Medicinrådet

Bilag til Medicinrådets anbefaling vedr. trastuzumab deruxtecan til behandling af voksne patienter med ikke-resekterbar eller metastatisk HER2-positiv brystkræft, som har fået en eller flere tidligere anti-HER2-baserede regimer

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. trastuzumab deruxtecan
2. Forhandlingsnotat fra Amgros vedr. trastuzumab deruxtecan
3. Ansøgers endelige ansøgning vedr. trastuzumab deruxtecan

Medicinrådet
Dampfærgevej 21 -23, 3. sal
2100 København Ø

Ballerup 15.12.2022

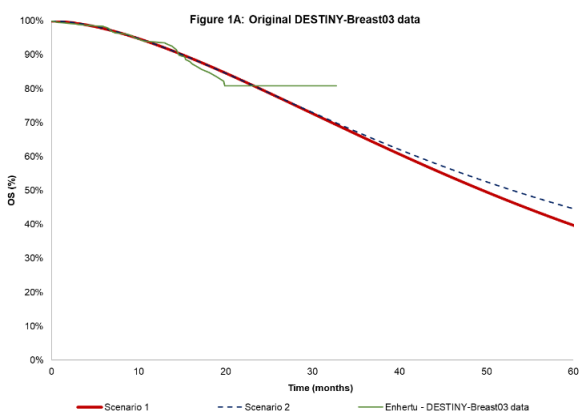
Daiichi-Sankyo(DS)/AstraZeneca(AZ) comment on *Medicinrådets anbefaling vedr. trastuzumab deruxtecan til behandling af voksne patienter med ikke-resekterbar eller metastatisk HER2-positiv brystkræft, som har fået en eller flere tidligere anti-HER2-baserede regimer.*

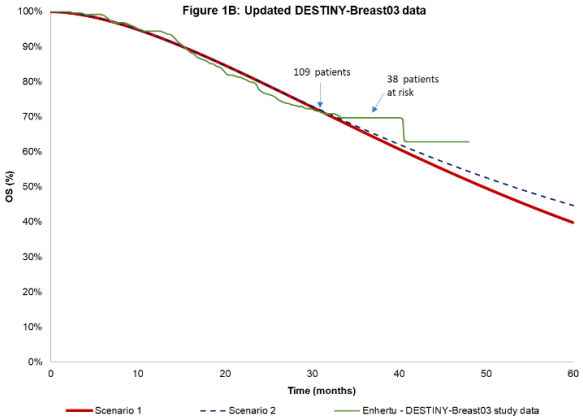
DS and AZ would like to thank Danish Medicine Council's (DMC) for a quick process regarding this assessment. The report is thorough, and the companies agree with the DMC assessment of the treatment effect for both T-DXd and T-DM1. We understand that it can be challenging to assess therapies like this, as it takes a long time to get mature data on overall survival (OS).

Concerning the method assessment report, DMC present a broad range of where they expect the real ICER will be. We acknowledge that DMC state that both of their scenarios are not realistic, but we believe that it is important to add some context of the likelihood of these scenarios and highlight the data that suggest that scenario 2 could be conservative. Finally, scenario 1 should be regarded as unsuitable for decision making based on study data and clinical plausibility.

Point 1: The DESTINY-Breast03 data suggest that Scenario 2 is a conservative assumption

We recognize that it was difficult for DMC to conclude which of the two scenarios that is the most probable, based on only the first data-cut (figure 1A). However, Scenario 1 has limited support with the additional data (figure 1B) that was requested and provided to DMC and recently presented at San Antonio breast cancer symposium, 2022[1]. With the additional follow-up, the data suggest that both models underestimate the survival in the T-DXd-arm. While DMC consider both scenario 1 and 2 to be extreme scenarios, the data actually support scenario 2 as a conservative scenario.



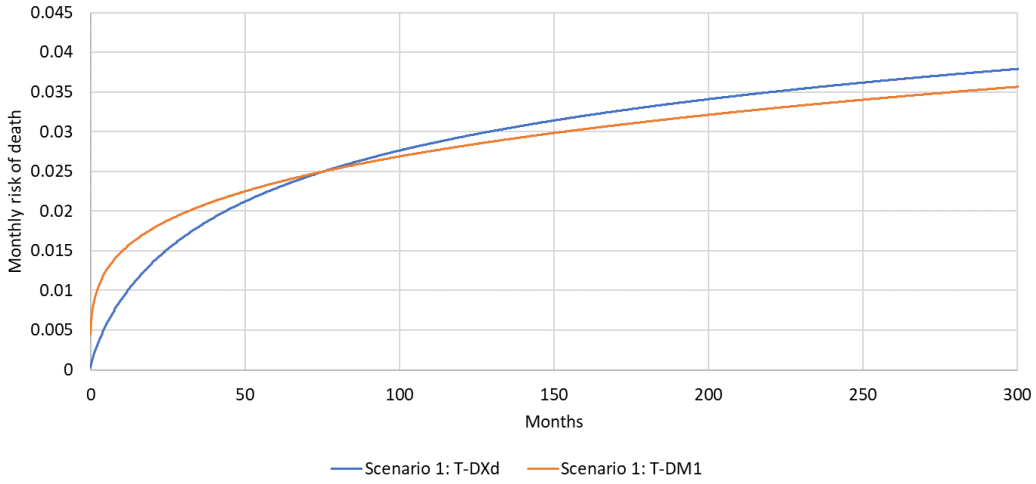


Point 2: PFS data show that scenario 2 provides a realistic OS gain

In the recent updated analysis, the median PFS gain in the study is confirmed to be 22 months, which is close to the estimated discounted OS gain in Scenario 2 (21.6m), but far from the estimated discounted OS gain in Scenario 1 (6.6m).[1] Given that there are more treatment options available after T-DXd (i.e. T-DM1) than after T-DM1 (T-DXd not reimbursed in 3L+ in Denmark), it is reasonable to assume that scenario 2 provide a conservative estimate in a Danish setting. As shown in figure 2, if scenario 1 is used the risk of dying would be higher for T-DXd treated patients than T-DM1 treated patients shortly after the end of study follow-up which does not make sense or have any scientific support. As DMC provide no clinical rationale for how this is plausible given the data from DESTINY-Breast03 and more effective treatment options available after T-DXd in Denmark, this scenario should be omitted from decision-making.

[1] Hurvitz, S. A., Hegg, R., Chung, W.-P., Im, S.-A., Jacot, W., Ganju, V., ...Cortés, J. (2022). Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet, 0(0). doi: 10.1016/S0140-6736(22)02420-5

Figure 2: Monthly risk of death in Scenario 1



Point 3: Scenario 1 is completely different than the assessment of other authorities with almost identical guidelines

In Norway, this indication has already been assessed using the same data and in with very similar assessment guidelines and treatment setting as Denmark. In Norway, Statens legemiddelverk estimated a gain of 1.63 QALY and 1.83 life-year in their base-case when T-DXd was funded, both gains are higher than Scenario 2 which DMC consider optimistic.[2] While AZ/DS views this HTA assessment as overly conservative the base-case ICER is in line with Scenario 2.

Summary

The scientific results show that the effect of T-DXd is of a different order of magnitude than what has been observed for other newer treatments for the same patient population in the past, and the Danish clinical environment has expressed great expectations to the overall survival of T-DXd.

- AZ/DS believes that the decision to introduce T-DXd should be based on costs and effects of treatment with T-DXd compared to T-DM1 that seems realistic based on the study data. The decision should not be based on groundless assumptions about a significantly higher mortality after T-DXd despite additional available treatment options. Based on this, we believe that the most realistic scenario is the company base-case.
- Alternatively, Scenario 2 can be used as a decision basis as it means less underestimation of the data and provides realistic and comparable ICERs to other similar HTA authorities.[3]
- Scenario 1 is not in line with good science, clinical plausibility and health economic practice and should be omitted as a basis for decision-making.

We ask for a decision to be made for T-DXd so patients at high risk for progression must be given access to a drug with a very strong documented effect, which is available for patients in neighbouring countries with similar health care and funding systems.

Kind Regards

Søren Clausen and Mattias Aronsson
AstraZeneca AS

Katja Lundberg Rand
Daiichi-Sankyo

[2] Numbers (1.36 QALYs and 1.65 life-yers) adjusted for Danish discount rate, Danish utility weights and DMC time horizon. https://nyemetoder.no/metoder/trastuzumabderukstekan-enhertu-indikasjon-iii (accessed 2022-12-14)

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

25. januar 2023
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	25. januar 2023
Leverandør	Daiichi-Sankyo i samarbejde med AstraZeneca
Lægemiddel	Enhertu (Trastuzumab deruxtecan, T-DXd)
Ansøgt indikation	Behandling af voksne patienter med ikke-resekterbar eller metastatisk HER2-positiv brystkræft, som har fået en eller flere tidligere anti-HER2-basrede regimer

Forhandlingsresultat

Amgros har opnået følgende pris på Enhertu (Trastuzumab deruxtecan, T-DXd):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP	Tidligere tilbudt SAIP	Forhandlet SAIP	Rabatprocent ift. AIP
Enhertu (T-DXd)	100 mg/pulver til konc.	1 stk.	11.630,1	[redacted]	[redacted]	[redacted]

Prisen er betinget af en anbefaling.

[redacted]

[redacted]

Omsætningen på Enhertu (T-DXd), til AIP-pris, har de sidste 12 måneder været på ca. 6,5 mio. DKK fordelt på alle regioner.

Konkurrencesituationen

Enhertu (T-DXd) sammenlignes med den nuværende 2. linje behandling Kadcyla (trastuzumab emtansin).

Kadcyla (trastuzumab emtansin) indgår i en behandlingsvejledning udarbejdet i RADS. Det er blevet besluttet, at Medicinrådet vil opdatere dele af behandlingsvejledningen.

Tabel 2: Sammenligning af den årlige lægemiddeludgift på Enhertu (T-DXd) og Kadcyla (trastuzumab emtansin)

Lægemiddel	Dosis	Frekvens	Pakning SAIP (DKK)	Antal pakninger	Samlet årspris SAIP (DKK)
Enhertu (T-DXd)	5,4 mg/kg*	IV hver 3 uge	[redacted]	[redacted]	[redacted]
Kadcyla (trastuzumab emtansin)	3,6 mg/kg*	IV hver 3 uge	[redacted]	[redacted]	[redacted]

*Vægt 71 kg

Status fra andre lande

Norge: Anbefalet i oktober 2022[1].
England: Under vurdering. Forventes færdig i januar 2023[2].

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/trastuzumabderukstekan-enhertu-indikasjon-iii
[2] https://www.nice.org.uk/guidance/indevelopment/gid-ta10804

Application for the assessment of Enhertu® (trastuzumab deruxtecan) as monotherapy for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received one or more prior anti HER2 based regimens

Submitted 01.07.2022
Updated 28.11.2022

Daiichi-Sankyo

AstraZeneca

Table of contents

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

1. Basic information

Contact information	
Company	**Astra Zeneca**
Name Title Responsibility Phone number E-mail	Søren Clausen Market Access Head Medicintilskud, forhandling og udbud +45 23 61 55 84 soren.clausen@astrazeneca.com
Name Title Responsibility Phone number E-mail	Mattias Aronsson Health Economist Health economics, Breast cancer +46 73 62 19 021 mattias.aronsson1@astrazeneca.com
Company	**Daiichi Sankyo**
Name Title Responsibility Phone number E-mail	Katja Lundberg Rand Head of Market Access/HEOR, Nordics Medicintilskud, forhandling og udbud, regulatory +45 27 21 10 72 katja.lundberg-rand@daiichi-sankyo.eu

Overview of the pharmaceutical	
Proprietary name	Enhertu
Generic name	Trastuzumab Deruxtecan (T-DXd)/DS-8201
Marketing authorization holder in Denmark	Daiichi Sankyo Europe GmbH Zielstattstrasse 48 81379 München Tyskland
ATC code	L01FD04 (2022)
Pharmacotherapeutic group	Antineoplastic agents, HER2 (Human Epidermal Growth Factor Receptor 2) inhibitors
Active substance(s)	Trastuzumab Deruxtecan

Overview of the pharmaceutical	
Pharmaceutical form(s)	One vial contains powder concentrate of 100 mg T-DXd for preparation of solution for infusion. After reconstitution, one vial of 5 ml solution contains 20 mg/ ml trastuzumab deruxtecan. The recommended dose is 5.4 mg / kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.
Mechanism of action	T-DXd is an antibody drug conjugate (ADC). It is composed of 3 components: a humanized anti-HER2 IgG1 monoclonal (mAb) with same amino acid sequence as trastuzumab covalently linked to a topoisomerase I inhibitor payload (an exatecan derivative). Following binding to Human Epidermal Receptor 2 (HER2) on the tumor cells and internalization, the payload is released through selective tumor protease mediated linker cleavage. Additionally, the payload has a high cell membrane permeability that enables elimination of both targeted tumor cells and the surrounding tumor cells.
Dosage regimen	5.4 mg/kg once every 3 weeks until disease progression or unacceptable toxicity.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	T-DXd as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.
Other approved therapeutic indications	Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti HER2 based regimens (3rd line and beyond is currently under evaluation in MC).
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Not applicable (n/a)
Packaging – types, sizes/number of units, and concentrations	1 vial of 100 mg powder for concentrate for solution for infusion
Orphan drug designation	No

2. Abbreviations

2L	Second line
3L	Third line
3L+	Third line and beyond
ADC	Antibody drug conjugate
AE	Adverse event
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
ATC	Anatomic Therapeutic Chemical classification system
AZ	AstraZeneca
BOR	best overall response
BIC	Bayesian information criterion
CBR	Clinical benefit rate
CEP17	chromosome enumeration probe 17
CI	Confidence interval
CR	Complete response
CT	Computed tomography
CTCAE	common terminology criteria for adverse events
DB01	DESTINY-Breast01 study
DB03	DESTINY-Breast03 study
DCR	Disease control rate
DoR	Duration of response
DS	Daiichi Sankyo
DXd	The payload of T-DXd, a potent topoisomerase I inhibitor
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
ESO	European school of Oncology
EWOC	Escalation with overdose control
FISH	Fluorescent in-situ hybridisation
HER2	Human Epidermal Growth Factor receptor 2
HR	Hormone Receptor
HR	Hazard ratio
HRQoL	Health Related Quality of Life
ICER	Incremental cost-effectiveness ratio
ICR	invasive cervical resorption
IHC	Immunohistochemistry
ILD	Interstitial lung disease

ISH	in-situ hybridisation
ITT	Intention to treat
IV	intravenous
LHRC	luteinizing hormone-releasing hormone
LY	Life years
MAPK	Mitogen-activated kinases
mBC	Metastatic Breast Cancer
mCRM	modified continuous reassessment method
N/A	Not available
NCCN	National Comprehensive Cancer Network
NE	Not evaluated
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI3K/AKT	Phosphatidylinositol-3-Kinase and Protein Kinase B
PK	Pharmacokinetics
Q3W	Every three weeks
QALY	Quality adjusted life years
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable Disease
SD	Standard deviation
DKK	Danish krone
SLR	Systematic literature research
SoC	Standard of Care
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment emergent adverse event
ToD	Treatment discontinuation
TDD	Time to definitive deterioration
TTD	Time to treatment discontinuation
TTR	Time to response
vs	Versus
WTP	Willingness to pay

3. Tables and Figures

Figures

Tables

4. Summary

Description of the indication

Breast cancer is the most common cancer among women in Denmark as well as worldwide (1). Approximately 12-14 percent of breast tumors have a gene amplification or protein overexpression of HER2 (HER2+, Human Epidermal Growth Factor Receptor 2) (2), which untreated leads to an increased aggressiveness of the tumor, high risk of recurrence and increased mortality (3). In the Danish Breast Cancer Cooperative Group (DBCG) database, 471 HER2+ breast cancer diagnoses were reported in 2020(2) and up to 20% of these are expected to develop into metastatic disease (4-7).

While the survival with second line (2L) treatment of HER2+ metastatic breast cancer (mBC) improved with the introduction of trastuzumab emtansine (T-DM1), these patients still live approximately 20 years shorter than women in the same age in the general population. In addition to the short survival, the disease progression increases patients' suffering, worsening symptoms such as fatigue, appetite loss and nausea, and further deteriorating their quality of life.

Patient Population and comparator

The patients eligible for trastuzumab deruxtecan (T-DXd) treatment should have HER2+, unresectable, and/or metastatic breast cancer and received one or more prior HER2 targeted therapies, including trastuzumab and taxane, i.e. in 2L and beyond. According to Danish clinical experts, patients eligible for T-DXd is today treated with T-DM1 in Denmark.

Intervention

T-DXd as monotherapy is expected to be indicated for the treatment of adult patients with unresectable and/or metastatic HER2+ breast cancer who have received one or more prior anti-HER2 based regimens. One vial of T-DXd contains powder concentrate of 100 mg T-DXd for preparation of solution for infusion. After reconstitution, one vial of 5 ml solution contains 20 mg/ ml trastuzumab deruxtecan. The recommended dose of T-DXd is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Outcomes

DESTINY-Breast03 (NCT03529110) is a Phase III, randomized, two-arm, multicenter, open-label, active-controlled study, designed to compare the efficacy and safety of T-DXd versus T-DM1 in HER2+, uBC and/or mBC patients previously treated with trastuzumab and a taxane (8).

The DESTINY-Breast03 included a female patient population as described above with a mean age of 54 years and where half of the population had hormone receptor–positive (HR+) tumors. The patient population characteristics and previous treatment regimens used in 2L mBC patients in this trial is aligned with current clinical practice in Denmark, as described in the treatment guidelines (9) and by Danish clinical experts.

Comparative effectiveness

In DESTINY-Breast03 the risk of death was reduced with 45% and the risk of progression or death was reduced with 72% in direct comparison with the current standard of care (SoC), T-DM1 (8). Nearly all patients (80%) responded to treatment with T-DXd compared with 34% for T-DM1. T-DXd delivered consistent benefit across all patient groups. At 12 months, 94% of T-DXd treated patients were alive and 86% of the T-DM1 patients. The safety profiles of T DXd and T DM1 in the target population of this study were generally manageable and tolerable. (8)

The unprecedented efficacy results for T-DXd in this trial have already led ESMO to update their clinical guidelines to replace the previous standard of care, T-DM1, with T-DXd as the recommended 2L therapy (10).

Cost-utility analysis

The company conducted a cost utility analysis (CUA) including Quality-adjusted life-years (QALYs). The model used in this submission contains four health states and used a partitioned survival analysis approach. The cost-effectiveness model is the first to evaluate the cost-effectiveness of T-DXd within this metastatic breast cancer indication. The analysis showed that the use of T-DXd implied a gain of 1.61 QALY versus T-DM1. This results in an ICER of 367 256 DKK per gained QALY.

Budget-impact analysis

The company also conducted a budget impact analysis (BIA) of a potential introduction of T-DXd. In the BIA, the following costs were considered: drug costs, administration costs, adverse event costs, subsequent treatment costs and disease management costs. The budget impact of introducing T-DXd was compared with the current Danish standard of care, T-DM1.

The BIA showed that at peak sales, the maximum budget impact of introducing T-DXd is estimated to be approximately 33 million DKK.

Enhertu application history and outlook

The current situation is:

3rd line+ treatment of HER2 positive breast cancer (based on DB01)

- AstraZeneca/Daiichi Sankyo has applied for recommendation of T-DXd for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti HER2 based regimens. It was rejected October 28th 2021.
- The rejection was for 3rd line patients (DB01) only and did not involve 2nd line (DB03)
- After a request from the chairman of the breast cancer fagudvalg, AstraZeneca/Daiichi Sankyo have May 19th 2022 submitted new data in 3rd line (subgroup analysis from the DB03 study) combined with a new confidential net price and thereby asked the Danish Medicine Council to reevaluate T-DXd in 3rd line.

2nd line+ treatment of HER2 positive breast cancer (based on DB03)

- The current application will cover the new indication for patients who have been treated with one or more previous anti-HER2 treatments and is independent of the possible reevaluation of 3rd line.

Treatment of HER2-low advanced breast cancer

- The DB04 data that is including patients with a low expression of HER2 (I.e. a different patient group) was presented at ASCO 2022 and simultaneously published in NEJM
- This will be a new separate application when CHMP is in place and do not influence applications for 2nd and 3rd line for HER2+ patients

Conclusions

T-DXd is a highly efficacious and cost-effective treatment when compared to T-DM1 for the treatment of unresectable or metastatic HER2+ breast cancer in patients previously treated with trastuzumab plus chemotherapy. The unprecedented results from DESTINY-Breast03 show that T-DXd, if funded in Denmark, has the potential to significantly improve outcomes for Danish breast cancer patients.

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

5.1 The medical condition and patient population

Breast cancer is the most common cancer among Danish women (1). In Denmark, ~5000 cases and ~1000 deaths are reported in women every year (11). Men are also affected, yet account for less than 1% of all cases (2). Breast cancer accounts for ~15% of all cancer cases reported in Denmark (12). Approximately 1 out of 10 women are expected to be affected by this disease in their lifetime.

Between 2015 and 2019, more than 40 000 women were diagnosed with breast cancer and in 2020 (Table 1).

The five-year relative survival in the period 2016 - 2019 is 90%. Survival for metastatic patients however is considerably lower (2). The course after a breast cancer diagnosis varies greatly depending on, amongst others, various known prognostic and predictive factors (13). These factors are important with regards to relapse, premature death and the effectiveness of a specific treatment (13).

In Denmark, ~5% of breast cancers are expected to be metastatic at diagnosis (13-16) and ~20% of existing Stage I-III cancers are expected to become metastatic during the course of the disease (6, 17, 18). Of all breast cancer cases in Denmark, ~12-14% are found to be HER2 positive (2).

Table 1. Prevalence and incidence of breast cancer in Denmark

	2015	2016	2017	2018	2019
Incidence in Denmark per 100 000	145,4	147,2	145,7	146,9	148,9
Prevalence in Denmark	64 546	66 517	68 325	70 164	72 188
Estimated prevalence of HER2+ cancer*	8391	8647	8882	9121	9384

Note: *Prevalence HER2+ assumed to be equal to incidence (~12-14%) (2). **Source:** Sundhetsdatastyrelsen (12)

Breast cancers with HER2 overexpression are called HER2 positive or HER2+. HER2 is a member of the HER superfamily that initiates signal transduction via the PI3K/AKT and RAS/MAPK pathways (19, 20). HER2+ breast cancers have historically been associated with more aggressive disease and worse outcomes compared with HER2-negative (HER2–) breast cancers (21). However, the introduction and expanded use of HER2-targeted treatments, along with other advances in care, have provided substantial survival gains for women with HER2+ mBC in the first- and second-line setting. A tumor would be considered HER2+ if it fulfils American Society of Clinical Oncology (ASCO) guidelines on HER2 testing; this would include tumors that are (22):

- Immunohistochemistry (IHC) 3+, defined as circumferential membrane staining that is complete, intense and in >10% of tumor cells, classed as a positive result for HER2 status
- IHC2+, defined as weak to moderate complete membrane staining observed in >10% of tumor cells, classified as equivocal and resulting in an additional in situ hybridization (ISH) test. HER2 positivity from ISH test is defined as ≥6.0 HER2 copy number signals per cell or a HER2 to chromosome enumeration probe 17 ratio ≥2.0. HER2 score would be IHC2+/ISH+

The main risk factors for breast cancer are female gender and older age, although patients with HER2+ disease are generally younger, than those with HER2– disease (23). Genetic and hormonal factors also increase the risk of breast cancer (24). In Denmark the average age for HER2+ breast cancer patients is less than 59 years (25), which was confirmed by clinical experts. Current evidence suggests that the HER2+ subtype of breast cancer is not hereditary so genetic predisposition is not a specific risk factor for HER2+ breast cancer (26, 27).

HER2+ mBC remains incurable with a median patient survival of 4 years, although this is affected by several prognostic factors (28, 29). For instance, the time between primary breast cancer diagnosis and the development of metastases is a known important prognostic factor (29).

The quality of life (QoL) of patients with breast cancer is important and has been extensively studied as it carries a substantial physical and psychological burden, which negatively impacts patients' QoL (30, 31). Following a diagnosis of breast cancer and during treatment, patients commonly develop psychological distress

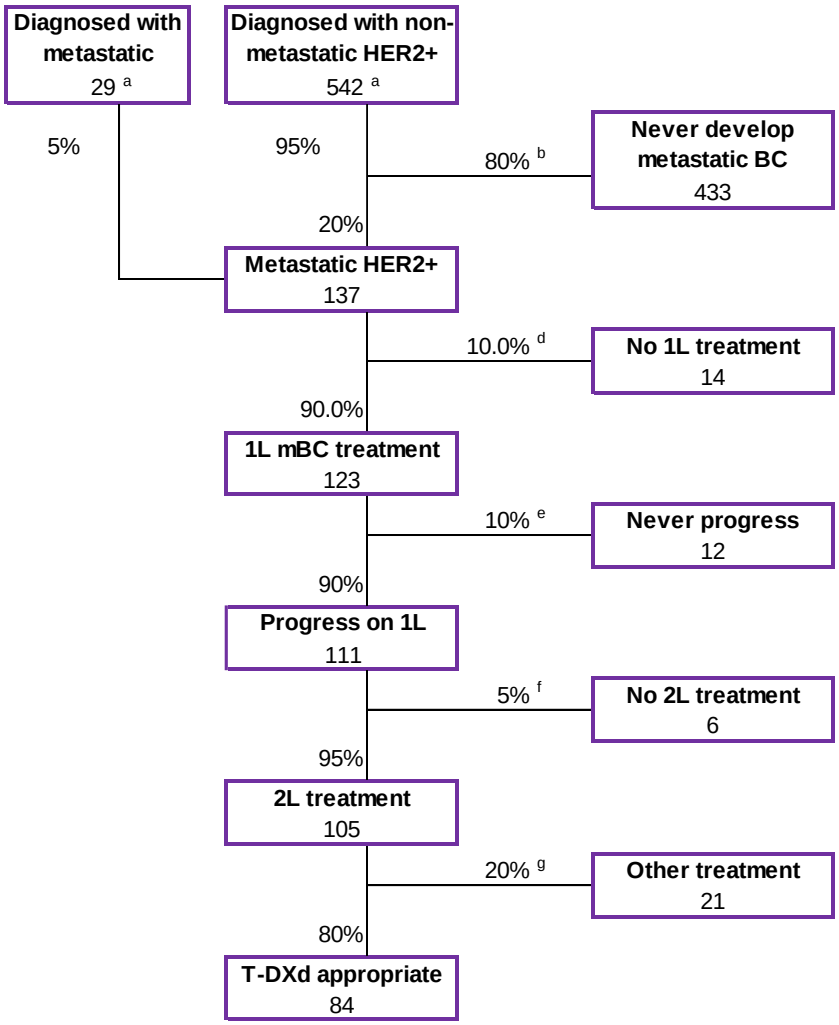
(including anxiety and depression) which substantially impair quality of life, particularly patients' emotional, social and physical functioning, as well as their mental health and adherence to treatment (31, 32). The symptoms of breast cancer – most commonly fatigue, lymphoedema, pain and menopausal symptoms – also contribute to distress in patients, and in turn have a severe impact on QoL (31).

5.2 Patient numbers in Denmark

To define the population that is eligible for treatment with T-DXd for HER2+ mBC, we have used an epidemiological approach starting with the incidence of HER2+ BC in Denmark.

- In Denmark 2020, 457 patients were diagnosed with HER2+ breast cancer (2) in the DBCG database. The DBCG database is not fully complete. Hence, this number was adjusted to 570 as the DBCG database is expected to cover ~80% of all Danish patients. This figure is slightly lower but more realistic than DMCs prior assessments of Enhertu and Tukysa.
- Only ~5% of these patients are metastatic at diagnosis (14), but 20% of the patients with stage I-III would be expected to develop metastatic disease during the course of the disease. Danish clinical experts consulted during the development of this application indicated that the improvements in screening, but also the addition of neo-/adjuvant treatments, have reduced the number of patients with metastatic relapse (4-7).
- Most HER2+ mBC patients are expected to receive 1L treatment according to Danish clinical experts (90%).
- Real-world data showed that approximately 80-85% of all metastatic 1L patients received 2L treatment. This was confirmed by Danish clinical experts. Danish clinical experts agreed that it is reasonable to assume that 10% will not progress on the first line treatment and 5% of those who progress will not get a 2L of treatment.
- Finally, not all patients will be fit enough to receive treatment. It is difficult to assess what proportion of the patients in 2L that would be appropriate for T-DXd, given that it is currently not used in Denmark. Danish experts estimated that ~80% will be appropriate for treatment with T-DXd.

Figure 1. Estimated number of eligible patients in Denmark



Key: [a] Invasive cancer cases in DBCG, [b] Conservatively estimated proportion by clinical experts based on HERA (DFS 70% at 11y) (6), APHINITY (iDFS 92.3% at 4y)(4) and the incidence of deaths in Danish registries (~1000/year), ExteNET (DDFS: 92.4% at 5y) (5), KATHERINE (iDFS ~83% at 5y) (7); [c] Proportion of HER2+ patients in DBCG (13), [d] Estimated proportion by clinical expert, [e] Estimated by clinical expert based on findings in CLEOPATRA (PFS 16% at 8y) (33), PERUSE (27% at 7y) (34), PERUSE (27% at 7y) (34), f = Clinical expert estimate, [g] Clinical expert estimate. HER2+: human epidermal growth factor receptor 2 positive, 1L: First line; 2L: Second line, T-DXd: Trastuzumab deruxtecan; T-DM1: ado-trastuzumab emtansine; mBC: Metastatic breast cancer.

5.2.1 Patient populations relevant for this application

The patient population relevant for this assessment cover the full population that is expected to be approved by European commission in July-Sept. 2022:

- T-DXd as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2+ breast cancer who have received one or more prior anti-HER2 based regimens.

In Denmark the average age for 2L HER2+ breast cancer patients is less than 59 years (25), which was confirmed by clinical experts. Additional details on the Danish population treated in 2L for HER2+ mBC are provided in section 8.2.

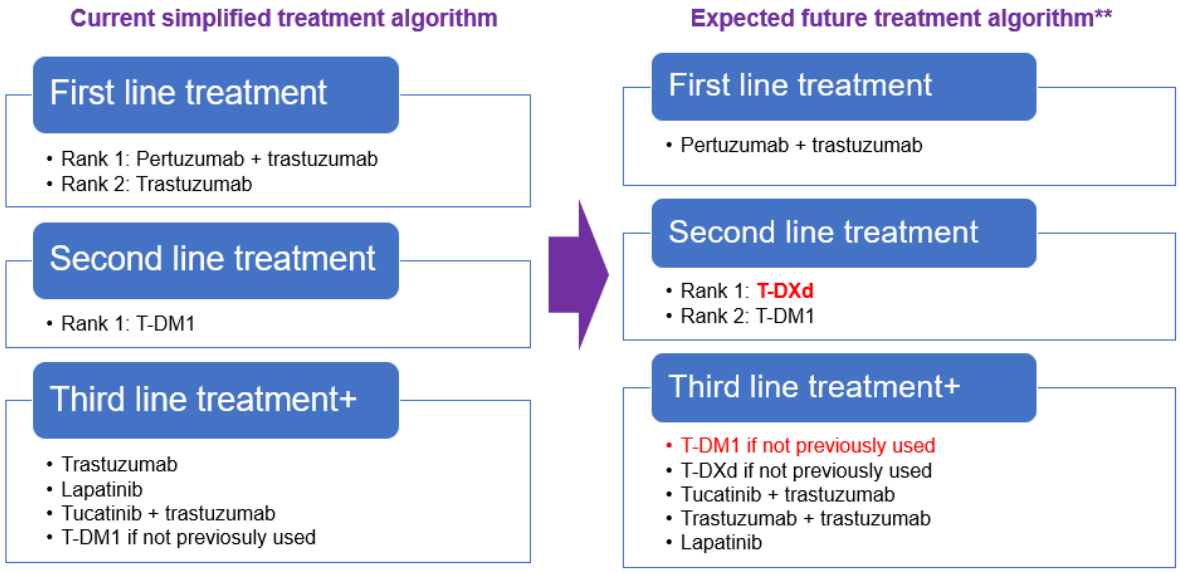
Treatment with T-DXd and T-DM1 is based on weight-based dosing, in DESTINY-Breast03 the mean weight was 62.4 kg in this pre-treated metastatic breast cancer population. (35)

5.3 Current treatment options and choice of comparator

5.3.1 Current treatment options

When it comes to HER2-positive metastatic breast cancer today's first-line recommendation is anti-HER2 monoclonal antibodies trastuzumab and pertuzumab given with a taxane or vinorelbine. Standard second-line therapy is the antibody-drug conjugate trastuzumab emtansine (T-DM1) (36) , see Figure 2 below.

Figure 2. Treatment overview metastatic HER2 positive breast cancer according to Danish Medicine Council



Reference: Adapted based on Medicinrådet(36)

5.3.2 Choice of comparator

As outlined in section 5.3.1, based on Danish guidelines and feedback from Danish clinical experts, the relevant comparator is T-DM1.

While T-DM1 has not been assessed by DMC, it has before the introduction of T-DXd been the clear standard of care in Denmark, since recommendation by KRIS in March 2014. It is recommended in DBCG and ESMO guidelines and there been a consensus that it is cost-effective in similar countries. Example of cost-effectiveness assessment from countries with similar health economic guidelines as Denmark:

- Finland (37)
- Sweden: (38)
- Norway: (39)
- England/Wales: (40)

Hence, we mean that it is not controversial to assume that T-DM1 is cost-effective also in Denmark. Comparing with anything else would be unscientific given that this has been the clear standard of care for a long time.

The expression of HER2-protein in breast cancer was described in the late 1980's. We are not aware of any studies describing outcomes on placebo in pre-treated HER2+ mBC patients and hence a comparison versus placebo is not possible to make.

That T-DM1 is the relevant comparator was also confirmed by the Danish clinical experts approached by the companies.

5.3.3 Description of the comparator – T-DM1 (Kadcyla)

Generic name and ATC code:

The comparator is trastuzumab emtansine (Kadcyla) with the ATC code L01FD03.

Mode of action:

Kadcyla, trastuzumab emtansine, is a HER2-targeted antibody-drug conjugate which contains the humanised anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitor DM1 (a maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex. An average of 3.5 DM1 molecules are conjugated to each molecule of trastuzumab.

Conjugation of DM1 to trastuzumab confers selectivity of the cytotoxic agent for HER2-overexpressing tumor cells, thereby increasing intracellular delivery of DM1 directly to malignant cells. Upon binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).

Trastuzumab emtansine has the mechanisms of action of both trastuzumab and DM1:

- Trastuzumab emtansine, like trastuzumab, binds to domain IV of the HER2 extracellular domain (ECD), as well as to Fcγ receptors and complement C1q. In addition, trastuzumab emtansine, like trastuzumab, inhibits shedding of the HER2 ECD, inhibits signalling through the phosphatidylinositol 3-kinase (PI3-K) pathway, and mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in human breast cancer cells that overexpress HER2.
- DM1, the cytotoxic component of trastuzumab emtansine, binds to tubulin. By inhibiting tubulin polymerization, both DM1 and trastuzumab emtansine cause cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death. Results from in vitro cytotoxicity assays show that DM1 is 20-200 times more potent than taxanes and vinca alkaloids.
- The MCC linker is designed to limit systemic release and increase targeted delivery of DM1, as demonstrated by detection of very low levels of free DM1 in plasma.

Pharmaceutical form:

Powder for concentrate for solution for infusion. White to off-white lyophilised powder.

Posology:

The recommended dose of trastuzumab emtansine is 3.6 mg/kg bodyweight administered as an intravenous infusion every 3 weeks (21-day cycle). The initial dose should be administered as a 90 minutes intravenous infusion. Patients should be observed during the infusion and for at least 90 minutes following the initial infusion for fever, chills, or other infusion-related reactions. The infusion site should be closely monitored for possible subcutaneous infiltration during administration. Cases of delayed epidermal injury or necrosis following extravasation have been observed in the post-marketing setting.

If the prior infusion was well tolerated, subsequent doses of trastuzumab emtansine may be administered as 30 minutes infusions. Patients should be observed during the infusion and for at least 30 minutes after infusion.

The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms. Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions.

In order to prevent medicinal product errors it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Kadcyla (trastuzumab emtansine) and not another trastuzumab-containing product (e.g. trastuzumab or trastuzumab deruxtecan).

Method of administration:

T-DM1 is for intravenous use. Trastuzumab emtansine must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. It must not be administered as an intravenous push or bolus.

Should the pharmaceutical (or other method) be administered with other medicines?:

No.

Treatment duration / Criteria for end of treatment:

Patients can continue treatment with T-DM1 until disease progression or unacceptable toxicity. The median treatment duration in DESTINY-Breast03 was 6.9 months while the mean modelled treatment duration is ~[redacted] months.

Necessary monitoring, both during administration and during the treatment period:

T-DM1 should only be prescribed by a physician and administered as an intravenous infusion under the supervision of a healthcare professional who is experienced in the treatment of cancer patients (i.e. prepared to manage allergic/anaphylactic infusion reactions and in an environment where full resuscitation facilities are immediately available.

Management of symptomatic adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of trastuzumab emtansine as per guidelines provided.

Trastuzumab emtansine dose should not be re-escalated after a dose reduction is made.

Need for diagnostic or other test:

Patients treated with T-DM1, should have documented HER2+ tumor status, defined as a immunohistochemic (ICH) score of 3+, or an ICH score of 2+ and a ratio ≥ 2.0 by in situ hybridization (ISH) or by fluorescence in situ hybridization (FISH) examined with CE marked medical equipment for in vitro diagnostics (IVD). If CE marked IVD is not available, HER2 status should be examined with another validated test.

IHC, ISH or FISH tests required are already performed on all patients in Denmark as a standardized diagnostic work-up.

Packaging

T-DM1 comes in two packages, see Table 2 more information.

Table 2 Packages for trastuzumab emtansine (Kadcyla)

Form	Strength	VNR	Package
Powder for conc. for infusion	100 mg	466278	1 pcs.
Powder for conc. for infusion	160 mg	121104	1 pcs.

5.4 The intervention – trastuzumab deruxtecan (Enhertu)

If T-DXd is recommended as standard treatment it would replace TDM-1 as the preferred 2L treatment. This would move TDM-1 down the treatment algorithm into the 3L according to ESMO guidelines (10) and Danish clinical experts.

Pharmaceutical form:

100 mg concentrate powder is provided in glass vial, where each vial reconstitutes a concentration of 20 mg/ mL.

Posology:

The recommended dose of T-DXd is 5.4 mg/ kg administered as an intravenous (IV) infusion once every 3 weeks. The initial dose of T-DXd will be infused for approximately 90 minutes; if there is no infusion-related reaction, the administration time will be approximately 30 minutes thereafter. Treatment with T-DXd should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. Dose reduction is performed according to the dose reduction schedule published in the SmPC for trastuzumab deruxtecan (Enhertu) seen in Table 3 (41).

Table 3 Dose reduction schedule for trastuzumab deruxtecan

Dose reduction schedule (Starting dose is 5.4 mg/kg)	Dose to be administered
First dose reduction	4.4 mg/kg
Second dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue treatment

Method of administration:

T-DXd, is an intravenously (IV) administered HER2-directed antibody drug conjugate.

Should the pharmaceutical be administered with other medicines?

No

Treatment duration / Criteria for end of treatment:

Patients can continue treatment with T-DXd until disease progression or unacceptable toxicity. The median treatment duration in DESTINY-Breast03 was 14.3 months while the modelled mean treatment duration is ~[redacted] months.

Necessary monitoring, both during administration and during the treatment period:

A higher incidence of grade 1 and 2 interstitial lung disease (ILDs) has been observed in patients with moderate renal impairment. Patients with moderate or severe renal impairment should be closely monitored. Cases of neutropenia, including febrile neutropenia, have been reported in clinical trials for T-DXd. A complete blood count should be performed before starting T-DXd and before each dose administration, and as otherwise clinically indicated. A standard cardiac function test (echocardiogram or MUGA scan) should be performed to evaluate LVEF before starting T-DXd and regularly during treatment as clinically indicated. Pregnancy status in women of childbearing potential should be checked before starting T-DXd.

Need for diagnostic or other test:

Patients treated with T-DXd, should have documented HER2 positive tumor status, defined as a score of 3+ by immunohistochemistry (IHC) or a ratio ≥ 2.0 by in situ hybridization (ISH) or by fluorescence in situ hybridization (FISH) examined with CE marked medical equipment for in vitro diagnostics (IVD). If CE marked IVD is not available, HER2 status should be examined with another validated test.

6. Literature search and identification of efficacy and safety studies

A systematic literature search was not deemed relevant but was conducted and is available in Appendix A. The only study that is relevant for the scope if this assessment is presented below.

6.1 Identification and selection of relevant studies

A systematic literature review was conducted and is presented in Appendix A. Only one study, DESTINY-Breast03 was deemed relevant for the scope of this assessment (Table 4). As that is a head-to-head study with the comparator relevant in Danish clinical practice, the literature search is omitted from the main part of this document.

