Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende trastuzumab deruxtecan til behandling af voksne patienter med ikke-resekterbar eller metastatisk HER2-lav brystkræft

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

Note on the DMC assessment report of Enhertu (T-DXd) as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC2+/ISH-) breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.

AstraZeneca (AZ) and Daiichi-Sankyo (DS) want to thank the Secretariat for having a good and open dialogue during the assessment process. Overall, the Secretariat and the Expert committee acknowledge the positive results from the Destiny Breast-04 (DB-04) trial on the HER2-low metastatic breast cancer (mBC) population. The trial demonstrates significant benefit from treatment with T-DXd in a head-to-head study compared to current standard of care in Denmark (chemotherapy) and mature progression-free survival (PFS) and overall survival (OS) data are available. The recently updated DBCG guidelines for mBC also reflect that Danish clinical experts acknowledge the DB-04 data by recommending T-DXd for patients with HER2-low mBC, in line with the approved EMA label for both HR+ and HR- patients.

In response to the DMC evaluation report, there are a few important errors and topics that we would like to highlight that we do not think the report addressed adequately. **The most important difference between the company and the Secretariat base-case is the selection of parametric curves for OS extrapolation. The only argument the DMC puts forward for considering the more pessimistic curves is the fit to updated data presented as ESMO 2023, which the Secretariat has digitalized, and present in Figure 10. However, data presented in this figure is not from the DB-04 trial, which is clearly shown by the crossing of the curves at ~12 months.** It is difficult to understand and follow the DMC validation process with regards to data used, consultation of clinical experts and how the selected parametric curves have been validated given the brief description. Consequently, the following should be noted regarding the currently preferred curves:

- DMC states that the OS curves are most 'clinically plausible'. However, in identified relevant studies (e.g., two registrational studies on eribulin by Twelves et al, requested by EMA) patients treated with chemotherapy, have approximately twice as high survival rate at 4 years compared to the curves DMC deem most clinically plausible. We are not aware of any data that supports these conclusions by the DMC. Yet, if this is in line with clinical expert opinion in Denmark, it should be noted in the report that the DMC expects the survival after T-DXd to be significantly worse than for those patients treated with chemotherapy today. **A rationale for this worse prognosis should also be added to the assessment report to inform decision-making.**
- While extrapolations of OS data in general are associated with some uncertainty, there are relevant external data on this specific patient population to apply to validate landmark survival rates, which the DMC do not present or discuss. We appreciate that it is appropriate to test the uncertainty of long-term outcomes in Danish clinical practice. However, the adjustments made to the company base-case rather represent extreme scenarios and are not reasonable for any base-case.
- DMC guidelines state that smoothed-hazard plots should be reviewed for curve fitting. DMC has selected curves, which after 35 months, indicates that there will be a higher risk of dying for T-DXd treated patients than for chemotherapy treated patients. Treatment effect may be reduced over time, but there is no evidence supporting that the treatment effect of T-DXd is lower than for TPC.
- Finally, the DMC did not request updated parametric models based on the latest data cut in DB-04. This could have been provided by AZ and DS and would have provided a more scientifically sound and transparent basis for decision-making. Parametric curves change when data are updated hence the best practice is to fit curves to the same study data used for selecting appropriate curves.
- Other curves have been put forward as appropriate to use in the base-case analysis to inform decision-making, by other HTA bodies. For example, the Norwegian Medicine Agency[1], which is the HTA authority with the most similar guidelines to DMC, preferred independent log-logistic curves. It is important to note that this is in line with prior published data for these patients, referenced to above. Consequently, if these were to be applied to the company base case in the Danish setting, we would see a cost of approx. 700k DKK per quality adjusted life year (QALY) gained (700k/LY), and 900k

[1] Beslutningsforum 25092023 https://www.nyemetoder.no/metoder/trastuzumabderukstekan-enhertu-indikasjon-iv/

(800k/LY) DKK using the DMC preferred base-case. The Swedish HTA body TLV preferred like the Norwegian Medicine Agency, log-logistic curves but assumed proportional hazards. This means that both HTA bodies have assessed T-DXd closer in line with our data and base case compared to this assessment (Norway: QALY: 0.72, Life-year: 0.86 and Sweden: 0.62 QALY, Life-year: 0.74 compared to Denmark (DMC): QALY: 0.31-0.56, Life-year: 0.35-0.66). The two scenarios presented by the DMC include more conservative assumptions on OS, compared to the evaluations in Norway and Sweden. To the best of our knowledge there are no clinical rationale or evidence to support the assumption that patients in Denmark would have worse survival outcomes.

- Patients included in DB-04 could have had 1 or 2 prior lines of chemotherapy in the metastatic setting. However, the EMA-approved indication and ESMO and DBCG guidelines recommend T-DXd to be used following 1 line of chemotherapy for mBC. The latest data cut from DB-04 (after this submission, but shared with the Secretariat), shows that the OS HR is trending most favorably for patients with 1 prior line of chemotherapy, compared to 2 prior lines. Hence, since T-DXd is to be implemented according to current DBCG guidelines in clinical practice, outcomes are more likely to trend more positive than expectations based on the whole of the DB04 population, showing again why the two scenarios presented by the DMC may be viewed as too pessimistic.

With regards to vial sharing, we would like to emphasize that it is an extreme scenario to assume 0% in the DMC base-case. According to clinical experts, we know that vial sharing, and treatment days are conducted and coordinated in clinical practice and will become more frequent with higher patient numbers, yet it is unclear to what extent. Hence the uncertainty associated with the costs of the intervention is overestimated and consequently the budget impact. In the evaluation of the T-DXd indication in HER2 positive patients (DB-03) the DMC stated that waste over time would be reduced due to planning and increase in patient numbers, why a sensitivity analysis was made where 50% of treatments could be performed without waste. An appropriate way to show the uncertainty associated with this parameter would therefore be to identify a reasonable assumption and show the implications of varying the value in scenario analyses. With the potential introduction of DB-04 in Danish clinical practice, more patients will be receiving T-DXd and hence it will become easier to coordinate administration in clinics.
After receiving the DMC draft assessment report, we reached out to clinicians in different Danish regions which again confirmed that clinical practice (also for T-DXd) would be to always optimize patient flow and thus sharing vials in departments to avoid waste.

We acknowledge that the size of the HR- population is small in our trial and that smaller populations may bring uncertainty to the results. However, the HR- population size in DB-04 is reflective of the prevalence of HR- mBC within the population of HER2-low mBC as a whole (approx. 10%). Most importantly, the hazard ratio for both PFS and OS in the HR- subgroup are numerically even more favourable than for HR+ and hence it was included in the EMA approved label. Furthermore, T-DXd is recommended for HR- HER2low mBC in recently updated ESMO 2023 and DBCG guidelines and is reimbursed for these patients by similar health care systems such as Norway, Sweden, and Finland.

Lastly, we consider it inappropriate to use the same utility values across treatment arms, especially in the progression-free health state. By not considering the positive impact of T-DXd on health-related quality of life, as demonstrated in DB-04 (DB-04 CSR), the economic analysis may not fully capture the health benefits of treating patients with T-DXd versus using TPC.

In summary there are decisions and assumptions in the draft evaluation report that we hope will be addressed differently in the final version. T-DXd has demonstrated significant OS benefit in HER2-low mBC compared to TPC. Lastly, T-DXd is already funded for HER2-low mBC patients in the other Nordic countries (Norway, Sweden, and Finland) and we ask for a decision to be made for T-DXd so patients in Denmark with HER2-low mBC may also be given access to a medicine with clinically significant impact on survival.

Kind Regards

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12.04.2024
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	24.04.2024
Leverandør	Daiichi Sankyo i samarbejde med AstraZeneca
Lægemiddel	Enhertu (trastuzumab deruxtecan, T-DXd)
Ansøgt indikation	Enhertu til behandling af voksne patienter med ikke-resekterbar eller metastatisk HER2-lav brystkræft
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende volumenbaserede aftale på Enhertu (trastuzumab deruxtecan, T-DXd):

Tabel 1: Forhandlingsresultat

Trin	Antal pakninger	Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
1	0-6000	Enhertu	100 mg	1 stk.	11.089	[redacted]	[redacted]
2	6001-12001	Enhertu	100 mg	1 stk.	11.089	[redacted]	[redacted]
3	12001-40000	Enhertu	100 mg	1 stk.	11.089	[redacted]	[redacted]

[redacted]

Tilbuddet med volumenbaseret aftale er betinget af Medicinrådets anbefaling.

[redacted]

Konkurrencesituationen

Enhertu er den eneste behandling til denne indikation.

[redacted]

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Trin	Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 12 mdr. (SAIP, DKK)**
1	Enhertu	100 mg	1 stk.	5,4 mg/kg IV hver tredje uge*	[redacted]	[redacted]
2	Enhertu	100 mg	1 stk.	5,4 mg/kg IV hver tredje uge*	[redacted]	[redacted]
3	Enhertu	100 mg	1 stk.	5,4 mg/kg IV hver tredje uge*	[redacted]	[redacted]

*Patientvægt 71 kg if. Medicinrådets vurderingsrapporten

[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
Sverige	Anbefalet	Link til anbefaling
England	Under vurdering	Link til vurdering

Konklusion

[redacted]

Medicinrådet

Application for the assessment of Enhertu (T-DXd) as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy

Submitted 12.04.2023
2nd version submitted 20.10.2023

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Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
[redacted]	**Confidential information**

1. Basic information

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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. Enhertu in breast cancer is handled in an alliance between Daiichi Sankyo and AstraZeneca.
ATC code	L01FD04 (2022)
Pharmacotherapeutic group	Antineoplastic agents, HER2 (Human Epidermal Growth Factor Receptor 2) inhibitors

Overview of the pharmaceutical	
Active substance(s)	Trastuzumab Deruxtecan
Pharmaceutical form(s)	I.V. 100mg in vial. For solution
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)	Enhertu (T-DXd) as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy (CHMP December 2022)
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 one or more prior anti-HER2-based regimens
Will dispensing be restricted to hospitals?	Yes labelled BEGR
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	100 mg concentrate powder is provided in glass vial, where each vial reconstitutes a concentration of 20 mg/ mL
Orphan drug designation	No

2. Abbreviations

2L	Second line		KM	Kaplan-Meier
2L+	Second line and beyond		LVEF	Left Ventricular Ejection Fraction
3L	Third line		LY	Life years
3L+	Third line and beyond		MAPK	Mitogen-activated kinases
ADC	Antibody drug conjugate		mBC	Metastatic Breast Cancer
AE	Adverse event		N/A	Not available
ASCO	American Society of Clinical Oncology		NE	Not estimable

ATC	Anatomic Therapeutic Chemical classification system		ORR	Overall response rate
AZ	AstraZeneca		OS	Overall survival
BICR	Blinded Independent Central Review		PC	Physician's choice
BOR	Best overall response		PD-1	Programmed Death protein 1
BRCA	Breast Cancer susceptibility gene		PD-L1	Programmed Death Ligand 1
CEP17	chromosome enumeration probe 17		PFS	Progression-free survival
CI	Confidence interval		PH	Proportional Hazard
CR	Complete response		PI3K/AKT	Phosphatidylinositol-3-Kinase and Protein Kinase B
CTCAE	common terminology criteria for adverse events		PS	Partial Response
DB04	DESTINY-Breast04 study		Q3W	Every three weeks
DB06	DESTINY-Breast06 study		QALY	Quality adjusted life years
DB08	DESTINY-Breast08 study		QoL	Quality of Life
DoR	Duration of response		RECIST	Response Evaluation Criteria in Solid Tumours
DS	Daiichi Sankyo		REML	Restricted maximum likelihood
DXd	The payload of T-DXd, a potent topoisomerase I inhibitor		RWE	Real World Evidence
ECOG	Eastern Cooperative Oncology Group		SD	Stable Disease
ESMO	European Society for Medical Oncology		SD	Standard deviation
FISH	Fluorescent in-situ hybridisation		SLR	Systematic literature research
HER2	Human Epidermal Growth Factor receptor 2		SoC	Standard of Care
HR	Hormone Receptor		T-DXd	Trastuzumab deruxtecan
HR	Hazard ratio		TEAE	Treatment emergent adverse event
HRQoL	Health Related Quality of Life		TNBC	Triple Negative Breast Cancer
ICER	Incremental cost-effectiveness ratio		TPC	Treating Physician's Choice
IHC	Immunohistochemistry		TTD	Time to treatment discontinuation
ILD	Interstitial lung disease		TTR	Time to response
ISH	in-situ hybridisation		uBC	Unresectable Breast Cancer
ITT	Intention to treat		vs	Versus
IV	intravenous		WTP	Willingness to pay

3. Tables and Figures

Figures

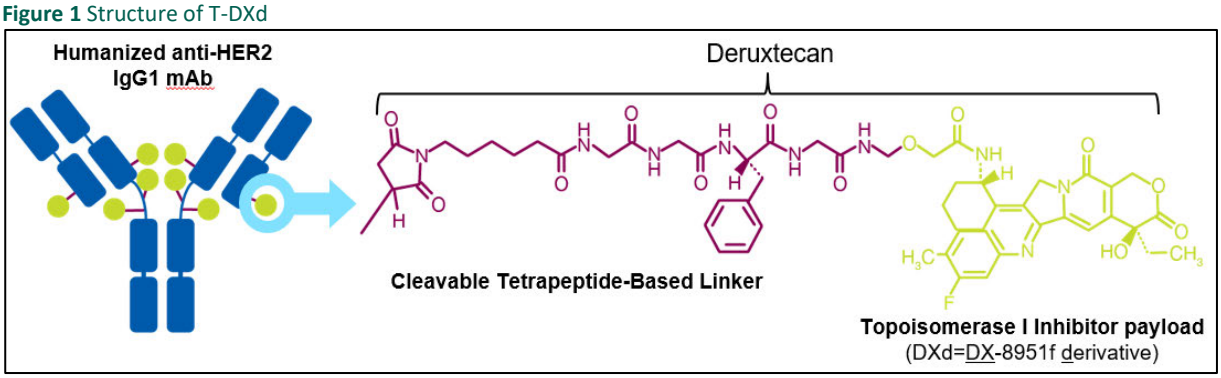
Tables

4. Summary effect, safety and QALY

Enhertu (T-DXd)

Trastuzumab Deruxtecan (T-DXd) is a novel next generation HER2-targeted antibody-drug conjugate designed to deliver optimal antitumor effect. T-DXd is composed of a humanized monoclonal antibody specifically targeting HER2, with the same amino acid sequence as trastuzumab, covalently linked to a camptothecin analogue (known as a topoisomerase I inhibitor) via a tetrapeptide-based cleavable linker. Specifically, deruxtecan is composed of the linker and the cytotoxic topoisomerase I inhibitor payload (a water-soluble exatecan derivative [DXd]), see Figure 1. T-DXd was designed to overcome the efficacy and toxicity limitations of earlier antibody drug conjugates (ADC). A key feature of T-DXd is that DXd is highly membrane permeable, enabling the elimination of both target-expressing tumor cells as well as surrounding tumor cells ("bystander-effect"). These unique features are likely the reason why T-DXd has succeeded in improving outcomes for HER2-low mBC patients, which no other HER2-targeted treatment has previously done.

Figure 1 Structure of T-DXd



Source: Daiichi Sankyo, Inc., 2019.

Applied indication and other EMA/DMC approved indications

On the 23rd of January 2023 Enhertu was approved as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior chemotherapy in

the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy (1).
Eligible patients should have documented HER2-low tumour status, defined as a score of 1+ by IHC or 2+ by IHC and negative ISH. IHC, ISH or Fluorescent ISH (FISH) tests are required, and already established as a standard element of diagnostics in Denmark. Hence, the introduction of T-DXd is not expected to result in additional costs for testing.
Patients can continue treatment with T-DXd until disease progression or unacceptable toxicity. The median treatment duration in DESTINY-Breast04 was 8.2 months.

Comparators in the clinical trial DB04 and Danish Clinical practice

HER2-low mBC patients, who have received one line of chemotherapy for metastatic disease, is the patient population in scope of this application. The next treatment option for these patients is another (second line) chemotherapy. Danish guidelines for chemotherapy in the metastatic setting make no clear recommendation on the sequence of the different chemotherapies. The therapies mentioned are taxanes, anthracyclines, capecitabine, eribulin, vinorelbine and gemcitabine. In addition, carboplatin can in certain cases be an option for HR- patients. Since anthracyclines are often used for neoadjuvant or adjuvant treatment of early-stage breast cancer, these agents are less frequently used in Danish clinical practice for mBC. Vinorelbine and gemcitabine have little or limited evidence to support their use ahead of other options and the evidence supporting carboplatin is, according to DBCG guidelines, “controversial” and it is mainly used as an option for HR- patients. Hence, taxanes, capecitabine and eribulin are the most commonly used chemotherapies for mBC in Denmark across both the HR+ and HR- mBC populations in the relevant setting (second line of chemotherapy).
Based on Danish guidelines and discussions with Danish clinical experts, the chemotherapy options of the control-arm of the DB04 study (i.e., eribulin, gemcitabine, capecitabine, paclitaxel, and nab-paclitaxel) are therefore well aligned with guideline recommendations and clinical practice for this patient group. In conclusion, the selection and frequency of the chemotherapies used in the DB04 control arm constitutes an appropriate comparator.

Efficacy DB04

DESTINY-Breast04 is a Phase III, multicentre, randomized, two-group, open-label, active controlled trial, designed to compare the efficacy and safety of T-DXd versus treating physician’s choice of chemotherapy (TPC) (2:1) for HER2-low, unresectable and/or metastatic breast cancer. The primary efficacy outcome of the study was progression-free survival (PFS) in the HR–positive cohort, and key secondary outcomes included PFS in the full analysis set and overall survival in the HR–positive cohort and full analysis set.
The results from DB04 demonstrate that the HER2-low population within breast cancer, significantly benefit from treatment with T-DXd.
In DB04 the risk of death was reduced with 36% and the risk of progression or death was reduced with 50% in direct comparison with TPC in the full analysis set. More than half of all patients (~52%) responded to T-DXd compared to ~16% of patients receiving TPC. T-DXd delivered consistent benefit across all patient groups.
T-DXd significantly prolonged progression-free survival (PFS) compared with TPC, median PFS was ~10 months for patients receiving T-DXd compared to ~5 months for patients who received TPC. In the full analysis set, median overall survival (mOS) was ~24 months for patients that received T-DXd versus 17.5 months in the TPC group (2). The treatment effect was statistically significant for both OS and PFS.

Safety

The safety profiles of T-DXd and TPC in the target population of this study were generally manageable and tolerable and consistent with the safety profile of previous clinical studies in the HER2 positive mBC setting. In DB04, no new safety concerns were identified. A total of 99.5% of the patients in the T-DXd group and 98.3% of those in the TPC group had at least one treatment-emergent adverse event (TEAE) that emerged or worsened after initiation of a trial drug until 47 days after the last dose of the trial drug, and the incidence of TEAEs ≥Grade 3 was 52.6% and 67.4%, respectively.
The incidence of TEAEs associated with discontinuation of treatment was 16.2% in the T-DXd group and 8.1% in the TPC group, and the incidence of AEs associated with dose reductions was 22.6% and 38.4%, respectively. A total of 14 patients (3.8%) in the T-DXd group and 5 patients (2.9%) in the TPC group had TEAEs that were associated with death.

Cost-effectiveness/Health economic analysis

The cost-effectiveness of T-DXd versus TPC in patients with HER2-low expression in the mBC setting was evaluated, and is aligned with previous economic analyses evaluated by DMC on the use of T-DXd in breast cancer (3). The analysis shows that the use of T-DXd results in a gain of 0.80 QALY versus TPC. This results in an ICER of ~695 000 DKK per QALY gained, at list price (AIP).

In conclusion, the results indicate that T-DXd could be considered a cost-effective treatment option with the potential to significantly improve outcomes for patients who currently have few effective treatment options.

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

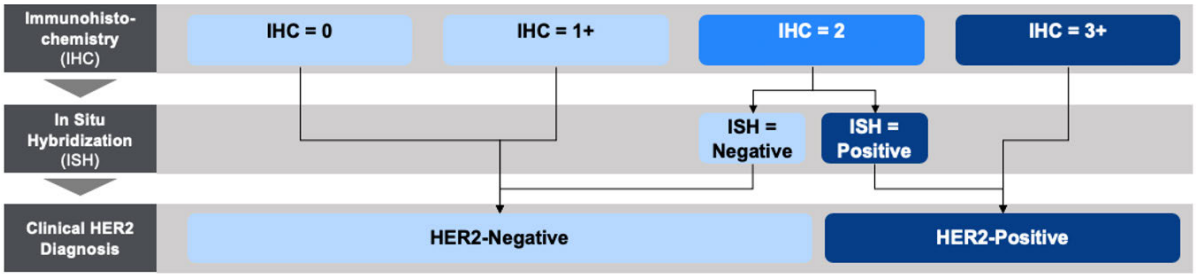
5.1 The medical condition and patient population (HER2-low)

Breast cancer is a biologically heterogeneous disease with histological subtypes categorized by the cell surface receptor expression profiles of the tumour. Estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) are key biomarkers for identification and treatment decision-making HER2 status is currently routinely assessed at diagnosis by immunohistochemistry (IHC) according to the American Society of Clinical Oncology (ASCO) CAP guidelines, which scores the IHC staining on a scale from 0-3 (IHC0, IHC1+, IHC2+ or IHC3+). Tumors that are IHC3+ OR IHC2+ with additional positive in-situ-hybridization (ISH) test are classed as HER2-positive. The remaining tumors have until recently been classed as HER2-negative (Figure 2A). However, in tumors with IHC scores of IHC1+ or IHC2+, a range of 100,000–500,000 HER2 receptor (4) molecules are still present on the cell surface of tumor cells; therefore, it seems reasonable to identify these low-expressing breast carcinomas as 'HER2-low'. The presence of elevated levels of HER2 receptors indicates that HER2-low patients may also benefit from HER2 targeted therapy. Approximately 60% of HER2 negative metastatic breast cancers are IHC1+ or IHC2+ (ISH-) with HER2-low expression (5) (Figure 2B)(5).

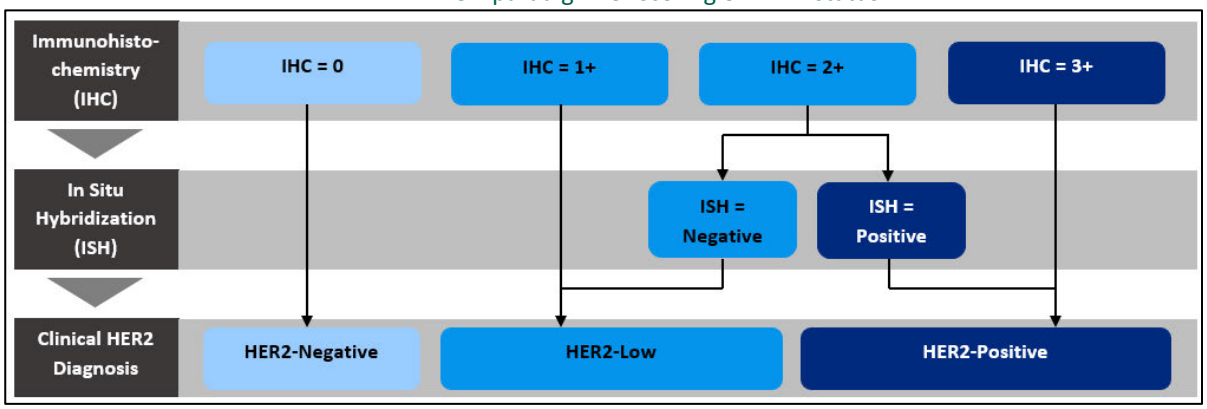
The HER2-low group includes both HR positive (HR+) and HR negative (HR-) breast cancers that vary in prognosis and sensitivity to systemic treatment. Within the HR+ patient population, the fraction of HER2-negative patients who can be classed as HER2-low has been estimated at around 65% whereas the corresponding percentage for the HR- patient population is estimated at 37% (5).

Figure 2 HER2 testing algorithm. A. Established testing paradigm. B. New emerging paradigm.

A. Current paradigm for scoring of HER2 status



B. New paradigm for scoring of HER2 status



***Source**: Produced by AstraZeneca based on ASCO guidelines*

Until the DESTINY-Breast04 (DB04) study, the currently approved HER2-directed therapies have not improved clinical outcomes in patients with HER2-low mBC and therefore, HER2-low breast cancer is traditionally treated as HER2-negative with the treatment allocated being primarily based on their HR status.
For HR+ mBC patients, endocrine therapy (ET) +/- CDK4/6 inhibitors is the first line standard of care and can prolong time to progression and provide a well-tolerated and widely used treatment option. However, once the cancer becomes resistant to ET, cytotoxic chemotherapy remains the only treatment option. HR- mBC TNBC (triple negative breast cancer) patients are insensitive to endocrine treatment and therefore chemotherapy is the standard treatment for this patient group, with the possibility of combination with anti-programmed death-ligand 1 (PD-L1) or anti-programmed death protein 1 (PD-1) based immunotherapy in first line for the PD-L1 positive subgroup of the HR- patients. Chemotherapies are typically given sequentially as single agent regimens with few strong and conclusive data to inform the sequencing and no biomarkers to guide selection of the specific chemotherapy. Despite a significant increase in the development of breast cancer therapies, the survival outcomes for HER2-negative mBC patients, including those of HER2-low patients, remains poor once the opportunities for endocrine therapy for HR+ patients have been exhausted. Real World Evidence studies of outcomes on chemotherapy in the 2L-3L setting report mOS in the range of 13-14 months from treatment with capecitabine or eribulin (6, 7), which are the treatments with the strongest documentation in the later line setting after treatment with anthracyclines and taxanes. As is well known, HR- (TNBC) patients have a particular poor survival with progression-free survival (PFS) of ~2-4 months and median OS from metastatic diagnosis of just ~14-15 months (8).

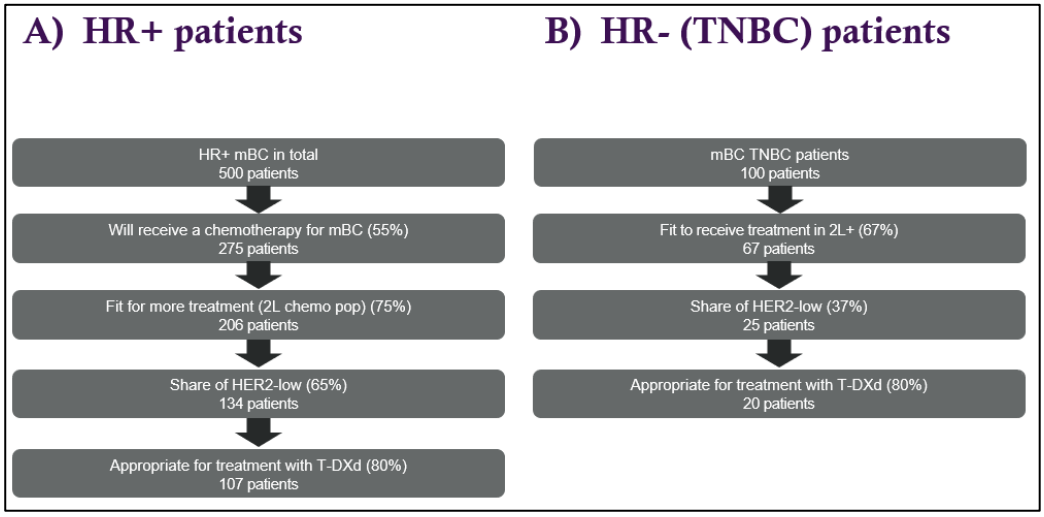
Danish guidelines for use of chemotherapy in mBC

Danish guidelines for chemotherapy for mBC are outlined by the Danish Breast Cancer Cooperative Group (DBCG) and are closely aligned with ESMO guidelines (9, 10). For details about detailed treatment recommendations see section 5.2.1“current treatment options”.

Patient estimate

In line with the recently approved indication for T-DXd for HER2-low mBC patients, we expect T-DXd to be incorporated into Danish clinical practise in place of a second chemotherapy in the metastatic setting for HR+ and HR- HER2-low patients.
To define the population that is eligible for treatment with T-DXd for HER2-low mBC, we have used a stepwise approach for the HR+ and HR- patient populations. With this stepwise approach we will define the mBC patient population that has 1) received at least one line of prior chemotherapy in the metastatic setting, 2) is fit for additional treatment and 3) have HER2-low IHC status.

Figure 3 Patient numbers by HR+/HR- status



Source: See text below

HR+ patients (Figure A)

- DBCG unpublished data on patients with diagnosis of metastatic/recurrent BC show that approximately 500 HR+ patients are treated per year in 1L[1].
- Of the patients getting treatment, an estimated 55% of HR+ patients will at some point receive a chemotherapy, resulting in 275 patients (11).
- Of the patients receiving a chemotherapy, around 75% will be fit for additional treatment, which then results in 206 patients (12).
- Of the 206 HR+ patients in scope, 65% are estimated to be HER2-low (5). Assuming they are all identified, this results in 134 patients.
- Of the 134 patients, ~80% are estimated to be considered appropriate for T-DXd. Not all patients will be deemed suitable for T-DXd treatment, main reasons being contraindications and patient or physicians' preference for other treatment options (ref: Danish clinical experts). Hence, we estimate 107 new HR+ HER2-low patients to be treated with T-DXd per year.

HR- patients (Figure B)

- Recent assessment reports from Medicinrådet estimate the number of new HR- (TNBC) mBC patients per year at approximately 100 new patients per year (13).
- After treatment in 1L with chemotherapy or immunotherapy + chemotherapy (if PD-L1-postive), the fraction of patients who will be fit for subsequent treatment is estimated at 2/3 (67%) by Danish clinical experts (12). This is very well aligned with the fraction of patients (67%) who received post-progression therapy in the IMPassion131 phase 3 trial. Consequently, 67 patients are estimated to be in scope for treatment in 2L (14).
- Of the 67 patients in scope, 37% are estimated to be HER2-low. Assuming they are all identified, this leaves 25 patients (5).
- Of the 25 patients, ~80% are estimated to be considered appropriate for T-DXd. Not all patients will be deemed suitable for T-DXd treatment, main reasons being contraindications and patient or physicians' preference for other treatment options (ref: Danish clinical experts). Hence, we estimate 20 new HR- HER2-low patients to be treated with T-DXd per year.

In conclusion we estimate that a total of 127 new patients per year may be treated with T-DXd according to the recently approved indication.

Table 1 Incidence and prevalence in the past 5 years

[1] DBCG unpublished nationwide data for HR+ patients with mBC diagnosis in 2018, shared by Tobias Berg and Ann Knop.

Year	2016	2017	2018	2019	2020
Incidence* in Denmark	4 860	4 896	4 998	5 168	4 900
Prevalence** in Denmark	66 517	68 269	70 164	72 188	73 926

* Men and Women ** Women only

Table 2 Age related incidence of breast cancer 2020

Age	15-29	30-44	45-59	60-74	75+	Total
Incidence**	24	382	1363	1786	1302	4857

** Women only

Table 3 Estimated number of patients eligible for treatment within the applied indication

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	127	128	128	129	129

Source: Medicinrådet and https://www.esundhed.dk/Emner/Kraeft/Nye-kraefttilfaelde

5.1.1 Patient populations relevant for this application

The patient population relevant for this assessment cover the full population that was approved by EMA in February 2023; T-DXd as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy)(15).
According to this indication, we therefore expect T-DXd to be implemented into Danish clinical practise as a new treatment option for mBC patients with HER2-low IHC status who have received one line of chemotherapy in the metastatic setting and who are fit for additional treatment. See also section 5.1 for more details on the patient population in scope for the assessment.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

As outlined previously, mBC patients with HER2-low IHC status are currently treated as HER2-negative patients according to both ESMO and Danish (DBCG) guidelines. These patients are thus currently primarily treated on the basis of their hormone receptor (HR) status. Danish guidelines clearly recommend that for HR+ patients, endocrine therapy (+/- CDK4/6i) is the first choice for as long as the cancer is sensitive to endocrine therapy. However, once the patient become refractory to endocrine therapy, the only recommended options are currently chemotherapy. Similarly, for HR- mBC patients, the recommendations after 1L, where IO + chemo is available for PD-L1+ patients, are chemotherapy. Since the expected implementation of the indication in scope for this assessment is as a second chemotherapy for patients who have received one line of chemotherapy in the metastatic setting, the relevant recommendations for current treatment are those for chemotherapy for mBC.

Danish guidelines for chemotherapy for mBC are outlined by DBCG and are closely aligned with ESMO guidelines (9, 10). DBCG guidelines thus outline a few simple recommendations and guiding principles for chemotherapy:

- There is no preferred 1L chemotherapy treatment. The choice of treatment depends on multiple factors such as prior treatment, toxicities, performance status, co-morbidities, and patient preferences.
- After 1L chemotherapy, additional lines of chemotherapy can be given in accordance with performance status.

