,597	2,215,266	3,836,111	3,185,562	5,160,671	3,419,978	6,297,041	3,360,734	7,325,228.35	3,149,056.16
Total	**37,731,429**	**15,158,410**	**54,972,371**	**17,532,086**	**65,383,362**	**17,052,734**	**73,392,205**	**15,680,169**	**80,506,077**	**13,948,815**
Total population	**52,889,839**		**72,504,457**		**82,436,096**		**89,072,375**		**94,454,892**	

Table 54. Costs if The Danish Medicines Council does not recommend the new pharmaceutical as a possible standard treatment for the indication being applied for

Costs category	Year 1		Year 2		Year 3		Year 4		Year 5	
	Tucatinib combination	TRASCAP	Tucatinib combination	TRASCAP	Tucatinib combination	TRASCAP	Tucatinib combination	TRASCAP	Tucatinib combination	TRASCAP
Tucatinib	-	-	-	-	-	-	-	-	-	-
Trastuzumab	-	8,065,716	-	8,859,578	-	9,022,755	-	9,048,411	-	9,052,444.86
Capecitabine	-	155,835	-	171,816	-	175,101	-	175,618	-	175,698.95
Administration	-	643,123	-	711,721	-	725,822	-	728,039	-	728,387.29
Antidiarrheals	-	4,211	-	4,211	-	4,211	-	4,211	-	4,211.04
Post prog. drugs	-	13,782,370	-	15,889,759	-	16,320,811	-	16,446,370	-	16,491,679.71
Adverse events	-	469,424	-	469,424	-	469,424	-	469,424	-	469,424.27
Death	-	2,765,609	-	5,175,166	-	6,264,185	-	6,781,826	-	7,058,088.10
Disease management and monitoring	-	4,430,532	-	6,814,177	-	7,964,427	-	8,642,381	-	9,083,264.00
Total	-	**30,316,820**	-	**38,095,853**	-	**40,946,736**	-	**42,296,280**	-	**43,063,198**
Total population	**30,316,820**		**38,095,853**		**40,946,736**		**42,296,280**		**43,063,198**	

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Table 55. Expected budget impact of introducing the pharmaceutical at the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is introduced	52,889,839	72,504,457	82,436,096	89,072,375	94,454,892
Minus: The pharmaceutical under consideration is NOT introduced	30,316,820	38,095,853	40,946,736	42,296,280	43,063,198
Budget impact of the recommendation	**22,573,019**	**34,408,604**	**41,489,360**	**46,776,095**	**51,391,694**

10. Discussion on the submitted documentation

10.1 Summary of submitted evidence

Tucatinib is an oral HER2-directed TKI used in combination with trastuzumab and capecitabine for treatment of patients with locally advanced or metastatic HER2+ BC who have received two HER2-directed regimens in any setting. For the health economic assessment of tucatinib in combination with trastuzumab and capecitabine a direct comparison was conducted using data from the pivotal trial HER2CLIMB. The comparator in the clinical trial, trastuzumab combined with capecitabine, was considered to be the most relevant comparator in Danish clinical practice.

The HER2CLIMB trial was rigorously designed as a large, double-blind, placebo-controlled, active-comparator trial with the primary endpoint assessed by BICR. The comparator in HERCLIMB, trastuzumab and capecitabine, is a recommended regimen and can be considered a standard of care in the metastatic setting [64]. Patients in HER2CLIMB were enrolled globally and were required to have received prior treatment with trastuzumab, pertuzumab, and T-DM1. These three agents were considered the standard of care at the time of study initiation. Thus, patients enrolled in HER2CLIMB would have received the best treatment, allowing the benefit of tucatinib to be observed in patients who had received "gold standard" care.

The strength of the HER2CLIMB results is reflected in the consistency of benefit observed in the total population and across all prespecified 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 prespecified patient subgroups including various ages, ECOG status, and geographic region.

10.2 Cost-effectiveness analysis

The discounted results of the base-case deterministic analysis for the all-comers population showed that the tucatinib combination was associated with higher per patient costs and benefits versus TRASCAP. The base-case ICER were DKK 886,942 per QALY gained and DKK 744,398 per life-year gained. The QALY benefit of tucatinib versus TRASCAP manifests predominantly from time spent in the progression-free health state. The incremental cost was due to additional drug acquisition costs associated with the tucatinib combination, which was impacted by drug pack prices, drug doses (including parameters for relative dose intensity and patient body weight or body surface area used in dose calculations), and treatment duration.

The univariate sensitivity analyses demonstrate that the ICER (QALYs) is most sensitive to changes in the relative dose intensity for the tucatinib combination.

The probabilistic sensitivity analysis results were very similar to the deterministic results which demonstrates the robustness of the analysis. The cost-effectiveness acceptability curves showed that the tucatinib combination has 50% probability of being cost-effective at a willingness-to-pay threshold of DKK 900,000 per QALY.

Over a lifetime time horizon, HER2-positve MBC patients treated with the tucatinib combination were estimated to incur mean total costs of DKK 1,230,634 in the base-case with a mean life expectancy of 3.01years and 2.40 total QALYs.