6.2 List of relevant studies

Table 4. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. Cortés J, et al New England Journal of Medicine, 2022	DESTINY-Breast03	03529110	July 20, 2018- April 2023

Table 5. Additional ongoing studies of T-DXd

Trial summary	Intervention(s) assessed	Expected primary completion date	Reference
Destiny Breast 02. A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-HER2-antibody Drug Conjugate, Versus Treatment of Investigator's Choice for HER2-positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated With T-DM1. N = 600	**Arm 1:** T-DXd administered initially as an intravenous (IV) infusion at a dose of 5.4 mg/kg on Day 1 of each 21-day cycle **Arm 2:** Trastuzumab+capecitabine or Lapatinib+capecitabine	Dec, '22	https://clinicaltrials.gov/ct2/show/NCT03523585
Destiny Breast 04. A Phase 3, Multicenter, Randomized, Open-label, Active Controlled Trial of DS-8201a, an Anti-HER2-antibody Drug Conjugate (ADC), Versus Treatment of Physician's Choice for HER2-low, Unresectable and/or Metastatic Breast Cancer Subjects. N = 557	**Arm 1:** T-DXd administered initially as an intravenous (IV) infusion at a dose of 5.4 mg/kg on Day 1 of each 21-day cycle **Arm 2:** Physician's choice (Capecitabine, Eribulin, Gemcitabine, Paclitaxel, Nab-paclitaxel)	Jun, '22	https://clinicaltrials.gov/ct2/show/NCT03734029
Destiny Breast 05. A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of Trastuzumab Deruxtecan (T-DXd) Versus Trastuzumab Emtansine (T-DM1) in Participants With High-Risk HER2-Positive Primary Breast Cancer Who Have Residual Invasive Disease in Breast or Axillary Lymph Nodes Following Neoadjuvant Therapy. N = 1,600	**Arm 1:** T-DXd administered initially as an intravenous (IV) infusion at a dose of 5.4 mg/kg on Day 1 of each 21-day cycle **Arm 2:** T-DM1 administered initially as an intravenous (IV) infusion at a dose of 3.6 mg/kg on Day 1 of each 21-day cycle	Dec, '25	https://clinicaltrials.gov/ct2/show/NCT04622319
Destiny Breast 06. A Phase 3, Randomized, Multi-	**Arm 1:** T-DXd administered initially as an intravenous	Jul, '23	https://clinicaltrials.gov/ct2/show/NCT04494425

center, Open-label Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice Chemotherapy in HER2-Low, Hormone Receptor Positive Breast Cancer Patients Whose Disease Has Progressed on Endocrine Therapy in the Metastatic Setting. N = 850	(IV) infusion at a dose of 5.4 mg/kg on Day 1 of each 21-day cycle **Arm 2:** Investigator's choice standard of care chemotherapy (capecitabine, paclitaxel, nab-paclitaxel)		
Destiny Breast 09. Phase III Study of Trastuzumab Deruxtecan (T-DXd) With or Without Pertuzumab Versus Taxane, Trastuzumab and Pertuzumab in HER2-positive, First-line Metastatic Breast Cancer. N = 1134	**Arm 1:** T-DXd administered initially as an intravenous (IV) infusion at a dose of 5.4 mg/kg on Day 1 of each 21-day cycle **Arm 2:** T-DXd administered initially as an intravenous (IV) infusion at a dose of 5.4 mg/kg on Day 1 of each 21-day cycle + pertuzumab **Arm 3:** doxorubicin and cyclophosphamide, followed by THP	Dec, '24	https://clinicaltrials.gov/ct2/show/NCT04784715
Destiny Breast 11. A Phase 3 Open-label Trial of Neoadjuvant Trastuzumab Deruxtecan (T-DXd) Monotherapy or T-DXd Followed by THP Compared to ddAC-THP in Participants With High-risk HER2-positive Early-stage Breast Cancer. N = 624	**Arm 1:** T-DXd administered initially as an intravenous (IV) infusion at a dose of 5.4 mg/kg on Day 1 of each 21-day cycle **Arm 2:** T-DXd, followed by THP **Arm 3:** Standard of care (Taxane (paclitaxel or docetaxel), trastuzumab, and pertuzumab)	Feb, '24	https://clinicaltrials.gov/ct2/show/NCT05113251
Destiny Breast 12. An Open-Label, Multinational, Multicenter, Phase 3b/4 Study of Trastuzumab Deruxtecan in Patients With or Without Baseline Brain Metastasis With Previously Treated Advanced/Metastatic HER2-Positive Breast Cancer. N = 500	T-DXd administered initially as an intravenous (IV) infusion at a dose of 5.4 mg/kg on Day 1 of each 21-day cycle	Jan, '24	https://clinicaltrials.gov/ct2/show/NCT04739761

For detailed information about included studies, please see appendix B.

7. Efficacy and safety

7.1 Efficacy and safety of T-DXd compared to T-DM1 for HER2+ mBC

7.1.1 Relevant studies

Table 6. The DESTINY-Breast03 trial

Parameter	Data

<table>
<tr><td>Study 1</td><td>Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer, Cortés, J et al., 2022 (8)</td></tr>
<tr><td>Sample size (n)</td><td>524</td></tr>
<tr><td>Study design</td><td>Phase III, randomized, two-arm, multicentre, open-label, active-controlled study</td></tr>
<tr><td>Patient population</td><td>HER2-positive, uBC and/or mBC patients previously treated with trastuzumab and a taxane.
<table>
<tr><th>Parameter</th><th>T-DXd (N = 261)</th><th>T-DM1 (N = 263)</th><th>Total (N = 524)</th></tr>
<tr><td>Age (years)</td><td></td><td></td><td></td></tr>
<tr><td>Mean (std dev)</td><td>54.5 (11.11)</td><td>54 2 (11.84)</td><td>54.4 (11.47)</td></tr>
<tr><td>Median</td><td>54.3</td><td>54.2</td><td>54.3</td></tr>
<tr><td>Minimum, Maximum</td><td>27.9, 83.1</td><td>20.2, 83.0</td><td>20.2, 83.1</td></tr>
<tr><td>Female sex</td><td>260 (99.6)</td><td>262 (99.6)</td><td>522 (99.6)</td></tr>
<tr><td>Region</td><td></td><td></td><td></td></tr>
<tr><td>Asia</td><td>149 (57.1)</td><td>160 (60.8)</td><td>309 (59.0)</td></tr>
<tr><td>Europe</td><td>54 (20.7)</td><td>50 (19.0)</td><td>104 (19.8)</td></tr>
<tr><td>Rest of World</td><td>41 (15.7)</td><td>36 (13.7)</td><td>77 (14.7)</td></tr>
<tr><td>North America</td><td>17 (6.5)</td><td>17 (6.5)</td><td>34 (6.5)</td></tr>
<tr><td>Weight (kg)</td><td></td><td></td><td></td></tr>
<tr><td>Mean (std dev)</td><td>62.8 (14.05)</td><td>62.0 (12.53)</td><td>62.4 (13.30)</td></tr>
<tr><td>Median</td><td>59.3</td><td>60.7</td><td>60.0</td></tr>
<tr><td>Body mass index (kg/m²)</td><td></td><td></td><td></td></tr>
<tr><td>Mean (std dev)</td><td>24.9 (5.15)</td><td>24.5 (4.65)</td><td>24.7 (4.90)</td></tr>
<tr><td>Median</td><td>24.0</td><td>23.6</td><td>23.9</td></tr>
<tr><td>Smoking status</td><td></td><td></td><td></td></tr>
<tr><td>Never</td><td>191 (73.2)</td><td>229 (87.1)</td><td>420 (80.2)</td></tr>
<tr><td>Former</td><td>50 (19.2)</td><td>20 (7.6)</td><td>70 (13.4)</td></tr>
<tr><td>Current</td><td>18 (6.9)</td><td>11 (4.2)</td><td>29 (5.5)</td></tr>
<tr><td>Missing</td><td>2 (0.8)</td><td>3 (1.1)</td><td>5 (1.0)</td></tr>
<tr><td>Reported history of CNS metastases</td><td>62 (23.8)</td><td>52 (19.8)</td><td>114 (21.8)</td></tr>
<tr><td>HER2 expression (IHC) – Central</td><td></td><td></td><td></td></tr>
<tr><td>1+</td><td>1 (0.4)</td><td>0</td><td>1 (0.2)</td></tr>
<tr><td>2+</td><td>25 (9.6)</td><td>30 (11.4)</td><td>55 (10.5)</td></tr>
<tr><td>3+</td><td>234 (89.7)</td><td>232 (88.2)</td><td>466 (88.9)</td></tr>
<tr><td>Not evaluable</td><td>1 (0.4)</td><td>1 (0.4)</td><td>2 (0.4)</td></tr>
<tr><td>HER2 gene amplification (ISH) – Central</td><td></td><td></td><td></td></tr>
<tr><td>Amplified</td><td>24 (9.2)</td><td>29 (11.0)</td><td>53 (10.1)</td></tr>
<tr><td>Non-amplified</td><td>2 (0.8)</td><td>2 (0.8)</td><td>4 (0.8)</td></tr>
<tr><td>Missing</td><td>235 (90.0)</td><td>232 (88.2)</td><td>467 (89.1)</td></tr>
<tr><td>Hormone receptor</td><td></td><td></td><td></td></tr>
<tr><td>Positive</td><td>133 (51.0)</td><td>139 (52.9)</td><td>272 (51.9)</td></tr>
<tr><td>Negative</td><td>126 (48.3)</td><td>122 (46.4)</td><td>248 (47.3)</td></tr>
<tr><td>Indeterminate</td><td>1 (0.4)</td><td>1 (0.4)</td><td>2 (0.4)</td></tr>
<tr><td>Missing</td><td>1 (0.4)</td><td>1 (0.4)</td><td>2 (0.4)</td></tr>
<tr><td>Estrogen receptors</td><td></td><td></td><td></td></tr>
<tr><td>Positive</td><td>129 (49.4)</td><td>132 (50.2)</td><td>261 (49.8)</td></tr>
<tr><td>Negative</td><td>130 (49.8)</td><td>128 (48.7)</td><td>258 (49.2)</td></tr>
<tr><td>Indeterminate</td><td>1 (0.4)</td><td>2 (0.8)</td><td>3 (0.6)</td></tr>
<tr><td>Missing</td><td>1 (0.4)</td><td>1 (0.4)</td><td>2 (0.4)</td></tr>
<tr><td>Progesterone receptors</td><td></td><td></td><td></td></tr>
<tr><td>Positive</td><td>81 (31.0)</td><td>92 (35.0)</td><td>173 (33.0)</td></tr>
<tr><td>Negative</td><td>177 (67.8)</td><td>168 (63.9)</td><td>345 (65.8)</td></tr>
</table></td></tr>
</table>

	Indeterminate	2 (0.8)	1 (0.4)	3 (0.6)
	Missing	1 (0.4)	2 (0.8)	3 (0.6)
	Prior pertuzumab			
	Yes	162 (62.1)	158 (60.1)	320 (61.1)
	No	99 (37.9)	105 (39.9)	204 (38.9)
	Lines of prior systemic therapy excluding hormone therapies			
	<3	188 (72.0)	191 (72.6)	379 (72.3)
	≥3	73 (28.0)	72 (27.4)	145 (27.7)
	Lines of therapy prior to pertuzumab			
	<3	156 (59.8)	152 (57.8)	308 (58.8)
	≥3	6 (2.3)	6 (2.3)	12 (2.3)
	Renal function at baseline			
	Within normal range	134 (51.3)	131 (49.8)	265 (50.6)
	Mild impairment	96 (36.8)	105 (39.9)	201 (38.4)
	Moderate impairment	27 (10.3)	25 (9.5)	52 (9.9)
	Missing	4 (1.5)	2 (0.8)	6 (1.1)
	Hepatic function at baseline			
	Within normal range	208 (79.7)	212 (80.6)	420 (80.2)
	Mild impairment	49 (18.8)	49 (18.6)	98 (18.7)
	Missing	4 (1.5)	2 (0.8)	6 (1.1)
	Baseline visceral disease	195 (74.7)	189 (71.9)	384 (73.3)
	Baseline CNS metastases	43 (16.5)	39 (14.8)	82 (15.6)
	ECOG Performance Status			
	0	154 (59.0)	175 (66.5)	329 (62.8)
	1	106 (40.6)	87 (33.1)	193 (36.8)
	Missing	1 (0.4)	1 (0.4)	2 (0.4)

Intervention	T-DXd
Comparator	T-DM1
Follow-up period	July 20, 2018 - May 21, 2021
Is the study used in the health economic model?	Yes
Reasons for use of the study in model	PFS and OS from DESTINY-Breast03 is the most relevant source of evidence for the scope of this assessment.
Primary endpoints	The primary endpoint is progression free survival (PFS) based on blinded independent central review (BICR)* (42):

Parameter	T-DXd (N = 261)	T-DM1 (N = 263)
PFS		
Median PFS, months (95% CI)	NE (18.5, NE)	6.8 (5.6, 8.2)
Stratified Cox hazard ratio (95% CI)	0.2840 (0.2165, 0.3727)	
Stratified log-rank *P*-value	<0.000001	
Percentage of subjects alive and progression-free over time		
3 months (95% CI)	96.1 (92.8, 97.9)	69.5 (63.3, 74.9)
6 months (95% CI)	88.4 (83.7, 91.8)	51.7 (45.1, 57.9)
9 months (95% CI)	79.9 (74.3, 84.4)	41.4 (34.9, 47.8)
12 months (95% CI)	75.8 (69.8, 80.7)	34.1 (27.7, 40.5)

	18 months (95% CI)	60.1 (52.5, 67.0)	27.3 (20.7, 34.2)
	24 months (95% CI)	50.5 (39.9, 60.2)	25.3 (18.4, 32.9)

Other outcomes reported

OS, ORR (BICR and investigator), DOR (BICR), PFS (investigator), Safety:

Parameter	T-DXd (N = 261)	T-DM1 (N = 263)
Overall survival		
Stratified Cox hazard ratio (95% CI)	0.55 (0.36, 0.86)	
Stratified log-rank test *P*-value	0.007172	
Percentage of subjects alive over time		
3 months (95% CI)	99.2 (96.9, 99.8)	96.9 (93.9, 98.4)
6 months (95% CI)	98.4 (95.9, 99.4)	94.5 (90.9, 96.7)
9 months (95% CI)	96.1 (92.8, 97.9)	91.3 (87.1, 94.2)
12 months (95% CI)	94.1 (90.3, 96.4)	85.9 (80.9, 89.7)
18 months (95% CI)	85.7 (79.8, 90.0)	76.5 (69.8, 81.8)
24 months (95% CI)	80.8 (73.0, 86.6)	73.7 (66.1, 79.9)
BOR by BICR		
Complete response, n (%)	42 (16.1)	23 (8.7)
Partial response, n (%)	166 (63.6)	67 (25.5)
Stable disease, n (%)	44 (16.9)	112 (42.6)
Progressive disease, n (%)	3 (1.1)	46 (17.5)
Not evaluable, n (%)	6 (2.3)	15 (5.7)
Confirmed ORR (complete response + partial response)		
Responders, n (%)	208 (79.7)	90 (34.2)
95% CI	74.3, 84.4	28.5, 40.3
P-value	<0.0001	
Difference in ORR (95% CI)	45.5 (37.6, 53.4)	

Key: BOR: best overall response, CI: confidence interval, CR: complete response, DOR: duration of response, IXRS: Interactive Web/Voice Response System, KM: Kaplan-Meier, NE: not estimable, std dev: standard deviation, TDM1: trastuzumab emtansine, T-DXd: trastuzumab deruxtecan, HER2: Human epidermal growth factor receptor 2, CNS: Central nervous system, ECOG: Eastern Cooperative Oncology group, IHC: Immunohistochemistry. ORR: overall response rate, OS: overall survival, PFS: progression-free survival, PS: partial response, SAP: Statistical Analysis Plan, T-DM1: trastuzumab emtansine, T-DXd: trastuzumab deruxtecan. **Source:** Daiichi Sankyo (2021) (35).

Randomization was stratified by: Hormone receptor status (positive, negative), Prior treatment with pertuzumab (yes, no), History of visceral disease (yes, no). These stratification factors were used for the stratified log-rank tests.

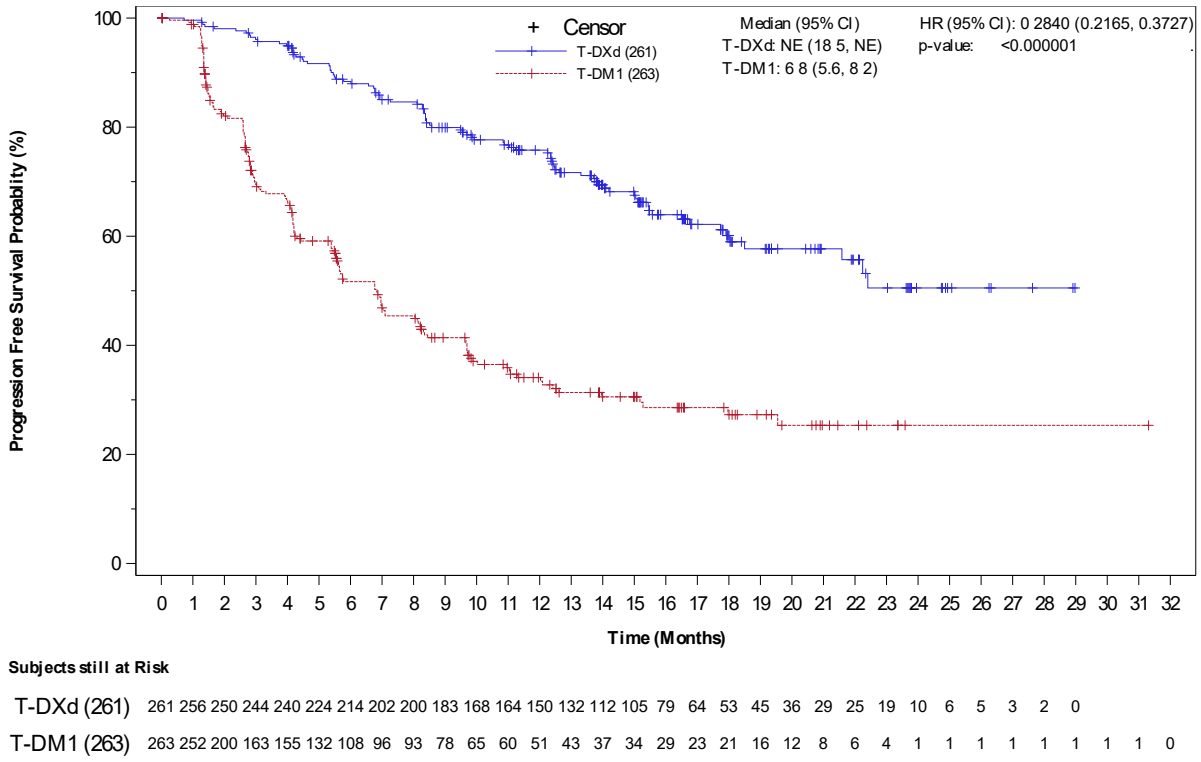
7.1.2 Efficacy and safety – results per study

The results in this section are taken from the 21 May 2021 data cut-off and are available for the full study population (8)(76).

In the full-analysis set of 524 subjects DESTINY-Breast03, treatment with T-DXd resulted in a highly statistically significant and clinically meaningful improvement in BICR-assessed PFS compared with T-DM1: the stratified HR was 0.28 (95% CI: 0.22, 0.37) in favor of the T-DXd arm, with a P-value of <0.000001, which was less than the prespecified threshold of 0.000204. The median PFS based on BICR was not estimable (95% CI: 18.5, NE) in the T-DXd arm vs. 6.8 months (95% CI: 5.6, 8.2) in the T-DM1 arm. There was an early separation of the PFS curves that was maintained throughout the study up to the DCO (data cutoff) (8). The 12-month PFS rate based on

investigator assessment was 75.8% (95% CI: 69.8-80.7) and 34.1% (95% CI: 27.7-40.5) in the T-DXd and T-DM1 arm, respectively (Figure 3). Median duration of PFS follow-up was 15.5 months and 13.9 months in the investigational and control arm, respectively.

Figure 3. Kaplan-Meier plot of PFS in DESTINY-Breast03.



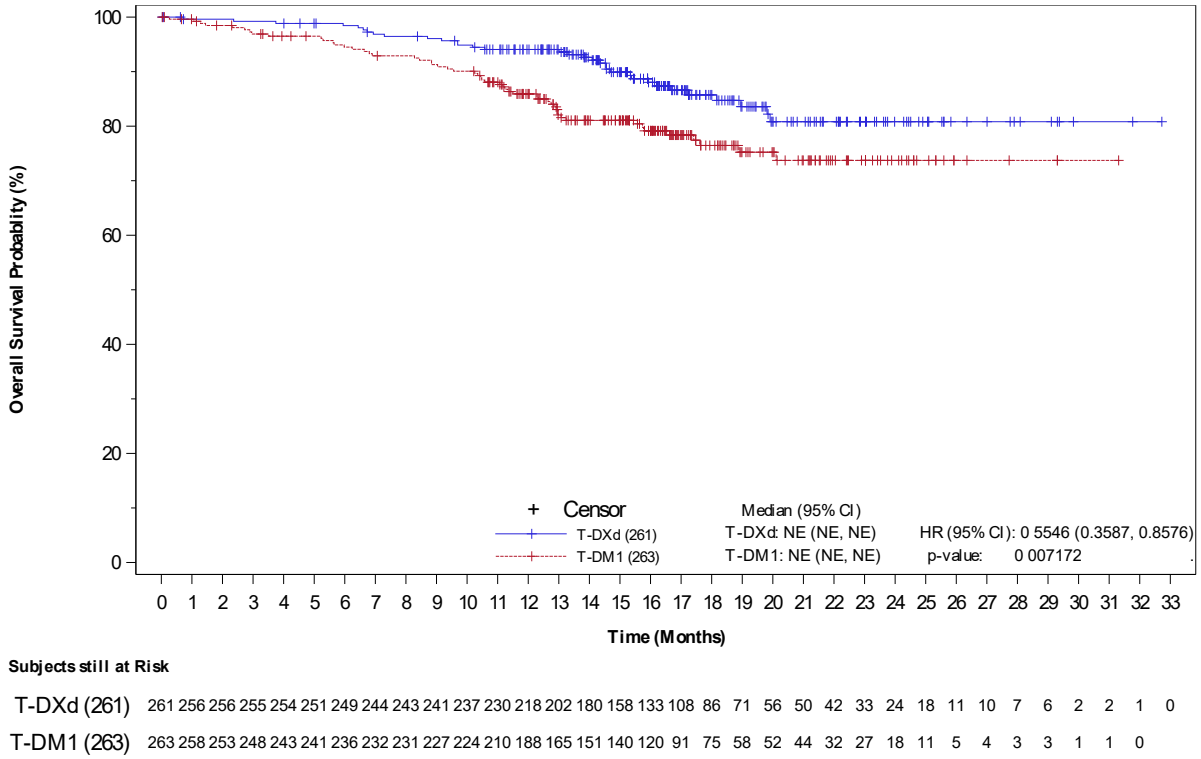
Key: CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. **Source**: Cortes et al., 2022 (8)

The efficacy benefit in BICR-assessed PFS provided by T-DXd over T-DM1 was observed consistently across key prespecified subgroups. Among these subgroups, the HR was 0.31 (95% CI: 0.22, 0.43) for subjects who had received prior pertuzumab; 0.32 (95% CI: 0.22, 0.46) for subjects with hormone receptor-positive status; and 0.28 (95% CI: 0.21, 0.38) for subjects with baseline visceral metastases, with similar results for subjects who had not received prior pertuzumab (HR 0.30 [95% CI: 0.19, 0.47]), subjects with hormone receptor-negative status (HR 0.30 [95% CI: 0.20, 0.44]), and subjects with no baseline visceral metastases (HR 0.32 [95% CI: 0.17, 0.58]) (76).

A prespecified interim OS analysis was conducted using the same data cut. An early separation of the OS curves in favor of T-DXd was observed, as supported by the estimated landmark 12month survival rate of 94.1% (95% CI: 90.3, 96.4) in the T-DXd arm compared with 85.9% (95% CI: 80.9, 89.7) in the TDM1 arm. The 24-month survival rate was 80.8% (95% CI: 73.0, 86.6) in the T-DXd arm compared with 73.7% (95% CI: 66.1,79.9) in the T-DM1 arm. The median OS was not estimable in either arm (Figure 4). The median duration of follow-up was 16.2 months (range, 0 to 32.7) with trastuzumab deruxtecan and 15.3 months (range, 0 to 31.3) with trastuzumab emtansine.

The stratified HR was 0.55 (95% CI: 0.36, 0.86). The results are currently not mature as OS is calculated based on only 86 observed events (33 (12.6%) subjects in the T-DXd arm and 53 (20.2%) subjects in the T-DM1 arm (76)).

Figure 4. Kaplan-Meier plot of OS in DESTINY-Breast03.



Subjects still at Risk

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

Key: CI, confidence interval; HR, hazard ratio; NE, not estimable; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Source: Cortes et al., 2022 (8)

Subgroup analyses of OS would not be uninformative with the current level of maturity of this data.

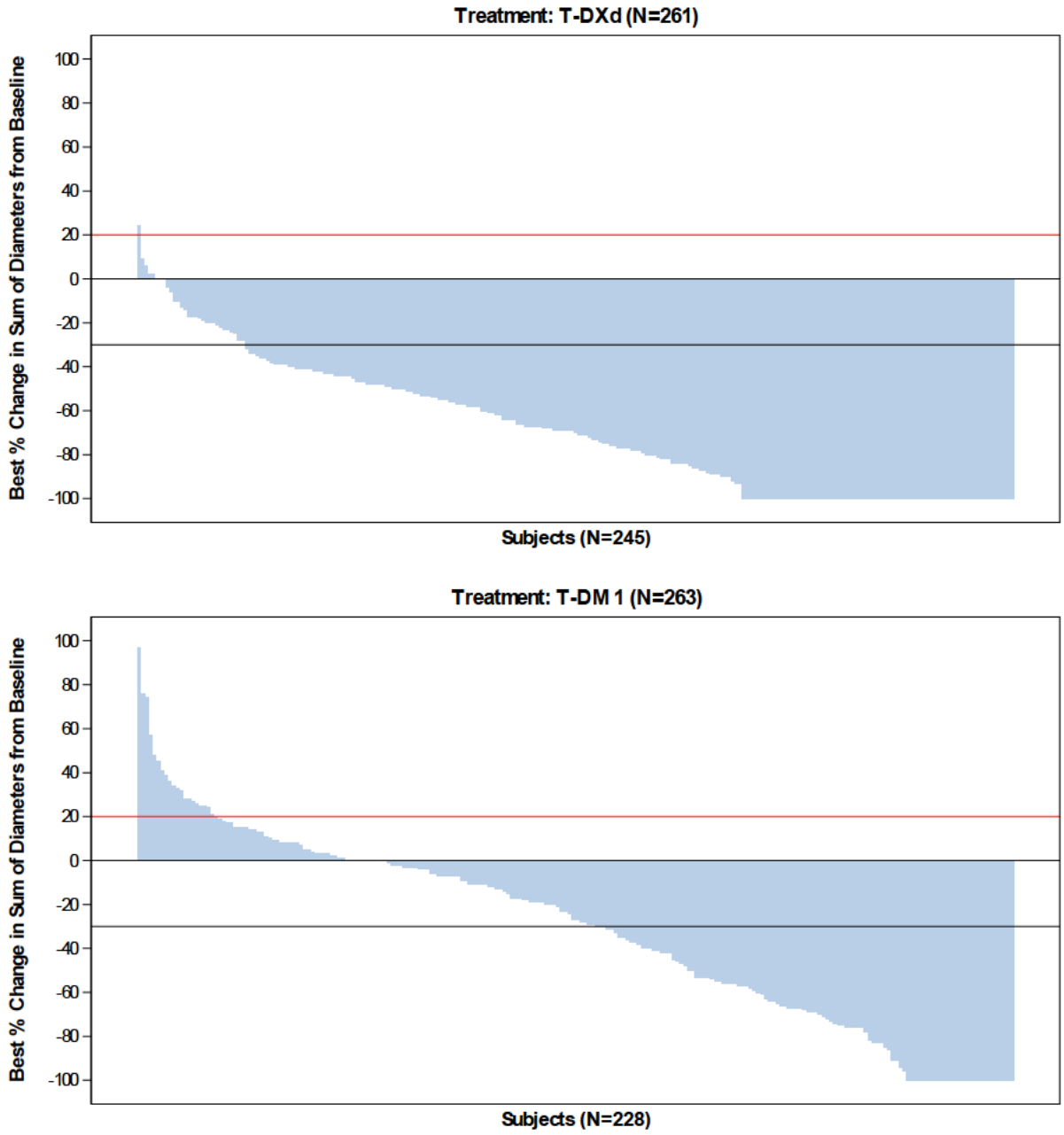
The T-DXd treatment benefit over T-DM1 was also observed for secondary endpoints:

- Median confirmed ORR was 79.7% (95% CI: 74.3, 84.4) in the T-DXd arm vs. 34.2% (95% CI: 28.5, 40.3) in the T-DM1 arm (P-value <0.0001) (76). The difference in ORR between the two treatment arms was 45.5% (95% CI: 37.6, 53.4).

- Results of analyses of PFS by investigator were consistent with those seen for the primary analysis of PFS by BICR. The median PFS based on investigator assessment estimated by the KM method was 25.1 months (95% CI: 21.1, NE) in the T-DXd arm and 7.2 months (95% CI: 6.8, 8.3) in the T-DM1 arm (76).

Furthermore, a waterfall plot of the percentage change from baseline to best post-baseline sum of diameters of target lesions based on BICR is shown for both treatment groups in Figure 5. As shown, almost all patients benefit from T-DXd treatment.

Figure 5. Waterfall Plot of Percentage Change in DESTINY-Breast03



Key: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. **Source**: Cortes et al., 2022 (8)

A summary of all efficacies as assessed by BICR is presented in Table 7.

Table 7. Summary of DESTINY-Breast03 results

Parameter	T-DXd (N = 261)	T-DM1 (N = 263)
PFS		
Median PFS, months (95% CI)	NE (18.5, NE)	6.8 (5.6, 8.2)
Stratified Cox hazard ratio (95% CI)	0.2840 (0.2165, 0.3727)	
Stratified log-rank *P*-value	<0.000001	
Percentage of subjects alive and progression-free over time		
3 months (95% CI)	96.1 (92.8, 97.9)	69.5 (63.3, 74.9)
6 months (95% CI)	88.4 (83.7, 91.8)	51.7 (45.1, 57.9)
9 months (95% CI)	79.9 (74.3, 84.4)	41.4 (34.9, 47.8)

12 months (95% CI)	75.8 (69.8, 80.7)	34.1 (27.7, 40.5)
18 months (95% CI)	60.1 (52.5, 67.0)	27.3 (20.7, 34.2)
24 months (95% CI)	50.5 (39.9, 60.2)	25.3 (18.4, 32.9)
Overall survival		
Stratified Cox hazard ratio (95% CI)	0.55 (0.36, 0.86)	
Stratified log-rank test *P*-value	0.007172	
Percentage of subjects alive over time		
3 months (95% CI)	99.2 (96.9, 99.8)	96.9 (93.9, 98.4)
6 months (95% CI)	98.4 (95.9, 99.4)	94.5 (90.9, 96.7)
9 months (95% CI)	96.1 (92.8, 97.9)	91.3 (87.1, 94.2)
12 months (95% CI)	94.1 (90.3, 96.4)	85.9 (80.9, 89.7)
18 months (95% CI)	85.7 (79.8, 90.0)	76.5 (69.8, 81.8)
24 months (95% CI)	80.8 (73.0, 86.6)	73.7 (66.1, 79.9)
BOR by BICR		
Complete response, n (%)	42 (16.1)	23 (8.7)
Partial response, n (%)	166 (63.6)	67 (25.5)
Stable disease, n (%)	44 (16.9)	112 (42.6)
Progressive disease, n (%)	3 (1.1)	46 (17.5)
Not evaluable, n (%)	6 (2.3)	15 (5.7)
Confirmed ORR (complete response + partial response)		
Responders, n (%)	208 (79.7)	90 (34.2)
95% CI	74.3, 84.4	28.5, 40.3
P-value	<0.0001	
Difference in ORR (95% CI)	45.5 (37.6, 53.4)	

Key: BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; IXRS, Interactive Web/Voice Response System; KM, Kaplan-Meier; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, partial response; SAP, Statistical Analysis Plan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. **Source:** Daiichi Sankyo (2021) (76).

The safety profiles of T-DXd and T-DM1 in the target population of this study were generally manageable and tolerable.

Overall, TEAEs were reported in 256 (99.6%) subjects in the T-DXd arm and 249 (95.4%) subjects in the T-DM1 arm. Drug-related TEAEs were reported in 252 (98.1%) and 226 (86.6%) subjects, respectively. Most of which were manageable through routine clinical practice, with no drug-related TEAEs associated with an outcome of death (76).The T-DXd arm had a longer treatment duration compared with the T-DM1 arm (292.86 vs. 174.48 patient-years) and a lower exposure-adjusted incidence rate (EAIR) for overall TEAEs, TEAEs ≥Grade 3, and treatment-emergent SAEs (76).

Compared to subjects in the T-DM1 arm, a numerically higher proportion (≥10 percentage points [pp]) of subjects in the T-DXd arm experienced TEAEs associated with study drug interruption (overall and drug related), primarily related to hematologic TEAEs. No relevant differences between the 2 treatment arms were found in the other parameters (76).

The most common TEAEs reported in the T-DXd arm were GI or hematologic in nature, which is in line with the known non-clinical and pharmacological profile of this class of drugs. Reported TEAEs included nausea, vomiting, constipation, diarrhea, abdominal pain and neutropenia, anemia, leukopenia. Overall, the TEAEs reported in the T-DXd arm were manageable by dose modification and routine clinical practice (76).

Adverse events of special interest

With regards to adverse events of special interest, the following points were noted:

- A total of 27 (10.5%) patients in the T-DXd arm and 5 (1.9%) subjects in the T-DM1 arm had events adjudicated as being drug-related ILD, none of which was adjudicated as Grade 4 or Grade 5. Most events in both treatment arms were resolved, with 1 fatal case reported in the T-DM1 arm (76).
- Ejection fraction decreased was reported in 6 (2.3%) subjects in the T-DXd arm and 1 (0.4%) patient in the T-DM1 arm (all were Grade 2 with no action taken; all except 1 T-DXd patient had outcome of resolved). Left ventricular dysfunction (Grade 1; resolved with no action taken) was reported in 1 patient in the T-DXd arm. 34 (13.5%) patients in the T-DXd arm and 24 (10.1%) subjects in the T-DM1 arm who had a post-baseline LVEF value met the laboratory criteria for a Grade 2 LVEF decrease, and 1 (0.4%) patient in each arm met the criteria for a Grade 3 decrease (76).

Table 8 summarizes drug related treatment-emergent AEs by system organ class which occurred in ≥20% of patients and the AEs of special interest in all patients.

Table 8. Summary of drug related treatment-emergent AEs*

System Organ Class, Preferred or grouped term	T-DXd (n=257)		T-DM1 (n=261)		Is the adverse reaction referred to as "important identified"?	Is the adverse reaction included in the model?
	Any grade (n,%)	Grade ≥3 (n,%)	Any grade (n,%)	Grade ≥3 (n,%)		
Blood and lymphatic system disorders						
Neutropenia[a]	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)	No	Yes
Anemia[b]	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)	No	Yes
Leukopenia [c]	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)	No	Yes
Thrombocytopenia [d]	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)	No	Yes
Gastrointestinal disorders						
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)	No	Yes
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)	No	No
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)	No	No
Constipation	58 (22.6)	0	25 (9.6)	0	No	No
General disorders						
Fatigue [e]	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)	No	Yes
Investigations						
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)	No	Yes
ALT increased	50 (19.5	4 (1.6)	71 (27.2)	12 (4.6)	No	No
Metabolism and nutrition disorders						
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0	No	No
Skin and subcutaneous tissue disorders						
Alopecia [f]	93 (36.2)	1 (0.4)	6 (2.3)	0	No	No

N (%)	Gr 1 n (%)	Gr 2 n (%)	Gr 3 n (%)	Gr 4 n (%)	Gr 5 n (%)	Any n (%)		
Adjudicated as drug-related ILD/pneumonitis[h]								
T-DXd (n=257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)	Yes	Yes
T-DM1 (261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)	Yes	Yes
LVEF disease								
T-DXd (n=257)	1 (0.4)[i]	6 (2.3)[j]	0	0	0	7 (2.7)	Yes	Yes
T-DM1 (261)	0	1 (0.4)[j]	0	0	0	1 (0.4)	Yes	Yes

Key: AE, adverse event; ILD, interstitial lung disease; LVEF, left-ventricular ejection fraction; T DM1, trastuzumab emtansine; T DXd, trastuzumab deruxtecan. **Note:** [a]This category includes the preferred terms neutrophil count decreased and neutropenia. [b]This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [c]This category includes the preferred terms white blood cell count decreased and leukopenia. [d]This category includes platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms fatigue, asthenia, and malaise. [f] Grade 1 alopecia: T-DXd = 26.5%, T-DM1 = 2.3%; grade 2, T-DXd = 9.3%. [h]Patients with prior history of ILD/pneumonitis requiring steroids were excluded. [i]Left ventricular dysfunction. [j]Decreased ejection fraction. * In 20% of patients and the AEs of special interest in all patients. **Source:** Cortes et al., 2022 (8).

Overall health status and QoL was maintained with T-DXd, based on mean change from baseline of EORTC QLQ-C30 global health status scale (primary patient reported outcome variable of interest). For all prespecified patient reported outcome variables of interest, the HR for time to definitive deterioration (TDD) numerically favored T-DXd over T-DM1 (HR range, 0.69-0.90), indicating T-DXd treatment delays the deterioration of QoL in patients with mBC. Delayed TDD of pain symptoms with T-DXd was statistically significant (HR, 0.75, 95% CI (0.59-0.95), p value 0.0146). Time to first

hospitalization was delayed with T-DXd versus T-DM1: median 219.5 days versus 60.0 days, respectively (interpretation limited by low rates of hospitalization in both arms).

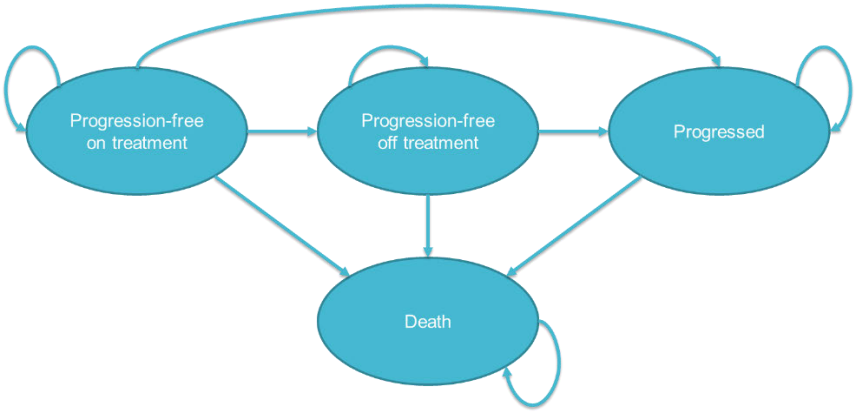
8. Health economic analysis

Cost-utility and budget impact models that follow the DMC guidelines are provided in this submission. A discount rate of 3.5% was used for both costs and benefits in line with the guidelines (2.5% after 35 years). A time horizon of 40 years was used in the base-case to ensure all relevant costs and health effects were included in the analysis. A restricted societal perspective was used in line with DMC guidelines. A 1-week cycle length was used to appropriately capture the dosing schedules of the included pharmaceuticals. Half-cycle corrections are available in the model but not implemented in the base-case as this was deemed redundant due to the short cycle length. Applying half-cycle corrections would add additional complexity without adding any additional accuracy.

8.1 Model

The cost-analysis model used in this submission contains four health states. Figure 6 presents the flow of patients in the model. All patients enter the model in the 'progression-free on treatment' state, receiving T-DXd or T-DM1 treatment. Patients may remain on-treatment while progression free, discontinue treatment while remaining progression-free, their disease may progress, or they may die. Patients whose disease has progressed can remain alive with progressed disease or die.

Figure 6: Model structure

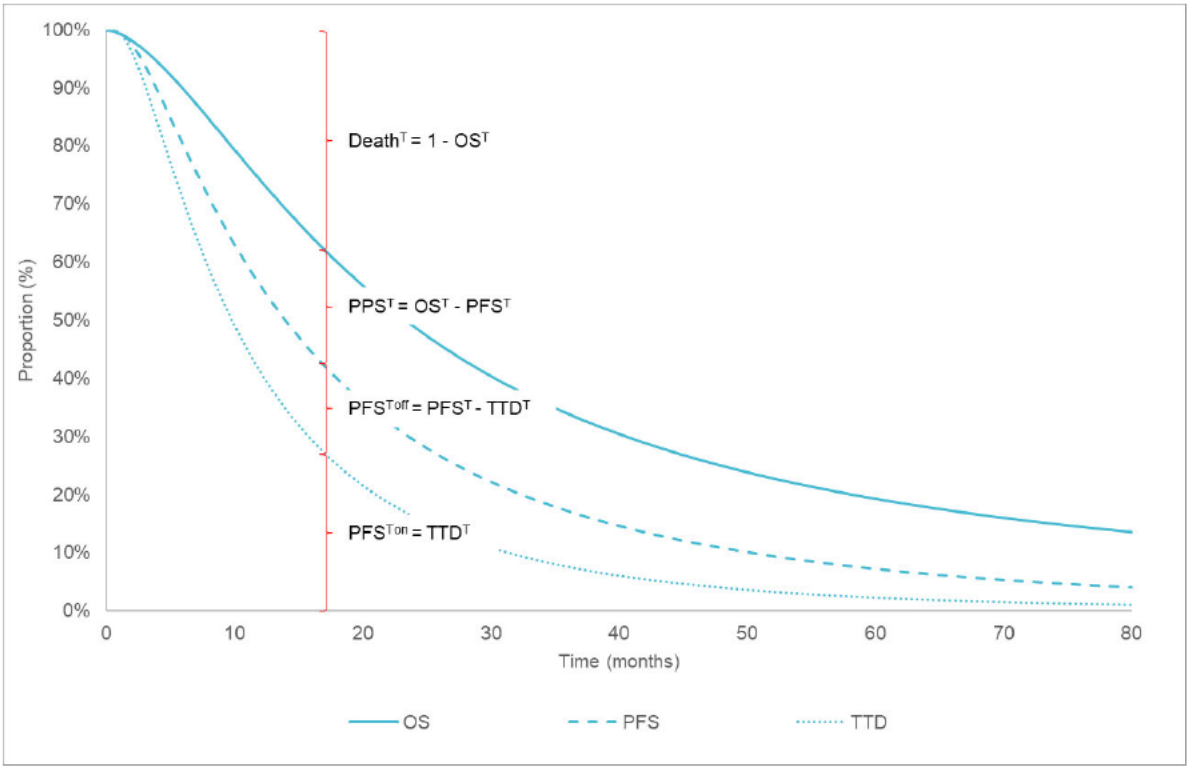


Health state membership is determined using a partitioned survival analysis approach, which is the most common type of economic modelling of oncology treatments and widely accepted. Other model types such as Markov models were considered to add complexity without improving the accuracy of the predictions. Compared with the most-standard three-state partitioned survival model, the model in this submission add additional functionality with a fourth state. This flexibility is used for a conservative assumption and we consider it relevant when treatments, like T-DXd, have shown that patients are often progression-free longer than the treatment duration. We believe that response rates and AE profiles will impact the utility while the patient are on treatment but not after the treatment is stopped. If DMC want to use the more optimistic assumption of a three-state model, the utility in the 'off-treatment' health state can be set to the same as the 'on-treatment' health state, the model then perform like a standard three-state model.

To inform the partitioned survival analysis model, parametric curves are fitted to OS, PFS and TTD data from DESTINY-Breast03. Parametric survival models are used to extrapolate outcomes beyond the observed data for a lifetime horizon. The 'standard' selection of parametric models was fitted, in line with guidance from various HTA authorities (43-45). These comprise exponential, Weibull, log-normal, log-logistic, Gompertz, and generalized gamma models.