- Sequential treatment with single-agent chemotherapy regimens is recommended rather than combination treatment.
- Each line of chemotherapy should be continued until progression or unacceptable toxicity.

DBCG guidelines emphasize that the optimal sequence of chemotherapies has never been established, but outline a number of agents that are used: Anthracyclines, taxanes, capecitabine, eribulin, gemcitabine, and vinorelbine (10). However, in Danish clinical practise, anthracyclines are most often used for neoadjuvant or adjuvant treatment of early stage BC and hence it is less frequently used in the metastatic setting since many patients have prior exposure to this class of drugs (12, 16). Additionally, anthracyclines are associated with substantial side-effects among these cardio-toxicities, and there is thus a defined maximum cumulative dose, limiting the use anthracyclines in the metastatic setting (10). Vinorelbine and gemcitabine are less frequently used in Danish clinical practise due to the absence of high-level evidence for their efficacy in later line treatment.
In conclusion, for HR+ mBC patients, the most frequently used agents are taxanes, capecitabine and eribulin (12, 16). Similarly for HR- (TNBC) patients, the guidelines recommend the same single agents as well as carboplatin. As mentioned previously, for PD-L1-positive TNBC patients, the combination of atezolizumab + nab-paclitaxel is also an option for 1L mTNBC (10).
In conclusion, Danish guidelines and clinical practise with chemotherapy for mBC in the 2L chemotherapy setting are very well aligned with the Treating Physician's Choice (TPC) options for chemo in the DESTINY-Breast04 study control arm (paclitaxel, nab-paclitaxel, capecitabine, eribulin, and gemcitabine), which has been confirmed by Danish clinical experts (12, 16).

5.2.2 Choice of comparator(s)

HER2-low mBC patients, who have received one line of chemotherapy for metastatic disease, is the patient population in scope of this application. The next treatment for such patients is thus another (second line) chemotherapy. Danish guidelines for chemotherapy in the metastatic setting emphasize that the optimal sequence of chemotherapies is unknown and thus make no clear recommendation on the sequence of the different chemotherapies. The therapies mentioned are taxanes, anthracyclines, capecitabine, eribulin, vinorelbine, gemcitabine and, as an option for HR- patients, carboplatin (17). Since anthracyclines are often used for neoadjuvant or adjuvant treatment of early-stage breast cancer, these agents are less frequently used in Danish clinical practise for mBC. Vinorelbine and gemcitabine have little or limited evidence to support their use ahead of other options, and the evidence for carboplatin is controversial according to DBCG guidelines with its use being mainly for HR- patients. Hence, the most commonly used chemotherapies for mBC in Denmark across both the HR+ and HR- mBC populations are taxanes, capecitabine and eribulin (12) (17).
The chemotherapies that constitute the comparator (TPC) have never been assessed by Medicinrådet (or KRIS/RADS). However, they have all been part of Danish clinical practise for many years. In relation to this, we refer to a conclusion made by DMC (document number 157603) in the assessment (cost-section) of sacituzumab govitecan vs TPC (broadly similar compounds as in DB04) "Medicinrådet accepterer ansøgers indsendte sundhedsøkonomiske analyse, herunder at ansøger ikke har udarbejdet separate analyser, der belyser omkostningseffektiviteten af de nuværende standardbehandlinger, på trods af at disse ikke tidligere er blevet vurderet og anbefalet af Medicinrådet (jf. Medicinrådets metodevejledning). Det skyldes, at standardbehandlingerne anses som etableret dansk behandlingspraksis, og at omkostningerne forbundet med disse behandlinger er lave".

Based on Danish guidelines, DMC Document-number 157603) and feedback from Danish clinical experts, the chemotherapy options of the control-arm of the DB04 study (i.e., eribulin, gemcitabine, capecitabine, paclitaxel, and nab-paclitaxel) are therefore well aligned with guideline recommendations and clinical practice for this patient group (3, 12, 16, 17).

In conclusion, the selection and frequency of the chemotherapies used in the DB04 control arm constitutes an appropriate comparator and is in line with Danish "standardbehandling".

5.2.3 Description of the comparator(s)

5.2.3.1 Eribulin

Pharmaceutical form:
0.44 mg/ml, clear colourless aqueous solution

Posology:
The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 which should be administered intravenously over 2 to 5 minutes on day 1 and day 8 every 21-day cycle.

Method of administration:
Intravenous use. The dose may be diluted in up to 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection.

Should the pharmaceutical be administered with other medicines:
As monotherapy or in combination with docetaxel.

Treatment duration / Criteria for end of treatment:
Eribulin is usually given on Day 1 and 8 of every 21-day cycle. The treating physician will determine how many cycles of treatment the patient should receive. Median duration of treatment was 15.9 weeks for breast cancer patients. Patients can continue treatment until disease progression or unacceptable toxicity

Necessary monitoring, both during administration and during the treatment period:
Caution and monitoring for adverse events is recommended with concomitant use of substances that have a narrow therapeutic window and that are eliminated mainly via CYP3A4-mediated metabolism (e.g., alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).

In patients treated concomitantly with oral coumarin-derived anticoagulants, coagulation parameters should be closely monitored, and the anticoagulant dose should be adjusted. The patient must be closely monitored for ophthalmic complications such as keratitis and corneal disease, especially if they have a history of eye disorders. For more details see SmPC.

Need for diagnostic or other test:
DPYD (dihydropyrimidin dehydrogenase) genotyping is required per national guidelines prior to commencing capecitabine.

5.2.3.2 Gemcitabine

Pharmaceutical form:
Gemcitabine Accord 100 mg/ml solution for injection

Posology:
In combination with paclitaxel, the recommended starting dose of paclitaxel for breast cancer is 175 mg/m2 on Day 1 over 3 hours, followed by gemcitabine 1250 mg/m2 which should be given intravenously over 30 minutes on Day 1 and 8 of every 21-day cycle. The dose can gradually be decreased per cycle, or within a cycle, based on toxicity of the patient.

Method of administration:
Intravenous use. The dose may be diluted in sodium chloride 9 mg/ml (0.9%) solution for injection.

Should the pharmaceutical be administered with other medicines?:
As combination with paclitaxel.
As monotherapy or in combination with docetaxel.

Treatment duration / Criteria for end of treatment:
Patients can continue treatment until disease progression or unacceptable toxicity.
Gemcitabine can suppress bone marrow function as manifested by leucopenia, thrombocytopenia and anaemia. Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte and granulocyte counts.

Necessary monitoring, both during administration and during the treatment period:
Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity. In patients treated concomitantly with oral coumarin-derived anticoagulants, coagulation parameters should be closely monitored, and the anticoagulant dose should be adjusted. The patient must be closely monitored for ophthalmic complications such as keratitis and corneal disease, especially if they have a history of eye disorders. For more details see SmPC.

Need for diagnostic or other test:
DPYD (dihydropyrimidin dehydrogenase) genotyping is required per national guidelines prior to commencing capecitabine.

5.2.3.3 Capecitabine

Pharmaceutical form:
150 mg and 500 mg film-coated tablets

Posology:
In combination with docetaxel, the recommended starting dose of capecitabine for metastatic breast cancer is 1250 mg/ m^2 twice daily for 14 days followed by a 7-day rest period, combined with docetaxel given at a dose of 75 mg/ m^2 as 1-fold IV infusion every 3 weeks.

Method of administration:
Oral administration.

Should the pharmaceutical be administered with other medicines?:
As monotherapy or in combination with docetaxel.

Treatment duration / Criteria for end of treatment:
Patients can continue treatment until disease progression or unacceptable toxicity

Necessary monitoring, both during administration and during the treatment period:
In patients treated concomitantly with oral coumarin-derived anticoagulants, coagulation parameters should be closely monitored, and the anticoagulant dose should be adjusted. The patient must be closely monitored for ophthalmic complications such as keratitis and corneal disease, especially if they have a history of eye disorders. For more details see SmPC.

Need for diagnostic or other test:
DPYD (dihydropyrimidin dehydrogenase) genotyping is required per national guidelines prior to commencing capecitabine.

5.2.3.4 Paclitaxel

Pharmaceutical form:
Paclitaxel Accord 6 mg/ml powder for dispersion for infusion 5

Posology:
Recommended dosage of paclitaxel is 175 mg/m2 administered intravenously over 30 minutes every 3 weeks.

Method of administration:

Intravenous administration.

Should the pharmaceutical be administered with other medicines?:
No.

Treatment duration / Criteria for end of treatment:
Patients can continue treatment until disease progression or unacceptable toxicity

Necessary monitoring, both during administration and during the treatment period:
Treatment must be carried out under supervision of treating physician. The patient must receive corticosteroids, antihistamines and H2-antagonists prior to receiving treatment. Common sides effect include; neutropenia, thrombocytopenia, neurotoxicity, and arthralgia or myalgia.

Need for diagnostic or other test:
No.

5.2.3.5 Nab-paclitaxel

Pharmaceutical form:
Abraxane 5 mg/ml white to yellow powder for dispersion for infusion.

Posology:
The recommended dose of Abraxane is 260 mg/m2 administered intravenously over 30 minutes every 3 weeks.

Method of administration:
Intravenous administration.

Should the pharmaceutical be administered with other medicines?:
No.

Treatment duration / Criteria for end of treatment:
Patients can continue treatment until disease progression or unacceptable toxicity

Necessary monitoring, both during administration and during the treatment period:
Treatment must be carried out under supervision of treating physician. The patient must receive corticosteroids, antihistamines and H2-antagonists prior to receiving treatment. Common sides effect include; neutropenia, thrombocytopenia, neurotoxicity and diarrhea.

Need for diagnostic or other test:
No.

5.3 The intervention (T-DXd)

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.

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-Breast04 was 8.2 months while the modelled mean treatment duration is ~8.3 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 left ventricular ejection fraction (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 should have documented HER2-low tumor status, defined as a score of 1+ by IHC or 2+ by IHC and negative ISH. IHC, ISH or Flourescent ISH (FISH) tests are required, and these are already established as a standard element of breast cancer diagnostics in Denmark. Hence, the introduction of T-DXd should not result in additional costs for testing. New updated SNOMED codes for Patobank have recently been added, which continues to support the registration of the IHC1+ and IHC2+/ISH- categories that make up the HER2-low category (18).

6. Literature search and identification of efficacy and safety studies

6.1 Overview of all included literature

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)	Used in comparison of*
N Engl J Med 2022; 387:9-20 DOI: 10.1056/NEJMoa2203690. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. Modi S et al.	Destiny-Breast 04	NCT03734029	Start date: Dec 18 End date: June 22	T-DXd vs TPC (”standardbehandling”)

Table 5 Ongoing studies within HER2- breast cancer (HER2 low marked with grey)

Trial summary	Intervention(s) assessed	Expected comple-tion 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 03. A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of DS-8201a (Trastuzumab Deruxtecan), an Anti-HER2 Antibody Drug Conjugate (ADC), Versus Ado Trastuzumab Emtansine (T-DM1) for HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated With Trastuzumab and Taxane. N =	**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:** Participants previously treated with trastuzumab and taxane who received T-DM1 in accordance with the approved label.	May, ’21	https://www.clinicaltrials.gov/ct2/show/NCT03529110
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-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	**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:** Investigator's choice standard of care chemotherapy (capecitabine, paclitaxel, nab-paclitaxel)	Jul, ’23	https://clinicaltrials.gov/ct2/show/NCT04494425
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	Dec, ’24	https://clinicaltrials.gov/ct2/show/NCT04784715

	Arm 3: doxorubicin and cyclophosphamide, followed by THP		
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

6.2 Identification and selection of relevant studies

DB04 is a phase 3, multicentre, randomized, open-label direct comparative study and this can according to the DMC guidelines in some cases cancel the requirement for a SLR.
The generation of clinical and economic evidence for the HER2-low patient population and T-DXd in this indication could require SLRs; however, because HER2-low as a patient group is only recently defined, the literature in this area will be limited. Since it is only recently with the positive results from the DB04 study that HER2-low has been established as a clinically relevant sub-classification of the HER2 negative population, an SLR should include the entire HER2-negative population to ensure all studies reporting HER2-low data are included. In current clinical practice, HER2-low patients are treated according to the guidelines for HER2-negative breast cancer and thus according to HR status. HER2-low-expressing patients are a subset of HER2-negative patients, and in clinical trials performed in patients with HER2-negative mBC, HER2-low patients are not differentiated from HER2-negative patients.
In the previous section it is has been documented through guidelines, clinical experts and DMC references that the comparator arm (TPC) can be considered as Danish "standardbehandling".
For the comparator arm (TPC) a number of studies have been performed in cohorts of HER2-positive, HER2-negative and TNBC patients, but none of these have information on HER2-low patients (Table 6). The HER2-low breast cancer population is not investigated in many studies, primarily in the early phase studies on T-DXd and the ongoing phase 3 study DB06 (Table 5). Based on the above, a SLR in HER2-low mBC has been performed for this application.

Table 6 Summary of survival outcomes for HER2-negative targeted therapies

Randomized clinical trials			
Study name **Study phase**	**Treatment** **Evaluable N**	**OS** **Median (range)** **months**	**PFS** **Median (range) months**
HR-positive, HER2-negative			
Yardley et al., 2016 (298) (NCT01427933) Phase II	Eribulin (1.4 mg/m2, days 1 and 8 of a 3-week cycle) N=60	11.5 95% CI 9.0 – 17.3	4.1 95% CI 3.2 – 5.6
Pivot et al., 2016 (299) (NR) Phase III	Eribulin (1.23 mg/m2, day 1 and 8 of a 3-week cycle) N=663	15.1 P=0.008	3.7 P=0.007
Cortes et al., 2011 (297) (NCT00388726)	Eribulin mesylate (1.4 mg/m2, day 1 and 8 of a 3-week cycle) N=508	13.2 95% CI 12.1 – 14.4	Investigator 3.6 95% CI

Phase III			[3.3 – 3.7] Independent 3.7 95% CI 3.3 – 3.9
Pivot et al., 2017 (300) (NCT00337103) Phase III	Eribulin (1.23 mg/m2, day 1 and 8 of a 3-week cycle) N=186	16.1 95% CI 15.2 – 18.6	4.2 95% CI 3.5 – 4.5
	Capecitabine (1,250 mg/m2, twice daily on the first 2 weeks of a 3-week cycle) N=206	13.5 95% CI 10.9 – 14.9	4.0 95% CI 3.2 – 4.5
Twelves et al., 2016 (301) (NCT00337103) Phase III	Eribulin (1.23 mg/m2, day 1 and 8 of a 3-week cycle) N=290	15.9	NR
	Capecitabine (1,250 mg/m2, twice daily on the first 2 weeks of a 3-week cycle) N=305	13.4	NR
Barrios et al., 2010 (302) Phase III	Capecitabine (1,250 mg/m2, twice daily during the first 2 weeks of a 3-week cycle) N=244	24.6	4.2 P=0.002
Decker et al., 2017 (303) (NCT01320111) Phase II	Paclitaxel (80 mg/m2, day 1, 8, and 15 of a 4-week cycle) N=30	20.7 95% CI 16.4 – 26.7	6.6 95% CI 5.1 – 9.0
TNBC			
Pivot et al., 2016 (299) (NR) Phase III	Eribulin (1.23 mg/m2, day 1 and 8 of a 3-week cycle) N=199	12.4 P=0.005	2.8 P=0.028
O'Shaughnessy et al., 2014 (304) (NCT00938652) Phase III	Gemcitabine (1,000 mg/m2) + Carboplatin (UAC=2) (days 1 and 8 of a 3-week cycle) + iniparib (5.6 mg/kg, on days 1, 4, 8, and 11 of a 3-week cycle) N=113	12.1	4.2
	Gemcitabine (1000 mg/m2) + Carboplatin (UAC=2) (days 1 and 8 of a 3-week cycle) N=109	8.1	2.9

7. List of relevant studies Efficacy and safety

7.1 Efficacy and safety of T-DXd compared to TPC for previously treated HER2-low advanced breast cancer

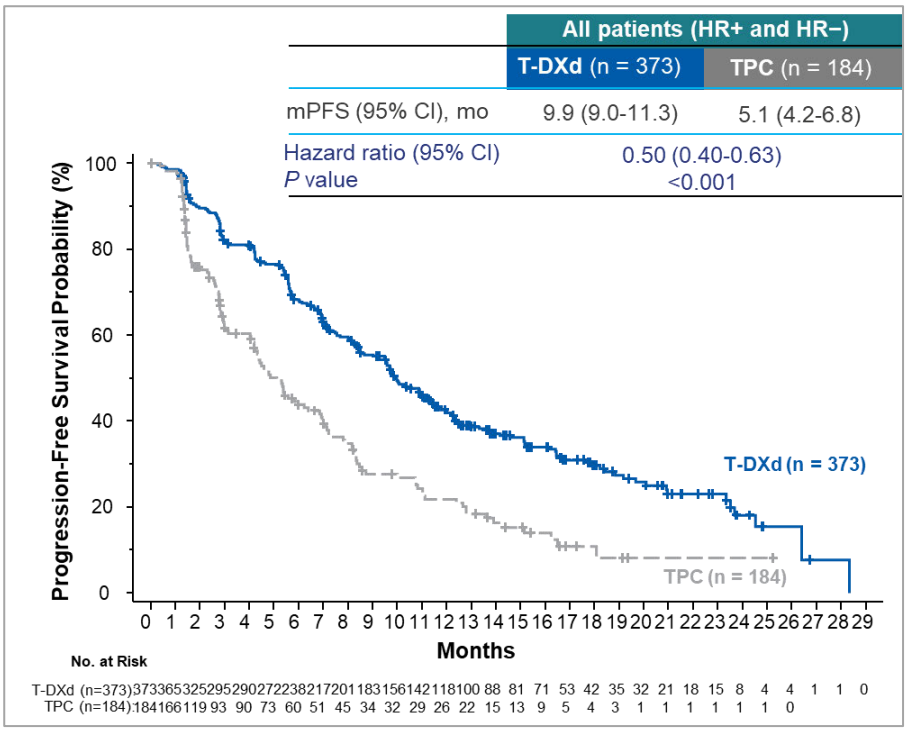
7.1.1 Relevant studies: Destiny-Breast04 (DB04)

Summary of design, patient-population and results from DB04 will follow in sections below

7.1.1.1 Progression-free survival

At the data-cut-off date (January 11, 2022), for the primary efficacy analysis, the median PFS was 9.9 months (95% CI, 9.0 to 11.3) in the T-DXd group and 5.1 months (95% CI, 4.2 to 6.8) in the TPC group (hazard ratio [HR] for disease progression or death, 0.50; 95% CI, 0.40 to 0.63; P<0.001)(2), see Figure 4.

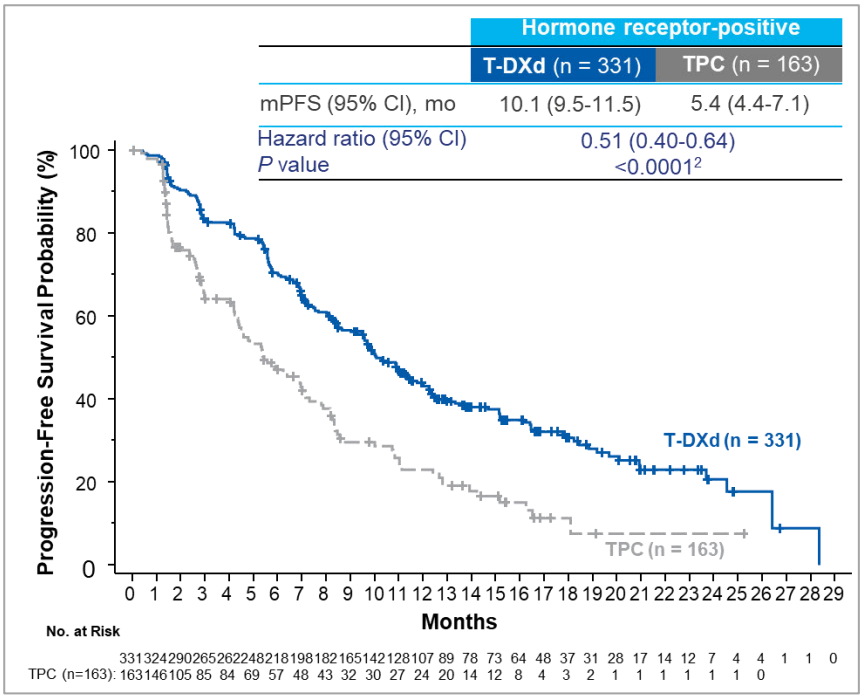
Figure 4 PFS all patients



Note: PFS was assessed by means of blinded independent central review.

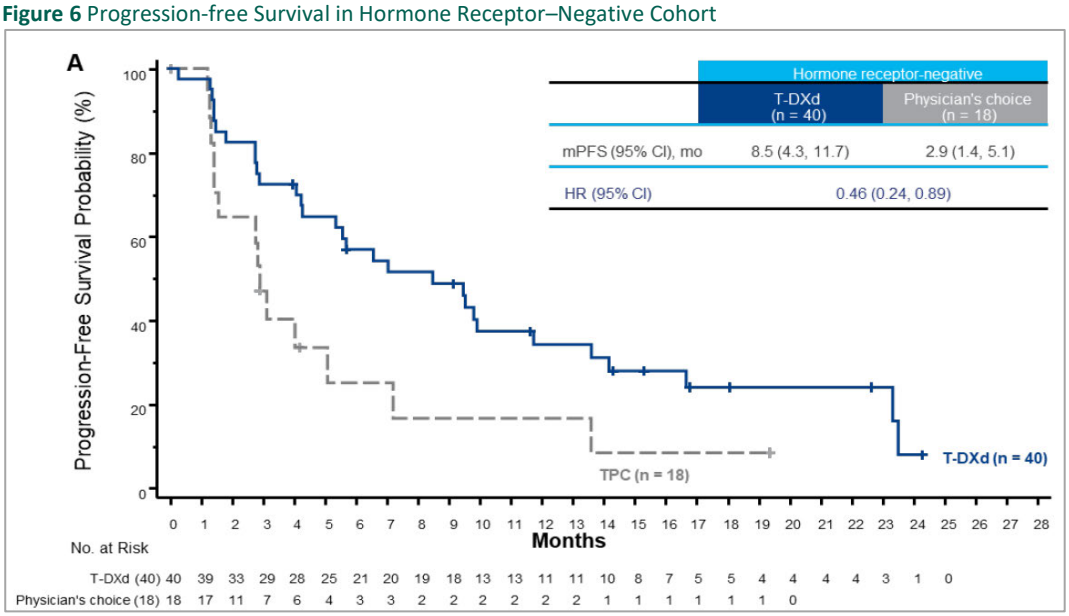
For the HR–positive cohort the median PFS was 10.1 months (95% CI, 9.5 to 11.5) in the T-DXd group and 5.4 months (95% CI, 4.4 to 7.1) in the TPC cohort (hazard ratio for disease progression or death, 0.51; 95% CI, 0.40 to 0.64; P<0.001)(2), see Figure 5.

Figure 5 Progression-free Survival in Hormone Receptor–Positive Cohort



In the HR–negative cohort the median PFS was 8.5 months (95% CI, 4.3 to 11.7) in the T-DXd group and 2.9 months (95% CI, 1.4 to 5.1) in the TPC group (hazard ratio, 0.46; 95% CI, 0.24 to 0.89), see Figure 6.

Figure 6 Progression-free Survival in Hormone Receptor–Negative Cohort

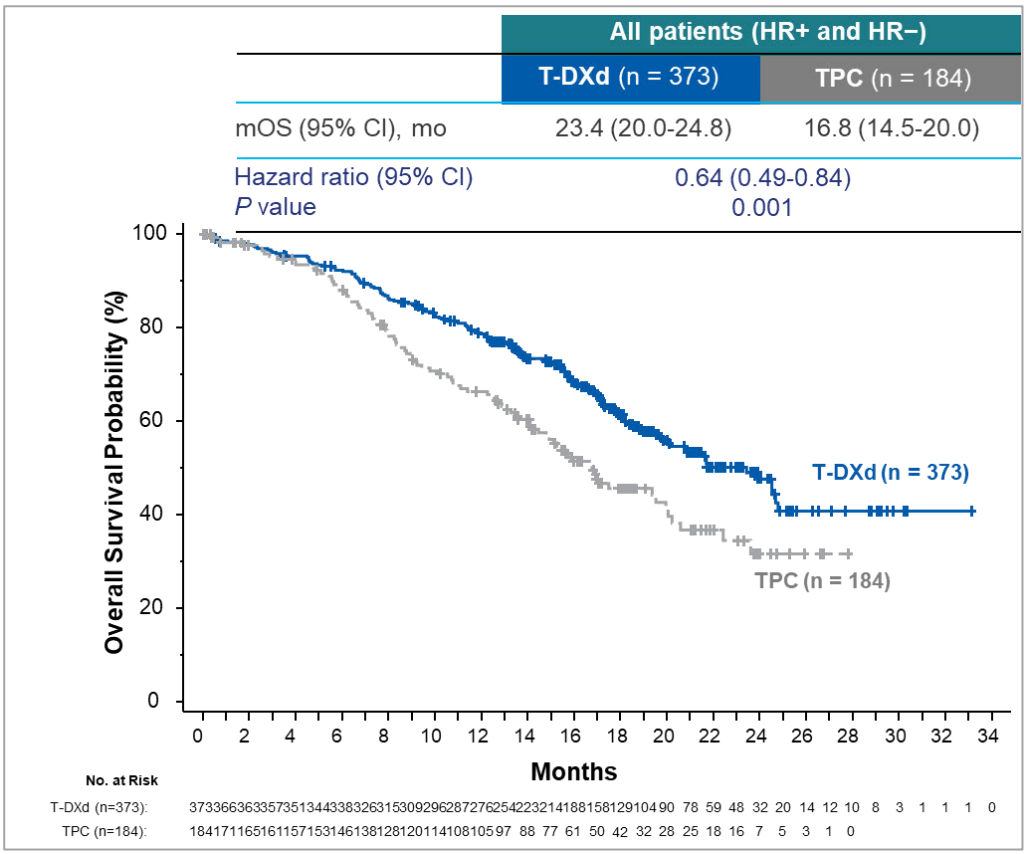


In DESTINY-Breast04, T-DXd resulted in a consistent and clinically meaningful improvement regarding PFS across the analysed subgroups. In the T-DXd group, the median PFS was 10.3 months among patients with a HER2 IHC score of 1+ and 10.1 months among those with a HER2 IHC score of 2+ and negative results on ISH. Among patients who had received previous treatment with CDK4/6 inhibitors, the median PFS was 10.0 months in the T-DXd group; without previous CDK4/6 inhibitor treatment, it was 11.7 months.

7.1.1.2 Overall survival

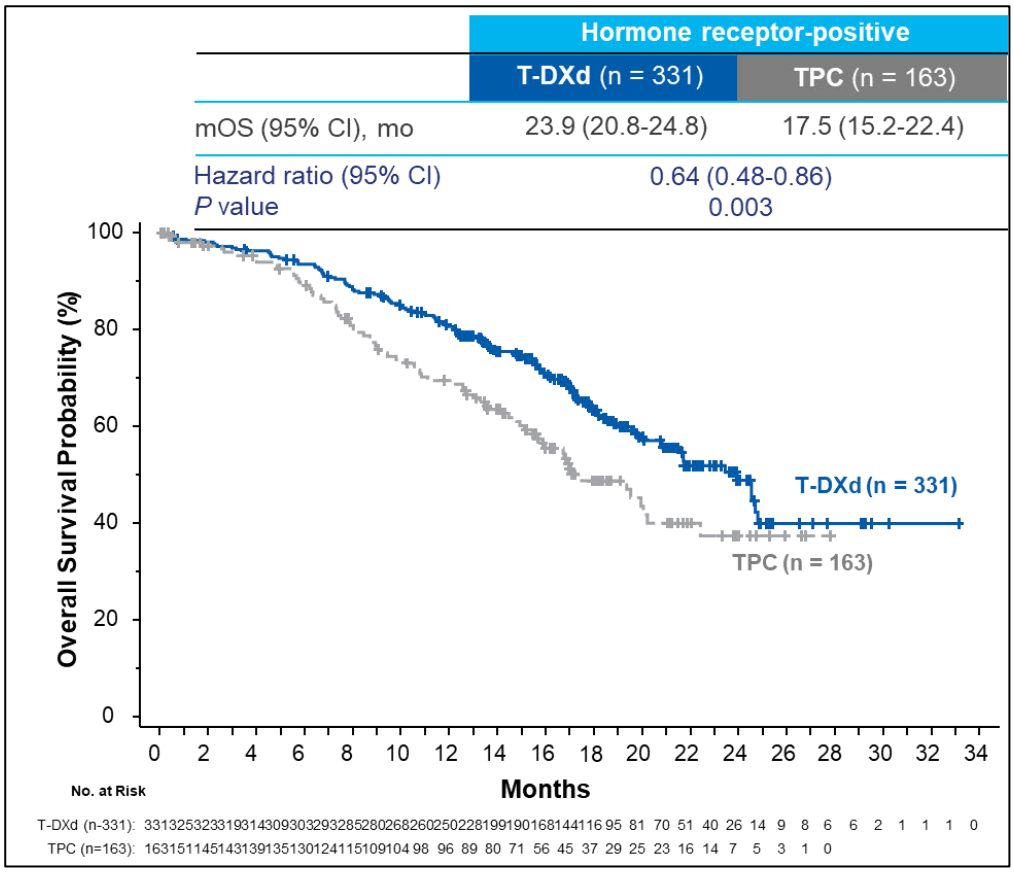
The median OS was 23.4 months (95% CI, 20.0 to 24.8) in the T-DXd group and 16.8 months (95% CI, 14.5 to 20.0) in the TPC group (hazard ratio, 0.64; 95% CI, 0.49 to 0.84; P = 0.001), see Figure 7. The P values crossed the interim stopping boundary of 0.0075 in both cohorts (2).

Figure 7 OS all patients



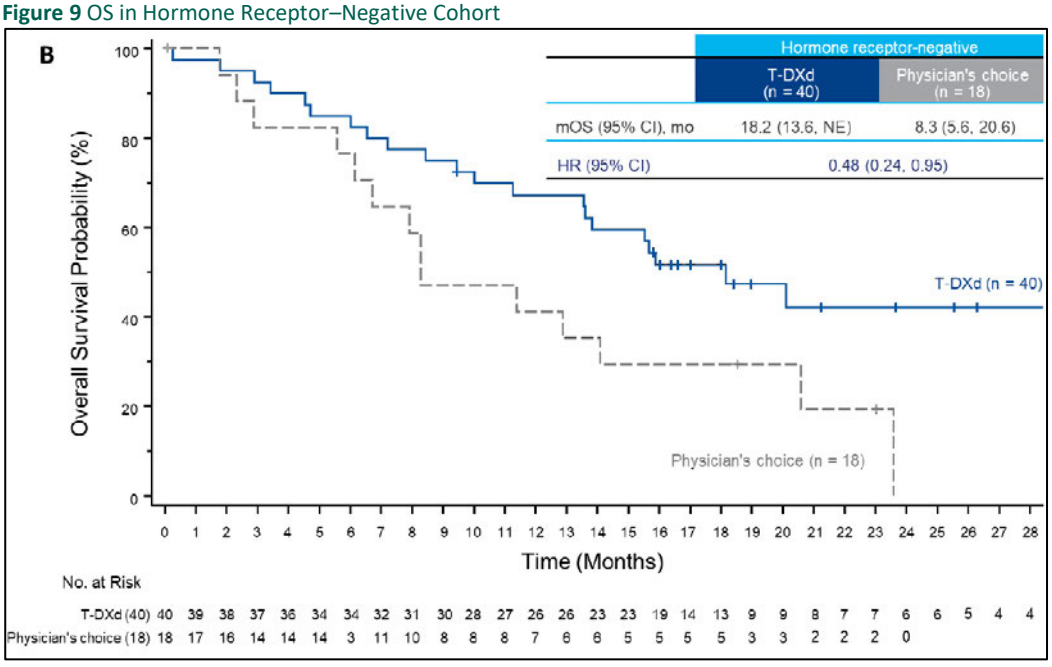
The median OS in the HR–positive cohort was 23.9 months (95% CI, 20.8 to 24.8) in the T-DXd group and 17.5 months (95% CI, 15.2 to 22.4) in the TPC group (HR for death, 0.64; 95% CI, 0.48 to 0.86; P = 0.003) (2), see Figure 8.

Figure 8 OS in Hormone Receptor–Positive Cohort



The median OS in the HR–negative cohort was 18.2 months (95% CI, 13.6, NE) in the T-DXd group and 8.3 months (95% CI, 5.6 to 20.6) in the TPC group (HR, 0.48; 95% CI, 0.24 to 0.95), see Figure 9.