10.2.1 Strengths of the analysis

A transparent, probabilistic cost-effectiveness model was developed in Microsoft Excel and Microsoft Visual Basic for Applications. The model was adapted to a Danish setting according to the DMC's guidelines. The three-health state partitioned survival model structure aligns with the approach used in previous technology appraisals in breast cancer. The model captures the lifetime of patients and uses a 7-day cycle length, which provides sufficient granularity to capture any important differences in costs and outcomes between comparator treatments.

Extensive research was performed to identify input data used in the model, including a systematic literature review of clinical evidence [89] and a systematic literature review of economic evidence [90, 91].

Where possible, data were used from the HER2CLIMB trial in the base-case analysis, which represents the target population. Extensive survival analyses were performed for PFS and OS, including various parametric models fitted to the trial data. There was good consistency between the results using different methodologies, highlighting the robustness of the analyses. Additionally, the model includes health state utility weights derived from EQ-5D data collected in the HER2CLIMB trial. Unit costs were taken from recognized national sources (where available). Extensive sensitivity analysis was performed, including univariate and probabilistic sensitivity analyses incorporating all model parameters.

10.3 Limitations

Some inputs to the analysis were based on assumptions and clinical expert opinion, such as the proportion of patients receiving different post-progression treatments. No treatment duration data for post-progression treatments were available from the HER2CLIMB trial; data was instead derived from literature.

Long-term extrapolation of OS curves from short-term clinical trials is always subject to uncertainty and hence should be validated against long-term data from other sources. However, long-term validation specifically for this patient population is difficult due to a lack of real-world evidence.

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Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

See attached SLR.

Appendix B Main characteristics of included studies

Table 56. Overview of HER2CLIMB

	Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer, Murthy et al. [52])
Sample size (n)	612
Study design	Randomized, double-blinded, international, multi-center study
Patient population	Patients with HER2-positive metastatic, breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1, who had or did not have brain metastases.
Intervention(s)	Administration of tucatinib, capecitabine, trastuzumab in treatment cycles of 21 days
Comparator(s)	Administration of capecitabine, trastuzumab, placebo in treatment cycles of 21 days
Follow-up period	January 28, 2016 – September 4, 2019 (Primary completion date)
Inclusion criteria	**The inclusion exclusion criteria for HER2CLIMB are given below:** Double-blind Phase Inclusion Criteria Histologically confirmed HER2-positive breast carcinoma, with HER2-positive defined by in situ hybridization (ISH), immunohistochemistry (IHC), or fluorescence in situ hybridization (FISH) methodology 1. Received previous treatment with trastuzumab, pertuzumab, and T-DM1 2. Progression of unresectable locally advanced or metastatic breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy 3. Have measurable or non-measurable disease assessable by RECIST 1.1 4. ECOG Performance Status of 0 or 1 5. Adequate hepatic and renal function and hematologic parameters 6. Left ventricular ejection fraction (LVEF) ≥ 50% 7. CNS Inclusion - Based on screening brain magnetic resonance imaging (MRI), patients must have one of the following: 1. No evidence of brain metastases 2. Untreated brain metastases not needing immediate local therapy 3. Previously treated brain metastases not needing immediate local therapy a. Brain metastases previously treated with local therapy may either be stable since treatment or may have progressed since prior local CNS therapy b. Patients treated with CNS local therapy for newly identified lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if the following criteria are met: i. Time since whole brain radiation therapy (WBRT) is ≥ 21 days prior to first dose of study treatment, time since stereotactic radiosurgery (SRS) is ≥ 7 days prior to first dose of study treatment, or time since surgical resection is ≥ 28 days. ii. Other sites of disease assessable by RECIST 1.1 are present 4. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions
Exclusion criteria	1. Previously been treated with: 1. 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 toxicity)

2. Neratinib, afatinib, or other investigational HER2/epidermal growth factor receptor (EGFR) or HER2 tyrosine kinase inhibitor (TKI) at any time previously
3. Capecitabine (or other fluoropyrimidine) for metastatic disease except in cases where capecitabine was given for < 21 days and was discontinued for reasons other than disease progression or toxicity. Patients who have received capecitabine for adjuvant or neoadjuvant treatment at least 12 months prior to starting study treatment are eligible.

2. Clinically significant cardiopulmonary disease
3. Carriers of Hepatitis B or Hepatitis C or have other known chronic liver disease
4. Positive for human immunodeficiency virus (HIV)
5. Unable for any reason to undergo MRI of the brain
6. 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
7. Have known dihydropyrimidine dehydrogenase deficiency (DPD)
8. CNS Exclusion - Based on screening brain MRI, patients must not have any of the following:
    1. Any untreated brain lesions > 2.0 cm in size, unless approved by medical monitor
    2. Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of > 2 mg of dexamethasone (or equivalent)
    3. Any brain lesion thought to require immediate local therapy. Patients who undergo local treatment for such lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described under CNS inclusion criteria
    4. Known or suspected leptomeningeal disease (LMD)
    5. Poorly controlled seizures Unblinded Phase Crossover Inclusion Criteria - Participants who were randomized to the control arm (placebo + trastuzumab + capecitabine) must meet the following criteria to be eligible to crossover to the experimental arm.
9. Have measurable or non-measurable disease assessable by RECIST 1.1
10. For patients who were randomized to the control arm and on the long-term follow-up period at the time of crossover screening: have progression of unresectable locally advanced or metastatic breast cancer after last systemic therapy (as confirmed by investigator) or be intolerant of last systemic therapy.
11. Have an ECOG Performance Status of 0 or 1
12. Have a life expectancy of at least 6 months
13. Have adequate hepatic and renal function and hematologic parameters
14. Left ventricular ejection fraction (LVEF) ≥ 50%
15. CNS Inclusion - Based on screening brain magnetic resonance imaging (MRI), patients must have one of the following:

    i. No evidence of brain metastases ii. Untreated brain metastases not needing immediate local therapy iii. Previously treated brain metastases not needing immediate local therapy
16. Brain metastases previously treated with local therapy may either be stable since treatment or may have progressed since prior local CNS therapy
17. Patients treated with CNS local therapy for newly identified lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if the following criteria are met:
    1. Time since whole brain radiation therapy (WBRT) is ≥ 21 days prior to first dose of study treatment, time since stereotactic radiosurgery (SRS) is ≥ 7 days prior to first dose of study treatment, or time since surgical resection is ≥ 28 days.
    2. Other sites of disease assessable by RECIST 1.1 are present Unblinded Phase Crossover Exclusion Criteria - Participants who were randomized to the control

arm (placebo + trastuzumab + capecitabine) will be excluded from the crossover to the experimental arm for any of the following reasons.

18. Discontinuation of study treatment due to an adverse event while on the double-blind phase of the study. If the adverse event leading to discontinuation of study treatment has resolved, the patient may be allowed to crossover with approval from the medical monitor.
19. History of exposure to the following cumulative doses of anthracyclines:
    1. Doxorubicin > 360 mg/m^2
    2. Epirubicin > 720 mg/m^2
    3. Mitoxantrone > 120 mg/m^2
    4. Idarubicin > 90 mg/m^2
    5. Liposomal doxorubicin > 550 mg/m^2
20. History of allergic reactions to trastuzumab, capecitabine, or compounds chemically or biologically similar to tucatinib

    o Exceptions for Grade 1 or 2 infusion related reactions to trastuzumab that were successfully managed, or known allergy to one of the excipients in the study drugs
21. Have received treatment with any systemic anti-cancer therapy, non-CNS radiation, or experimental agent within 3 weeks prior to start of crossover therapy
22. Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
    1. Alopecia and neuropathy (must have resolved to ≤ Grade 2)
    2. CHF (must have been ≤ Grade 1 in severity at the time of occurrence and must have resolved completely)
    3. Anemia (must have resolved to ≤ Grade 2)
23. Have clinically significant cardiopulmonary disease
24. Have known myocardial infarction or unstable angina within 6 months prior to start of crossover therapy
25. Require therapy with warfarin or other coumarin derivatives
26. Inability to swallow pills or significant gastrointestinal disease which would preclude the adequate oral absorption of medications
27. Have used a strong CYP2C8 inhibitor within 5 half-lives of the inhibitor or have used a strong CYP2C8 or CYP34A inducer within 5 days prior to start of the crossover (tucatinib) treatment.
28. Known dihydropyrimidine dehydrogenase deficiency
29. Unable to undergo contract MRI of the brain
30. Have evidence within 2 years prior to start of crossover therapy of another malignancy that required systemic treatment
31. CNS Exclusion:
32. CNS Exclusion - Based on screening brain MRI, patients must not have any of the following:
    1. Any untreated brain lesions > 2.0 cm in size, unless approved by medical monitor
    2. Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of > 2 mg of dexamethasone (or equivalent)
    3. Any brain lesion thought to require immediate local therapy. Patients who undergo local treatment for such lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described under CNS inclusion criteria
    4. Known or suspected leptomeningeal disease (LMD)
    5. Poorly controlled seizures