Figure 7 graphically demonstrates how parametric survival curves are used to calculate health state occupancy. The proportion of patients in the death health state at time *T* is calculated as one minus OS^T, where OS^T is the probability, a patient is alive at time *T*. The proportion of patients in the progressed disease state is equal to OS^T minus PFS^T, where PFS^T is the probability of being alive and progression-free at time *T*. TTD is used to separate the pre-progression health state into on and off treatment periods, allowing costs and health outcomes to be modelled more accurately. The proportion of patients alive, progression-free and off treatment is equal to PFS^T minus TTD^T, and the proportion of patients who are progression-free and on treatment is equal to TTD^T.

Figure 7: Partitioned survival analysis - health state membership at time *T*



Key: OS: overall survival, PFS: progression-free survival, TTD: time to treatment discontinuation.

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

A summary of input data and how the data were obtained is presented in Table 9.

Table 9. Presentation of input data used in the model and how they were obtained

Name of estimates	Results from DESTINY-Breast03	Input value used in the model	How is the input value (column 3) obtained/estimated
Age	54.4	54.4	Obtained from DESTINY-Breast03 (35)
Weight	62.4	62.4	Obtained from DESTINY-Breast03 (35)
OS HR	0.55	0.55	Obtained from DESTINY-Breast03 (35)
Progression-free, T-DXd - utility	[redacted]	[redacted]	Obtained from DESTINY-Breast03 (35)

Progression-free, T-DM1 - utility	[redacted]	[redacted]	Obtained from DESTINY-Breast03 (35)
Progression-free, off-treatment - utility	[redacted]	[redacted]	Obtained from DESTINY-Breast03 (35)
Progressive disease, T-DXd + T-DM1 - utility	[redacted]	[redacted]	Obtained from DESTINY-Breast03 (35)
Neutrophil count decreased - T-DXd	19.10%	19.10%	Obtained from DESTINY-Breast03 (35)
Anaemia -T-DXd	5.80%	5.80%	Obtained from DESTINY-Breast03 (35)
White blood cell count decreased -T-DXd	6.60%	6.60%	Obtained from DESTINY-Breast03 (35)
Platelet count decreased -T-DXd	7.00%	7.00%	Obtained from DESTINY-Breast03 (35)
Nausea -T-DXd	6.60%	6.60%	Obtained from DESTINY-Breast03 (35)
Increased AST -T-DXd	0.80%	0.80%	Obtained from DESTINY-Breast03 (35)
Interstitial lung disease -T-DXd	0.80%	0.80%	Obtained from DESTINY-Breast03 (35)
Left ventricular ejection fraction (LVEF) decrease -T-DXd	0.00%	0.00%	Obtained from DESTINY-Breast03 (35)
Neutrophil count decreased – T-DM1	3.10%	3.10%	Obtained from DESTINY-Breast03 (35)
Anaemia	4.20%	4.20%	Obtained from DESTINY-Breast03 (35)
White blood cell count decreased– T-DM1	0.40%	0.40%	Obtained from DESTINY-Breast03 (35)
Platelet count decreased– T-DM1	24.90%	24.90%	Obtained from DESTINY-Breast03 (35)
Nausea– T-DM1	0.40%	0.40%	Obtained from DESTINY-Breast03 (35)
Increased AST– T-DM1	5.00%	5.00%	Obtained from DESTINY-Breast03 (35)
Interstitial lung disease– T-DM1	0.00%	0.00%	Obtained from DESTINY-Breast03 (35)
Ejection fraction decreased– T-DM1	0.00%	0.00%	Obtained from DESTINY-Breast03 (35)
OS	KM-data	KM-data	Obtained from DESTINY-Breast03 (35)
PFS	KM-data	KM-data	Obtained from DESTINY-Breast03 (35)
Treatment duration	KM-data	KM-data	Obtained from DESTINY-Breast03 (35)
Frequency - Specialist physician/ Oncologist	Not available	0.10	Average of the answers from Danish clinical expert opinion. In line with the DMC assessment of Tucatinib.
Frequency - Blood tests	Not available	0.34	Average of the answers from Danish clinical expert opinion. In line with the DMC assessment of Tucatinib.
Frequency - ECHO/MUGA-scanning, cardiological examination	Not available	0.01	Average of the answers from Danish clinical expert opinion. In line with the DMC assessment of Tucatinib.
Frequency - CT-scanning	Not available	0.10	Average of the answers from Danish clinical expert opinion. In line with the DMC assessment of Tucatinib.

Key: T-DXd: trastuzumab deruxtecan, T-DM1: trastuzumab emtansine,.

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

The direct comparison with T-DM1, which is currently in use in Danish clinical practice is outlined in section 7.1. The most relevant study of T-DXd (DESTINY-breast03) is used in the direct comparisons, with the purpose to assess the relative efficacy versus T-DM1.

8.2.2.1 Patient population

The patients expected to be treated with T-DXd are diagnosed with HER2+ mBC cancer and have been treated with trastuzumab, chemotherapy and often pertuzumab. These patients will be treated with T-DXd as 2L of therapy or later. Hence, the patient population considered in this submission is therefore fully aligned with the DESTINY-Breast03 study population and the approved indication of T-DXd.

Danish clinical practice:

T-DM1 is a clear standard of care for these patients in Danish clinical practice. The treatment options that are recommended in Danish guidelines and used is clinical practice are presented in detail in section 5. Most patients are expected to be treated with T-DM1 and most patients are treated with trastuzumab, chemotherapy and pertuzumab before T-DM1.

While T-DM1 has not been assessed by DMC it has before the introduction of T-DXd been the clear standard of care in Denmark, since recommendation by KRIS in March 2014. It is recommended in DBCG and ESMO guidelines and there been a consensus that it is cost-effective in all similar countries. Example of cost-effectiveness assessment from countries with similar health economic guidelines as Denmark:

- Finland (37)
- Sweden: (38)
- Norway: (39)
- England/Wales: (40)

Hence, we mean that it is not controversial to assume that T-DM1 is cost-effective also in Denmark. Comparing with anything else would be unscientific given that this has been the clear standard of care for a long time.

The expression of HER2-protein in breast cancer was described in the late 1980's. We are not aware of any studies describing outcomes on placebo in pre-treated HER2+ mBC patients and hence a comparison versus placebo is not possible to make.

That T-DM1 is the relevant comparator was also confirmed by the Danish clinical experts approached by the companies.

Clinical documentation submitted in relation to clinical practice:

Clinical documentation for the patient population can be found in section 5. The main source of evidence for this submission, DESTINY-breast03, was deemed reflective of patient population in clinical practice by Danish clinical experts. The main difference pointed out by the experts was that they would expect more (~90%) patients to be treated with pertuzumab prior to third line. They also meant that less patients are Asian in Denmark. None of these differences highlighted in the table above are expected to have an impact on the generalizability of the results from the study.

Table 10. Clinical documentation submitted in relation to clinical practice – patient population

Parameter	Clinical documentation (35)	Used in the model	Danish clinical practice
Age (years) Mean (std dev)	54.4 (11.47)	54.4	Similar
Female sex	522 (99.6)	100%	Similar
Region		N/A	Less Asian patients (<5%)
Asia	309 (59.0)		
Europe	104 (19.8)		
Rest of World	77 (14.7)		
North America	34 (6.5)		

Weight (kg)			Similar
Mean (std dev)	62.4 (13.30)	62.4	
Median	60.0	N/A	
Smoking status		N/A	Similar
Never	420 (80.2)		
Former	70 (13.4)		
Current	29 (5.5)		
Missing	5 (1.0)		
Reported history of CNS metastases	114 (21.8)	N/A	Similar
HER2 expression (IHC) - Central		N/A	Similar
1+	1 (0.2)		
2+	55 (10.5)		
3+	466 (88.9)		
Not evaluable	2 (0.4)		
Hormone receptor - Derived [a]		N/A	Similar
Positive	272 (51.9)		
Negative	248 (47.3)		
Indeterminate	2 (0.4)		
Missing	2 (0.4)		
Prior pertuzumab - Derived [c]		N/A	Higher in Denmark (90%)
Yes	320 (61.1)		
No	204 (38.9)		
Lines of prior systemic therapy excluding hormone therapies		1	1 prior line expected in most patients
<3	379 (72.3)		
≥3	145 (27.7)		
Renal function at baseline [d]		N/A	Higher in Denmark
Within normal range	265 (50.6)		
Mild impairment	201 (38.4)		
Moderate impairment	52 (9.9)		
Missing	6 (1.1)		
Hepatic function at baseline [e]		N/A	Similar
Within normal range	420 (80.2)		
Mild impairment	98 (18.7)		
Missing	6 (1.1)		
Baseline visceral disease [f]	384 (73.3)	N/A	Similar
ECOG Performance Status		N/A	More with ECOG 2 in Denmark (5-10%)
0	329 (62.8)		
1	193 (36.8)		
Missing	2 (0.4)		

Key: HER2: Human epidermal growth factor receptor 2, CNS: Central nervous system, ECOG: Eastern Cooperative Oncology group, IHC: Immunohistochemistry.

8.2.2.2 Intervention

T-DXd is intended to be used as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

Danish clinical practice:

T-DXd is expected to be used within its indication and in accordance with Danish clinical practice. The mean dose in clinical practice is expected to be similar to the dose in DESTINY-Breast03.

Clinical documentation submitted (in relation to clinical practice):

Clinical documentation for the intervention can be found in section 7.1.2. The potential use in clinical practice is expected to follow the use in the study.

Table 11. Clinical documentation submitted in relation to clinical practice – intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	[redacted] (35)	[redacted]	[redacted] mg/kg capture expected dose-reductions and interuptions that will also take place in clinical practice.
Length of treatment (extrapolated)	[redacted]	[redacted]	Treatment duration in the DESTINY-Breast03, which was deemed reflective by Danish clinical experts.
The pharmaceutical's position in the Danish clinical practice	2L	2L	T-DXd will, if approved, be used where T-DM1 is used today. That is in 2L according to Danish clinical experts.

8.2.2.3 Comparators

DESTINY-Breast03 provide data of T-DXd versus Danish standard of care (T-DM1). Additional clinical documentation of T-DM1 is provided in section 7.1.1. The relative effectiveness results based on a head-to-head study are provided in section 7.1.2.

Danish clinical practice:

According to clinical experts, the Danish clinical practice for 2L treatment (+/and beyond) of HER2+ mBC follows the Danish guidelines and are presented in section 5.3.1. In summary most patients appropriate for treatment with T-DXd based on DESTINY-Breat03 are currently treated with T-DM1.

Clinical documentation submitted (in relation to clinical practice):

The comparator presented in the clinical documentation is in line with Danish clinical practice according to Danish clinical experts.

Table 12. Clinical documentation submitted in relation to clinical practice – comparator

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	[redacted]	[redacted]	[redacted]mg/kg capture expected dose-reductions and interuptions that will also take place in clinical practice.
Length of treatment (extrapolated)	[redacted] (35))	[redacted]	Treatment duration in the DESTINY-Breast03, which was deemed reflective by Danish clinical experts.
The pharmaceutical's position in the Danish clinical practice	2L	2L	2L

8.2.2.4 Relative efficacy outcomes

DESTINY-Breast03 showed that T-DXd results in significantly more effective than the treatment currently used in Danish standard of care (see section 7.1.2).

Table 13. Clinical documentation submitted in relation to clinical practice – Relative efficacy - value

Clinical efficacy outcome	Used in the model	Clinical documentation
Primary endpoint in the study: • Median progression free survival (PFS)	T-DXd: 23 months (extrapolated) T-DM1: 7.8 months (extrapolated)	T-DXd: Median not reached. T-DM1: 6.8
Secondary endpoint: • Median OS	T-DXd: 63 months (extrapolated) T-DM1: 40 months (extrapolated)	T-DXd: Median not reached. T-DM1: Median not reached.

Key: T-DXd: trastuzumab deruxtecan, T-DM1: trastuzumab emtansine, OS: Overall survival, PFS, Progression-free survival.

Table 14. Clinical documentation submitted in relation to clinical practice – Relative efficacy - 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 (PFS)	BIRC, KM-method	Highly relevant	Progression is known to impact the patients' quality of life. Progression-free survival is also a frequently used surrogate endpoint for overall survival, which often is the main goal of the treatment.
Secondary endpoint: • Median OS	KM-method	Highly relevant	Prolonging overall survival is the main goal of the treatment for HER2+ mBC.

8.2.2.5 Adverse reaction outcomes

A safety profile of T-DXd and T-DM1 is presented in section 7.1.2. The clinical documentation submitted is fully aligned with the health economic model as shown in 8.5.4.

8.3 Extrapolation of relative efficacy

8.3.1 Time to event data – summarized:

Where data are not sufficiently mature, extrapolated survival curves were used to inform health state occupancy over a lifetime horizon in the model. Time-to-event data used to model the T-DM1 and T-DXd arms were taken from DESTINY-Breast03. For PFS, OS and TTD, standard parametric models (Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Generalized gamma) were fitted to the data from DESTINY-Breast03 in line with best practice.

Curve selection for extrapolations of OS, PFS and TTD curves were carried out systematically in line with guidelines from DMC and other HTA authorities (44-47):

- Assessment of proportional hazards.
- Statistical methods; Akaike information criterion (AIC) and Bayesian information criterion (BIC).
- Graphic evaluations to study which of the parametric functions that visually fitted the trial data from DESTINY-Breast03.
- Clinical validity and biologically plausibility were assessed using feedback from Danish HER2+ mBC experts.

There are no guidelines or standards for what should be considered in the assessment of clinical validity. Hence, the following criteria was developed together with Danish clinical experts:

- Crossing between TDD, PFS and OS should be minimized in the treatment arms as this indicates that the modelling is not clinically possible. It is unlikely that many patients die without first having progressed.
- The long-term extrapolations, assessed at 5 and 10 years, should be plausible given previous experience and publications in 2L+ HER2+ mBC.

Criteria 1 can be objectively assessed using the model developed for this submission while criteria 2 is more difficult to assess, as Danish clinical experts have limited experience of new treatments with no available long-term data (such as T-DXd). The last point was, therefore, used to disregard extreme cases.

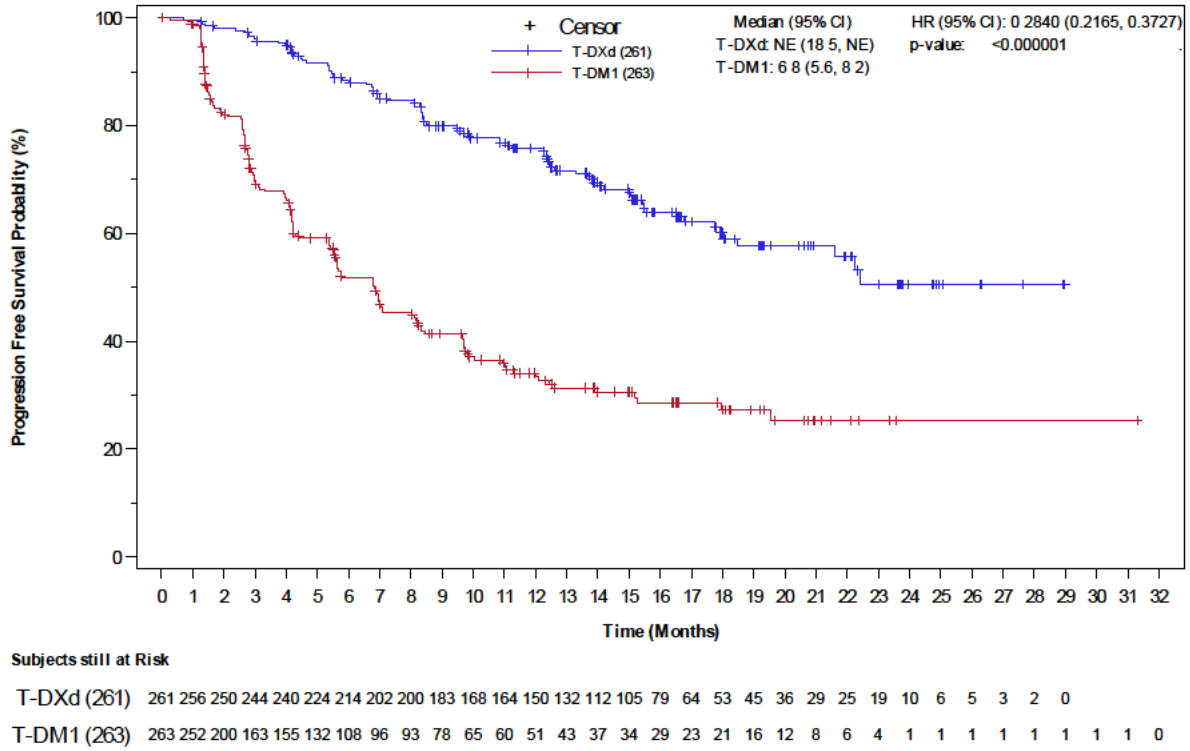
Additional details of the parameterization is provided in Appendix G.

8.3.1.1 Progression-free survival

Proportional hazards

Independent survival models are used in the model as the proportional hazard assumption did not hold for PFS when it was tested, which is indicated by the shape of the curves in Figure 8 and assessed in detail in appendix G.

Figure 8. Kaplan–Meier (KM) data for progression-free survival in DESTINY-Breast03



Key: OS: overall survival, PFS: progression-free survival, TTD: time to treatment discontinuation. T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Source: Cortes et al., 2022 (8)

Statistical fit

As shown in Table 15, the Generalized gamma and Log-normal curve has the best statistical fits to the observed data for PFS for T-DM1 and T-DXd, respectively.

Table 15. T-DXd – progression-free survival – AIC/BIC

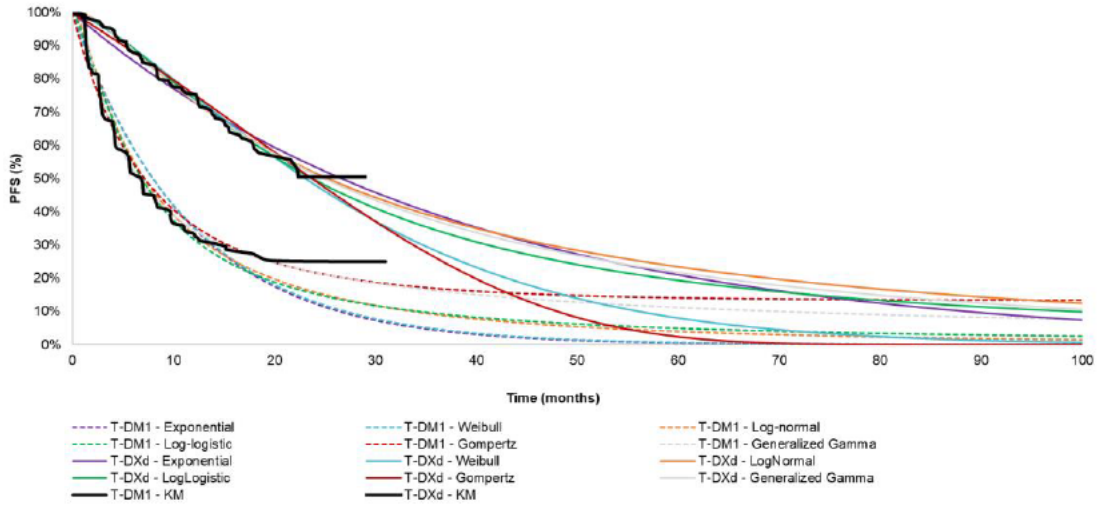
Model	T-DM1		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	1091.10	1094.67	811.15	814.72
Weibull	1093.03	1100.17	804.18	811.31
Gompertz	1081.18	1088.33	809.64	816.77
Log-Logistic	1067.40	1074.54	802.00	809.13
Log normal	1058.42	1065.56	800.83	807.96
Generalized gamma	1045.19	1055.91	802.77	813.46

Key: AIC: Akaike information criterion, BIC: Bayesian information criterion, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Post – study follow-up: Visual fit

Figure 9 show all parametric curves for PFS based the DESTINY-Breast03 study. The visual fit to the observed data is similar for most of the parametric models during the study period but varied during the long-term follow-up.

Figure 9. Progression-free survival (PFS) – parametric models



Key: KM: Kaplan-Meier, PFS: progression-free survival, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Post – study follow-up: Clinical plausibility

As can be observed in the figure above, generalized gamma and Gompertz had an unrealistic flat shape for T-DM1 (not trending towards zero). Exponential, LogNormal and the LogLogistic model provided extrapolations that seems to overestimate the survival for T-DXd with the evidence available today.

Table 16. Clinical plausibility according to Danish clinical experts - PFS

Model	T-DM1		T-DXd		Plausibility according to Danish medical experts
	5-year PFS (%)	Mean	5-year PFS (%)	Mean	
Exponential	0.5%	11.6	21.0%	38.6	Overestimating
Weibull	0.6%	11.8	8.0%	27.9	Conservative but most realistic
Log-normal	4.0%	14.9	23.5%	49.7	Overestimating
Log-logistic	4.9%	17.3	19.3%	45.8	Overestimating
Gompertz	14.1%	72.5	2.4%	25.5	Unrealistic
Generalised Gamma	11.2%	34.2	21.7%	45.0	Unrealistic

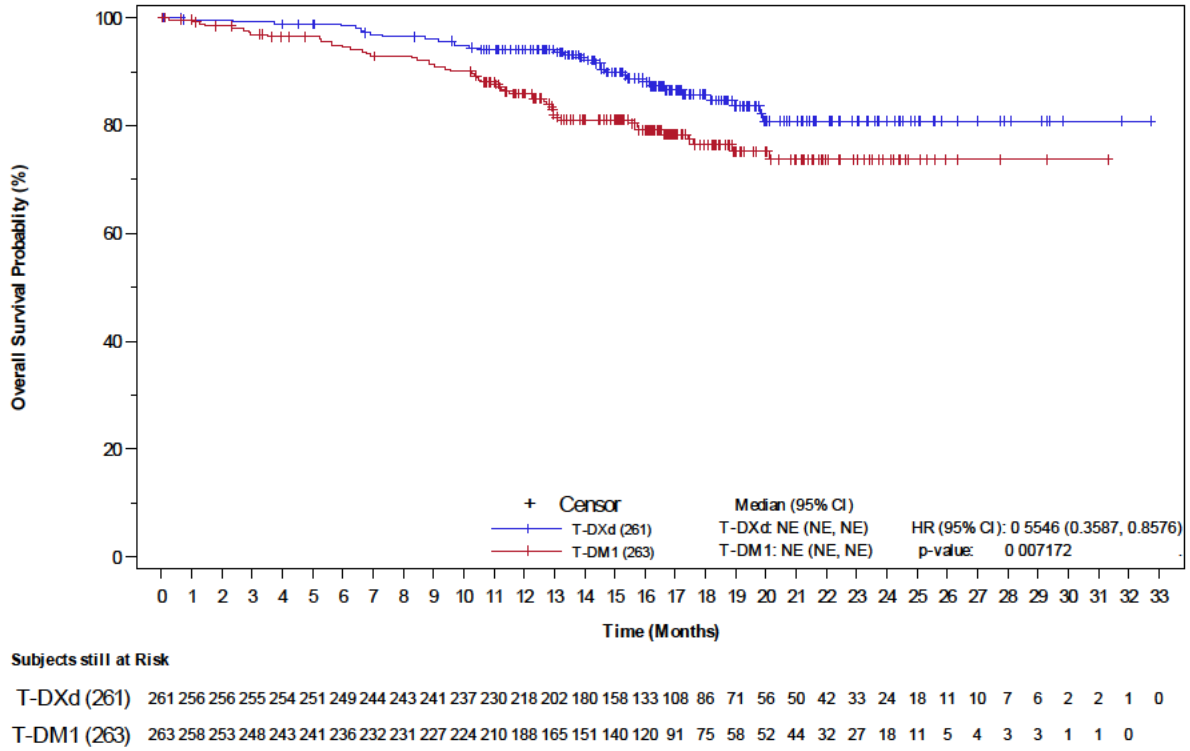
Key: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

8.3.1.2 Overall survival

Proportional hazards

Proportional hazard is used in the model as the assumption hold for OS when it was tested. This is shown in Figure 10 and assessed in detail in appendix G. Hence, AFT/dependent models were considered.

Figure 10. Overall survival – KM curves



Key: KM: Kaplan-Meier, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Statistical fit

The Log-Logistic, Weibull and Generalized gamma curve had the best statistical fit to the observed data as shown in Table 17.

Table 17. Overall survival – AIC/BIC

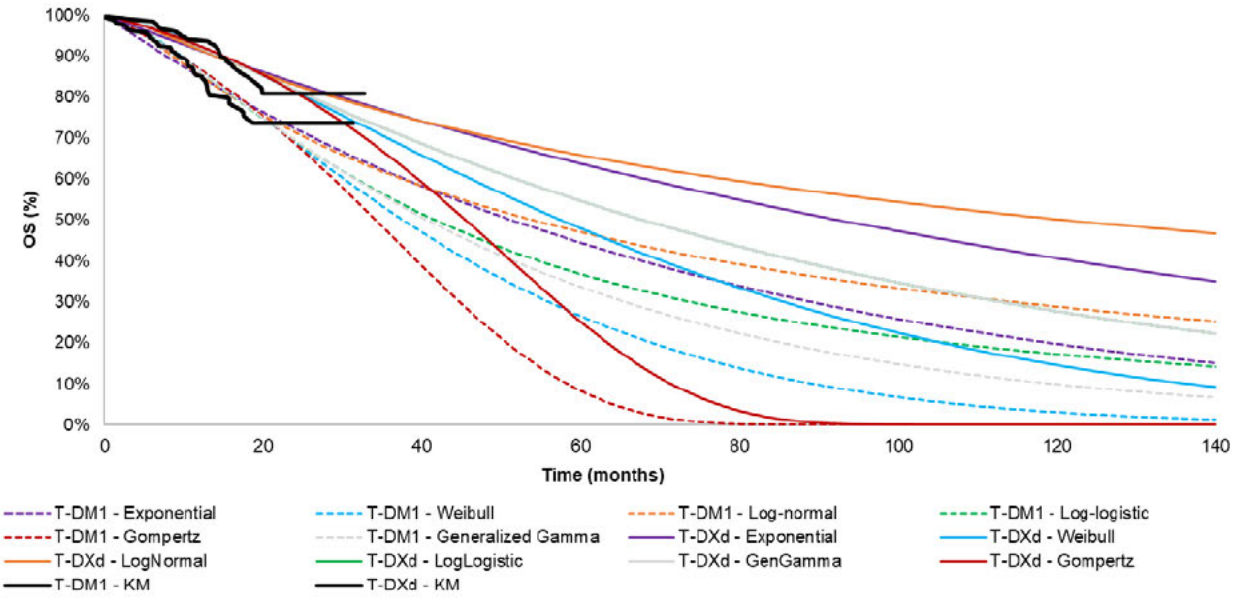
Model	AIC	BIC
Exponential	953.05	961.58
Weibull	945.44	958.22
Gompertz	949.14	961.93
Log-Logistic	944.44	957.22
Log normal	947.91	960.69
Generalized gamma	946.98	964.02

Key: AIC: Akaike information criterion, BIC: Bayesian information criterion

Post – study follow-up: Visual fit

Figure 11 show all parametric curves for OS. The visual fit is similar for most of the parametric models during the study period but varied in the long-term follow-up.

Figure 11. Overall survival – parametric models of full follow-up



Key: KM: Kaplan-Meier, OS: overall survival, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

8.3.1.3 Post – study follow-up: Clinical plausibility

It is difficult for Danish clinical experts to assess the clinical plausibility of the OS extrapolation of T-DXd given the unprecedented PFS in DESTINY-Breast03 and no available long-term data. However, for the T-DM1 curve Gompertz was deemed unrealistically pessimistic by Danish clinical experts. They stated that they believed that some patients will survive for ten years with T-DM1 but especially with T-DXd given the long PFS shown in DESTINY-Breast03. However, the Log-Normal curve was ruled out as it is expected to overestimate the survival.

Table 18. Clinical plausibility according to Danish clinical experts - OS

Model	T-DM1			T-DXd		Plausibility according to Danish medical experts
	10-year OS (%)	Mean	Better than T-DM1 arm in EMILIA	10-year OS (%)	Mean	
Exponential	19.7%	74.0	Yes	39%	126.1	Overestimating
Weibull	3.1%	44.8	No	14%	67.9	Plausible
Log-normal	28.9%	111.6	Yes	43%	160.2	Unrealistic
Log-logistic	17.3%	77.3	Yes	29%	110.6	Overestimating
Gompertz	0.0%	34.3	No	0%	44.4	Unrealistic
Generalized Gamma	9.9%	55.3	Yes	24%	86.1	Plausible

Key: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

8.3.2 Curve selection

The curve selection for the base-case analysis is provided in Table 19.

Table 19. Curve selection in the base-case

Parameter	Selected curve	Summary of rationale
Progression-free survival	Weibull	• Good visual fit for both arms

		• One of the best statistical fits for the T-DXd arm • Clinically plausible for both arms • Conservative estimates
Overall survival	Generalized gamma	• Good visual fit • One of the best statistical fits • Clinically plausible • One of the most conservative estimates

Key: T-DXd, trastuzumab deruxtecan

8.3.2.1 Progression-free survival

For the PFS extrapolation of the T-DM1 arm, only the Weibull and Exponential survival curves were deemed clinically plausible by Danish clinical experts. Weibull also had good statistical and visual fit to T-DXd data and provided clinically plausible but conservative estimates. Hence, Weibull was chosen to extrapolate PFS for both treatment arms.

8.3.2.2 Overall survival

For OS, the Danish clinical experts expect that the long-term survival for the T-DXd patient population will be long considering the unprecedented PFS shown in DESTINY-Breast03. New and additional treatment options will also be available in later lines (T-DM1, pertuzumab, tucatinib, neratinib, etc.). There is no other treatment with comparable PFS to what T-DXd showed in DESTINY-Breast03, which makes it difficult to validate the long-term extrapolation of the T-DXd OS results versus other published studies. The treatment available for HER2+ mBC patients that most closely matched the T-DXd results is pertuzumab and trastuzumab in combination with chemotherapy, which had a PFS of 18.7 (33) vs ~25.1 (8) with T-DXd. However, while the PFS is better and there are more effective subsequent treatment options, the patients in DESTINY-Breast03 are more pre-treated and the long-term OS should conservatively be assumed to be worse than in CLEOPATRA. This is the case when the base-case curve, Generalized gamma, is used to model T-DXd.

With the improvements seen during the last ten years in treating mBC (both pharmaceuticals and other technologies), the survival in the T-DM1 arm in DESTINY-Breast03 should be longer than the T-DM1 arm in the EMILIA study. As a reference, the five-year survival with mBC in Norway was 24% when the EMILIA trial was initiated and ~34% when DESTINY-Breast03 started (48). Generalized gamma was the only curve that fulfilled this criterion of the curves and was deemed clinically plausible (five year survival 33.7% in the model versus ~26% in the EMILIA study).

Hence, to not overestimate the clinical benefits, we have selected a Generalized gamma model for both T-DXd and T-DM1, which is one of the most conservative curves. In addition to good visual fit, Generalized gamma also had one of the best statistical fit to the data from DESTINY-breast03.

Table 20. External validation of the modelling

	Progression-free survival			Overall survival		
Source	**1 year**	**3 years**	**5 years**	**1 year**	**3 years**	**10 years**
T-DM1						
Modelled T-DM1 arm	**36%**	5%	1%	**86%**	55%	10%
EMILIA study (49)	**39%**			**86%**	**43%**	
T-DXd						

Modelled T-DXd arm	**75%**	28%	8%	**92%**	71%	24%
CLEOPATRA study (33) (1L)	**67%**	**30%**	**20%**	**94%**	**69%**	**29%**
PERUSE study (34) (1L)	**67%**	**35%**	**30%**	**93%**	**72%**	

Key: T-DXd: trastuzumab deruxtecan, T-DM1: trastuzumab emtansine. Note: Blue values indicate extrapolated data.

8.3.2.3 Long term treatment effect

Long-term and stable treatments effects have been observed in a large number of trials of HER2+ mBC treatments. In general, when studies have shown important treatment effects versus standard of care, these effects have been long lasting for HER2-acting agents. For instance, the CLEOPATRA study of pertuzumab plus trastuzumab and chemotherapy versus trastuzumab plus chemotherapy, showed a stable (or even improving) hazard ratio throughout the 8-9 years follow-up (33).

In late line studies of T-DM1 (49, 50), the proportional hazards assumption was verified, and the shapes of the curves do not suggest a violation of the proportional hazards during the follow-up. These studies indicated that the treatment effect has not changed significantly up to six years.

Long-lasting treatment effects have also been observed with HER2 treatments in an adjuvant setting, where the HERA trial showed consistent treatment effect of trastuzumab throughout the 11-year follow-up when adjusting for the crossover (6).

Based on these results with therapies employing trastuzumab-targeting of HER2-receptors and the long PFS and DoR in DESTINY-Breast03, a long-term treatment effect (at least 7 years) should be expected from T-DXd.

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

8.4.1 Overview of health state utility values (HSUV)

Utility weights were collected in the DESTINY-Breast03 trial using EQ-5D-5L. Utility scores for the EQ-5D-5L dimensions was computed using the Danish value sets (51). A systematic literature review was also conducted to identify health state utility values, but no relevant data was identified (appendix H). Details of the analysis of the utility data from DESTINY-Breast03 are provided in appendix I.

In the progression-free health states the completion rate of the EQ-5D questionnaires was high in both arms (97.3% and 99.2%) in DESTINY-Breast03. Patients with T-DXd had a slightly higher utility than patients with T-DM1. This is likely explained by the lower time-adjusted rate of AEs, (i.e., patients with T-DXd had a trend of lower rate of AE per months of treatment) and the higher response rates to the treatment (52).

Table 21. Relevant health state utility values

Health state utilities	Instrument	Tariff (value set) used	Utility weight (95% CI)	Reference
Progression-free, T-DXd	EQ-5D-5L	Danish	[redacted]	DESTINY-Breast03 (35)
Progression-free, T-DM1	EQ-5D-5L	Danish	[redacted]	DESTINY-Breast03 (35)

Progressive disease, T-DXd	EQ-5D-5L	Danish	[redacted]	DESTINY-Breast03 (35)
Progressive disease, T-DM1	EQ-5D-5L	Danish	[redacted]	DESTINY-Breast03 (35)

Key: T-DXd: trastuzumab deruxtecan, T-DM1: trastuzumab emtansine, CI: confidence interval.

8.4.1.1 Overview of health state utility values (HSUV) - Details

In DESTINY-Breast03, EQ-5D-5L, EORTC QlQ-BR45 and EORTC QLQ-C30 questionnaires were administered to patients to measure HRQoL. EQ-5D-5L questionnaires were completed by patients on day 1 of cycles 1, 2 and 3 and then every 2 cycles thereafter until the end of treatment assessments. Patients were then followed up at the Day 40 (+ 7 days) first follow-up assessment (after last study drug administration) or before initiation of new anti-cancer treatment, whichever came first, and then at the first long-term/survival follow-up assessments three months later. Patients were required to complete questionnaires before any other study assessments or procedures were performed on the day.

The PRO completion compliance rate at baseline was 97.3% in the T-DXd arm and 99.2% in the T-DM1 arm for the QLQ-C30; 97.7% and 98.9%, respectively, for the QLQ-BR45; and 97.3% and 99.2%, respectively, for the EQ-5D-5L questionnaire. From Cycle 3 onward, the minimum compliance rate across the questionnaires was 82.8% in the T-DXd arm and 86.6% in the T-DM1 arm:

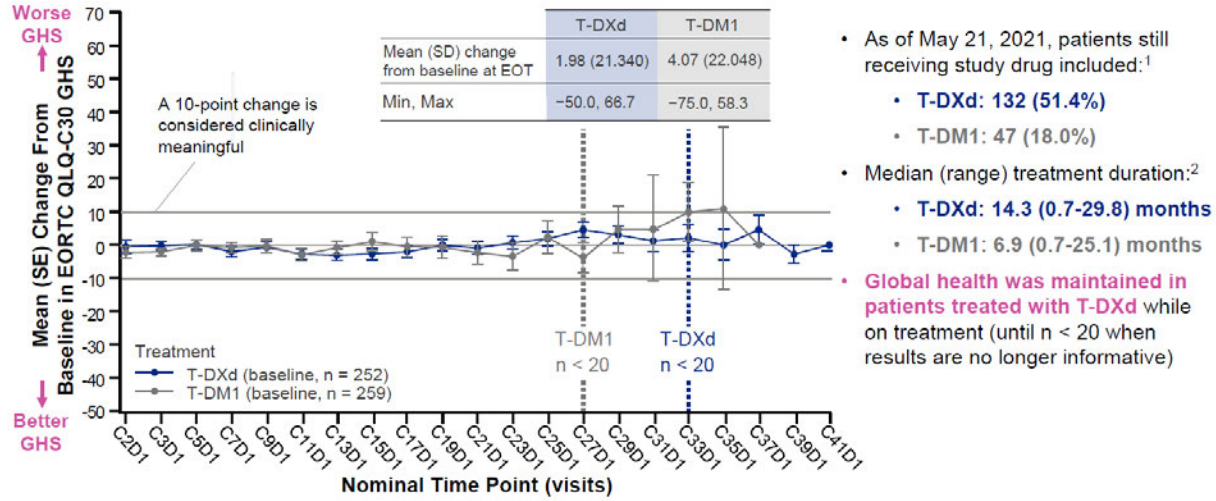
- Post-baseline compliance rates from Cycle 3 through Cycle 33 (n = 20) in the T-DXd arm ranged from 82.8% to 100.0% for EORTC-QLQ-C30, from 83.3% to 100.0% for EORTC QLQ-BR45, and from 83.3% to 97.6% for the EQ-5D-5L.
- Post-baseline compliance rates from Cycle 3 through Cycle 27 (n = 21) in the T-DM1 arm ranged from 87.1% to 98.2% for EORTC-QLQ-C30, from 86.6% to 98.2% for
- EORTC-QLQ-BR45, and from 87.1% to 98.2% for the EQ-5D-5L.

In both treatment arms, PRO completion compliance across the EORTC questionnaires were low at Cycle 2 (38.2% in the T-DXd arm and 43.8% in the T-DM1 arm), which is expected to be related to the fact that the requirement to conduct HEOR assessments at Cycle 2 Day 1 was implemented in Protocol Amendment 2.

Patients at risk at different time points for EORTC QLQ-C30, EQ-5D-5L VAS are provided in the figures below based on data presented at ASCO 2022. Patient numbers at all EQ-5D-5L timepoints are provided in

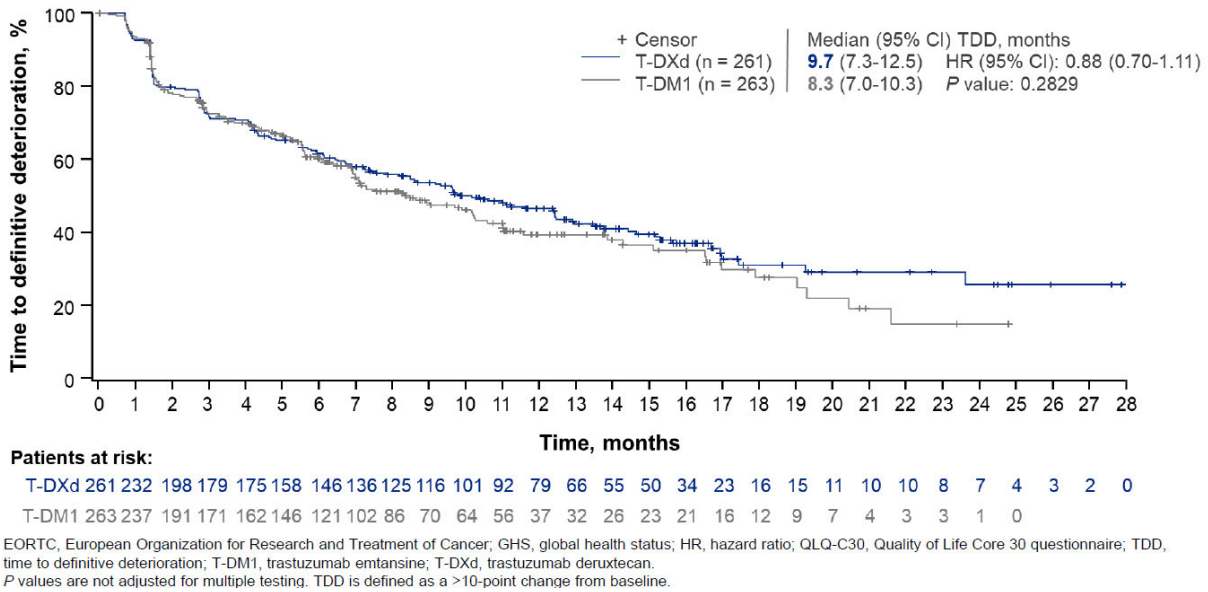
Table 22. Reporting closely followed the Consolidated Standards of Reporting Trials (CONSORT) extension on reporting PROs. The base-line outcome is reported versus the end of treatment in those subjects where this data is available (n in T-DXd arm: 97 versus n in T-DM1 arm: 172).

Figure 12. Overall health status and QoL on treatment



C, cycle; D, day; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; GHS, global health scale; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Scores range from 0 to 100; a linear transformation was applied to the raw GHS score, thus a higher score represents lower ("worse") GHS/overall QoL
1. Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 16-21, 2021. Presentation 2525. 2. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154.

