Medicinrådet

Bilag til Medicinrådets vurdering af trastuzumab deruxtecan til behandling af ikke-resekterbar eller metastatisk ER+/HER2-lav eller ER+/HER2-ultralav brystkræft

Patienter, der har fået mindst én endokrin behandling i metastatisk regi og som ikke anses for at være egnede til endokrin behandling som næste behandlingslinje

Vers. 1.0

Bilagsoversigt

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

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

22.12.2025

Note on the DMC evaluation report of Enhertu (trastuzumab deruxtecan) for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who received at least one endocrine therapy (ET) in the metastatic setting and who are not considered suitable for ET as the next line of treatment.

AstraZeneca (AZ) and Daiichi-Sankyo (DS) would like to thank the DMC for the evaluation of Enhertu; we appreciate the opportunity to comment on the draft evaluation report. The open dialogue with the Secretariat during the evaluation process has also been appreciated.

Overall, the secretariat and the Expert committee acknowledge the positive results from the Destiny Breast-06 (DB06) trial on HER2-low and HER2-ultralow metastatic breast cancer. The trial demonstrates significant benefit of treating patients with Enhertu in a head-to-head study compared to current standard of care in Denmark; data are available on progression-free-survival (PFS) and overall survival (OS). In response to the DMC evaluation report, there are some concerns to be highlighted, that may bias decision-making on DB06 in Denmark if not considered in a comprehensive context.

Key implications of the DMC evaluation of DB06

- The DMC approach on modelling OS in the DB06 evaluation implies that the benefit of treating with Enhertu one line earlier is nearly lost compared to treating in the DB04 setting.
- The OS extrapolation of the DMC base case does not consider the fact that not all patients, such as those with HER2-ultralow disease, will get the opportunity of receiving Enhertu in later lines.
- The overly conservative DMC base case risks understating the intervention's clinical value. Nonetheless, we agree that it is appropriate to evaluate sensitivity scenarios that adjust the comparator arm to reflect increased use of Enhertu in later treatment lines in Denmark.
    - Ideally these should be informed by clinical trial evidence and plausible real-world use patterns in Denmark to provide bounded estimates for decision-making.

These implications are explained in more detail below,

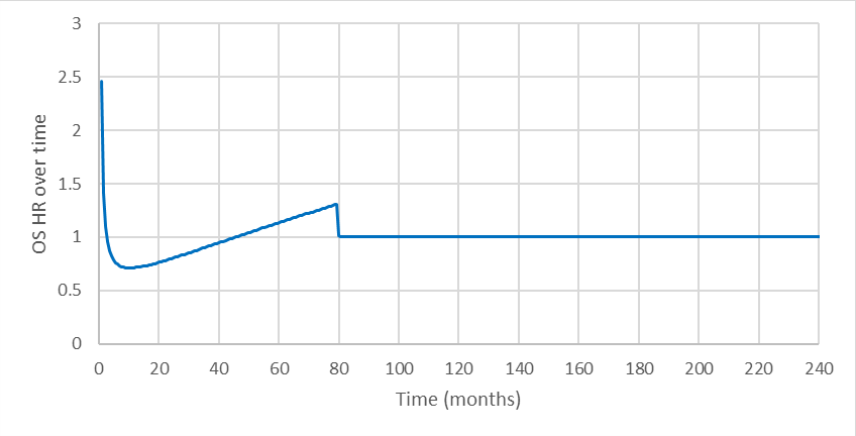
AZ/DS acknowledge that the breast cancer landscape is quickly changing and the current clinical practice in Denmark differs from the situation of DB06. Mature OS data have been central in informing the extrapolations in the economic evaluation of DB06. It should be noted that performing survival adjustments that are not informed by DB06 data involves tampering with the results of a randomized controlled trial. While there is no single appropriate method for making such adjustments, there are no data to suggest that the OS adjustments implemented by the DMC are appropriate or clinically plausible. [redacted]

While Enhertu is available for use in later lines in Denmark, not all patients will have access to the treatment i.e., patients with ultralow HER2 expression (15% of the cohort). Furthermore, not all patients will be fit or survive to receive Enhertu in later lines. Regarding ultralow patients, results from DB06 show benefits consistent with the HER2-low population. The benefits gained from treating ultralow in the DB06 setting should therefore be expected to manifest as durable benefits, further supporting the argument that OS curve convergence would be clinically implausible given the disease trajectory.

The DMC acknowledges that, in line with clinical expert opinion, the implementation of Enhertu in the DB06 setting into Danish clinical practice will focus on patients with the greatest unmet need for effective treatment. The DMC estimate of 70% is higher than the estimate of 40-50% from clinical experts consulted by AZ/DS with substantial experience with Enhertu. In any case, the patient population that would be prioritized for treatment with Enhertu in the DB06 setting is a population with higher risk of not being able to receive Enhertu or other treatments in subsequent lines. For this relatively small population, the flexibility of treating with Enhertu in earlier lines to ensure disease control and durable responses will be crucial.

The AZ/DS view is that the DMC modelling approach is conservative and not reflective of trial data. While we acknowledge that the treatment mix in DB06 underestimates the subsequent use of Enhertu in the control arm within a Danish clinical setting, the modelling chosen by DMC to compensate for this, overestimates the comparative efficacy in the control arm. This can best be demonstrated by examining how the relative mortality in the DMC modelling evolves over time (see Figure 1).

Figure 1 Development of relative mortality (hazard rate) between the Enhertu arm and the control arm over time, DMC base case.



Based on the DMC approach, there is an initial advantage in relative mortality (HR<1) for Enhertu from 4 to 45 months. The average HR from 0 to 45 months is 0.86 in the DMC modelling, compared with HR=[redacted] in the latest DB06 clinical trial data (Figure 7 in the DMC report). Thereafter the advantage in relative mortality switches over to the control arm from 45 to 80 months (HR>1). After this point, the modelled OS curves cross (Figure 10 in the DMC report), and DMC sets survival as equal in both arms thereafter (hence HR=1 beyond 80 months).

While there is some uncertainty on what happens after 80 months, **it is important to note that over the initial period up to 80 months in the DMC modelling, the average HR is 0.99, i.e. very close to one**. In practice, this implies very little advantage of treating earlier with Enhertu, as the modelled efficacy in later line treatment is high enough to compensate for the lack of first-line usage.

We find that this is a clinically implausible implication of the DMC modelling, based on clinical trial data and the fact that not all patients will survive to receive second line treatment, and not all patients will get Enhertu in later lines in the Danish clinical setting.

Furthermore, it should be noted that the DMC modelling curve selection of the Enhertu arm does not fully consider predominantly reported 5-year survival rates in the literature, which fall within a range of 15–25% for patients receiving chemotherapy (page 36 of the DMC evaluation report). The DMC curve selection yields a 5-year survival of 16% in the Enhertu arm, comparable with patients at the lower bound when receiving conventional chemotherapy.

To conclude, the DMC modelling is overly conservative and should be considered an extreme scenario analysis rather than a clinically plausible base case. It is important that the value of Enhertu is recognized when treating patients in the first line, because there are patients who will not survive or remain eligible for second-line treatment, and early use maximizes the chance of durable response before resistance and declining performance status erode benefit.

Kind regards,

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19.12.2025
DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.01.2026
Leverandør	Daiichi Sankyo i samarbejde med AstraZeneca
Lægemiddel	Enhertu (trastuzumab deruxtecan)
Ansøgt indikation	Voksne patienter med ikke-resekterbar eller metastatisk hormonreceptor (HR)-positiv, HER2-lav eller HER2-ultralav brystcancer, som har fået mindst én endokrin terapi i metastatisk regi, og som ikke anses for at være egnede til endokrin terapi som næste behandlingslinje.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Enhertu (trastuzumab deruxtecan):

Tabel 1: Forhandlingsresultat [redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Enhertu	100 mg (1 stk.)	10.856,99	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Anbefaler Medicinrådet ikke Enhertu, har leverandøren tilbudt en anden pris. Se tabel 3.

Enhertu er tidligere anbefalet til følgende to indikationer:

Tabel 2: Tidligere anbefalede indikationer på Enhertu

Indikation	Anbefalingstidspunkt	Pris der ligger til grund for anbefaling, SAIP, DKK
Voksne patienter med ikke-resekterbar eller metastatisk HER2-positiv brystkræft, som har fået en eller flere tidligere anti-HER2-baserede regimer	25. januar 2023	[redacted]
Voksne patienter med ikke-resekterbar eller metastatisk HER2-lav brystkræft	24. april 2024	[redacted]

Tabel 3: Forhandlingsresultat [redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Enhertu	100 mg (1 stk.)	10.856,99	[redacted]	[redacted]

[redacted]

Tabel 4: [redacted]

Trin	Antal pakninger	Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
[redacted]	[redacted]	Enhertu	100 mg (1 stk.)	10.856,99	[redacted]	[redacted]
[redacted]	[redacted]	Enhertu	100 mg (1 stk.)	10.856,99	[redacted]	[redacted]

[redacted]	[redacted]	Enhertu	100 mg (1 stk.)	10.856,99	[redacted]	[redacted]
[redacted]				10.856,99	[redacted]	[redacted]

[redacted]

[redacted]

Tabel 5: [redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Udbuds-SAIP (DKK)	Rabatprocent ift. AIP
Enhertu	100 mg (1 stk.)	10.856,99	[redacted]	[redacted]

[redacted]

Tabel 6: [redacted]

Prispunkt (aftaleperiode)	AIP (DKK)	SAIP (DKK)	Rabatprocent ift. AIP
[redacted]	10.856,99	[redacted]	[redacted]
[redacted]	10.856,99	[redacted]	[redacted]
[redacted]	10.856,99	[redacted]	[redacted]
[redacted]	10.856,99	[redacted]	[redacted]
[redacted]	10.856,99	[redacted]	[redacted]

Informationer fra forhandlingen

[redacted]

[redacted]

Konkurrencesituationen

Enhertu er den eneste behandling til denne indikation. Enhertu er godkendt til to andre brystkræftindikationer og indgår i Medicinrådet behandlingsvejledning for HER2-positiv brystkræft. Tabel 7 viser den årlige lægemiddeludgift for Enhertu, baseret på den forhandlet pris betinget af anbefaling af igangværende vurdering.

Tabel 7: Lægemiddeludgift pr. patient pr. år

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Enhertu	100 mg, 1 stk.	5,4 mg/kg* hver tredje uge, i.v.	[redacted]	[redacted]

*Patientvægt 71 kg if. Medicinrådets vurdering af trastuzumab deruxtecan til behandling af ikke-resekterbar eller metastatisk ER+/HER2-lav eller HER2-ultralav brystkræft

Status fra andre lande

Tabel 8: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til status
Sverige	Under vurdering	[redacted]	Link til status
England	Ikke ansøgt		

Opsummering

[redacted]

[redacted]

Application for the assessment of Enhertu (T-DXd) as monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2 ultralow breast cancer who received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment

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

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Tables and Figures

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Abbreviations

Abbreviation	Definition	Abbreviation	Definition
1L	First line	**ICER**	Incremental cost-effectiveness ratio
2L	Second line	**IHC**	Immunohistochemistry
2L+	Second line and beyond	**ILD**	Interstitial lung disease
3L	Third line	**ISH**	in-situ hybridisation

Abbreviation	Definition	Abbreviation	Definition
ADC	Antibody drug conjugate	**ICC**	Treating investigators' choice of chemotherapy
AE	Adverse event	**ITT**	Intention to treat
AIC	Akaike information criterion	**IV**	intravenous
ATC	Anatomic Therapeutic Chemical classification system	**KM**	Kaplan-Meier
AZ	AstraZeneca	**LVEF**	Left Ventricular Ejection Fraction
BICR	Blinded Independent Central Review	**mBC**	Metastatic Breast Cancer
BIC	Bayesian information criterion	**N/A**	Not applicable
CI	Confidence interval	**ORR**	Overall response rate
CT	Computed tomography	**OS**	Overall survival
CTCAE	common terminology criteria for adverse events	**PFS**	Progression-free survival
DB04	DESTINY-Breast04 study	**PH**	Proportional Hazard
DB06	DESTINY-Breast06 study	**PR**	Progesterone receptor
DMC	Danish Medicine Council	**Q3W**	Every three weeks
DoR	Duration of response	**QALY**	Quality adjusted life years
DS	Daiichi Sankyo	**QoL**	Quality of Life
DXd	Deruxtecan - a potent topoisomerase I inhibitor	**RECIST**	Response Evaluation Criteria in Solid Tumours
ECOG	Eastern Cooperative Oncology Group	**RWE**	Real World Evidence
ET	Endocrine treatment	**SD**	Standard deviation
FAS	Full Analysis Set	**SLR**	Systematic literature review

Abbreviation	Definition	Abbreviation	Definition
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	**TTD**	Time to treatment discontinuation

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Enhertu
Generic name	Trastuzumab Deruxtecan (T-DXd)
Therapeutic indication as defined by EMA	ENHERTU as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one ET in the metastatic setting and who are not considered suitable for ET as the next line of treatment
Marketing authorization holder in Denmark	Daiichi Sankyo Europe GmbH Zielstattstrasse 48 81379 München Tyskland. Enhertu is handled in an alliance between Daiichi Sankyo and AstraZeneca.
ATC code	L01FD04
Combination therapy and/or co-medication	No
Date of EC approval	April 4th 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No