Primary endpoints reported	PFS (Per RECIST 1.1[3] as determined by Blinded Independent Central Review (BICR)) among the first 480 patients who underwent randomization defined as the time from randomization to documented disease progression or death from any cause, whichever occurs earlier. Results: PFS at 1 year was 33.1% in the tucatinib-combination group and 12.3% in the placebo-combination group (hazard ratio for disease progression or death, 0.54; 95% confidence interval [CI], 0.42 to 0.71; P<0.001), and the median duration of PFS was 7.8 months and 5.6 months, respectively.
Key secondary outcomes	Key secondary end points were assessed in the total population and included: • OS defined as the time from randomization to death from any cause • PFS (Per RECIST 1.1 as determined by Blinded Independent Central Review (BICR)) among the patients with brain metastases at baseline (same definition as primary end point) • cORR (Per RECIST 1.1. as determined by BICR) defined as the percentage of patients with measurable disease at baseline who had a confirmed complete response or partial response, as assessed by means of blinded independent central review Results: OS at 2 years was 44.9% in the tucatinib-combination group and 26.6% in the placebo combination group (hazard ratio for death, 0.66; 95% CI, 0.50 to 0.88; P=0.005), and the median overall survival was 21.9 months and 17.4 months, respectively. Among the patients with brain metastases, PFS at 1 year was 24.9% in the tucatinib-combination group and 0% in the placebo-combination group (hazard ratio, 0.48; 95% CI, 0.34 to 0.69; P<0.001), and the median PFS was 7.6 months and 5.4 months, respectively. Among the 511 patients with measurable disease at baseline, as assessed by means of blinded independent central review, the percentage who had a confirmed objective response was 40.6% (95% CI, 35.3 to 46.0) in the tucatinib-combination group and 22.8% (95% CI, 16.7 to 29.8) in the placebo-combination group (P<0.001)
Other secondary efficacy endpoints	• PFS (Per RECIST 1.1. as determined by investigator assessment) defined as primary endpoint • PFS in patients without BM • cORR (Per RECIST 1.1. as determined by investigator assessment) • DOR (Per RECIST 1.1. as determined by BICR and investigator assessment) • CBR (Per RECIST 1.1. as determined by BICR and investigator assessment)
Safety endpoints	• Incidence of 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	• Cumulative HRU, including LOS, hospitalizations, and ED visits • HRQoL/health status using the EQ-5D-5L
Exploratory endpoints	• ORR in brain per RANO-BM as determined by BICR • DOR in brain per RANO-BM as determined by BICR • Time to brain progression in patients with BM at baseline per RANO-BM as determined by BICR • Presence of HER2 mutations or other potential biomarkers of response

BICR, blinded independent central review; BM, brain metastases; CBR, clinical benefit rate; cORR: confirmed objective response rate; DOR, duration of response; ED, emergency department; EQ-5D-5L, EuroQoL 5 Dimensions 5 Levels; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; HRU, healthcare resource utilization; ITT, intent to treat; LOS, length of stay; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RANO-BM, Response Assessment in Neuro-Oncology – Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors

[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 6 (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: [52, 53]

[3] Response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) 92. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.

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Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 57. Patient characteristics in HER2CLIMB

	Primary Endpoint Population[a] (N=480)		Total Population[a] (N=612)	
	Tucatinib Combination (n=320)	Placebo Combination (n=160)	Tucatinib Combination (n=410)	Placebo Combination (n=202)
Female sex – no. (%)	317 (99.1)	158 (98.8)	407 (99.3)	200 (99.0)
Age – no. (%)				
<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 – no. (%)				
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 – no. (%)				
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 – no. (%)				
ER and/or PR-positive	190 (59.4)	99 (61.9)	243 (59.3)	127 (62.9)
ER and PR-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] – no. (%)				
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 – no. (%)	108 (33.8)	67 (41.9)	143 (34.9)	77 (38.1)

Presence or history of BM – no. (%)	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 – no. (%)				
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)

BM, brain metastases; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ITT, intent to treat; no, number; OS, overall survival; PR, progesterone receptor; US, United States. [a]The primary end-point 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 randomization. Randomization 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).
Source [52, 53]

Appendix D Efficacy and safety results per study

Table 58. Summary of results from HER2CLIMB

	Primary Endpoint Population[a] (N=480)		Total Population[a] (N=612)	
	Tucatinib Combination (n=320)	**Placebo Combination (n=160)**	**Tucatinib Combination (n=410)**	**Placebo Combination (n=202)**
Progression free survival Median months (PFS) (95% CI)	7.8 (7.5-9.6)	5.6 (4.2-7.1)	8.1 (7.6-9.6)	5.6 (4.3-6.9)
Hazard ratio PFS (95% CI)	0.54 (0.42-0.71))		0.54 (0.42-0.68)	
Overall survival (OS) Median months (95% CI)			21.9 (18.3-31.0)	17.4 (13.6-19.9)
Hazard ratio OS (95% CI)			0.66 (0.50-0.88)	
Confirmed objective response per BICR in patients with measurable disease			**Tucatinib Combination (n=340)**	**Placebo Combination (n=171)**
Objective response, n (%)			138 (40.6)	39 (22.8)
95% CI[c]			35.3, 46.0	16.7, 29.8
Stratified CMH p-value[d]			<0.001	

Best confirmed response 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[b]	20 (5.9)	7 (4.1)
Clinical benefit rate (CBR) % 95% CI*	59.8% (54.8, 64.5)	38.1% (31.4, 45.2)
Duration of response Median, months, 95% CI**	8.3 (6.2, 9.7)	6.3 (5.8, 8.9)
Confirmed objective response per investigator in patients with measurable disease	**Tucatinib Combination (N=357)**	**Placebo-Combination (N=173)**
Objective response, n (%)	146 (40.9)	37 (21.4)
95% CI[a]	(35.8, 46.2)	(15.5, 28.3)
Stratified CMH p-value[b]	0.00001	
Best confirmed response n (%)		
Complete response	8 (2.2)	2 (1.2)
Partial response	138 (38.7)	35 (20.2)
Stable disease	151 (42.3)	96 (55.5)
Progressive disease	39 (10.9)	33 (19.1)
Not evaluable	0	1 (0.6)
Not available[d]	21 (5.9)	6 (3.5)
Clinical benefit rate (CBR) % 95% CI*	58.0% (53.1, 62.9)	37.6% (30.9, 44.7)
Duration of response Median, months, 95% CI**	6.9 (6.2, 8.3)	6.9 (4.2, 8.9)

BICR, blinded independent central review; BM, brain metastases; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ECOG, Eastern Cooperative Oncology Group; ITT, intent to treat; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; US, United States

[a] Confirmed best overall response assessed per RECIST 1.1.