Figure 13. Time to definitive deterioration (TTD) of QLQ-C30 GHS

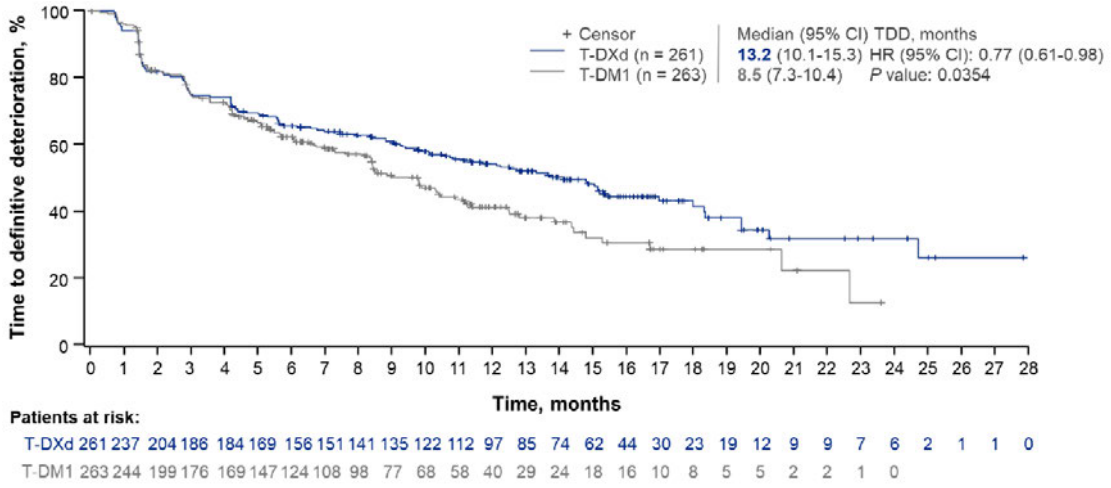


Patients at risk:

T-DXd	261	232	198	179	175	158	146	136	125	116	101	92	79	66	55	50	34	23	16	15	11	10	10	8	7	4	3	2	0
T-DM1	263	237	191	171	162	146	121	102	86	70	64	56	37	32	26	23	21	16	12	9	7	4	3	3	1	0			

EORTC, European Organization for Research and Treatment of Cancer; GHS, global health status; HR, hazard ratio; QLQ-C30, Quality of Life Core 30 questionnaire; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
P values are not adjusted for multiple testing. TDD is defined as a >10-point change from baseline.

Figure 14. TDD of EQ-5D-5L VAS[a]



EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; HR, hazard ratio; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale.
P values are not adjusted for multiple testing. TDD is defined as a >10-point change from baseline. [a]VAS of self-rated overall health and quality of life, measured on a scale from 0 to 100.

[redacted]

Note: C, cycle; D, day;

8.4.1.1.1 Overview of health state utility values (HSUV) - Details

[redacted]

EQ-5D-5L utility scores based on *'progression-free'* and *'progressed disease'* health states were derived using generalized estimating equations (GEE) regressions. EQ-5D-5L scores from all available time points, including baseline, were included in the GEE as dependent variables. Treatment and treatment response status (progressed disease vs. progression-free) were included as independent variables. The mean utility values and associated 95% confidence intervals for the progression-free and progressed health states for each treatment group are derived from the model using least squares means. The GEEs are fitted with an independence working correlation structure and a robust

sandwich variance estimator to account for the fact that we considered several visits per patient. Two regression models were considered:

- Utility ~ progressed
- Utility ~ progressed + treatment

Table 23 presents the regression coefficients for the models including only progression status (model 1) and both treatment arm and progression status (model 2). For both models, progression significantly reduces the utility (regression coefficients (95% CI) -0.043 (-0.072, -0.014) for model 1 and -0.040 (-0.068, -0.013) for model 2). T-DXd is seen to non-significantly increase utility in model 2 (0.008 (-0.014, 0.031)). Based on QIC criterion, Model 1 including only progression status is favored.

[redacted]

	Model 1	Model 2
[redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]

Table 24 presents the utility values by health-state progressed and non-progressed overall (model 1) and by treatment group (model [redacted]

	T-DXd		T-DM1		Total		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[a] Number of visits/timepoints without and with progression, respectively. LSM: Least Square Means obtained from Generalized Estimating Equations, CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease.

A longitudinal model was chosen over cross-sectional analysis using a pooled sample as it better aligns with the design of the

8.4.1.1.2 Missing data handling and sensitivity analysis using the UK value set

A display of the missing data pattern per patient and visit for the EQ-5D-5L questionnaire is presented below. We see that the missing data pattern is monotone over time, i.e., we observe more missing questionnaires as time into the study progresses.

[redacted]

Generalized Estimating Equations (GEE) regressions were used to derive health-state utilities and no missing data imputation was performed. GEE requires the assumption of missing completely at random (MCAR), i.e., the fact that the data are missing is independent of the observed and unobserved data.

To assess whether bias was introduced by assuming missing data to be MCAR, a sensitivity analysis was performed for Models 1 and 2 defined above by using a linear mixed model instead of GEE. The former requires the data to be Missing At Random (MAR), which is less strong than MCAR. For these models, the optimal random effects (subject or subject and timing of questionnaire) were identified based on the lowest AIC and BIC. An unstructured correlation matrix was used to model the correlation within patients.

The model including subject and timing of questionnaire as random effects, and progression status as fixed effect, provided the lowest AIC and was considered as the best model (see Table 25Table 26). Figure 16 displays the health-utilities per health state (progressed, non-progressed) overall and by treatment arm, obtained as Least Square Means from GEE and the linear mixed model including subject and timing of questionnaire as random effect. Estimates of utilities are similar between models, and GEE provides slightly larger 95% confidence intervals, thus comforting our conclusions. Please note that the assessment of the robustness of the results used the UK value set, but the same conclusions would naturally apply for the Danish value set.

[redacted]

CI: [redacted]

[redacted]

[redacted]			
[redacted]			
[redacted]	[redacted]		[redacted]
	[redacted]		[redacted]
[redacted]			[redacted]
			[redacted]
[redacted]	[redacted]		[redacted]
	[redacted]		[redacted]
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]		[redacted]
		[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

8.4.2 Health state utility values used in the health economic model

Utilities collected in the DESTINY-Breast03 study were used throughout the model. The baseline utility values used in the model are then adjusted for age over time using the age-matched general population utility values presented by DMC (53).

It was shown in DESTINY-Breast03 that for all prespecified PRO variables of interest, the HR for time to definitive deterioration numerically favoured T-DXd over T-DM1 (HR range, 0.69-0.90), indicating T-DXd treatment delays the deterioration of QoL in patients with mBC. Delayed TDD of pain symptoms with T-DXd (HR, 0.75) is particularly salient, given its profound impact on QoL.

Still, it is expected that the main driver for the utility is if the patient is progression-free or not, which also showed to be a significant parameter in the utility estimation (see above). But it was deemed appropriate to use treatment specific utilities to capture differences between the treatment arms in especially response rate and AE profile.

For breast cancer, it has been shown that responding to a treatment is an important parameter for predicting the utility (54). The large difference in response in DESTINY-Breast03 (ORR: 79.7% vs. 34.2%) could be an explanation to the observed trend towards higher EQ-5D generated utility in the T-DXd arm. The AE profile is also different between T-DXd and T-DM1.

Table 27. Health state utility values used in model

Health state utilities	Utility weight (CI)	Reference
Progression-free, T-DXd	[redacted]	DESTINY-Breast03 (35)
Progression-free, T-DM1	[redacted]	DESTINY-Breast03 (35)
Progression-free, off-treatment	[redacted]	Average of T-DXd and T-DM1 values of the above was used to use a more conservative value when

		patients are no longer on treatment and experience different AE profiles, DESTINY-Breast03 (35)
Progressive disease, T-DXd + T-DM1	[redacted]	Average of the utility values of T-DXd and T-DM1, DESTINY-Breast03 (35). The average was used instead of the overall utility as more subjects previously treated would otherwise inform this health state.

Key: T-DXd: trastuzumab deruxtecan, T-DM1: trastuzumab emtansine,. **Notes:** *((0.8711 (0.8559, 0.8864) + 0.8793 (0.8625, 0.8960))/2), **((0 8390 (0.8092, 0.8687)+ 0.8308 (0.7995, 0.8621)/2)

The utility weights from DESTINY-Breast03 are expected to capture disutility from AEs. Hence, to avoid double counting, no AE utilities were included in the base-case. Information about AE disutilities for scenario analyses is available in the submitted Excel-model. These utilities are based on disutilities in the published literature.

8.5 Resource use and costs

The model uses 2022 prices in Danish kroner (DKK) (55). The model includes the following costs:

- Drug acquisition costs (section 6.4.1)
- Drug administration costs (section 6.4.2)
- Disease management costs (section 6.4.3)
- Adverse event costs (section 6.4.4)
- Subsequent treatment and terminal care costs (section 6.4.5)
- Time and transportation costs (section 8.5.6)

8.5.1 Drug acquisition

The AIP of T-DXd of DKK 11 928,31 per 100 mg vial and the recommended dose is 5.4 mg/kg every 3 weeks was used in the model. Drug acquisition costs for T-DM1 in the model were sourced from medicinepriser.dk drug cost data base and the dosing information (3.6mg/kg) was sourced from the SmPC. The actual dose the patients received in DESTINY-Breast03 trial was used as the basis for the drug cost calculation as this is the dose that is the basis for the clinical effect used throughout this submission. The number of vials needed per administration was based on the weight distribution in DESTINY-Breast03. Price reductions for T-DXd and T-DM1 in line with the agreement between the companies and the Danish government was incorporated in the model assuming that T-DXd is approved after November 1, 2022. [redacted]

Table 28. Vials per patient if wastage is included

	Patient numbers (n=518)	Proportion of population	T-DXd vials
Weight intervals (kg)			
0 – 36.9	1	0.2%	2
37.0 – 55.5	185	35.7%	3
55.6 – 74.0	252	48.6%	4

74.1 – 92.5 92.6+	59 51	11.4% 4.1%	5 6
Maximum number of vials with 100% wastage			3.83
Maximum number of vials without wastage			3.37

Key: T-DXd: trastuzumab deruxtecan, T-DM1, trastuzumab emtansine.

Table 29 presents the resulting costs per dose and indicates whether the cost includes wastage.

Table 29. Drug costs per dose

Treatment	Relative dose intensity (RDI)	Cost per dose (with RDI, DKK)	Cost per day (with RDI, DKK)	Reference
T-DXd (q3w)	[redacted]	[redacted]	[redacted]	RDI: DESTINY-Breast03 (35), Price: medicinpriser.dk
T-DM1 (q3w)	[redacted]	[redacted]	[redacted]	

Key: IV: intravenous, q3w: every three weeks, T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan.

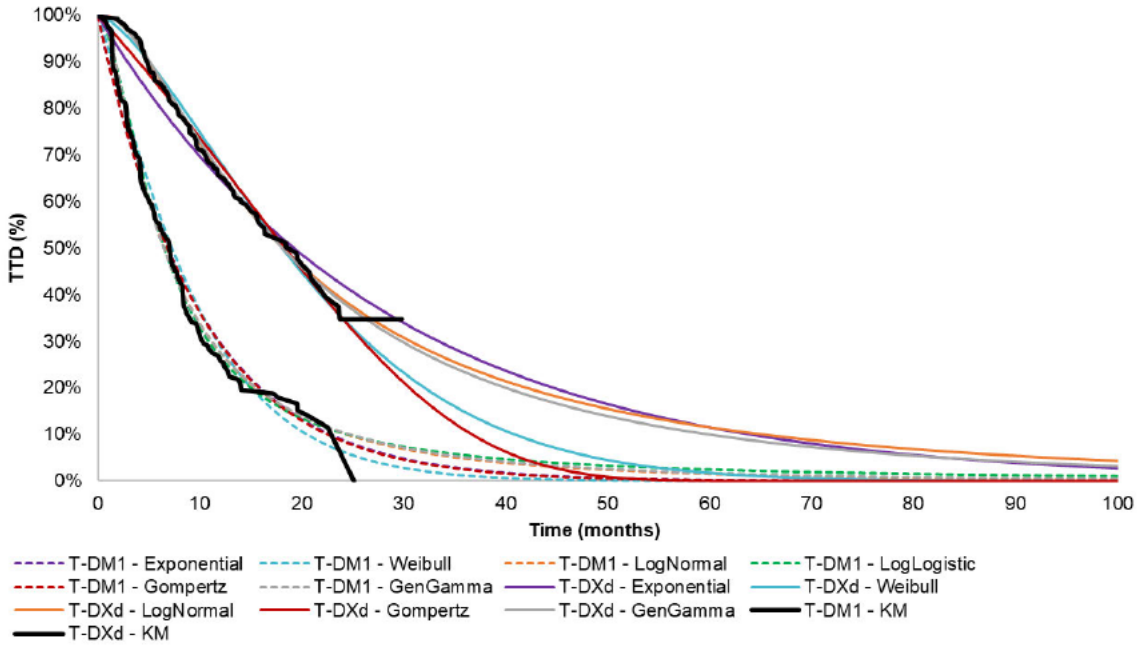
The mean relative dose intensity in DESTINY-Breast03 was [redacted] for T-DXd and [redacted] for T-DM1 when dose-interruptions and dose-adjustments were taken into consideration. Based on feedback from clinical experts, no wastage was assumed as the base-case in this submission. According to clinical experts, as for other treatments, the clinics try to minimize the wastage by coordinating specific treatment days for these patients or rounding the doses to a specific number of vials.

The treatment durations in the model (~[redacted] months of treatment with T-DXd and ~[redacted] months for T-DM1) are based on the actual treatment durations in DESTINY-Breast03. In DESTINY-Breast03, the time-to-discontinuation was shorter than the PFS, especially for T-DXd. This is expected as, while some patients discontinued the treatment due to toxicity in progression-free health states in the T-DM1 arm (7%), this was more common in the T-DXd arm (14%).

Figure 17 shows the parametric curves for the time to treatment discontinuation in the DESTINY-Breast03 population. It is logical that the treatment duration should follow the same parametric shape as PFS (Weibull) and be the same or shorter than the PFS given that most patients discontinue due to progression.

Hence, the same parametric curve, Weibull, was used for the base-case. Weibull was also in line with the expectations of Danish clinical experts, who did not expect to treat many patients for more than a couple of years, regardless of progression status.

Figure 17. Time to treatment discontinuation in DESTINY-Breast03



Key: KM: Kaplan-Meier, T-DXd: trastuzumab deruxtecan, T-DM1: trastuzumab emtansine, TTD: time to treatment discontinuation.

Table 30. Statistical fit to time to treatment discontinuation in DESTINY-Breast03

Model	T-DM1		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	1409.80	1413.38	1084.75	1088.31
Weibull	1405.39	1412.53	1066.07	1073.20
Gompertz	1411.80	1418.94	1077.34	1084.47
Log-Logistic	1386.80	1393.95	1061.20	1068.33
Log normal	1384.04	1391.19	1059.57	1066.70
Generalized gamma	1386.01	1396.72	1061.39	1072.09

Key: AIC: Akaike information criterion, BIC: Bayesian information criterion, T-DXd: trastuzumab deruxtecan, T-DM1: trastuzumab emtansine.

8.5.2 Drug administration

The drug administration costs are based on what was deemed appropriate by DMC in the assessment of Tukysa and are taken from Sørensen et al., (56) (Table 31).

Sørensen et al. estimated the administration cost of trastuzumab in a Danish setting using a micro-cost approach. Sørensen et al., for instance, include the costs for time spent for a physician and nurse per IV administration following the first administration. The physician was estimated to be involved for 30 minutes and the nurse for 10 minutes in relation to the IV administration and following observation time. The cost of this time is retrieved from 'Medicinrådets værdisætning af enhedsomkostninger' (57). A physician's hourly rate of DKK 1.316 (Overlæger) and a nurses (Sygeplejersker) hourly rate of DKK 554 was assumed and adjusted to 2022 prices with the Netto price index (55).

Trastuzumab is used in the same patient population as T-DXd and is administered in the same way as T-DXd. Hence, this reference is expected to be an accurate estimate of the administration cost. Administration costs are applied to all patients on treatment with IV treatments.

Table 31: Drug administration costs

Method	Cost (DKK)*	Source
IV infusion 30 min	744	Sørensen J.et al.,. (56) Danmarks Statistik, Nettoprisindeks, updated in March 2022. 'Medicinrådets værdisætning af enhedsomkostninger' V1.3 2020

Key: IV, intravenous.
*2020 price average to March 2022, index factor 1,0596

8.5.3 Monitoring costs

Monitoring costs are based on what was deemed appropriate by DMC in the assessment of Tukysa.

The disease management costs are split into progression-free and progressed disease health state costs per week in the model. However, in the base-case the frequency of visits was considered to be the same regardless of progression status. Table 32 summarizes the routine follow-up resource use and costs associated with pre- and post- progression obtained from Danish DRG system 2022 (58). The types and frequencies of medical resource use were informed by DMC assessment of tucatinib and were validated by Danish clinical experts. However, clinical experts expected patients to continue to receive CT scans as this is for a second line treatment and the majority of patients are expected to also be treated in third line.

Table 32: Unit cost of Routine Follow-up

Resource	Frequency in pre-progression health state	Frequency in post-progression health state	Cost (DKK)	Source
Specialist physician/ Oncologist	Once per month	Once per month	1 379	"Medicinrådets værdisætning af enhedsomkostnigner v. 1.4. 2020"*
Specialist nurse	Every three weeks	Every three weeks	581	"Medicinrådets værdisætning af enhedsomkostnigner v. 1.4. 2020"*
Blood tests	Once per month	Once per month	244	Rigshospitalets Labportal 2021**
ECHO/MUGA-scanning, cardiological examination	Every three months	Every three months	1 910	DRG 2022 (05PR04) "Kardiologisk undersøgelse, udvidet "
CT-scanning	Every three months	Every three months*	1 979	DRG 2022 (30PR07) "CT-scanning, ukompliceret"

Key: CT: computed tomography, ECHO: Echocardiogram, MUGA: multigated acquisition. * As this is second line patients are likely to get additional treatment and, therefore, continue to get CT scans according to clinical experts *2020 price average to March 2022, index factor 1,0596. **2021 price average to March 2022, index factor 1,0446.

8.5.4 Adverse event costs

Adverse event costs are based on what was deemed appropriate by DMC in the assessment of Tukysa and in relation to the DMC Guidelines.

Table 33 shows the costs associated with the management of AEs sourced from the price list of the Danish DRG system 2021 (58).

All AEs with a grade of 3 or more and that had an incidence of above 5% in either arm was assigned a cost in line with what is reported in Table 33. Only grade 3+ events were assumed to require health care resources.

AE probabilities were sourced from the DESTINY-Breast03 patient level data. The product of the probability of experiencing an AE and the cost per event is summed across all AEs to calculate an average AE cost per patient.

In line with previous DMC assessments (59), the cost for AEs such as *neutropenia* and l*eukopenia* were set to zero under the assumption that these are only treated in the occurrence of fever or infection.

Table 34 present average per-patient AE management costs for each arm of the model.

Table 33: Adverse events –cost per event

Adverse event	Cost per event (DKK)	Source (DRG 2022)
Neutropenia	0	Assumption, only treated in case of fever
Anaemia	61 074	Mean of DRG 2022 16MA05 (41 278) and DRG 16MP06 (80 869)
Leukopenia	0	Assumption, only treated in case of fever
Thrombocytopenia	0	Assumption, only treated in case of fever
Nausea	2 041	DRG 2022 – 09MA98
Fatigue	2 041	DRG 2022 – 09MA98
Increased AST	0	Assumption, only treated in case of fever
ILD	45 635	DRG 2022 – 04MA17 Interstitielle lungesygdomme
LVEF decreased	31 725	DRG 2022 – 05MP42 Hjertesvigt, herunder kardiogent shock, proceduregrp. A

Key: AE, adverse event; ILD, interstitial lung disease; LVEF, left-ventricular ejection fraction; T DM1, trastuzumab emtansine; T DXd, trastuzumab deruxtecan.

Table 34: Total adverse event costs in both arms

Action	T-DXd	T-DM1
Total adverse event cost (DKK)	4 146	2 590

Key: T DM1, trastuzumab emtansine; T DXd, trastuzumab deruxtecan.

8.5.5 Subsequent treatment and terminal care

A one-off terminal care inflation-adjusted cost of 71 610 DKK in line with the DMC assessment of Tucatinib and T-DM1 was used in the base-case (60).

The cost is derived from the UK study which estimates the end-of-life costs for four different types of cancer, including breast cancer. The study is based in a UK setting and includes patients starting palliative treatment to death. The estimate is the most relevant data identified as an end-of-life cost for these patients. Only the costs for health care and social care were included thereby excluding the informal care and Charity care costs included in the study. The currency exchange rate conversion was done 28.01.2022 and the Danish "nettoprisindeks excl. Energy" was used to project the 2021 value from 2015, which is when the UK study was conducted (60, 61).

Danish clinical experts stated that subsequent treatment should be assumed in the modelling as these are used in clinical practice. Accounting for subsequent treatment costs also reduces the need for crossover- and other adjustments.

Hence, subsequent treatment after 2L was assumed in 90% of the patients in the base-case in this assessment based on feedback from Danish clinical experts and the DMCs estimates in their assessment of tucatinib.

T-DXd is the preferred 3L option after T-DM1 in most patients (~70%) according to these experts. When submitting this dossier (for 2L) price discussions are still ongoing with DMC/Amgros for the 3L indication. Hence, to be conservative, the modelled proportion of subsequent T-DXd after T-DM1 was 0%. However, in their assessment of tucatinib 70% were assumed to be treated with the tucatinib combination after T-DM1.

Clinical experts indicated that they expect that most patients will be treated with T-DM1 after T-DXd in Denmark.

More patients received a novel subsequent treatment in DESTINY-Breast03 than what was assumed in the model. When patients progressed, most patients went on to treatment with another novel HER2+ targeted treatment. The subsequent use of T-DXd and T-DM1 was similar in the study where 43 patients in the T-DXd arm received T-DM1 treatment and 30 in the T-DM1 arm received T-DXd treatment. In the study, it was observed that other novel treatments such as tucatinib, pertuzumab etc. were used after T-DM1 due to the lack of availability of T-DXd in many countries.

Table 35. Subsequent treatment proportion

Action	T-DXd arm	T-DM1 arm
Patients with progression, n,	80	152
T-DXd, n, (%)	0 (0%)	30 (20%)
T-DM1, n, (%)	43 (54%)	17 (11%)
Other novel treatments (Other ADCs, Pertuzumab, Tucatinib, neratinib, other TKIs), n, (%)	27 (34%)	98 (64%)
Total proportion novel treatments T-DM1, T-DXd and other in DESTINY-Breast03	88%	95%

Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan.

Cost of subsequent treatment is shown in Table 36.

Table 36. Subsequent treatment costs after T-DM1 and T-DXd

Action	Cost per patient	T-DXd %	T-DM1 %	Source
Trastuzumab + chemo	89 366	10%	30%	DMCs assessment of Tukysa (62)
T-DM1	199 111	70%	0%	DMC+ DB03*, Danish experts.
Tucatinib combination	760 756	20%	70%	DMCs assessment of Tukysa (62)
Total costs subsequent treatments		**300 466**	**559 339**	

Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan

Table 37. Subsequent treatment costs after T-DM1 and T-DXd

					Source:
Tucatinib combo costs	**Pack size**	**PPP**	**units per 3 weeks**		
Tucatin b PPP	84	45930.8	84		Medicinpriser.dk

Trastuzumab PPP	1	11114	1		Medicinpriser.dk
Capecitabine PPP	120	250	93		Medicinpriser.dk,Mosteller formula
IV admin			1		
RDI					
Tucatin b RDI	88.50%				DMCs assessment of Tukysa (62)
Capecitabine (tucatin b arm)	73.90%				DMCs assessment of Tukysa (62)
Trastuzumab IV Tikysa arm	73.90%				DMCs assessment of Tukysa (62)
Capecitabine (TRASCAP)	79%				DMCs assessment of Tukysa (62)
Trastuzumab (TRASCAP)	79%				DMCs assessment of Tukysa (62)
Tukysa regime	**Cost per 3 weeks**	**Total cost**	**Cycles**	**Discounted months of exposure**	
Tucatin b PPP	40 649	625387	15	11	Calculation to match: DMCs assessment of Tukysa (62)
Trastuzumab PPP	8 213	122253	15	10	Calculation to match: DMCs assessment of Tukysa (62)
Capecitabine PPP	143	2388	17	12	Calculation to match: DMCs assessment of Tukysa (62)
IV admin	712	10728	15	10	Calculation to match: DMCs assessment of Tukysa (62)
Total		**760 756**			
TRASCAP regime	**Cost per 3 weeks**	**Total cost**	**Cycles**	**Discounted months of exposure**	
Trastuzumab PPP	8 780	81253	9	6	Calculation to match: DMCs assessment of Tukysa (62)
Capecitabine PPP	153	1577	10	7	Calculation to match: DMCs assessment of Tukysa (62)
IV admin	712	6536	9	6	Calculation to match: DMCs assessment of Tukysa (62)
Total		**89 366**			
	Cost per 3 weeks	**Total cost**	**Cycles**	**Treatment months**	
T-DM1	[redacted]	**199 111**	8	5.6	See above for monthly cost, KAMILLA study (63) for treatment duration after Pertuzumab.

Key: T-DM1: Trastuzumab emtansine,PPP: Pharmacy purchasing price.

The number of discounted month of treatment was calculated baesd on the total cost in the DMC assessment of Tukysa. As the patient weight in DESTINY-Breast03 and HER2Climb do not fully match. The number of month of treatment do not fully match either.

8.5.6 Time and transportation costs

Time and transportation costs are based on what was deemed appropriate by DMC in the assessment of Enhertu in 3L.

Transportation costs are calculated by applying 3.51 DKK/km which is the tax-free driving allowance for 2021 according to "Skattestyrelsen". This cost per kilometer is applied to the average distance of 20 km to a nearby hospital assumed to take 45 minutes each way. (64)

Patient time costs are estimated to 181 DKK/hour according to DMC guidelines (64). A round trip to the hospital including visit will amount to 2 hours per visit. This cost is applied to hospital visit for the patient. It is assumed that in most cases specialist visits and scans will be done in the same visit as when blood tests are taken. Thus, in order to not overestimate the patient costs, the visit with the highest frequency per week was used to calculate the number of visits for the patients.

Patients experiencing an AE requiring an action were assumed to do an additional visit to the hospital.

Table 38: Time and transportation costs

Action	Units	DKK	Source
Proportion of patients that incur costs	100 %	-	Medicinrådets værdisætning af enhedsomkostninger v. 1.6. 2022
Average distance to hospital	20 km		Medicinrådets værdisætning af enhedsomkostninger v. 1.6. 2022
Cost per km		3.51	Medicinrådets værdisætning af enhedsomkostninger v. 1.6. 2022
Average visits per week	0.33		
Total transport costs per week		46.8	Calculation
Time spent per visit	2 hours		Assumption
Patient cost per hour		181	Medicinrådets værdisætning af enhedsomkostninger v. 1.6. 2020
Total patient time cost per week		120.67	Calculation
Total patient cost per week		167.54	Calculation

Key: km: kilometer.

8.6 Results

8.6.1 Base case overview

All economic models include approximations, and cost-analysis results are dependent on assumptions and choices with respect to methodology and inputs. In this analysis, key assumptions were necessary because of the clinical trial data that is currently not available for the full follow-up.

As endpoints are modelled independently, partitioned survival analysis models can produce logically inconsistent scenarios, for example it is possible for the extrapolated PFS curves to fall above the extrapolated OS curve. However,

the model accounts for this by capping the PFS curve to be the minimum of the PFS extrapolation and the OS extrapolation.

Other key base-case settings and assumptions used in the model are presented in Table 39.

Table 39. Key settings and assumptions used in the model

Parameter	Base case Value / Assumption	Section for justification
Model settings		
Intervention	T-DXd	5.4
Comparators	T-DM1	5.3
Discount rate	3.5%	8.1
Time horizon	40	8.1
Year length	52 weekly cycles, and thus, each month is 4.33 weeks long	8.1
Population / Indication	Patients in second line treatment of HER2-Positive Metastatic Breast cancer who been treated with trastuzumab and pertuzumab	5.2.1
Start age	54	7.1.1
Perspective	Restricted societal	8
Cycle length	1 week	8.1
% Female	100%	7.1.1
Clinical inputs		
Weight	62.4 kg	7.1.1
OS curve fit	Generalized gamma	8.3.1.2
PFS curve fit	Weibull	8.3.1.1
Treatment duration	Weibull in line with PFS	8.5.1
Main source for AE	DESTINY-Breast03	8.5.4
Cost inputs		
Wastage	Not included	8.5.1
Dose intensity	~93%/~94%	8.5.1

Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan. PFS: Progression-free survival, PD: Progressed disease.

8.6.2 Base case results

The cost-effectiveness result for the base-case is presented in Table 40. T-DXd is predicted to gain 1.61 QALYs to an incremental cost of approximately 600 000 DKK, which results in an ICER of 367 256 versus T-DM1. As expected, the major cost-driver is the drug cost (~67% of total incremental cost) while almost all the gain in QALYs was in a pre-progression health state (~69% of total gained QALYs).

Table 40. Deterministic results – incremental analysis

	T-DXd	T-DM1
Total LYs	5.96	4.10
Incremental LYs	1.86	
Total QALYs	5.07	3.45
Incremental QALYs	1.61	
Total direct costs (DKK)	1 710 545	1 118 490
Incremental direct costs (DKK)	592 055	
ICER per QALY	**367 256**	

ICER per LY	**317 575**	

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan.

Table 41. Disaggregated costs for T-DXd and T-DM1

Cost category	T-DXd	T-DM1	Increment
Drug costs	1 050 502	328 090	722 412
Administration costs	22 400	10 444	11 955
Resource use costs	268 917	184 795	84 123
AE costs	4 146	2 590	1 557
Subsequent tx & EOL costs	312 482	556 770	-244 288
Transportation & patient costs	52 098	35 801	16 297
Total	**1 710 545**	**1 118 490**	**592 055**

Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan.

Table 42. Disaggregated QALYs for T-DXd and T-DM1

Health state	T-DXd	T-DM1	Increment
Pre-progression (on)	1.51	0.69	0.819
Pre-progression (off)	0.45	0.15	0.292
Post progression	3.11	2.61	0.501
Total	**5.07**	**3.45**	**1.61**

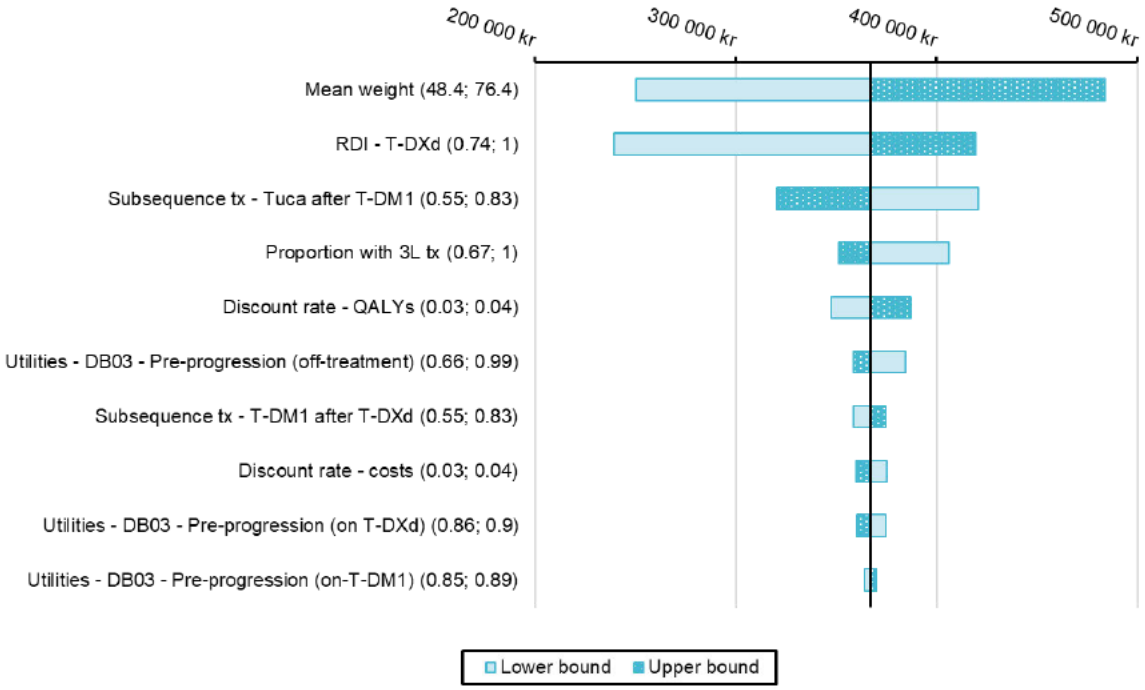
Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan.

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

In the one-way sensitivity analysis, each parameter was varied in turn at its lower and upper bound, which is obtained from the 95% confidence interval. Figure 18 presents a summary of the most influential parameters with corresponding ICERs. The results show that the patient weight, utility values, particularly for progression-free, are the parameters most likely to generate significant changes in the ICER. In all the analyses, the ICERs are well-below commonly used thresholds for cost-effectiveness in Denmark.

Figure 18. Tornado diagram – T-DXd versus T-DM1 (ICER)



Key: HR: hazard ratio, ICER: incremental cost-effectiveness ratio, IV: intravenous, PFS: progression-free survival, T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan., RDI: Relative Dose Intensity.

Table 43 reports the results from the ten most influential parameters. A more detailed table with all varied parameters is available in the model in the sheet "OWSA".

Table 43. Deterministic sensitivity analyses

Parameter	Input value		Reason	Results		
	Lower bound	Upper bound	Assumption	Lower bound	Upper bound	Difference
Mean weight	48.40	76.40	Upper/lower CI	250 296	484 215	233 919
RDI - T-DXd	0.74	1.00	SE =10%	239 538	419 406	179 868
Subsequence tx - Tuca after T-DM1	0.55	0.83	SE =10%	420 705	320 461	100 244
Proportion with 3L tx	0.67	1.00	SE =10%	406 044	351 217	54 826
Discount rate - QALYs	0.03	0.04	SE =10%	347 721	387 124	39 403
Utilities - DB03 - Pre-progression (off-treatment)	0.66	0.99	SE =10%	384 430	358 874	25 556
Subsequence tx - T-DM1 after T-DXd	0.55	0.83	SE =10%	358 882	374 587	15 705
Discount rate - costs	0.03	0.04	SE =10%	375 056	359 915	15 141
Utilities - DB03 - Pre-progression (on T-DXd)	0.86	0.90	SE =10%	374 823	360 437	14 386
Utilities - DB03 - Pre-progression (on-T-DM1)	0.85	0.89	SE =10%	364 066	370 321	6 255

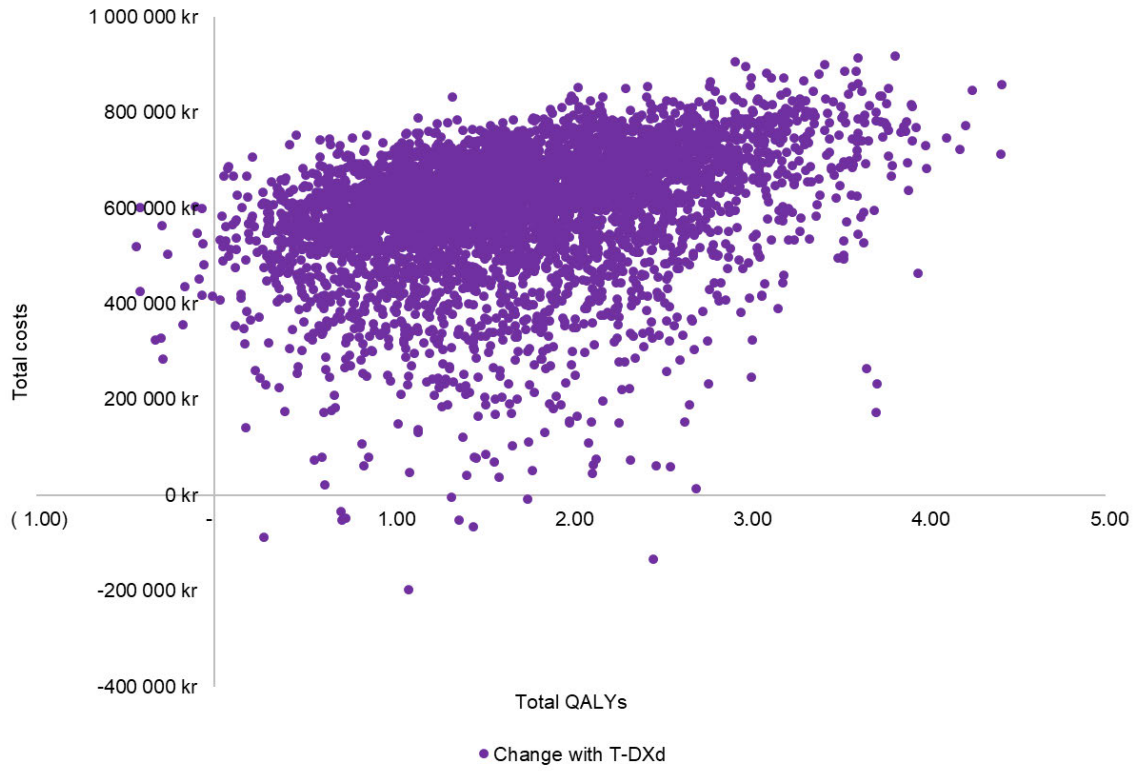
Key: HR: hazard ratio, ICER: incremental cost-effectiveness ratio, IV: intravenous, PFS: progression-free survival, T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan., RDI: Relative Dose Intensity.

[redacted]

8.7.2 Probabilistic sensitivity analyses

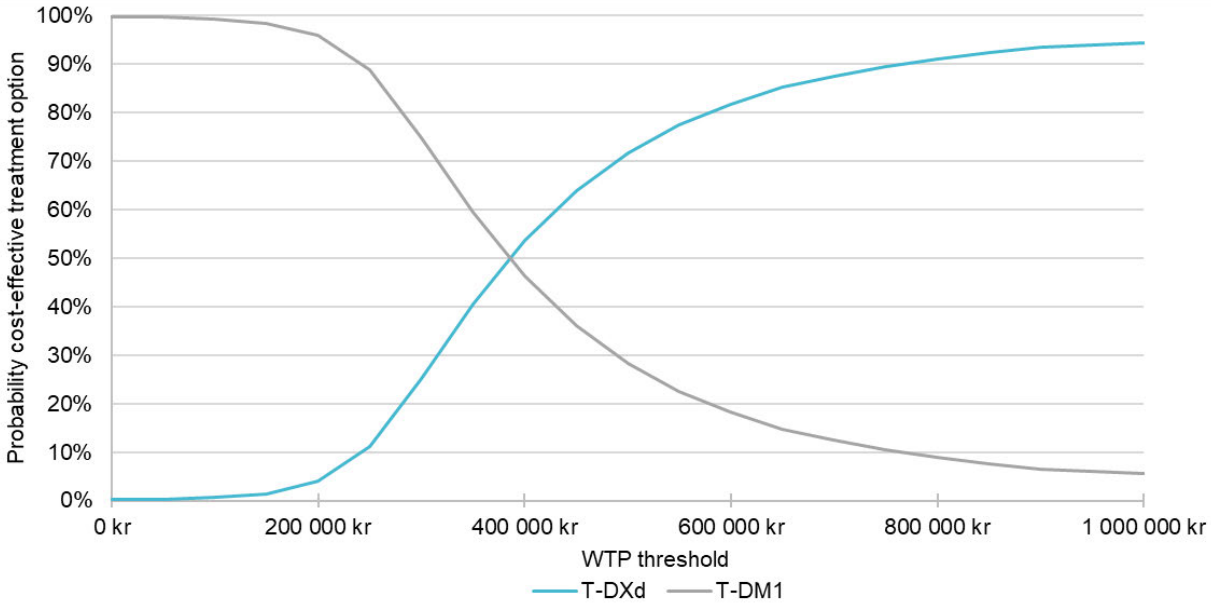
A PSA using 10 000 iterations was run for T-DXd compared to T-DM1 using the base-case settings as detailed above. The average results of all PSA iterations showed similar results (<1% difference) as the base case deterministic results. The probability of cost-effectiveness for all the treatment arms are presented in Figure 20 and Figure 21. As shown in the figure, T-DXd has the highest probability of being cost-effective if a QALY is considered to be worth more than approximately 380 000 DKK.

Figure 20: Cost-effectiveness plane for both treatments



Key: T-DXd: trastuzumab deruxtecan, WTP: willingness-to-pay.

Figure 21: Cost-effectiveness acceptability curves for both treatments



Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan, WTP: willingness-to-pay. **Note:** Value of perfect information is available in the model on sheet: PSA calcs.

9. Budget impact analysis

The analysis below shows the budget impact if T-DXd is recommended as standard of care. We assumed a market share of 40%, 60%, 80%, 80% and 80% for the first five years.

Table 44. 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
T-DXd	34	51	68	69	69
T-DM1	51	34	17	17	17

Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan..

As of today, eligible patients in need of treatment are expected to get treated with T-DM1. Therefore, if T-DXd is not approved for reimbursement, the patients in Table 44 are assumed to get T-DM1 as shown in Table 45.

Table 45. 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
T-DXd	0	0	0	0	0
T-DM1	84	85	85	86	87

Key T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan..

9.1 Expenditure per patient

The drug expenditure using AIP is presented in Table 46 and Table 47. As stated above, the treatment durations in the model ([redacted] months of treatment with T-DXd and ~[redacted] months for T-DM1) are based on the actual treatment durations in DESTINY-Breast03 and the calculation of a treatment course is outlined in section 8.5.1

Table 46. Drug expenditure per patient per year - if the pharmaceutical is introduced.

	Year 1	Year 2	Year 3	Year 4	Year 5
T-DXd	557 136	298 824	144 285	52 242	18 504

Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan..

Table 47. Drug expenditure per patient per year - if the pharmaceutical is NOT introduced.

	Year 1	Year 2	Year 3	Year 4	Year 5
T-DM1	257 502	58 611	12 532	2 083	369

Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan..

Table 48. Expenditure per patient per year by cost component (related cost components for specialist health services other than the drug expenditure) - if the pharmaceutical is used

	Year 1	Year 2	Year 3	Year 4	Year 5
Administration costs	11 605	6 445	3 192	1 185	420
Resource use costs	44 380	39 091	34 197	29 579	25 434
EOL and subsequent treatment costs	72 537	80 428	61 463	41 583	26 475
AE costs	4 146	-	-	-	-

Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan.

Table 49. Expenditure per patient per year by cost component (related cost components for specialist health services other than the drug expenditure) - if the pharmaceutical is NOT used

	Year 1	Year 2	Year 3	Year 4	Year 5
Administration costs	8 120	1 919	421	72	13
Resource use costs	43 156	34 955	27 861	21 937	17 191
EOL and subsequent treatment costs	333 816	125 903	51 784	23 652	12 327
AE costs	2 590	-	-	-	-

Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan.

Table 50. Budget impact per patient - summary

Cost per patient	2023	2024	2025	2026	2027
T-DXd introduced	689 805	424 787	243 138	124 589	70 833
T-DXd not introduced	645 183	221 387	92 597	47 744	29 899
Net budget impact	44 621	203 400	150 540	76 845	40 934

Key: T-DM1: Trastuzumab emtansine, T-DXd: trastuzumab deruxtecan.

9.2 Budgetary consequences

The budget impact for T-DXd is presented in Table 51. The budget impact in Year 5 if all expected T-DXd patients get T-DXd versus if all these patients get T-DM1 is approximately 33 million DKK. The main driver for the budget impact is the drug cost. This is expected as patients are progression-free and, therefore, treated for a longer time with T-DXd compared to the patients today treated with T-DM1.