Overview of the medicine	
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	<u>Breast cancer</u> • *HER2-positive breast cancer* 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. • *HER2-low breast cance*r Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. <u>Non-small cell lung cancer (NSCLC)</u> • Enhertu as monotherapy is indicated for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy. <u>Gastric cancer</u> • Enhertu as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.
Other indications that have been evaluated by the DMC (yes/no)	Yes, all breast cancer indications.
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No there are some differences noted in the treatment landscape Is the product suitable for a joint Nordic assessment? No If no, why not? HTA assessments already ongoing in Norway and Sweden.
Dispensing group	BEGR
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

2. Summary table

Summary	
Indication relevant for the assessment	ENHERTU as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one ET in the metastatic setting and who are not considered suitable for ET as the next line of treatment.
Dosage regiment and administration	5.4 mg/kg once every 3 weeks until disease progression or unacceptable toxicity. Intravenous (IV) administration.
Choice of comparator	Investigator's choice of chemotherapy (ICC)
Prognosis with current treatment (comparator)	Although endocrine treatment (ET) (with or without CDK4/6i) has improved outcomes for the first-line treatment of HR-positive mBC, treatment options for patients are very limited after ET, with chemotherapy still being the standard. Outcomes on chemotherapy for mBC are generally poor with typical OS of 12-24 months and a real-world PFS of 6.9 months for first line of chemotherapy and progressively shorter PFS in following lines of treatment (1). Although T-DXd is now recommended as standard treatment after 1 prior line of chemotherapy for HER2-low mBC by DBCG guidelines and the DMC as per the DB04 study, many patients may never be in a position to receive this treatment due to their health and performance status deteriorating while on their 1L chemotherapy. T-DXd will likely be used more selectively for the patients with the greater unmet need such as patients with visceral disease and patients with CNS metastasis.
Type of evidence for the clinical evaluation	Head-to-head study, Destiny Breast-06 study
Most important efficacy endpoints (Difference/gain compared to comparator)	T-DXd performed significantly better than ICC in PFS in the ITT population (HER2-low and ultra-low). At the time of the first interim analysis (March 2024), OS data were 39.6% mature (i.e., 282 events/713 patients). Although T-DXd had not yet demonstrated a statistically significant difference between the treatment arms, there was a numerical improvement, suggesting an early trend of OS favouring the T-DXd arm. Median PFS was 13.2 months (95% CI: 11.4, 15.2) in patients treated with T-DXd and 8.1 months (95% CI: 7.0, 9.0) in patients treated with ICC. Thus, T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS as assessed by blinded independent central review (BICR) compared with ICC in HER2-low patients (HR: 0.62; [95% CI: 0.52, 0.75]; $p < 0.0001$). (2)

Summary	
	The improvement in median PFS was further supported by the analysis of other secondary endpoints in the ITT population: Median DoR based on BICR was longer in the T-DXd arm (13.7 months) than in the chemotherapy arm (7.3 months) (2), median PFS2 was 20.3 months for T-DXd vs 14.7 months for ICC (2). At the second interim OS analysis (March 2025) where data were [redacted] mature, a positive trend favouring the T-DXd arm was maintained in the ITT population [redacted](3).
Most important serious adverse events for the intervention and comparator	The 3 most frequent SAEs in the T-DXd arm were ILD (1.8%), pneumonitis (1.8%), and COVID-19 (1.6%), and in the chemotherapy arm were cellulitis (1.2%), pleural effusion (1.2%), and febrile neutropenia (0.5%) (2).
Impact on health-related quality of life	Clinical documentation: EORTC QLQ-30 and EQ-5D-5L EQ-5D-5L: T-DXd Pre-progression [redacted] ICC Pre-progression: [redacted] T DXd post progression: [redacted] ICC post progression: 0.8082 [redacted] Health economic model: Better than comparator
Type of economic analysis that is submitted	Type of analysis: cost-utility Type of model: Partitioned survival model
Data sources used to model the clinical effects	DB06 data
Data sources used to model the health-related quality of life	DB06 data
Life years gained	0.48 years
QALYs gained	0.45 QALY
Incremental costs	297,985 DKK
ICER (DKK/QALY)	661,992 DKK/QALY
Uncertainty associated with the ICER estimate	Survival extrapolation, subsequent treatment
Number of eligible patients in Denmark	HER2-low or HER2-ultralow patients: 206 patients Appropriate for T-DXd: 165 patients
Budget impact (in year 5)	53,049,512 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Breast cancer is a heterogenous disease, and the patients have different levels of expression of the hormone receptors; oestrogen receptor positive/negative (HR) and progesterone receptor positive/negative (PR), as well as HER2. However, in Danish clinical practice, PR is not assessed, so HR status is solely dependent on ER positivity.

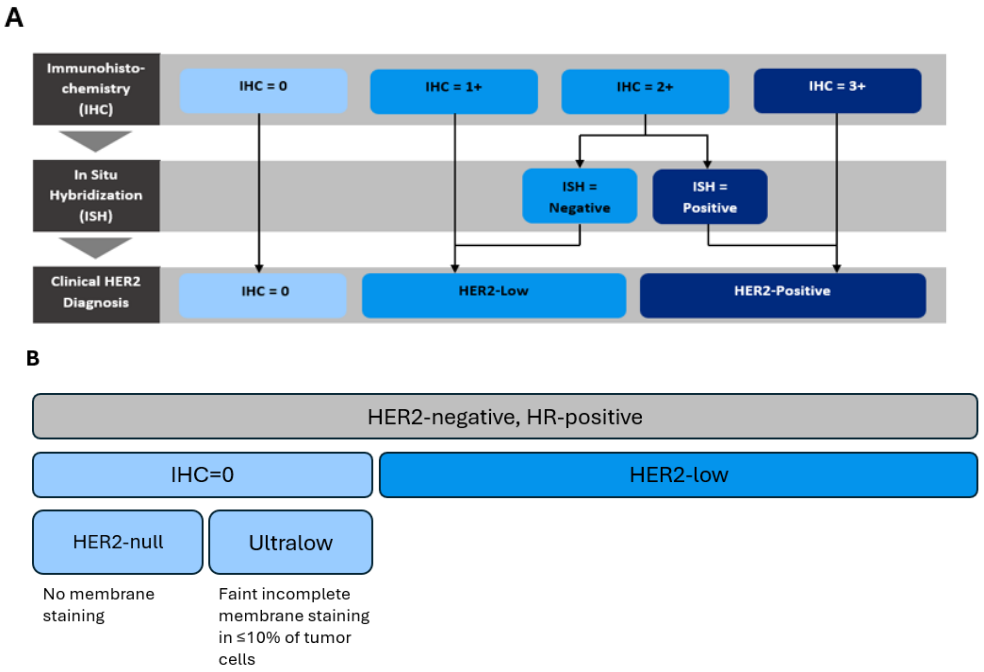
In Denmark, HER2 status is assessed at diagnosis using immunohistochemistry (IHC), scored from 0 to 3 as well as *in-situ* hybridisation (ISH). Historically, HER2 has been categorized into HER2-positive and HER2-negative based on the results of the IHC and ISH score. IHC3+ or IHC2+ with positive ISH (ISH+) is classed as HER2-positive. HER2-negative then included IHC0, IHC1+, and IHC2+ (ISH-) (Figure 1). To further nuance the traditional HER2-negative spectrum, the HER2-low category was introduced, which includes IHC1+ and IHC2+(ISH-), which became clinically relevant with the introduction of T-DXd for HER2-low mBC.

Within the HR-positive patient population, the fraction of HER2-negative patients who can be classed as HER2-low has previously been estimated at approx. 65% with the remaining 35% being IHC0 (4) (Figure 1B). Recently, IHC0 was divided into HER2-ultralow (IHC0 with membrane staining) and HER2-null (IHC0 with no membrane staining) in order to identify a lower boundary for response to HER2-directed antibody drug conjugates (ADC) therapy such as T-DXd (Figure 1B) (5-7).

There are currently few published data describing the prevalence of HER2-ultralow. One study found that HER2-ultralow comprise 43%-45% of the traditional IHC0 (35%), making ultralow approx. 15% of the whole HER2-negative spectrum. Data from the Nordic REVISIT study, which assessed the HER2-ultralow population in two small cohorts of Swedish and Danish mBC patients, found HER2-ultralow to be 20%-21% of the HER2-negative HR-positive mBC (8). Importantly, as of 2024, DBCG pathology guidelines now include HER2-Ultralow and SNOMED codes in patobank have been changed to include this category, thereby enabling the practical identification and registration of this patient group (9). Consequently, the DBCG annual report for 2024 contains real world scorings from Danish clinical practice of 4287 patients. These recently reported numbers from the DBCG annual report from scoring of a large population in Danish clinical practice showing a 8,8% prevalence of HER2-ultralow across all patients and 10,0% of the traditional HER2-negative spectrum thus appear to be the most appropriate estimate for estimation

of HER2-ultralow. The DBCG report estimate for HER2-low as percentage of the whole HER2-negative spectrum is similarly be estimated at 79%(10).

Figure 1 HER2 testing system. A; current HER2 testing paradigm. B; New HER2 testing paradigm with HER2-low as treatable subgroup



3.1.1 Predictive and prognostic factors

The course after a breast cancer diagnosis varies greatly depending on, amongst others, various prognostic and predictive factors (11-13). These factors are important with regards to relapse, premature death and the effectiveness of a specific treatment (14). The time between primary breast cancer diagnosis and the development of metastases is another known important prognostic factor (13). Line of therapy is also a strong prognostic factor; patients with mBC who are eligible for 3L treatment typically survive for less than 2 years (15). Differences in survival also depend on the site of metastases (16-18): if bone was the first site of metastases, median overall survival (OS) was 42 months; if it was visceral metastases OS was further reduced to 25 months, and to 12 months in patients where the brain was the first site of metastases (19).

3.1.2 Unmet need

Although endocrine treatment (with or without CDK4/6i) has improved outcomes for the first-line treatment of HR-positive mBC, treatment options for patients are very limited after ET, with chemotherapy still being the standard. Outcomes on chemotherapy for mBC are generally poor with typical OS of 12-24 months and a real-world PFS of 6.9 months for first line of chemotherapy and progressively shorter PFS in following lines of treatment (1). Attrition rates should also be accounted for, meaning that for each line there will be a proportion of patients that will be too worn down or even die before

being able to receive next line of therapy (1, 20). According to a recent large real-world evidence study from the United States around 25% of mBC patients died having only received 1 line of chemotherapy and were thus never able to receive the 2L chemotherapy (1). This is a reason why a guiding principle in oncology is to use the best treatment first in order to secure optimal response, disease control and symptom relief. Although T-DXd is now recommended as standard treatment after 1 prior line of chemotherapy for HER2-low mBC by DBCG guidelines and the DMC as per the DB04 study, many patients may never be in a position to receive this treatment due to their health and performance status deteriorating while on their 1L chemotherapy.

Particularly for patients with visceral disease or CNS metastasis it is of critical importance to have the best and most effective treatment options available as early as possible. With DB06 demonstrating the superiority of T-DXd over 1L chemotherapy for both PFS and PFS2, T-DXd may now fulfil this significant unmet need for patients. Moreover, Danish HER2-Ultralow patients currently have no access to T-DXd or other innovative treatments, leaving them with just chemotherapy after ET-CDK4/6i, so this patient group have an even greater unmet need for new effective treatment options. With DB06 showing consistent benefit of T-DXd for HER2-ultralow patients, this patient group will now be able to get access to a novel and effective treatment (21).

In conclusion, despite recent progress with the introduction of T-DXd for HER2-low after one line of chemotherapy for mBC, there is still a great unmet need for improved treatment options for HER2-low and HER2-Ultralow patients and for the novel, effective treatments to be made available to a broader segment of patients and in earlier lines, when patients are still fit to receive them.

3.2 Patient population

The prevalence of breast cancer cases in 2022 was around 77.000 for women (22, 23) and around 430 for men in Denmark (22). Breast cancer incidence for men and women across all ages was 4.981 in 2021 and increased to 5.085 in 2022 (24). Incidences and prevalences for the past years based on a 2024 data report from the Danish Cancer registry are described in Table 1.

Table 1 Incidence and prevalence (in women) in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark per 100.000*	146,7	149,3	139,7	143,3	145,0
Prevalence in Denmark*	70 238	72 263	73 976	75 645	77 263

*Note: * Age-standardized incidence rate (to the age composition of the Danish population in 2000) (per 100,000 women) and prevalence of breast cancer in women based on annual rapport from cancer registry (23)*

The Danish patient population eligible for treatment with T-DXd is aligned with the approved EMA-indication, i.e. for the treatment of adult patients with unresectable or

metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one ET in the metastatic setting and who are not considered suitable for ET as the next line of treatment.

According to Danish clinical experts, the median age of HR-positive mBC patients is somewhat higher than the median age of the patients in the DB06 study (25) . However, the patient population that is HER2-low or HER2-ultralow, chemotherapy-eligible and relevant for treatment with T-DXd following ET is expected to be younger, as some older patients are less likely to receive treatment due to frailty, performance status, and comorbidities, as commonly observed in clinical practice. 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 (26, 27).

A large retrospective study collected data from 3689 patients previously classified as HER2-negative. Of these patients, 1486 were reclassified as HER2 0 and 2203 patients were reclassified as HER2-low, with the median ages of the groups being 55 and 59 years, respectively (4). This aligns with the average age observed in the DB06 trial (58.2 years), which was confirmed as generalizable to the Danish population during interviews with Danish clinical experts (25).