Figure 9 OS in Hormone Receptor–Negative Cohort



7.1.1.3 Overall response and duration of response

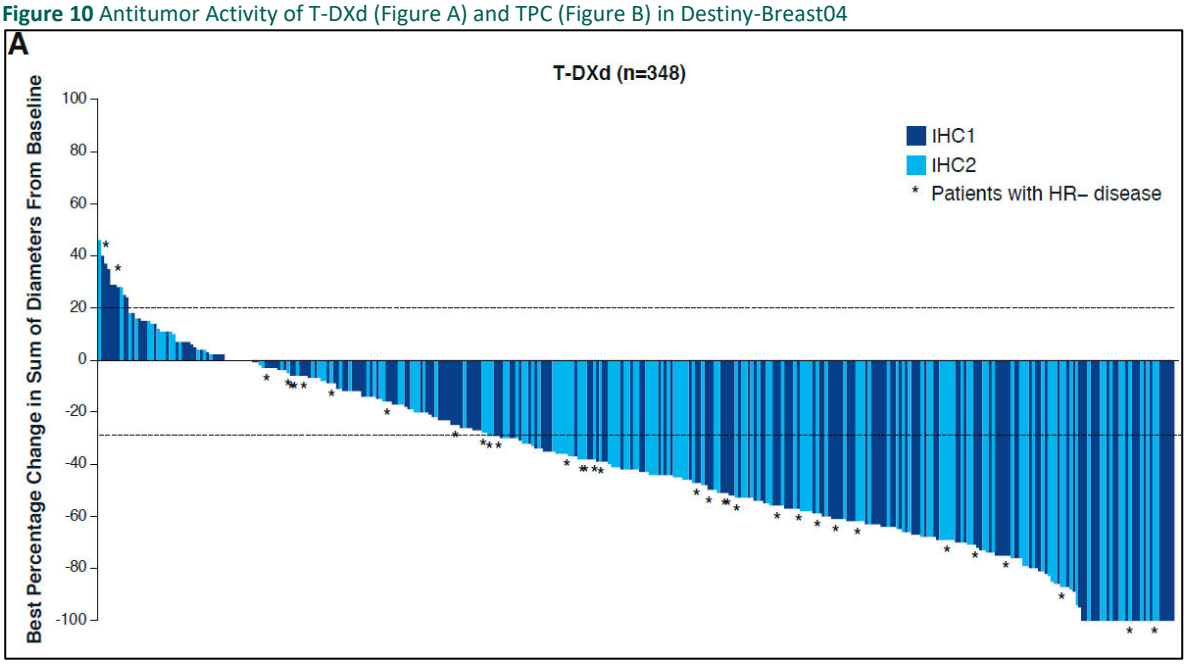
Secondary endpoints of DB04 included overall response and duration of response. The T-DXd treatment benefit over TPC was also observed for these endpoints, see Figure 10.

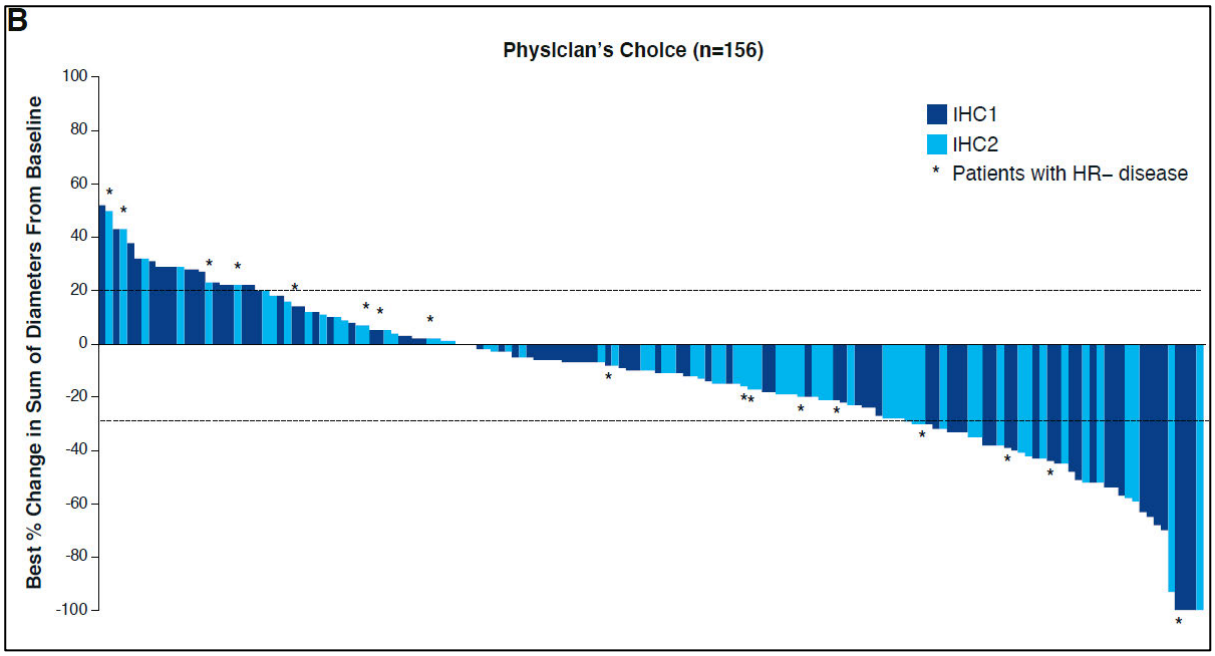
Confirmed objective response (COR) among all patients was 52.3% (95% CI, 47.1 to 57.4) in the T-DXd group and 16.3% (95% CI, 11.3 to 22.5) in the TPC group. Similar results are noted in the HR–positive cohort, in which COR was 52.6% (95% CI, 47.0 to 58.0) in the T-DXd group and 16.3% (95% CI, 11.0 to 22.8) in the TPC group.

Among all patients, median duration of response (DoR) was 10.7 months (95% CI, 8.5 to 13.2) in the T-DXd group and 6.6. months (95% CI, 6.0 to 9.9) in the TPC group.

Waterfall plots are presented in Figure 7 which show the best percentage change from baseline in the sum of the largest diameters of measurable tumours in patients for whom data from both baseline and postbaseline assessments of target lesions by independent central review. As shown, almost all patients benefit from T-DXd treatment. Median duration of response is presented illustrating that T-DXd show significantly longer median duration of response compared to TPC in all patients, but also in HR+ and HR- subgroups.

Figure 10 Antitumor Activity of T-DXd (Figure A) and TPC (Figure B) in Destiny-Breast04





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Note: *Patients with tumours categorized HER2 IHC1+ are shown in light blue and HER2 IHC2+/ISH- is shown in dark blue. Patients with HR-negative tumours are designated with an asterisk.*

Table 7 and Table 8 show a summary of outcomes assessed by the BICR.

Table 7 Summary of DESTINY-Breast04 results all patients

Parameter	T-DXd (N = 373)	TPC (N = 184)
Progression-free survival		
Median PFS, months (95% CI)	9.9 (9.0–11.3)	5.1 (4.2–6.8)
Stratified Cox hazard ratio (95% CI)	0.50 (0.40-0.63)	
Stratified log-rank *P*-value	<0.001	
Percentage of subjects alive and progression-free over time		
3 months (95% CI)	84.2 (80.0, 87.5)	58.0 (50.1, 65.1)
6 months (95% CI)	67.0 (61.9, 71.6)	27.3 (20.6, 34.4)
9 months (95% CI)	49.9 (44.6, 55.0)	14.0 (9.1, 20.0)
12 months (95% CI)	34.6 (29.5, 39.6)	8.9 (5.0, 14.2)
18 months (95% CI)	22.7 (18.0, 27.7)	4.2 (1.5, 8.9)
24 months (95% CI)	14.2 (9.1, 20.5)	0.0 (NE, NE)
Overall survival		
Median OS, months (95% CI)	23.4 (20.0–24.8)	16.8 (14.5–20.0)
Stratified Cox hazard ratio (95% CI)	0.64 (0.49-0.84)	
Stratified log-rank test *P*-value	0.001	
Percentage of subjects alive over time		
3 months (95% CI)	96.2 (93.7, 97.8)	95.3 (90.9, 97.6)
6 months (95% CI)	92.4 (89.2, 94.7)	88.1 (82.2, 92.2)
9 months (95% CI)	85.3 (81.3, 88.5)	74.0 (66.6, 80.0)
12 months (95% CI)	78.8 (74.3, 82.7)	66.5 (58.8, 73.2)
18 months (95% CI)	61.7 (55.9, 66.9)	45.9 (37.5, 54.0)
24 months (95% CI)	48.1 (40.8, 54.9)	32.0 (21.9, 42.4)
Best overall response by BICR		
Complete response, n (%)	13 (3.5)	2 (1.1)
Partial response, n (%)	183 (49.1)	28 (15.2)
Stable disease, n (%)	129 (34.6)	91 (49.5)
Progressive disease, n (%)	31 (8.3)	41 (22.3)
Not evaluable, n (%)	17 (4.6)	22 (12.0)
Disease control – (%)	325 (87.1)	121 (65.8)
Clinical benefit (%)	262 (70.2)	62 (33.7)
Median DoR – mo.	10.7	6.8
Median TTR – mo.	2.73	2.22
Confirmed ORR (complete response + partial response)		
No of patients evaluated	373	184
Responders, n (%)	195 (52.3)	30 (16.3)
95% CI	47.1–57.4	11.3–22.5
P-value	<0.0001	
Difference in ORR (95% CI)	36.0 (28.2, 43.7))	

[b] Disease control was a composite of complete response, partial response, and stable disease.

[c] Clinical benefit was a composite of complete response, partial response, and more than 6 months of stable disease, according to blinded independent central review. **Source:** Daiichi Sankyo (2022) (2, 19).

Table 8 Overall Efficacy in HR-positive and HR-negative patients.

Variable	HR-positive Cohort		HR-negative Cohort	
	T-DXd	TPC	T-DXd	TPC
No. of patients evaluated	331	163	40	18
Median PFS (95% CI) — months	10.1 (9.5–11.5)	5.4 (4.4–7.1)	8.5 (4.3–11.7)	2.9 (1.4–5.1)
Hazard ratio for disease progression or death (95% CI)	0.51 (0.40–0.64)		0.46 (0.24–0.89)	
P value	<0.001		—	
Median OS (95% CI) — months	23.9 (20.8–24.8)	17.5 (15.2–22.4)	18.2 (13.6–NE)	8.3 (5.6–20.6)
Hazard ratio for death (95% CI)	0.64 (0.48–0.86)		0.48 (0.24–0.95)	
P value	0.003		—	
No. of patients evaluated	333	166	40	18
No. with response	175	27	20	3
Percent (95% CI)	52.6 (47.0–58.0)	16.3 (11.0–22.8)	50.0 (33.8–66.2)	16.7 (3.6–41.4)
Complete response	12 (3.6)	1 (0.6)	1 (2.5)	1 (5.6)
Partial response	164 (49.2)	26 (15.7)	19 (47.5)	2 (11.1)
Stable disease	117 (35.1)	83 (50.0)	12 (30.0)	8 (44.4)
Progressive disease	26 (7.8)	35 (21.1)	5 (12.5)	6 (33.3)
Not evaluable	14 (4.2)	21 (12.7)	3 (7.5)	1 (5.6)
Disease control — no. (%)[b]	293 (88.0)	110 (66.3)	32 (80.0)	11 (61.1)
Clinical benefit — no. (%)[c]	237 (71.2)	57 (34.3)	25 (62.5)	5 (27.8)
Median DoR — mo	10.7	6.8	8.6	4.9
Median TTR — mo	2.76	2.73	1.51	1.41

Data cut-off was 22 January 2022, 58 patients (15.6%) of the T-DXd arm, and 3 patients (1.7%) of the TPC arm were still receiving the study drug. For the primary endpoint (progression-free survival in the hormone receptor–positive cohort) and key secondary endpoints (progression-free survival among all patients and overall survival in the hormone receptor–positive cohort and among all patients), the hormone-receptor status is based on data collected with the use of the interactive Web-response and voice-response system at the time of randomization, which includes patients who were mis-stratified. For the other end points, hormone-receptor status is based on data from the electronic data capture that was corrected for mis-stratification.

In the full analysis set, the median study duration (i.e., duration of follow-up) was 16.1 months (range: 0.3 to 33.1) in the T-DXd arm and 13.5 months (range: 0.0 to 27.8) in the TPC arm, with a median follow up of 18.4 months. The proportion of subjects still on treatment was greater in the T-DXd arm than in the TPC arm (15.6% vs. 1.7%, respectively).

7.2 Safety

7.2.1 Intervention and comparator

The safety profiles of T-DXd and TPC in the target population of this study were generally manageable and tolerable and consistent with the safety profile of previous clinical studies in the HER2 positive mBC setting. In DB04, no new safety concerns were identified.

Table 9 presents the overall safety summary for DB04, of the safety analysis set including both HR-positive and HR-negative patients. Treatment Emergent Adverse Events (TEAE) were reported in 99.5% of the patients in the T-DXd group and 98.3% of those in the TPC group had at least one adverse event (AE) that emerged or worsened after initiation of a trial drug until 47 days after the last dose of the trial drug.

The incidence of serious treatment emergent adverse events (TEAEs) was 27.8% in the T-DXd group and 25.0% in the TPC group, and the incidence of AEs of grade 3 or higher was 52.6% and 67.4%, respectively. The incidence of AEs associated with discontinuation of treatment was 16.2% in the T-DXd group and 8.1% in the TPC group, and the incidence of AEs associated with dose reductions was 22.6% and 38.4%, respectivelyTable 8.

A total of 14 patients (3.8%) in the T-DXd group and 5 patients (2.9%) in the TPC group had TEAEs that were associated with death. Drug-related deaths in the T-DXd group (1.9%) were due to pneumonitis (in 2 patients [0.5%]) and ischemic colitis, disseminated intravascular coagulation, dyspnoea, febrile neutropenia, and sepsis (in 1 patient [0.3%] each); there were no drug related deaths in the TPC group.

Table 9 Overall Safety Summary, Safety Analysis Set

Type of Adverse Events, n (%)	**T-DXd (n = 371)**		**TPC (n = 172)**	Difference, % (95 % CI)
Number of adverse events, n	369	169		
Number and proportion of patients with ≥1 adverse events, n (%)	369 (99.5)	169 (98.3)	0.01205 [-0.008884 , 0.03299].	
Number of serious adverse events*, n	103	43		
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	103 (27.8)	43 (25.0)	0.02763 [-0.05152 , 0.1068].	
Number of CTCAE grade ≥ 3 events, n	195	116		
Number and proportion of patients with ≥ 1 CTCAE grade 3 events § , n (%)	195 (52.6)	116 (67.4)	-0.1488 [-0.2353 , -0.06229].	
Number of adverse reactions, n	357	162		
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	357 (96.2)	162 (94.2)	0.0204 [-0.01958 , 0.06039].	
Number and proportion of patients who had a dose reduction, n (%)	86 (23.2)	80 (46.5)	-0.2333 [-0.3193 , -0.1473].	
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	313 (84.4)	169 (98.3)	-0.1389 [-0.1807 , -0.09708]	
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	60 (16.2)	14 (8.1)	0.08033 [0.02489 , 0.1358]	

In the T-DXd group, the most common drug-related AEs of any grade included nausea, fatigue, and alopecia, all of which were more frequent than in the physician's choice group.

7.2.2 Adverse events of special interest

Drug-related interstitial lung disease (ILD) or pneumonitis as adjudicated by an independent committee occurred in 45 patients (12.1%) who received T-DXd, including 13 (3.5%) with a grade 1 event, 24 (6.5%) with a grade 2 event, 5 (1.3%) with a grade 3 event, and 3 (0.8%) of which was adjudicated as a grade 5 event. Of the grade 5 events, 1 event was an investigator-assessed grade 3 event in a patient who died due to disease progression (>47 days after the last dose of T-DXd) and was adjudicated by the independent committee as being a grade 5 event. ILD or pneumonitis occurred in 1 patient (0.6%) who received the TPC; this patient, who received eribulin, had a grade 1 event. In the T-DXd group, the median time to onset in patients with ILD or pneumonitis was 129 days (range, 26 to 710).

Another AE of special interest is left ventricular ejection fraction (LVEF), which comprises *decreased ejection fraction* and *cardiac failure*. In the T-DXd group, left ventricular dysfunction was reported in 17 patients (4.6%) (decreased ejection fraction of grade 1 in 1 patient, of grade 2 in 14 patients, and of grade 3 in 1 patient and cardiac failure of grade 2 in 1 patient and of grade 3 in 1 patient). One patient initially had a decreased ejection fraction, then later had cardiac failure. Based on laboratory values of the left ventricular ejection fraction (LVEF), grade 2 events (10 to 19% decrease from baseline) were observed in 44 of 371 patients (11.9%) in the T-DXd group and in 10 of 172 patients (5.8%) in the TPC group. Grade 3 events (>20% decrease from baseline) were observed in 5 patients (1.5%) in the T-DXd group and no patients in the TPC group.

7.2.3 Comparative analyses of efficacy and safety

DB04 is a head to head study vs chemotherapy (TPC). The involved TPC regimens used in DB04 are in line with Danish clinical practice. With a direct comparing study vs established comparators it is not relevant to perform indirect comparisons (MAIC's etc.).

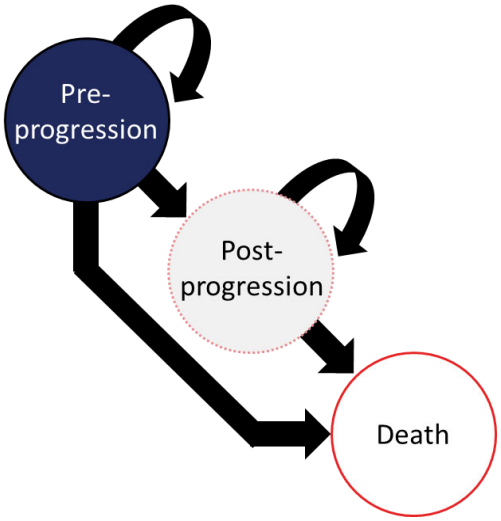
8. Health economic analysis

A cost-utility model that follow the DMC guidelines is provided in this submission, which is aligned with previous economic models of T-DXd that DMC has previously evaluated. An annual discount rate of 3.5% was used for both costs and benefits. A time horizon of 30 years was used in the base-case to ensure all relevant costs and health effects were included in the analysis. A three-week cycle length was selected as the most appropriate to reflect the treatment period for T-DXd and TPC. Half-cycle correction was applied in the base-case.

8.1 Model

The cost-utility model used in this submission contains three health states. Figure 11 presents the flow of patients in the model. All patients enter the model in the 'progression-free on treatment' state, receiving T-DXd or TPC. 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.

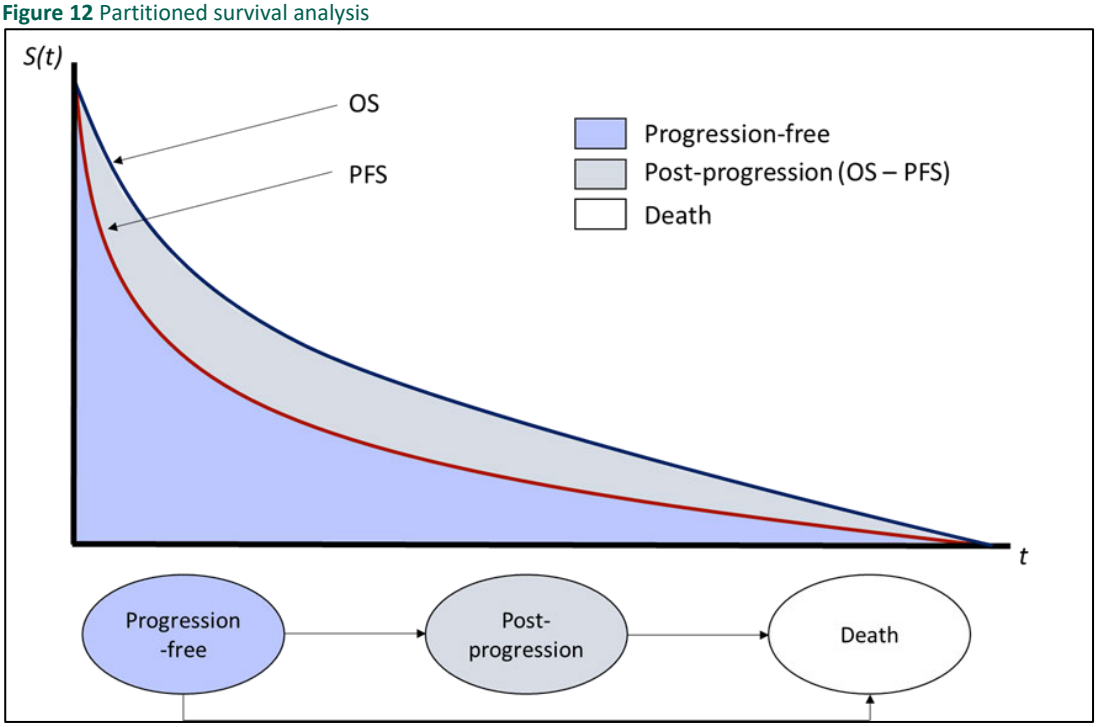
Figure 11 Model structure



Health state membership is determined using a partitioned survival analysis approach, which is a standard modelling approach for oncology products. To inform the partitioned survival analysis, parametric curves are fitted to OS, PFS and TTD data from DB04. 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 for various HTA authorities (20-22). These comprise of Exponential, Weibull, Log-normal, Log-logistic, Gompertz, Gamma, and Generalised gamma models.

Figure 12 graphically demonstrates how parametric survival curves are used to calculate health state occupancy. In the model, state membership is determined from a set of non-mutually exclusive survival curves using the area under the curve approach in PartSA (23). The curves that determine state membership are the PFS and OS curves reported in the clinical trial literature. The first curve, PFS, shows the proportion of patients remaining in the progression-free health state over time. The second curve, OS, provides insight into the survival of all patients still alive (i.e., the sum of patients in the progression-free and post-progression health states) as well as information about the membership in the death state. For the post-progression health state, state membership is derived from the difference between the OS curve and the PFS curve at each time point; this provides the proportion of patients who are alive but not progression-free.

Figure 12 Partitioned survival analysis



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

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

Table 10 shows a summary of the model input data and how they were obtained.

Table 10 Input data used in the model and how they were obtained

Name of estimates	Results from DESTINY-Breast04	Input value used in the model	How is the input value (column 3) obtained/estimated
Age	56.5	56.5	Obtained from DESTINY-Breast04 (19)
Weight	63.4	63.4	Obtained from DESTINY-Breast04
OS HR	0.6432	NA	Obtained from DESTINY-Breast04
[redacted]	[redacted]	[redacted]	Obtained from DESTINY-Breast04
[redacted]	[redacted]	[redacted]	Obtained from DESTINY-Breast04
[redacted]	[redacted]	[redacted]	Obtained from DESTINY-Breast04
[redacted]	[redacted]	[redacted]	Obtained from DESTINY-Breast04

Name of estimates	Results from DESTINY-Breast04	Input value used in the model	How is the input value (column 3) obtained/estimated
OS (months); T-DXd + TPC	23.4 (20.0-24.8) 16.8 (14.5-20.20)	24.8 17.3	Obtained from DESTINY-Breast04 and extrapolated in the model
PFS (months); T-DXd + TPC	9.9 (9.0-11.3) 5.1 (4.2-6.8)	9.7 4.8	Obtained from DESTINY-Breast04 and extrapolated in the model
[redacted]	[redacted]	[redacted]	Obtained from DESTINY-Breast04 and extrapolated in the model
Frequency per cycle - Specialist physician/ Oncologist	Not available	0.69	Average of expert opinion.
Frequency per cycle - Blood tests	Not available	0.69	Average of expert opinion.
Frequency per cycle - ECHO/MUGA-scanning, cardiological examination	Not available	0.23	Average of expert opinion.
Frequency per cycle - CT-scanning	Not available	0.23	Average of expert opinion.

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

The comparison with TPC, is aligned with current Danish clinical practice, as outlined in section 5.2. The most relevant study of T-DXd (DESTINY-Breast04) is used for the comparisons, with the purpose to assess the relative efficacy versus TPC.

8.2.2.1 Patient population

Patients expected to be treated with T-DXd are diagnosed with HER2-low mBC and have received one prior line of chemotherapy. These patients will be treated with T-DXd as the next line of therapy or later. Hence, the patient population considered in this submission is fully aligned with the DB04 study population and the approved indication of T-DXd.

Danish clinical practice:

As previously outlined and summarized in section 5, Danish standard of care for this patient group is currently to treat with a second line of chemotherapy. Based on Danish guidelines and feedback from Danish clinical experts, the TPC options of the control-arm of the DB04 study (i.e., eribulin, gemcitabine, capecitabine, paclitaxel, and nab-paclitaxel) are aligned with Danish guideline recommendations and real-world clinical practice for this patient group (12, 16, 17). See also sections 5.2.1 and 5.2.2 for additional discussions on the comparators and Danish clinical practice. Treatment options recommended in Danish guidelines and used in clinical practice are presented in detail in section 5.2.3.

Clinical documentation submitted in relation to clinical practice:

Clinical documentation for the studied patient population can be found in section 5. DESTINY-Breast04 is the main source of evidence for this submission, which was deemed reflective of the patient population in clinical practice by Danish clinical experts (12, 16).

Minor differences were pointed out by the clinical experts, including that they would expect more (~90%) HR+ patients to be treated with CDK4/6 inhibitors (compared with ~70% in DB04), and that and a smaller proportion of patients would be Asian in Denmark. These differences are not expected to have an impact on the generalisability of the results of DB04 to the Danish setting (12, 16).

Danish clinical experts stated that the proportion of patients with liver metastasis in DB04 (71.3% in T-DXd and 66.8% in the TPC arm) is higher than what they would expect to see in the Danish setting.

Table 11 Clinical documentation submitted in relation to clinical practice – Patient population

Parameter	Clinical documentation (2)	Used in the model	Danish clinical practice
Age (years) Mean (std dev)	56.5	56.5	Similar
Female sex (%)	99.6%	99.6%	Similar
Region		N/A	Less Asian patients (<5%)
Asia	213 (38.2)		
Europe or Israel	251 (45.1)		
North America	93 (16.7)		
Weight (kg)			Similar
Mean (std dev)	63.4	63.4	
Median		N/A	
Height (cm)			
Mean	160	160	Slightly taller
Median	160	N/A	
Stratification factor HER2 status by IHC/ISH			
IHC 1+	321 (57.6)	N/A	
IHC 2+/ISH-	236 (42.2)		
Hormone receptor - no (%) [a]		N/A	Similar
Positive	499 (98.6)		
Negative	58 (10.4)		
Creatinine Clearance at Baseline		N/A	
Mean (SD)	93.6 (30.26)	N/A	
Median	91.9	N/A	
Baseline CNS metastases		N/A	
Yes	32 (5.7)	N/A	
No	525 (94.3)	N/A	
ECOG Performance Status		N/A	More with ECOG 2 in Denmark (5-10%)
0	305 (54.8)	N/A	
1	252 (45.2)		
≥2	0		

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-low breast cancer regardless of HR status. T-DXd is given as intravenous infusion once every 3 weeks until disease progression.

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-Breast04 ([redacted]/kg when considering dose-reductions).

Clinical documentation submitted in relation to clinical practice:
Clinical documentation for the intervention can be found in section 7. The potential use in clinical practice is expected to follow the use in the study (12, 16).

Table 12 Clinical documentation submitted in relation to clinical practice – intervention

Intervention	Clinical documentation (including source) (2)	Used in the model (number/value includings source)	Expected Danish clinical practice (including source if known)
Posology	[redacted] kg (19)	[redacted] kg	[redacted] mg/kg capture expected dose-reductions and interruptions that will also take place in clinical practice.
Length of treatment (median, extrapolated)	[redacted] months	[redacted] months	Treatment duration in the DESTINY-Breast04.
The pharmaceutical's position in the Danish clinical practice	2L+	2L+	T-DXd will, if approved, be used where TPC is used today. That is in 2L+ according to Danish clinical experts.

Key: RDI: relative dose intensity

8.2.2.3 Comparators

DESTINY-Breast04 provides data of T-DXd versus standard of care (physicians choice of chemotherapy, TPC). Additional clinical documentation of TPC is provided in section 5.2. The relative effectiveness results based on a head-to-head study are provided in section 7.

Danish clinical practice:
According to clinical experts, the Danish clinical practice for 2L treatment (+/and beyond) of HER2-low mBC follows the Danish guidelines and are presented in section 5.2.2. In summary most patients appropriate for treatment with T-DXd, based on DESTINY-Breast04, are currently treated with chemotherapies such as eribulin, capecitabine, and paclitaxel.

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 (12, 16).

Table 13 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	Capecitabine: 1250 mg/m2 Eribulin: 1.23 mg/m2 Gemcitabine: 1250 mg/m2 (24) Paclitaxel: 175 mg/m2 (25) Nab-paclitaxel: 260 mg/m2	Capecitabine: 1250 mg/m2 (16) Eribulin: 1.23 mg/m2 (25) Gemcitabine: 1250 mg/m2 (26) Paclitaxel: 175 mg/m2 (26) Nab-paclitaxel: 260 mg/m2 (26)	RDI obtained from DB04 expected to capture expected dose-reductions and interruptions that will also take place in clinical practice.
Length of treatment (extrapolated)	[redacted] months	[redacted] months	Treatment duration in the DESTINY-Breast04, 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-Breast04 showed that T-DXd is more effective than the treatment currently used in Danish standard of care (see section 7).

Table 14 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: 9.7 months (extrapolated) TPC: 4.8 months (extrapolated)	T-DXd: 9.9 months TPC: 5.1 months
Secondary endpoint: Median OS	T-DXd: 24.8 months (extrapolated) TPC: 17.3 months (extrapolated)	T-DXd: 23.4 months TPC: 16.8 months

Table 15 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)	BICR, KM-method	Highly relevant	Progression is known to impact the patients' quality of life. Progression-free survival is also a frequently used surrogate enpoint for overall surival, which often is the main goal of the treatment.
Secondary endpoint: • Median OS	KM-method	Highly relevant	Prolonging overall surival is the main goal of the treatment for HER2-low mBC.

8.2.2.5 Adverse reaction outcomes

The safety profile of T-DXd and TPC is presented in section 7.2. The clinical documentation submitted is fully aligned with the health economic model as shown in section 8.5.4.

8.3 Extrapolation of relative efficacy

8.3.1 Time to event data – summarized:

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 TPC and T-DXd arms were taken from DESTINY-Breast04. For PFS, OS and time to treatment discontinuation (TTD), standard parametric models (Exponential, Weibull, Log-normal, Log-logistic, Gompertz, Generalised gamma and Gamma) were fitted to the data from DESTINY-Breast04 in line with best practice.

Curve selection for extrapolations of OS, PFS and TTD curves were carried out systematically in line with guidelines from HTA authorities (21, 22, 27, 28):

- 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-Breast04.

- Clinical validity and biologically plausibility were assessed using feedback from Danish mBC experts and published literature.

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 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.

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 when modelling the TPC arm.

Additional details of the parameterization are provided in Appendix G Extrapolation.

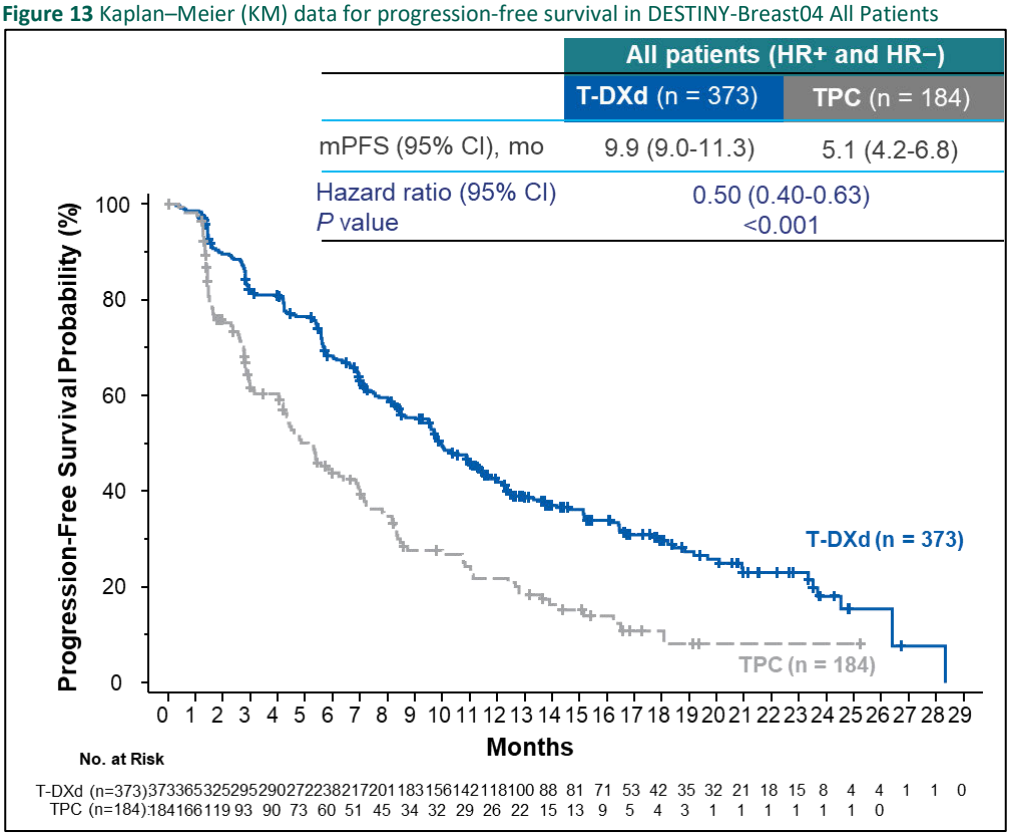
8.3.1.1 Progression-free survival

This section provides the distributions chosen for the extrapolation of T-DXd and TPC and justification for the choices based on AIC values, BIC values, visual inspection, and clinical plausibility. This information can be used to select the distributions in the 'Set Distributions' tab. Given that the PH assumption holds, the same distribution was chosen for both treatment arms.