[b] Patients with no post-baseline response assessment.

[c] Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934).

[d] 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 randomization.

*The clinical benefit rate (CBR) was defined as achieving stable disease (SD) or non-CR/non-PD for ≥6 months (i.e., no documented PD or death within 6 months from date of randomization) or a best overall response of CR or PR as determined by BICR review using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
** Duration of response (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.
Source: [54]

For safety see section 7.

Appendix E Safety data for intervention and comparator(s)

See section 7.

Appendix F Comparative analysis of efficacy and safety

Not applicable

Appendix G – Extrapolation

See section 8.3

Appendix H – Literature search for HRQoL data

See attached SLR.

Appendix I Mapping of HRQoL data

Not applicable.

Appendix J Probabilistic sensitivity analyses

In order to evaluate uncertainty associated with parameter precision, probabilistic sensitivity analyses were conducted to establish the impact of such uncertainty. Probabilistic sensitivity analyses included all model parameters; estimates of uncertainty were based on the uncertainty in the source data where data availability permitted this. In those cases, exact data were used to capture the upper and lower bounds; in instances of a lack of data, 10% variability from mean values was applied.
All parameters were varied simultaneously, and multiple sets of parameter values were sampled from predefined probability distributions to characterize the uncertainty associated with the precision of mean parameter values.
Parameters can be sampled from appropriate statistical distributions, such as the following:

- Survival function parameters can be sampled from correlated distributions defined by their mean, standard error, and covariance.
- Mean costs can be sampled from a gamma distribution defined by the mean and standard error.

Table 59. Summary of base case variables applied in the economic model

Variable	Value	Measurement of Uncertainty (Distribution)
Analysis settings		
Time horizon	20 years	Fixed (no associated parameter uncertainty)
Discount rate: costs	3.5%	Fixed (no associated parameter uncertainty)
Discount rate: outcomes	3.5%	Fixed (no associated parameter uncertainty)
Patient characteristics		
Mean starting age	54 years	Normal (central limit theorem, CLT)
Mean body surface area	1.8 m2	Normal (CLT)
Mean body weight	69.5 kg	Normal (CLT)
Survival analysis (within-trial comparison)		
PFS survival model	Lognormal	Multivariate normal (CLT)
OS survival model	Log-logisitic	Multivariate normal (CLT)
Treatment duration: investigational treatments		
Tucatinib + trastuzumab + capecitabine	TTD: Extended mean	Multivariate normal (CLT)
Trastuzumab + capecitabine	TTD: Extended mean	Multivariate normal (CLT)
External comparators	Assume = PFS	Multivariate normal (CLT)
Treatment duration: post-progression treatments		
Trastuzumab	5.70 months	Normal (CLT)
Lapatinib	4.4 months	Normal (CLT)
Vinorelbine	8.66 months	Normal (CLT)
Eribulin	4.50 months	Normal (CLT)
Pertuzumab	10.3 months	Normal (CLT)

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Treatment duration: antidiarrheals (loperamide)		
Tucatinib combination	21.63 days	Normal (CLT)
TRASCAP	5.80 days	Normal (CLT)
Relative dose intensity: tucatinib combination		
Tucatinib	88.5%	Beta (probability/proportion [0,1])
Capecitabine	73.9%	Beta (probability/proportion [0,1])
Trastuzumab	73.9%	Beta (probability/proportion [0,1])
Relative dose intensity: TRASCAP		
Capecitabine	79.0%	Beta (probability/proportion [0,1])
Trastuzumab	79.0%	Beta (probability/proportion [0,1])
Incidence of grade 3+ adverse events		
Hand-foot syndrome	13.1%	Beta (probability/proportion [0,1])
Diarrhoea	12.9%	Beta (probability/proportion [0,1])
Alanine aminotransferase increased	5.4%	Beta (probability/proportion [0,1])
Fatigue	4.7%	Beta (probability/proportion [0,1])
Aspartate aminotransferase increased	4.5%	Beta (probability/proportion [0,1])
Anaemia	3.7%	Beta (probability/proportion [0,1])
Nausea	3.7%	Beta (probability/proportion [0,1])
Vomiting	3.0%	Beta (probability/proportion [0,1])
Stomatitis	2.5%	Beta (probability/proportion [0,1])
Adverse events incidence: TRASCAP		
Hand-foot syndrome	9.1%	Beta (probability/proportion [0,1])
Diarrhoea	8.6%	Beta (probability/proportion [0,1])
Alanine aminotransferase	0.0%	Beta (probability/proportion [0,1])