In terms of prognosis, the experts commented that in Danish clinical practice patients may have somewhat less aggressive disease compared to those in the DB06 study. This is because in clinical practice, around 26% of HR-positive mBC patients have bone-only disease (28), whereas only 3% in the DB06 trial had bone-only disease, with a higher percentage of DB06 patients having liver/visceral metastasis (7). Given the uncertainty around the implications of these comments, and to ensure that the modelled results are internally consistent with the DB06 trial data, no adjustments have been made to the patient characteristics or efficacy data informing the model.

The Danish clinical experts also suggested that even with T-DXd available in one line earlier, not all patients would be given treatment with T-DXd in this earlier, post-ET chemo-naive setting of DB06 and that T-DXd will likely be used more selectively for the patients with the greater unmet need such as patients with visceral metastasis and patients with CNS metastasis. Danish clinical experts estimate that the patient population who would likely receive T-DXd in the chemo-naïve (DB06) setting corresponds to around 30-60% of the overall post-ET HR-positive HER2-low or HER2-Ultralow mBC population that are in scope for chemotherapy (25).

The patient population in the DB06 trial is representative of the patient profile the Danish clinical experts have described as candidates for treatment with T-DXd in the DB06 setting. For instance, the proportion of patients with bone-only disease in DB06 was just 3%, while it is 26% in the Danish real-world population. Along similar lines, in DB06, 85% of patients had visceral disease while it is 54% in the Danish real-world cohort. Also, 56% of patients in DB06 had 3 or more metastasis while there are 29% of patients in the Danish real-world cohort with 3 or more metastasis at baseline.

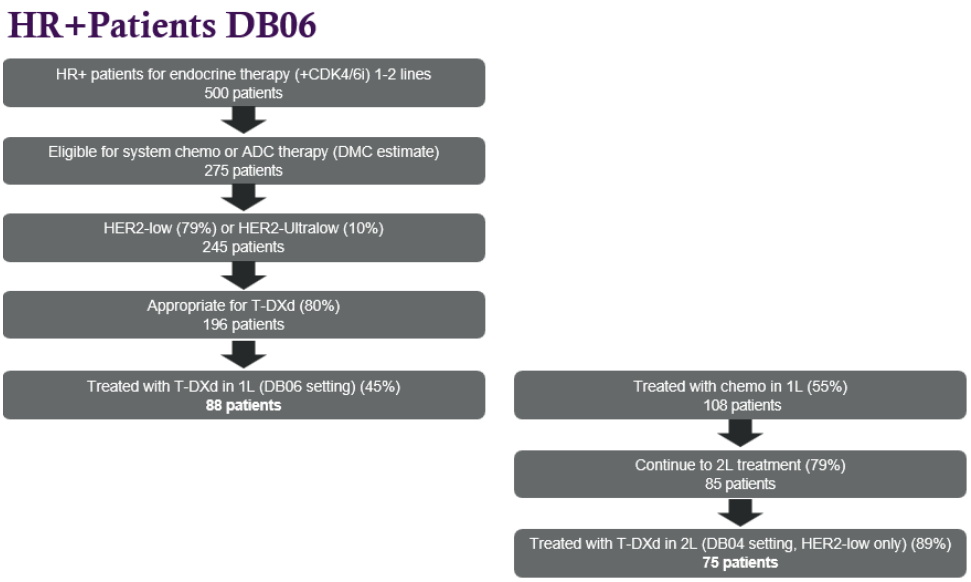
To sum up, the majority of patients in DB06 are patients with visceral disease and often several metastases which corresponds well to the patient profile that Danish clinical

experts want to treat with T-DXd in this setting. This is further emphasized by the fact that DB06 recruited a significant number of Danish patients.

The patient funnel is outlined in the following text and schematically illustrated in Figure 2.

- DMC estimates from the assessment of DB04 indicate that approximately 500 HR+ patients are treated per year in 1L with ET+CDK4/6i. This is consistent with DBCG unpublished data. (29, 30)
- According to DMCs assessment of DB04, of the patients getting treatment, an estimated 55% of HR+ patients will at some point receive a chemotherapy, resulting in 275 patients (29).
- Of the 275 HR+, 79% are estimated to be HER2-low and 10% are estimated to be HER2-Ultralow according to DBCG reporting (10). Assuming they are all identified, this results in 245 patients.
- Of the 245 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, frailty or poor performance status (25, 29). Hence, we estimate 196 new HR+ HER2-low and HER2 Ultralow who could potentially receive T-DXd instead of 1L chemotherapy post progression on ET+CDK4/6i.
    - Of the 196 patients, we estimate that 45% of patients (average of 30% and 60% which were estimated by the clinical experts) would receive T-DXd instead of 1L chemotherapy while 55% would still receive chemotherapy in the 1L setting. Consequently 88 patients would be treated with T-DXd in the 1L setting while 108 patients would receive chemotherapy. This estimate is based on input from Danish clinical experts on which patient groups they would prioritize for T-DXd vs chemotherapy, which includes patients with greater unmet need such as patients with visceral disease or patients with CNS metastasis (25).
- Of the 108 patients receiving chemotherapy in 1L after progression on ET+CDK4/6i, 85 patients (79%) will receive another line of treatment in 2L. This attrition rate (79%) corresponds to the rate of subsequent treatment in the DB06 study (7).
- Of the 85 HER2-low and HER2-Ultralow patients who will receive a treatment in 2L after 1L chemotherapy, 75 patients (89%) are estimated to be HER2-low and will thus receive T-DXd as per the DB04 current DMC recommendation (4, 10).

Figure 2 Schematic illustration of patient funnel. The columns represent the HR+ patients, where the left column illustrates 1L use of T-DXd in the chemo-naïve setting (DB06) and the right column illustrates 2L (DB04)



Estimated number of patients eligible for treatment in the upcoming years are depicted in Table 2 with an estimated 196 patients in year 1 growing to 200 patients being eligible for treatment in Year 5.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	196	197	198	199	200

3.3 Current treatment options

As mentioned above, the population in scope for this application is *"metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one ET in the metastatic setting and who are not considered suitable for ET as the next line of treatment"*

The standard of care for HR+ mBC patients is ET, which is most often given in combination with CDK4/6-inhibitors as a 1L treatment.

However, once the patients become refractory to ET, the available options for the following line of treatment are chemotherapy. DBCG guidelines clearly state that for HR+ HER2-negative/HER2-low mBC there is no preferred 1L chemotherapy. Treatment is

decided based on multiple factors including previous treatment, toxicity, performance status, comorbidities and patient preferences (10). For patients who have not received (neo)adjuvant taxanes or anthracyclins in early-stage BC, these regimens should be considered. Sequential use of single-agent chemotherapy is generally recommended over combination chemotherapy since more toxicity is seen with combinations without any increase in overall survival (10). In Danish clinical practice, the most commonly used option in the post-ET setting is capecitabine, followed by taxanes and anthracyclines (unless received in (neo)adjuvant setting), which is generally well aligned with the physicans choice options in the DB06 control-arm. This was confirmed by Danish clinical experts (25).

After progression on 1L chemotherapy for mBC, the recommended treatment for HER2-low patients is T-DXd, since this was approved by DMC in April 2024 and stated in DBCG guidelines (10). HER2-Ultralow patients do not currently have access to T-DXd, so for this patient group, another line of chemotherapy is typically given after the first chemotherapy for mBC. The choice of 2L chemotherapy typically depends on what has been used previously as well as performance status of the patient, the presence of co-morbidities, and the patient's preferences (10). If taxanes, anthracyclines, or capecitabine have not already been used for early breast cancer or as first chemotherapy for mBC, then those are potential options in 2L, but eribulin, vinorelbine and gemcitabine are also options in later line chemotherapy (10).

The efficacy of fulvestrant after progression on CDK4/6i is, however, limited and for this reason, the often rapid progression on fulvestrant in this setting is not thought to significantly impact on the sensitivity of the tumor towards neither chemotherapy or T-DXd since the cytotoxic mechanisms of action of these drugs are fundamentally different from that of endocrine treatment and consequently the mechanisms of resistance to endocrine treatment are different as well. Consistent with this assumption, a clear PFS benefit was observed in the forest plot in favor of T-DXd across all subgroups of patients with 1, 2, or 3+ lines of prior endocrine treatment for metastatic disease (See Figure XX of Appendix **Error! Reference source not found.**). Therefore, there is no reason to believe that the prior lines of endocrine treatment have any impact on the overall interpretation of the results of DB06. A clinical expert consulted, agrees with this conclusion.

Importantly, the recently updated ESMO living guidelines for mBC as well as NCCN guidelines now include T-DXd for HER2-low and HER2-Ultralow patients in the chemo-naive setting with reference to the DB06 study (31, 32). However, current DBCG guidelines for mBC are from march 2024 and therefore do not yet include reference to DB06 (10).

3.4 The intervention

T-DXd is an IV administered HER2-directed antibody drug conjugate. The dose is 5.4 mg/kg administered as an IV infusion once every 3 weeks. Treatment with T-DXd can be continued until disease progression, unless there is evidence of unacceptable toxicity.

Overview of intervention	
Indication relevant for the assessment	ENHERTU as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one ET in the metastatic setting and who are not considered suitable for ET as the next line of treatment
ATMP	N/A
Method of administration	T-DXd, is intravenously (IV) administered
Dosing	5.4 mg/kg administered as an IV infusion once every 3 weeks. Initial dose: infused for about 90 minutes; if no infusion-related reaction occurs, subsequent doses infused over approximately 30 minutes If necessary, dose reduction may be required. The dose reduction schedule is provided in the SmPC.
Dosing in the health economic model (including relative dose intensity)	5.02 mg/m^2; RDI: 92.9%
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Median duration in the DB06 trial: 10.4 months / Treatment with T-DXd can be continued until disease progression, unless there is evidence of unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	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 diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	In Danish clinical practice, HER2 status is assessed at diagnosis using IHC, scored from 0 to 3. IHC3+ or IHC2+ with positive ISH is HER2-positive. HER2-negative includes IHC0, IHC1+, and IHC2+ (ISH-). T-DXd was recently assessed for HR+, HER2-low mBC. Within the HR+ patient population, the fraction of HER2-negative patients who can be classed as HER2-low has

Overview of intervention	
	previously been estimated at approx. 65% with the remaining 35% being IHC0 [22]. Recently, IHC0 was divided into HER2-ultralow (IHC0 with membrane staining) and HER2-null (IHC0 with no membrane staining) to identify a lower boundary for response to HER2-directed ADC therapy such as T-DXd [23-25]. In the most recent DBCG report, HER2-low and HER2-Ultralow have been estimated at 10% and 79% respectively (10). Testing has not been included in the model as it is part of standard practice already.
Package size(s)	1 x 100 mg vial 100 mg concentrate powder is provided in glass vial, where each vial reconstitutes a concentration of 20 mg/ mL

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

As discussed in Section 3.3, for patients who are no longer eligible for ET, the currently recommended first-line chemotherapy is either anthracyclines or taxanes (if not used before or within the last 12-24 months). However, since anthracyclines and taxanes are used according to Danish guidelines as part of standard adjuvant or neo-adjuvant treatments for early breast cancer, these agents are less likely to be of benefit to patients with recent prior exposure. Hence, oncologists will look to the next line of treatment options for a suitable chemotherapy option for such patients, including capecitabine. Of note, anthracyclines are associated with cardiotoxicity and therefore, Danish guidelines have defined a maximum cumulative dose limit and advice caution and cardiac monitoring in the event of re-challenge [1]. For those patients deemed eligible for treatment, T-DXd will replace single agent chemotherapies, including anthracyclines, taxanes and capecitabine.

3.5 Choice of comparator(s)

The DB06 trial examined T-DXd versus ICC. The ICC comparator comprised several single treatment chemotherapeutic agents, including capecitabine (59.8%), nab-paclitaxel (24.4%) and paclitaxel (15.8%). This was deemed representative of Danish clinical practice in line with guidelines and as confirmed by Danish clinical experts (25). The appropriateness of the chemotherapy comparator options is further validated by the fact that the study was actively recruiting in Denmark at multiple sites and included a substantial number of Danish mBC patients (16 patients).

Overview of comparator	
Generic name	Capecitabine

Overview of comparator	
ATC code	L01BC06
Mechanism of action	The active substance in Capecitabine Accord, capecitabine, is a cytotoxic medicine (a medicine that kills rapidly dividing cells, such as cancer cells) that belongs to the group 'anti-metabolites'.
Method of administration	Oral administration
Dosing	As monotherapy, 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.
Dosing in the health economic model (including relative dose intensity)	1250 mg/m^2 (RDI: 87.1%)
Should the medicine be administered with other medicines?	As monotherapy.
Treatment duration/ criteria for end of treatment	Patients can continue treatment until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	DPYD (dihydropyrimidin dehydrogenase) genotyping is required per national guidelines prior to commencing capecitabine.
Package size(s)	150 mg (in a 60 blister pack), 300 mg (in a 60 blister pack), and 500 mg (in a 120 blister pack) film-coated tablets

Overview of comparator	
Generic name	Paclitaxel
ATC code	L01CD01
Mechanism of action	The exact mechanism of the antitumour activity of paclitaxel is not known. It is generally believed that paclitaxel promotes the assembly of microtubules from tubulin dimer and prevents depolymerization. (33)
Method of administration	Intravenous administration.
Dosing	Recommended dosage of paclitaxel is 175 mg/m2 administered intravenously over 30 minutes every 3 weeks.