Proportional hazards

Dependent survival models are used in the model as the proportional hazard (PH) assumption did hold for PFS when it was tested.

Figure 13 Kaplan–Meier (KM) data for progression-free survival in DESTINY-Breast04 All Patients



Source: Modi et al. 2022. (2)

Post – study follow-up: statistical fit

Table 16 shows that the log normal distribution seems to be the best-fitting extrapolation for the PFS data of T-DXd and TPC, based on the AIC and BIC values, closely followed by the generalised gamma distribution.

Table 16 Progression-free survival All Patients – AIC/BIC

Distribution		
	AIC	BIC
Exponential	2567.474	2576.119
Weibull	2557.302	2570.269
Gompertz	2566.837	2579.805
Log-Logistic	2543.761	2556.728
Log normal	**2537.006**	**2549.974**
Generalised gamma	2538.175	2555.465
Gamma	2552.155	2565.122

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

Economic modelling experts were consulted in the process of developing this dossier, who advised that other criteria such as clinical plausibility should be assessed to support the selection of curves, given that the differences in AIC scores are very marginal.

Post – study follow-up: visual fit

Visual inspection of the log normal, log-logistic, and generalised gamma extrapolations (the best fits based on AIC and BIC) of the T-DXd PFS curve confirmed a good fit, Figure 14.

Figure 14 Log-logistic, log normal, and generalised gamma extrapolations of T-DXd PFS with KM curve of DB04 All Patients

Similarly, the log normal, log-logistic, and generalised gamma extrapolations of the TPC arm for PFS confirmed a good fit, Figure 15.

Figure 15 Log-logistic, log normal, and generalised gamma extrapolations of TPC PFS with KM curve of DB04 All Patients

Post – study follow-up: Clinical plausibility

Table 17 shows the results of the extrapolations on median PFS (months) and 5-year PFS (%). Minor differences were observed on median PFS in both treatment arms, as PFS data from DB04 is mature.

Clinical experts in Denmark and the Nordics found this challenging to assess. While log-normal provided best scores based on goodness of fit, it was also pointed out that it may overestimate the extrapolation as there are few patients in this setting with PFS at 5 years. When exploring clinically plausible options, by looking at the 5-year PFS in the TPC arm in discussions with clinical experts, it was suggested that Generalised gamma could be another preferred choice as it yielded five-year PFS slightly lower than log normal.

Table 17 Clinical plausibility according to Danish clinical experts – PFS All Patients

Model	TPC		T-DXd	
	5-year PFS (%)	Median (months)	5-year PFS (%)	Median (months)
Exponential	0.04	4.8	1.7	9.7
Weibull	0.002	5.5	0.5	10.4
Log-normal	1.2	4.8	4.8	9.0
Log-logistic	1.9	4.8	5.6	9.7
Gompertz	0.0001	5.5	0.02	10.4
Generalised Gamma	0.7	4.8	3.8	9.7
Gamma	0.01	5.5	0.6	10.4

Considering expert opinion, goodness of fit and visual inspection, the generalised gamma distribution was selected for modelling both the T-DXd and TPC cohort in the model. Furthermore, it is noted that the use of this distribution produces a median PFS of 9.7 months for T-DXd and 4.8 months for TPC in the model, and median PFS in DB04 was 9.9 (95% CI, 9.0–11.3) and 5.1 (95% CI, 4.2–6.8) in the T-DXd and TPC arm, respectively.

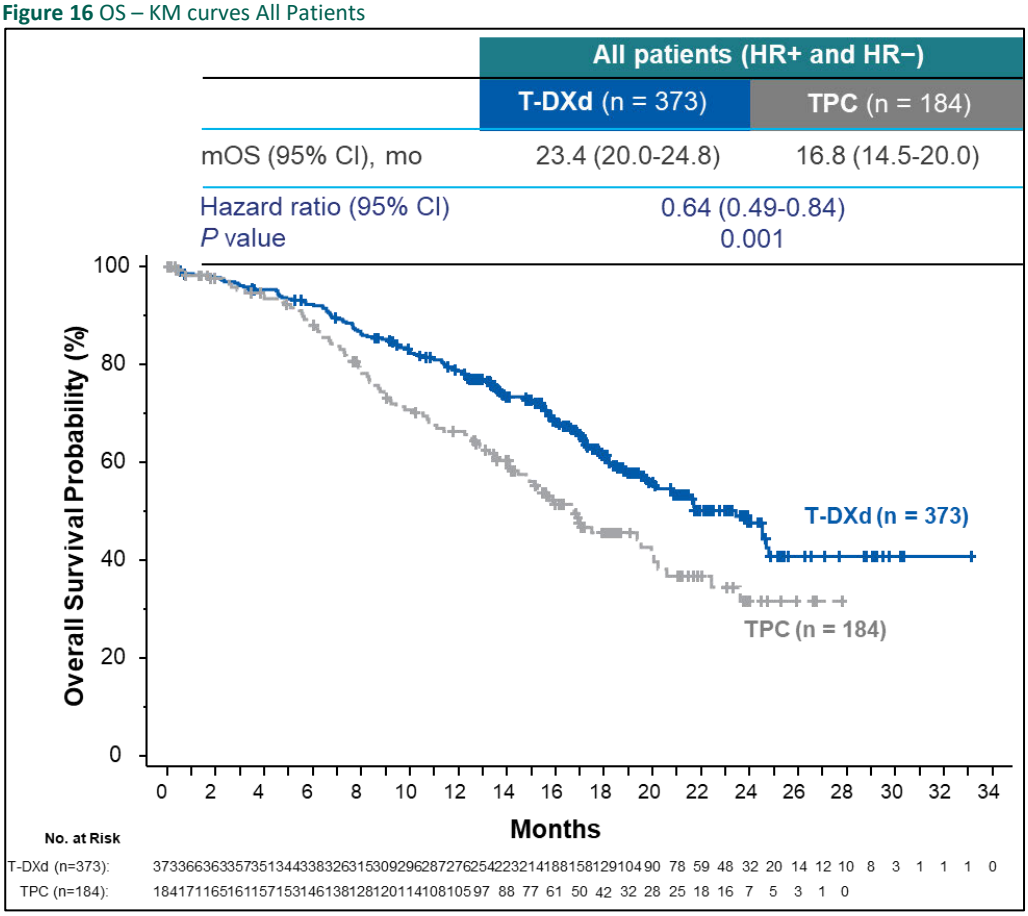
See section 8.5.1 for the approach taken on selecting the distribution to model time to treatment discontinuation (TTD).

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. Schoenfeld residuals results do not show a clear trend over time, and the associated statistical test for proportionality shows a p-value that is not significant (p=0.093); this means that the hypothesis that the assumption holds cannot be rejected, this is shown in Figure 16 and assessed in detail in Appendix G Extrapolation.

Figure 16 OS – KM curves All Patients



Source: Modi et al. 2022. (2)

Post – study follow-up: statistical fit

In general, there is a small difference between the AIC values of most of the curve distributions, as shown in Table 18.

Table 18 OS All Patients – AIC/BIC

Model	AIC	BIC
Exponential	2155.504	2164.149
Weibull	2116.056	2129.023
Gompertz	2121.115	2134.082
Log-logistic	2120.827	2133.794
Log normal	2149.354	2162.321
Generalised gamma	2117.657	2134.947
Gamma	2118.648	2131.616

Post – study follow-up: Visual fit

Visual inspection of the extrapolations of the T-DXd OS curve confirmed a good fit specifically for the extrapolations using the exponential, log normal and log logistic models, see Figure 17.

Figure 17 All extrapolations of T-DXd OS with KM curve of DB04 All Patients

Similarly, the extrapolations of the TPC OS curve confirmed a good fit for the extrapolations using the exponential, log normal and log logistic models, Figure 18.

Figure 18 All extrapolations of TPC OS with KM curve of DB04 All Patients

Median OS is 23 to 26 months for patients treated with T-DXd when using the various extrapolation methods, which is close to the median OS of 23.4 months (95% CI, 20.0–24.8) observed in the DB04 trial. For patients in the TPC arm, the median OS is 16 to 17 months depending on extrapolated distribution, and the median OS observed in the DB04 trial was 16.8 months (95% CI, 14.5–20.0).
Hence, published long-term follow-up, Nordic registry data and input from clinical experts were also considered in the selection of the most appropriate curve for modelling the base case.

Post – study follow-up: Clinical plausibility

It is difficult for Danish and Nordic clinical experts to assess the clinical plausibility of the OS extrapolation of T-DXd given the unprecedented PFS in DESTINY-Breast04 and limited available long-term data. They described that few patients are alive at 5 years; however, it was noted that the 5-year OS is likely to be somewhere around 10-20% in the overall cohort, which was true for all curves except for the Gompertz, Weibull and Generalised gamma curves. The clinical experts also noted that there were only minor differences in the extrapolated median OS (12, 16).

Table 19 Clinical plausibility according to Danish clinical experts – OS All Patients

Model	TPC		T-DXd	
	5-year OS* (%)	Median (months)	5-year OS* (%)	Median (months)
Exponential	9.4	17.3	20.9	26.2
Weibull	1.1	16.6	5.9	22.8
Log-normal	14.4	17.9	22.7	25.5
Log-logistic	10.0	16.6	16.8	23.5
Gompertz	0.0001	17.3	0.02	22.8
Generalised Gamma	0.5	16.6	4.0	22.8
Gamma	3.0	16.6	9.6	23.5

*Adjusted for background mortality

The selection between the clinically plausible curves was then based on how the extrapolation matched up with the best available long-term data.

Overall survival versus long-term data: TPC arm

Supported by clinical experts two recent and relevant registration studies of eribulin, EMBRACE and eribulin Study 301, were used to validate the extrapolation of the TPC arm given the use of similar treatments in these studies. Twelves et al. (29) published a long-term pooled analysis of these trials, where the effect of eribulin versus a control arm is reported. The OS outcomes reported in this study, for both the eribulin and comparator arms, are expected to be worse compared to the long-term OS of the TPC arm in the DESTINY-Breast04 trial. This is expected for the following reasons:

- Improvements have been seen during the last ten years in treating mBC (both with regards to pharmaceuticals and other technologies).
- The five-year survival for patients with mBC has improved over the past decade. Data from Norway show that five-year survival was 24.5% when the EMBRACE/Study 301 trial was initiated and ~36.6% when the DESTINY-Breast04 trial started (30). Norwegian data is deemed to be an appropriate proxy for Denmark, as data on mBC is not captured in Danish registries.
- There were more patients with TNBC status in the pooled analysis (~23%) (29) than in the DESTINY-Breast04 trial and what is expected in a HER-low population (<10%) (31). These patients are well-known to have a poorer prognosis (32).
- Twelves et al reported median PFS values of 4.0 and 3.4 months for the eribulin and control arms respectively (29), while the median PFS value for the TPC arm in the DESTINY-Breast04 study was 5.1 months (2). This indicates that the patients in the study by Twelves et al are expected to have poorer prognosis compared to the patients in the TPC arm in DESTINY-Breast04.

An OS validation curve was constructed using the DESTINY-Breast04 KM data of the TPC arm up to 19.4 months and the long-term data from the Twelves et al. study beyond that timepoint. For constructing the OS validation curve, the DB04 TPC KM curve was used up to 19.4 months to avoid including the immature tail of the KM curve. It was noted that beyond this timepoint less than 20% of the patient population is at risk.

Considering the poorer prognosis of the patients in the Twelves study, it is reasonable to assume that a clinically plausible OS extrapolation generated by the health economic model for the TPC arm should lie above the OS validation curve.

In the TPC arm of DB04, 51.1% of patients received eribulin and the remaining proportion of patients received other treatment options. Therefore, it was considered relevant to include both curves by Twelves et al. to generate the OS validation curve (Figure 19).

Both the eribulin and control OS KM curves were digitized, and a weighted average of the survival estimates was calculated by time point, i.e., “eribulin survival at time x” * 51.1% + “control survival at time x” * 48.9% (Figure 20). Then, the conditional survival rates per time point extracted from the digitization were applied to the proportion of patients having survived to 19.4 months in DB04. The OS validation curve is presented in Figure 21.

Figure 19 OS KM curves presented by Twelves et al. (top) and digitized OS KM curves using Twelves et al. with weighted average OS curve (51.1% on eribulin based on DB04) (bottom)

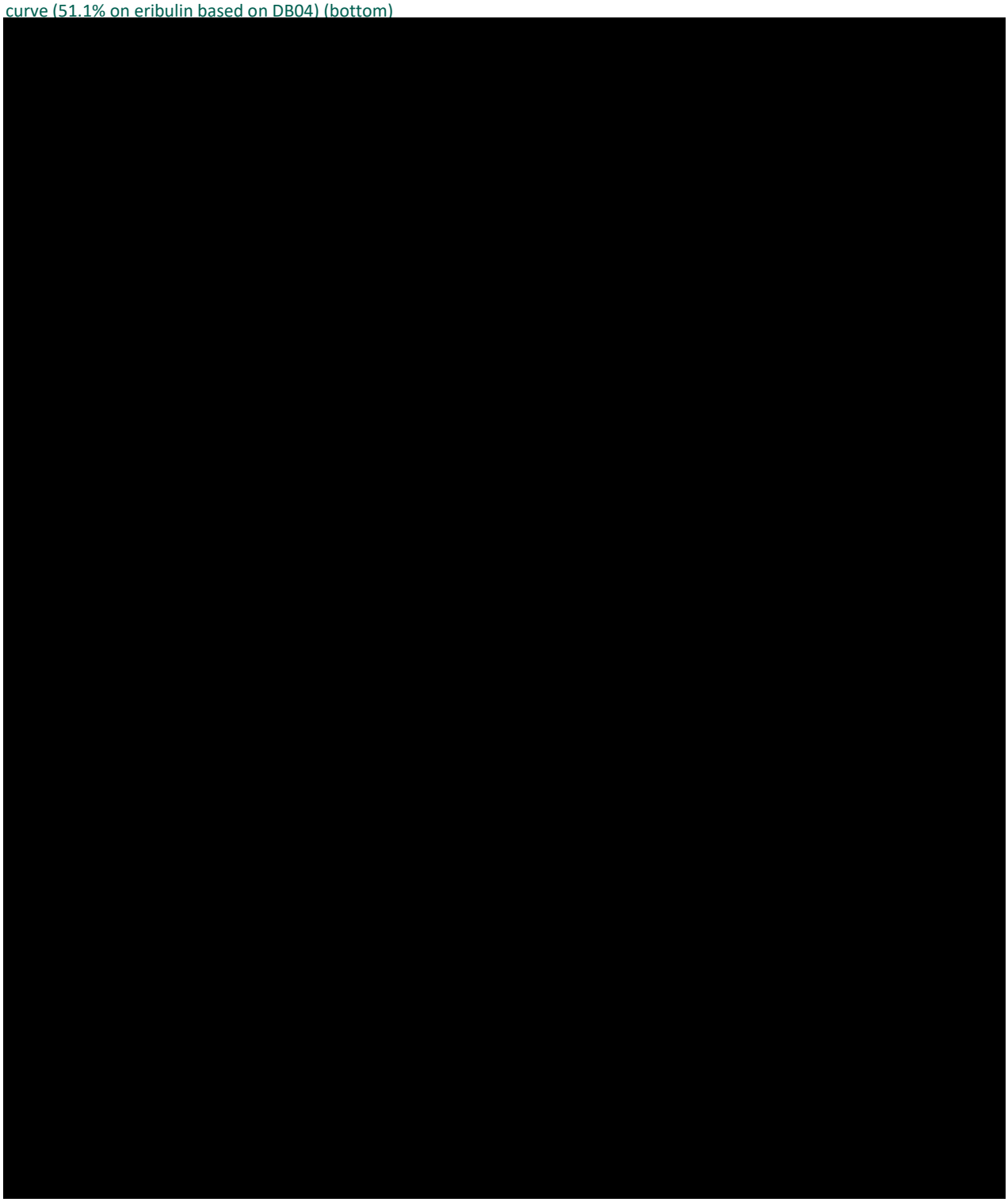


Figure 20 Curves used for the validation of the DB04 extrapolated TPC OS

While the Log-logistic and Exponential distributions provided a reasonably good fit only the log normal distribution generated long-term OS estimates that were lying above both the OS validation curve and the Twelves weighted average OS curve (51.1% on eribulin based on DB04) and could therefore be deemed clinically plausible, see Figure 21 and Figure 22.

Figure 21 TPC OS extrapolations with KM curve of DB04 All Patients and OS validation curve

Figure 22 TPC OS extrapolations with KM curve of DB04 All Patients, OS validation curve and Twelves weighted average OS curve (51.1% on eribulin based on DB04)

Overall survival versus long-term data: T-DXd arm

The Danish clinical experts expect that the long-term survival for the T-DXd patient population will be longer compared to that of the population treated with TPC (12, 16).

There is no other treatment with comparable PFS to what T-DXd showed in DESTINY-Breast04, which makes it difficult to validate the long-term extrapolation of the T-DXd OS results versus other published studies.

However, it is reasonable to assume that the hazard should be lower when extrapolating T-DXd than with chemotherapy given the proportional hazards shown in DB04. Hence, survival extrapolations that are below this curve or with a steeper slope can been ruled out (Weibull, Gompertz, Generalised Gamma and Gamma). As the log-logistic closely matches the extrapolated survival according to the eribulin study, we believe that it is overly conservative to assume that the long-term survival with T-DXd would not be higher than that with eribulin, see Figure 23. Further the slope of the extrapolated Log-logistic curve is also steeper than of the curve based on eribulin data from Twelves et al., therefore, Log-Logistic was also ruled out as an appropriate model to extrapolate T-DXd OS data.

Considering these aspects with regards to the T-DXd arm, the log normal curve was deemed appropriate and clinically plausible.

Figure 23 TPC OS extrapolations with KM curve of DB04 All Patients, OS validation curve and Twelves Eribulin-arm

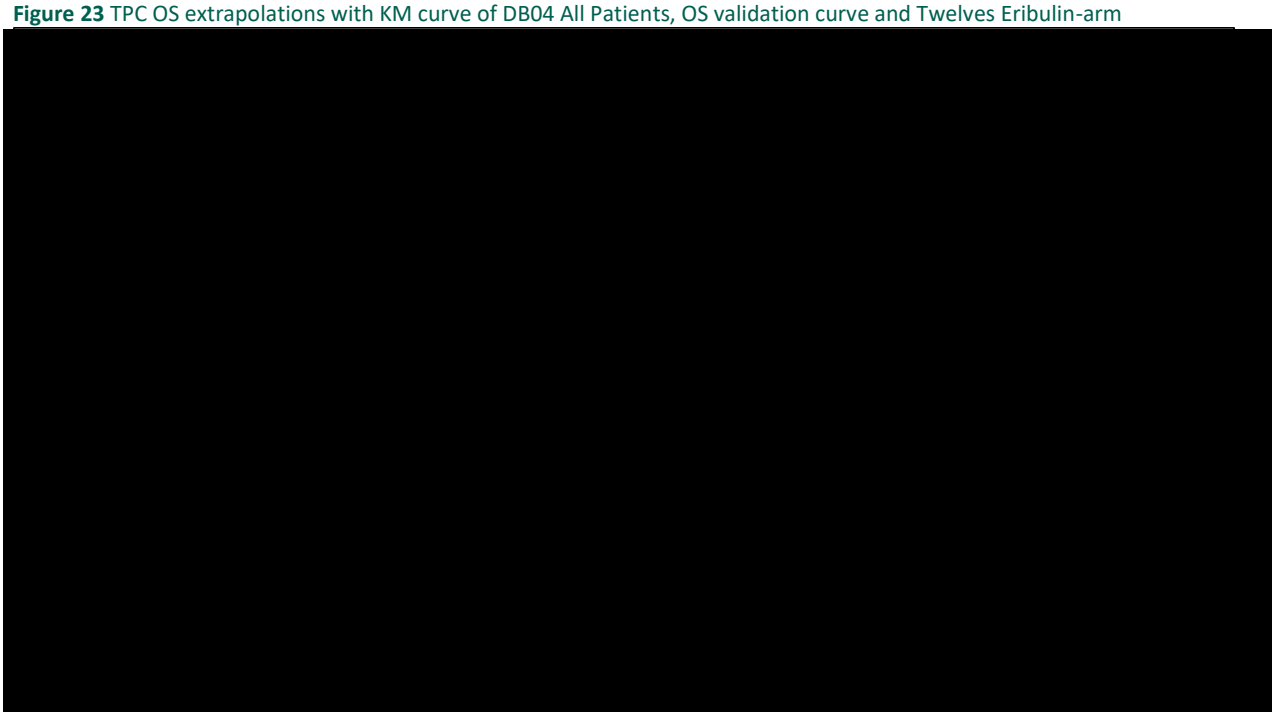


Table 20 shows a summary of the external data used to validate the extrapolations.

Table 20 External validation of the modelling

	Progression-free survival			Overall survival			
Source	**1 year**	**3 years**	**5 years**	**1 year**	**3 years**	**4 years**	**5 years**
TPC							
Modelled TPC arm	**21%**	2.7%	0.7%	**65%**	27%	19%	14%
OS validation curve				**66%**	20%	15%	
Twelves et al. (29) weighted average OS				**59%**	**17%**	13%	
T-DXd							
Modelled T-DXd arm	**43%**	10%	3.8%	**75%**	38%	29%	23%

Based on the rationale above, and the visual fit of the different distributions, the log-normal model was selected for both T-DXd and TPC, as it is the only model with good visual fit which also provides clinically plausible extrapolations for TPC and T-DXd.

Curve selection

The curve selection for the base-case analysis is provided in Table 21.

Table 21 Curve selection in the base-case

Parameter	Selected curve	Summary of rationale
Progression-free survival	Generalised gamma	Good visual fit One of the best statistical fits Clinically plausible for both arms
Overall survival	Log-normal	Good visual fit Best fit considering published literature of long-term follow-up

Parameter	Selected curve	Summary of rationale
		Most clinically plausible

Selection of the appropriate curves was informed by multiple criteria. For the PFS extrapolation, the Generalised gamma survival curve had good statistical fit and good visual fit and was deemed clinically plausible. The Generalised gamma curves were also deemed relevant to use for extrapolating TTD, which should follow the same pattern as PFS as they are closely linked.

The rationale for extrapolation of OS is described in detail in section 8.3.1.2.

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

In DESTINY-Breast04, EQ-5D-5L, EORTC QlQ-BR45 and EORTC QLQ-C30 questionnaires were administered to patients to measure HRQoL, similar to the study design of DESTINY-Breast03.
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.
Reasons for missing questionnaires were not collected in the study. No additional methods were applied to adjust for missing data in the analyses.

8.4.1 Response rates and compliance

The PROM completion compliance rate in the FAS at baseline was 97.1% in the T DXd arm and 92.9%% in the TPC arm for the EORTC QLQ-C30 (Table 22); 96.4% for T-DXd and 92.6% for TPC for the EORTC QLQ-BR45 (Table 23); and 96.1% for T-DXd and 92.0% for TPC for the EQ 5D 5L questionnaire (Table 24).
Post-baseline compliance rates from Cycle 2 through Cycle 49 (n = 222) in the T-DXd arm ranged from 94.6% to 89.5% for the EORTC QLQ-C30, from 94.9% to 89.9% for the EORTC QLQ-BR45, and from 94% to 89.5% for the EQ-5D-5L.
Post-baseline compliance rates from Cycle 3 through Cycle 27 (n = 117) in the TPC arm ranged from 97.1% to 86.8% for the EORTC QLQ-C30, from 97.1% to 86.8% for the EORTC QLQ-BR45, and from 97.1% to 86.0% for the EQ-5D-5L.

Table 22 Summary of QoL completion compliance - Full Analysis Set EORTC QLQ-C30

		T-DXd (N=373)		TPC (N=184)	
Questionnaire	Visit	n(%) [a]	Compliance Rate (%) [b]	n(%) [a]	Compliance Rate (%) [b]
EORTC QLQ-C30 v3	Baseline	362 (97.1)	362/373 (97.1)	171 (92.9)	171/184 (92.9)
	C2D1	336 (90.1)	336/355 (94.6)	154 (83.7)	154/159 (96.9)
	C3D1	321 (86.1)	321/328 (97.9)	132 (71.7)	132/137 (96.4)
	C5D1	279 (74.8)	279/301 (92.7)	83 (45.1)	83/93 (89.2)
	C7D1	256 (68.6)	256/267 (95.9)	55 (29.9)	55/66 (83.3)
	C9D1	217 (58.2)	217/233 (93.1)	34 (18.5)	34/42 (81.0)
	C11D1	189 (50.7)	189/200 (94.5)	25 (13.6)	25/29 (86.2)
	C13D1	148 (39.7)	148/162 (91.4)	20 (10.9)	20/21 (95.2)
	C15D1	131 (35.1)	131/141 (92.9)	13 (7.1)	13/13 (100)
	C17D1	103 (27.6)	103/116 (88.8)	10 (5.4)	10/10 (100)
	C19D1	90 (24.1)	90/100 (90.0)	9 (4.9)	9/10 (90.0)
	C21D1	73 (19.6)	73/82 (89.0)	8 (4.3)	8/9 (88.9)
	C23D1	58 (15.5)	58/66 (87.9)	6 (3.3)	6/6 (100)
	C25D1	48 (12.9)	48/56 (85.7)	4 (2.2)	4/4 (100)
	C27D1	37 (9.9)	37/39 (94.9)	1 (0.5)	1/1 (100)
	C29D1	26 (7.0)	26/29 (89.7)	0	0
	C31D1	17 (4.6)	17/21 (81.0)	0	0
	C33D1	15 (4.0)	15/17 (88.2)	0	0
	C35D1	12 (3.2)	12/13 (92.3)	0	0
	C37D1	3 (0.8)	3/6 (50.0)	0	0
EORTC QLQ-C30 v3	C39D1	3 (0.8)	3/3 (100)	0	0
	C41D1	3 (0.8)	3/3 (100)	0	0
	C43D1	1 (0.3)	1/1 (100)	0	0
	C45D1	1 (0.3)	1/1 (100)	0	0
	C47D1	1 (0.3)	1/1 (100)	0	0
	C49D1	1 (0.3)	1/1 (100)	0	0
	End of Treatment	254 (68.1)	254/284 (89.4)	133 (72.3)	133/156 (85.3)
	40 Day Follow-Up	89 (23.9)	89/110 (80.9)	60 (32.6)	60/74 (81.1)
	3 Months Follow-Up	140 (37.5)	140/140 (100)	76 (41.3)	76/76 (100)

Notes: Visit is based on window rule specified in SAP. Compliance rate is calculated from the number of subjects completing the QoL form at the specified visit. [a] Percentages are based on total number of subjects in the Full Analysis Set as denominator.[b] Percentages are based on number of on-going subjects in the Full Analysis Set as denominator at each visit.

Table 23 Summary of QoL completion compliance - Full Analysis Set - EORTC QLQ-BR45

		T-DXd (N=373)		TPC (N=184)	
Questionnaire	Visit	n(%) [a]	Compliance Rate (%) [b]	n(%) [a]	Compliance Rate (%) [b]
EORTC QLQ-BR45 v3	Baseline	360 (96.5)	360/373 (96.5)	170 (92.4)	170/184 (92.4)
	C2D1	337 (90.3)	337/355 (94.9)	154 (83.7)	154/159 (96.9)
	C3D1	322 (86.3)	322/328 (98.2)	132 (71.7)	132/137 (96.4)
	C5D1	279 (74.8)	279/301 (92.7)	83 (45.1)	83/93 (89.2)
	C7D1	257 (68.9)	257/267 (96.3)	55 (29.9)	55/66 (83.3)
	C9D1	216 (57.9)	216/233 (92.7)	34 (18.5)	34/42 (81.0)
	C11D1	188 (50.4)	188/200 (94.0)	25 (13.6)	25/29 (86.2)
	C13D1	147 (39.4)	147/162 (90.7)	20 (10.9)	20/21 (95.2)
	C15D1	132 (35.4)	132/141 (93.6)	13 (7.1)	13/13 (100)
	C17D1	103 (27.6)	103/116 (88.8)	10 (5.4)	10/10 (100)
	C19D1	90 (24.1)	90/100 (90.0)	9 (4.9)	9/10 (90.0)
	C21D1	74 (19.8)	74/82 (90.2)	8 (4.3)	8/9 (88.9)
	C23D1	58 (15.5)	58/66 (87.9)	6 (3.3)	6/6 (100)
	C25D1	48 (12.9)	48/56 (85.7)	4 (2.2)	4/4 (100)
	C27D1	37 (9.9)	37/39 (94.9)	1 (0.5)	1/1 (100)
	C29D1	26 (7.0)	26/29 (89.7)	0	0
	C31D1	17 (4.6)	17/21 (81.0)	0	0
	C33D1	15 (4.0)	15/17 (88.2)	0	0
	C35D1	12 (3.2)	12/13 (92.3)	0	0
	C37D1	3 (0.8)	3/6 (50.0)	0	0
EORTC QLQ-BR45 v3	C39D1	3 (0.8)	3/3 (100)	0	0
	C41D1	3 (0.8)	3/3 (100)	0	0
	C43D1	1 (0.3)	1/1 (100)	0	0
	C45D1	1 (0.3)	1/1 (100)	0	0
	C47D1	1 (0.3)	1/1 (100)	0	0
	C49D1	1 (0.3)	1/1 (100)	0	0
	End of Treatment	255 (68.4)	255/284 (89.8)	133 (72.3)	133/156 (85.3)
	40 Day Follow-Up	89 (23.9)	89/110 (80.9)	60 (32.6)	60/74 (81.1)
	3 Months Follow-Up	140 (37.5)	140/140 (100)	76 (41.3)	76/76 (100)

Notes: Visit is based on window rule specified in SAP. Compliance rate is calculated from the number of subjects completing the QoL form at the specified visit.

[a] Percentages are based on total number of subjects in the Full Analysis Set as denominator.

[b] Percentages are based on number of on-going subjects in the Full Analysis Set as denominator at each visit.