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increased		
Fatigue	4.1%	Beta (probability/proportion [0,1])
Aspartate aminotransferase increased	0.0%	Beta (probability/proportion [0,1])
Anaemia	2.5%	Beta (probability/proportion [0,1])
Nausea	3.0%	Beta (probability/proportion [0,1])
Health state utilities		
Progression-free	0.84	Beta (values between 0,1)
Progressed disease	0.77	Beta (values between 0,1)
Dead	0.00	Fixed (by definition)
Indirect costs		
Progression-free	3307.17	Gamma (Positvely skewed >0)
Progressed w.o. brain mets	3461.71	Gamma (Positvely skewed >0)
Progressed w. brain mets	3975.83	Gamma (Positvely skewed >0)
Dead	0	Gamma (Positvely skewed >0)
Adverse-event unit costs		
Hand-foot syndrome	13366.00	Gamma (Positvely skewed >0)
Diarrhea	22115.00	Gamma (Positvely skewed >0)
Alanine aminotransferase increase	13366.00	Gamma (Positvely skewed >0)
Fatigue	3987.00	Gamma (Positvely skewed >0)
Aspartate aminotransferase increase	13366.00	Gamma (Positvely skewed >0)
Anemia	69514.00	Gamma (Positvely skewed >0)
Nausea	5130.00	Gamma (Positvely skewed >0)
Vomiting	22115.00	Gamma (Positvely skewed >0)
Stomatitis	1186.00	Gamma (Positvely skewed >0)

Drug costs		
Tucatinib (150 mg x 84)	45,930.80	Fixed (no associated parameter uncertainty)
Capecitabine (500 mg x 120)	250	Fixed (no associated parameter uncertainty)
Trastuzumab (150 mg)	10,506.64	Fixed (no associated parameter uncertainty)
Pertuzumab (420 mg)	19,144.78	Fixed (no associated parameter uncertainty)
Vinorelbin	1,650.40	Fixed (no associated parameter uncertainty)
Eribulin	2,462.67	Fixed (no associated parameter uncertainty)
Loperamide (2 mg)	218.40	Fixed (no associated parameter uncertainty)
Post-progression treatment: following tucatinib combination		
Trastuzumab	70.0%	Beta (probability/proportion [0,1])
Lapatinib	15.0%	Beta (probability/proportion [0,1])
Vinorelbin	35.0%	Beta (probability/proportion [0,1])
Eribulin	35.0%	Beta (probability/proportion [0,1])
Pertuzumab	4.0%	Beta (probability/proportion [0,1])
Post-progression treatment: following TRASCAP		
Trastuzumab	70.0%	Beta (probability/proportion [0,1])
Lapatinib	15.0%	Beta (probability/proportion [0,1])
Vinorelbin	35.0%	Beta (probability/proportion [0,1])
Eribulin	35.0%	Beta (probability/proportion [0,1])
Pertuzumab	4.0%	Beta (probability/proportion [0,1])
Drug administration costs		
Tucatinib	0	Gamma (Positvely skewed >0)
Capecitabine	0	Gamma (Positvely skewed >0)
Trastuzumab	712	Gamma (Positvely skewed >0)
Vinorelbin	0	Gamma (Positvely skewed >0)
Eribulin	712	Gamma (Positvely skewed >0)

Lapatinib	0	Gamma (Positvely skewed >0)
Pertuzumab	712	Gamma (Positvely skewed >0)

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MGK/CAF

08.03.2022

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.03.2022
Leverandør	Seagen B.V.
Lægemiddel	Tucatinib (Tukysa)
Ansøgt indikation	Tucatinib er indiceret i kombination med trastuzumab og capecitabin til behandling af voksne patienter med HER2-positiv lokalt fremskreden eller metastatisk brystkræft, der har fået mindst 2 tidligere anti-HER2 behandlingsregimer.

[redacted]

[redacted]

[redacted]

Forhandlingsresultat

Amgros har opnået en ny pris på tucatinib (Tukysa):

Tabel 1: Forhandlingsresultat

Læge-middel	Styrke/form	Pakkings-størrelse	AIP (DKK)	Nuværende SAIP (DKK)	Tidligere forhandlet SAIP (DKK)	NY forhandlet SAIP (DKK)	Rabat-procent ift. AIP
Tucatinib	150 mg/tablet	84 stk.	45.930,80	[redacted]	[redacted]	[redacted]	[redacted]
Tucatinib	50 mg/tablet	88 stk.	16.039,33	[redacted]	[redacted]	[redacted]	[redacted]

*Prisen er betinget af en godkendelse i Medicinrådet.

[redacted]

Konkurrencesituationen

Enhertu søgte samme indikation i 2021, men fik en afvisning til standardbehandling af Medicinrådet. Nedenstående tabel viser de årlige lægemiddelpriser for sammenlignelige lægemidler til behandling af HER2-positiv brystkræft. Det bør bemærkes, at Kadcyla er godkendt til standardbehandling i 2. linje i september 2020. Amgros er bevidst omkring behandlingslængden på 10,8 måneder for tucatinib jfr. Medicinrådets vurderingsrapport. Nedenstående tabel er er for sammenlignelighedens skyld dog opgjort med en årlig lægemiddelpris per produkt.