Overview of comparator	
Dosing in the health economic model (including relative dose intensity)	175 mg/m2 (82.3%)
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Patients can continue treatment until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	6 mg/ml powder for dispersion for infusion in 16.7 ml, 25 ml or 50 ml.

Overview of comparator	
Generic name	Nab-paclitaxel
ATC code	L01CD01
Mechanism of action	See “Paclitaxel” above.
Method of administration	Intravenous administration.
Dosing	The recommended dose of nab-paclitaxel is 260 mg/m2 administered intravenously over 30 minutes every 3 weeks.
Dosing in the health economic model (including relative dose intensity)	260 mg/m2 (92.2%)
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Patients can continue treatment until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	5 mg/ml white to yellow powder for dispersion for infusion. 1 vial contains 100 mg.

3.6 Cost-effectiveness of the comparator(s)

The basket of chemotherapy comparators has not been evaluated by the DMC, however these are low-cost, well-established treatments that form part of standard Danish treatment practice. Therefore, it is reasonable to assume these are cost-effective.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Efficacy analyses sets: The ITT population, also termed as FAS, included all randomized patients. HER2-low: The HER2-low population comprised the subset of patients included in the ITT population with HER2 IHC 2+/ISH- and IHC 1+ as determined by central laboratory testing. HER2-ultra-low: The HER2-ultra-low population comprised the subset of patients included in the ITT population with HER2 IHC >0 <1+ as determined by central laboratory testing and who were randomized ≥ 24 weeks prior to interim futility DCO. (2)

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression free survival (PFS) – By BICR [DB06]	Q6W for the first 48 weeks, then Q9W thereafter)	PFS was defined as the time from date of randomization until the date of objective radiological disease progression by BICR according to RECIST 1.1 or death (by any cause in the absence of progression).	PFS distribution was compared between T-DXd and Investigator's choice chemotherapy using a stratified log-rank test adjusting for prior CDK4/6 inhibitor use (yes vs. no), and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-).
Overall survival (OS) [DB06]		OS was defined as the time from the date of randomization until death due to any cause regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy (i.e. date of death or censoring – date of randomization + 1).	OS was estimated using Kaplan -Meier estimate.
Objective Response Rate (ORR) [DB06]		ORR was defined as the percentage of patients with at least one visit response of complete or	ORR were analyzed by logistic regression.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		partial response (using RECIST 1.1). Data obtained up until progression, or last evaluable assessment in the absence of progression, was to be included in the assessment of ORR.	
Health-related quality of life/EQ-5D-5L [DB06]		The EQ-5D is a standardized measure of self-reported health, developed by the EuroQol Group. There are 5 dimensions or domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. In the 5-level ('5L') version of the questionnaire, there are 5 possible levels of response that a subject can give for each dimension: no, mild, moderate, severe, and severe/unable to.	The EQ-5D-5L score was collected by the investigator at every study visit.

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

All outcome measures are standard, internationally used and valid measures for assessing the efficacy of treatment in oncology trials. They have been used in numerous previous assessments by the DMC, including of Enhertu for metastatic breast cancer (DB04).

4. Health economic analysis

4.1 Model structure

The cost-utility model used in this submission was a standard partitioned survival model (PSM) structure containing three health states. The health states included are Progression-free, Post-progression, and Death. Patients enter the model in the progression-free health state and receive either T-DXd or ICC.

In the model, health state membership is determined from a set of survival curves, using the area under the curve approach [34]. Parametric models are fitted to PFS and OS survival data from the DB06 study and are used to determine state membership.

Regression analyses with individual patient-level data (IPD) from the DB06 trial are used to extrapolate OS and PFS curves for both T-DXd and ICC. The parametric survival modelling followed the approach recommended by the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) technical support document 14. The flexsurv package in R was used to conduct the survival analysis [Latimer, N., NICE DSU Technical Support Document 14: Survival Analysis for Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-Level Data. 2013, NICE Decision Support Unit].

4.2 Model features

The main features of the model are described in Table 4.

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one ET in the metastatic setting and who are not considered suitable for ET as the next line of treatment	Trial population relevant for clinical practice (No deviation from section 0)
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (30 years)	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	3 weeks	Consistent with length of treatment cycle.
Half-cycle correction	Yes	Implemented for all outcomes and costs, except one-off costs.
Discount rate	3.5 %	The DMC applies a discount rate of 3.5% for all years
Intervention	T-DXd	Intervention in scope for application.
Comparator(s)	ICC	According to DB06 trial, treatment guidelines, and

Model features	Description	Justification
		validated by Danish clinical experts.
Outcomes	OS, PFS, TTD	Used to inform the health state transitions in the model.

5. Overview of literature

The primary trial informing the clinical and health economic analysis is the DB06 trial. A systematic literature search was also conducted to identify any evidence relevant for this application (health-related quality of life and key model inputs), however no external information was incorporated in the submission.

5.1 Literature used for the clinical assessment

The clinical assessment is based on the DB06 trial, a head-to-head study of T-DXd versus investigator's choice chemotherapy (ICC), which is the relevant comparator for Danish clinical practice. In preparation for this assessment, a systematic literature search was conducted on September 13, 2023, with no other studies identified which are relevant for this assessment. The search was updated on February 21st 2025 to cover the period Sep 13 2023 to February 21st 2025, and no additional studies relevant for this assessment were identified.

Due to an update in the CSR after the publication of Bardia et al, there are some very minor differences in some of the efficacy endpoints reported in Bardia et al. In this application, the EPAR is therefore primarily used. (7)

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Bardia, A., et al., Trastuzumab Deruxtecan after ET in Metastatic Breast Cancer. N Engl J Med, 2024. 391(22): p. 2110-2122.(7) Note that the EPAR is used to report data due	Destiny Breast 06	NCT04494425	Start: 24/07/2020 Completion: 19/06/2026 Primary analysis: 18/03/2024 Second interim: 24/03/2025 Final analysis: Event-driven. The final OS analysis will be performed	T-DXd vs. ICC for adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have

Reference	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
to a data update in the CSR after the publication of Bardia et al. (2)			when approximately 489 OS events have been observed in the HER2-low population.	received at least one ET in the metastatic setting

5.2 Literature used for inputs for the health-related quality of life

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference	Health state/Disutility	Reference to where in the application the data is described/applied
Data on file: Destiny-Breast06: Daiichi-Sankyo Inc., DB06 Clinical Study Report: Trastuzumab Deruxtecan - D9670C00001. 2024. (34)	EQ-5D-5L based HSUV for pre-progressed and post-progressed health state derived from linear mixed model based on clinical trial data.	10.1, 10.2, 10.3
Hu et al. Patient-reported outcomes with trastuzumab deruxtecan in hormone receptor-positive, HER2-low or HER2-ultralow metastatic breast cancer: results from the randomized DESTINY-Breast06 trial. ESMO 2025. Available online 15 May, 105082. (35)	EORTC QLQ-30	10.1, 10.2

5.3 Literature used for inputs for the health economic model

All clinical inputs used to inform the health economic model were sourced from the DB06 trial. Some AE disutilities were sourced from the DB04 trial (29).

Table 7 Relevant literature used for input to the health economic model

Reference	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Bardia, A., et al., Trastuzumab Deruxtecan after ET in Metastatic Breast Cancer. N Engl J Med, 2024. 391(22): p. 2110-2122. (7)	PFS, OS, TTD, AE, HSUV	Clinical trial of interest for comparison, plus targeted literature review	Section 8, 9, 10
Data on file: Destiny-Breast06: Daiichi-Sankyo Inc., DB06 Clinical Study Report: Trastuzumab Deruxtecan - D9670C00001. 2024. (34)	AE disutility		
Data on file: Destiny-Breast04: Daiichi-Sankyo Inc., DB04 Clinical Study Report: Trastuzumab Deruxtecan . 2022. (36)			

6. Efficacy

The efficacy of T-DXd versus chemotherapy in patients with HR-positive, HER2-low or HER2-ultralow mBC was established in the clinical trial DB06 in the ITT population. At the March 2024 data cutoff, the majority of patients in both arms (79.5% in the T-DXd arm and 92.8% in the ICC arm) had discontinued study treatment. In the ITT population, the median (95% CIs) treatment duration was 10.4 (9.4, 11.8) months in the T-DXd arm and 5.5 (5.3, 6.7) months in the ICC arm. (2) T-DXd performed significantly better than ICC on the key secondary outcome of PFS in the ITT population (HER2-low and ultra-low). (2)

At the time of the first interim analysis, OS data were 39.6% mature (i.e., 282 events/713 patients). Although T-DXd had not yet demonstrated a statistically significant difference between the treatment arms, there was a numerical improvement, suggesting an early trend of OS favouring the T-DXd arm. (2)

The improvement in median PFS was further supported by the analysis of other secondary endpoints in the ITT population:

Median DoR based on BICR was longer in the T-DXd arm (13.7 months) than in the chemotherapy arm (7.3 months), median PFS2 was 20.3 months for T-DXd vs 14.7 months for ICC. (2)

At the second interim OS analysis (March 2025) where data were 56% mature, a positive trend favouring the T-DXd arm was maintained in the ITT population [redacted] (3).

6.1 Efficacy of T-DXd compared to chemotherapy in patients with HR-positive, HER2-low or HER2-ultralow mBC

6.1.1 Relevant studies

DESTINY-Breast06 (DB06, NCT04494425) is a phase III, multicenter, randomized, open-label, active controlled trial, designed to compare the efficacy and safety of T-DXd versus treating investigators' choice of chemotherapy (ICC) (1:1) for HER2-low or HER2-ultralow, unresectable or mBC. (7)

The primary purpose of the DB06 trial is to determine the efficacy and safety of T-DXd compared with ICC in the target population.

A total of 866 patients with advanced/metastatic HR+ breast cancer (713 patients with HER2 IHC 1+/2+ expression [HER2-Low] and 152 patients with HER2 IHC>0 <1+ [HER2-Ultralow] expression) were randomized 1:1 across approximately 314 centres globally to receive either 5.4 mg/kg T-DXd Q3W or single agent ICC (i.e., paclitaxel, nab-paclitaxel or capecitabine) until Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 defined progressive disease (PD)—unless unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation was met. (7)

The patients needed to have progressed after two prior ET +/- targeted therapy, or within 6 months of 1L ET+CDK4/6i. Of note with regard to the ≥ 2 lines of previous ET requirement: disease recurrence while on the first 24 months of starting adjuvant ET was considered a line of therapy; these patients only required 1 line of ET in the metastatic setting.

The randomisation was stratified by:

- prior CDK4/6 inhibitor use (Yes vs No)
- HER2 IHC expression (IHC 2+/ISH- [HER2-Low] vs IHC 1+ vs IHC >0 <1+ [HER2-Ultralow])
- prior taxane use in the non-metastatic setting (Yes vs No)

Inclusion and exclusion criteria are shown in Appendix A and the study design is illustrated in Figure 3. A consort flow diagram for the patient disposition can be found in Appendix K.2.

Figure 3 DESTINY-Breast06 study design scheme (7)

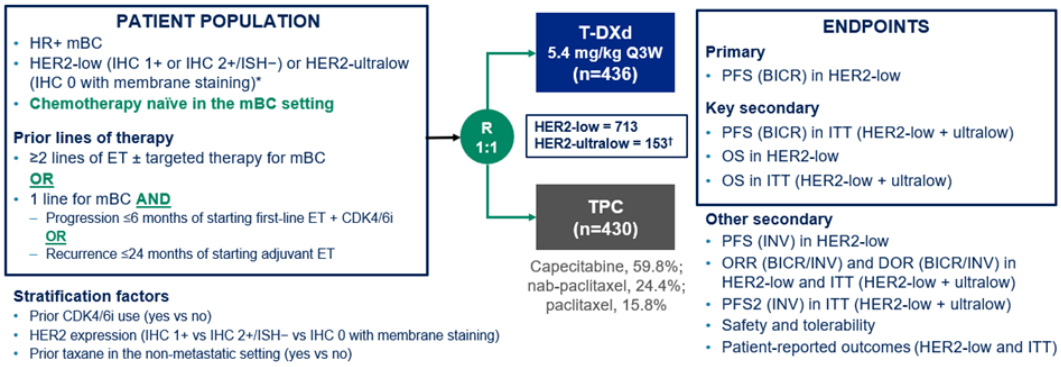


Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (2, 7)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
DESTINY-Breast06, NCT04494425	Phase III, randomized, open-label study	First patient enrolled: 24 July 2020 Last patient enrolled: 13 April 2023 Data cut-off: 18 March 2024 (IA1) and 24th March 2025 (IA2)	Patients with hormone receptor–positive, HER2-low or HER2-ultralow metastatic breast cancer.	Trastuzumab deruxtecan (IV) 5.4 mg/kg every 3 weeks	Investigator's choice of chemotherapy; capecitabine (oral) 1000 or 1250 mg/m^2 Twice daily for two weeks followed by a 1-week rest period in 3-week cycles, paclitaxel (IV) 80 mg/m^2 every week in 3-week cycles, nab-paclitaxel (IV) 100 mg/m^2 every week for 3 weeks followed by a 1-week rest period in 4-week cycles	Progression-Free Survival (PFS) in HR+, HER2-low population by BICR per RECIST 1.1 or death Progression Free Survival (PFS) - in intent to treat (ITT) population (HER2-Low and HER2 IHC >0<1+ [HER2-Ultralow]) Overall Survival - in intent to treat (ITT) population (HER2-Low and HER2 IHC >0<1+ [HER2-Ultralow]) Overall Survival (OS) - in HR+, HER2-low population Primary analysis: 18.03.2024 Second interim analysis of OS (March 24th 2025) Final analysis: Event-driven. The final OS analysis will be performed when approximately 489 OS events have been observed in the HER2-low population.