Table 51. Expected budget impact of introducing T-DXd at the current indication.

	Year 1	Year 2	Year 3	Year 4	Year 5
If T-DXd is introduced	**55 836 618**	**82 479 861**	**100 138 191**	**113 475 690**	**122 041 330**
Of which: Primary drug expenditure	31 778 634	45 028 659	50 837 432	53 058 340	54 071 697
Of which: Other related costs including subsequent treatment drug costs	24 057 983	37 451 202	49 300 759	60 417 349	67 969 632

Minus: **If T-DXd is NOT introduced**	**54 333 521**	**73 357 762**	**81 669 276**	**86 261 690**	**89 383 468**
Of which: Primary drug expenditure	8 674 101	15 076 573	20 996 331	22 427 068	22 833 430
Of which: Other related costs including subsequent treatment drug costs	45 659 419	58 281 189	60 672 946	63 834 622	66 550 038
Budget impact of the recommendation	**1 503 097**	**9 122 099**	**18 468 914**	**27 214 000**	**32 657 862**

Key: T-DXd: [fam-]trastuzumab deruxtecan.

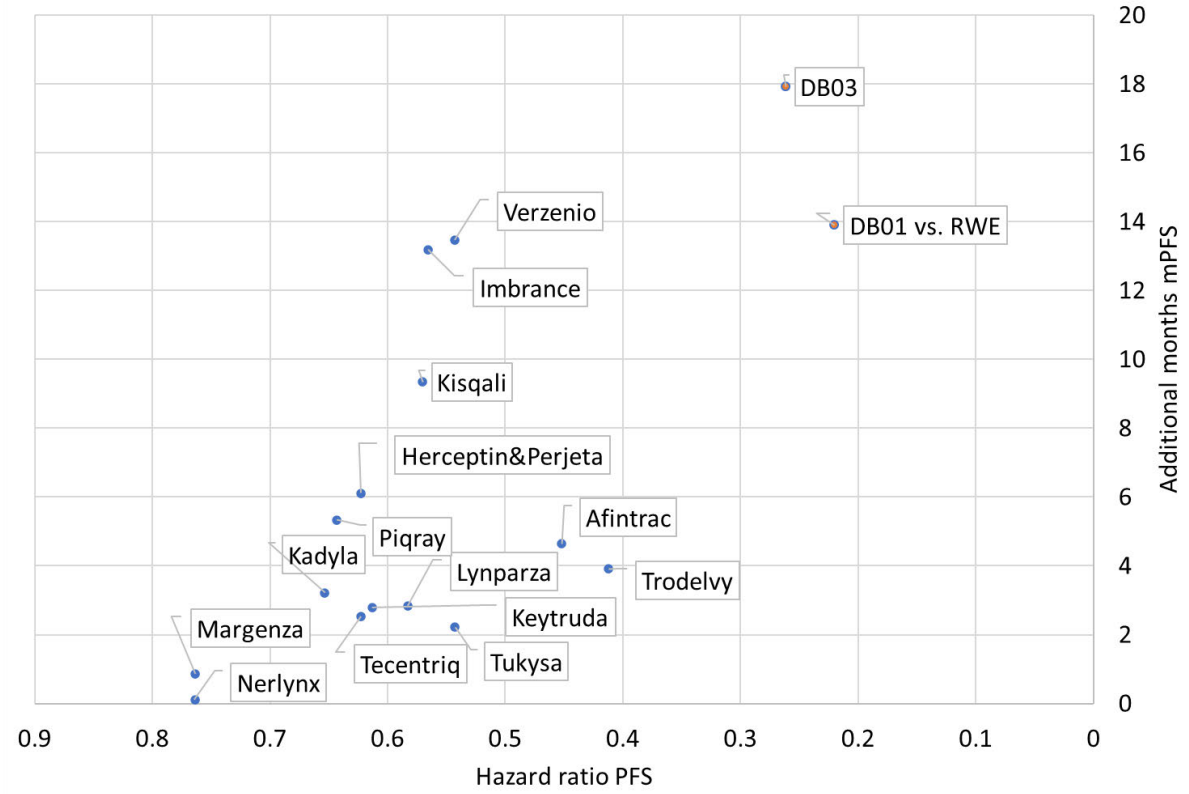
10. Discussion on the submitted documentation

Breast cancer is a leading cause of death in Danish women, and HER2+ mBC represents a particularly aggressive form of the disease. Although the availability of HER2-targeted therapies has improved outcomes in these patients, more efficacious options are needed after treatment fails; this need is especially relevant after 1L treatment where the time to progression is currently short (49). T-DXd has demonstrated in DESTINY-Breast03 that the risk of death can be reduced by 45% and the risk of progression or death can be reduced by 72% in direct comparison with T-DM1, the current SoC in Denmark in 2L HER2+ mBC (8).

Results in context

The DESTINY-Breast03 study confirmed the efficacy of T-DXd in HER2+ mBC that was also shown in DESTINY-Breast01, a study investigating T-DXd in 3L and later line HER2+ mBC. The results highlight that T-DXd will deliver one of the most important shifts in treatment for BC in 20 years (Figure 22).

Figure 22: DESTINY-Breast03 results versus other BC drugs at the time of introduction



Source: AZ-DS. Data on file.

Methods

In line with previous oncology models in HER2+ mBC, a partitioned survival model was developed to assess the cost-effectiveness of T-DXd within its mBC indication. The structure of the cost-utility model comprised four health states: progression-free on treatment, progression-free off treatment, progressed disease, and death.

The analysis uses the available DESTINY-Breast03 trial data to inform safety, quality of life and treatment effectiveness and uses the latest relevant data sources for other inputs such as costs. In the model we tested a range of different models for extrapolation, Weibull (PFS and TTD) and Generalized gamma models (OS) fitted the DESTINY-Breast03 data well and provided sometimes conservative but clinically plausible predictions according to clinical experts while more optimistic (LogNormal/Loglogistic) and pessimistic models (Gompertz) provided unlikely predictions.

Results

The analysis shows that the use of T-DXd results in a gain of 1.61 QALYs versus T-DM1. This implies ICERs of 367 256 DKK versus T-DM1. Drug cost represented ~67% of the total incremental cost of T-DXd while ~69% of total gained QALYs was gained in a progression-free health state. The cost-effectiveness results were tested in a large number of sensitivity and scenario analyses, which showed that these results were robust and, in most cases, varied with less than +/-20%.

The probabilistic sensitivity analysis was run for 10,000 iterations and showed that if a QALY is considered to be worth more than approximately 380 000 DKK, T-DXd has the highest probability of being cost-effective of the two 2L treatment options in HER2+ mBC.

Further, it is plausible that T-DXd lead to productivity gains and a lower caregiver burden given the prolonged PFS in many young patients. However, no good data on productivity loss for patients with 2L+ HER2+ mBC or their caregivers are available for Denmark, which makes the assumptions around the productivity losses uncertain.

Conclusion

T-DXd is a highly efficacious and cost-effective treatment when compared to T-DM1 for the treatment of unresectable or metastatic HER2+ breast cancer in patients previously treated with trastuzumab and chemotherapy in Denmark. The results from DESTINY-Breast03 show that T-DXd, if funded in Denmark, has the potential to significantly improve outcomes for patients that today have a poor prognosis.

11. List of experts

The following experts were consulted during the preparation of this submission. These are throughout references as 'Danish clinical experts:

[redacted]

Professor, consultant

12. References

1. Globocan. Breast Cancer Fact Sheet.2020. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf. Accessed: 30 July 2020.
2. DBCG. DBCG Kvalitetsdatabase for Brystkræft. National årsrapport 2020. https://www.sundhed.dk/content/cms/79/4679_dbcg_aarsrapport_2020_publiceret_final.pdf. 2021.
3. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235(4785):177-82.
4. Piccart M, Procter M, Fumagalli D, de Azambuja E, Clark E, Ewer MS, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. J Clin Oncol. 2021:JCO2001204.
5. Martin M, Holmes FA, Ejlertsen B, Delaloge S, Moy B, Iwata H, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(12):1688-700.
6. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-205.
7. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-28.
8. Cortés J, Kim S-B, Chung W-P, Im S-A, Park YH, Hegg R, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. 2022;386(12):1143-54.
9. DBCG. Systemisk behandling af brystkræft III – palliativ og systemisk behandling af metastaserende brystkræft (MBC). https://www.dmcg.dk/siteassets/kliniske-retningslinjer---skabeloner-og-vejledninger/kliniske-retningslinjer-opdelt-pa-dmcg/dbcg/dbcg_pall-syste-bh-mbc_v1.2_admgodk091221.pdf. 2021.
10. Gennari A, Andre F, Barrios CH, Cortes J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Annals of oncology : official journal of the European Society for Medical Oncology. 2021;32(12):1475-95.

11. NORDCAN. Denmark. Breast. https://gco.iarc.fr/media/nordcan/factsheets/91/en/countries/208/breast-180-denmark-208.pdf. 2022.

12. Sundhedsdatastyrelsen. Nye kræfttilfælde i Danmark. Cancerregisteret. https://sundhedsdatastyrelsen.dk/-/media/sds/filer/find-tal-og-analyser/sygdomme-og-behandlinger/kraeft/kraft_nye-tilfaelde/kraefttilfaelde-2019.pdf. 2021.

13. DBCG. DBCG Kvalitetsdatabase for Brystkræft. National årsrapport 2019. https://dbcg.dk/images/PDF/Rapporter/DBCG_%C3%A5rsrapport_2019_final210820.pdf. 2020.

14. Trewin CB, Johansson ALV, Hjerkind KV, Strand BH, Kiserud CE, Ursin G. Stage-specific survival has improved for young breast cancer patients since 2000: but not equally. Breast cancer research and treatment. 2020;182(2):477-89.

15. Cancer.Net. Breast cancer - metastatic: statistics2019. Available from: https://www.cancer.net/cancer-types/breast-cancer-metastatic/statistics. Accessed: 29 July 2019.

16. Metastatic Breast Cancer Network. Incidence and incidence rates. 2019.2019. Available from: http://mbcn.org/incidence-and-incidence-rates/. Accessed: 29 July 2019.

17. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist. 2005;10 Suppl 3:20-9.

18. Mariotto AB ER, Hurlbert M, et al. Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2017;26(6):809-15.

19. Esteva FJ, Guo H, Zhang S, Santa-Maria C, Stone S, Lanchbury JS, et al. PTEN, PIK3CA, p-AKT, and p-p70S6K status: association with trastuzumab response and survival in patients with HER2-positive metastatic breast cancer. The American journal of pathology. 2010;177(4):1647-56.

20. Archer SG, Eliopoulos A, Spandidos D, Barnes D, Ellis IO, Blamey RW, et al. Expression of ras p21, p53 and c-erbB-2 in advanced breast cancer and response to first line hormonal therapy. Br J Cancer. 1995;72(5):1259-66.

21. Wilcken N, Zdenkowski N, White M, Snyder R, Pittman K, Mainwaring P, et al. Systemic treatment of HER2-positive metastatic breast cancer: a systematic review. Asia-Pacific journal of clinical oncology. 2014;10 Suppl S4:1-14.

22. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Archives of pathology & laboratory medicine. 2018;142(11):1364-82.

23. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LAG, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014;106(5):dju055.

24. Mehrgou A, Akouchekian M. The importance of BRCA1 and BRCA2 genes mutations in breast cancer development. Med J Islam Repub Iran. 2016;30:369-.

25. Asbjørn Due, Tobias Berg, Maj Britt Jensen, Ann Knoop, Klaus Kaae Andersen , Kümler SRdaI. A retrospective population based observational study in metastatic HER2 positive breast cancer patients in Denmark previously treated with T DM1. ESMO congress. 2021.

26. Institute HLMCCR. What Causes HER2 Positive Breast Cancer? [Available from: https://moffitt.org/cancers/her2-positive-breast-cancer/causes/.

27. Chun C. Is HER-2 Positive Breast Cancer Hereditary? 2019 [updated 27 March 2019. Available from: https://www.healthline.com/health/her2-positive-breast-cancer-genes-hereditary.

28. Deluche E, Antoine A, Bachelot T, Lardy-Cleaud A, Dieras V, Brain E, et al. Contemporary outcomes of metastatic breast cancer among 22,000 women from the multicentre ESME cohort 2008-2016. Eur J Cancer. 2020;129:60-70.

29. Lobbezoo DJA, van Kampen RJW, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ, et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? British journal of cancer. 2015;112(9):1445-51.

30. Ahadzadeh AS, Sharif SP. Uncertainty and Quality of Life in Women With Breast Cancer: Moderating Role of Coping Styles. Cancer Nurs. 2018;41(6):484-90.

31. Montazeri A. Quality of Life in Breast Cancer Patients: An Overview of the Literature. New York: Springer; 2010.

32. Jones SM, LaCroix AZ, Li W, Zaslavsky O, Wassertheil-Smoller S, Weitlauf J, et al. Depression and quality of life before and after breast cancer diagnosis in older women from the Women's Health Initiative. J Cancer Surviv. 2015;9(4):620-9.

33. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21(4):519-30.

34. Miles D, Ciruelos E, Schneeweiss A, Puglisi F, Peretz-Yablonski T, Campone M, et al. Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication. Annals of oncology : official journal of the European Society for Medical Oncology. 2021;32(10):1245-55.

35. Daiichi-Sankyo Inc. CSR DESTINY-Breast03. 2021.

36. Medicinrådet. Lægemiddelrekommandation for anti-HER2 behandling af brystkræft. https://medicinraadet.dk/media/fjlhijns/l%C3%A6gemiddelrekommandation_for_anti-her2_behandling_af_brystkr%C3%A6ft-vers-_3-3_adlegacy.pdf. 2021.

37. Fimea. TRASTUTSUMABIEMTANSIINI HER2-POSITIIVISEN RINTASYÖVÄN HOIDOSSA. JULKAISUSARJA 3/2015. 2015.

38. TLV. Hälsoekonomiskt kunskapsunderlag . Kadcyla (trastuzumab emtansin). 2014.

39. statens legemiddelverk. Hurtig metodevurdering. Trastuzumabemtansin (Kadcyla) til behandling av HER2-positiv, inoperabel lokalavansert eller metastatisk brystkreft. 2014.

40. NICE. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane. https://www.nice.org.uk/guidance/TA458. 2017.

41. EMA. SmPC. 2021.

42. Javier Cortés, SBK, Wei Pang Chung, Seock Ah Im , Yeon Hee Park, Roberto Hegg , et al. Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients With HER2+ Metastatic Breast Cancer: Results of the Randomized, Phase 3 Study DESTINY Breast03. ESMO Congress 2021. 2021.

43. Pharmaceutical pricing board. Guidelines for preparing a health economic evaluation. 2019.

44. N Latimer. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data 2011 [Available from: http://www.nicedsu.org.uk.

45. Medicinrådet. Anvendelse af forløbsdata i sundhedsøkonomiske analyser. v1.1. 2020.

46. Latimer NR. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Med Decis Making. 2013;33(6):743-54.

47. Statens legemiddelverk. Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals. 2020.

48. Kreftregisteret. Årsrapport 2020. https://www.kreftregisteret.no/Generelt/Rapporter/Cancer-in-Norway/cancer-in-norway-2020/. 2021.

49. Dieras V, Miles D, Verma S, Pegram M, Welslau M, Baselga J, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(6):732-42.

50. Krop IE, Kim SB, Martin AG, LoRusso PM, Ferrero JM, Badovinac-Crnjevic T, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol. 2017;18(6):743-54.

51. Jensen CE, Sorensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Appl Health Econ Health Policy. 2021.

52. Hurvitz S, Kim S-B, Chung W-P, Im S-A, Park YH, Hegg R, et al. Trastuzumab Deruxtecan (T-DXd) Versus Trastuzumab Emtansine (T-DM1) in Patients With HER2+ Metastatic Breast Cancer: Subgroup Analyses From the Randomized Phase 3 Study DESTINY-Breast03. San Antonio Breast Cancer Symposium®, December 7-10, 2021. 2021.

53. Medicinrådet. Appendiks: Aldersjustering for sundhedsrelateret livskvalitet. https://medicinraadet.dk/media/mbtgpjjl/efter-1-januar-2021-appendiks-til-medicinr%C3%A5dets-metodevejledning-aldersjustering-adlegacy.pdf. 2022.

54. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683-90.

55. Danmark statistik. Nettopris-indeks. https://www.dst.dk/da/Statistik/emner/priser-og-forbrug/forbrugerpriser/nettoprisindeks. 2022.

56. Sørensen J. Analyse af forskelle i ressourceforbrug og omkostninger ved intravenøs og subkutan administration af Herceptin til behandling af HER2 positiv brystkræft. Hosp (Lond 1886) 2014;(978). 2014.

57. Medicinrådet. Medicinrådets værdisætning af enhedsomkostninger version 1.4. 2020. 2020.

58. Sundhedsdatastyrelsen. DRG-takster 2022. https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2022. 2022.

59. Medicinrådet. Tisagenlecleucel (Kymriah). Available from: https://medicinraadet.dk/media/jkccmyej/baggrund-for-medicinraadets-anbefaling-vedr-tisagenlecleucel-til-diffust-storcellet-b-celle-lymfom-vers-1-0_adlegacy.pdf. 2019.

60. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med. 2015;29(10):899-907.

61. Skattestyrelsen. Kørselsfradraget og befordringsgodtgørelsen falder i 2021. https://www.sktst.dk/aktuelt/pressemeddelelser/koerselsfradraget-og-befordringsgodtgoerelsen-falder-i-2021/. 2020.

62. Medicinrådet. Bilag til Medicinrådets anbefaling vedrörande tucatinib i kombination med trastuzumab of capecitabin til behandling af lokalt fremskreden inoperabel eller metastatisk HER2+ brystkräft efter progression på to HER2-rettede behandlnger. 2022.

63. Wuerstlein R, Ellis P, Montemurro F, Anton Torres A, Delaloge S, Zhang Q, et al. Final results of the global and Asia cohorts of KAMILLA, a phase IIIB safety trial of trastuzumab emtansine in patients with HER2-positive advanced breast cancer. ESMO Open. 2022;7(5):100561.

64. Medicinrådet. Værdisætning af enhedsomkostninger. v.1.6. 2022.

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

DESTINY-Breast03 is the only study that compared T-DXd with T-DM1 in the relevant study population. Hence, a SLR was not deemed to provide additional insights. However, for completeness, a detailed report of the conducted systematic literature review (SLR) is provided in the separate file named Appendix A - Clinical SLR. Please see the attached report for the reference list. A summary in line with the guidelines is provided below:

Objective

Asc Academics has conducted a clinical SLR to identify and describe all relevant clinical information (i.e., efficacy, safety, tolerability, and QoL) on the available treatments for second-line unresectable and/or metastatic HER2-positive breast cancer.

The specific objectives of this clinical SLR were as follows:

- To systematically review and describe the body of literature that exists on trastuzumab deruxtecan and relevant comparators as second-line treatments for patients with HER2-positive metastatic breast cancer.
- To critically appraise all relevant studies using validated appraisal tools.
- To prepare summaries of the included studies in accordance with the guidelines outlined in the DMC guidelines.

Bibliographic databases included in the literature search

Electronic databases

The searches for the clinical SLRs were designed with a combination of sensitivity and specificity as per the requirements of global HTA agencies. The following electronic databases were searched (i.e., standard evidence sources used in UK HTA assessments):

- MEDLINE and Embase (Embase.com)
- MEDLINE In-Process (PubMed.com)
- The Cochrane Library, including:
    - The Cochrane Database of Systematic Reviews (CDSR)
    - The Cochrane Central Register of Controlled Trials (CENTRAL)

The updated Embase search strategy for the clinical SLRs is presented in Table 53. This Embase search strategy was adapted to search other electronic databases. Search terms for the online resource searches were drawn from the lists presented below, as appropriate for the search features of individual sites.

Grey literature search

A grey literature search was conducted to help identify the most recent abstracts, posters, and podium presentations that may not have been indexed in medical literature databases. These searches were restricted to the last two years (2018–2020), to capture the most recent unpublished or ongoing trials. The search covered the following conferences:

- ASCO Annual meeting
- ASCO-Society for Immunotherapy of Cancer (SITC) Clinical Immuno-Oncology Symposium
- ASCO Quality Care Symposium

- European Society for Medical Oncology (ESMO) Breast Cancer Congress
- European Breast Cancer Conference (EBCC)
- San Antonio Breast Cancer Symposium (SABCS)
- JSCO Annual meetings
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR): ISPOR Europe, ISPOR-FDA, ISPOR Asia Pacific, ISPOR Latin America, ISPOR Warsaw, ISPOR Dubai

Asc Academics also conducted bibliographic searches of identified key systematic review and meta-analysis (including network meta-analysis) articles to ensure that the initial searches captured all relevant clinical studies.

Methods

Study selection methodology

All retrieved studies were assessed against eligibility criteria for the clinical search. The study selection process was performed in the following two phases:

- Primary (Level 1) screening: titles and abstracts of studies identified from the electronic databases and internet searches were double screened by two independent researchers to determine eligibility according to the inclusion and exclusion criteria described below. If there was disagreement about study relevance, consensus was reached through a discussion between the two researchers.
- Secondary (Level 2) screening: full texts of studies selected at level 1 were obtained and double screened by two independent researchers to determine eligibility according to the inclusion and exclusion criteria described below. If there was disagreement about study relevance, consensus was reached through a discussion between the two researchers.

This inclusion and exclusion process was documented and clearly defined and presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram below. A document containing detailed information on the reasons for exclusion was sent to the primary contact person of Daiichi Sankyo and AstraZeneca for this project.

Study selection criteria

Potentially relevant publications were reviewed and assessed to collate a final set of studies that formed the main body of clinical evidence. To determine the final set of studies eligible for review, explicit inclusion and/or exclusion criteria were applied to the literature search results. The inclusion and exclusion criteria are specified in Table 52..

Table 52. PICOS criteria for the inclusion and exclusion of studies.

Category	Inclusion criteria	Exclusion criteria
Population (P) [a]	Adult (age ≥18 years) HER2-positive uBC and/or mBC patients who had 1 prior systemic treatment in the metastatic setting[f] or have progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane[g]. Furthermore, the studies that assess a mixed population will be included regardless of the percentage of the study population[b]	Healthy volunteers Patients <18 years Diseases other than unresectable and/or metastatic HER2-positive breast cancer Patients with HER2-negative breast cancer Non-invasive or Stage 0 breast cancer
Intervention (I)	Any	None
Comparators (C)	Any	None
Outcomes (O) (tentative list, not exhaustive) [c]	PFS EFS DFS OS TTR DoR TTP ToT ORR BOR (CR, PR, SD, PD, CBR) AEs of treatment Health-related QoL	Studies that do not report at least one of the outcomes of interest
Study design (S)	RCTs – both parallel-group and crossover (double-blind, single-blind, open-label) Systematic reviews and meta-analyses of RCTs [d] Non-RCTs Retrospective and prospective cohort studies Single-arm trials Real-world evidence studies	In vitro studies Preclinical studies Reviews, comments, letters, and editorials Case reports, case series Dose-escalation studies
Language	English language [e]	None
Time limit	No restriction	None
Country	No restriction	None

Abbreviations: RCT, randomized clinical trial; PFS, progression-free survival; EFS, event-free survival; DFS, disease-free survival; OS, overall survival; TTR, time to response; DoR, duration of response; TTP, time to progression; ToT, time on treatment; ORR, objective response rate; BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CBR, clinical benefit rate; AEs, adverse events; QoL, quality of life.

Note: If it is unclear whether a study meets any criterion during the Level 1 screening process, the study will be progressed to full-text screening to confirm its inclusion in the review.

[a] At the screening stage, the studies reporting data for a previously treated population will be included and flagged. However, these studies will be processed further after agreement with Daiichi Sankyo and AstraZeneca and in accordance with the numbers agreed in the proposal.

[b] Mixed populations containing a HER2-positive subgroup will be included and flagged. In the Level 2 screening, studies need to report outcomes for HER2-positive subgroups separately. Studies that report a population with a median treatment line >2 will be excluded. Studies of which treatment line- or setting is not reported, will be flagged, and reported to Daiichi Sankyo and AstraZeneca.

[c] Outcome criteria will be used at Level 2 screening

[d] Systematic reviews and meta-analyses will be included at Level 1 screening, used for identification of primary studies, and then excluded at Level 2 screening.

[e] At the screening stage, the studies published in non-English will be flagged and reported to Daiichi Sankyo and AstraZeneca. These studies will be progressed further in accordance with Daiichi Sankyo and AstraZeneca.

[f] Patients who progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane will be flagged.

[g] Additional population inclusion criteria were introduced with the update of literature review from August 2020 to October 2021.

Search strategy

Embase search strategy

Table 53. Clinical SLR Embase updated search strategy.

String Number	Query
1	'breast cancer'/exp OR ((breast NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti) OR ((mammary NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti)
2	'cancer recurrence'/exp OR relapse/exp OR 'cancer resistance'/exp OR '2nd line':ab,ti OR 'second line':ab,ti OR '2 l':ab,ti OR '2 line':ab,ti OR 2l:ab,ti OR relaps*:ab,ti OR refrac*:ab,ti OR resist*:ab,ti OR recurr*:ab,ti OR progress*:ab,ti OR (((previ* OR prior* OR heav* OR post*) NEAR/4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ab,ti) OR treated:ab,ti OR pretreat*:ab,ti OR pre-treat*:ab,ti OR failed:ab,ti OR failure:ab,ti OR reocur*:ab,ti OR 're ocur*':ab,ti OR reoccur*:ab,ti OR 're occur*':ab,ti
3	'epidermal growth factor receptor 2'/exp OR 'epidermal growth factor receptor 2':ab,ti OR cd340:ab,ti OR erbb2*:ab,ti OR 'erbb 2*':ab,ti OR her2*:ab,ti OR 'her 2*':ab,ti OR ((neu NEAR/1 (protein* OR oncoprotein* OR receptor*)):ab,ti) OR 'differentiation factor receptor':ab,ti OR 'neuregulin receptor':ab,ti OR (((immunohistochemistry OR ihc) NEAR/2 (3 OR 2)):ab,ti) OR 'hr positive':ab,ti OR 'hormone receptor positive':ab,ti
4	'case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'veterinary clinical trial'/exp OR 'abstract report'/exp OR letter/exp OR note/exp OR 'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR note:it OR 'veterinary clinical trial':it OR 'case study':ab,ti OR 'case report':ab,ti OR 'abstract report':ab,ti OR editorial:ab,ti OR letter:ab,ti OR comment:ab,ti OR note:ab,ti OR 'veterinary clinical trial':ab,ti
5	animal/exp NOT (animal/exp AND human/exp)
6	(review:it OR 'literature review':it) NOT 'meta-analysis':it OR 'meta-analysis (topic)':it OR 'systematic review':it OR 'systematic literature review':it OR 'meta-analysis':ab,ti OR 'systematic review':ab,ti OR 'systematic literature review':ab,ti
7	#4 OR #5 OR #6
8	stages:ab,ti OR ((stage* NEAR/2 ('3' OR 'iii' OR '3c' OR 'iiic' OR '3b' OR 'iiib' OR '4' OR 'iv')):ab,ti)
9	metasta*:ab,ti OR advanc*:ab,ti OR unresect*:ab,ti OR 'un resect*':ab,ti OR nonresect*:ab,ti OR 'non resect*':ab,ti OR inoperable:ab,ti OR (((non OR 'not') NEAR/2 (amenabl* OR suit*) NEAR/2 (surge* OR surgi* OR opera*)):ab,ti)
10	#8 OR #9

11	#1 AND #2 AND #3 AND #6
12	#11 NOT #7

PubMed search strategy

Table 54. Clinical SLR PubMed updated search strategy.

String Number	Query
1	"breast neoplasms"[MeSH Terms] OR (breast[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab])) OR (mammary[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab]))
2	"Neoplasm Recurrence, local"[MeSH] OR recurrence[MeSH] OR "disease resistance"[MeSH] OR "2nd line"[tiab] OR "second line"[tiab] OR "2 l"[tiab] OR "2 line"[tiab] OR 2l[tiab] OR relaps*[tiab] OR refrac*[tiab] OR resis*[tiab] OR recurr*[tiab] OR progress*[tiab] OR (previ*[tiab] AND (chemo*[tiab] OR line*[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (prior*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (heav*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (post*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR treated[tiab] OR pretreat*[tiab] OR pre-treat*[tiab] OR failed[tiab] OR failure[tiab] OR reoccur*[tiab] OR reocur*[tiab] OR "re occur"[tiab]
3	"receptor, erbb-2"[MeSH] OR "genes, erbb-2"[MeSH] OR "epidermal growth factor receptor 2"[tiab] OR cd340[tiab] OR erbb2*[tiab] OR "erbb 2*"[tiab] OR her2*[tiab] OR "her 2*"[tiab] OR (neu[tiab] AND protein*[tiab]) OR (neu[tiab] AND oncoprotein*[tiab]) OR (neu[tiab] AND receptor*[tiab]) OR "differentiation factor receptor"[tiab] OR "neuregulin receptor"[tiab] OR "neu receptor"[tiab] OR (immunohistochemistry[tiab] AND (2[tiab] OR 3[tiab])) OR (ihc[tiab] AND (2[tiab] OR 3[tiab])) OR hr positive[tiab] OR "hormone receptor positive"[tiab]
4	"case reports"[pt] OR editorial[pt] OR letter[pt] OR comment[pt] OR "clinical trial, veterinary"[pt]
5	Animals[MeSH] NOT (animals[MeSH] AND humans[MeSH])
6	review[pt] NOT ("meta-analysis"[pt] OR "systematic review"[pt] OR meta-analysis[tiab] OR "systematic review"[tiab] OR "systematic literature review"[tiab])
7	#4 OR #5 OR #6
8	"clinical study"[pt] OR "random allocation"[MeSH] OR "placebo effect"[MeSH] OR placebos[MeSH] OR "control groups"[MeSH] OR "single-blind method"[MeSH] OR "cross-over studies"[MeSH] OR "double-blind method"[MeSH] OR "cohort studies"[MeSH] OR "comparative study"[pt] OR "follow-up studies"[MeSH] OR "medical records"[MeSH] OR "cross-sectional studies"[MeSH] OR "observational study"[pt] OR registries[MeSH] OR randomization[tiab] OR "control group"[tiab] OR "crossover procedure"[tiab] OR "cohort analysis"[tiab] OR "comparative study"[tiab] OR "follow up"[tiab]
9	"clinical audit"[MeSH] OR "clinical trials data monitoring committees"[MeSH] OR ("case control"[tiab] AND stud*[tiab]) OR ("case control"[tiab] AND trial*[tiab]) OR (observational[tiab] AND stud*[tiab]) OR (observational[tiab] AND trial*[tiab]) OR ("cross sectional"[tiab] AND stud*[tiab]) OR ("cross sectional"[tiab] AND trial*[tiab]) OR retrospectiv*[tiab] OR registry[tiab] OR (hospital[tiab] AND record*[tiab]) OR (hospital[tiab] AND chart*[tiab]) OR (medical[tiab] AND record*[tiab]) OR (medical[tiab] AND chart*[tiab]) OR (electronic[tiab] AND record*[tiab]) OR (electronic[tiab] AND chart*[tiab]) OR "non random"[tiab] OR "single arm"[tiab] OR "real world"[tiab] OR "real life"[tiab] OR "controlled clinical trial"[tiab] OR "randomized controlled trial"[tiab] OR "randomised controlled trial"[tiab] OR rct[tiab] OR (random[tiab] AND alloca*[tiab]) OR (random[tiab] AND assign*[tiab]) OR (single[tiab] AND blind*[tiab]) OR (double[tiab] AND blind*[tiab]) OR (triple[tiab] AND blind*[tiab]) OR (treble[tiab] AND blind*[tiab]) OR (single[tiab] AND

	mask*[tiab]) OR (double[tiab] AND mask*[tiab]) OR (triple[tiab] AND mask*[tiab]) OR (treble[tiab] AND mask*[tiab]) OR placebo[tiab] OR “clinical study”[tiab] OR “clinical article”[tiab]
10	#8 OR #9
11	#10 NOT #7
12	Stages[tiab] OR (stage*[tiab] AND (3[tiab] OR iii[tiab] OR 3c[tiab] OR iiic[tiab] OR 3b[tiab] OR iiib[tiab] OR 4[tiab] OR iv[tiab]))
13	metasta*[tiab] OR advance*[tiab] OR unresect*[tiab] OR “un resect*”[tiab] OR nonresect*[tiab] OR “non resect*”[tiab] OR inoperable[tiab] OR (non[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (non[tiab] AND suit*[tiab] AND surg*[tiab]) OR (non[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (non[tiab] AND suit*[tiab] AND opera*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (not[tiab] AND suit*[tiab] AND surg*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (not[tiab] AND suit*[tiab] AND opera*[tiab])
14	#12 OR #13
15	#1 AND #2 AND #3 AND #14
16	#11 AND #15

Cochrane search strategy

Table 55. Clinical SLR Cochrane updated search strategy.

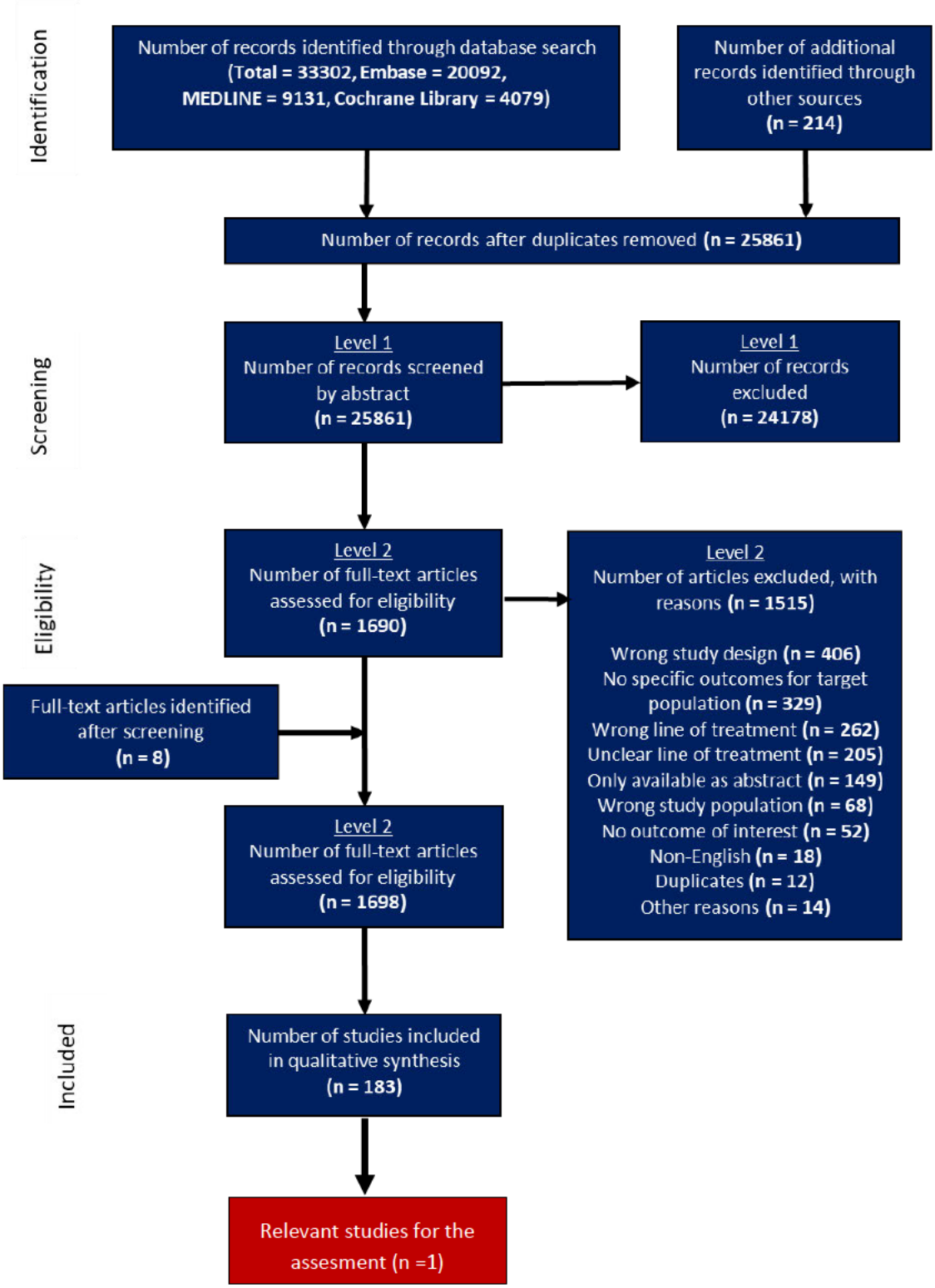
String Number	Query
1	MeSH descriptor: [Breast neoplasm] explode all trees
2	((breast NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti) OR ((mammary NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti)
3	#1 OR #2
4	MeSH descriptor: [Recurrence] explode all trees
5	'2nd line':ab,ti OR 'second line':ab,ti OR '2 l':ab,ti OR '2 line':ab,ti OR 2l:ab,ti OR relaps*:ab,ti OR refrac*:ab,ti OR resist*:ab,ti OR recurr*:ab,ti OR progress*:ab,ti OR (((previ* OR prior* OR heav* OR post*) NEAR/4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ab,ti) OR treated:ab,ti OR pretreat*:ab,ti OR 'pre treat*':ab,ti OR failed:ab,ti OR failure:ab,ti OR reocur*:ab,ti OR 're ocur*':ab,ti OR reoccur*:ab,ti OR 're occur*':ab,ti
6	#4 OR #5
7	MeSH descriptor: [ErbB Receptors] explode all trees
8	'epidermal growth factor receptor 2':ab,ti OR cd340:ab,ti OR erbb2*:ab,ti OR 'erbb 2*':ab,ti OR her2*:ab,ti OR 'her 2*':ab,ti OR ((neu NEAR/1 (protein* OR oncoprotein* OR receptor*)):ab,ti) OR 'differentiation factor receptor':ab,ti OR 'neuregulin receptor':ab,ti OR (((immunohistochemistry OR ihc) NEAR/2 (3 OR 2)):ab,ti) OR 'hr positive':ab,ti OR 'hormone receptor positive':ab,ti
9	#7 OR #8
10	stages:ab,ti OR ((stage* NEAR/2 ('3' OR 'iii' OR '3c' OR 'iiic' OR '3b' OR 'iiib' OR '4' OR 'iv')):ab,ti)
11	metasta*:ab,ti OR advanc*:ab,ti OR unresect*:ab,ti OR 'un resect*':ab,ti OR nonresect*:ab,ti OR 'non resect*':ab,ti OR inoperable:ab,ti OR (((non OR 'not') NEAR/2 (amenabl* OR suit*) NEAR/2 (surge* OR surgi* OR opera*)):ab,ti)
12	#10 OR #11
13	#3 AND #6 AND #9 AND #12
14	MeSH descriptor: [Surveys and Questionnaires] explode all trees
15	MeSH descriptor: [Quality of Life] explode all trees
16	MeSH descriptor: [Patient Preference] explode all trees
17	MeSH descriptor: [Visual Analog Scale] explode all trees
18	utilit*:ab,ti OR disutilit*:ab,ti OR 'sf 6':ab,ti OR sf6:ab,ti OR 'short form 6':ab,ti OR 'shortform 6':ab,ti OR 'sf six':ab,ti OR 'sfsix':ab,ti OR 'shortform six':ab,ti OR 'short form six':ab,ti OR 'sf 36':ab,ti OR sf36:ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'sf thirtysix':ab,ti OR 'sfthirtysix':ab,ti OR 'shortform thirtysix':ab,ti OR 'short form thirtysix':ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti OR eq5d:ab,ti OR 'eq 5d':ab,ti OR 'health utilities index':ab,ti OR hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR ((standard NEXT/1 gamble*):ab,ti) OR 'quality of life*':ab,ti OR 'time trade off':ab,ti OR 'time tradeoff':ab,ti OR tto:ab,ti OR 'visual analog scale':ab,ti OR 'patient preference':ab,ti OR 'european quality of life 5 dimensions questionnaire':ab,ti
19	#14 OR #15 OR #16 OR #17 OR #18
20	price*:ti OR pricing:ti OR economic*:ti OR cost:ti OR costs:ti OR 'cost control':ti

21	'health economics':ti OR 'quality adjusted life year':ti OR 'decision tree':ti OR 'hidden markov model':ti OR 'economic model':ti OR 'markov chain':ti OR qaly*:ti OR (((cost OR costs) NEAR/1 (variable* OR unit* OR estimate*)):ti) OR (((cost OR costs) NEAR/3 (increment* OR conseq* OR minim*)):ti) OR icer:ti OR 'incremental cost effectiveness ratio':ti OR ((decision NEXT/2 (analy* OR tree*)):ti) OR ((model* NEAR/3 (simulat* OR decisio* OR analy* OR 'area under curve' OR partition* OR transitio* OR state* OR discrete* OR individual* OR cohort*)):ti) OR (monte:ti AND carlo:ti) OR economic:ti OR pharmacoeconomic:ti OR markov:ti OR 'cost effect*':ti OR 'cost utilit*':ti OR 'cost benefit*':ti
22	(#20 OR #21) NOT #19
23	#13 NOT #22

* No limits are applied to the chain.

Systematic selection of studies

Figure 23. PRISMA figure



Note: the fact that only one reason for exclusion is reported for every excluded article in Level 2 screening does not indicate there are not multiple exclusion criteria present in the record.