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Tucatinib	150 mg/300 mg. to gange dagligt/tablet	150 mg, 84 stk.	[redacted]	[redacted]	[redacted]
Enhertu	100 mg/5,4 mg/kg/IV	100 mg, 1 stk.	[redacted]	[redacted]	[redacted]
Kadcyla	160 mg/3,6 mg/kg/IV	160 mg, 1 stk.	[redacted]	[redacted]	[redacted]

*Betinget af godkendelse i Medicinrådet til hele populationen

** 2. linje behandling. Kadcyla gives i maksimalt 14 cykler, svarende til en behandlingslængde på 9,6 måneder.

Status fra andre lande

Norge: Under behandling[1]
Sverige: Under behandling
England: Under behandling[2]

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/tucatinib-tukysa-
[2] https://www.nice.org.uk/guidance/indevelopment/gid-ta10708

Kbh. 8. marts 2022

Kære Andreas

Vi forhandlede med Amgros i starten af året på baggrund af den ansøgning vi havde indsendt til Medicinrådet i foråret 2021. Da ansøgningen gjaldt hele indikationen for Tukysa, forhandlede vi baseret på en anbefaling af denne. Vores tilbud om konfidentiel rabat, givet til Amgros den 4. januar, er således ikke gældende for subpopulationen med hjernemetastaser i performance status 0-1 alene.

Som fremført af fagudvalgsformanden på Medicinrådets møde den 26. januar, screenes der ikke systematisk i Danmark for at identificere patienter med hjernemetastaser, i modsætning til procedurerne i studiet. Der blev i HER2CLIMB studiet gennemført en række tests for a identificerer patienter med hjernemetastaser for at muliggøre at der kunne vises effekt i denne sub-population. Det er Seagens opfattelse, at præmissen for kun at give adgang af Tukysa til en undergruppe af patienter er forkert.

HER2CLIMB studiet er per protokol designet og poweret i forhold til følgende mål for patienter, som behandles for lokal fremskreden inoperabel eller metastaserende HER2+ brystkræft efter progression på to HER-2 rettede behandlinger:

Primært mål:

- At undersøge effekten af tucatinib i forhold til placebo I kombination med capecitabin og trastuzumab på progressionsfri overlevelse (PFS) målt ved RECIST 1.1 baseret på blindet uafhængigt central review (BICR)

Sekundære mål:

- At undersøge effekten af tucatinib i forhold til placebo I kombination med capecitabin og trastuzumab på PFS i patienter med tidligere hjernemetastase, aktuel hjernemetastase eller forandringer i hjernen forenelige med hjernemetastase målt ved RECIST 1.1 baseret på BICR
- At undersøge effekten af tucatinib i forhold til placebo I kombination med capecitabin og trastuzumab på overlevelse (OS)

(https://clinicaltrials.gov/ProvidedDocs/94/NCT02614794/SAP_000.pdf)

Resultatet af studiet har givet entydige svar:

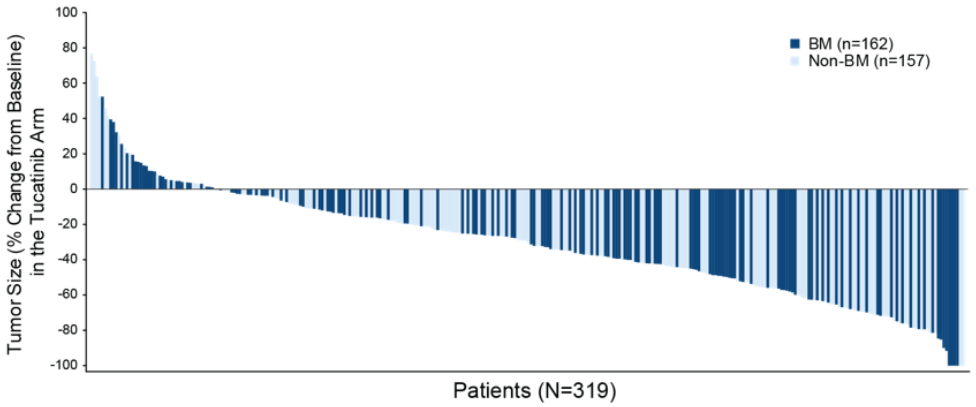
- For alle inkluderede patienter (ITT-populationen) er der en signifikant forbedret PFS og OS efter tucatinib behandling, som er klinisk særdeles meningsfyldt.
- For patienterne i gruppen hjernemetastaser er resultatet det samme.

Som dokumenteret i ansøgningen, fandt man i et eksplorativt endepunkt effekt på udviklingen af hjernemetastaser både for patienter der ved randomisering havde- hhv. ikke havde hjernemetastaser.

En undersøgelse af tumorstørrelse på tværs af patienter med og uden hjernemetastaser viste en konsekvent effekt på tværs af grupperne (mørkeblå=hjernemetastaser, lyseblå=ikke hjernemetastaser).