6.1.2 Comparability of studies

N/A (H2H study).

6.1.2.1 Comparability of patients across studies

The key baseline demographic and disease characteristics of patients in the ITT population for the DB06 trial are shown in Table 9. The majority of patients were HER2-low (81.7%) with 17.6% of patients HER2-ultralow. Demographic and disease characteristics were broadly balanced across treatment arms. Bone only metastatic sites were present in 13 patients (3%) in the both arms and visceral disease was present in 376 patients (86.2%) in the T-DXd arm and 364 (84.7%) in the ICC arm. In both treatment arms, patients had received a median of two lines of ET for metastatic disease.

Table 9 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (2)

	DESTINY-Breast06	
	T-DXd (n = 436)	**ICC (n = 430)**
Age (Years), mean	58.2 (28-87)	58.2 (32-83)
Weight (kgs), mean	64.1	66.1
Race no. (%)†		
White	231 (53)	230 (53.5
Black	4 (0.9)	3 (0.7)
Asian	154 (35.3)	151 (35.1)
Other	7 (1.6)	12 (2.8)
Not reported	39 (8.9)	34 (7.9)
HER2 status (%)		
ICH >0 < 1+ (HER2-ultra low)	76 (17.4)	76 (17.7)
IHC 1+ (HER2-low)	239 (54.8)	234 (54.4)
IHC 2+ and ISH-negative (HER2-Low)	117 (26.8)	118 (27.4)
Metastases – n (%)		
Do-novo disease at diagnosis n. (%)	133 (30.5)	132 (30.7)
Bone only disease at baseline n. (%)	13 (3.0)	13 (3.0)
Visceral disease at baseline n. (%)	376 (86.2)	364 (84.7)

	DESTINY-Breast06	
	T-DXd (n = 436)	ICC (n = 430)
Liver metastases at baseline n. (%)	296 (67.9)	283 (65.8)
Brain or CNS metastasis n. (%)	37 (8.5)	33 (7.7)
ET in the metastatic setting		
Number of lines, median (range)	2.0 (1-4)	2.0 (1-5)
1 line — no./total no. (%)	65/435 (14.9)	82/428 (19.2)
First-line ET with CDK4/6 inhibitor for ≤6 months — no./total no. (%)	37/435 (8.5)	40/428 (9.3)
2 lines — no./total no. (%)	295/435 (67.8)	288/428 (67.3)
≥3 lines — no./total no. (%)	75/435 (17.2)	58/428 (13.6)
Previous therapies for metastatic disease — no. (%)		
Endocrine monotherapy	230 (52.8)	223 (51.9)
Any ET‖	435 (99.8)	428 (99.5)
ET with CDK4/6 inhibitor	388 (89.0)	385 (89.5)
ET with targeted therapy other than CDK4/6 inhibitor**	143 (32.8)	127 (29.5)
Prior endocrine treatments in metastatic setting – type (%)		
Anastrazole/Letrozole	315 (72.2)	322 (74.9)
Fulvestrant	326 (74.8)	310 (72.1)
Tamoxifen	55 (12.6)	44 (10.2)
Exemestane	148 (33.9)	124 (28.8)
Adjuvant/neoadjuvant setting		
ET	275 (63.1)	256 (59.5)
Cytotoxic chemotherapy	228 (52.3)	234 (54.4)
Taxane	179 (41.1)	177 (41.2)
Anthracycline	197 (45.2)	206 (47.9)

† Race was reported by the patients.
‖ Any ET included both monotherapy and combination therapy.
**Other targeted therapies in the trastuzumab deruxtecan group and chemotherapy group in the intention-to-treat population included mammalian target of rapamycin inhibitors (in 23.9% of the patients in the trastuzumab deruxtecan group and in 23.7% of those in the chemotherapy group), phosphoinositide 3-kinase inhibitors (in 5.5% and 2.8%, respectively), or poly (adenosine diphosphate–ribose) polymerase inhibitors (in 0.7% and 1.2%, respectively).

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The Danish patient population eligible for treatment with T-DXd is aligned with the EMA-indication and reflects the DB06 trial population.

In terms of overall prognosis, the Danish clinical experts commented that in Danish clinical practice patients may have somewhat less aggressive disease compared to those in the DB06 study. This is because in clinical practice, many patients have bone-only disease, whereas only 3% of patients in the DB06 trial had bone-only disease, with a higher percentage having liver/visceral metastasis.

At the same time, the Danish clinical experts also suggested that even with T-DXd available a line earlier in the post-ET chemo-naïve setting as per DB06, approximately 30-60% of patients would be given treatment with T-DXd in first-line, depending on treatment preferences and patient and disease characteristics. Those most likely to receive T-DXd in this setting in Danish clinical practice would be younger patients, patients with brain metastasis and/or patients with visceral metastasis. For these patients there is a higher risk of not getting to the next line of subsequent treatment, so it is important to use T-DXd as early as possible.

According to Danish clinical experts, the average age for metastatic breast cancer patients in Denmark is older than the study population in the DB06 study. However, the patient population that is HER2-low or HER2-ultralow, chemotherapy-eligible and relevant for treatment with T-DXd following ET is, as previously mentioned, expected to be younger than the average HR-positive mBC patient, as some older patients are less likely to receive cytotoxic treatment due to frailty and/or comorbidities, as commonly observed in clinical practice and would thus not be in scope for treatment with chemotherapy or T-DXd. For example, an observational population-based study including all women diagnosed with HER2-positive mBC in Denmark, previously treated with another ADC (T-DM1) in the metastatic setting, found that the mean age of patients was 59 years. (37)

This aligns with the average age observed in the DB06 trial (58.2 years), which was confirmed as generalizable to the Danish population during interviews with Danish clinical experts (25). DB06 also recruited patients in Denmark, and it should also be noted that the DMC accepted that the average age from the DB04 application (54.4 years) was generalizable to the Danish metastatic breast cancer population, where patients would be treated one line later than for the DB06 indication (29).

Danish clinical experts also considered the average patient weight in DB06 generalizable to Danish clinical practice (25).

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model
Age	59 (37)	58.2 years (7)
Gender	99.4 (38)	99.8% female (7)
Patient weight	Not available	65.1 kgs (7)
BSA	Not available	1.695 (7)

6.1.4 Efficacy – results per DESTINY-Breast06

This section presents efficacy data from the final analysis of PFS, the first interim analysis of OS (March 2024), the second interim analysis of OS (March 2025), and the objective response rate (ORR), PFS2, and duration of response (DoR), for the ITT population, analysed according to multiple testing procedures. For the HER2-low population, only the primary outcome is shown in this section.

Primary outcome – Progression-free survival (PFS) by BICR in HER2-low patients

The primary endpoint of DB06 was met, with T-DXd demonstrating a statistically significant and clinically meaningful improvement in PFS as assessed by blinded independent central review (BICR) compared with ICC in HER2-low patients (HR: 0.62; [95% CI: 0.52, 0.75]; p < 0.0001). Median PFS was 13.2 months (95% CI: 11.4, 15.2) in patients treated with T-DXd and 8.1 months (95% CI: 7.0, 9.0) in patients treated with ICC (Figure 4). Number of events were 225 (62.7%) for the T-DXd arm and 232 (65.6%) for the ICC arm. (2) A full analysis of PFS by BICR at specific time points can be found in Appendix K.3.

Key secondary outcomes

PFS by BICR in the ITT population

The primary endpoint of DB06 was met, with T-DXd demonstrating a statistically significant and clinically meaningful improvement in PFS as assessed by blinded independent central review (BICR) compared with ICC in HER2-low patients (HR: 0.64; [95% CI: 0.54, 0.76]; p < 0.0001). Median PFS was 13.2 months (95% CI: 12, 15.2) in patients treated with T-DXd and 8.1 months (95% CI: 7.0, 9.0) in patients treated with ICC (Figure 5). Number of events were 269 (61.7%) for the T-DXd arm and 271 (63%) for the ICC arm (2). A full analysis of PFS by ITT at specific time points can be found in Appendix K.3. PFS by BICR for T-DXd versus ICC for the HER2-ultralow population can be found in Appendix K.4.

Overall survival in the ITT population

Based on the first interim OS analysis (data cut-off March 2024), in the ITT set, 161 (36.9%) of patients died in the T-DXd arm vs 174 (40.5%) of patients died in the ICC arm.

The median (95% CIs) OS from the Kaplan-Meier analysis was 28.9 (26.4, 32.7) months in the T-DXd arm and 27.4 (23.9, 29.9) months in the ICC arm. The HR (95% CIs) was equal to 0.81 (0.66, 1.01), suggesting better survival for T-DXd than for ICC, albeit non-statistically significant. (2) A full analysis of OS at specific time points can be found in Appendix K.3.

At 12 months from randomization, the percentage of patients alive was 87.0% (95% CI: 83.5, 89.9) in the T-DXd arm vs 81.1% (95% CI: 77.0, 84.6) in the ICC arm. At 18 months from randomization, the percentage of patients alive was 74.8% (95% CI: 70.3, 78.8) in the T-DXd arm vs 68.7% (95% CI: 63.8, 73.1) in the ICC arm (Figure 6). (2)

The second interim OS analysis (with XXX data maturity) supported the preliminary OS findings, with T-DXd-treated patients maintaining a positive OS trend vs the ICC arm (Figure 7). [redacted] of patients died in the T-DXd arm vs [redacted] Of patients died in the ICC arm. Median OS was [redacted] in the T-DXd arm and XXX [redacted] in the ICC arm [redacted] (3)

The second interim OS analysis for the sup-populations with HER-low and HER2-ultralow can be found in appendix K.4.

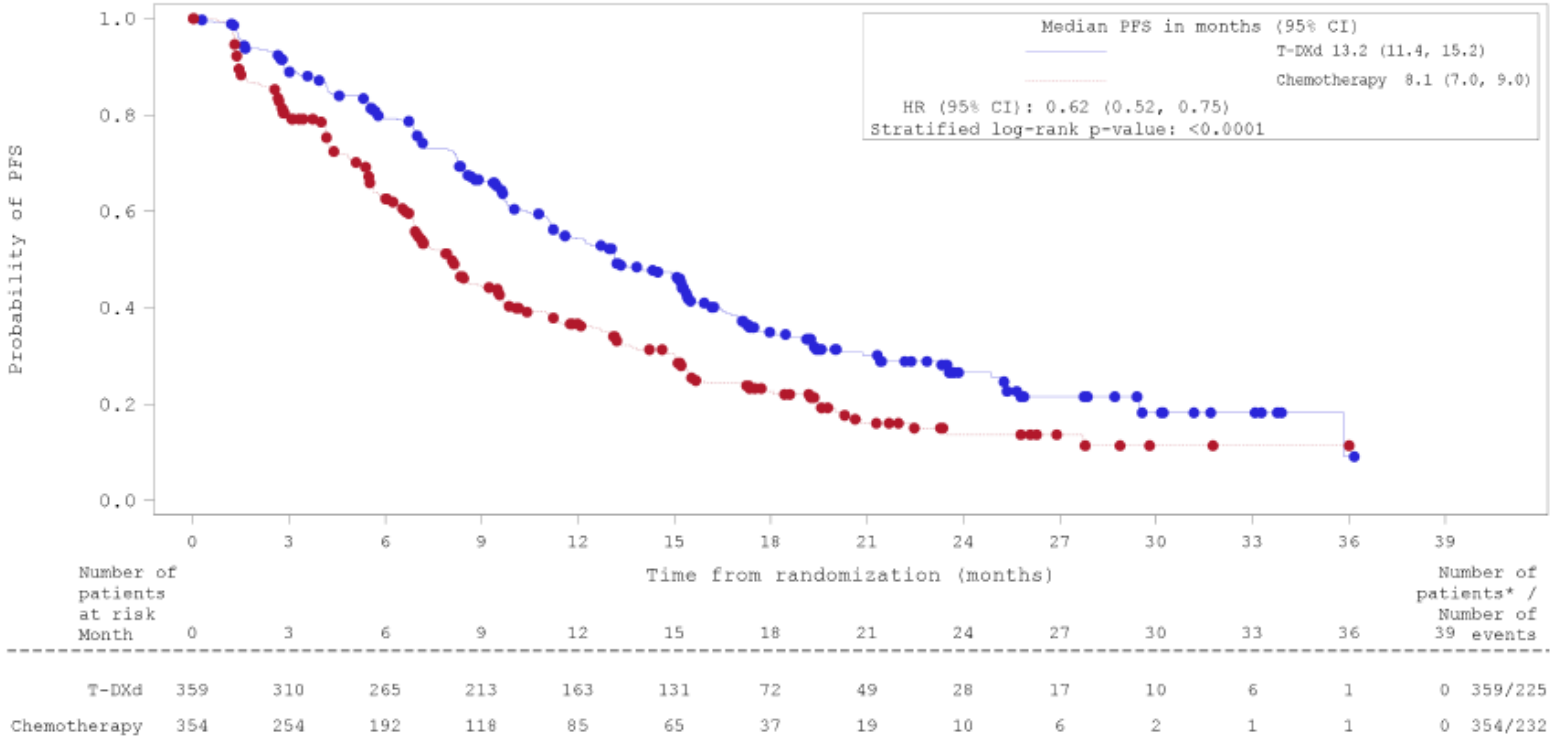
Duration of response in the ITT population