Table 24 Summary of QoL completion compliance - Full Analysis Set - EQ-5D-5L

		T-DXd (N=373)		TPC (N=184)	
Questionnaire	Visit	n(%) [a]	Compliance Rate (%) [b]	n(%) [a]	Compliance Rate (%) [b]
EQ-5D-5L	Baseline	359 (96.2)	359/373 (96.2)	170 (92.4)	170/184 (92.4)
	C2D1	335 (89.8)	335/355 (94.4)	154 (83.7)	154/159 (96.9)
	C3D1	322 (86.3)	322/328 (98.2)	132 (71.7)	132/137 (96.4)
	C5D1	279 (74.8)	279/301 (92.7)	81 (44.0)	81/93 (87.1)
	C7D1	255 (68.4)	255/267 (95.5)	55 (29.9)	55/66 (83.3)
	C9D1	215 (57.6)	215/233 (92.3)	34 (18.5)	34/42 (81.0)
	C11D1	187 (50.1)	187/200 (93.5)	25 (13.6)	25/29 (86.2)
	C13D1	146 (39.1)	146/162 (90.1)	20 (10.9)	20/21 (95.2)
	C15D1	130 (34.9)	130/141 (92.2)	13 (7.1)	13/13 (100)
	C17D1	103 (27.6)	103/116 (88.8)	10 (5.4)	10/10 (100)
	C19D1	90 (24.1)	90/100 (90.0)	9 (4.9)	9/10 (90.0)
	C21D1	74 (19.8)	74/82 (90.2)	8 (4.3)	8/9 (88.9)
	C23D1	58 (15.5)	58/66 (87.9)	6 (3.3)	6/6 (100)
	C25D1	48 (12.9)	48/56 (85.7)	4 (2.2)	4/4 (100)
	C27D1	37 (9.9)	37/39 (94.9)	1 (0.5)	1/1 (100)
	C29D1	27 (7.2)	27/29 (93.1)	0	0
	C31D1	17 (4.6)	17/21 (81.0)	0	0
	C33D1	15 (4.0)	15/17 (88.2)	0	0
	C35D1	11 (2.9)	11/13 (84.6)	0	0
	C37D1	3 (0.8)	3/6 (50.0)	0	0
EQ-5D-5L	C39D1	3 (0.8)	3/3 (100)	0	0
	C41D1	3 (0.8)	3/3 (100)	0	0
	C43D1	1 (0.3)	1/1 (100)	0	0
	C45D1	1 (0.3)	1/1 (100)	0	0
	C47D1	1 (0.3)	1/1 (100)	0	0
	C49D1	1 (0.3)	1/1 (100)	0	0
	End of Treatment	254 (68.1)	254/284 (89.4)	132 (71.7)	132/156 (84.6)
	40 Day Follow-Up	89 (23.9)	89/110 (80.9)	60 (32.6)	60/74 (81.1)
	3 Months Follow-Up	140 (37.5)	140/140 (100)	76 (41.3)	76/76 (100)

Notes: Visit is based on window rule specified in SAP. Compliance rate is calculated from the number of subjects completing the QoL form at the specified visit.

[a] Percentages are based on total number of subjects in the Full Analysis Set as denominator.

[b] Percentages are based on number of on-going subjects in the Full Analysis Set as denominator at each visit.

More information on HRQoL is available in Appendix I Documentation and mapping of HRQoL data.

8.4.2 Baseline utility values

Table 25 Summary of baseline HRQoL values at baseline – Full Analysis Set

	T-DXd	TPC
EORTC QLQ-C30 Global Health status	[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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	T-DXd	TPC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

8.4.3 Overview of health state utility values (HSUV)

In the DESTINY-Breast04 trial, health related quality of life (HRQoL) was captured using EQ-5D-5L. For this economic evaluation, utilities were calculated from DB04 using a data driven mixed model approach. Utility scores for the EQ-5D-5L dimensions were computed using the Danish value set (33). A systematic literature review was also conducted to identify health state utility values, but no relevant data was identified (Appendix H – Literature search for HRQoL data).

EQ-5D-5L utility scores from all available timepoints in the DB04 trial, including baseline, were included in a linear mixed model as a dependent variable. The model selection was based on a backward elimination approach. The initial full model included treatment, age, number of metastatic sites, ECOG performance status, progression status (progression versus progression-free) at the corresponding visit, treatment status (on-treatment versus off-treatment) at the corresponding visit, and interaction terms between each health state of interest and treatment (i.e., progression status*treatment, treatment status*treatment). For the model constructed using the Full Analysis Set (All Patients), HR status (HR-positive versus HR-negative) was equally included in the model. A complete overview of mixed models used are reported in Appendix I Documentation and mapping of HRQoL data.

Starting with the full model, the variable with the highest p-value based on the t-statistic was eliminated in a stepwise fashion until all variables in the model were significant at a 5% level.

Using the initial full model, the optimal random effects (subject, timing of questionnaire, or both) were identified based on the lowest AIC and BIC values. The full model with the optimal random effects was then used to identify the most appropriate of the following covariance matrix structure based on the lowest AIC and BIC: unstructured, autoregressive (AR(1)), and compound symmetry.

The fit of the final model was then assessed by plotting the conditional studentized residuals against the predicted values. The normality of the residuals was evaluated graphically through histograms of the residuals. If the residuals showed heterogeneity or non-normality, then a log-normal distribution of modelling utility decrements (1-utility) was considered (34).

The mean utility values, associated 95% CIs, and p-values for the different health states from the best fitting models, were derived from the model using least square means and regression coefficients.

The trajectory of the average utility values along with the 95% CIs over time were presented separately for each health state in the final model. All mixed models were estimated using restricted maximum likelihood (REML).

Table 26 shows the regression coefficients for the best fitting model, including progression status at the corresponding visit and treatment status at the corresponding visit as independent covariates. The regression coefficients correspond to utility decrements using a log-normal distribution; as such, a negative regression coefficient denotes an improvement in QoL. Patients with a ECOG performance of 1, progressed patients, and patients that are off treatment have reduced utility scores.

Table 26 Regression coefficients of best-fitting mixed model of utility decrements (log-normal distribution) – Denmark – Full Analysis Set

	Regression coefficients (95% CI) p-value
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Notes: Mixed model selection based on optimal random effects structure identified in the full initial model. Utility decrements (1-utility) were modelled with a log-normal distribution. A negative regression coefficient denotes an improvement in quality of life.

Table 27 presents the utility values by treatment group for All Patients. T-DXd patients have higher mean utilities compared to TPC in both the progression-free and progressed health states. This could be explained by a lower rate of grade 3+ AEs and a higher response rate to treatment.

Table 27 Health state utility values derived from DB04 for T-DXd and TPC Danish value set, All patients

Health status	T-DXd		TPC	
	n[1]	LSM, (95% CI)	n[1]	LSM, (95% 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]

1 Number of visits/timepoints with the condition **Source:** DESTINY-Breast04 (2), Danish value set

The LSM is estimated at the mean timepoint, equal to 164.5 days and assumes that the distribution between the other variables (ECOG- and treatment status) are the actual values from the DB04 at the mean timepoint.

8.4.4 Health state utility values used in the health economic model

Utilities collected in the DESTINY-Breast04 study were used throughout the model. It is expected that the main driver for the utility gain is associated with whether the patient is progression-free or not, which also showed to be a significant parameter in the utility estimation (see above).

The baseline utility values used in the model are then adjusted for age over time using the age- and sex-matched general population utility values, following DMC guidelines (35).

Table 28 HSUV used in the model

Health state utilities	Utility weight	Reference
Progression-free, T-DXd	[redacted]	DESTINY-Breast04 (2, 19), using the Danish value set
Progression-free, TPC	[redacted]	
Progressed disease, T-DXd	[redacted]	
Progressed disease, TPC	[redacted]	

It was deemed appropriate to use treatment specific utilities to capture differences between the treatment arms, such as response rate and AEs. It has been shown that responding to a treatment and not only not progressing is an important parameter for predicting the utility (36).
The utility weights from DESTINY-Breast04 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.

8.5 Resource use and costs

The model uses 2023 prices in Danish kroner (DKK). Cost inputs are based on Danish sources. Older costs were inflated to present values using the consumer price index when needed. The model includes the following costs:

- Drug acquisition costs (section 8.5.1)
- Drug administration costs (section 8.5.2)
- Disease management costs (section 8.5.3)
- Adverse event costs (section 8.5.4)
- Subsequent treatment and terminal care costs (section 8.5.5)

8.5.1 Drug acquisition

The model uses the AIP of T-DXd of DKK 11 339,35 per 100 mg vial and the recommended dose is 5.4 mg/kg every 3 weeks. Drug acquisition costs for chemotherapies in the model were sourced from the drug cost data base of the Danish Medicines Agency and the dosing information was sourced from the SmPC. The actual dose the patients received in DESTINY-Breast04 trial [redacted] mg/kg) 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-Breast04.

The mean relative dose intensity in DESTINY-Breast04 was [redacted] for T-DXd. For the TPC arm the RDI differed between treatments: ranging from [redacted] to [redacted] when dose-interruptions and dose-adjustments were taken into consideration.

According to clinical expert, the clinics try to minimise wastage by coordinating specific treatment days for these patients or rounding doses to a specific number of vials. Clinical practice on vial sharing differs across Denmark, and it is likely to be more common in more densely populated areas such as in the region of Copenhagen. Vial sharing of 50% was conservatively applied in the base case of this economic evaluation as broad use of T-DXd started in February 2023 in Denmark. This estimate considers both vial sharing and rounding of doses, as clinical experts have suggested that this may occur in clinical practice when vial sharing is not an option, to minimise wastage. Table 29 shows the resulting costs per 3-week cycle and cost per day.

Table 29 Drug costs per dose

Treatment	Package size and form	Units (mg)	Cost per pack (DKK)	Relative dose intensity (RDI)*	Mean dose per 3 weeks (with RDI, mg/kg)	Cost per cycle (with RDI, DKK)	Cost per day (with RDI, DKK)	Weight in arm
T-DXd	1 vial	100	11 339	[redacted]	[redacted]	[redacted]	[redacted]	100%
Capecitabine	60 Tablets 120 Tablets	150 500	928 834	[redacted]	[redacted]	[redacted]	[redacted]	20%
Eribulin	1 Vial	1	3 075	[redacted]	[redacted]	[redacted]	[redacted]	51%
Gemcitabine	1 Vial 1 Vial 1 Vial 1 Vial 1 Vial 1 Vial	1200 1400 1600 1800 2000 2200	432 459 486 513 533 580	[redacted]	[redacted]	[redacted]	[redacted]	10%
Paclitaxel	1 Vial 1 Vial 1 Vial	100 150 300	165 2 027 287	[redacted]	[redacted]	[redacted]	[redacted]	8%
Nab-Paclitaxel	1 Vial	100	2 578	[redacted]	[redacted]	[redacted]	[redacted]	10%

Source: DESTINY-Breast04 (2, 19).

In DESTINY-Breast04, the time-to-discontinuation (TTD) was shorter than the PFS, especially for T-DXd. It was more common that patients in the T-DXd arm (16.2%) discontinued treatment due to toxicity, compared to the TPC arm (8.1%). Hence the TTD- curve should be below the PFS curve.

Figure 24 and Figure 25 show the parametric curves for TTD in the DESTINY-Breast04 population for T-DXd and TPC respectively. It is logical that the treatment duration should be the same form but shorter than the PFS given that most patients discontinue due to progression, see section 8.3.1.1.

Figure 24 Time to treatment discontinuation in DESTINY-Breast04 for T-DXd All Patients

Figure 25 Time to treatment discontinuation in DESTINY-Breast04 for TPC All Patients

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Based on AIC values, the generalised gamma distribution shows the best statistical fit for the T-DXd arm. Based on BIC values the log-logistic distribution shows the best statistical fit, followed by gamma and generalised gamma. For the

TPC arm a similar pattern is observed based on statistical fit, with the additional of log normal which also shows a reasonably good fit to the data.

Table 30 Statistical fit to time to treatment discontinuation in DESTINY-Breast04 All Patients

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	900.677	903.892	2137.869	2141.791
Weibull	893.620	900.050	2115.293	2123.136
Gompertz	902.675	909.105	2132.040	2139.883
Log-Logistic	870.593	877.023	2108.927	2116.770
Log normal	875.687	882.117	2116.240	2124.083
Generalised gamma	876.462	886.107	2108.900	2120.665
Gamma	886.685	893.115	2110.390	2118.234

Statistical test for proportionality indicates that the PH assumption does not hold hence independent parametric curves for each treatment group could be used for modelling TTD. However, for consistency, the same distribution was used to model the TPC arm.

TTD data from the DESTINY-Breast04 are very mature and therefore all the distributions fitted, especially for TPC, and showed an exceptionally good fit visually. As PFS and TTD are closely linked, the model chosen for PFS was considered in the selection of distribution to model TTD, and vice versa. The Generalised gamma model provided good AIC and BIC values and good visual fit across PFS and TTD and hence it was opted in the base case to model both treatment arms using the Generalised gamma distribution.

To conclude, the selected base case distributions resulted in a median TTD of [redacted] in the T-DXd arm, which closely approximates the median TTD observed in the DB04 trial of [redacted] months. For the TPC arm, the median TTD was [redacted] months resulting from the extrapolations, compared with [redacted] as observed in the DB04 trial. Notably, all distributions gave the same median TTD ([redacted] months) in the TPC arm, indicating the completeness of the TTD data. Therefore, the curve selection for TTD was predominantly based on the fit of the survival distributions to the T-DXd arm.

A gamma distribution was tested in scenario analyses as generalised gamma seemed to overestimate the treatment duration in the tail of the T-DXd arm.

8.5.2 Drug administration

The drug administration cost used in the model is based on what was deemed appropriate by DMC in the most recent evaluation of T-DXd (3). In the evaluation, the DMC used the cost of administration using the DRG code 09MA98: MDC09 1-dagsgruppe, patienter på mindst 7 år. Hence, for the analysis of the current indication of T-DXd the 2023 DRG list is used, in which 09MA98 amounts to 1 634 DKK (Table 31).

For oral administration no associated costs were assumed.

Table 31 Drug administration costs

Method	Cost (DKK)	Source
Oral	0	Assumption
IV infusion	1 634	DRG-taksten 09MA98: MDC09 1-dagsgruppe, patienter på mindst 7 år

Key: IV, intravenous.

8.5.3 Monitoring costs

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 summarises the routine follow-up resource use and costs associated with pre- and post- progression obtained from the 2023 DRG list, and previous DMC evaluations.

Monitoring costs in this economic analysis are the same as were used in the recent DMC evaluation of T-DXd DB03 and have been reconfirmed by clinical experts in Denmark (12, 16), in addition these have also been deemed appropriate by DMC in the recent evaluation of Tukysa (37).

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	1 634	DRG 2023 (09MA98) "MDC09 1-dagsgruppe, patienter på mindst 7 år" DMC evaluation of DB03
Specialist nurse	Every three weeks	Every three weeks	0	DMC evaluation of DB03
Blood tests	Once per month	Once per month	0	DMC evaluation of DB03
ECHO/MUGA-scanning, cardiological examination	Every three months	Every three months	1 975	DRG 2023 (05PR04) "Kardiologisk undersøgelse, udvidet "
CT-scanning	Every three months	Every three months	2 023	DRG 2023 (30PR07) "CT-scanning, ukompliceret"

Key: CT: computed tomography, ECHO: Echocardiogram, MUGA: multigated acquisition.

8.5.4 Adverse event costs

Costs associated with the management AEs were sourced from the Danish DRG list 2023 (38), and are aligned with the previous DMC evaluation of T-DXd and the DMC Guidelines. AE probabilities were sourced from the DESTINY-Breast04 patient level data, using treatment-emergent adverse events of CTCAE ≥Grade 3 reported in ≥2% of subjects in either treatment arm. These were included as the impact associated with managing these AEs is noticeable.

The product of the probability of experiencing an AE, the cost per event is summed across all AEs to calculate an average AE cost per patient. Table 33 presents the average per-patient AE management costs used in the model.

In line with previous DMC assessments (3), the cost of some AEs such as *neutropenia* and *leukopenia* were set to zero under the assumption that these are only treated in the occurrence of fever or infection and managed at administration visit.

Table 33 Adverse events –cost per event

Adverse event	Incidence*		Cost per event (DKK)	Source / Assumption
	T-DXd N=371 (%)	TPC N=172 (%)		
Neutropenia / Neutrophil count decreased	8.1%	27.9%	0	Assumption, managed at administration visit DMC assessment of trastuzumab deruxtecan (DB03)
Anaemia	9.4%	4.7%	1 634	DRG-2023: 09MA98 "MDC09 1-dagsgruppe, patienter på mindst 7 år" DMC assessment of Trastuzumab deruxtecan (DB03)
White blood cell decrease / Leukopenia	6.7%	17.4%	0	Assumption, managed at administration visit DMC assessment of trastuzumab deruxtecan (DB03)
Thrombocytopenia / Platelet count decreased	4.9%	0.6%	0	Assumption, managed at administration visit DMC assessment of trastuzumab deruxtecan (DB03)
Febrile neutropenia	0.3%	2.3%	14 514	DRG 2023 48PR02 + 16PR02 / DMC assessment of sacituzumab-govitecan
Palmar-Plantar Erythrodysesthesia	0.0%	4.1%	1 634	DRG 2023 09MA98 "MDC09 1-dagsgruppe, patienter på mindst 7 år"
Nausea	4.3%	0.0%	0	Assumption, managed at administration visit DMC assessment of Trastuzumab deruxtecan (DB03)
Peripheral neuropathy	0.0%	2.3%	2 321	DRG 2023 01MA98 "MDC01 1-dagsgruppe, pat. mindst 7 år"
Decreased appetite	2.4%	1.2%	0	Assumption, managed at administration visit
Fatigue	5.4%	1.7%	0	Assumption, managed at administration visit DMC assessment of Trastuzumab deruxtecan (DB03)
Asthenia	1.9%	2.3%	0	Assumption, managed at administration visit
Increased ALT	1.1%	5.2%	0	Assumption, same as "Increased AST"
Increased AST	3.2%	4.7%	0	Assumption, managed at administration visit DMC assessment of Trastuzumab deruxtecan (DB03)
Gamma-glutamyltransferase increased	1.3%	2.9%	0	Assumption, managed at administration visit
Lymphocyte count decreased	4.9%	2.9%	0	Assumption, managed at administration visit
Hypokalaemia	2.4%	1.2%	2 005	MDC17 1-dagsgruppe, pat. mindst 7 år (DMC assessment of venetoclax)
Interstitial lung disease	2.2%	0	45 905	DRG-2023: 04MA17 DMC assessment of Trastuzumab deruxtecan (DB03)
Ejection fraction decreased	0.5%	0	31 680	DRG 2023 – 05MP42 Hjertesvigt, herunder kardiogent shock, proceduregrp. A

Table 34 summarises the total adverse event costs in the treatment arms included in the analysis.

Table 34 Total adverse event costs in both arms

Action	T-DXd	TPC
Total adverse event cost (DKK)	1 403	544

8.5.5 Subsequent treatment and terminal care

Danish clinical experts stated that subsequent treatment should be assumed in the modelling as these are used in clinical practice (12, 16). Accounting for subsequent treatment costs also reduce the need for crossover and other adjustments. The subsequent treatment used in DESTINY-Breast04 was similar across the arms and this is expected to be the case also in Danish clinical practice according to experts consulted when preparing this submission.

Subsequent treatments included in the model are based on what patients have received after progressing in the DB04 trial, Table 35. For details see the tab 'Set_Costs' of the model.

Based on DB04 data it was assumed that 63.1% of patients in the T-DXd arm and 75.5% in the TPC arm received subsequent treatment.

The base-case used a one-off terminal care inflation-adjusted cost of 71 610 DKK in line with the DMC assessment of T-DXd DB03, Tucatinib and T-DM1 (3, 37, 39).

Table 35 Proportion of patients receiving a treatment option in both the T-DXd and the comparator arm

Treatment group	Proportion of subsequent treatments – T-DXd arm	Proportion of subsequent treatments – Comparator arm	Tablet dose / vial concentration	Package size	Pack cost (kr)	Units	Doses per cycle	Total cost per cycle T-DXd arm (kr)	Total cost per cycle TPC arm (kr)
Capecitabine	13.3%	12.3%	Tablet	60	928.05	150.00 mg	28	802.09	741.79
Eribulin	11.8%	9.8%	Vial	1	3 075.45	0.88 mg	2	2 080.82	1 728.14
Gemcitabine	7.6%	12.9%	Vial	1	459.05	1200.00 mg	2	369.82	627.72
Paclitaxel	15.1%	13.5%	Vial	1	164.90	100.00 mg	1	319.55	285.69
Vinorelbine	4.2%	10.4%	Vial	1	690.60	20.00 mg	3	642.09	1 589.95
Fulvestrant	9.7%	12.9%	Vial	2	4 572.85	250.00 mg	1	602.06	800.68
Epirubicin	2.1%	3.1%	Vial	1	165.05	50.00 mg	1	45.90	67.75
Carboplatin	5.7%	11.0%	Vial	1	129.40	150.00 mg	1	126.00	243.17
Tamoxifen	1.8%	1.8%	Tablet	100	229.90	20.00 mg	21	0.87	0.87

.Reference treatments are chosen, assumed to be representative of each treatment in the treatment group.

8.5.6 Patient time and transportation costs

Transportation costs are calculated by applying 3.73 DKK/km which is the tax-free driving allowance for 2023 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 (Table 36).

Patient time costs are estimated to 203 DKK/hour according to DMC guidelines (Medicinrådet. Værdisætning af enhedsomkostninger. v.1.7. 2023.). 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 (Table 36).

Table 36 Time and transportation cost

	Units	DKK	Source
Proportion of patients that incur costs	100%		Medicinrådets værdisætning af enhedsomkostninger v. 1.7. 2023
Average distance to hospital (one way)	20 km		Medicinrådets værdisætning af enhedsomkostninger v. 1.7. 2023
Cost per km		3.73	Medicinrådets værdisætning af enhedsomkostninger v. 1.7. 2023
Average visits per week	0.33		Assumption
Total transport costs per week		49.2	Calculation
Time spent per visit	2 hours		
Patient cost per hour		203	
Total patient time cost per week		135.2	Calculation
Total patient cost per week		**185.4**	**Calculation**

8.6 Results

8.6.1 Base case overview

Key base-case settings and assumptions used in the model are presented in Table 37.

Table 37 Base case overview

Parameter	Base case Value / Assumption	Section for justification
Model settings		
Intervention	T-DXd	8.2.2.2
Comparators	TPC (capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel)	5.2
Perspective	Payer	8
Discount rate	3.5%	8
Time horizon	30	8
Cycle length	3 weeks	8
Population / Indication	Adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy	5.1.1
Start age	56.5	8.2.1
% Female	99.6%	8.2.1
Weight	63.4 kg	8.2.1
Clinical inputs		
OS curve fit	Log normal	8.3.1.2
PFS curve fit	Generalised gamma	8.3.1.1
Treatment duration	Generalised gamma in line with PFS	8.5.1
Main source for AE	DESTINY-Breast04	8.5.4
Cost inputs		
Wastage	50%	8.5.1
Dose intensity	T-DXd: [redacted] Capecitabine: [redacted] Eribulin: [redacted] Gemcitabine: [redacted] Paclitaxel: [redacted] Nab-paclitaxel: [redacted]	8.5.1

Key: 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 38. T-DXd is predicted to gain 0.80 QALYs to an incremental cost of approximately 560 000 DKK, which results in an ICER of 695 886 DKK versus TPC. As expected, the major cost-driver is the drug cost and the gain in QALYs was mainly in the pre-progression health state.

Table 38 Base case results

	T-DXd	TPC
Total LYs	3.32	2.47
Incremental LYs	0.85	
Total QALYs	2.80	2.00
Incremental QALYs	**0.80**	
Total direct costs (DKK)	967 569	409 261
Incremental direct costs (DKK)	**558 309**	

	T-DXd	TPC
ICER per QALY	**695 886**	
ICER per LY	658 365	

Key: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; TPC, Physician's choice; T-DXd, trastuzumab deruxtecan.

Table 39 Disaggregated costs for T-DXd and TPC

Cost category	T-DXd	TPC	Increment
Drug costs	616 505	71 539	544 966
Administration costs	25 462	17 068	8 394
Resource use costs	118 054	87 877	30 177
AE costs	1 403	544	859
Subsequent tx & EOL costs	174 668	208 762	-34 093
Societal costs	**31 477**	**23 471**	**8 006**
Total (DKK)	**967 569**	**409 261**	**558 309**

Key: TPC: Physician's choice, T-DXd: trastuzumab deruxtecan.

Table 40 Disaggregated QALYs for T-DXd and TPC

Health state	T-DXd	TPC	Increment
Pre-progression	1.11	0.58	
Post progression	1.68	1.41	
Total	**2.80**	**2.00**	**0.80**

Key: TPC: Physician's choice, 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 26 presents a summary of the most influential parameters with corresponding ICERs, showing that utility values and the cost of T-DXd are the parameters most likely to generate significant changes in the ICER.

Figure 26 Tornado diagram – T-DXd versus TPC (ICER)

Table 41 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 "OSA" and "OSA_Calc".

Table 41 One-way sensitivity analyses results

Parameter	Input value		Reason	Results		
	Lower bound	Upper bound		Lower bound	Upper bound	Difference
Utilities - Progressed - T-DXd	[redacted]	[redacted]	SE =20%	[redacted]	[redacted]	[redacted]
Utilities - Progressed - TPC	[redacted]	[redacted]	SE =20%	[redacted]	[redacted]	[redacted]
Utilities - Progression-free - T-DXd	[redacted]	[redacted]	SE =20%	[redacted]	[redacted]	[redacted]
Drug cost - T-DXd	9 185	13 717	SE =20%	525 725	834 196	-308 471
Utilities - Progression-free - TPC	[redacted]	[redacted]	SE =20%	[redacted]	[redacted]	[redacted]
Drug cost - Eribulin	2 491	3 720	SE =20%	686 213	657 058	29 155
Administration cost – T-DXd	1 324	1 977	SE =20%	690 241	702 116	- 11 875
Administration cost - TPC	1 870	2 793	SE =20%	699 391	692 017	7 374
Health state cost - Progression-free - Specialist physician/ Oncologist	1 324	1 977	SE =20%	693 038	699 029	-5 991
Drug cost - Nab-paclitaxel	2 088	3 118	SE =20%	674 317	670 188	4 129

Key: ICER: incremental cost-effectiveness ratio, PFS: progression-free survival, T-DXd: trastuzumab deruxtecan

8.7.2 Scenario analysis

Table 42Table 42 shows the scenario analyses that were deemed relevant to the decision problem. As shown in the table, the base-case results were robust. Scenario analyses of the subgroups HR-positive and HR-negative patients show that the results are consistent across subgroups.

Extrapolation of PFS, and TTD were further explored in scenario analyses. While several parametric models were deemed relevant based on goodness of fit and visual fit, other criteria were also considered to identify the best fitting model. Models that generated cross-over of the TTD and PFS curves were not deemed clinically plausible, these include using the log logistic and log normal models to model TTD (see the tab 'Set_Distributions' in the model). Hence a scenario was explored in which PFS was extrapolated based on log logistic and TTD was extrapolated using Gamma. This scenario yielded curves that were deemed clinically plausible.

Alternative curves for extrapolation of OS data were also considered for the scenario analyses. Extrapolation using Log-logistic is included as it provided the best fit considering solely the statistical fit of the data.

Table 42 Scenario analysis (DKK)

#	Scenario name	ICER
	Base-case	**695 886**
1	Discount rates – 0%	589 299
2	Discount rates – 5%	740 278
3	HR-positive cohort	710 311
4	HR-negative cohort	597 430
5	PFS: Log-logistic TTD: Gamma	672 434
6	OS: Log logistic	794 577

8.7.3 Probabilistic sensitivity analyses

For the complete list of the parameters used in the probabilistic analysis see the model sheet: 'Parameters'.

A PSA using 10 000 iterations was run for T-DXd compared to TPC 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 the treatment arms are presented in Figure 27 and Figure 28.

Figure 27 Cost-effectiveness plane for both treatments

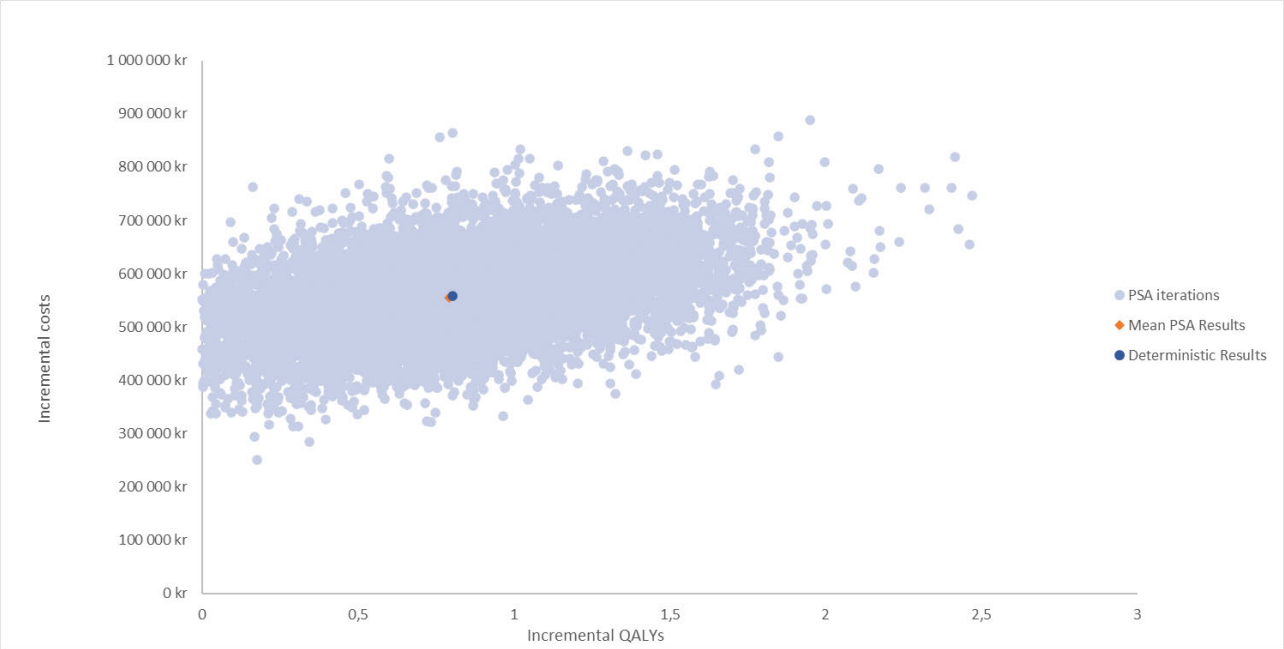
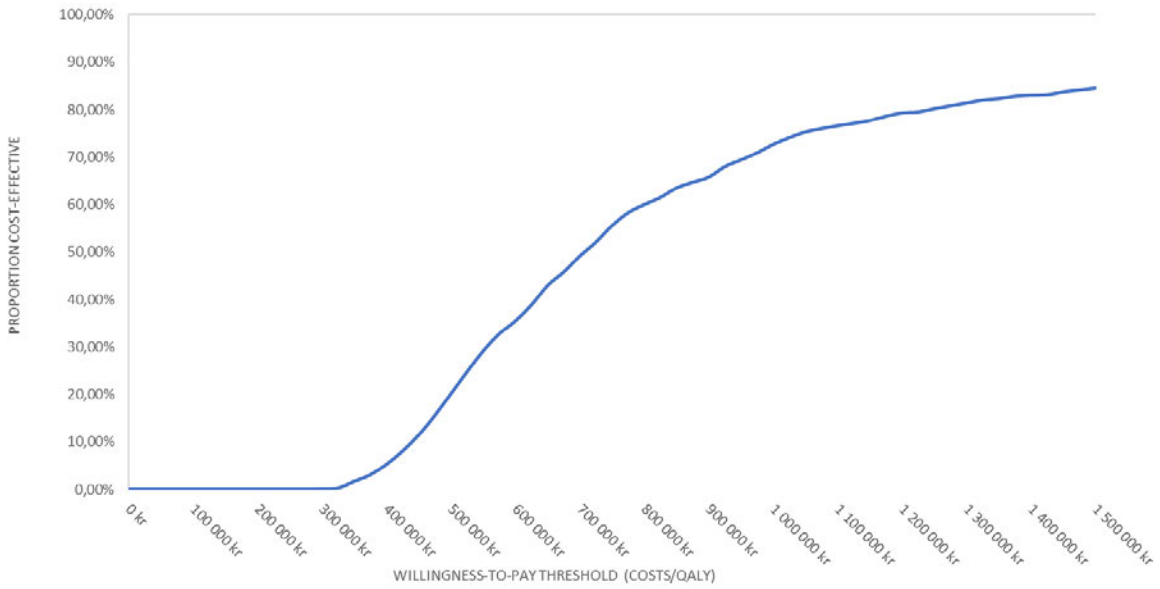


Figure 28 Cost-effectiveness acceptability curves for T-DXd versus TPC



9. Budget impact analysis

9.1 Number of patients

Table 43 shows the number of patients expected to be treated over the next five-year period, if T-DXd is approved for reimbursement. Assumed treatment durations are reported in detail in section 8.5.1.

Table 43 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	102	115	115	116	116
TPC	25	13	13	13	13

As of today eligible patients in need of treatment are expected to get treated with TPC. Expected numbers if T-DXd is not approved for reimbursement is shown in Table 44.

Table 44 Number of patients expected to be treated over 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
TPC	127	128	128	129	129

9.2 Expenditure per patient

The drug expenditure using AIP is presented in Table 45 and Table 46. Calculation of a treatment course is outlined in section 8.5.1.