Change in Tumor Size in the Tucatinib Arm Regardless of the Presence or Absence of Brain Metastases

- The DCR was 92% in the tucatinib arm and 85% in the placebo arm.*



*DCR calculated from all evaluable patients as: ([CR + PR + SD] / [CR + PR + SD + PD]) * 100

Seagen

Bachelot T, et al. Ann Oncol. 2020;31 (suppl_4):S348-S395:Abstract 293P

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I Tyskland blev tucatinib af G-BA klassificeret til "Considerable additional benefit" (den næsthøjeste merværdikategori) for hele populationen af patienter med lokal fremskreden inoperabel eller metastaserende HER2+ brystkræft efter progression på to HER-2 rettede behandlinger. Som en del af ansøgningen i Tyskland skal der per protokol gennemføres interaktionsanalyse for samtlige subpopulationer i studiet. Resultatet af denne analyse viste at der ikke var interaktion (statistisk signifikant effekt) på nogen af de specificerede subpopulationer, inklusiv hjernemetastase gruppen. Der var således en konsistent effekt på tværs af samtlige subpopulationer.

Tabelle 4-66: Ergebnisse der Interaktionsterme für Subgruppenanalysen von Endpunkten der Kategorien Mortalität und Morbidität aus HER2CLIMB zum Zeitpunkt der primären Analyse

Primäre Analyse	p-Wert des Interaktionstests[1]					
Endpunktkategorie Endpunkt	**Alter**	**Region**	**Abstammung**	**ECOG-PS**	**Hormonrezeptor-Status**	**Hirnmetastasen zu Baseline**
Mortalität						
Gesamtüberleben	0,4023	0,8306	0,5174	0,1152	0,0607	0,3257
Morbidität						
EQ5D-VAS (MID 7)	0,8430	0,6711	0,7342	0,8691	0,6319	0,0645
EQ5D-VAS (MID 10)	0,9955	0,8668	0,8131	0,9905	0,4628	0,0699
Datenschnitt: 04.09.2019; **Fett** = statistisch signifikanter Interaktions-p-Wert						

(se side 183 i: https://www.g-ba.de/downloads/92-975-4537/2021-03-12_Modul4A_Tucatinib.pdf)

Vi mener på baggrund af ansøgningen for tucatinib, at en anbefaling alene for patientgruppen med hjernemetastaser i performance status 0-1, ville begrænse værdien af behandlingen unødigt for en patientpopulation med stort medicinsk behov.

HER2CLIMB studiet viste en signifikant, vedvarende overlevelsesgevinst for såvel alle patienterne (ITT-populationen) som for patienter med hjernemetastaser. Det er det eneste og første studie, som viser dette. I Danmark er standardbehandlingen i 3. linie kombinationen af capecitabin og trastuzumab, hvilket er identisk med komparator i studiet.

At studiet viste en fornem gevinst for patienter med hjernemetastaser over standardbehandling i Danmark, bør ikke medføre at patienter uden hjernemetastaser som havde den samme gevinst over standardbehandling i Danmark, udelukkes fra en signifikant bedre behandling.

På baggrund af dette og referatet fra Rådets møde i januar har vi forhandlet en ny konfidentiel pris glædende for hele indikationen med Amgros. Vi håber at denne ny pris kan indgå i Rådets overvejelser på Medicinrådets møde den 23. marts.

De bedste hilsner

Ole

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09.10.2023
CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	25.10.2023
Leverandør	Seagen B.V
Lægemiddel	Tukysa (tucatinib)
Ansøgt indikation	Tucatinib er indiceret i kombination med trastuzumab og capecitabin til behandling af voksne patienter med HER2-positiv lokalt fremskreden eller metastatisk brystkræft, der har fået mindst 2 tidligere anti-HER2 behandlingsregimer.
Nyt lægemiddel / indikationsudvidelse	Revurdering af nyt lægemiddel

Aftaleforhold og prisinformation

[redacted]

Amgros har indgået en aftale med en parallelimportør, som gælder fra d. 01.01.2024 til d. 31.03.2025. Parallelimportøren har mulighed for at sætte prisen ned i hele aftaleperioden.

[redacted]

Amgros har følgende aftalepris på Tukysa (tucatinib):

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Rabatprocent ift. AIP	SAIP (DKK) pr. 01.01.2024	Rabatprocent ift. AIP
Tukysa	150 mg	84 stk.	45.930,34	[redacted]	[redacted]	[redacted]	[redacted]
Tukysa	50 mg	88 stk.	16.039,34	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 2: Lægemiddeludgifter pr. patient med nuværende aftalepris og aftaleprisen pr. 01.01.2024

Lægemiddel	Styrke	Pakkings-størrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Tukysa	150 mg	84 stk.	300 mg PO 2 gange dagligt	[redacted]	[redacted]
Tukysa (parallelimportør) pris pr. 01.01.2024	150 mg	84 stk.	300 mg PO 2 gange dagligt	[redacted]	[redacted]

Konklusion

[redacted]