Median DoR by BICR was 13.7 months in the T-DXd arm which was significantly longer than vs 7.3 months seen in the ICC arm (Figure 8) (2)

PFS2 in the ITT population

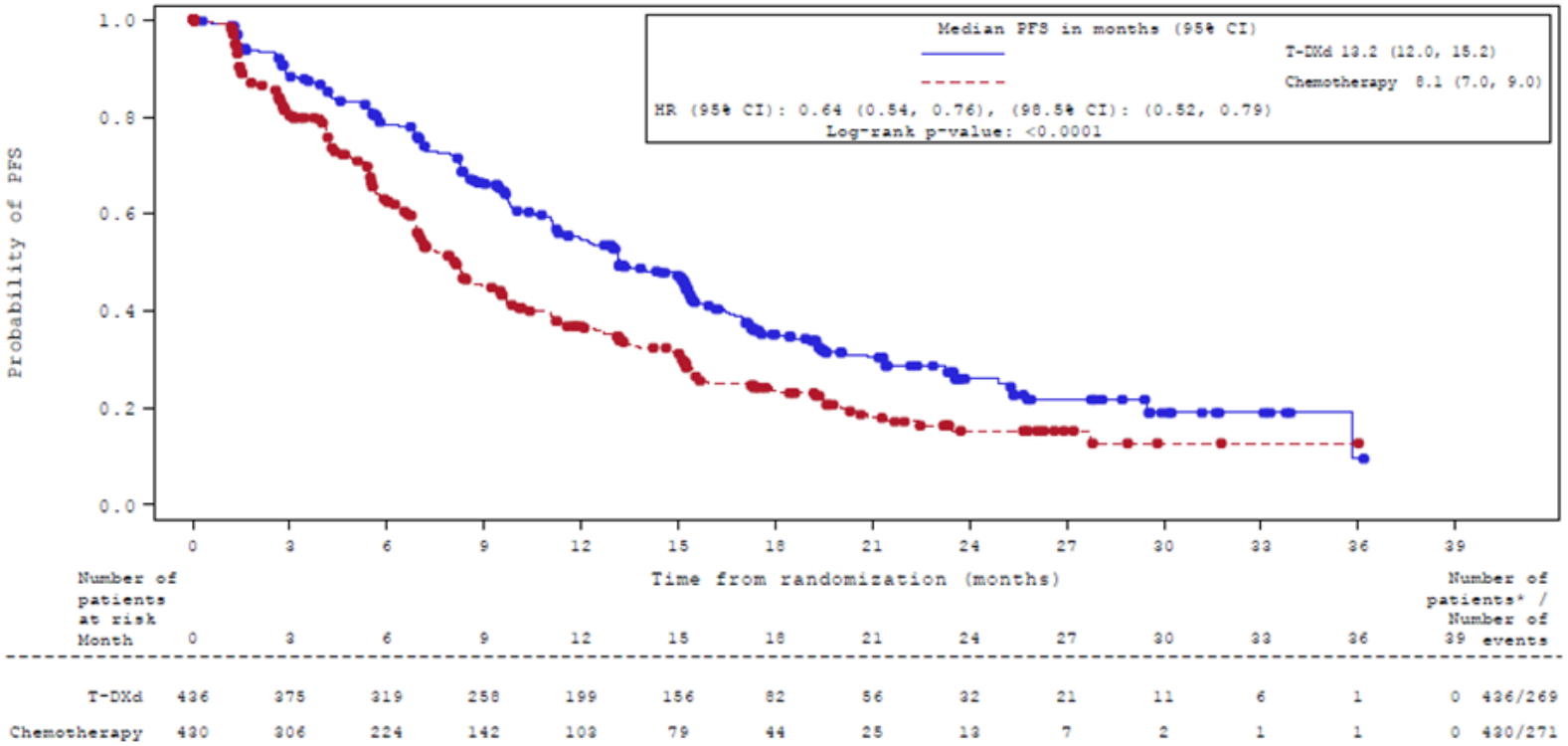
At the time of data cut-off, there were 228 PFS2 events in the T-DXd arm compared with 278 events in the ICC arm. The median PFS2 in the T-DXd arm was 20.3 months vs 14.7 months in the ICC arm (p-value < 0.0001), which is a significant and clinically meaningful improvement (Figure 9). (2)

Figure 4 PFS by BICR for T-DXd versus ICC by BICR in DB06, Kaplan-Meier plot (HER2-low population) (2)



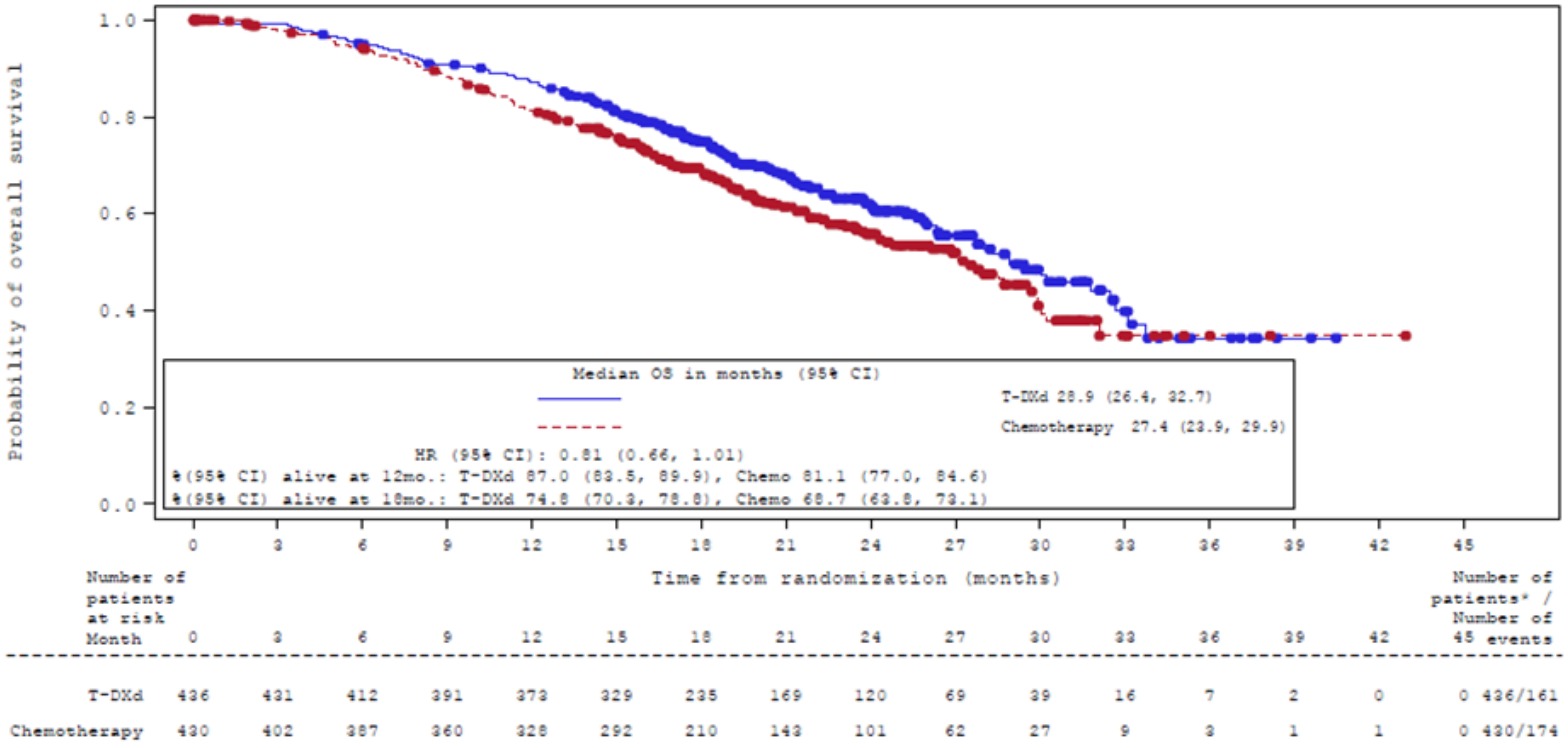
Circle indicates a censored observation. 2-sided p-value. A p-value < 0.05 is significant

Figure 5 PFS by BICR for T-DXd versus ICC in DB06, Kaplan-Meier plot (ITT population) (2)



Circle indicates a censored observation. 2-sided p-value. A p-value < 0.05 is significant

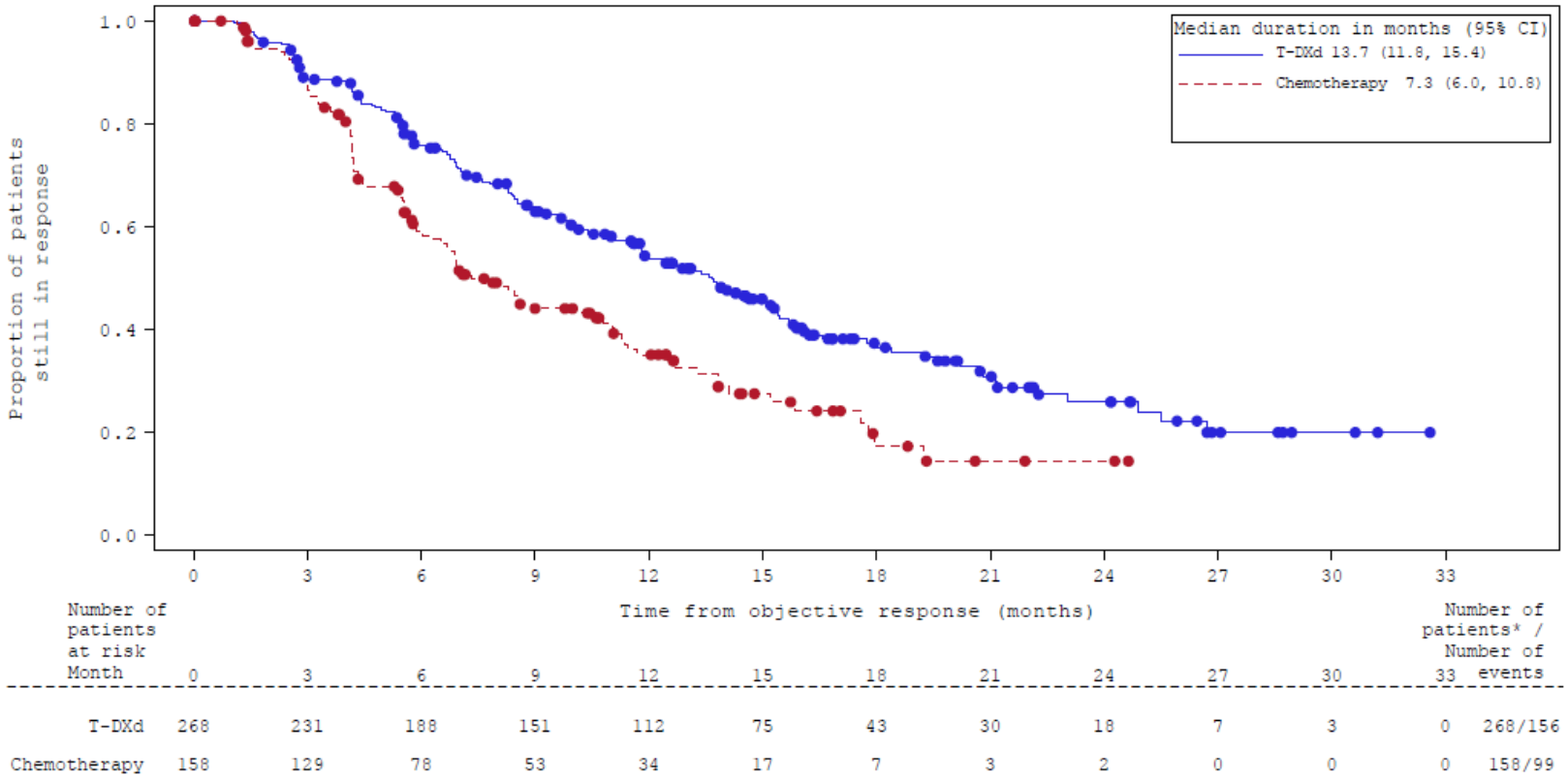
Figure 6 OS for the T-DXd versus ICC in DB06, Kaplan-Meier plot (ITT population) based on IA1 (data cutoff: March 2024) (2)



Circle indicates a censored observation. 2-sided p-value. A p-value < 0.05 is significant