Table 45 Costs per patient per year - if the pharmaceutical is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
T-DXd	450 289	119 497	37 670	11 484	4 148

Table 46 Costs per patient per year - if the pharmaceutical is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
TPC	65 439	5 160	931	208	64

Table 47 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	18 597	4 935	1 556	474	171
Subsequent tx costs	11 409	17 937	17 073	13 399	11 057

	Year 1	Year 2	Year 3	Year 4	Year 5
Resource use costs	18 450	12 177	9 203	6 460	5 002
EOL costs	18 305	15 748	10 414	6 430	4 469
AE costs	1 403	0	0	0	0

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 NOT used

	Year 1	Year 2	Year 3	Year 4	Year 5
Administration costs	15 613	1 231	222	50	15
Subsequent tx costs	27 575	30 075	23 438	16 188	12 219
Resource use costs	17 161	9 807	6 756	4 432	3 259
EOL costs	26 115	16 752	9 556	5 359	3 476
AE costs	544	0	0	0	0

9.3 Budgetary consequences

The budget impact for T-DXd is presented in Table 48. The budget impact in Year 5 if all expected T-DXd patients get T-DXd versus if all these patients get TPC is approximately 61 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 TPC.

Table 49 Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
If T-DXd is introduced	56 583 542	80 394 692	90 842 543	96 208 014	99 756 072
Of which: Drug expenditure for the specialist health services	47 442 169	64 822 121	70 327 836	72 238 882	73 158 800
Of which: Other related costs in the specialist health services	9 141 372	15 572 571	20 514 707	23 969 133	26 597 272

	Year 1	Year 2	Year 3	Year 4	Year 5
Minus:					
If T-DXd is NOT introduced	19 373 212	27 460 138	32 768 020	36 233 234	38 797 047
Of which: Drug expenditure for the specialist health services	8 316 105	9 005 151	9 159 514	9 222 632	9 267 657
Of which: Other related costs in the specialist health services	11 057 107	18 454 987	23 608 505	27 010 603	29 529 390
Budget impact of the recommendation	37 210 330	52 934 554	58 074 523	59 974 780	60 959 025

10. Discussion on the submitted documentation

Breast cancer is one of the most prevalent cancer diseases and a leading cause of death in Denmark. Although the availability of new therapies, such as CDK4/6 inhibitors has improved outcomes in mBC patients, more efficacious options are needed after progression of earlier treatments. In patients with HER2-low mBC, T-DXd (DESTINY-Breast04) demonstrated that the risk of death can be reduced by 36% and the risk of progression or death can be reduced by 50% in direct comparison with different chemotherapy regimens (TPC). These regimens are all evaluated by Danish guidelines or oncologists as standard treatments for patients with HER2-low mBC. Some of the involved products have been implemented in the past and have not been evaluated by Medicinrådet.

The DESTINY-Breast04 population is considered representative of patients that are eligible for T-DXd in clinical practice. The proportion of patients with HER2-Low/HR- (TNBC) and HER2-low/HR+ breast cancer in DESTINY-Breast04 were ~10% and ~90%, respectively. The relatively low proportion of HR- in DESTINY-Breast04 is in line what is expected in Danish clinical practice according to clinical experts consulted. The age in DESTINY-Breast04 is also in line with, and representative for what would be expected considering that patients must have received prior chemotherapy and be fit for additional treatment Patients who are unfit for chemotherapy tend to be older patients, and hence the chemo-eligible patients are younger than the overall mBC population in median terms (40, 41). The proportion of Asian patients in DESTINY-Breast04 is higher at 40% than a corresponding Danish patient population, but Danish clinical experts do not believe that this should detract from the overall generalizability of the results to Danish clinical practise.

The DESTINY-Breast04 study confirmed the efficacy of T-DXd, previously shown in HER2+ mBC with DESTINY-Breast01 and DESTINY-Breast03. T-DXd is the first targeted treatment for these patients who have historically been treated as HER2 negative patients.

The cost-effectiveness of T-DXd versus TPC in the metastatic/unresectable breast cancer setting in patients with HER2-low expression was evaluated and is aligned with previous economic analyses evaluated by DMC on the use of T-DXd in the breast cancer setting (3). The analysis shows that the use of T-DXd results in a gain of 0.80 QALY versus chemotherapy. This results in an ICER of ~695 000 DKK per QALY gained, at list price (AIP).

In conclusion, the results indicate that T-DXd could be considered a cost-effective treatment option with the potential to significantly improve outcomes for patients who currently have few effective treatment options.

11. List of experts

The following experts were consulted during the preparation of this submission. They are throughout the document referred to as 'Danish clinical experts':

[redacted]

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

Please see section 6 for details around SLE and selection of literature. The EPAR has also been consulted.

Systematic selection of studies

Table 50 Overview of study design for studies included in the technology assessment/analysis:

Study/ID45	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
NCT03734029/DB04	Evaluate the efficacy and safety of trastuzumab deruxtecan as compared with the physician's choice of chemotherapy in patients with HER2-low metastatic breast cancer	Phase III, multicentre, randomized, open-label, active-controlled trial of T-DXd versus TPC (Treatment of Physcians Choice) for HER2-low uBC and/or mBC	HER2-low uBC and/or mBC	Intervention n=373 Comparator N=184	See appendix B	See appendix B

Appendix B Main characteristics of included studies (DB04)

Trial name: DB04	NCT number: NCT03734029
Objective	Evaluate the efficacy and safety of trastuzumab deruxtecan as compared with the physician's choice of chemotherapy in patients with HER2-low metastatic breast cancer
Publications – title, author, journal, year	Modi S et al. N Engl J Med .2022 Jul 7. N Engl J Med 2022; 387:9-20 https://www.nejm.org/doi/10.1056/NEJMoa2203690?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
Study type and design	Phase III, multicentre, randomized, open-label, active-controlled trial of T-DXd versus TPC (Treatment of Physcians Choice) for HER2-low uBC and/or mBC • Study start date: December 27, 2018 • Estimated study completion date: January 1, 2023
Sample size (n)	Intervention n=373 Comparator N=184

Main inclusion and exclusion criteria

Inclusion criteria:

- Must be competent and able to comprehend, sign and date an IRB or IEC approved ICF before performance of any study-specific procedures or tests
- Adults ≥ 18 years old. Please follow local regulatory requirements if the legal age of consent for study participation is > 18 years old
- Pathologically documented breast cancer that
- Is unresectable or metastatic
- Has a history of low HER2 expression, defined as IHC 2+/ISH- or IHC 1+ (ISH- or untested).
- Assessed as low HER2 expression, defined as IHC 2+/ISH- or IHC 1+ according to ASCO-CAP 2018 guidelines (adapted by Daiichi Sankyo Inc. and Ventana) evaluated at a central laboratory.
- Is HR-positive or HR-negative. Approximately 60 HR-negative subjects are to be enrolled, the remaining subjects will be HR-positive (positive for oestrogen receptor or progesterone receptor if finding of ≥1% of tumour cell nuclei are immunoreactive).
- If HR-positive, is documented refractory to endocrine therapy, defined as having progressed on at least 1 endocrine therapy and determined by the Investigator that subject would no longer benefit from further treatment with endocrine therapy. Presence of at least one measurable lesion per RECIST Version 1.1
- If HR-positive, has or has not been treated with a CDK4/6 inhibitor. Not more than 240 HR-positive subjects who have not had prior therapy with a CDK4/6 inhibitor and at least 240 HR-positive subjects who have had prior therapy with a CDK4/6 inhibitor will be enrolled.
- Has been treated with at least 1 and at most 2 prior lines of chemotherapy in the recurrent or metastatic setting. If recurrence occurred within 6 months of(neo)adjuvant chemotherapy, (neo)adjuvant therapy would count as 1 line of chemotherapy. Targeted agents (such as mTOR inhibitors, PARP inhibitors, PD-L inhibitors, or PD-L1 inhibitors) and endocrine therapies on their own do not contribute to the count of prior lines of chemotherapy, although regimens with such agents in combination with chemotherapy would still count as 1 line of chemotherapy.

Exclusion criteria:

- Ineligible for all 5 of the options in the physician's choice arm either because of previously having received treatment in the metastatic setting with the same comparator or having a contraindication to treatment.
- Prior treatment with antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor.
- Uncontrolled or significant cardiovascular disease, including any of the following:
- History of myocardial infarction within 6 months before randomization, troponin levels consistent with myocardial infarction as defined according to the manufacture 28 days prior to randomization
- History of symptomatic congestive heart failure (New York Heart Association Class II to IV)

Trial name: DB04	NCT number: NCT03734029
	• Corrected QT interval (QTc) prolongation to >470 ms (females) or >450 ms (male) based on average of Screening triplicate 12 lead ECGs • Has a history of (non-infectious) 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 metastases, defined as untreated or symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. • Subjects 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 enrolment. • Has multiple primary malignancies within 3 years, except adequately resected nonmelanoma skin cancer, curatively treated in situ disease, or contralateral breast cancer.
Intervention	T-DXd IV at a dosage of 5.4 mg/kg initially as an IV infusion over 30 to 90 minutes every 21 days (±2 days) n=331
Comparator(s)	Capecitabine, Eribulin, Gemcitabine, Paclitaxel, Nab-paclitaxel n=163. All product were administered according to label.
Follow-up time	The median duration of follow-up for survival was 18.4 months (95% confidence interval [CI], 17.7 to 18.9). Data cut-off date was January 11, 2022
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints	**Primary objective:**
	• Compare the PFS benefit of T-DXd to physician's choice in HER2-low/HR-positive breast cancer, based on blinded independent central review (BICR)
	Secondary objective:
	• To investigate the efficacy of T-DXd compared to physician's choice on the following parameters:
	  • PFS in HR-positive subjects, based on Investigator assessment
	  • OS in HR-positive subjects
	  • Confirmed overall response rate (ORR), based on BICR and Investigator assessment in HR-positive subjects
	  • Duration of response (DoR), based on BICR and Investigator assessment in HR-positive subjects
	  • PFS, OS, confirmed ORR, and DoR in all subjects, regardless of HR status
	• To evaluate the safety of T-DXd compared to physician's choice

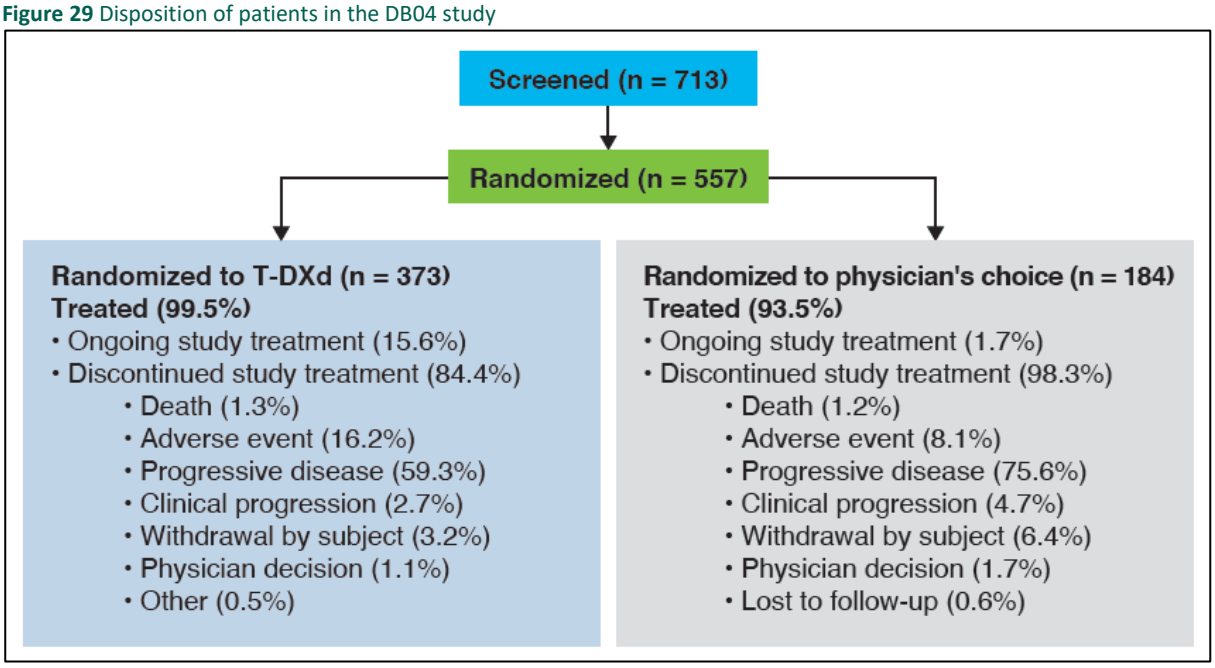
Trial name: DB04	NCT number: NCT03734029
Method of analysis	The primary efficacy analysis compared progression-free survival in the hormone receptor-positive cohort between the two trial groups with the use of a stratified log-rank test at a two-sided significance level of 0.05. The final efficacy analysis for progression-free survival was to be performed after approximately 318 patients had disease progression or died in the hormone receptor-positive cohort; this number of events would ensure a power of 90%, under the assumption of a hazard ratio of 0.68 and a two-sided alpha level of 0.05. Group sequential testing using a stratified logrank test to compare overall survival between the trial groups, provided that superiority with respect to progression-free survival was significant in the hormone receptor-positive cohort and among all patients. The hazard ratios and 95% confidence intervals for progression-free and overall survival were estimated with the use of a stratified Cox regression analysis. Efficacy analyses were performed in the intention-totreat population. Safety analyses were performed in patients who received at least one dose of a trial drug.
Subgroup analyses	Predefined subgroups included: • Prior CDK 4/6 inhibitors • IHC status • Prior lines of chemotherapy in the metastatic setting • Age • Race • Region • ECOG performance status • Visceral disease at baseline
Other relevant information	No

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

Patient disposition and baseline characteristics

From December 27, 2018, through December 31, 2021, a total of 713 patients with HER2-low mBC were screened for potential trial entry. Of the 373 patients who were randomly assigned to the T-DXd group and the 184 patients who were assigned to the TPC group, 331 (88.7%) and 163 (88.6%), respectively, comprised the HR–positive cohort. In the TPC group, patients received eribulin (51.1%), capecitabine (20.1%), nab-paclitaxel (10.3%), gemcitabine (10.3%), or paclitaxel (8.2%). An imbalance in randomization of patients (those not treated) occurred, primarily due to withdrawal of consent in the control arms prior to initiating treatment, see Figure 29.

Figure 29 Disposition of patients in the DB04 study



The demographic and clinical characteristics of the patients at baseline were similar in the two trial groups and were largely representative of the overall population of patients with HER2-negative breast cancer. Patients in both groups had a median of 3 lines of treatment for metastatic disease. The median duration of follow-up for survival was 18.4 months (95% confidence interval [CI], 17.7 to 18.9). The key baseline demographic and clinical characteristics are summarized in Table 51.

Table 51 Key baseline demographic and clinical characteristics of patients in the DESTINY-Breast04 trial.

	HR-positive Cohort		HR-negative cohort		All Patients	
Parameter[a]	**T-DXd (N = 331)**	**TPC (N = 163)**	**T-DXd (N = 42)**	**TPC (N = 21)**	**T-DXd (N = 373)**	**TPC (N = 184)**
Age (years)						
Median	56.8	55.7	[redacted]	[redacted]	57.5	55.9
Minimum, Maximum	31.5, 80.2	28.4, 80.0	[redacted]	[redacted]	31.5, 80.2	28.4, 80.5
Female sex						

No. (%)	329 (99.4)	163 (100)	[redacted]	[redacted]	371 (99.5)	184 (100)
Race[b] – no. (%)						
Asian	131 (39.6)	66 (40.5)	[redacted]	[redacted]	151 (40.5)	72 (39.1)
White	156 (47.1)	78 (47.9)	[redacted]	[redacted]	176 (47.2)	91 (49.5)
Black	7 (2.1)	2 (1.2)	[redacted]	[redacted]	7 (1.9)	3 (1.6)
Other	37 (11.2)	16 (9.8)	[redacted]	[redacted]	39 (10.5)	17 (9.2)
Missing data	0	1 (0.6)	[redacted]	[redacted]	0	1 (0.5)
Ethnic group[b] – no. (%)						
Hispanic/Latino	14 (4.2)	5 (3.1)	[redacted]	[redacted]	14 (3.8)	7 (3.8)
Non-Hispanic/Non-Latino	267 (80.7)	137 (84.0)	[redacted]	[redacted]	308 (82.6)	153 (83.2)
Unknown	9 (2.7)	4 (2.5)	[redacted]	[redacted]	9 (2.4)	7 (3.8)
Not applicable	41 (12.4)	17 (10.4)	[redacted]	[redacted]	42 (11.3)	17 (9.2)
Region						
Asia	128 (38.7)	60 (36.8)	[redacted]	[redacted]	147 (39.4)	66 (35.9)
Europe or Israel	149 (45.0)	73 (44.8)	[redacted]	[redacted]	166 (44.5)	85 (46.2)
North America	54 (16.3)	30 (18.4)	[redacted]	[redacted]	60 (16.1)	33 (17.9)
HER2-low status[c] – no. (%)						
IHC 1+	193 (58.3)	95 (58.3)	[redacted]	[redacted]	215 (57.6)	106 (57.6)
IHC 2+ and ISH-negative	138 (41.7)	68 (41.7)	[redacted]	[redacted]	158 (42.4)	78 (42.4)
gBRCA1m status – no. (%)						
Mutated	3 (0.9)	2 (1.2)	[redacted]	[redacted]	3 (0.8)	2 (1.1)
Wild type	93 (28.1)	56 (34.4)	[redacted]	[redacted]	112 (30.0)	65 (35.3)
Unknown	235 (71.0)	105 (64.4)	[redacted]	[redacted]	258 (69.2)	117 (63.5)
gBRCA2m status – no. (%)						
mutated	11 (3.3)	8 (4.9)	[redacted]	[redacted]	15 (4.0)	8 (4.3)
Wild type	87 (26.3)	50 (30.7)	[redacted]	[redacted]	103 (27.6)	59 (32.1)

Unknown	233 (70.4)	105 (64.4)	[redacted]	[redacted]	255 (68,4)	117 (63.6)
ECOG performance status score[d]						
0	187 (56.5)	95 (58.3)	[redacted]	[redacted]	200 (53.6)	105 (57.1)
1	144 (43.5)	68 (41.7)	[redacted]	[redacted]	173 (46.4)	79 (42.9)
Hormone receptor status[e]						
Positive	328 (99.1)	162 (99.4)	[redacted]	[redacted]	333 (89.3)	166 (90.2)
Negative	3 (0.9)	1 (0.6)	[redacted]	[redacted]	40 (10.7)	18 (9.8)
***De novo* mBC at initial diagnosis**						
Yes	76 (23.0)	35 (21.5)	[redacted]	[redacted]	88 (23.6)	39 (21.2)
Metastasis – no. (%)						
Brain	18 (5.4)	7 (4.3)	[redacted]	[redacted]	24 (6.4)	8 (4.3)
Liver	247 (74.6)	116 (71.2)	[redacted]	[redacted]	266 (71.3)	123 (66.8)
Lung	98 (29.6)	58 (35.6)	[redacted]	[redacted]	120 (32.3)	63 (34.2)
Previous cancer therapy — no. (%)						
Targeted therapy	259 (78.2)	132 (81.0)	[redacted]	[redacted]	279 (74.8)	140 (76.1)
CDK4/6 inhibitor	233 (70.4)	115 (70.6)	[redacted]	[redacted]	239 (64.1)	119 (64.7)
Immunotherapy	10 (3.0)	8 (4.9)	[redacted]	[redacted]	20 (5.4)	12 (6.5)
Other	128 (38.7)	70 (42.9)	[redacted]	[redacted]	140 (37.5)	76 (41.3)
Endocrine therapy	330 (99.7)	160 (98.2)	[redacted]	[redacted]	347 (93.0)	165 (89.7)
Chemotherapy	331 (100)	162 (99.4)	[redacted]	[redacted]	373 (100)	183 (99.5)
Capecitabine	177 (53.5)	83 (50.9)	[redacted]	[redacted]	191 (51.2)	95 (51.2)
Carboplatin	14 (4.2)	13 (8.0)	[redacted]	[redacted]	24 (6.4)	19 (10.6)
Cyclophosphamide	196 (59.2)	92 (56.4)	[redacted]	[redacted]	223 (59.8)	100 (54.3)

Docetaxel	109 (32.9)	62 (38.0)	[redacted]	[redacted]	126 (33.8)	68 (37.0)
Doxorubicin	84 (25.3)	31 (19.0)	[redacted]	[redacted]	94 (25.2)	33 (18.0)
Epirubicin	99 (29.9)	52 (31.9)	[redacted]	[redacted]	115 (30.8)	58 (31.5)
Eribulin	24 (7.2)	18 (11.0)	[redacted]	[redacted]	29 (7.8)	22 (12.0)
Fluorouracil	64 (19.3)	34 (20.9)	[redacted]	[redacted]	69 (18.5)	35 (19.0)
Nab-paclitaxel	23 (6.9)	11 (6.7)	[redacted]	[redacted]	33 (8.8)	15 (8.2)
Paclitaxel	161 (48.6)	82 (50.3)	[redacted]	[redacted]	187 (50.1)	93 (50.5)
Vinorelbine	36 (10.8)	14 (8.6)	[redacted]	[redacted]	40 (10.8)	17 (9.2)
Lines of therapy for metastatic disease						
Median no. of lines (range)	3 (1–9)	3 (1–8)	[redacted]	[redacted]	3 (1–9)	3 (1–8)
No. of lines — no. of patients (%)						
1	23 (6.9)	14 (8.6)	[redacted]	[redacted]	39 (10.5)	19 (10.3)
2	85 (25.7)	41 (25.2)	[redacted]	[redacted]	100 (26.8)	53 (28.8)
≥3	223 (67.4)	108 (66.3)	[redacted]	[redacted]	234 (62.7)	112 (60.9)

[a] Percentages may not total 100 because of rounding. CDK4/6 denotes cyclin-dependent kinases 4 and 6.
[b] Race and ethnic group were reported by the patients. For available options, see the Methods section in the Supplementary Appendix.
[c] Low expression of human epidermal growth factor receptor 2 (HER2) was defined as a score of 1+ on immunohistochemical (IHC) analysis or as an IHC score of 2+ and negative results on in situ hybridization (ISH).
[d] Performance-status scores on the Eastern Cooperative Oncology Group (ECOG) scale range from 0 (no disability) to 5 (death).
[e] For the intention-to-treat analyses in the hormone receptor–positive cohort, hormone-receptor status is based on data collected with the use of the interactive Web-response and voice-response system at the time of randomization, which includes patients who were mis-stratified.
Source: Modi *et al.* (2022)(2)

Comparability of patients across studies

Comparability of the study populations with Danish patients eligible for treatment

As mentioned previously in Section 10, the DESTINY-Breast04 study population is considered representative of patients that are eligible for T-DXd in Danish clinical practice if implemented according to the approved indication. The proportion of patients with HER2-Low/HR- (TNBC) and HER2-low/HR+ breast cancer in DESTINY-Breast04 were ~10% and ~90%, respectively. The relatively low proportion of HR- in DESTINY-Breast04 is in line what is expected in Danish clinical practice according to clinical experts consulted. The age of patients in DESTINY-Breast04 is in line with, and representative for what would be expected, considering that patients must have received prior chemotherapy and be fit for additional treatment. The prior treatments received are also very similar to Danish clinical practise with around 70% of HR+ patients in DESTINY-Breast04 having received prior CDK4/6 inhibitors. The proportion of Asian patients in

DESTINY-Breast04 is higher at 40% than a corresponding Danish patient population, but Danish clinical experts do not believe that this should detract from the overall generalizability of the results to Danish clinical practise.

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.
Median PFS BICR	PFS based on BICR is defined as the time from the date of randomization to the earliest date of the first objective documentation of radiographic disease progression via BICR according to RECIST Version 1.1 or death due to any cause.	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.
PFS based on investigator assessment	PFS (based on investigator assessment) is defined as the time from the date of randomization to the earliest date of the first objective documentation of radiographic disease progression via investigator-assessed disease progression according to RECIST Version 1.1 or death due to any cause.	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	ORR is defined as the sum of CR and PR rate based on BICR and based on investigator assessment.	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.
DoR	DoR, defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression based on BICR and based on investigator assessment. DoR will be measured for responding patients (PR or CR) only.	Standard outcome in oncology. DoR will be measured for responding patients (PR or CR) only.	

Results per study

Table A3a Results of DB04 NCT03734029

				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 PFS(all ptt)	T-DXd	373	9.9(9.0–11.3)	4.8m	(2.229-7.371)		HR: 0.50	(0.40–0.63)	<0.001	PFS based on BICR is defined as the time from the date of randomization to the earliest date of the first objective	
	TPC	184	5.1(4.2–8.8)								

Table A3a Results of DB04 NCT03734029

									documentation of radiographic disease progression via BICR according to RECIST Version 1.1 or death due to any cause.	
Median PFS(HR+)	T-DXd	331	10.1(9.5-11.5)	4.7m	(3.02-6.38)	HR: 0.51	(0.40–0.64)	<0.001	See above	
	TPC	163	5.4(4.4-7.1)							
Median PFS(HR-)	T-DXd	40	8.5(4.3-11.7)	5.6m	(1.463-9.737)	HR: 0.46	(0.24-0.89)	NA	See above	
	TPC	18	2.9(1.4-5.1)							
Median OS(all ptt)	T-DXd	373	23.4(20.0-24.8)	6.6m	(2.950-10.250)	HR: 0.64	(0.49-0.84)	0.001	OS is defined as the time from the date of randomization to the date of death for any cause.	
	TPC	184	16.8)14.5-20.0)							
Median OS(HR+)	T-DXd	331	23.9(20.8-24.8)	6.4m	(2.282-10.518)	HR: 0.64	(0.48-0.86)	0.003	See above	
	TPC	163	17.5(15.2-22.4)							
Median OS(HR-)	T-DXd	40	18.2(13.6-NE)	9.9m	NA	HR: 0.48	(0.24-0.95)	NA	See above	
	TPC	18	8.3(5.6-20.6)							
Median DoR(all)	T-DXd	373	10.7m(8.5-13.2)	4.1m	NA	NA	NA		See definition in previous table	
	TPC	184	6.6m(6.0-9.9)							

Table A3a Results of DB04 NCT03734029									
Median DoR(HR+)	T-DXd	331	10.7m(8.5-13.7)	3.9m	NA	NA	NA	See definition in previous table	
	TPC	163	6.8m(6.5-9.9)						
Median DoR(HR-)	T-DXd	40	8.6m(7.1-13.9)	3.7m	NA	NA	NA	See definition in previous table	
	TPC	18	4.9m(3.7-6.0)						
Confirmed ORR %(all)	T-DXd	373	52.3(47.1-57.4)	36%	(28.2-43.7)	RR=3.2	(2.24-4.59)	RR and CI Calculated by AstraZeneca	
	TPC	184	16.3(11.3-22.5)						
Confirmed ORR % (HR+)	T-DXd	331	52.6(47.0-58.0)	36,3%	(28.4-44.2)	RR=3.2	(2.22-4.69)	RR and CI Calculated by AstraZeneca	
	TPC	163	16.3(11.0-22.8)						
Confirmed ORR % (HR-)	T-DXd	40	50.0(33.8-66.2)	33.3%	(8.2-58.4)	RR=2.9	(0.9-9.88)	RR and CI Calculated by AstraZeneca	
	TPC	18	16.7(3.6-41.4)						
TEAE(all) %	T-DXd	371	99.5(NA,NA)	1.2 %	NA	RR=1.01	(0.99_1.03)	RR and CI Calculated by AstraZeneca	
	TPC	172	98.3(NA,NA)						
TEAE(all) % Grade >3	T-DXd	371	52.6(NA,NA)	14.8%	NA	RR=0.78	(0.68-0.90)	RR and CI Calculated by AstraZeneca	
	TPC	172	67.4(NA,NA)						
STEAE(all) %	T-DXd	371	27.8(NA,NA)		NA	RR=1.11	(0.82-1.51)		

Table A3a Results of DB04 NCT03734029								
	TPC	172	25.0(NA,NA)				RR and CI Calculated by AstraZeneca	
TEAEs associated with dose discontinuations	T-DXd	371	16.2(NA,NA)	NA	RR=1.99	(1.14-3.45)	RR and CI Calculated by AstraZeneca	
	TPC	172	8.1(NA,NA)					

Appendix E Safety data for intervention and comparators

See section 7.2.

Appendix F Comparative analysis of efficacy and safety

No ITC has been included in the application.

Appendix G Extrapolation

Distribution parameters

Table 52 Distribution parameters – DB04 TPC

Modelling method	DB04 data	TPC		
Distribution	Parameter	PFS	OS	TTD
Exponential	Rate	0.1300	0.0391	[redacted]
Weibull – PH	Scale	0.0914	0.0100	
	Shape	1.1656	1.4918	
Weibull – AFT	Scale	7.7900	21.8599	
	Shape	1.1656	1.4918	
Gompertz	Scale	0.1196	0.0222	
	Shape	0.0162	0.0607	
Log-Logistic	Scale	4.8674	17.0803	
	Shape	1.5600	1.7340	
Log normal	Meanlog	1.6029	2.8940	
	Sdlog	1.0999	1.1434	
Generalised gamma	Mu	1.6725	3.1112	
	Sigma	1.0681	0.6155	
	Q	0.1616	1.1553	
Gamma	Scale	5.5997	12.5664	
	Shape	1.3144	1.6785	

Table 53 Distribution parameters – DB04 T-DXd

Modelling method	DB04 data	T-DXd		
Distribution	Parameter	PFS	OS	TTD
Exponential	Rate	0.0682	0.0258	[redacted]
Weibull - PH	Scale	0.0449	0.0063	
	Shape	1.1656	1.4918	
Weibull - AFT	Scale	14.3295	29.9534	
	Shape	1.1656	1.4918	
Gompertz	Scale	0.0607	0.0137	
	Shape	0.0162	0.0607	
Log-Logistic	Scale	9.8446	24.1581	
	Shape	15600	1.7340	
Log normal	Meanlog	2.2622	3.2523	
	Sdlog	1.0999	1.1434	
Generalised gamma	Mu	2.3350	3.4166	
	Sigma	1.0681	0.6155	
	Q	0.1616	1.1553	
Gamma	Scale	10.3971	17.5135	
	Shape	1.3144	1.6785	

Proportional hazards and fit assessment

Proportional hazard and fit —PFS, All patients

In Figure 30 the log-cumulative hazard plot for T-DXd and TPC is shown for PFS. The log-cumulative hazards plots are relatively parallel, particularly after approximately the 1 month.