Table 56. Excluded references/full text papers because not in line with PICO

AA_ID	Study name (Trial name/NCT)	• LoT • Country	• Blinding • Randomization	• Study phase • Study setting	Treatment / Comparator • Number enrolled • Number meeting cSLR criteria	Secondary publications
9	Cortés et al., 2020 (1) (TRAXHER2 / NCT01702558)	• Mixed-line • Argentina, Brazil, Canada, France, Germany, Greece, Italy, Portugal, Russian Federation, Serbia, Slovakia, Spain	• Open-label • Randomized	• Phase I/II • Multicenter	T-DM1 (3.6 mg/kg q3w) + capecitabine (700 mg/m2 bid on days 1-14) • 81 • 100% T-DM1 (3.6 mg/kg q3w) • 80 • 100%	
65	Ma et al. 2019 (2) (NCT02422199)	• Mixed-line • China	• Open-label • Randomized	• Phase II • Multicenter	Pyrotinib (400 mg od) + capecitabine (1000 mg/m2 bid on days 1-14) • 65 • 100% Lapatinib (1250 mg od) + capecitabine (1000 mg/m2 bid on days 1-14) • 63 • 100%	
110	Bischoff et al. 2019 (3) (NCT01534455)	• Mixed-line • Germany	• Open-label • Randomized	• Phase II • Multicenter	Eribulin (1.23 mg/m2 [equivalent to 1.4 mg/m2 eribulin mesylate] on days 1 and 8) + lapatinib (1000 mg bid) • 21 • 100% Eribulin (1.76 mg/m2 [equivalent to 2.0 mg/m2 eribulin mesylate] on day 1) + lapatinib (1000 mg bid) • 20 • 100%	
146	Takano et al. 2018 (4) (WJOG6110B/ELTOP / UMIN000005219)	• Mixed-line • Japan	• Open-label • Randomized	• Phase II • Multicenter	Trastuzumab (4 mg/kg loading dose followed by 2 mg/kg qw OR 8 mg/kg loading dose followed by 6 mg/kg q3w) +	AA_ID1270

AA_ID	Study name (Trial name/NCT)	• LoT • Country	• Blinding • Randomization	• Study phase • Study setting	Treatment / Comparator • Number enrolled • Number meeting cSLR criteria	Secondary publications
					capecitabine (2500 mg/m2 qd on days 1-14) • 43 • 100%	
					Lapatinib (1250 mg qd) + capecitabine (2500 mg/m2 qd on days 1-14) • 43 • 100%	
176	Johnston et al. 2017 (5) (ALTERNATIVE / NCT01160211)	• Mixed-line • Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Croatia, France, Germany, Greece, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, South Korea, Lithuania, Norway, Peru, Philippines, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, Singapore, South Africa, Spain, Taiwan, Turkey, Ukraine, UK, USA	• Open-label • Randomized	• Phase III • Multicenter	Lapatinib (1000 mg od) + trastuzumab (8 mg/kg loading dose followed by 6 mg/kg q3w) • 120 • 100%	
					Trastuzumab (8 mg/kg loading dose followed by 6 mg/kg q3w) + letrozole (2.5 mg od) OR anastrazole (1 mg od) OR exemestane (25 mg od) • 117 • 100%	

AA_ID	Study name (Trial name/NCT)	• LoT • Country	• Blinding • Randomization	• Study phase • Study setting	Treatment / Comparator • Number enrolled • Number meeting cSLR criteria	Secondary publications
					Lapatinib (1500 mg od) + letrozole (2.5 mg od) OR anastrazole (1 mg od) OR exemestane (25 mg od) • 118 • 100%	
222	Urruticoechea et al. 2017 (6) (PHEREXA / NCT01026142)	• 2nd-line & Mixed-line • Argentina, Austria, Belgium, Brazil, Canada, Croatia, Czech Republic, Estonia, France, Germany, Hong Kong, Hungary, Italy, Mexico, Netherlands, Peru, Poland, Romania, Russian Federation, South Korea, Spain, Thailand, UK	• Open-label • Randomized	• Phase III • Multicenter	Trastuzumab (8 mg/kg loading dose followed by 6 mg/kg q3w) + capecitabine (1250 mg/m2 bid on days 1-14) • 224 • 100%	
					Pertuzumab (840 mg loading dose followed by 420 mg q3w) + capecitabine (1250 mg/m2 bid on days 1-14) • 228 • 100%	

AA_ID	Study name (Trial name/NCT)	• LoT • Country	• Blinding • Randomization	• Study phase • Study setting	Treatment / Comparator • Number enrolled • Number meeting cSLR criteria	Secondary publications
251	Diéras et al. 2017 (7) (EMILIA / NCT00829166)	• Mixed-line • Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Denmark, Finland, France, Germany, Hong Kong, India, Italy, Mexico, New Zealand, Philippines, Poland, Portugal, Russian Federation, Singapore, Slovenia, South Korea, Spain, Sweden, Switzerland, Taiwan, UK, USA	• Open-label • Randomized	• Phase III • Multicenter	T-DM1 (3.6 mg/kg q3w) • 495 • 100% Lapatinib (1250 mg od) + capecitabine (1000 mg/m2 bid on days 1-14) • 496 • 100%	AA ID612, AA ID649, AA_ID1145
325	Harbeck et al. 2016 (8) (LUX-BREAST 1 / NCT00470704)	• Mixed-line • Argentina, Australia, Austria, Belarus, Belgium, Brazil, Canada, China, Czech Republic, Egypt, France, Germany, India, Ireland, Israel, Italy, Japan, Latvia, Lebanon, Lithuania, Mexico, Netherlands, Peru, Poland, Portugal, Russian Federation,	• Open-label • Randomized	• Phase III • Multicenter	Afatinib (40 mg od) + vinorelbine (25 mg/m2 qw) • 332 • >99% Trastuzumab (4 mg/kg loading dose followed by 2 mg/kg qw) + vinorelbine (25 mg/m2 qw) • 168 • 99%	

AA_ID	Study name (Trial name/NCT)	• LoT • Country	• Blinding • Randomization	• Study phase • Study setting	Treatment / Comparator • Number enrolled • Number meeting cSLR criteria	Secondary publications
		Singapore, Slovakia, Slovenia, South Africa, South Korea, Spain, Sri Lanka, Taiwan, Turkey, UK, USA				
456	Cortés et al. 2015 (9) (LUX-Breast 3 / NCT01441596)	• Mixed-line • Canada, Finland, France, Germany, Italy, Spain, USA	• Open-label • Randomized	• Phase II • Multicenter	Afatinib (40-50 mg od) • 40 • 100% Afatinib (40 mg od) + vinorelbine (25 mg/m2 qw) • 38 • 100% Investigator's choice of treatment (see supplement) • 43 • 100%	
509	Janni et al. 2014 (10) (VITAL / NCT01013740)	• Mixed-line • Bulgaria, Chile, France, Germany, Greece, Italy, Mexico, Poland, Serbia, Spain	• Open-label • Randomized	• Phase II • Multicenter	Lapatinib (1250 mg od) + vinorelbine (20 mg/m2 on days 1 and 8 q3w) • 75 • 100% Lapatinib (1250 mg od) + capecitabine (2000 mg/m2 qd on days 1-14) • 37 • 100%	AA_ID1274
519	André et al. 2014 (11) (BOLERO-3 / NCT01007942)	• Mixed-line • Argentina, Australia, Belgium, China, Czech Republic, France, Germany,	• Double-blind • Randomized	• Phase III • Multicenter	Everolimus (5 mg qd) + vinorelbine (25 mg/m2) + trastuzumab (4 mg/kg loading dose followed by 2 mg/kg qw) • 284 • 100%	

AA_ID	Study name (Trial name/NCT)	• LoT • Country	• Blinding • Randomization	• Study phase • Study setting	Treatment / Comparator • Number enrolled • Number meeting cSLR criteria	Secondary publications
		Greece, Hungary, Israel, Italy, Japan, Mexico, Poland, Singapore, Spain, Thailand, Turkey, UK, USA			Placebo (qd) + vinorelbine (25 mg/m2) + trastuzumab (4 mg/kg loading dose followed by 2 mg/kg qw) • 285 • 100%	
549	Gómez et al. 2016 (12) (GLICO-0801 / NCT01050322)	• Mixed-line • Argentina, Brazil, Peru	• Open-label • Randomized	• Phase II • Multicenter	Lapatinib (1250 mg od) + vinorelbine (25 mg/m2 qd on days 1 and 8) • 45 • 100%	
					Lapatinib (1250 mg od) + gemcitabine (1000 mg/m2 on days 1 and 8) • 46 • 100%	
					Lapitinib (1250 mg od) + capecitabine (2000 mg/m2 qd on days 1-14) • 51 • 100%	
557	Martin et al. 2013 (13) (NCT00777101)	• Mixed-line • Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czechia, France, Germany, Greece, Hong Kong, Hungary, Italy, Japan, Jordan, Mexico, Poland, Puerto Rico, Romania, Russian Federation, Serbia,	• Open-label • Randomized	• Phase II • Multicenter	Neratinib (240 mg qd) • 117 • 100%	
					Lapatinib (1250 mg qd) + capecitabine (2000 mg/m2 qd on days 1-14) • 116 • 100%	

AA_ID	Study name (Trial name/NCT)	• LoT • Country	• Blinding • Randomization	• Study phase • Study setting	Treatment / Comparator • Number enrolled • Number meeting cSLR criteria	Secondary publications
		Singapore, Slovenia, South Africa, South Korea, Spain, Switzerland, Taiwan, Thailand, UK, USA				
612	Baselga et al. 2016 (14) (EMILIA / NCT00829166)	• Mixed-line • Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Denmark, Finland, France, Germany, Hong Kong, India, Italy, Mexico, New Zealand, Philippines, Poland, Portugal, Russian Federation, Singapore, Slovenia, South Korea, Spain, Sweden, Switzerland, Taiwan, UK, USA	• Open-label • Randomized	• Phase III • Multicenter	T-DM1 (3.6 mg/kg q3w) • 495 • 100% Capecitabine (1000 mg/m2 bid on days 1-14) + lapatinib (1250 mg od) • 496 • 100%	AA ID251, AA ID649, AA_ID1145
649	Verma et al. 2012 (EMILIA / NCT00829166)	• Mixed-line • Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Denmark, Finland, France, Germany, Hong Kong, India, Italy, Mexico, New Zealand, Philippines, Poland, Portugal, Russian Federation, Singapore, Slovenia,	• Open-label • Randomized	• Phase III • Multicenter	T-DM1 (3.6 mg/kg q3w) • 495 • 100% Capecitabine (1000 mg/m2 bid on days 1-14) + lapatinib (1250 mg od) • 496 • 100%	AA ID251, AA ID612, AA_ID1145

AA_ID	Study name (Trial name/NCT)	• LoT • Country	• Blinding • Randomization	• Study phase • Study setting	Treatment / Comparator • Number enrolled • Number meeting cSLR criteria	Secondary publications
		South Korea, Spain, Sweden, Switzerland, Taiwan, UK, USA				
736	Lin et al. 2011 (15) (EGF107671 / NCT00437073)	• Mixed-line • Canada, EU, Israel, USA	• Open-label • Randomized	• Phase II • Multicenter	Lapatinib (1250 mg od) + capecitabine (2000 mg/m2 qd on days 1-14) • 13 • 100% Lapatinib (1250 mg od) + topotecan (3.2 mg/m2 on days 1, 8, and 15) • 9 • 100%	
739	Von Minckwitz et al. 2011 (16) (GBG 26/BIG 3-05)	• 2nd-line & Mixed-line • Multinational (countries NR)	• Open-label • Randomized	• Phase III • Multicenter	Capecitabine (1250 mg/m2 bid on days 1-14) • 78 • 100% Capecitabine (1250 mg/m2 bid on days 1-14) + trastuzumab (6 mg/kg q3w) • 78 • 100%	AA_ID934
816	Cameron et al. 2010 (17) (EGF100151)	• Mixed-line • Multinational (countries NR)	• Open-label • Randomized	• Phase III • Multicenter	Lapatinib (1250 mg od) + capecitabine (2000 mg/m2 on days 1-14) • 207 • 100% Capecitabine (2500 mg/m2 qd on days 1-14) • 201 • 100%	AA_ID994
934	Von Minckwitz et al. 2009 (18) (GBG 26/BIG 3-05)	• 2nd-line & Mixed-line • Austria, Denmark, Germany, Netherlands, Slovenia, UK	• Open-label • Randomized	• Phase III • Multicenter	Capecitabine (1250 mg/m2 bid on days 1-14) • 78 • 100% Capecitabine (1250 mg/m2 bid on days 1-14) + trastuzumab (6 mg/kg q3w)	AA_ID739

AA_ID	Study name (Trial name/NCT)	• LoT • Country	• Blinding • Randomization	• Study phase • Study setting	Treatment / Comparator • Number enrolled • Number meeting cSLR criteria	Secondary publications
					• 78 • 100%	
994	Geyer et al. 2006 (19) (NCT00078572)	• Mixed-line • NR	• Open-label • Randomized	• Phase III • Multicenter	Lapatinib (1250 od) + capecitabine (1000 mg/m2 bid on days 1-14) • 163 • 100% Capecitabine (1250 mg/m2 bid on days 1-14) • 161 • 100%	AA_ID816
1145	Welslau et al. 2014 (20) (EMILIA / NCT00829166)	• Mixed-line • Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Denmark, Finland, France, Germany, Hong Kong, India, Italy, Mexico, New Zealand, Philippines, Poland, Portugal, Russian Federation, Singapore, Slovenia, South Korea, Spain, Sweden, Switzerland, Taiwan, UK, USA	• Open-label • Randomized	• Phase III • Multicenter	T-DM1 (3.6 mg/kg q3w) • 495 • 100% Capecitabine (1000 mg/m2 bid on days 1-14) + lapatinib (1250 mg qd) • 496 • 100%	AA ID251, AA ID612, AA_ID649
1223	Tryfonidis et al. 2017 (21) (NCT00036868)	• Mixed-line • Belgium, Denmark, Egypt, France, Netherlands, Poland, Serbia, South Africa, UK	• Open-label • Randomized	• Phase II • Multicenter	Cyclophosphamide (600 mg/m2 on days 1 and 8) + methotrexate (40 mg/m2 on days 1 and 8) + 5-fluorouracil (600 mg/m2 on days 1 and 8) + trastuzumab (4 mg/kg loading dose followed by 2 mg/kg qw; after completion of	

AA_ID	Study name (Trial name/NCT)	• LoT • Country	• Blinding • Randomization	• Study phase • Study setting	Treatment / Comparator • Number enrolled • Number meeting cSLR criteria	Secondary publications
					chemotherapy 6 mg/kg q3w) • 70 • 100%	
					Cyclophosphamide (1000 mg/m2 on days 1-14) + methotrexate (40 mg/m2 on days 1 and 8) + 5-fluorouracil (600 mg/m2 on days 1 and 8) • 19 • 100%	
1274	Janni et al. 2015 (22) (VITAL / NCT01013740)	• Mixed-line • Bulgaria, Chile, France, Germany, Greece, Italy, Mexico, Poland, Serbia, Spain	• Open-label • Randomized	• Phase II • Multicenter	Lapatinib (1250 mg od) + vinorelbine (20 mg/m2 on days 1 and 8) • 75 • 100%	AA_ID509
					Lapatinib (1250 mg od) + capecitabine (2000 mg/m2 qd on days 1-14) • 37 • 100%	
1316	Pivot et al. 2015 (23) (CEREBEL / NCT00820222)	• Mixed-line • Belgium, Denmark, France, Germany, Greece, Hungary, Italy, Poland, Russian Federation, Spain, Sweden, Thailand, UK, USA	• Open-label • Randomized	• Phase III • Multicenter	Lapatinib (1250 mg od) + capecitabine (2000 mg/m2 qd on days 1-14) • 271 • 100%	
					Trastuzumab (8mg/kg loading dose followed by 6 mg/kg q3w) + capecitabine (2000 mg/m2 qd day on days 1-14) • 269 • 100%	
3103	Lipton et al. 2002 (24) (NR)	• 2nd-line & Mixed-line • NR	• Double-blind • Randomized	• NR • Multicenter	1. Fadrozole (1 mg bid) + placebo vs. megestrol acetate (40 mg orally qid) + placebo 2. Fadrozole (1 mg bid) + placebo vs. megestrol acetate (40 mg orally qid) + placebo	

AA_ID	Study name (Trial name/NCT)	• LoT • Country	• Blinding • Randomization	• Study phase • Study setting	Treatment / Comparator • Number enrolled • Number meeting cSLR criteria	Secondary publications
					3. Letrozole (2.5 mg bid) + placebo vs. megestrol acetate (40 mg orally qid) + placebo • 719 • 219 (30%)	
4004	Xu et al. 2021 (75) (PHOEBE / NCT03080805)	• 2nd-line • China	• Open-label • Randomized	• Phase III • Multicenter	Pyrotinib (400 mg od) + capecitabine (1000 mg/m² bid on days 1–14) • 134 • 100%	
					Lapatinib (1250 mg od) + capecitabine (1000 mg/m² bid on days 1–14) • 132 • 100%	
4005	Emens et al. 2020 (76) (KATE2 / NCT02924883)	• 2nd-line • Australia, Canada, Germany, Italy, South Korea, Spain, Taiwan, UK, USA	• Double-blind • Randomized	• Phase II • Multicenter	T-DM1 (3.6 mg/kg q3w) + atezolizumab (1200 mg q3w) • 133 • 100%	
					T-DM1 (3.6 mg/kg q3w) + placebo (q3w) • 69 • 100%	

Appendix B Main characteristics of included studies

Trial name: DESTINY-Breast03	NCT number:
Objective	This study is designed to compare the anti-tumor activity as well as the safety and efficacy of DS-8201a versus T-DM1 in HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane.
Publications – title, author, journal, year	Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer, Cortés, J et al., 2022 (8)
Study type and design	Phase III, randomized, two-arm, multicentre, open-label, active-controlled study

Trial name: DESTINY-Breast03	NCT number:
Sample size (n)	524
Main inclusion and exclusion criteria	Inclusion Criteria: • Is the age of majority in their country • Has pathologically documented breast cancer that: 1. is unresectable or metastatic 2. has confirmed HER2-positive expression as determined according to American Society of Clinical Oncology - College of American Pathologists guidelines evaluated at a central laboratory 3. was previously treated with trastuzumab and taxane in the advanced/metastatic setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane • Has documented radiologic progression (during or after most recent treatment or within 6 months after completing adjuvant therapy) • Is HER2 positive as confirmed by central laboratory assessment of most recent tumor tissue sample available. If archived tissue is not available, agrees to provide a fresh biopsy. • If of reproductive/childbearing potential, agrees to use a highly effective form of contraception or avoid intercourse during and upon completion of the study for 7 months after the last dose of DS-8201a (females); 4.5 months after last dose of DS-8201a (males) or 7 months after the last dose of T-DM1 • Has adequate renal and hepatic function Exclusion Criteria: • Has previously been treated with an anti-HER2 antibody drug conjugate (ADC) in the metastatic setting. Prior treatment in the adjuvant/neo-adjuvant setting would be allowed if progression of disease did not occur within 12 months of end of adjuvant therapy • Has uncontrolled or significant cardiovascular disease • Has a history of (noninfectious) interstitial lung disease (ILD)/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening • Has spinal cord compression or clinically active central nervous system (CNS) metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. 1. Participants with clinically inactive brain metastases may be included in the study. 2. Participants with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment.
Intervention	T-DXd

Trial name: DESTINY-Breast03		NCT number:
Comparator(s)	T-DM1	
Follow-up time	July 20, 2018 - May 21, 2021	
Is the study used in the health economic model?	Yes	

Trial name: DESTINY-Breast03	NCT number:

Primary, secondary and exploratory endpoints

The primary endpoint is progression free survival (PFS) based on blinded independent central review (BICR)* (42):

Parameter	T-DXd (N = 261)	T-DM1 (N = 263)
PFS		
Median PFS, months (95% CI)	NE (18.5, NE)	6.8 (5.6, 8.2)
Stratified Cox hazard ratio (95% CI)	0.2840 (0.2165, 0.3727)	
Stratified log-rank *P*-value	<0.000001	
Percentage of subjects alive and progression-free over time		
3 months (95% CI)	96.1 (92.8, 97.9)	69.5 (63.3, 74.9)
6 months (95% CI)	88.4 (83.7, 91.8)	51.7 (45.1, 57.9)
9 months (95% CI)	79.9 (74.3, 84.4)	41.4 (34.9, 47.8)
12 months (95% CI)	75.8 (69.8, 80.7)	34.1 (27.7, 40.5)
18 months (95% CI)	60.1 (52.5, 67.0)	27.3 (20.7, 34.2)
24 months (95% CI)	50.5 (39.9, 60.2)	25.3 (18.4, 32.9)

OS, ORR (BICR and investigator), DOR (BICR), PFS (investigator), Safety:

Parameter	T-DXd (N = 261)	T-DM1 (N = 263)
Overall survival		
Stratified Cox hazard ratio (95% CI)	0.28 (0.22, 0.37)	
Stratified log-rank test *P*-value	0.007172	
Percentage of subjects alive over time		
3 months (95% CI)	99.2 (96.9, 99.8)	96.9 (93.9, 98.4)
6 months (95% CI)	98.4 (95.9, 99.4)	94.5 (90.9, 96.7)
9 months (95% CI)	96.1 (92.8, 97.9)	91.3 (87.1, 94.2)
12 months (95% CI)	94.1 (90.3, 96.4)	85.9 (80.9, 89.7)
18 months (95% CI)	85.7 (79.8, 90.0)	76.5 (69.8, 81.8)
24 months (95% CI)	80.8 (73.0, 86.6)	73.7 (66.1, 79.9)
BOR by BICR		
Complete response, n (%)	42 (16.1)	23 (8.7)
Partial response, n (%)	166 (63.6)	67 (25.5)
Stable disease, n (%)	44 (16.9)	112 (42.6)
Progressive disease, n (%)	3 (1.1)	46 (17.5)
Not evaluable, n (%)	6 (2.3)	15 (5.7)
Confirmed ORR (complete response + partial response)		
Responders, n (%)	208 (79.7)	90 (34.2)
95% CI[f]	74.3, 84.4	28.5, 40.3
P-value[h]	<0.0001	
Difference in ORR (95% CI)	45.5 (37.6, 53.4)	

Trial name: DESTINY-Breast03	NCT number:
Method of analysis	*The planned sample was 500 patients. We performed the interim analysis of progression-free survival using the data cutoff date of May 21, 2021, after 245 events of disease progression (as determined by blinded independent central review) or death had occurred; the interim analysis was based on an information fraction of approximately 70%. The independent data and safety monitoring committee recommended that the trial be unblinded on July 30, 2021, after the prespecified efficacy boundary of superiority (P<0.000204) had been crossed. A stratified logrank test with an overall two-sided significance level of 0.05 was used to compare the two treatment groups. If the analysis of the primary end point showed a significant difference between the two groups, overall survival was to be tested. The prespecified boundary for overall survival (P<0.000265) was based on the occurrence of 86 deaths.* *All endpoints were ITT population and Kaplan-Meier method was used for PFS and OS.*
Subgroup analyses	Subgroups defined according to hormone-receptor status, previous treatment with pertuzumab, baseline visceral disease, lines of previous therapy, and stable brain metastases (as defined by documentation of central nervous system metastases in the patient's medical history).
Other relevant information	*N/A*

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

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety			
Parameter	**T-DXd (N = 261)**	**T-DM1 (N = 263)**	**Total (N = 524)**
Age (years) [a]			
Mean (std dev)	54.5 (11.11)	54.2 (11.84)	54.4 (11.47)
Median	54.3	54.2	54.3
Minimum, Maximum	27.9, 83.1	20.2, 83.0	20.2, 83.1
Female sex	260 (99.6)	262 (99.6)	522 (99.6)
Race			
Asian	152 (58.2)	162 (61.6)	314 (59.9)
White	71 (27.2)	72 (27.4)	143 (27.3)
Black or African American	10 (3 8)	9 (3.4)	19 (3.6)
Multiple	2 (0.8)	0	2 (0.4)
Other	26 (10.0)	20 (7.6)	46 (8.8)
Region			
Asia	149 (57.1)	160 (60.8)	309 (59.0)
Europe	54 (20.7)	50 (19.0)	104 (19.8)
Rest of World	41 (15.7)	36 (13.7)	77 (14.7)
North America	17 (6.5)	17 (6.5)	34 (6.5)
Weight (kg)			
Mean (std dev)	62.8 (14.05)	62.0 (12.53)	62.4 (13.30)
Median	59.3	60.7	60.0
Body mass index (kg/m²)			
Mean (std dev)	24.9 (5.15)	24.5 (4.65)	24.7 (4.90)
Median	24.0	23.6	23.9
Smoking status			
Never	191 (73.2)	229 (87.1)	420 (80.2)
Former	50 (19.2)	20 (7.6)	70 (13.4)
Current	18 (6 9)	11 (4.2)	29 (5.5)
Missing	2 (0.8)	3 (1.1)	5 (1.0)
Reported history of CNS metastases	62 (23.8)	52 (19.8)	114 (21.8)
HER2 expression (IHC) – Central			
1+	1 (0.4)	0	1 (0.2)
2+	25 (9 6)	30 (11.4)	55 (10.5)
3+	234 (89.7)	232 (88.2)	466 (88.9)
Not evaluable	1 (0.4)	1 (0.4)	2 (0.4)
HER2 gene amplification (ISH) – Central			
Amplified	24 (9 2)	29 (11.0)	53 (10.1)
Non-amplified	2 (0.8)	2 (0.8)	4 (0.8)
Missing [b]	235 (90.0)	232 (88.2)	467 (89.1)
Hormone receptor - Derived [c]			
Positive	133 (51.0)	139 (52.9)	272 (51.9)
Negative	126 (48.3)	122 (46.4)	248 (47.3)
Indeterminate	1 (0.4)	1 (0.4)	2 (0.4)
Missing	1 (0.4)	1 (0.4)	2 (0.4)
Estrogen receptors			

Positive	129 (49.4)	132 (50.2)	261 (49.8)
Negative	130 (49.8)	128 (48.7)	258 (49.2)
Indeterminate	1 (0.4)	2 (0.8)	3 (0.6)
Missing	1 (0.4)	1 (0.4)	2 (0.4)
Progesterone receptors			
Positive	81 (31.0)	92 (35.0)	173 (33.0)
Negative	177 (67.8)	168 (63.9)	345 (65.8)
Indeterminate	2 (0.8)	1 (0.4)	3 (0.6)
Missing	1 (0.4)	2 (0.8)	3 (0.6)
Prior pertuzumab - Derived [d]			
Yes	162 (62.1)	158 (60.1)	320 (61.1)
No	99 (37.9)	105 (39.9)	204 (38.9)
Lines of prior systemic therapy excluding hormone therapies			
<3	188 (72.0)	191 (72.6)	379 (72.3)
≥3	73 (28.0)	72 (27.4)	145 (27.7)
Lines of therapy prior to pertuzumab			
<3	156 (59.8)	152 (57.8)	308 (58.8)
≥3	6 (2.3)	6 (2.3)	12 (2.3)
Renal function at baseline [e]			
Within normal range	134 (51.3)	131 (49.8)	265 (50.6)
Mild impairment	96 (36.8)	105 (39.9)	201 (38.4)
Moderate impairment	27 (10.3)	25 (9.5)	52 (9.9)
Missing	4 (1.5)	2 (0.8)	6 (1.1)
Hepatic function at baseline [f]			
Within normal range	208 (79.7)	212 (80.6)	420 (80.2)
Mild impairment	49 (18.8)	49 (18.6)	98 (18.7)
Missing	4 (1.5)	2 (0.8)	6 (1.1)
Baseline visceral disease [g]	195 (74.7)	189 (71.9)	384 (73.3)
Baseline CNS metastases	43 (16.5)	39 (14.8)	82 (15 6)
ECOG Performance Status			
0	154 (59.0)	175 (66.5)	329 (62.8)
1	106 (40.6)	87 (33.1)	193 (36.8)
Missing	1 (0.4)	1 (0.4)	2 (0.4)

a) Age (years) was calculated using the date of birth and the date of informed consent

b) During tissue screening, tissue samples were first tested for HER2 IHC Only the samples with HER2 IHC2+ were tested by HER2 gene amplification (ISH)

c) Derived from locally determined estrogen and progesterone receptors. Hormone receptor: positive = estrogen receptor-positive and/or progesterone receptor-positive; negative = estrogen receptor-negative and progesterone receptor-negative; indeterminate = (neither estrogen receptor- nor progesterone receptor-positive) and (estrogen receptor-indeterminate or progesterone receptorindeterminate) based on estrogen receptors and progesterone receptors reported from EDC.

d) Derived based on prior cancer systemic therapy.

e) Within normal range, mild, and moderate impairment are presented for subgroup analyses.

f) Subjects within normal range and mild impairment are presented for subgroup analyses

g) Baseline visceral disease was determined with any target or non-target tumour in the lesion locations specified in the SAP. Baseline was defined as the last non-missing value taken before the first dose of study drug.

Comparability of patients across studies

N/A

Comparability of the study populations with Danish patients eligible for treatment

See section 10.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Median overall survival	*The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	Standard outcome of oncology studies. Widely accepted.	Overall survival is a key outcome for clinicians and patients.
1-year survival	*The absolute difference in effect is estimated using a two-sided t-test*	Standard outcome of oncology studies. Widely accepted.	Overall survival is a key outcome for clinicians and patients.
Median PFS independent	*The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	Standard outcome of oncology studies. Widely accepted.	PFS is a key outcome for clinicians and patients. PFS is also often strongly linked to overall survival.
Median PFS investigator	*The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	Standard outcome of oncology studies. Widely accepted.	PFS is a key outcome for clinicians and patients. PFS is also often strongly linked to overall survival.
1-year PFS	*The absolute difference in effect is estimated using a two-sided t-test*	Standard outcome of oncology studies. Widely accepted.	PFS is a key outcome for clinicians and patients. PFS is also often strongly linked to overall survival.

Outcome measure	Definition	Validity	Clinical relevance
ORR	*The absolute difference in effect is estimated using a two-sided t-test*	Standard outcome of oncology studies. Widely accepted.	ORR provides a direct measure of antitumor activity in an objective manner that can be directly attributable to drug effect without the need to account for differing subsequent lines of treatments between the two treatment arms.

Results per study

Table A3a Results of DESTINY-Breast03 (NCT03529110)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	T-DXd	261	NE (NE, NE)	NE	NE	NE	HR: 0.55	0.36, 0.86	0.007172	*The median survival is based on the Kaplan–Meier estimator. 2-sided P-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: Hormone receptor status, Prior treatment with pertuzumab, and History of visceral disease, as defined by IXRS.*	(8)
	T-DM1	263	NE (NE, NE)								
1-year survival	T-DXd	261	94.1 (90.3, 96.4)	0.082	0.0311, 0.1329	0.0018				*Estimate and CI for OS rate at the specified timepoint are from KM analysis.* Confidence intervals of difference in the proportion is calculated with Z-test using the following formula: = (p1 – p2) +/- z*√(p1(1-p1)/n1 + p2(1-p2)/n2)	(8)
	T-DM1	263	85.9 (80.9, 89.7)								

Table A3a Results of DESTINY-Breast03 (NCT03529110)											
Median PFS independent	T-DXd	261	NE (18.5, NE)	NE	NE	NE	HR: 0.28	0.22, 0.37	<0.000001	*The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	(8)
	T-DM1	263	6.8 (5.6, 8.2)								
Median PFS investigator	T-DXd	261	25.1 (22.1 NE)	17.9	NE	NE	0.26	0.20, 0.35	<0.000001	*The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	(8)
	T-DM1	263	7.2 (6.8 8.3)								
1-year PFS independent	T-DXd	261	75.8% (69.8, 80.7)	0.417	0.3397, 0.4943	< .00001				*Estimate and CI for OS rate at the specified timepoint are from KM analysis.* Confidence intervals of difference in the proportion is calculated with Z-test using the following formula: = (p1 – p2) +/- z*√(p1(1-p1)/n1 + p2(1-p2)/n2)	(8)
	T-DM1	263	34.1% (27.7, 40.5)								
ORR	T-DXd	261	0.797 (0.743–0.844)	0.455	0.376, 0.534	P<0.0001	RR: 2.3288	1.9483, 2.7837	< 0.0001	*Based on the Clopper-Pearson method for single proportion and for the difference of 2 proportions with continuity correction.*	(8)
	T-DM1	263	0.342 (0.285–0.403)								

Table A3a Results of DESTINY-Breast03 (NCT03529110)											
										Relative effectiveness: 2-sided P-value based on the Cochran-Mantel-Haenszel test adjusted for stratification factors: Hormone receptor status, Prior treatment with pertuzumab, and History of visceral disease, as defined by the IXRS.	
Grade 3/4 AEs	T-DXd	257	0.451 (0.389-0.514)	0.053	-0.0317, 0.1377	P=0.22246	RR: 1.1327	0.9265, 1.3849	0.2241	Confidence intervals of difference in the proportion with AE calculated with Z-test using the following formula: = (p1 – p2) +/- z*√(p1(1-p1)/n1 + p2(1-p2)/n2) The relative risk (RR), its standard error and 95% confidence interval are calculated according to Altman, 1991.	(8)
	T-DM1	261	0.398 (0.339-0.461)								

Appendix E Safety data for intervention and comparator(s)

See section 7.

Appendix F Comparative analysis of efficacy and safety

N/A

Appendix G Extrapolation

Distribution parameters

Table 57. Distribution parameters – DB03 T-DM1

Modelling method	DB03 data	T-DM1		
Distribution	**Parameter**	**PFS**	**OS**	**TTD**
Exponential	Rate	0.0870	0.0135	0.1010
Weibull	Scale	11.5800	48.9908	9.9910
	Shape	0.9830	1.3873	1.1580
Gompertz	Scale	0.1190	0.0091	0.1010
	Shape	-0.0590	0.0422	0.0010
Log-Logistic	Scale	6.8670	41.6770	6.5180
	Shape	1.3660	1.4806	1.6570
Log normal	Meanlog	1.9630	3.9886	1.8730
	Sdlog	1.2140	1.4342	1.0310
Generalized gamma	Mu	1.3950	3.9234	1.8550
	Sigma	1.1980	0.9079	1.0360
	Q	-1.0880	0.6883	-0.0400

Abbreviations: DB03, DESTINY-Breast03; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TTD, time to treatment discontinuation

Notes: -

Table 58. Distribution parameters – DB03 T-DXd

Modelling method	DB03 data	T-DXd		
Distribution	**Parameter**	**PFS**	**OS**	**TTD**
Exponential	Rate	0.0260	0.0077	0.0360
Weibull	Scale	30.2720	74.2561	23.2250
	Shape	1.3510	1.3873	1.4740
Gompertz	Scale	0.0190	0.0051	0.0240
	Shape	0.0340	0.0422	0.0460
Log-Logistic	Scale	23.7560	64.7971	17.8220
	Shape	1.5400	1.4806	1.7710
Log normal	Meanlog	3.2310	4.5229	2.9010
	Sdlog	1.1930	1.4342	0.9960
Generalized gamma	Mu	3.2600	4.3685	2.9390
	Sigma	1.1410	0.9079	0.9570
	Q	0.1190	0.6883	0.1310

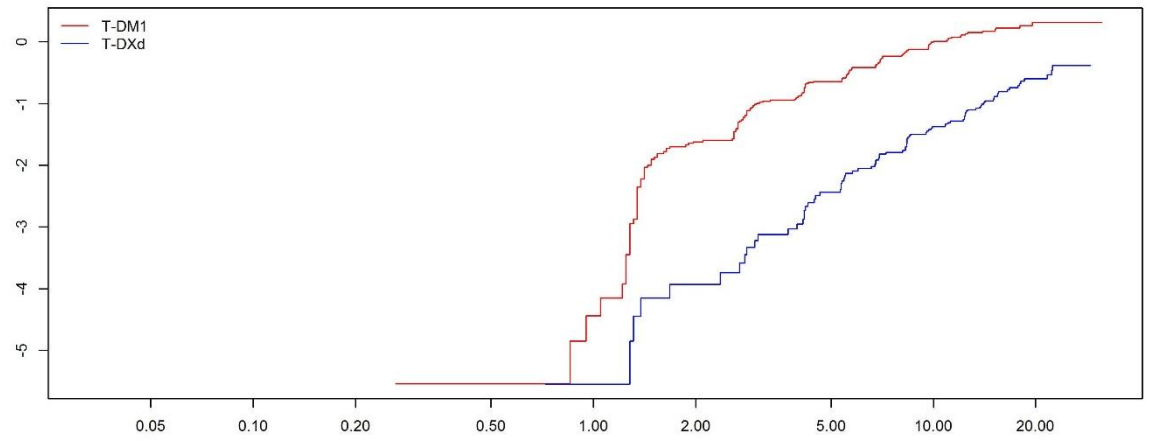
Abbreviations: DB03, DESTINY-Breast03; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TTD, time to treatment discontinuation

Proportional hazards and fit assessment

Proportional hazard and fit —PFS

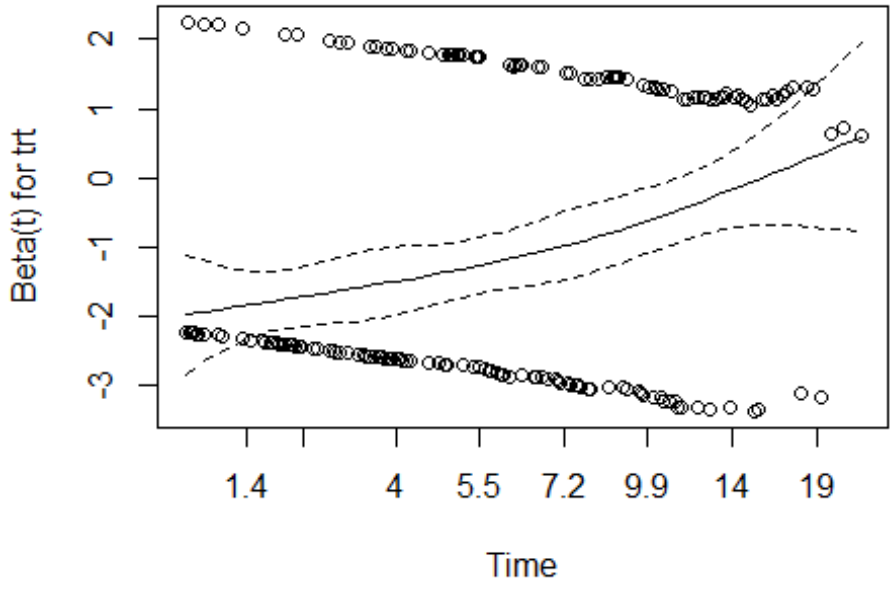
In Figure 24 the log-cumulative hazard plot for T-DXd and T-DM1 is shown for PFS. The lines are not parallel. The gap between the lines shrinks continuously from 2 months onwards. Prior to two months the lines are also not parallel, as the gap between them initially shrinks, and is followed by a large increase.

Figure 24. Log-cumulative hazard plot of PFS assessed by BICR



In Figure 25 the Schoenfeld residuals are shown for PFS. To indicate that the proportional hazards assumption holds, the line in the middle of the graph should be horizontal, indicating independence from time. However, the line is continuously increasing, indicating that the proportional hazards assumption does not hold. The associated statistical test for proportionality has a p-value <0.001, which means that the hypothesis that the proportional hazards assumption holds is rejected.

Figure 25. Schoenfeld residuals for PFS assessed by BICR



Both the log-cumulative hazards plot and the Schoenfeld residuals indicate that the proportional hazards assumption does not hold. Therefore, PH/AFT models with treatment group included as a covariate are considered unsuitable for PFS modelling.

Figure 26. Hazard function, smoothed and unsmoothed of PFS- based on BICR

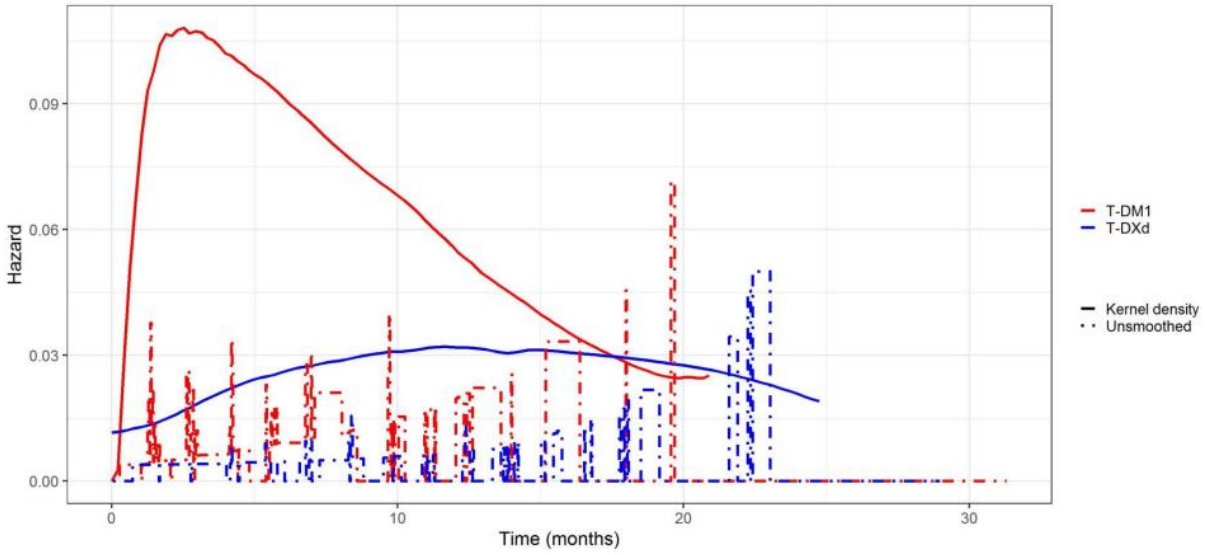
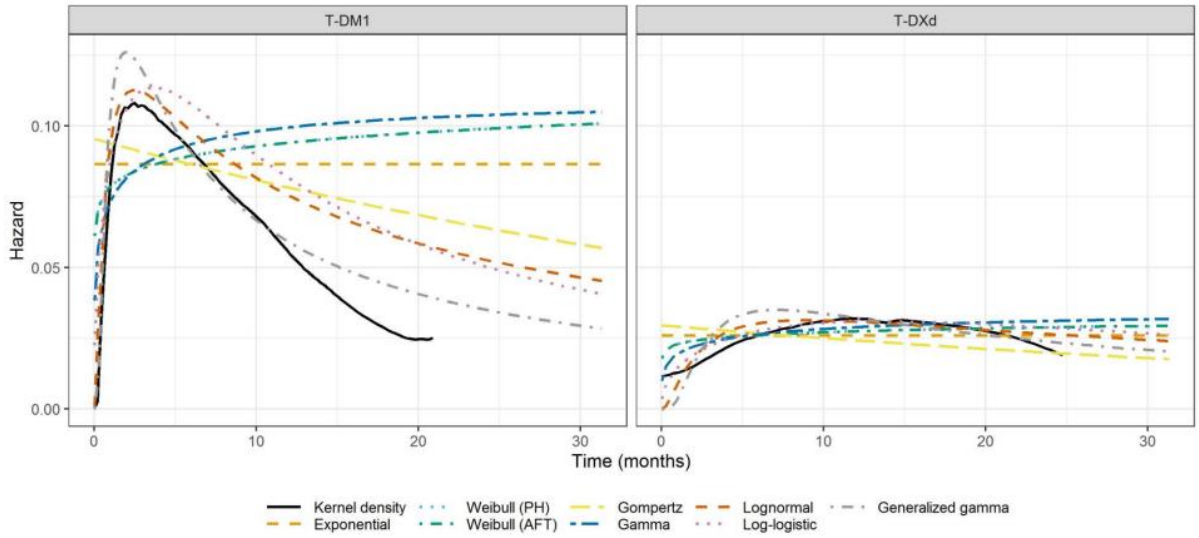


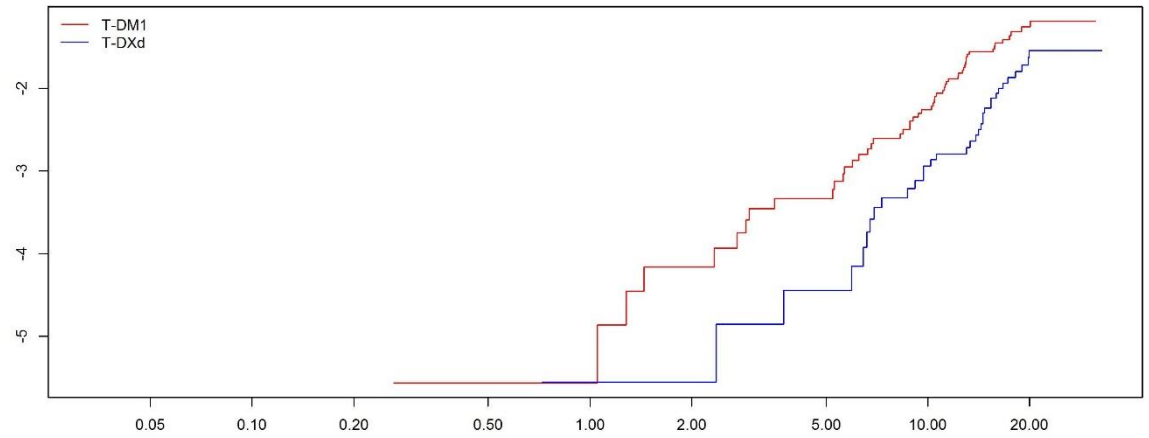
Figure 27. Hazard function, smoothed and by extrapolation model of PFS- based on BICR



Proportional hazard and fit —OS

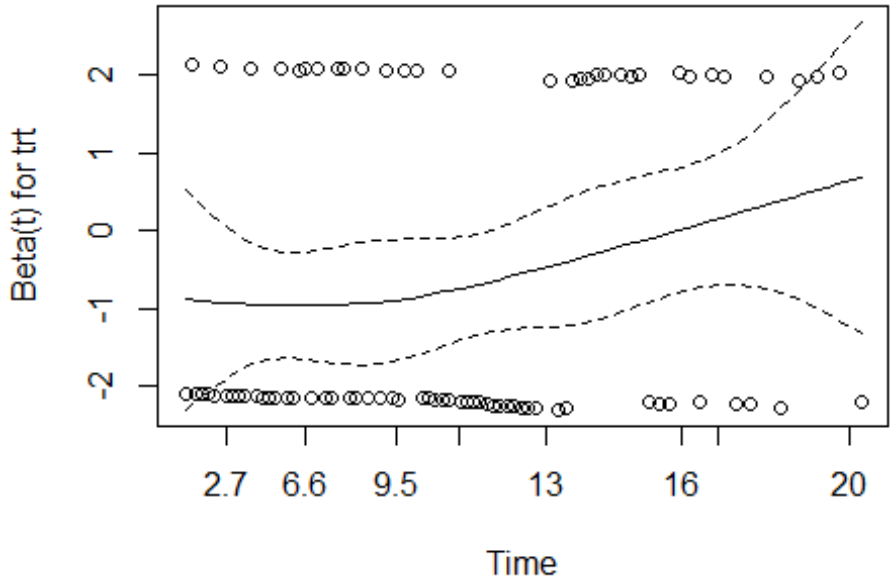
In Figure 28 the log-cumulative hazard plot for T-DXd and T-DM1 is shown for OS. While the lines show a trend with the gap between the lines narrowing, the lines are approximately parallel. From the log-cumulative hazard plot, it is not possible to determine with certainty whether the proportional hazard assumption holds.