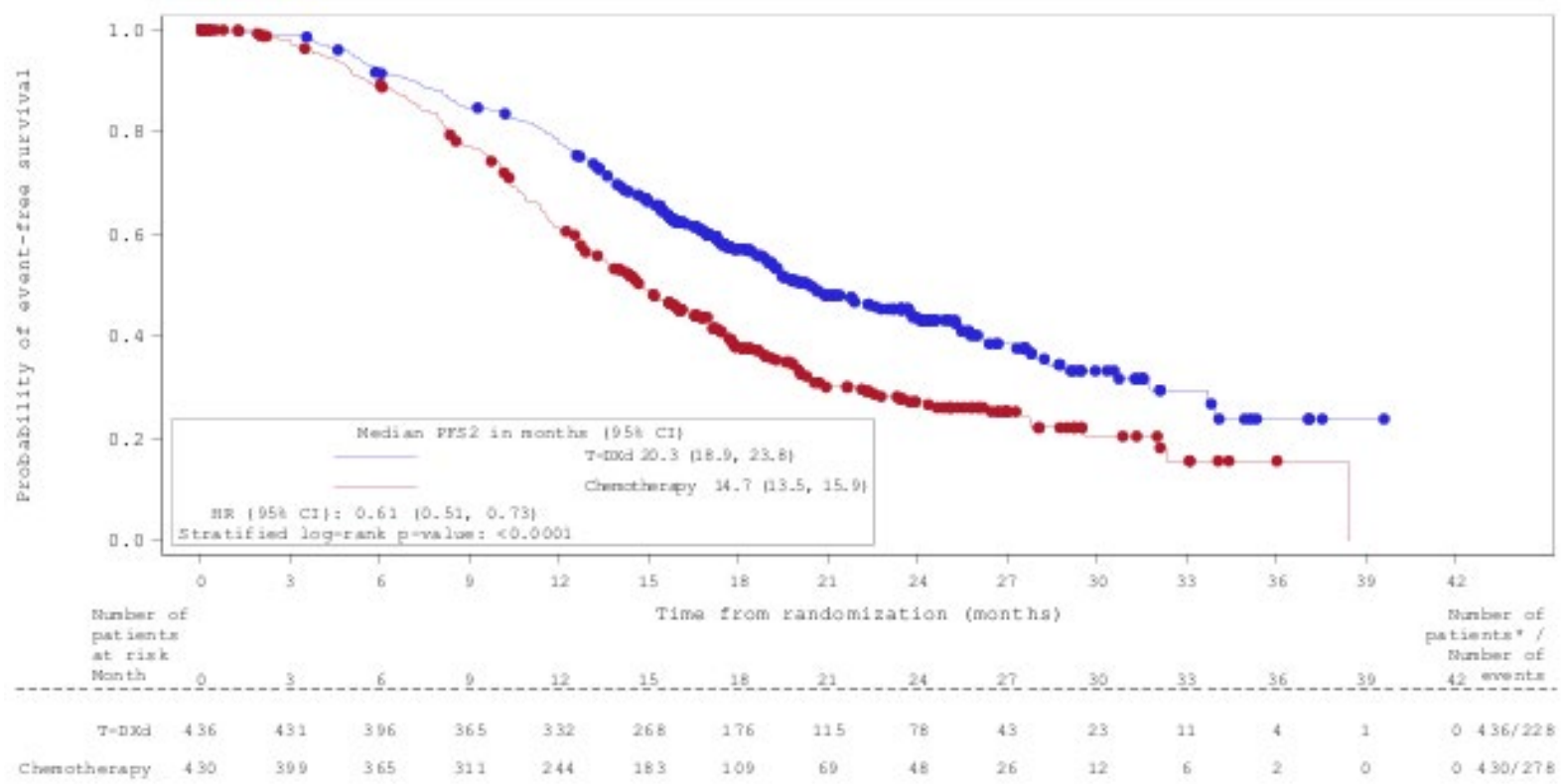
Figure 7 OS for the T-DXd versus ICC in DB06, Kaplan-Meier plot (ITT population) at IA2 (DCO: March 2025) (3)

Figure 8 DoR by BICR for T-DXd versus ICC in DB06, Kaplan-Meier plot (ITT population) (2)



Circle indicates a censored observation. 2-sided p-value. A p-value < 0.05 is significant

Figure 9 Time from randomization to second progression or death, Kaplan-Meier plot (ITT population) (2)



Circle indicates a censored observation. 2-sided p-value. A p-value < 0.05 is significant

7. Comparative analyses of efficacy

Table 11 shows an overview of efficacy outcomes, assessed by blinded independent central review (BICR) in the ITT population. Since the results are based on a H2H study and no ITC has been performed, some sections are not applicable. Efficacy outcomes can be found in Section 6.

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

N/A

Table 11 Results from the comparative analysis of T-DXd vs. ICC for patients with hormone receptor-positive, HER2-low or HER2 ultralow mBC, ITT population (2, 3)

Outcome measure, ITTpopulation	T-DXd (N=436)	ICC (N=430)	Result
Median PFS, months (95% CI), DCO March 18 2024	13.2 (12.0, 15.2)	8.1 (7.0, 9.0)	5.1 HR: 0.64 (0.54, 0.76) P-value < 0.0001
Median OS, months (95% CI), DCO March 18 2024	28.9 (26.4, 32.7)	27.4 (23.9, 29.9)	1.5 HR: 0.81 (0.66, 1.01)
Median OS, months (95% CI), DCO March 24 2025.	[redacted]	[redacted]	[redacted]
ORR (N [%]), DCO March 18 2024	268 (61.5)	158 (36.7)	Odds ratio: 2.76 (2.10, 3.64) P-value < 0.0001

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Data from the DB06 trial (IA1 and IA2) were used to inform efficacy estimations for T-DXd and ICC. The PSM used time to PFS, OS and general population mortality to model transitions between the PF, PP and dead health states. Parametric survival modelling was used to extrapolate these results after the trial follow-up period and over a 30-year (lifetime) horizon. A summary of the trial data used to model the transition between health states is provided in Table 12.

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of PFS data

A summary of the extrapolation of PFS is presented in Table 12. Please refer to Appendix D for a full description of extrapolation choice.

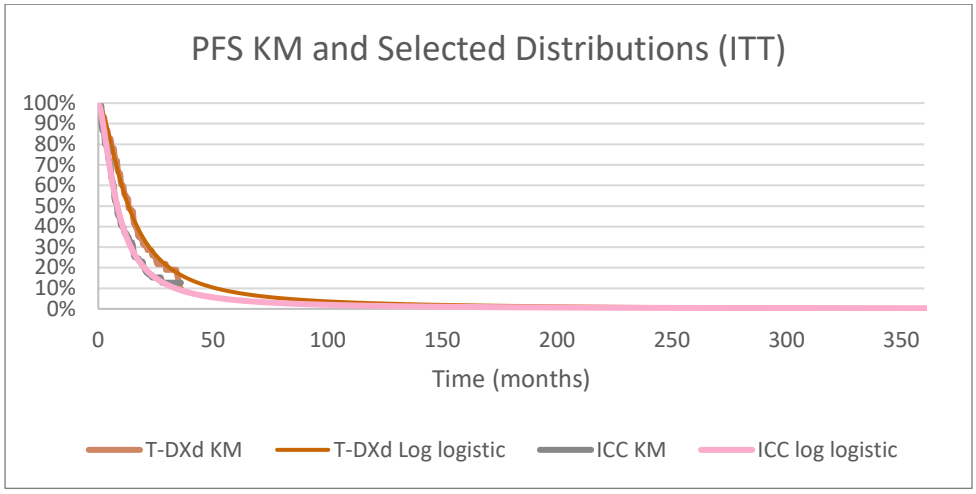
Table 12 Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	DB06
Survival models	- Exponential - Weibull - Gompertz - Log-logistic - Log-normal - Generalised-gamma - Gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	T-DXd: Gamma ICC: Log-normal
Function with best BIC fit	T-DXd: Gamma ICC: Log-normal
Function with best visual fit	T-DXd: Log-logistic ICC: Log-logistic

Method/approach	Description/assumption
Function with best fit according to evaluation of smoothed hazard assumptions	T-DXd: Log-logistic ICC: Log-logistic
Validation of selected extrapolated curves (external evidence)	Clinical experts' opinion on clinical plausibility
Function with the best fit according to external evidence	T-DXd: Log-logistic ICC: Log-logistic
Selected parametric function in base case analysis	T-DXd: Log-logistic ICC: Log-logistic
Adjustment of background mortality with data from Statistics Denmark	No (applied to OS)
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

The selected PFS curves and KM data for the modelled time horizon are shown in Figure 10 with all available distributions for PFS shown in Appendix D.

Figure 10 Base-case extrapolations of PFS overlayed with observed KM data from DB06



8.1.1.2 Extrapolation of OS

A summary of the extrapolation of OS is presented in Table 13 and the selected OS curves and KM data for the modelled time horizon are shown in Figure 11. Please refer to Appendix D for a full description of extrapolation choice.

Table 13. Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	DB06
Survival models	- Exponential - Weibull - Gompertz - Log-logistic - Log-normal - Generalised-gamma - Gamma
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	T-DXd: Log-logistic ICC: Log-logistic
Function with best BIC fit	T-DXd: Log-logistic ICC: Log-logistic
Function with best visual fit	T-DXd: Log-logistic ICC: Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	T-DXd: Log-logistic ICC: Log-logistic
Validation of selected extrapolated curves (external evidence)	Clinical experts' opinion on clinical plausibility and RWE ((39-41)
Function with the best fit according to external evidence	T-DXd: Log-logistic ICC: Log-logistic
Selected parametric function in base case analysis	T-DXd: Log-logistic ICC: Log-logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 11 Base-case extrapolations of OS overlayed with observed KM data from DB06

8.1.1.3 Extrapolation of TTD

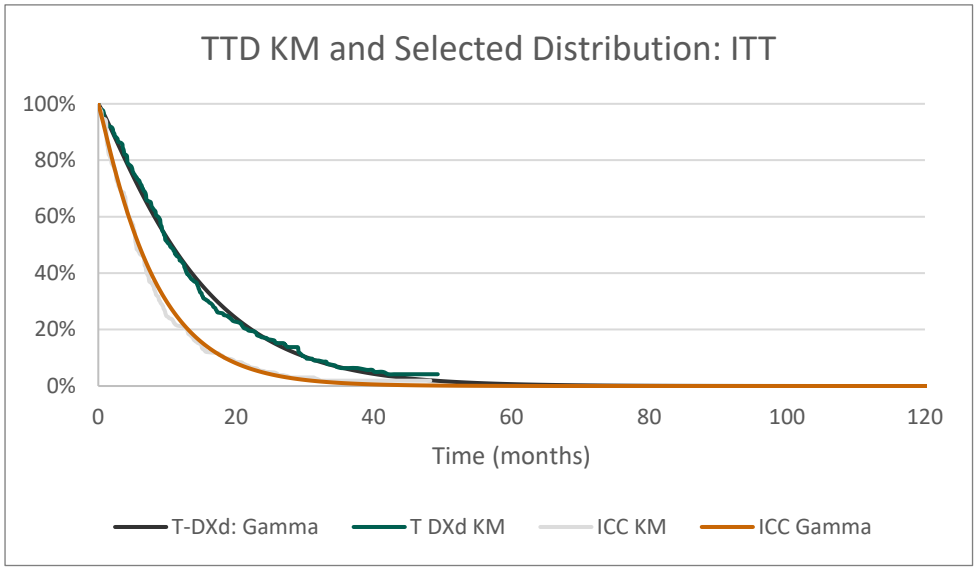
A summary of the extrapolation of TTD is presented in Table 14 and the selected TTD curves and KM data for the modelled time horizon are shown in Figure 12. Please refer to Appendix D for a full description of extrapolation choice.

Table 14. Summary of assumptions associated with extrapolation of TTD

Method/approach	Description/assumption
Data input	DB06
Survival models	- Exponential - Weibull - Gompertz - Log-logistic - Log-normal - Generalised-gamma - Gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	T-DXd: Weibull ICC: Generalised Gamma
Function with best BIC fit	T-DXd: Weibull ICC: Exponential
Function with best visual fit	T-DXd: Gamma ICC: Gamma
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	Clinical expert opinion
Function with the best fit according to external evidence	T-DXd: Gamma ICC: Gamma
Selected parametric function in base case analysis	T-DXd: Gamma ICC: Gamma
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A

Method/approach	Description/assumption
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

Figure 12 Base-case extrapolations of TTD overlayed with observed KM data from DB06



8.1.2 Calculation of transition probabilities

The PFS and OS curves are used to calculate the health state membership for the three health states, with the PFS curve indicating the probability that patients remain progression-free over time, with the OS curve determining the probability of survival over time from the initial treatment.

Table 15. Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Progression free	Post progression	OS - PFS	(42), DB06
Post progression	Dead	1 - OS	(42), DB06

Health state occupancy in the health economic model is presented in Figure 13 and Figure 14 for the T-DXd and ICC arm respectively.