Figure 30 Log-cumulative hazard plot of PFS, All Patients

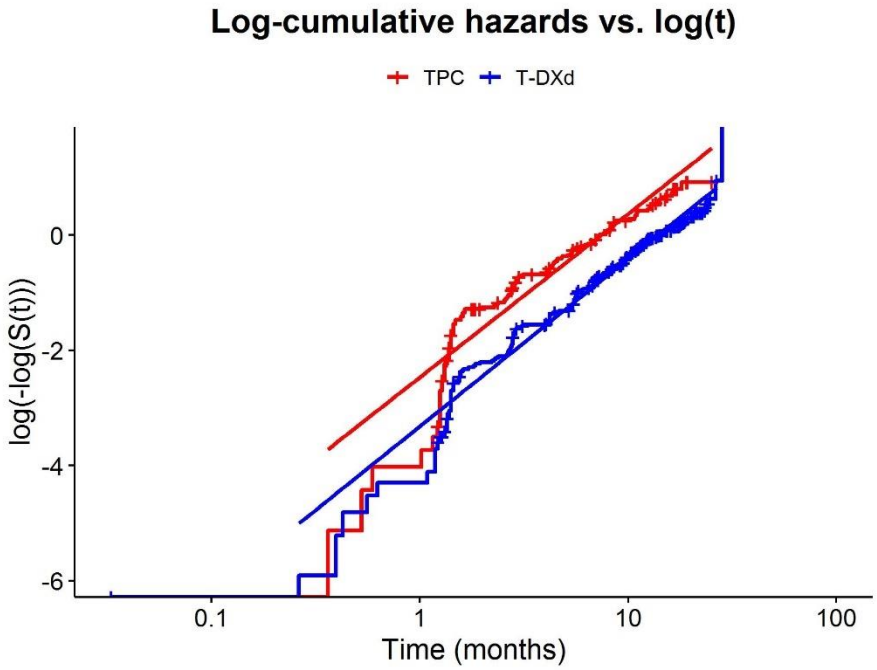
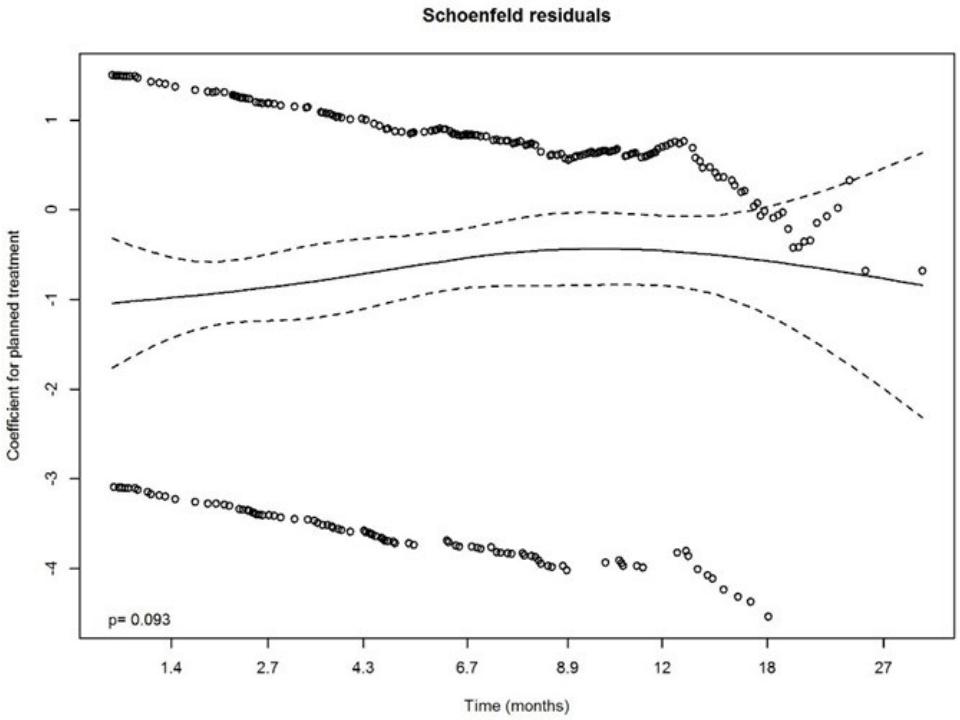


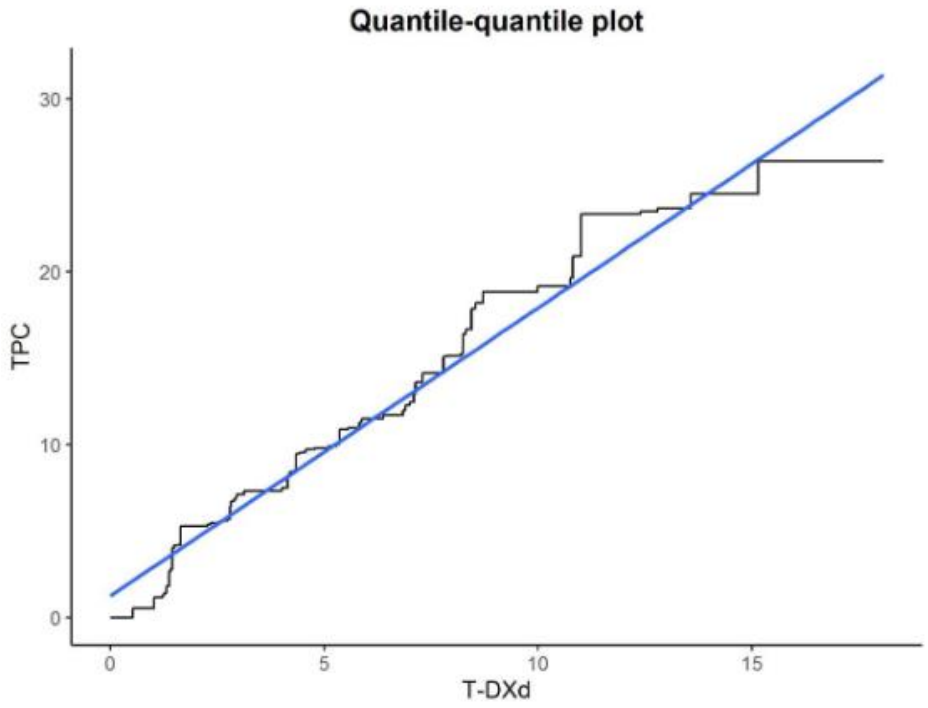
Figure 31 shows the Schoenfeld residuals for PFS. If the PH assumption holds, the line in the middle of the graph should be horizontal, indicating independence from time. These Schoenfeld residuals results do not show a clear trend over time, and the associated statistical test for proportionality shows a p-value that is not significant (p=0.093); this means that the hypothesis that the PH assumption holds cannot be rejected.

Figure 31 Schoenfeld residuals for PFS assessed by BICR, All Patients



Key: BICR, blinded independent central review; PFS, progression-free survival.

Figure 32 Quantile-Quantile-plot PFS based on BICR, All Patients



The results of the log-cumulative hazards plot, the Schoenfeld residuals, and the quantile-quantile plot all indicate that the PH assumption holds. Therefore, dependent survival distributions are considered suitable for PFS modelling.

Figure 33 Log($S(t)$/(1−$S(t)$)) vs. log(t) PFS based on BICR, All Patients

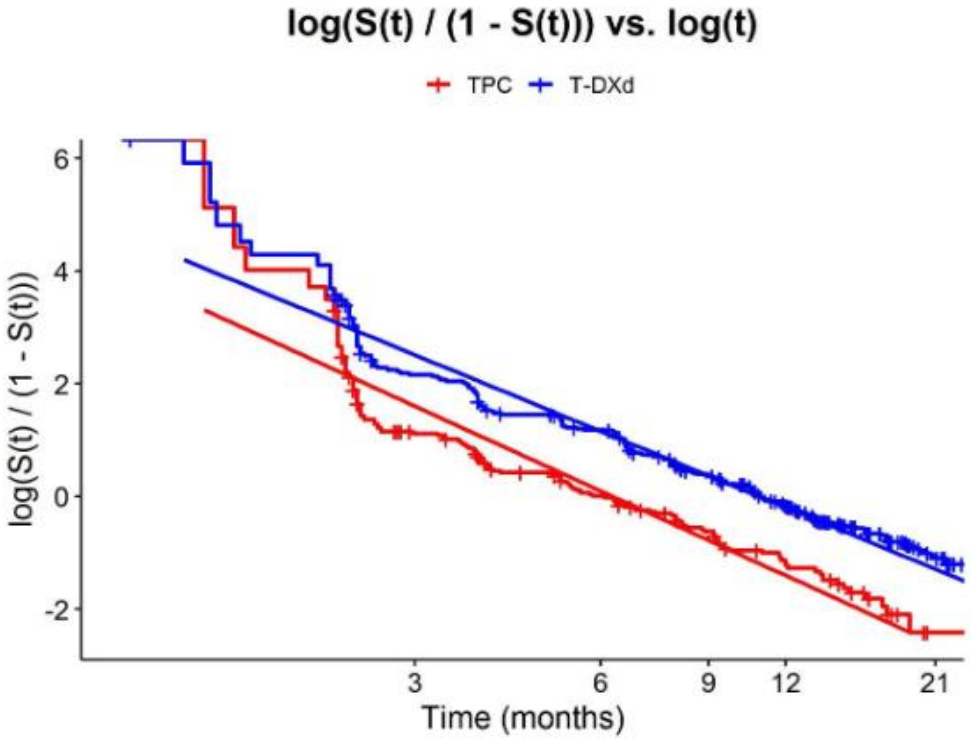


Figure 34 Inverse.normal(1−$S(t)$) vs. log(t) PFS based on BICR, All Patients

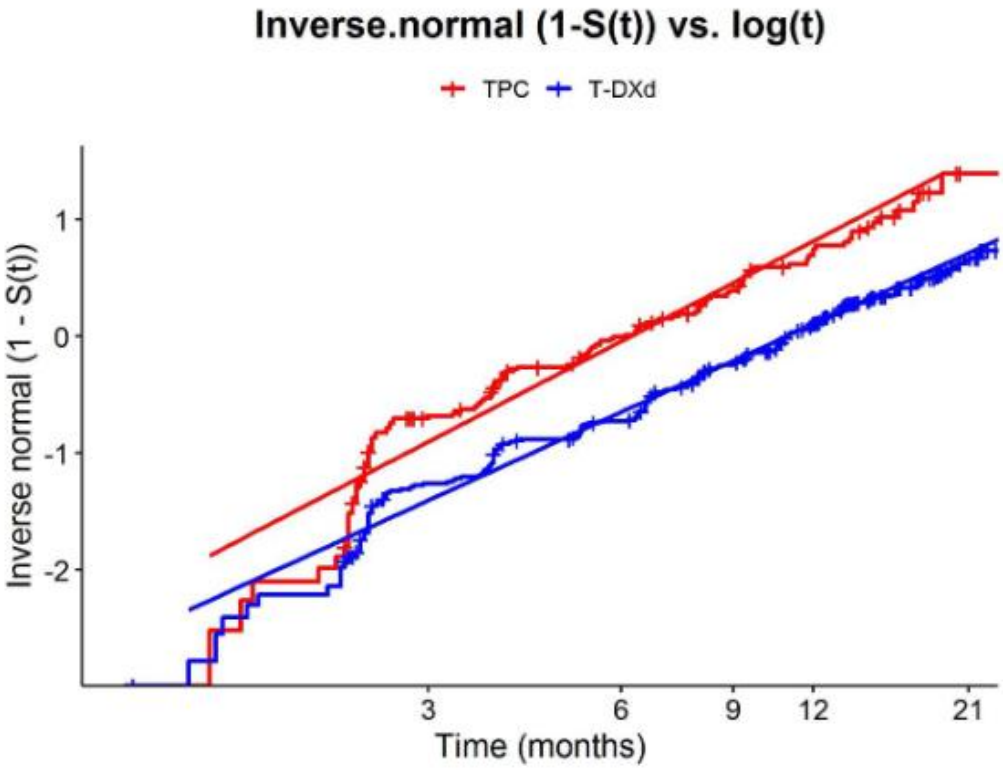


Figure 35 Hazard function, smoothed and unsmoothed of PFS- based on BICR, All Patients

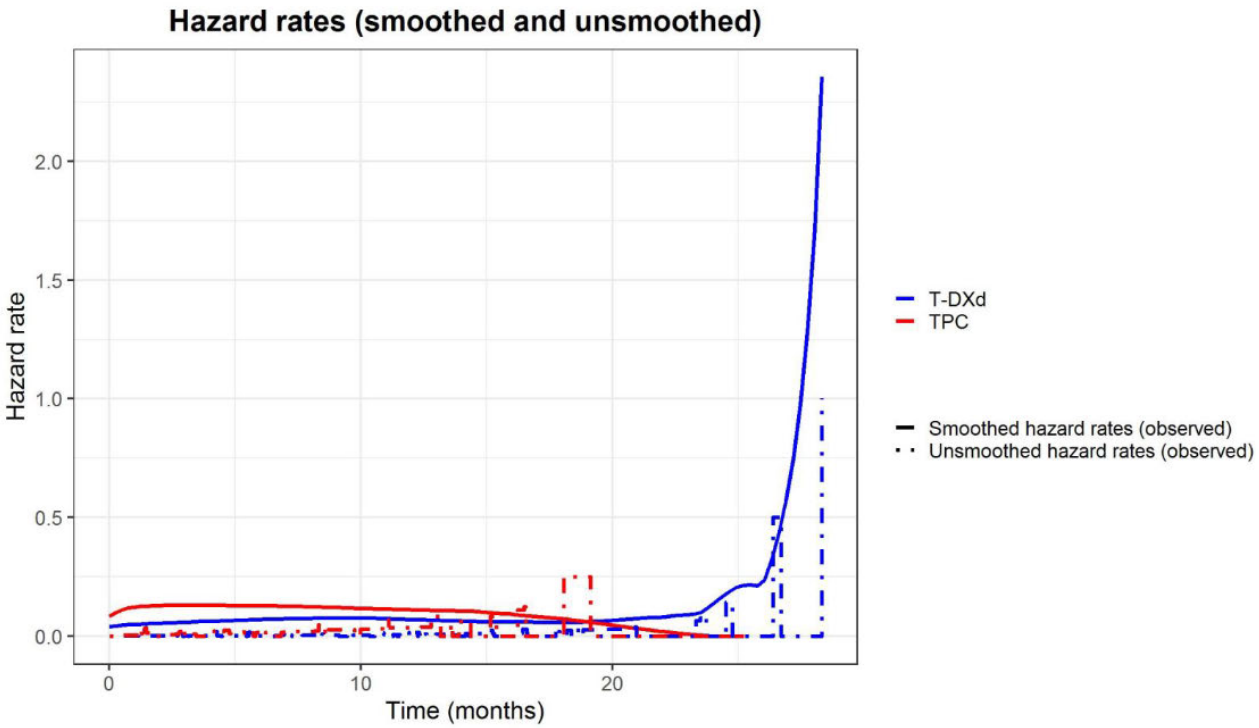
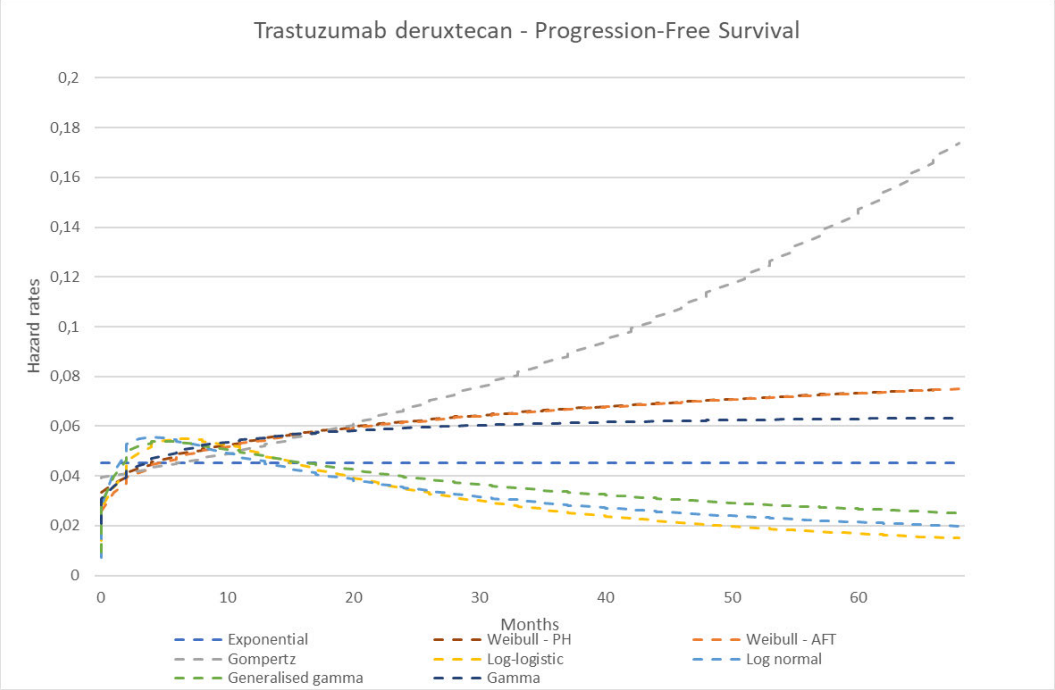
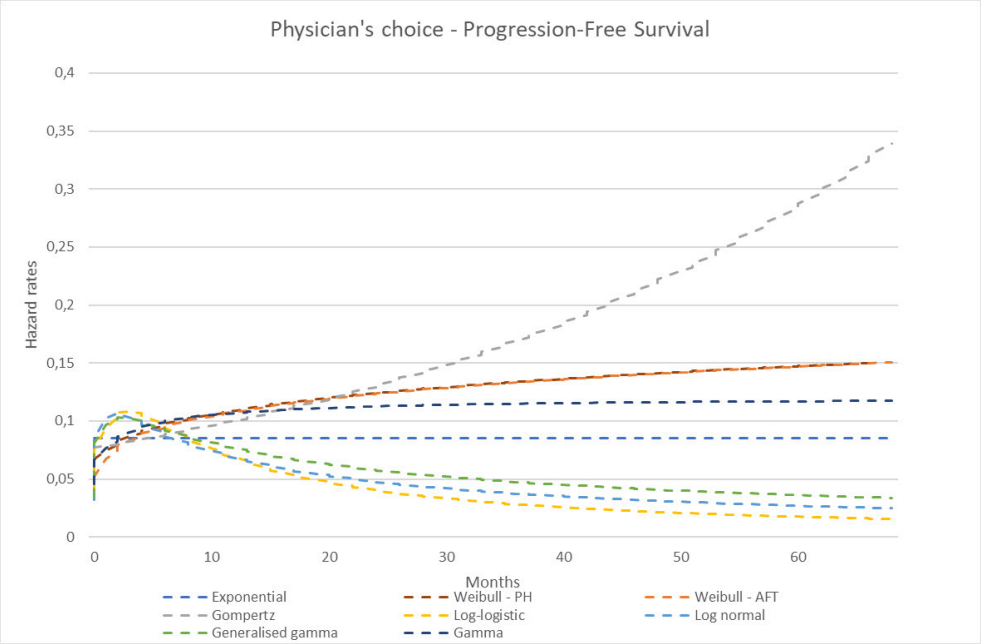


Figure 36 Hazard function, smoothed and by extrapolation model of PFS- based on BICR A. T-DXd B. TPC

A.



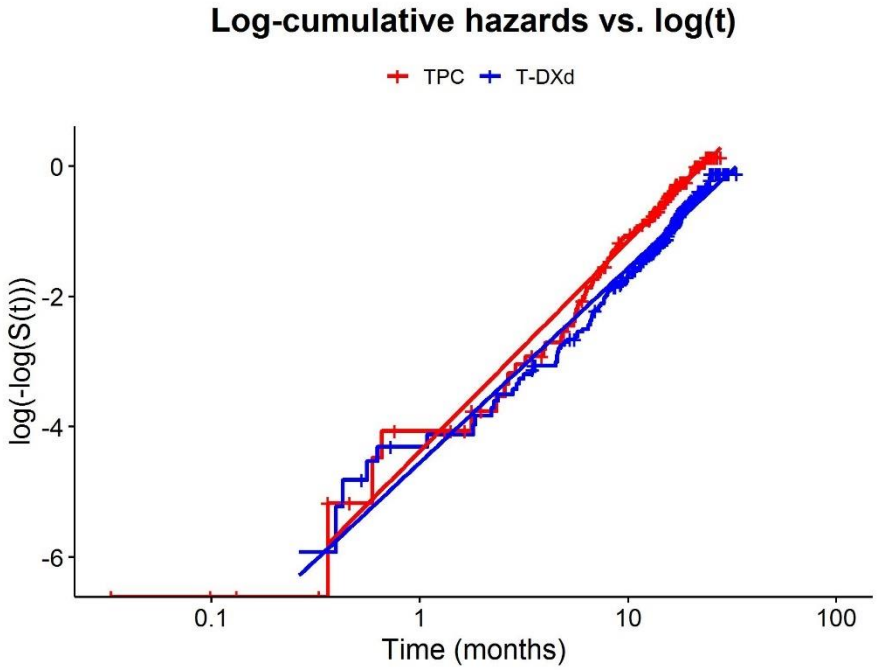
B.



Proportional hazard and fit —OS, All Patients

In Figure 37 the log-cumulative hazard plot for T-DXd and TPC is shown for OS. A change in hazards at approximately 5 months means that the log-cumulative hazards plots are not parallel at all time points, though the hazards are reasonably proportional after the change at 5 months.

Figure 37 Log-cumulative hazard plot of OS, All Patients



Key: OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

In Figure 38 the Schoenfeld residuals are shown for OS. Similar to the PFS data, the Schoenfeld residuals do not show a clear trend over time, and the associated statistical test for proportionality shows a p-value that is not significant (p=0.421), which means that the hypothesis that the PH assumption holds cannot be rejected.

Figure 38 Schoenfeld residuals for OS, All Patients

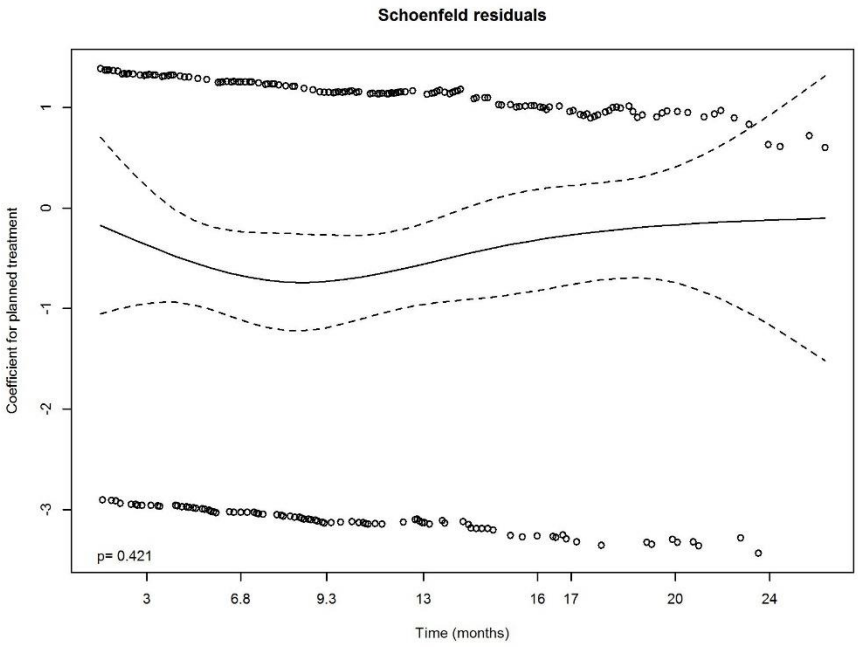
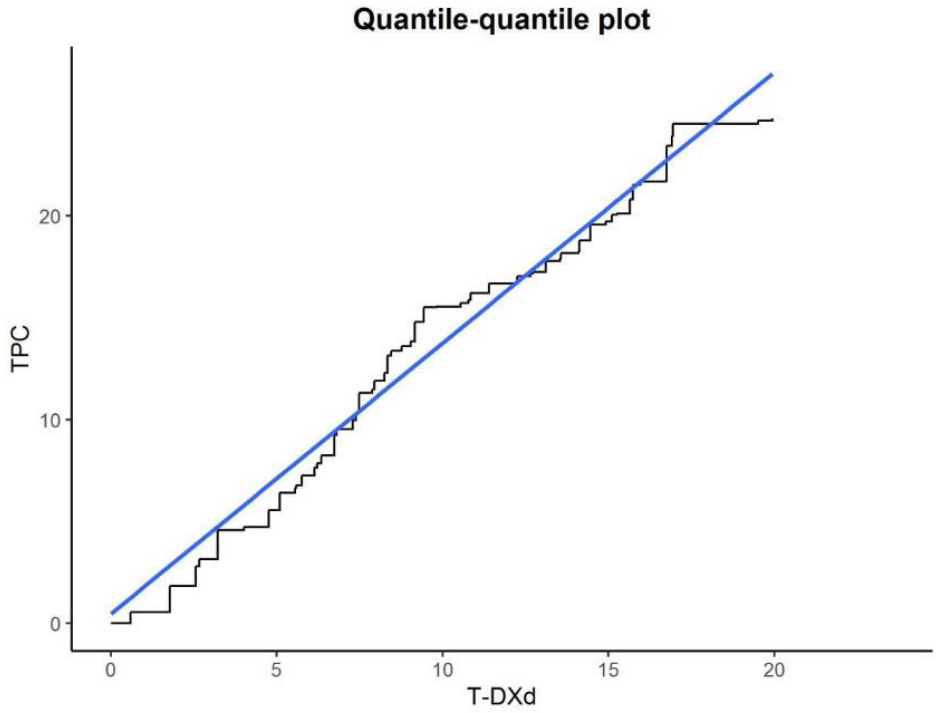


Figure 39 Quantile-Quantile-plot OS, All Patients



The results of the log-cumulative hazards plot, the Schoenfeld residuals, and the quantile-quantile plot indicate that the PH assumption holds. Therefore, dependent survival distributions are considered suitable for OS modelling.

Figure 40 Log($S(t)$/(1−$S(t)$))vs. log(t) OS, All Patients

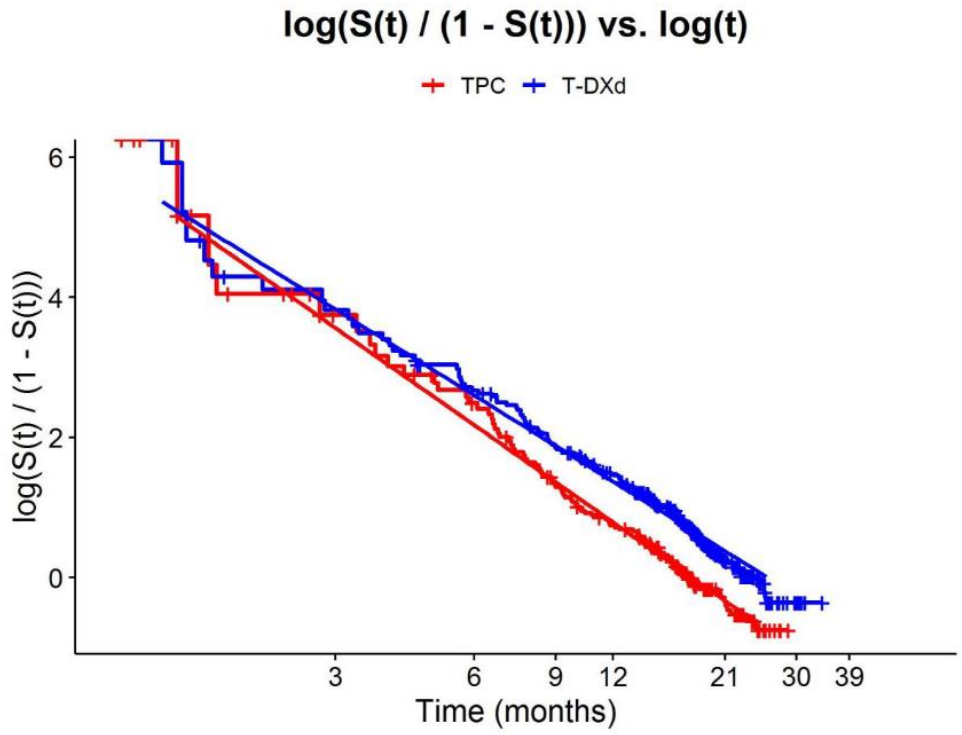


Figure 41 Inverse.normal(1−$S(t)$) vs. log(t) OS, All Patients

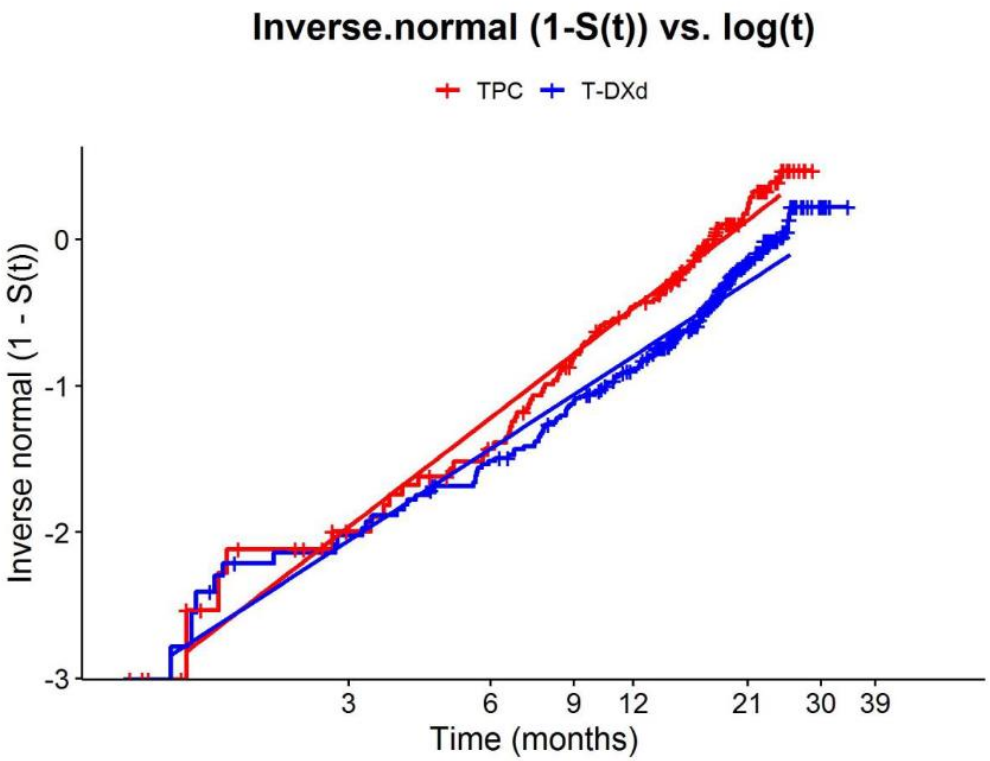


Figure 42 Hazard function, smoothed and unsmoothed of OS, All Patients

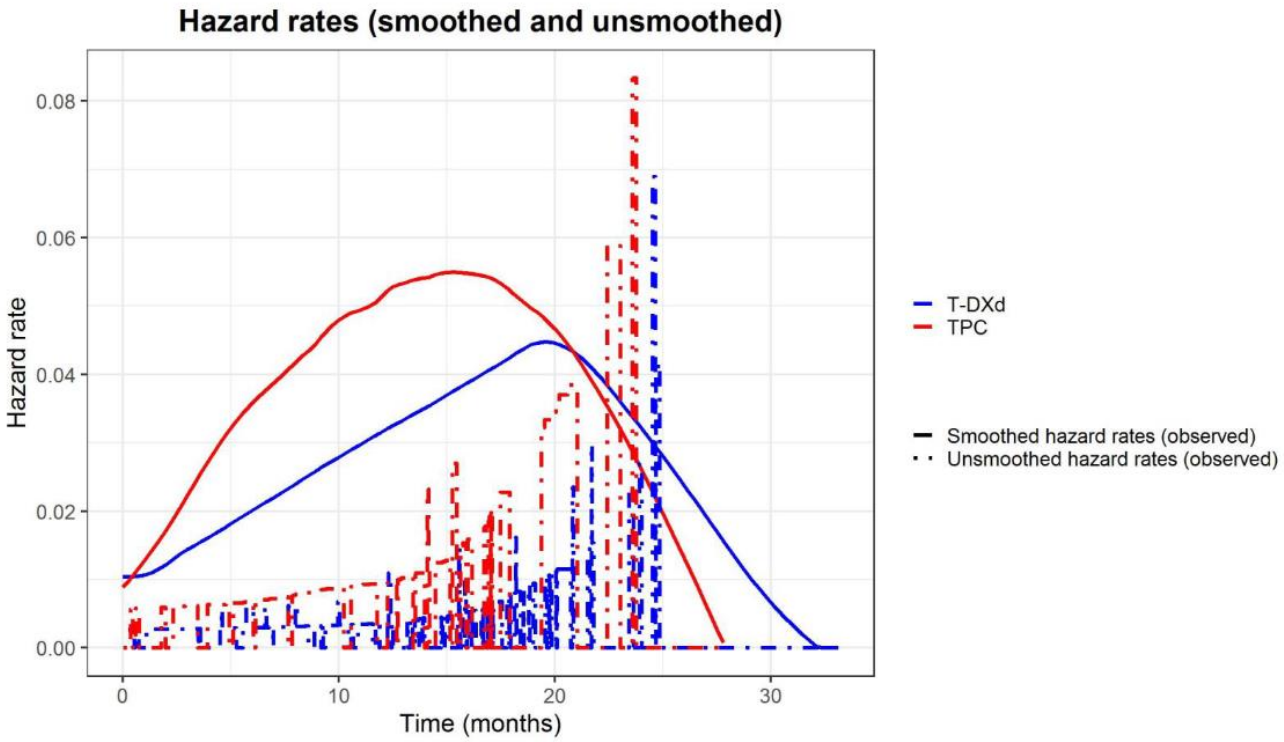
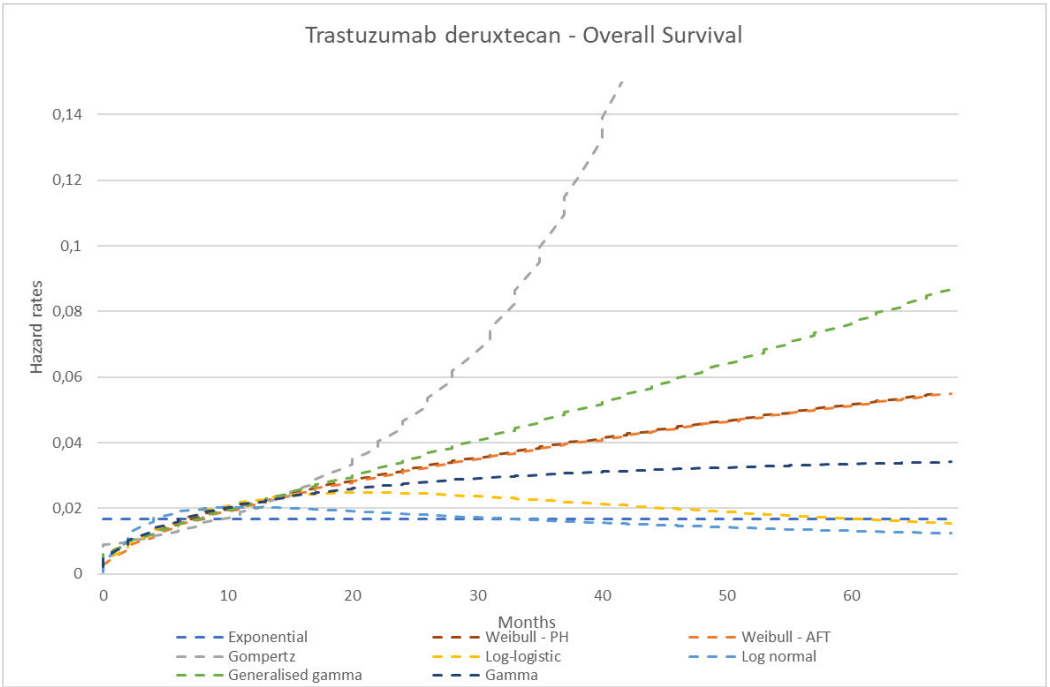
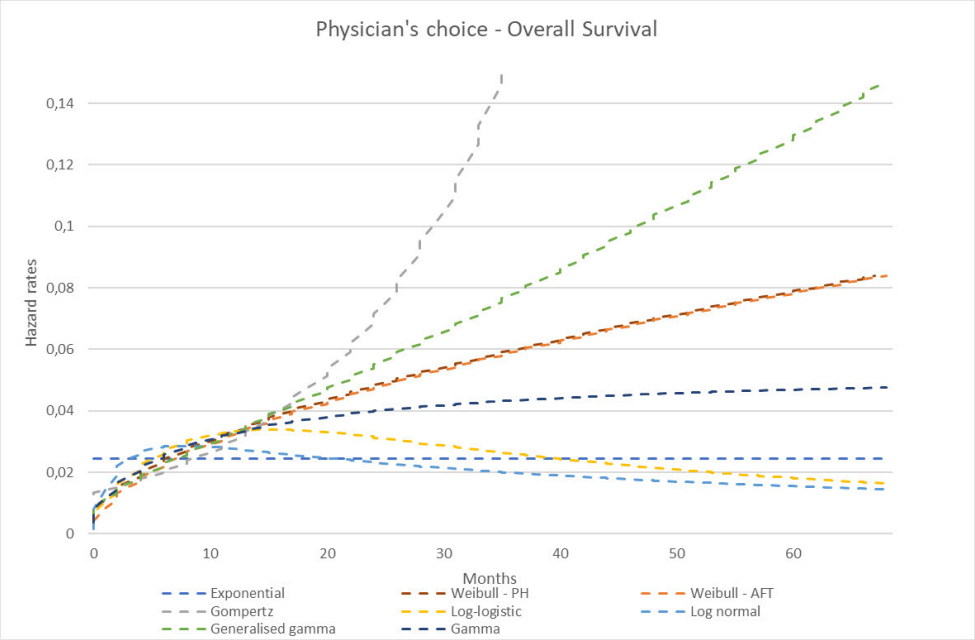


Figure 43 Hazard function, smoothed and by extrapolation model of OS, All Patients A. T-DXd B. TPC

A.