Figure 28. Log-cumulative hazard plot of OS



In Figure 29 the Schoenfeld residuals are shown for OS. The line has a slight upward trend. However, the statistical test for proportionality has a p-value of 0.05309. The statistical test fails to reject the hypothesis that the proportional hazard assumption holds.

Figure 29. Schoenfeld residuals for OS



Based on the information above, it is likely that the proportional hazard assumption holds. Therefore, PH/AFT models with treatment group included as a covariate could be considered suitable for OS modelling.

Figure 30. Hazard function, smoothed and unsmoothed of OS

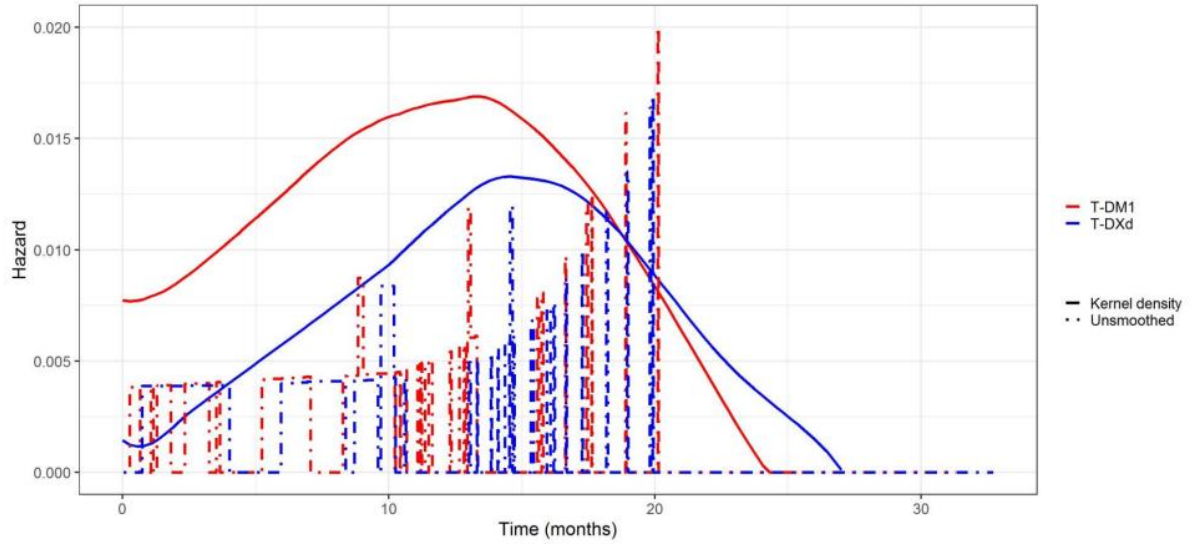
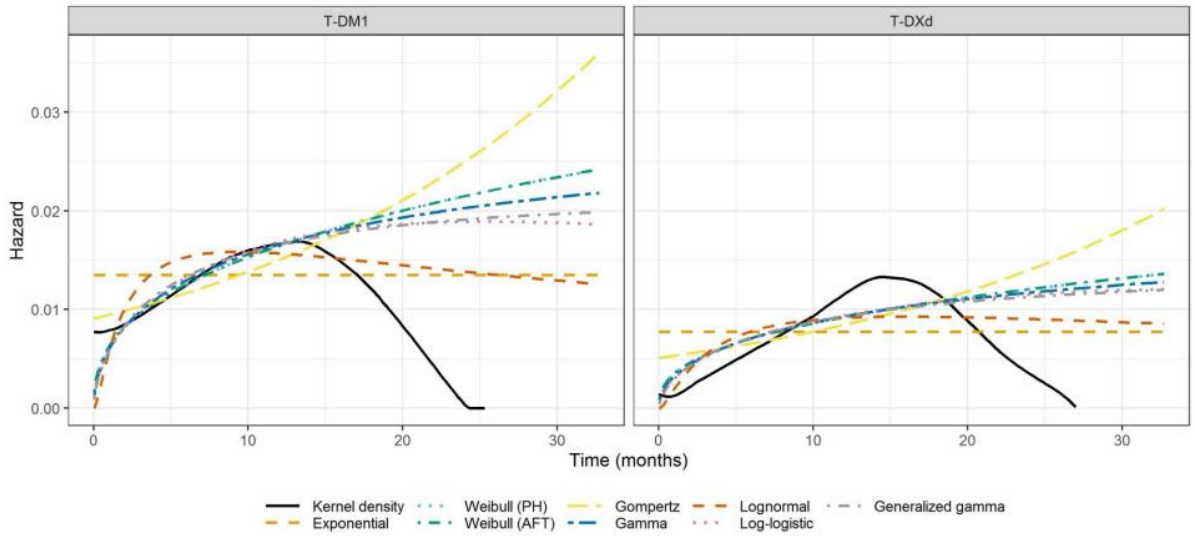


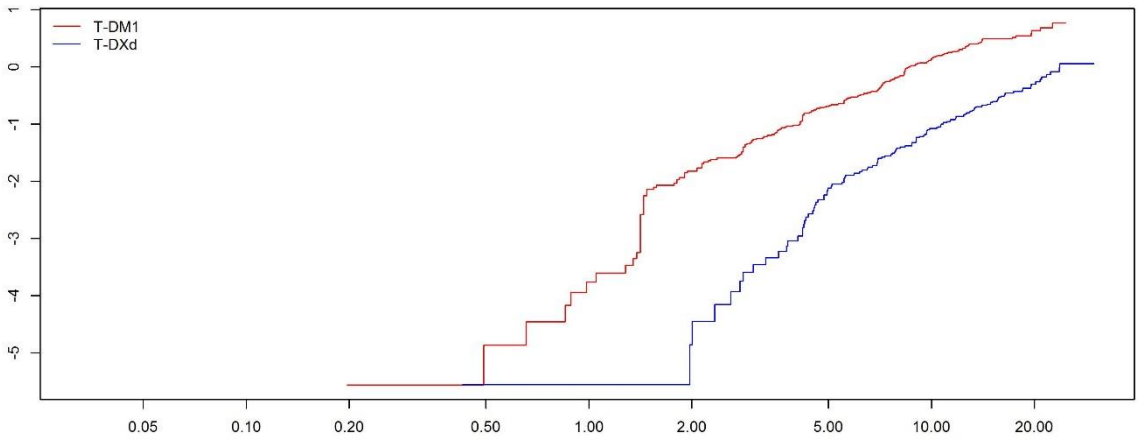
Figure 31. Hazard function, smoothed and by extrapolation model of OS



Proportional hazard and fit —TTD

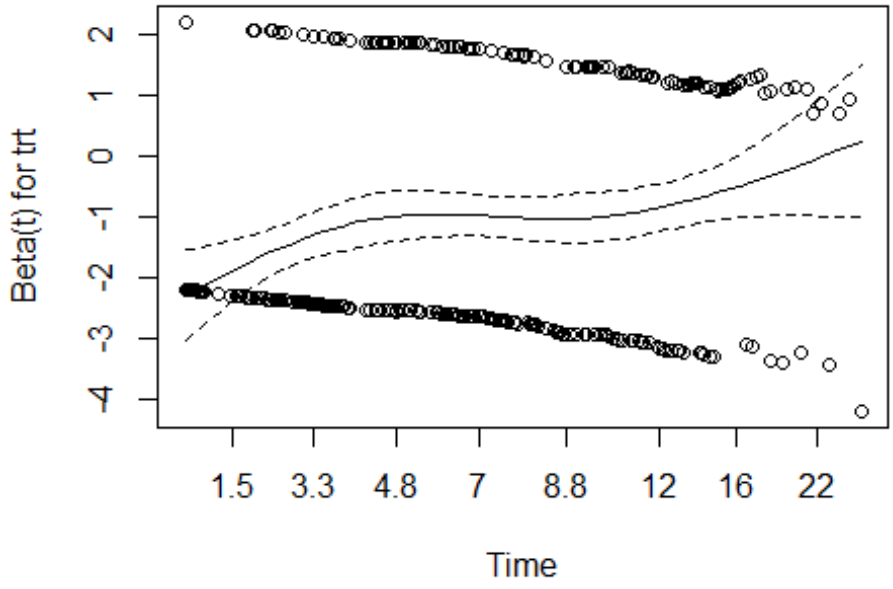
In Figure 32 the log-cumulative hazard plot for T-DXd and T-DM1 for TTD is shown. The lines seem to show a trend, since the gap between them is narrowing. From the log-cumulative hazard plot it is not possible to determine with certainty whether the proportional hazard assumption holds.

Figure 32. Log-cumulative hazard plot of TTD



In Figure 33 the Schoenfeld residuals are shown for TTD. The line in the plot is not horizontal. The Schoenfeld residuals plot indicates that the proportional hazards assumption does not hold. The p-value for the statistical test for proportionality is <0.001. This means that the hypothesis that the proportional hazard assumption holds is rejected.

Figure 33. Schoenfeld residuals for TTD



The information above indicates that the proportional hazards assumption does not hold. Therefore, PH/AFT models with treatment group included as covariate are considered unsuitable for TTD modelling.

Figure 34. Hazard function, smoothed and unsmoothed of TTD

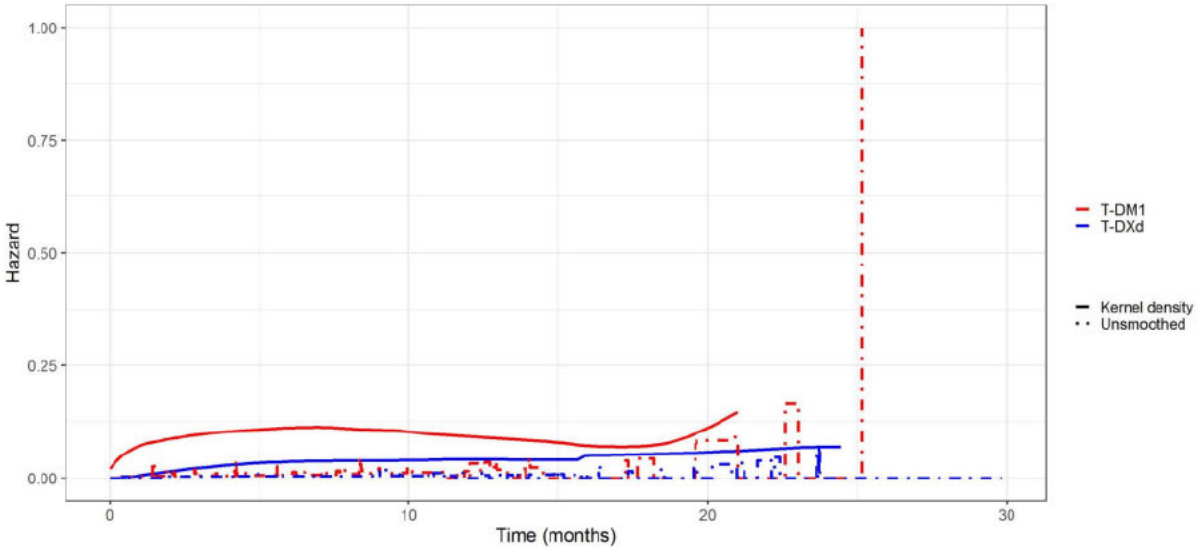


Figure 35. Hazard function, smoothed and by extrapolation model of TTD

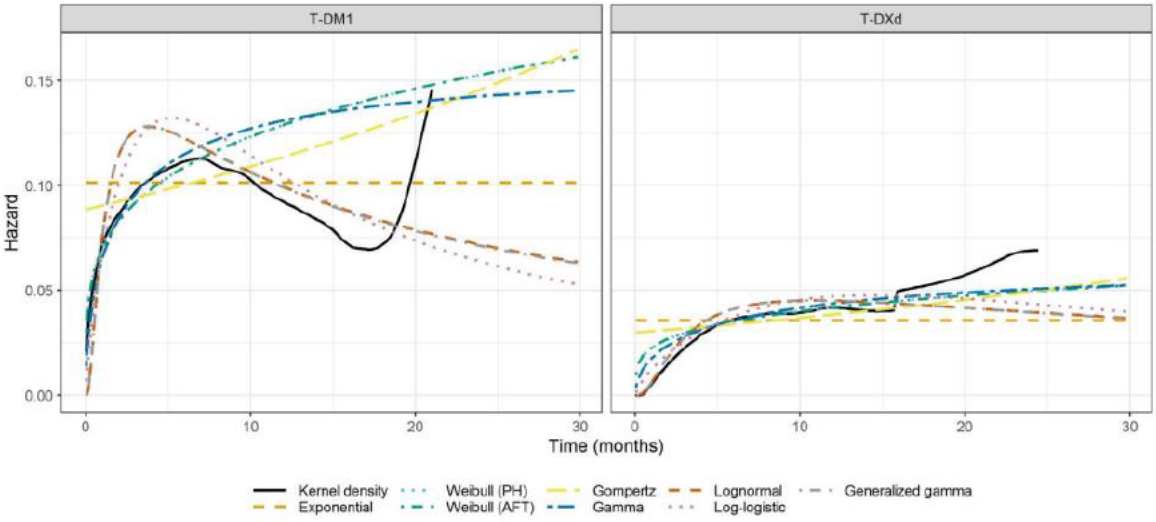


Figure 36. Independent OS fits

Model	Parameter	T-DM1	T-DXd
Exponential	Rate	0.0135	0.0077
Weibull	Scale	54.5681	59.0146
	Shape	1.2582	1.6597
Log-normal	meanlog	4.0853	4.3161
	sdlog	1.5284	1.2722
Log-logistic	log(shape)	45.6491	53.0629
	log(scale)	1.3538	1.7473
Gompertz	shape	0.0107	0.0039

	rate	0.0252	0.0658
Generalised Gamma	mu	4.0284	4.1082
	sigma	0.9777	0.6892
	Q	0.7089	0.8283

Appendix H – Literature search for HRQoL data

The only study that collected HRQoL data in line with the scope of this assessment was DESTINY-Breast03. Hence, no SLR for these data was deemed appropriate. Please see the attached report for the reference list. However, for completeness a SLR has been conducted and is provided in this section.

Objectives

Asc Academics has conducted an economic SLR to understand the economic value of second-line treatments for unresectable and/or metastatic HER2-positive breast cancer by searching for previously published economic evidence relevant to the development of an economic model.

The specific objectives of this economic SLR were the following:

- Identify economic modeling studies for second-line treatment of unresectable and/or metastatic HER2-positive breast cancer
- Identify utility studies for second-line treatment of unresectable and/or metastatic HER2-positive breast cancer
- Identify cost and resource use studies for second-line treatment of unresectable and/or metastatic HER2-positive breast cancer
- Critically appraise the studies using validated appraisal tools.
- Prepare summaries of the included studies in accordance with the guidelines set forth in Specification for Manufacturer or Sponsor Submission of Evidence (26).

Methods

Electronic databases

The searches for the economic SLRs were designed with a combination of sensitivity and specificity as per the requirements of global HTA agencies. The following electronic databases were searched (i.e., standard evidence sources used in UK HTA assessments):

- MEDLINE® and Embase® (using Embase.com)
- MEDLINE® In-Process (using PubMed.com)
- EconLit®
- School of Health and Related Research Health Utilities Database (ScHARRHUD)
- Centre for Reviews and Dissemination (CRD) York (archived records until 2015), including:
    - Health Technology Assessment Database (HTAD)
    - National Health Service (NHS) Economic Evaluation Database

Searches for the update were limited to articles published between 8 August 2020 (date of the primary eSLR) to 24 November 2021. The search strategies for the SLRs are presented below.

Grey literature search

A grey literature search was conducted to help identify the most recent abstracts, posters, and podium presentations that may not yet have been indexed in the medical literature databases. For the initial document, these searches were restricted to 2018–2020, with the update covering 2020 – 24 November 2021, to capture the most recent unpublished or ongoing trials. The search covered the following conferences:

- ASCO Breast Cancer Symposium
- European Society for Medical Oncology (ESMO)
- European Breast Cancer Conference (EBCC)
- San Antonio Breast Cancer Symposium (SABCS)
- Japan Society of Clinical Oncology Annual meetings (JSCO)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

Where possible, data identified within the review was supplemented by data available on HTA body websites (i.e., clinical trials on which manufacturer submissions are based). The HTA body websites were searched for relevant comparators by searching for HER2 and breast cancer, and the list of HTA agencies that were searched is presented in below.

To ensure all relevant studies were captured, Asc Academics also conducted bibliographic searches of identified key systematic reviews and meta-analyses (including network meta-analyses).

Study selection methodology

All retrieved studies were assessed against eligibility criteria for the economic search. The study selection process was performed in the following two phases:

- Primary (Level 1) screen: Titles and abstracts of studies identified from the electronic databases and Internet searches were double-screened by two independent researchers to determine eligibility according to the inclusion and exclusion criteria described below. If there was disagreement about study relevance, consensus was reached through a discussion between the two researchers.
- Secondary (Level 2) screen: Full texts of studies selected at Level 1 were obtained and double-screened by two independent researchers to determine eligibility according to the inclusion and exclusion criteria described below. If there was disagreement about study relevance, consensus was reached through a discussion between the two researchers.

This inclusion and exclusion process was documented and clearly defined and presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in Figure 6. (27). A document containing detailed information on the reasons for exclusion will be sent to the primary contact person of Daiichi Sankyo and AstraZeneca for this project.

Study selection criteria

Potentially relevant publications were reviewed and assessed to collate a final set of studies that formed the main body of the economic evidence. To determine the final set of studies eligible for review, explicit inclusion and/or exclusion criteria were applied to the literature search results for each of the economic SLRs.

Utility evidence

The inclusion and exclusion criteria for the utility studies are specified in Table 3.1 in terms of population, interventions, comparators, outcomes, and other criteria. The study population includes adult patients with HER2-positive mBC. No restriction was applied to the intervention and comparator to allow all the relevant papers to be identified. The included studies reported utility values that are measured by using a generic, preference-based, disease-specific measure, or any other type of measure.

Table 3.1. PICOS Criteria for the inclusion and exclusion of the utility studies.

Category	Inclusion criteria	Exclusion criteria

Population (P)	Adult (age ≥18 years) patients undergoing second-line treatment for unresectable and/or metastatic HER2-positive breast cancer [a], or have progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane. [b] Furthermore, the studies that assess a mixed population will be included regardless of the percentage of the study population [c]	Healthy volunteers Patients <18 years Diseases other than unresectable and/or metastatic HER2-positive breast cancer Patients with HER2-negative breast cancer Non-invasive or Stage 0 breast cancer
Interventions (I)	Any	None
Comparators (C)	Any	None
Outcomes (O) (tentative list, not exhaustive)	Utility weights by health state (e.g., EuroQol 5 dimensions [EQ-5D], Quality-of-life Questionnaire Core 30 [QLQ-C30], Health Utilities Index [HUI], Short-Form 6-D [SF-6D]) [d]	Not reporting utility values
Study design (S)	Studies reporting utility/disutility data – QoL Economic modeling studies Systematic reviews [e] Studies reporting utility values (EQ-5D, QLQ-C30, etc.) Studies reporting mapped utility values Studies reporting elicited utility data from the general population	*In vitro* studies Preclinical studies Reviews, comments, letters, and editorials Case reports, case series Clinical studies reporting only efficacy and safety data
Language	English language [f]	None
Time limit	Published after August 1, 2010 [g]	Published before August 1, 2010 [g]
Country	No restriction	None

Abbreviations: HER2, Human epidermal growth factor receptor 2; EQ-5D, EuroQol 5 dimensions; QLQ-C30, Quality-of-life Questionnaire Core 30; HUI, Health utilities index; SF-6D, Short-Form 6D; QoL, Quality of life.

Note: If it is unclear whether a study meets any criterion during the Level 1 screening process, the study will be progressed to full-text screening to confirm its inclusion in the review.

[a] Studies not reporting second-line treatment were flagged and reported to Daiichi Sankyo and AstraZeneca. These studies were excluded at Level 2 screening in accordance with Daiichi Sankyo's and AstraZeneca's wishes.

[b] Addition to study population was only included in update covering 8 August '20 – 24 November '21.

[c] Studies reporting a mixed HER2 population were flagged and reported to Daiichi Sankyo and AstraZeneca. These studies were only included at Level 2 screening if outcomes were reported separately for the HER2-positive subgroup, in accordance with Daiichi Sankyo's and AstraZeneca's wishes.

[d] The following utility list is not exclusive, all PROs that provide utility values were included.

[e] Systematic reviews were included at Level 1 screening, used for identification of primary studies, and then excluded at Level 2 screening.

[f] At the screening stage, the studies published in a non-English language were flagged and reported to Daiichi Sankyo and AstraZeneca. These studies were excluded at Level 2 screening in accordance with Daiichi Sankyo's and AstraZeneca's wishes.

[g] Articles published before August 1, 2010, were flagged and reported to Daiichi Sankyo and AstraZeneca. These studies were excluded at Level 2 screening in accordance with Daiichi Sankyo's and AstraZeneca's wishes.

Search strategy

When performing the searches for the update, the timeframe was limited to articles published between August 11, 2020 and November 24, 2021. The number of hits mentioned under update reflect this time period.

ScharrHud returned no relevant articles because the search for the relevant receptor status of HER2 and HR returned zero results (Table 9.1).

Table 59. Receptor status search strategy (August 11, 2020).

String Number	Query	Hits
1	'epidermal growth factor receptor 2':AB,TI OR cd340:AB,TI OR erbb2*:AB,TI OR 'erbb 2*':AB,TI OR her2*:AB,TI OR 'her 2*':AB,TI OR ((neu NEAR (protein* OR oncoprotein* OR receptor*)):AB,TI) OR 'differentiation factor receptor':AB,TI OR 'neuregulin receptor':AB,TI OR (((immunohistochemistry OR ihc) NEAR (3 OR 2)):AB,TI) OR 'hr positive':AB,TI OR 'hormone receptor positive':AB,TI	0

Table 60. Utility Embase search strategy (August 11, 2020. Updated November 24, 2021).

String Number	Query	Hits
1	'breast cancer'/exp OR ((breast NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti) OR ((mammary NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti)	585,148 Update: 63,654
2	metasta*:ab,ti OR advanc*:ab,ti OR unresect*:ab,ti OR 'un resect*':ab,ti OR nonresect*:ab,ti OR 'non resect*':ab,ti OR inoperable:ab,ti OR (((non OR 'not') NEAR/2 (amenabl* OR suit*) NEAR/2 (surge* OR surgi* OR opera*)):ab,ti)	1,773,747 Update: 237,888
3	'cancer recurrence'/exp OR relapse/exp OR 'cancer resistance'/exp OR relaps*:ab,ti OR refrac*:ab,ti OR resist*:ab,ti OR recurr*:ab,ti OR progress*:ab,ti OR (((previ* OR prior* OR heav* OR post*) NEAR/4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ab,ti) OR treated:ab,ti OR pretreat*:ab,ti OR pre-treat*:ab,ti OR failed:ab,ti OR failure:ab,ti OR reocur*:ab,ti OR 're ocur*':ab,ti OR reoccur*:ab,ti OR 're occur*':ab,ti	7,074,288 Update: 761,845
4	'epidermal growth factor receptor 2'/exp OR 'epidermal growth factor receptor 2':ab,ti OR cd340:ab,ti OR erbb2*:ab,ti OR 'erbb 2*':ab,ti OR her2*:ab,ti OR 'her 2*':ab,ti OR ((neu NEAR/1 (protein* OR oncoprotein* OR receptor*)):ab,ti) OR 'differentiation factor receptor':ab,ti OR 'neuregulin receptor':ab,ti OR (((immunohistochemistry OR ihc) NEAR/2 (3 OR 2)):ab,ti) OR 'hr positive':ab,ti OR 'hormone receptor positive':ab,ti	100,420 Update: 14,029
5	'case report'/exp OR 'case study'/exp OR 'abstract report'/exp OR 'editorial'/exp OR 'veterinary clinical trial'/exp OR letter/exp OR note/exp OR (animal/exp NOT (animal/exp AND human/exp)) OR 'meta-analysis (topic)'/exp OR 'case study':it OR 'case study':ab,ti OR 'case report':it OR 'case report':ab,ti OR 'abstract report':it OR 'abstract report':ab,ti OR editorial:it OR editorial:ab,ti OR 'veterinary clinical trial':it OR 'veterinary clinical trial':ab,ti OR letter:it OR letter:ab,ti OR note:it OR note:ab,ti OR ((review:it OR review:ab,ti OR 'literature review':it OR 'literature review':ab,ti) NOT ('meta-analysis':it OR 'meta-analysis':ab,ti OR 'meta-analysis (topic)':it OR 'systematic review':it OR 'systematic literature review':it OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti))	13,886,323 Update: 1,090,134
6	'european quality of life 5 dimensions questionnaire'/exp OR 'short form 36'/exp OR 'patient preference'/exp OR 'visual analog scale'/exp OR 'quality of life'/exp OR utilit*:ab,ti OR disutilit*:ab,ti OR 'sf 6':ab,ti OR sf6:ab,ti OR 'short form 6':ab,ti OR 'shortform 6':ab,ti OR 'sf six':ab,ti OR 'sfsix':ab,ti OR 'shortform six':ab,ti OR 'short form six':ab,ti OR 'sf 36':ab,ti OR sf36:ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'sf thirtysix':ab,ti OR 'sfthirtysix':ab,ti OR 'shortform thirtysix':ab,ti OR 'short form thirtysix':ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti OR eq5d:ab,ti OR 'eq 5d':ab,ti OR 'health utilities index':ab,ti OR hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR ((standard NEXT/1	972,401 Update: 148,839

String Number	Query	Hits
	gamble*):ab,ti) OR 'quality of life*':ab,ti OR 'time trade off':ab,ti OR 'time tradeoff':ab,ti OR tto:ab,ti OR 'visual analog scale':ab,ti OR 'patient preference':ab,ti OR 'european quality of life 5 dimensions questionnaire':ab,ti	
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	1,101 Update: 235

Table 61. Utility PubMed search strategy (August 7, 2020. Updated November 24, 2021).

String Number	Query	Hits
1	"breast neoplasms"[MeSH Terms] OR (breast[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab])) OR (mammary[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab]))	431,753 Update: 36,169
2	metasta*[tiab] OR advance*[tiab] OR unresect*[tiab] OR "un resect*"[tiab] OR nonresect*[tiab] OR "non resect*"[tiab] OR inoperable[tiab] OR (non[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (non[tiab] AND suit*[tiab] AND surg*[tiab]) OR (non[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (non[tiab] AND suit*[tiab] AND opera*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (not[tiab] AND suit*[tiab] AND surg*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (not[tiab] AND suit*[tiab] AND opera*[tiab])	1,269,826 Update: 155,452
3	"Neoplasm Recurrence, local"[MeSH] OR recurrence[MeSH] OR "disease resistance"[MeSH] OR "2nd line"[tiab] OR "second line"[tiab] OR "2 l"[tiab] OR "2 line"[tiab] OR 2l[tiab] OR relaps*[tiab] OR refrac*[tiab] OR resis*[tiab] OR recurr*[tiab] OR progress*[tiab] OR (previ*[tiab] AND (chemo*[tiab] OR line*[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (prior*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (heav*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (post*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR treated[tiab] OR pretreat*[tiab] OR pre-treat*[tiab] OR failed[tiab] OR failure[tiab] OR reoccur*[tiab] OR reocur*[tiab] OR "re occur"[tiab]	6,060,425 Update: 571,756
4	"receptor, erbb-2"[MeSH] OR "genes, erbb-2"[MeSH] OR "epidermal growth factor receptor 2"[tiab] OR cd340[tiab] OR erbb2*[tiab] OR "erbb 2*"[tiab] OR her2*[tiab] OR "her 2*"[tiab] OR (neu[tiab] AND protein*[tiab]) OR (neu[tiab] AND oncoprotein*[tiab]) OR (neu[tiab] AND receptor*[tiab]) OR "differentiation factor receptor"[tiab] OR "neuregulin receptor"[tiab] OR "neu receptor"[tiab] OR (immunohistochemistry[tiab] AND (2[tiab] OR 3[tiab])) OR (ihc[tiab] AND (2[tiab] OR 3[tiab])) OR hr positive[tiab] OR "hormone receptor positive"[tiab]	132,672 Update: 14,785
5	"case reports"[pt] OR editorial[pt] OR letter[pt] OR comment[pt] OR "clinical trial, veterinary"[pt]	3,771,946 Update: 224,136
6	"Patient Health Questionnaire"[MeSH] OR "patient preference"[MeSH] OR "quality of life"[MeSH] OR "visual analog scale"[MeSH] OR utilit*[tiab] OR disutilit*[tiab] OR "sf 6"[tiab] OR sf6[tiab] OR "short form 6"[tiab] OR "sf	579,413

String Number	Query	Hits
	six"[tiab] OR "sfsix"[tiab] OR "short form six"[tiab] OR "sf 36"[tiab] OR sf36[tiab] OR "short form 36"[tiab] OR "shortform 36"[tiab] OR euroqol[tiab] OR "euro qol"[tiab] OR eq5d[tiab] OR "eq 5d"[tiab] OR "health utilities index"[tiab] OR hui[tiab] OR hui1[tiab] OR hui2[tiab] OR hui3[tiab] OR (standard[tiab] AND gamble*[tiab]) OR "quality of life*"[tiab] OR "time trade off"[tiab] OR "time tradeoff"[tiab] OR tto[tiab] OR "visual analog scale"[tiab] OR "patient preference"[tiab]	Update: 78,260
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	512 Update: 99

Table 62. Utility EconLit search strategy (August 11, 2020. Updated November 24, 2021).

String Number	Query			Hits
S1	AB ('breast cancer' OR ((breast N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*))) OR ((mammary N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)))) AND TI ('breast cancer' OR ((breast N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*))) OR ((mammary N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*))))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	103
S2	AB (metasta* OR advanc* OR unresect* OR 'un resect*' OR nonresect* OR 'non resect*' OR inoperable OR (((non OR 'not') N2 (amenabl* OR suit*) N2 (surge* OR surgi* OR opera*)))) AND TI (metasta* OR advanc* OR unresect* OR 'un resect*' OR nonresect* OR 'non resect*' OR inoperable OR (((non OR 'not') N2 (amenabl* OR suit*) N2 (surge* OR surgi* OR opera*))))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	1,290
S3	AB ('cancer recurrence' OR relapse OR 'cancer resistance' OR relaps* OR refrac* OR resist* OR recurr* OR progress* OR (((previ* OR prior* OR heav* OR post*) N4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*))) OR treated OR pretreat* OR pre-treat* OR failed OR failure OR reocur* OR 're ocur*' OR reoccur* OR 're occur*') AND TI ('cancer recurrence' OR relapse OR 'cancer resistance' OR relaps* OR refrac* OR resist* OR recurr* OR progress* OR (((previ* OR prior* OR heav* OR post*) N4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*))) OR treated OR pretreat* OR pre-treat* OR	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	4,664

String Number	Query			Hits
	failed OR failure OR reocur* OR 're ocur*' OR reoccur* OR 're occur*')			
S4	AB ('epidermal growth factor receptor 2' OR 'epidermal growth factor receptor 2' OR cd340 OR erbb2* OR 'erbb 2*' OR her2* OR 'her 2*' OR ((neu N1 (protein* OR oncoprotein* OR receptor*))) OR 'differentiation factor receptor' OR 'neuregulin receptor' OR (((immunohistochemistry OR ihc) N2 (3 OR 2))) OR 'hr positive' OR 'hormone receptor positive') AND TI ('epidermal growth factor receptor 2' OR 'epidermal growth factor receptor 2' OR cd340 OR erbb2* OR 'erbb 2*' OR her2* OR 'her 2*' OR ((neu N1 (protein* OR oncoprotein* OR receptor*))) OR 'differentiation factor receptor' OR 'neuregulin receptor' OR (((immunohistochemistry OR ihc) N2 (3 OR 2))) OR 'hr positive' OR 'hormone receptor positive')	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	4
S5	AB ('european quality of life 5 dimensions questionnaire' OR 'short form 36' OR 'patient preference' OR 'visual analog scale' OR 'quality of life' OR utilit* OR disutilit* OR 'sf 6' OR sf6 OR 'short form 6' OR 'shortform 6' OR 'sf six' OR 'sfsix' OR 'shortform six' OR 'short form six' OR 'sf 36' OR sf36 OR 'short form 36' OR 'shortform 36' OR 'sf thirtysix' OR 'sfthirtysix' OR 'shortform thirtysix' OR 'short form thirtysix' OR euroqol OR 'euro qol' OR eq5d OR 'eq 5d' OR 'health utilities index' OR hui OR hui1 OR hui2 OR hui3 OR ((standard N1 gamble*)) OR 'quality of life*' OR 'time trade off' OR 'time tradeoff' OR tto OR 'visual analog scale' OR 'patient preference' OR 'european quality of life 5 dimensions questionnaire') AND TI ('european quality of life 5 dimensions questionnaire' OR 'short form 36' OR 'patient preference' OR 'visual analog scale' OR 'quality of life' OR utilit* OR disutilit* OR 'sf 6' OR sf6 OR 'short form 6' OR 'shortform 6' OR 'sf six' OR 'sfsix' OR 'shortform six' OR 'short form six' OR 'sf 36' OR sf36 OR 'short form 36' OR 'shortform 36' OR 'sf thirtysix' OR 'sfthirtysix' OR 'shortform thirtysix' OR 'short form thirtysix' OR euroqol OR 'euro qol' OR eq5d OR 'eq 5d' OR 'health utilities index' OR hui OR hui1 OR hui2 OR hui3 OR ((standard N1 gamble*)) OR 'quality of life*' OR 'time trade off' OR 'time tradeoff' OR tto OR 'visual analog scale' OR 'patient preference' OR 'european quality of life 5 dimensions questionnaire')	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	4,233
S6	S1 AND S2 AND S3 AND S4 AND S5	Expanders - Apply equivalent subjects	Interface - EBSCOhost Research Databases Search Screen -	0

String Number	Query			Hits
		Search modes - Boolean/Phrase	Advanced Search Database - EconLit	

Table 63 Utility CRD search strategy (August 11, 2020).

String Number	Query	Hits
1	(MeSH DESCRIPTOR breast neoplasms EXPLODE ALL TREES) OR ((breast NEAR2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ti) OR ((mammary NEAR2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ti)	1,978
2	metasta*:ti OR advanc*:ti OR unresect*:ti OR un resect*:ti OR nonresect*:ti OR non resect*:ti OR inoperable:ti OR ((non OR 'not') NEAR2 (amenabl* OR suit*) NEAR2 (surge* OR surgi* OR opera*)):ti	2,197
3	(MeSH DESCRIPTOR neoplasm recurrence, local EXPLODE ALL TREES) OR (MeSH DESCRIPTOR recurrence EXPLODE ALL TREES) OR (MeSH DESCRIPTOR disease resistance EXPLODE ALL TREES) OR relaps*:ti OR refrac*:ti OR resist*:ti OR recurr*:ti OR progress*:ti OR (((previ* OR prior* OR heav* OR post*) NEAR4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ti) OR treated:ti OR pretreat*:ti OR pre-treat*:ti OR failed:ti OR failure:ti OR reocur*:ti OR re ocur*:ti OR reoccur*:ti OR re occur*:ti	4,650
4	(MeSH DESCRIPTOR receptor, erbb-2 EXPLODE ALL TREES) OR (MeSH DESCRIPTOR genes, erbb-2 EXPLODE ALL TREES) OR epidermal growth factor receptor 2:ti OR cd340:ti OR erbb2*:ti OR erbb 2*:ti OR her2*:ti OR her 2*:ti OR ((neu NEAR1 (protein* OR oncoprotein* OR receptor*)):ti) OR differentiation factor receptor:ti OR neuregulin receptor:ti OR (((immunohistochemistry OR ihc) NEAR2 (3 OR 2)):ti) OR hr positive:ti OR hormone receptor positive:ti	165
5	(MeSH DESCRIPTOR case reports EXPLODE ALL TREES) OR (MeSH DESCRIPTOR editorial EXPLODE ALL TREES) OR (MeSH DESCRIPTOR letter EXPLODE ALL TREES) OR ((MeSH DESCRIPTOR animal EXPLODE ALL TREES) NOT ((MeSH DESCRIPTOR animal EXPLODE ALL TREES) AND (MeSH DESCRIPTOR human EXPLODE ALL TREES))) OR (MeSH DESCRIPTOR meta-analysis as topic EXPLODE ALL TREES) OR case study:ti OR case report:ti OR abstract report:ti OR editorial:ti OR veterinary clinical trial:ti OR letter:ti OR note:ti OR ((review:ti OR literature review:ti) NOT (meta-analysis:ti OR systematic review:ti OR systematic literature review:ti OR meta analysis:ti))	3,574
6	(MeSH DESCRIPTOR surveys and questionnaires EXPLODE ALL TREES) OR (MeSH DESCRIPTOR patient preference EXPLODE ALL TREES) OR (MeSH DESCRIPTOR quality of life EXPLODE ALL TREES) OR (MeSH DESCRIPTOR visual analog scale EXPLODE ALL TREES) OR utilit*:ti OR disutilit*:ti OR sf 6:ti OR sf6:ti OR short form 6:ti OR shortform 6:ti OR sf six:ti OR sfsix:ti OR shortform six:ti OR short form six:ti OR sf 36:ti OR sf36:ti OR short form 36:ti OR shortform 36:ti OR sf thirtysix:ti OR sfthirtysix:ti OR shortform thirtysix:ti OR short form thirtysix:ti OR euroqol:ti OR euro qol:ti OR eq5d:ti OR eq 5d:ti OR health utilities index:ti OR hui:ti OR hui1:ti OR hui2:ti OR hui3:ti OR ((standard NEAR1 gamble*):ti) OR quality of life*:ti OR time trade off:ti OR time tradeoff:ti OR tto:ti OR visual analog scale:ti OR patient preference:ti OR european quality of life 5 dimensions questionnaire:ti	7,553
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	0

HTA bodies' website search

Country	Database	Date	Date (update)
US	Institute for Clinical and Economic Review	2-Oct, 2020	28-Dec, 2021
Japan	Central Social Insurance Medical Council (Chuikyo)	2-Oct, 2020	28-Dec, 2021
EU-5	European Medicines Agency (EMA)	5-Oct, 2020	28-Dec, 2021
France	The French National Authority for Health (HAS)	5-Oct, 2020	28-Dec, 2021
Germany	The German Institute for Health Technology Assessment (DAHTA)	5-Oct, 2020	28-Dec, 2021
Italy	Italian Medicine Agency (AIFA)	5-Oct, 2020	28-Dec, 2021
Spain	Spanish Medicine Agency (AEMPS)	5-Oct, 2020	28-Dec, 2021
United Kingdom	National Institute for Health and Care Excellence (NICE)	5-Oct, 2020	28-Dec, 2021
United Kingdom	Scottish Medicines Consortium (SMC)	5-Oct, 2020	28-Dec, 2021
United Kingdom	All Wales Medicines Strategy Group (AWMSG)	5-Oct, 2020	28-Dec, 2021
Netherlands	Dutch National Health Care Institute (ZIN)	5-Oct, 2020	28-Dec, 2021
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH)	5-Oct, 2020	28-Dec, 2021
Australia	Medicare Services Advisory Committee (MSAC)	5-Oct, 2020	28-Dec, 2021
Brazil	National Commission for the Incorporation of Technologies in the Unified Health (CONITEC)	5-Oct, 2020	28-Dec, 2021
China	State Food and Drug Administration (SFDA)	5-Oct, 2020	28-Dec, 2021
South-Korea	National Evidence-based Healthcare Collaborating Agency (NECA)	5-Oct, 2020	28-Dec, 2021
Taiwan	Bureau of National Health Insurance (BNHI)	5-Oct, 2020	28-Dec, 2021
Sweden	Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	5-Oct, 2020	28-Dec, 2021
Denmark	Danish Medicines Council	5-Oct, 2020	28-Dec, 2021
Norway	The Norwegian Knowledge Centre for Health Services	5-Oct, 2020	28-Dec, 2021
Finland	Finnish Coordinating Center for Health Technology Assessment (FinCCHTAn)	5-Oct, 2020	28-Dec, 2021

Quality assessment and generalizability of estimates

A quality check of the utility studies was performed using the methodology from the Guide to the Methods of Technology Appraisal: The Reference Case (2013) (228). The results of the quality check are presented in Table 64.