B.



Proportional hazard and fit —TTD, All Patients

In Figure 44 the log-cumulative hazard plot for T-DXd and TPC for TTD is shown. The log-cumulative hazard plots are relatively parallel until near the end of follow-up, from which point the gap in hazards decreases.

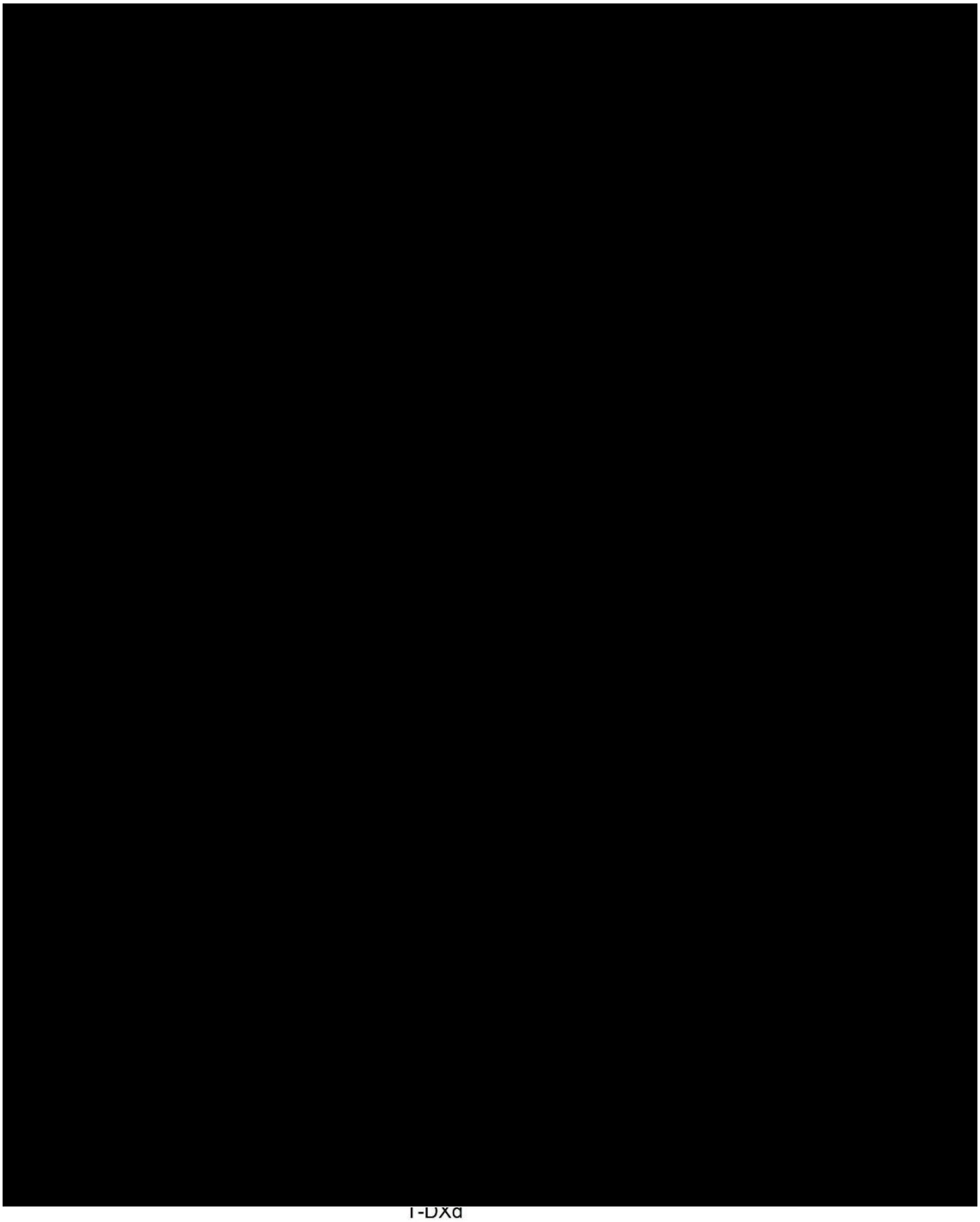
Figure 44 Log-cumulative hazard plot of TTD, All Patients

[redacted]

Key: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TTD, time to treatment discontinuation.

In Figure 45 the Schoenfeld residuals are shown for TTD. The Schoenfeld residuals do not appear constant over time, and the statistical test for proportionality shows a p-value that is significant (p=0.008). This means that the hypothesis that the PH assumption holds can be rejected.

Figure 45 Schoenfeld residuals for TTD, All Patients



On the basis of the log-cumulative hazards plot, the Schoenfeld residuals, and the quantile-quantile plot, it cannot be concluded with certainty that the PH assumption is valid. Separate parametric curves for each treatment group are more suitable for modelling TTD.

Figure 47 Log($S(t)$/(1−$S(t)$))vs. log(t) TTD, All Patients

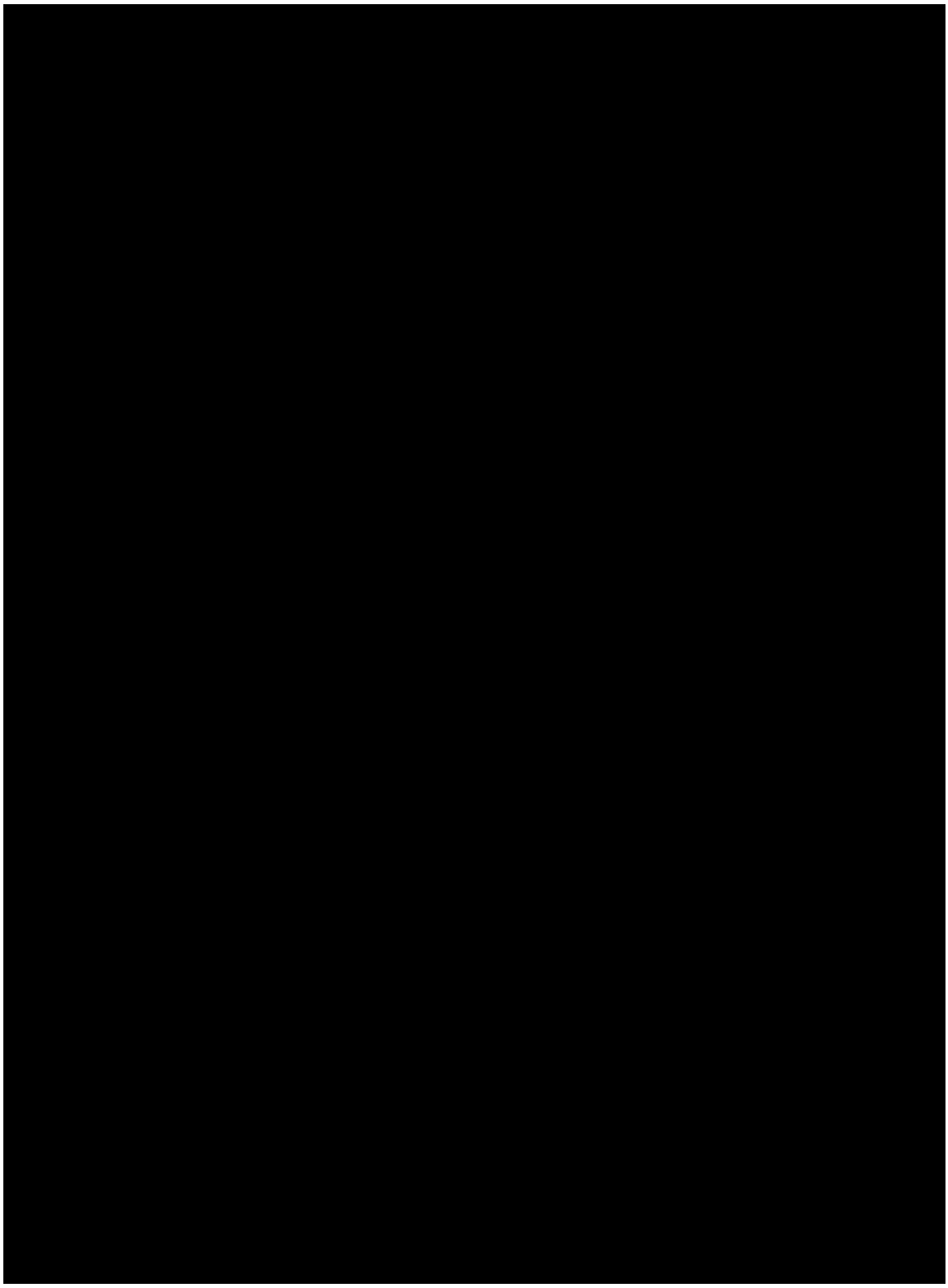


Figure 49 Hazard function, smoothed and unsmoothed of TTD

Figure 50 Hazard function, smoothed and by extrapolation model of TTD A. T-DXd B. TPC

Appendix H – Literature search for HRQoL data

See section 6.

Appendix I Documentation and mapping of HRQoL data

Utility scores for the EQ-5D-5L dimensions were computed using the Danish value set in the base-case.

Mixed model selection

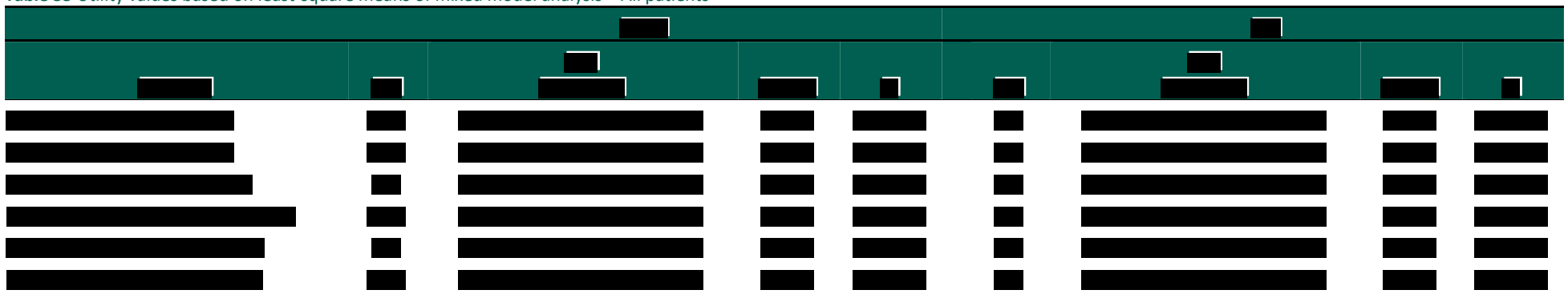
Table 54 Mixed model selection of utility values – All Patients – Denmark

Output driven mixed model analysis per subgroup

Table 55 presents the utility values by health state, for the full analysis set, included in the final model based on the least-square means estimated at the mean timepoint, equal to [redacted] days. It was assumed that the coefficients are proportional to those found in DESTINY-Breast04. Average utility values ranging from [redacted] for progressed health state in the TPC arm to [redacted] for ECOG performance status of zero in the T-DXd arm. Lower utility values were observed among the progressed and off-treatment health states. Table 56 and

Table 57 show results by subgroup.

Table 55 Utility values based on least-square means of mixed model analysis – All patients



Notes:
[a] Number of visits/timepoints per category.
[b] LSM based on generalized linear mixed model of utility decrements (1-utility) with log-normal distribution using backward elimination. LSMs are reported on the scale of the mean utilities (back transformation applied) with the coefficients proportional to those in the dataset rather than to a balanced population.
* Unstructured covariance matrix was used to model the correlation within subjects.
† AR(1) covariance structure used to model correlation within subjects.
‡ Compound symmetry covariance structure used to model correlation within subjects.

Table 56 Utility values based on least-square means of mixed model analysis – HR-positive population

Notes:
[a] Number of visits/timepoints per category.
[b] LSM based on generalized linear mixed model of utility decrements (1-utility) with log-normal distribution using backward elimination. LSMs are reported on the scale of the mean utilities (back transformation applied) with the coefficients proportional to those in the dataset rather than to a balanced population.
* Unstructured covariance matrix was used to model the correlation within subjects.
† AR(1) covariance structure used to model correlation within subjects.
‡ Compound symmetry covariance structure used to model correlation within subjects.

Table 57 Utility values based on least-square means of mixed model analysis – HR- negative population

Notes: TPC: treatment of physician's choice; LSM: least-square means; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease. Table 1.16.9.
[a] Number of visits/timepoints without and with progression, respectively.
[b] LSM based on linear mixed model with progression status and planned treatment as independent variables.
[c] LSM based on linear mixed model with progression status as only independent variable.
* Unstructured covariance matrix was used to model the correlation within subject.

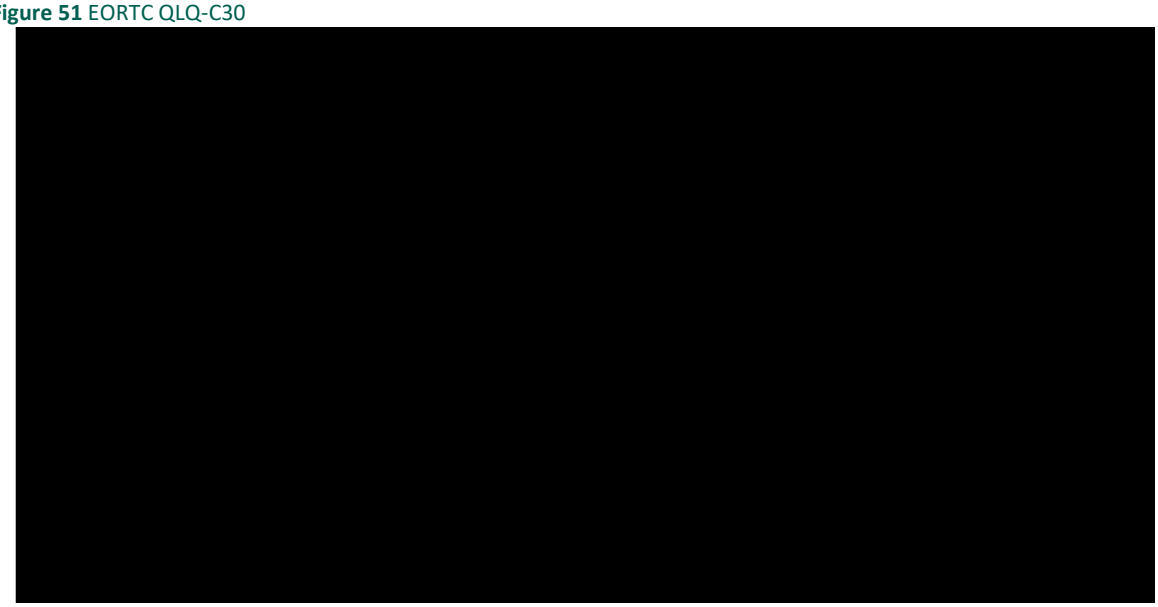
Compliance

The PROM completion compliance rate in the FAS at baseline was 97.1% in the T DXd arm and 92.9%% in the TPC arm for the EORTC QLQ-C30; 96.4% for T-DXd and 92.6% for TPC for the EORTC QLQ-BR45; and 96.1% for T-DXd and 92.0% for TPC for the EQ 5D 5L questionnaire (2).

Post-baseline compliance rates from Cycle 2 through Cycle 49 (n = 222) in the T-DXd arm ranged from 94.6% to 89.5% for the EORTC QLQ-C30, from 94.9% to 89.9% for the EORTC QLQ-BR45, and from 94% to 89.5% for the EQ-5D-5L. Post-baseline compliance rates from Cycle 3 through Cycle 27 (n = 117) in the TPC arm ranged from 97.1% to 86.8% for the EORTC QLQ-C30, from 97.1% to 86.8% for the EORTC QLQ-BR45, and from 97.1% to 86.0% for the EQ-5D-5L.

Median time to definitive deterioration was numerically longer in the T-DXd arm than the TPC arm for QLQ-C30 global health status (defined as the primary PRO variable of interest), see Figure 51, and the QLQ-C30 subscales prespecified as secondary PRO variables of interest.

Figure 51 EORTC QLQ-C30



Significant results (P <0.05) were seen in the QLQ-C30 scales global health status, emotional functioning, cognitive functioning, fatigue, nausea and vomiting, and financial difficulties, and significant results (P <0.0001) were seen in the scales physical functioning, role functioning, social functioning, insomnia, and pain.

Additionally, median time to definitive deterioration was significantly longer in the T DXd arm than in the TPC arm for the body image (P < 0.0001), sexual functioning (P<0.05), future perspective (P<0.05), systemic therapy side effects (P < 0.05), and arm symptoms (P < 0.05) scales in the QLQ-BR45 questionnaire.

The EQ-5D VAS scale (defined as a secondary PRO variable of interest) showed a significantly longer median time to definitive deterioration in the T-DXd arm compared to the TPC arm, see Figure 52.

Figure 52 Kaplan-Meier plot of time to definitive deterioration of EQ-5D-5L - VAS in Full Analysis Set

HRQoL in DESTINY-Breast04 was maintained for patients in the HR-positive cohort during the treatment period of T-DXd ( ) or TPC ( ). The mean change from baseline for QLQ-C30 GHS remained stable with T-DXd up to cycles and with TPC up to cycles.

The impact of T-DXd over time on nausea and vomiting was worse compared to TPC; however, with T-DXd, an increase in nausea and vomiting scores was only clinically significant in early cycles. Change from baseline in fatigue symptoms were similar between T-DXd and TPC and did not worsen over time with T-DXd.

The hazard ratios for time to definitive deterioration favoured T-DXd over TPC for almost all PRO variables of interest (range,), including pain symptoms (hazard ratio,). The HRQoL benefit observed confirm the efficacy and safety results of DESTINY-Breast04.

Appendix J Probabilistic sensitivity analyses

For the complete list of the parameters used in the probabilistic analysis see the model sheet: 'Parameters'.

Table 58 Probabilistic parameters

Parameter	Mean/ Basecase	SE	α	β	Distribution
Mean age (years)	56,5	5,765306			Not varied
Proportion female	0,996	0,101633			Not varied
Average weight (kg)	63,4	6,469388			Not varied
Average height (cm)	160,1	16,33673			Not varied
Average body surface (m2)	1,671	0,17051			Not varied
Discount rate for costs	0,035	0,003571			Not varied
Discount rate for health gains	0,035	0,003571			Not varied
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE - Incidence - Neutrophil count decreased - T-DXd	0,08	88,2	1000,5	0,90	Beta
AE - Incidence - Anaemia - T-DXd	0,09	86,9	837,7	0,27	Beta
AE - Incidence - White blood cell decrease / Leukopenia - T-DXd	0,07	89,5	1246,9	0,84	Beta
AE - Incidence - Platelet count decreased / Thrombocytopenia - T-DXd	0,05	91,3	1771,7	0,82	Beta
AE - Incidence - Febrile neutropenia - T-DXd	0,003	95,7	31820,5	0,76	Beta
AE - Incidence - Nausea - T-DXd	0,04	91,9	2044,6	0,66	Beta
AE - Incidence - Decreased appetite - T-DXd	0,02	93,7	3810,9	0,03	Beta
AE - Incidence - Fatigue - T-DXd	0,05	90,8	1590,7	0,03	Beta
AE - Incidence - Asthenia - T-DXd	0,02	94,2	4863,5	0,07	Beta
AE - Incidence - Increased ALT - T-DXd	0,01	95,0	8538,9	0,15	Beta
AE - Incidence - Increased AST - T-DXd	0,03	92,9	2811,3	0,67	Beta
AE - Incidence - Interstitial lung disease (ILD)- T-DXd	0,02	93,9	4174,5	0,56	Beta
AE - Incidence - Left ventricular ejection fraction (LVEF) decrease - T-DXd	0,01	95,6	19015,4	0,36	Beta
AE - Incidence - Gamma-glutamyltransferase increased - T-DXd	0,01	94,8	7195,9	0,51	Beta
AE - Incidence - Lymphocyte count decreased - T-DXd	0,05	91,3	1771,7	0,59	Beta
AE - Incidence - Hypokalaemia - T-DXd	0,02	93,7	3810,9	0,84	Beta
AE - Incidence - Neutrophil count decreased - TPC	0,28	69,0	178,2	0,62	Beta
AE - Incidence - Anaemia - TPC	0,05	91,5	1854,9	0,49	Beta
AE - Incidence - White blood cell decrease / Leukopenia - TPC	0,17	79,2	375,8	0,33	Beta

Parameter	Mean/ Basecase	SE	α	β	Distribution
AE - Incidence - Platelet count decreased / Thrombocytopenia - TPC	0,01	95,5	15814,2	0,13	Beta
AE - Incidence - Febrile neutropenia - TPC	0,02	93,8	3984,8	0,74	Beta
AE - Incidence - Palmar-Plantar Erythrodysesthesia - TPC	0,04	92,1	2153,3	0,25	Beta
AE - Incidence - Peripheral neuropathy - TPC	0,02	93,8	3984,8	0,41	Beta
AE - Incidence - Decreased appetite - TPC	0,01	94,9	7811,4	0,85	Beta
AE - Incidence - Fatigue - TPC	0,02	94,4	5458,0	0,85	Beta
AE - Incidence - Asthenia - TPC	0,02	93,8	3984,8	0,00	Beta
AE - Incidence - Increased ALT - TPC	0,05	91,0	1658,9	0,36	Beta
AE - Incidence - Increased AST - TPC	0,05	91,5	1854,9	0,48	Beta
AE - Incidence - Gamma-glutamyltransferase increased - TPC	0,03	93,2	3121,5	0,15	Beta
AE - Incidence - Lymphocyte count decreased - TPC	0,03	93,2	3121,5	0,49	Beta
AE - Incidence - Hypokalaemia - TPC	0,01	94,9	7811,4	0,89	Beta
Number of resources per cycle - Specialist physician/ Oncologist	0,7	0,1			Gamma
Number of resources per cycle - Blood tests	0,7	0,1			Gamma
Number of resources per cycle - Cardiac assessment: ECHO scan	0,2	0,0			Gamma
Number of resources per cycle - CT-scanning	0,2	0,0			Gamma
Number of resources per cycle - Nurse	1,0	0,1			Gamma
Patients receiving subsequent treatment - T-DXd	0,6		34,8	20,4	Beta
Patients receiving subsequent treatment – Comps	0,8		22,8	7,4	Beta
Vial sharing	0,5		47,5	47,5	Beta
[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]
HR T-DXd vs TPC – PFS	0,50	1,1			Log-normal
HR T-DXd vs TPC – OS	0,64	1,1			Log-normal
[redacted]	[redacted]	[redacted]			[redacted]
Proportion of Capecitabine as subsequent treatment - T-DXd arm	0,13		83,1	541,9	Beta
Proportion of Eribulin as subsequent treatment - T-DXd arm	0,12		84,6	632,3	Beta
Proportion of Gemcitabine as subsequent treatment - T-DXd arm	0,08		88,7	1078,0	Beta
Proportion of Paclitaxel as subsequent treatment - T-DXd arm	0,15		81,4	457,6	Beta
Proportion of Vinorelbine as subsequent treatment - T-DXd arm	0,04		92,0	2097,7	Beta
Proportion of Fulvestrant as subsequent treatment - T-DXd arm	0,10		86,6	806,4	Beta

Parameter	Mean/ Basecase	SE	α	β	Distribution
Proportion of Epirubicin as subsequent treatment - T-DXd arm	0,02		94,0	4382,3	Beta
Proportion of Carboplatin as subsequent treatment - T-DXd arm	0,06		90,5	1497,4	Beta
Proportion of Tamoxifen as subsequent treatment - T-DXd arm	0,02		94,3	5144,2	Beta
Proportion of Capecitabine as subsequent treatment - TPC arm	0,12		84,1	599,7	Beta
Proportion of Eribulin as subsequent treatment - TPC arm	0,10		86,5	796,4	Beta
Proportion of Gemcitabine as subsequent treatment - TPC arm	0,13		83,5	563,9	Beta
Proportion of Paclitaxel as subsequent treatment - TPC arm	0,14		82,9	531,4	Beta
Proportion of Vinorelbine as subsequent treatment - TPC arm	0,10		85,9	740,5	Beta
Proportion of Fulvestrant as subsequent treatment - TPC arm	0,13		83,5	563,9	Beta
Proportion of Epirubicin as subsequent treatment - TPC arm	0,03		93,0	2908,0	Beta
Proportion of Carboplatin as subsequent treatment - TPC arm	0,11		85,4	690,7	Beta
Proportion of Tamoxifen as subsequent treatment - TPC arm	0,02		94,3	5144,2	Beta

Table 59 Probabilistic parameters – PFS – T-DXd

T-DXd - PFS	Basecase	Variance - Covariance matrix		
Exponential				
Rate	0,068178204	0,004115226		
Weibull – PH				
Scale	0,044909384	0,002905656	-0,000296451	
Shape	1,165565167	-0,000296451	0,002889957	
Weibull – AFT				
Scale	14,32950786	0,002905656	-0,000296451	
Shape	1,165565169	-0,000296451	0,002889957	
Gompertz				
Scale	0,060706242	0,011498394	-0,000964319	

T-DXd - PFS	Basecase	Variance - Covariance matrix		
Shape	0,01615976	-0,000964319	0,000125949	
Log-logistic				
Scale	9,844604766	0,003816008	-0,00042518	
Shape	1,559979457	-0,00042518	0,002890861	
Log-normal				
Meanlog	2,262154229	0,004203504	0,000758289	
Sdlog	1,09993786	0,000758289	0,002275817	
Generalized gamma				
Mu	2,335023053	0,012044358	-0,005659862	0,021212562
Sigma	1,068146853	-0,005659862	0,007078879	-0,01566802
Q	0,161570339	0,021212562	-0,01566802	0,053574701
Gamma				
Scale	10,3970637	0,01229927	0,007606636	
Shape	1,314404542	0,007606636	0,00618427	

Table 60 Probabilistic parameters – PFS – TPC

TPC - PFS	Basecase	Variance - Covariance matrix		
Exponential				
Rate	0,129978564	0,007874014		
Weibull – PH				
Scale	0,091381326	0,006339967	0,000472913	
Shape	1,165565167	0,000472913	0,004782691	
Weibull – AFT				
Scale	7,789962122	0,006339967	0,000472913	
Shape	1,165565169	0,000472913	0,004782691	
Gompertz				
Scale	0,119563449	0,018014967	-0,002057733	
Shape	0,01615976	-0,002057733	0,000417579	
Log-logistic				

TPC - PFS	Basecase	Variance - Covariance matrix		
Scale	4,867409612	0,00773195	-0,000609298	
Shape	1,559979457	-0,000609298	0,005107035	
Log-normal				
Meanlog	1,602949	0,007160416	0,000840392	
Sdlog	1,09993786	0,000840392	0,004126643	
Generalized gamma				
Mu	1,672500726	0,029265264	0,002636683	0,045821979
Sigma	1,068146853	0,002636683	0,004220172	0,002362955
Q	0,161570339	0,045821979	0,002362955	0,095481039
Gamma				
Scale	5,599660243	0,021380897	0,013437501	
Shape	1,314404542	0,013437501	0,011710382	

Table 61 Probabilistic parameters – OS – T-DXd

T-DXd - OS	Basecase	Variance - Covariance matrix		
Exponential				
Rate	0,025799627	0,006711408		
Weibull – PH				
Scale	0,006272199	0,004358167	-0,002682537	
Shape	1,491812255	-0,002682537	0,005407103	
Weibull – AFT				
Scale	29,9533893	0,004358167	-0,002682537	
Shape	1,491812259	-0,002682537	0,005407103	
Gompertz				
Scale	0,013746014	0,02698326	-0,001726275	
Shape	0,060748133	-0,001726275	0,000147003	
Log-logistic				
Scale	24,15807531	0,004685557	-0,002302875	
Shape	1,734048053	-0,002302875	0,005294861	

T-DXd - OS	Basecase	Variance - Covariance matrix		
Log-normal				
Meanlog	3,252291851	0,00761516	0,00303058	
Sdlog	1,143352381	0,00303058	0,003999574	
Generalized gamma				
Mu	3,416559752	0,005479734	-0,008745609	0,020349643
Sigma	0,615514826	-0,008745609	0,078538878	-0,131621833
Q	1,15533194	0,020349643	-0,131621833	0,237620787
Gamma				
Scale	17,51354205	0,023609216	0,013980431	
Shape	1,678487896	0,013980431	0,009717344	

Table 62 Probabilistic parameters – OS – TPC

TPC - OS	Basecase	Variance - Covariance matrix		
Exponential				
Rate	0,039076987	0,01111111		
Weibull – PH				
Scale	0,010034489	0,005615825	-0,002342721	
Shape	1,491812255	-0,002342721	0,008403476	
Weibull – AFT				
Scale	21,85993936	0,005615825	-0,002342721	
Shape	1,491812259	-0,002342721	0,008403476	
Gompertz				
Scale	0,022181444	0,041323948	-0,002916336	
Shape	0,060748133	-0,002916336	0,000281503	
Log-logistic				
Scale	17,08027469	0,006684027	-0,002048726	
Shape	1,734048053	-0,002048726	0,008202913	
Log-normal				
Meanlog	2,893957893	0,009362967	0,003010658	

TPC - OS	Basecase	Variance - Covariance matrix		
Sdlog	1,143352381	0,003010658	0,006368146	
Generalized gamma				
Mu	3,111150485	0,010673075	-0,008593857	0,023167277
Sigma	0,615514826	-0,008593857	0,033836327	-0,054005667
Q	1,15533194	0,023167277	-0,054005667	0,113677622
Gamma				
Scale	12,56638801	0,034112612	0,022127203	
Shape	1,678487896	0,022127203	0,017136501	