For the reference case, it is required that the measurement of changes in HRQoL should be reported directly from patients, and the utility of these changes should be based on public preferences using a choice-based method. Moreover, the EQ-5D is the preferred measure of HRQoL in adults.

None of the 15 studies that were assessed using this reference case, used the EQ-5D measurement for all the relevant utilities. The four primary quality of life studies were the only studies reporting all of their outcomes directly from patients (197–200). These studies did not assign any utility values to these changes. Of the 11 cost-utility studies, eight studies based their utility values on public preferences using a choice-based method (32–35,38,39,103,196). They all used the study from Lloyd et al. (2006), who used the standard gamble technique with members of the general UK public (208). Besides Lloyd et al. (2006), the studies from Diaby et al. (32,33,35) also referred to two studies estimating utilities in non-small cell lung cancer (215,216). Three studies based their utilities on assessments from oncology nurses, rather than the general public (36,63,65). The cost-utility studies all failed to use changes in HRQoL that were all reported directly from patients. Rather, utility values were often directly used from public preference studies or from preferences as reported by oncology nurses.

Most studies used a utility-scale ranging from zero to one, except for two studies that utilized a utility-scale ranging from zero to one hundred (203,204).

Table 64. Utility studies compliance with the NICE reference case.

Study name	Is it reported directly from patients?	Is it based on public preferences using a choice-based method?	Is the EQ-5D measurement used?	Utility-scale
Garrison et al., 2019 (205)	N	Y	N	0–1
Tono et al., 2018 (201)	Y	N	N	0–1
Diaby et al., 2016 (55)	N	Y	N	0–1
Durkee et al., 2016 (83)	N	N	N	0–1
Wu et al., 2011 (200)	Y	N	N	0–1
Rugo et al., 2010 (204)	Y	N	N	0–100
Welslau et al., 2013 (203)	Y	N	N	0–100
Spolverato et al., 2017 (57)	N	N	N	0–1
Delea et al., 2012 (58)	N	Y	N	0–1
Diaby et al., 2020 (52)	N	Y	N	0–1
Diaby et al., 2017 (53)	N	Y	N	0–1
Mosegui et al., 2017 (54)	N	Y	N	0–1

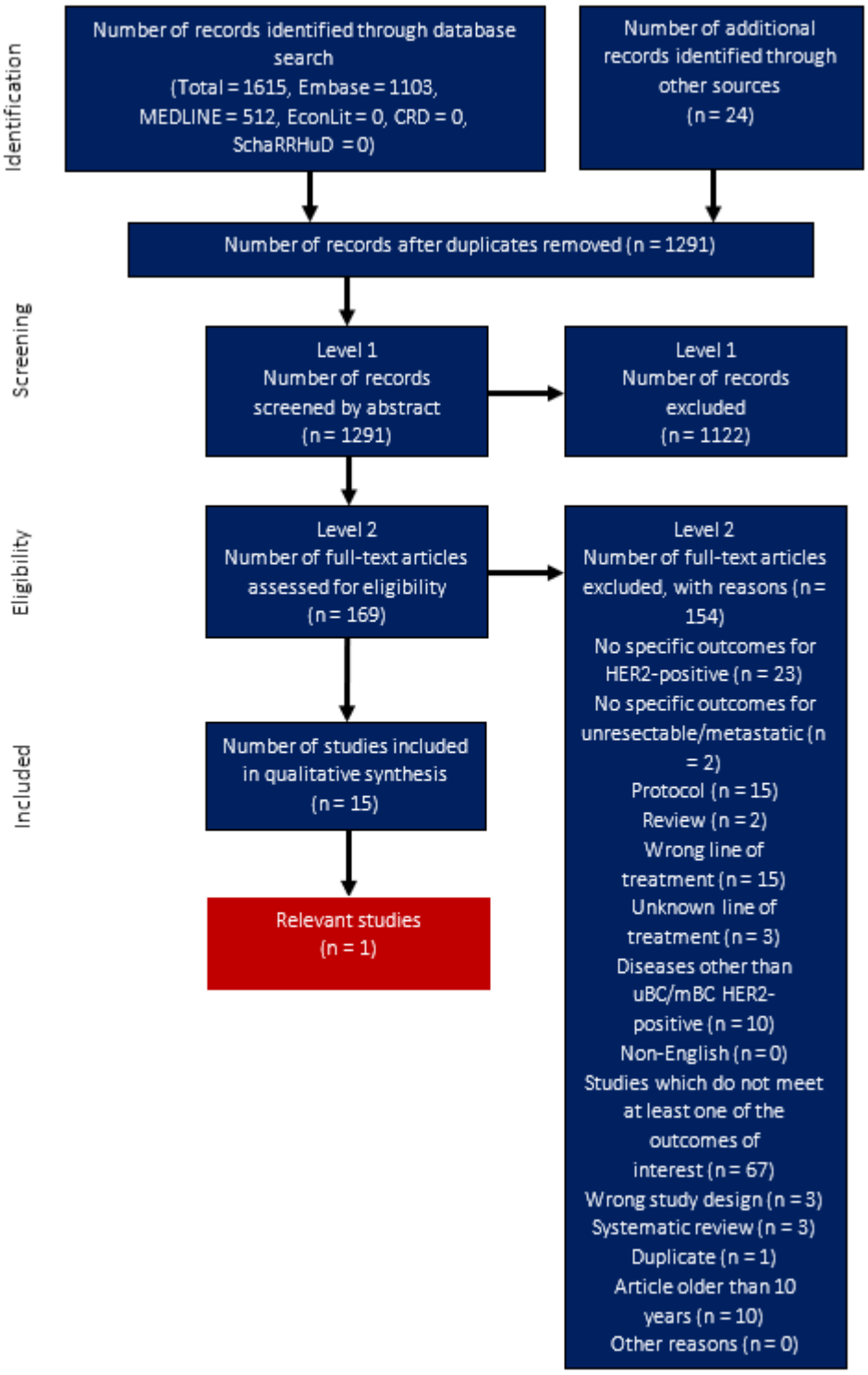
Study name	Is it reported directly from patients?	Is it based on public preferences using a choice-based method?	Is the EQ-5D measurement used?	Utility-scale
Le et al., 2016 (36)	N	N	N	0–1
Machado et al., 2012 (56)	N	Y	N	0–1
NICE, 2017 (51)	N	Y	N	0–1

Unpublished data

No relevant unpublished data was included.

Results

Figure 6.1. PRISMA flow diagram for economic utility SLR



Note: The fact that only one reason for exclusion is reported for every excluded article in Level 2 screening does not indicate that there are not multiple exclusion criteria present in the record.

Table 65. Study details and results from included utilities.

Study name	▪ Intervention ▪ Patient population	▪ Country ▪ Type of study	▪ Cohort size (response rate) ▪ Health states	▪ Method of elicitation ▪ Method of valuation	Utility and quality of life data	Source
Diaby et al., 2020 (52)	▪ Intervention: Sequence 1. 1st line: THP; 2nd line: T-DM1; 3rd line: capecitabine plus lapatinib Comparator 1: Sequence 2. 1st line: THP; 2nd line: trastuzumab plus lapatinib; 3rd line: trastuzumab plus capecitabine Comparator 2: Sequence 3. 1st line: TH; 2nd line: T-DM1; 3rd line: trastuzumab plus lapatinib Comparator 3: Sequence 4. 1st line: TH; 2nd line: trastuzumab plus lapatinib; 3rd line: trastuzumab plus capecitabine ▪ Patients with HER2-positive mBC	▪ Taiwan ▪ Cost-utility	▪ NR ▪ Markov model: – Progression-free under treatment – Treatment response ▪ Disease progression under treatment	▪ NR ▪ Adjusted based on progression status, therapy lines, and Aes. Also accounted for utility decrements associated with disease progression and treatment-related Aes	▪ Health state utilities (SD; range or 95% CI) – Progression free under treatment: 0.786 (0.113; 0.485-0.935) – Disease progression under treatment: 0.538 (0.163; 0.196-0.848) – Treatment response: +0.061 (0.012; 0.025-0.074) ▪ Disutility associated with disease progression (SD; range or 95% CI): 0.248 (0.0504; 0.289-0.087) ▪ Disutilities associated with treatment-related Aes – THP: 0.056 (0.0201; 0.098-0.016) – TH: 0.040 (0.0117; 0.058-0.011) – T-DM1: 0.009 (0.0025; 0.013-0.002) – Lapatinib plus capecitabine: 0.018 (0.007; 0.032-0.004) – Trastuzumab plus lapatinib: 0.017 (0.006; 0.026-0.004) ▪ Trastuzumab plus capecitabine: 0.040 (0.016; 0.075-0.009)	Lloyd et al., 2006 (206) Geyer et al., 2006 (207)
Garrison et al., 2019 (205)	▪ Intervention: pertuzumab plus trastuzumab and chemotherapy Comparator: trastuzumab and chemotherapy ▪ Female patients with HER2-positive BC in the adjuvant treatment	▪ United States ▪ Cost-utility	▪ NR ▪ Markov model – Invasive disease-free survival – Non-metastatic recurrence – Remission – Metastatic first line	▪ NR ▪ Adjusted by US/UK ratio	▪ Health state utilities – Metastatic first line: 0.716 – Metastatic subsequent lines: 0.472	Lloyd et al., 2006 (208)

Study name	▪ Intervention ▪ Patient population	▪ Country ▪ Type of study	▪ Cohort size (response rate) ▪ Health states	▪ Method of elicitation ▪ Method of valuation	Utility and quality of life data	Source
			– Metastatic subsequent line – Death			
Tono et al., 2018 (201)	▪ Pertuzumab, trastuzumab, and eribulin mesylate therapy ▪ Female patients with previously treated advanced HER2-positive BC	▪ Japan ▪ Feasibility	▪ 10 (20%) ▪ NR	▪ FACT-B TOI, FACT-G, FACT-B total score ▪ NR	▪ QoL scores – FACT-B TOI – At baseline: 51.3 – After 3 months: 58.3 – FACT-G – At baseline: 65.3 – After 3 months: 72.0 – FACT-B total score – At baseline: 84.7 – After three months: 93.2	Primary study
Diaby et al., 2017 (53)	▪ Intervention: Sequence 1. 1st line: THP; 2nd line: T-DM1; 3rd line: capecitabine plus lapatinib Comparator 1: Sequence 2. 1st line: THP; 2nd line: trastuzumab plus lapatinib; 3rd line: trastuzumab plus capecitabine Comparator 2: Sequence 3. 1st line: TH; 2nd line: T-DM1; 3rd line: trastuzumab plus lapatinib Comparator 3: Sequence 4. 1st line: TH; 2nd line: trastuzumab plus lapatinib; 3rd line: trastuzumab plus capecitabine ▪ Newly diagnosed patients with HER2-positive mBC	▪ Mexico ▪ Cost-utility	▪ NR ▪ Markov model: – Progression-free under treatment – Treatment response – Disease progression under treatment ▪	▪ NR ▪ Adjusted based on progression status, therapy lines, and Aes. Also accounted for utility decrements associated with disease progression and treatment-related Aes	▪ Health state utilities (SD; range or 95% CI) – Progression free on treatment: 0.786 (0.113; 0.485-0.935) – Disease progression on treatment: 0.538 (0.163; 0.196-0.848) – Treatment response: +0.061 (0.012; 0.025-0.074) ▪ Disutility associated with disease progression (SD; range or 95% CI): 0.248 (0.0504; 0.289-0.087) ▪ Disutilities associated with treatment-related Aes – THP: 0.056 (0.0201; 0.098-0.016) – TH: 0.040 (0.0117; 0.058-0.011) – T-DM1: 0.009 (0.0025; 0.013-0.002) – Lapatinib plus capecitabine: 0.018 (0.007; 0.032-0.004) – Trastuzumab plus lapatinib: 0.017 (0.006; 0.026-0.004) ▪ Trastuzumab plus capecitabine: 0.040 (0.016; 0.075-0.009)	Attard et al., 2014 (209) Doyle et al., 2008 (210) Lloyd et al., 2006 (206) Nafees et al., 2008 (211)

Study name	Intervention Patient population	Country Type of study	Cohort size (response rate) Health states	Method of elicitation Method of valuation	Utility and quality of life data	Source
Mosegui et al., 2017 **(54)**	▪ Intervention: T-DM1 ▪ Comparator: lapatinib plus capecitabine ▪ Female patients with HER2-positive mBC previously treated with trastuzumab, aged 50 or older	▪ Brazil ▪ Cost-utility	▪ 1000 ▪ Markov model: – Overall survival – Progression ▪ Death	▪ NR	▪ Health state utilities – Stable disease: 0.715 ▪ Death: 0	Lloyd et al., 2006 **(206)**
Spolverato et al., 2017 **(57)**	▪ Intervention: liver resection followed by docetaxel plus trastuzumab Comparator 1: docetaxel plus trastuzumab Comparator 2: THP ▪ Patients with BC and liver metastases	▪ NR ▪ Cost-utility	▪ NR ▪ Markov model: – Stable state – Progressing state – Hospice state ▪ Dead	▪ NR	▪ Health state utilities – Stable state: 0 65 – Progressing state: 0.29 – Hospice state: 0.48 ▪ Toll for major toxicity: -0.28	Durkee et al., 2016 **(83)** Launois et al., 1997 **(212)** Casarett et al., 2008 **(213)**
Diaby et al., 2016 **(55)**	▪ Intervention: Sequence 1 (optimal clinical sequence). 1st line: THP; 2nd line: T-DM1; 3rd line: capecitabine plus lapatinib Comparator 1: Sequence 2 (pertuzumab, no T-DM1). 1st line: THP; 2nd line: trastuzumab plus lapatinib; 3rd line: trastuzumab plus capecitabine Comparator 2: Sequence 3 (T-DM1, no pertuzumab). 1st line: TH; 2nd line: T-DM1; 3rd line: trastuzumab plus lapatinib Comparator 3: Sequence 4 (No T-DM1 or pertuzumab). 1st line: TH; 2nd line: trastuzumab plus lapatinib; 3rd line: trastuzumab plus capecitabine ▪ Newly diagnosed patients with HER2-positive mBC	▪ United States ▪ Cost-utility	▪ NR ▪ Markov model – PFS 1st line – PFS 2nd line – PFS 3rd line – Death	▪ NR ▪ Adjusted based on progression status, therapy lines, and Aes. Also accounted for utility decrements associated with disease progression and treatment-related Aes	▪ Utilities (range or 95% CI) – Progression-free: 0.786 (0.484-0.935) – Treatment response: +0.061 (0.025-0.074) ▪ Disutility associated with disease progression (range or 95% CI): -0.248 (0.087-0.289) ▪ Disutilities due to sAEs – Diarrhea: -0.088 – Neutropenia: -0.066 – Febrile neutropenia: -0.131 – Thrombocytopenia: -0.066 – Hand-foot syndrome/skin changes: -0.100 – Rash: -0.05 – Nausea/vomiting: -0.088 – Fatigue: -0.099 – Dyspnea: - 0.020 – Cardiovascular disorder: -0.058 ▪ Weighted disutilities due to sAEs, THP – Diarrhea: -0.00616 – Neutropenia: -0.03234 – Febrile neutropenia: -0.01703	Lloyd et al., 2006 **(206)** Attard et al., 2014 **(214)** Nafees et al., 2008 **(215)** Doyle et al., 2008 **(216)**

Study name	▪ Intervention ▪ Patient population	▪ Country ▪ Type of study	▪ Cohort size (response rate) ▪ Health states	▪ Method of elicitation ▪ Method of valuation	Utility and quality of life data	Source
					– Total: -0.05553 ▪ Weighted disutilities due to sAEs, TH – Neutropenia: -0.03036 – Febrile neutropenia: -0.00917 – Total: -0.03953 ▪ Weighted disutilities due to sAEs, T-DM1 – Thrombocytopenia: -0.008514 – Total: -0.00851 ▪ Weighted disutilities due to sAEs, lapatinib plus capecitabine – Diarrhea: -0.011264 – Hand-foot syndrome/skin changes: -0.007 – Total: -0.018264 ▪ Weighted disutilities due to sAEs, trastuzumab plus lapatinib – Diarrhea: -0.00616 – Rash: -0.011 – Total: -0.01716 ▪ Weighted disutilities due to sAEs, trastuzumab plus capecitabine – Diarrhea: -0.00469 – Hand-foot syndrome/skin changes: -0.03247 – Cardiovascular disorder: -0.003010 – Total: -0.04017	
Durkee et al., 2016 **(83)**	▪ Intervention: first-line pertuzumab plus docetaxel and trastuzumab ▪ Comparator: first-line docetaxel and trastuzumab ▪ Patients with HER2-positive metastatic or recurrent BC	▪ United States ▪ Cost-utility	▪ NR ▪ Markov model – Stable – Progressing (next-line therapy) – Hospice – Dead	▪ Standard gamble and visual analog scale ▪ NR	▪ Health state utilities (95% CI) – Stable: 0 65 (0.50-0.80) – Progressing: 0.29 (0.16-0.41) – Hospice: 0.48 ▪ Toll for major toxicity: -0 28	Hedden et al., 2012 **(217)** Attard et al., 2015 **(218)** Casarett et al., 2008 **(219)** Launois et al., 1996 **(220)**
Le et al., 2016 **(36)**	▪ Intervention: T-DM1 Comparator 1: lapatinib plus capecitabine Comparator 2: capecitabine monotherapy	▪ United States ▪ Cost-utility	▪ NR ▪ Markov model: – Stable disease – Respond-to-therapy	▪ NR	▪ Health state utilities (lower value-upper value) – Stable disease: 0.7 (0.5-0.8) – Respond-to-therapy: 0.84 (0.57-0.93)	Le et al., 2009 **(221)** Lloyd et al., 2006 **(206)** Elkin et al., 2004 **(222)** Montero et al., 2012 **(223)** Tolley et al., 2013 **(224)**

Study name	▪ Intervention ▪ Patient population	▪ Country ▪ Type of study	▪ Cohort size (response rate) ▪ Health states	▪ Method of elicitation ▪ Method of valuation	Utility and quality of life data	Source
	▪ Patients with progressive HER2-positive locally advanced BC or mBC, previously treated with trastuzumab and a taxane		– Disease progression ▪ Death		– Disease-progression: 0.5 (0.45-0.72) ▪ Disutilities due to Aes – Febrile neutropenia: -0.150 – Thrombocytopenia: -0.122 – Anemia: -0.120 – Nausea/vomiting: -0.103 ▪ Diarrhea: -0.103	Matza et al., 2015 (225)
Welslau et al., 2013 (203)	▪ Intervention: T-DM1 Comparator: capecitabine plus lapatinib ▪ Patients with HER2-positive, unresectable locally advanced BC or mBC, previously treated with trastuzumab and a taxane	▪ NR ▪ Clinical study (EMILIA)	▪ Intervention: 495 (NR) Comparator: 496 (NR) ▪ NR	▪ FACT-B TOI-PFB; DAS ▪ NR	▪ QoL scores (95% CI), least-squares mean difference with capecitabine plus lapatinib (reverse-scaled) – Lack of energy – Week 6: 0.22 (0.09-0.35) – Week 12: 0.13 (-0.01-0.27) – Week 18: 0.12 (-0.03-0.27) – Week 24: 0.19 (0.02-0.36) – Have nausea – Week 6: 0.32 (0.21-0.43) – Week 12: 0.15 (0.03-0.27) – Week 18: 0.07 (-0.06-0.20) – Week 24: 0.15 (-0.01-0.30) – Trouble meeting needs of family – Week 6: 0.23 (0.11-0.36) – Week 12: 0.11 (-0.02-0.23) – Week 18: 0.03 (-0.11-0.17) – Week 24: 0.07 (-0.09-0.23) – Have pain – Week 6: 0.13 (0.01-0.25) – Week 12: 0.06 (-0.07-0.19) – Week 18: 0.03 (-0.11-0.18) – Week 24: 0.04 (-0.12-0.21) – Bothered by side effects – Week 6: 0.58 (0.44-0.72) – Week 12: 0.42 (0.27-0.56) – Week 18: 0.41 (0.25-0.57) – Week 24: 0.34 (0.16-0.52) – Feel ill – Week 6: 0.31 (0.19-0.43) – Week 12: 0.23 (0.10-0.35) – Week 18: 0.16 (0.03-0.30)	Primary study

Study name	▪ Intervention ▪ Patient population	▪ Country ▪ Type of study	▪ Cohort size (response rate) ▪ Health states	▪ Method of elicitation ▪ Method of valuation	Utility and quality of life data	Source
					– Week 24: 0.13 (-0.02-0.28) – Forced to spend time in bed – Week 6: 0.17 (0.05-0.28) – Week 12: 0.19 (0.07-0.31) – Week 18: 0.03 (-0.10-0.16) – Week 24: 0.04 (-0.11-0.18)	
Delea et al., 2012 **(58)**	▪ Intervention: lapatinib plus capecitabine Comparator 1: capecitabine monotherapy Comparator 2: trastuzumab plus capecitabine ▪ Female patients with HER2-positive mBC who have received prior treatment with trastuzumab	▪ United Kingdom ▪ Cost-utility	▪ NR ▪ Partitioned survival model: – Pre-progression – Post-progression	▪ EQ-5D ▪ NR	▪ Health state utilities (SD) – Pre-progression: 0.694 (0.01) ▪ Disutility for disease progression: 32% or 0.22 in absolute terms (0.07)	Lloyd et al., 2006 **(206)** Johnson et al., 2005 **(226)**
Machado et al., 2012 **(56)**	▪ Intervention: lapatinib plus capecitabine Comparator 1: capecitabine monotherapy Comparator 2: trastuzumab plus capecitabine ▪ Brazilian female patients with HER2-positive mBC who were previously treated with trastuzumab	▪ Brazil ▪ Cost-utility	▪ NR ▪ Partitioned survival model: – Progression-free survival – Disease progression – Death	▪ EQ-5D ▪ NR	▪ Health state utilities (range of variation) – Progression-free survival: 0.694 (±10%) ▪ Disutility for disease progression: 32% or 0.22 in absolute terms (±10%) –	Zhou et al., 2009 **(227)** Lloyd et al., 2006 **(206)**
Wu et al., 2011 **(200)**	▪ Intervention: lapatinib plus trastuzumab Comparator: lapatinib ▪ Female patients with HER2-positive mBC who progressed on at least one T-containing regimen in the metastatic setting ▪	▪ NR ▪ Clinical study (EGF104900)	▪ 148 RR at baseline: – Lapatinib plus trastuzumab: 142/148 (96%) – Lapatinib: 141/148 (95%) RR at week 4: – Lapatinib plus trastuzumab: 108/139 (78%) – Lapatinib: 120/143 (84%) RR at week 12:	▪ FACT-B, FACT-G NR	▪ QoL scores (SD), intervention – FACT-B total scores at baseline (0-114): 98.7 (21.17) – FACT-G total scores at baseline (0-108): 76.3 (16.92) – TOI scores at baseline (0-92): 60.7 (14.70) – Physical well-being (0-28) – Baseline: 20.5 (5.30) – Changes relative to baseline – Week 4: -0.5 (3.49) – Week 12: -0.4 (3.36) – Week 16: -0.6 (3.65) – Week 24: -0.1 (3.20)	Primary study

Study name	▪ Intervention ▪ Patient population	▪ Country ▪ Type of study	▪ Cohort size (response rate) ▪ Health states	▪ Method of elicitation ▪ Method of valuation	Utility and quality of life data	Source
			– Lapatinib plus trastuzumab: 60/78 (77%) – Lapatinib: 54/79 (68%) RR at week 16: – Lapatinib plus trastuzumab: 46/70 (66%) – Lapatinib: 41/55 (75%) RR at week 24: – Lapatinib plus trastuzumab: 30/42 (71%) – Lapatinib: 29/32 (91%) RR at week 32: – Lapatinib plus trastuzumab: 19/30 (63%) – Lapatinib: 18/26 (69%) RR at week 40: – Lapatinib plus trastuzumab: 10/10 (100%) – Lapatinib: 7/14 (50%) RR at week 48: – Lapatinib plus trastuzumab: 5/7 (71%) – Lapatinib: 3/8 (38%) RR at withdrawal: – Lapatinib plus trastuzumab: 66/137 (48%)		– Withdrawal: -2.7 (5.36) – Social/family well-being (0-28) – Baseline: 22.7 (4.93) – Changes relative to baseline – Week 4: -0.5 (3.38) – Week 12: -0.1 (3.01) – Week 16: -0.6 (2.80) – Week 24: -0.6 (2.75) – Withdrawal: -0.9 (4.27) – Emotional well-being (0-24) – Baseline: 15.5 (4.97) – Changes relative to baseline – Week 4: 0.5 (3.16) – Week 12: 0.7 (3.54) – Week 16: 0.5 (3.76) – Week 24: 0.2 (4.55) – Withdrawal: -2.0 (3.68) – Functional well-being (0-28) – Baseline: 17.6 (6.21) – Changes relative to baseline – Week 4: -0.0 (3.93) – Week 12: -0.1 (4.02) – Week 16: -0.2 (4.09) – Week 24: -0.6 (5.67) – Withdrawal: -2.2 (5.23) – Breast cancer subscale (0-36) – Baseline: 22.7 (5.85) – Changes relative to baseline – Week 4: 0.3 (3.86) – Week 12: 1.3 (4.01) – Week 16: 0.8 (4.09) – Week 24: 1.3 (3.96) – Withdrawal: -0.3 (4.16) ▪ QoL scores (SD), comparator – FACT-B total scores at baseline (0-144): 97.2 (21.85) – FACT-G total scores at baseline (0-108): 74.8 (18.56) – TOI scores at baseline (0-92): 59.8 (15.03)	

Study name	▪ Intervention ▪ Patient population	▪ Country ▪ Type of study	▪ Cohort size (response rate) ▪ Health states	▪ Method of elicitation ▪ Method of valuation	Utility and quality of life data	Source
			– Lapatinib: 71/132 (54%) – NR		– Physical well-being (0-28) – Baseline: 20.0 (6.20) – Changes relative to baseline – Week 4: -1.0 (3.96) – Week 12: -1.6 (3.68) – Week 16: -0.7 (4.72) – Week 24: -1.2 (4.28) – Withdrawal: -3.0 (5.50) – Social/family well-being (0-28) – Baseline: 22.3 (5.46) – Changes relative to baseline – Week 4: 0.2 (4.53) – Week 12: -1.0 (4.86) – Week 16: 0.4 (6.89) – Week 24: -0.2 (5.15) – Withdrawal: -0.1 (3.64) – Emotional well-being (0-24) – Baseline: 15.1 (5.37) – Changes relative to baseline – Week 4: -0.1 (3.50) – Week 12: -0.3 (3.01) – Week 16: -0.1 (3.28) – Week 24: 0.4 (3.92) – Withdrawal: -2.0 (4.09) – Functional well-being (0-28) – Baseline: 17.4 (6.29) – Changes relative to baseline – Week 4: -0.5 (4.11) – Week 12: -1.3 (4.49) – Week 16: -1.3 (6.41) – Week 24: -1.2 (5.13) – Withdrawal: -2.2 (4.52) – Breast cancer subscale (0-36) – Baseline: 22.3 (5.68) – Changes relative to baseline – Week 4: 0.9 (3.91) – Week 12: 1.0 (3.72) – Week 16: 1.0 (3.65) – Week 24: 1.0 (4.07) – Withdrawal: 0.0 (4.52)	

Study name	Intervention Patient population	Country Type of study	Cohort size (response rate) Health states	Method of elicitation Method of valuation	Utility and quality of life data	Source
Rugo et al., 2010 (204)	▪ Trastuzumab monotherapy ▪ Female patients with HER2-positive mBC	▪ NR ▪ Clinical study (H0649)	▪ 222 (NR) – NR	▪ QLQ-C30; BR-23 ▪ NR	▪ QoL scores (SD), up to disease progression – Global QoL – Baseline: 62.2 (21.0) – Change from baseline: – Week 12: 4.3 (20.1) – Week 24: 1.1 (21.3) – Week 36: -0.5 (21.7) – Physical functioning – Baseline: 75.7 (24.6) – Change from baseline: – Week 12: 0.0 (22.8) – Week 24: -0.3 (24.4) – Week 36: -2.2 (24.4) – Social functioning – Baseline: 70.4 (29.5) – Change from baseline: – Week 12: 6.5 (24.8) – Week 24: 4.8 (26.0) – Week 36: 1.9 (25.3) – Role functioning – Baseline: 67.7 (38.1) – Change from baseline: – Week 12: 1.0 (32.8) – Week 24: 0.0 (33.7) – Week 36: -1.4 (32.5) – Fatigue – Baseline: 33.9 (23.4) – Change from baseline: – Week 12: -0.1 (23.3) – Week 24: 0.4 (23.0) – Week 36: 2.0 (23.2) ▪ QoL scores (SD), up to and beyond disease progression – Global QoL – Baseline: 62.2 (20.6) – Change from baseline: – Week 12: 3.6 (20.1) – Week 24: -3.2 (23.8) – Week 36: -6.5 (24.3)	Primary study

Study name	▪ Intervention ▪ Patient population	▪ Country ▪ Type of study	▪ Cohort size (response rate) ▪ Health states	▪ Method of elicitation ▪ Method of valuation	Utility and quality of life data	Source
					– Physical functioning – Baseline: 75.8 (24.4) – Change from baseline: – Week 12: -1.0 (23.4) – Week 24: -5.5 (27.6) – Week 36: -9.1 (28.2) – Social functioning – Baseline: 70.6 (29.1) – Change from baseline: – Week 12: 5.7 (24.6) – Week 24: 0.5 (29.2) – Week 36: -4.4 (28.0) – Role functioning – Baseline: 67.1 (37.8) – Change from baseline: – Week 12: 0.3 (33.4) – Week 24: -3.3 (34.0) – Week 36: -7.2 (35.2) – Fatigue – Baseline: 34.2 (23.3) – Change from baseline: – Week 12: 0.8 (23.5) – Week 24: 4.8 (24.8) Week 36: 7.6 (25.2)	
NICE, 2017 **(51)**	▪ Intervention: T-DM1 Comparator 1: lapatinib plus capecitabine Comparator 2: trastuzumab plus capecitabine ▪ Adult patients with HER2-positive unresectable locally advanced BC or mBC who previously received trastuzumab and a taxane, separately or in combination	▪ United Kingdom ▪ Cost-utility	▪ NR ▪ Partitioned survival model: – Progression-free survival – Progressed disease – Death	NR	▪ Health state utilities – Progression-free survival – T-DM1: 0.807 – Lapatinib plus capecitabine: 0.8 – Trastuzumab plus capecitabine: 0.8 – Capecitabine: 0.792 – Progressed disease: 0.53	Lloyd et al., 2006 **(206)**
Note: NR – Not reported; CI – Confidence Interval; SD – Standard Deviation; RR – Response Rate; sAE – serious Adverse Event						

Appendix I Mapping of HRQoL data

No mapping was conducted. Utility scores for the EQ-5D-5L dimensions was computed using the Danish value sets.

From DB03, Utility scores based on progression-free and progression health states were derived using Generalized Estimating Equations (GEE) regressions. GEEs gives similar results to mixed models in the case of linear models and provides consistent estimates even if the correlation structure is misspecified. EQ-5D-5L utility scores from all available timepoints, including baseline, were included in the GEE as dependent variable. Treatment response (progressed versus progression-free) status at the corresponding visit and treatment arm were included as independent variables in a stepwise fashion, starting with treatment response. The model with lowest quasi-likelihood under the independence model criterion (QIC) – an metric similar to AIC for models based on quasi-likelihood such as GEEs – was retained as the best fitting model. The mean utility values and associated 95% CIs for health states progression and progression-free were derived from the model using least square means. The GEEs were fitted with an independence working correlation structure and a robust sandwich variance estimator was be used (76).

Table 66 presents the utility values by health-state progressed and non-progressed overall (model 1) and by treatment group (model 2).

Table 66. Health state utility values derived from DB03 for T-DXd and T-DM1

Health-Status	T-DXd		T-DM1	
	n[1]	LSM (SE) (95% CI)	n[1]	LSM (SE) (95% CI)
Progression-free (CR/PR/SD)	2495	0.8793 (0.8625, 0.8960)	1479	0.8711 (0.8559, 0.8864)
Progressed (PD)	204	0.8390 (0.8092, 0.8687)	466	0.8308 (0.7995, 0.8621)

Abbreviations: CR, complete response, CI, confidence interval; PD, progressed disease; PR, partial response; SD, stable disease; SE, standard error; LSM, least square mean T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Notes: 1) Number of visits/timepoints with the condition

Appendix J Probabilistic sensitivity analyses

Parameters for the probabilistic analysis is provided in Table 67 to Table 70.

To assess the uncertainty associated with parameters, probabilistic sensitivity analyses were conducted. Probabilistic sensitivity analyses included all relevant 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% standard error 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 normal distribution defined by the mean and standard error.
- Most other probabilities can be sampled based on beta distribution defined by the estimated alpha and beta value.

Table 67. Probabilistic parameters

Parameter label	Mean/Base case	SE	α	β	Distribution
OS HR - T-DXd versus T-DM1	0.55	0.06			Log normal
RDI - T-DXd	0.9259		6.48	0.52	Beta
RDI - T-DM1 - q3w	0.9444		4.62	0.27	Beta
IV administration cost	744.00	74.40			Normal
Specialist visit - frequency (per week)	0.23	0.02			Normal
Blood tests - frequency (per week)	0.23	0.02			Normal
ECHO-scanning - frequency (per week)	0.08	0.01			Normal
CT-scanning - frequency (per week)	0.10	0.01			Normal
Specialist visit - unit cost	1 379.00	137.90			Normal
Blood tests - unit cost	244.00	24.40			Normal
ECHO-scanning - unit cost	1 979.00	197.90			Normal
CT-scanning - unit cost	1 910.00	191.00			Normal
Terminal care cost	71 609.64	7 160.96			Normal
AE - T-DXd - Neutrophil count decreased - events	19.1%		49	208	Beta
AE - T-DXd - Anemia - events	5.8%		15	242	Beta

AE - T-DXd - White blood cell count decreased - events	6.6%		17	240	Beta
AE - T-DXd - Platelet count decreased - events	7.0%		18	239	Beta
AE - T-DXd - Nausea - events	6.6%		17	240	Beta
AE - T-DXd - Increased AST	0.8%		2	255	Beta
AE - T-DXd - Interstitial lung disease	0.8%		2	255	Beta
AE - T-DXd - Left ventricular ejection fraction decrease	0.0%		0	257	Beta
AE - T-DM1 - Neutrophil count decreased	3.1%		8	253	Beta
AE - T-DM1 - Anemia	4.2%		11	250	Beta
AE - T-DM1 - White blood cell count decreased*	0.4%		1	260	Beta
AE - T-DM1 - Platelet count decreased	24.9%		65	196	Beta
AE - T-DM1 - Nausea	0.4%		1	260	Beta
AE - T-DM1 - Increased AST	5.0%		13	248	Beta
AE - T-DM1 - Interstitial lung disease	0.0%		0	261	Beta
AE - T-DM1 - Ejection fraction decreased	0.0%		0	261	Beta
AE cost - Neutrophil count decreased	-	0.00			Normal
AE cost - Anemia	61 074.00	6 107.40			Normal
AE cost - White blood cell count decreased	-	0.00			Normal
AE cost - Nausea	2 041.00	204.10			Normal
AE cost - Increased AST	-	0.00			Normal
AE cost - Interstitial lung disease	45 635.00	4 563.50			Normal
AE cost - Ejection fraction decreased	31 725.00	3 172.50			Normal
Utilities - DB03 - PF (on T-DXd)	0.879		1 055.27	144.86	Beta
Utilities - DB03 - PF (on-T-DM1)	0.871		1 233.96	182.59	Beta
Utilities - DB03 - PF (off-treatment)	0.875		11.60	1.65	Beta
Utilities - DB03 - Progressed disease	0.83		539.06	106.60	Beta
Proportion with 3L treatment	0.90		4	0.21	Beta
Subsequence treatment - Tucatinib after T-DM1	0.70		29.3	12.56	Beta
Subsequence treatment - Tucatinib after T-DXd	0.20		29.3	12.56	Beta

Key: AE: adverse event, OS: overall survival, PFS: progression-free survival, IV: Intravenous, T-DXd: trastuzumab deruxtecan, T-DM1: trastuzumab emtansine.

See CEA model sheet 'Cholesky' for details on the survival curves.

Table 68. Probabilistic parameters - OS

T-DXd & T-DM1 - OS				
Exponential	Variance			
Rate	0.049170947	-0.01887		
	-0.018867922	0.018868		
Weibull	Covarience matrix (C)			
Scale	0.0205	-0.0102	-0.006	
Shape	-0.0102	0.0098	-0.0036	
	-0.006	-0.0036	0.0269	
Gompertz	Covarience matrix (C)			
Scale	0.049240659	-0.00296	-0.01723	
Shape	-0.00296159	0.000289	-0.00016	
	-0.017233394	-0.00016	0.049259	
Log-logistic	Covarience matrix (C)			
Scale	0.019983224	-0.00936	-0.00764	
Shape	-0.009358411	0.009654	-0.00337	
	-0.007642324	-0.00337	0.028059	
Log-normal	Covarience matrix (C)			
Meanlog	0.031511729	0.011243	-0.01089	
Sdlog	0.011243448	0.007651	0.00279	
	-0.010889623	0.00279	0.035936	
Generalized gamma	Covarience matrix (C)			
Mu	0.025681724	0.025205	-0.01961	-0.00479
Sigma	0.025205335	0.098872	-0.12154	0.016976
Q	-0.019609466	-0.12154	0.164983	-0.01835
	-0.004792864	0.016976	-0.01835	0.030798

Table 69. Probabilistic parameters – PFS – TDM1

Trastuzumab emtansine - PFS			
Exponential	Variance		

Rate	0.006329		
Weibull	**Covarience matrix (C)**		
Scale	0.004156	-0.0007	
Shape	-0.0007	0.006667	
Gompertz	**Covarience matrix (C)**		
Scale	0.000328	-0.00155	
Shape	-0.00155	0.013676	
Log-logistic	**Covarience matrix (C)**		
Scale	0.004243	-0.00111	
Shape	-0.00111	0.007448	
Log-normal	**Covarience matrix (C)**		
Meanlog	0.007259	0.001421	
Sdlog	0.001421	0.003566	
Generalized gamma	**Covarience matrix (C)**		
Mu	0.022943	0.004093	0.031267
Sigma	0.004093	0.003774	0.003779
Q	0.031267	0.003779	0.061684

Table 70. Probabilistic parameters – PFS – TDXd

Trastuzumab deruxtecan - PFS			
Exponential	**Variance**		
Rate	0.011494		
Weibull	**Covariance matrix (C)**		
Scale	0.008899	-0.00582	
Shape	-0.00582	0.010105	
Gompertz	**Covariance matrix (C)**		
Scale	0.000313	-0.00288	
Shape	-0.00288	0.037948	
Log-logistic	**Covariance matrix (C)**		

Scale	0.008652	-0.00501	
Shape	-0.00501	0.010157	
Log-normal	**Covariance matrix (C)**		
Meanlog	0.013522	0.006097	
Sdlog	0.006097	0.007049	
Generalized gamma	**Covariance matrix (C)**		
Mu	0.025371	-0.0138	0.05163
Sigma	-0.0138	0.039583	-0.08395
Q	0.05163	-0.08395	0.217902

Table 71. Probabilistic parameters – OS independent -TDM1

Exponential			**Variance**		
Rate	0.013511		0.018868		
Weibull			**Covarience matrix (C)**		
Scale	54.56813		0.016044	-0.0187	
Shape	1.258169		-0.0187	0.033709	
Gompertz			**Covarience matrix (C)**		
Scale	0.010724		0.000508	-0.00488	
Shape	0.025242		-0.00488	0.065751	
Log-logistic			**Covarience matrix (C)**		
Scale	45.64906		0.015701	-0.01683	
Shape	1.35382		-0.01683	0.031016	
Log-normal			**Covarience matrix (C)**		
Meanlog	4.085276		0.047645	0.019456	
Sdlog	1.528415		0.019456	0.012392	

Generalized gamma			Covarience matrix (C)		
Mu	4.028403		0.022943	0.004093	0.031267
Sigma	0.977675		0.004093	0.003774	0.003779
Q	0.708918		0.031267	0.003779	0.061684

Table 72. Probabilistic parameters – OS independent -TDXd

Exponential			**Variance**		
Rate	0.007745		0.030303		
Weibull			**Covarience matrix (C)**		
Scale	59.01456		0.024758	-0.02868	
Shape	1.659739		-0.02868	0.044231	
Gompertz			**Covarience matrix (C)**		
Scale	0.003895		0.000672	-0.00796	
Shape	0.065829		-0.00796	0.124576	
Log-logistic			**Covarience matrix (C)**		
Scale	53.06295		0.024717	-0.02721	
Shape	1.747268		-0.02721	0.041525	
Log-normal			**Covarience matrix (C)**		
Meanlog	4.316125		0.068254	0.032486	
Sdlog	1.272249		0.032486	0.020032	
Generalized gamma			**Covarience matrix (C)**		
Mu	4.108		0.025371	-0.0138	0.05163
Sigma	0.68919		-0.0138	0.039583	-0.08395
Q	0.82827		0.05163	-0.08395	0.217902