Figure 13 Health state occupancy – T-DXd

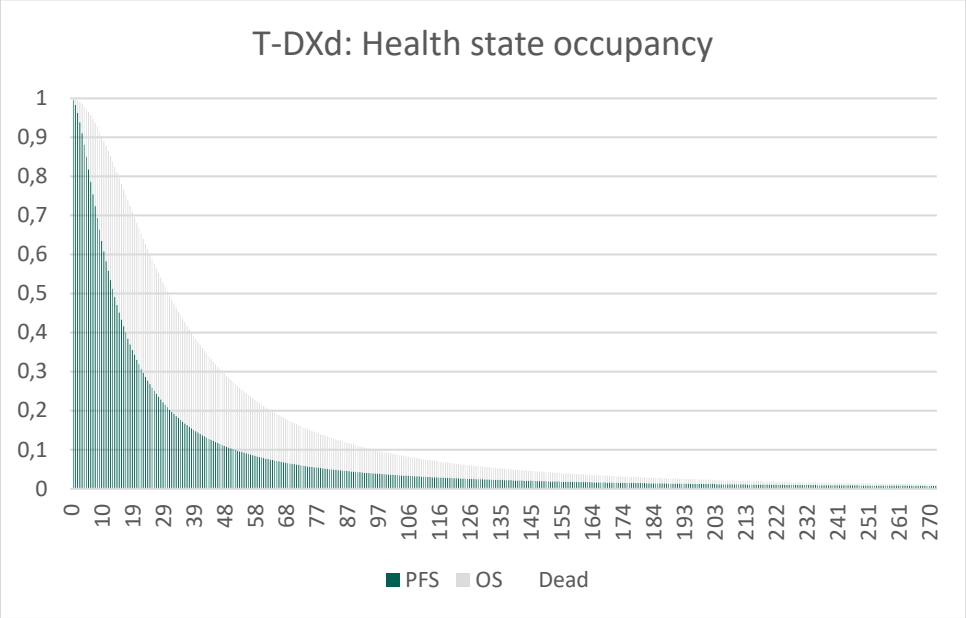
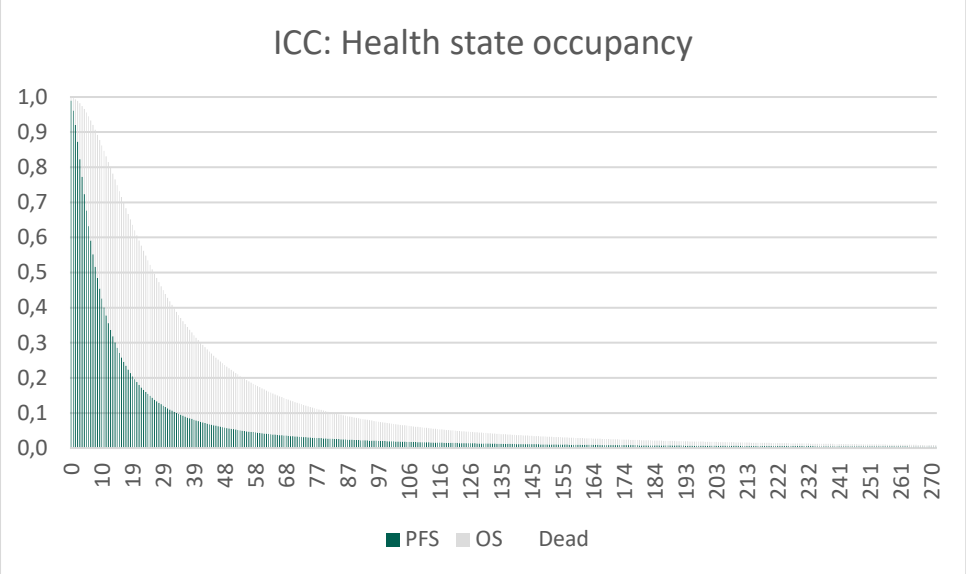


Figure 14 Health state occupancy - ICC



8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

After discussions with clinical experts to validate the curve selection for the extrapolations of T-DXd and ICC, it was decided that no adjustments due to subsequent treatments should be made to the extrapolated clinical effect.

The two clinical experts interviewed stated that the 2, 3 and 5 year landmark survival estimates produced by the selected curves were reasonable, given the Danish clinical landscape and current use of T-DXd following chemotherapy (25).

While significantly more patients in Denmark would have access to T-DXd in later lines (compared to what is observed in DB06), clinical experts discussed whether the two intervention arms would have the same risk of dying at some point in time. They concluded that it is reasonable to believe that the curves may never converge over time, as there is a preference to lead with the strongest treatment option and it is challenging to recover the impact on OS by receiving T-DXd in later lines as patients progress (25). Furthermore, some patients will likely be too fragile to receive T-DXd should they be subject to chemotherapy first.

Table 7676 in Appendix K.5 shows the treatment options based on DB-06 IA2, and the reference treatments chosen.

Based on IA2, this proportion was calculated from the patients with post-discontinuation cancer treatment after disease progression, which accounted for [redacted] of patients in the T-DXd arm and [redacted] in ICC. Please note that multiple treatment options can be used by one patient, causing the total percentage of treatments used to exceed 100%.

In Danish clinical practice, no patient is assumed to be rechallenged with T-DXd in later treatment lines or receive another ADC, such as sacituzumab govitecan, in later treatment lines.

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

An overview of modelled average and median PFS, OS and time on treatment is shown in Table 16, as well as the observed median for each from the DB06 trial. The modelled estimates have not been discounted or had half-cycle correction applied.

Table 16 Estimates in the model

	Modelled average (reference in Excel)	Modelled median (reference in Excel)	Observed median from relevant study
PFS			
T-DXd	25.47 months (='Traces_T-DXd!L1312)	13.11 months (='Set_Distributions'!H6)	13.2 months
ICC	17.13 months ('Traces_Comps!L1312)	7.59 months (='Set_Distributions'!H12)	8.1 months
OS			
T-DXd	49.96 months (='Traces_T-DXd!Q1312)	31.1 months (='Set_Distributions'!H8)	30.5 months
ICC	42.63 months ('Traces_Comps!Q1312')	26.2 months (='Set_Distributions'!H14)	27.2 months
TTD			
T-DXd	14.55 months (='Traces_T-DXd!M1312)	10.4 (='Set_Distributions'!H10)	10.4 months
ICC	8.52 months ('Traces_Comps!M1312')	5.5 (='Set_Distributions'!H16)	5.5 months

Note: Modelled OS outcomes have been adjusted for background mortality as per DMC guidance.

The modelled average treatment length and time in each model health state are shown in Table 17.

Table 17 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	Progression free [months]	Progressed [months]
T-DXd	14.55 months	25.47 months	24.48 months
ICC	8.52 months	17.13 months	25.49 months

9. Safety

The safety profiles of T-DXd and ICC in the ITT population of DB06 were generally manageable and tolerable. The nature and incidence of drug-related AEs reported in the

T-DXd arm were consistent with the established safety profile of T-DXd, as reviewed by the DMC for the DB04 indication (2, 29).

In DB06, the adverse event profile of T-DXd was generally consistent with that observed in previous studies with T-DXd such as DB03 and DB04. Similarly, the adverse events in the chemotherapy arm were consistent with the known safety profiles of the chemotherapy options. The incidence of adverse events that occurred during the treatment period was similar in the two groups (98.8% for T-DXd and 95.2% for the chemotherapy group). The three most common drug-related adverse events were nausea, fatigue, and alopecia in the T-DXd group and fatigue, palmar–plantar erythrodysesthesia syndrome (hand-foot syndrome), and neutropenia in the chemotherapy group. Adverse events of grade 3 or higher occurred in 52.8% of the patients in the T-DXd group and in 44.4% of those in the chemotherapy group; the three most common adverse events of grade 3 or higher that occurred in both treatment groups were neutropenia, leukopenia, and anemia. Adverse events associated with dose reductions occurred in 24.7% of the patients in the T-DXd group and in 38.6% of those in the chemotherapy group. Adverse events leading to discontinuation occurred in 14.3% of the patients in the T-DXd group and in 9.4% of those in the chemotherapy group. Serious adverse events occurred in 20.3% and 16.1%, respectively. Fatal adverse events occurred in 2.5% of the patients in the T-DXd group and in 1.4% of those in the chemotherapy group; fatal drug-related adverse events occurred in 5 patients (1.2%) who received T-DXd and in none who received chemotherapy. Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 49 patients (11.3%) who received T-DXd, including 7 (1.6%) with a grade 1 event, 36 (8.3%) with a grade 2 event, 3 (0.7%) with a grade 3 event, and 3 (0.7%) with a grade 5 event. Of these patients, 20 were reported as having recovered, 2 were reported as having recovered with sequelae, and 3 were reported as having recovered at the time of data cutoff. Interstitial lung disease occurred in 1 patient (0.2%) in the chemotherapy group; this was a grade 2 event that resolved after treatment discontinuation. Left ventricular dysfunction was reported in 35 patients (8.1%) in the T-DXd group and in 16 patients (3.8%) in the chemotherapy group. In the T-DXd group, the frequency of left ventricular dysfunction was primarily driven by decreased ejection fraction, which was grade 1 in severity in 1 patient, grade 2 in 31 patients, and grade 3 in 3 patients. Cardiac failure was not reported in any patients in the T-DXd group but was reported in 3 patients (0.7%) in the chemotherapy group (one event each of grades 2, 3, and 4). (7)

9.1 Safety data from the clinical documentation

The safety analysis set (SAF) consists of 851 patients whose tumors were HER2 IHC 1+, IHC 2+/ISH- and IHC > 0 < 1+ who received at least 1 dose of study treatment. Safety data were summarized using the SAF according to the study treatment received.

Table 18 presents the overall safety summary for DB06, based on the safety analysis set. The proportion of patients with ≥1 adverse events was 96.1% of patients in the T-DXd group and 89.4% in the ICC group. The incidence of AEs of grade 3 or higher was 52.8% and 44.4% for T-DXd and ICC, respectively. A higher proportion of patients discontinued study treatment for any reason in the ICC arm compared to the T-DXd arm (92.8% vs.

79.5%, respectively). The proportion of patients who had dose reductions was 24.7% and 38.6% for the T-DXd and ICC arm, respectively. (2, 7)

Table 18 Overview of safety events; DCO: 18-03-2024. (2)

	T-DXd (N=434) (Median duration: 11.02 months)	ICC (N=x417) (Median duration: 5.62 months)	Difference, % (95 % CI)
Number of adverse events, n	429 (98.8%)	397 (95.2%)	3.6% (1.31%, 5.89%)
Number and proportion of patients with ≥1 adverse events, n (%)	417 (96.1%)	373 (89.4%)	6.68% (3.21%, 10.15%)
Number of serious adverse events*, n	88 (20.3%)	67 (16.1%)	4.2% (-0.97%, 9.37%)
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	229 (52.8%)	185 (44.4%)	8.4% (1.71%, 15.09%)
Number and proportion of patients who had a dose reduction, n (%)	107 (24.7%)	161 (38.6%)	-13.9% (-20.1%, -7.7%)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	345 (79.5%)	387 (92.8%)	-13.3% (-17.82%, -8.78%)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	62 (14.3%)	39 (9.4%)	4.9% (0.59% to 9.21%)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). § CTCAE v. 5.0 must be used if available.

SAEs were reported in a similar proportion of patients in both treatment arms (20.3% and 16.1% for T-DXD and ICC, respectively). The 3 most frequent SAEs in the T-DXd arm were ILD, pneumonitis, and COVID-19, and in the chemotherapy arm were cellulitis,

pleural effusion, and febrile neutropenia. Serious Adverse Events reported in at Least 1% of patients by preferred term (SAF) are shown in Table 19.

Table 19 Serious adverse events (≥ 1 %); DCO: 18-03-2024. (2)

Adverse events	T-DXd (N=434)		ICC (N=417)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	88 (20.3%)	NR	67 (16.1%)	NR
Interstitial lung disease	8 (1.8%)	NR	0	NR
Pneumonitis	8 (1.8%)	NR	0	NR
COVID-19	7 (1.6%)	NR	1 (0.2%)	NR
Febrile neutropenia	5 (1.2%)	NR	2 (0.5%)	NR
Hypokalaemia	5 (1.2%)	NR	1 (0.2%)	NR
Cellulitis	1 (0.2%)	NR	5 (1.2%)	NR
Pleural effusion	0	NR	5 (1.2%)	NR

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect.

AE probabilities were sourced from the DB06 patient level data, using treatment-emergent adverse events of CTCAE ≥Grade 3 reported in ≥2% of subjects in either treatment arm. For AEs of special interest (ILD + LVEF decrease) all cases were considered in the health economic analysis. The probability of experiencing an AE and the cost per event (Table 35) is summed across all AEs to calculate an average AE cost per patient. Many of the included AEs were considered manageable at routine visits and therefore were not associated with additional cost for the purpose of the economic evaluation.

Table 20 Adverse events used in the health economic model (7). Summary of AEs of Maximum CTCAE Grade ≥ 3, Reported in at Least 2% of Patients in Either Treatment Arm by Preferred Term (SAF).

Adverse events	Intervention	Comparator		
	Frequency used in economic	Frequency used in economic model for comparator	Source	Justification

Adverse events	Intervention	Comparator		
	model for intervention			
Adverse event, (%)				
Neutrophil count decreased	13.8%	8.6%	DB06	≥2% of subjects
Anaemia	8.8%	4.3%	DB06	≥2% of subjects
White blood cell decrease / Leukopenia	5.8%	4.8%	DB06	≥2% of subjects
Thrombocytopenia / Platelet count decreased	4.1%	0%	DB06	≥2% of subjects
Palmar-Plantar Erythrodysesthesia	0%	7.4%	DB06	≥2% of subjects
Nausea	2.1%	0.5%	DB06	≥2% of subjects
Diarrhea	2.3%	2.6%	DB06	≥2% of subjects
Fatigue	2.1%	1.4%	DB06	≥2% of subjects
Asthenia	2.3%	1.2%	DB06	≥2% of subjects
Hypertension	2.8%	2.6%	DB06	≥2% of subjects
Gamma-glutamyltransferase increased	2.3%	0.5%	DB06	≥2% of subjects
Lymphocyte count decreased	2.3%	0.5%	DB06	≥2% of subjects
Neutropenia	8.5%	8.4%	DB06	≥2% of subjects
Hypokalaemia	4.4%	1.2%	DB06	≥2% of subjects
ILD*	1.4%	0%	DB06	Special interest/Costly to treat

Adverse events	Intervention	Comparator		
Ejection fraction decreased*	0.7%	0.7%	DB06	Special interest/Costly to treat

* ILD & LVEF: Number of patients with adverse events of special interest by group term, preferred term and maximum reported CTCAE grade.

9.2 Safety data from external literature applied in the health economic model

N/A. No external safety data was applied in the health economic model.

Table 21 Adverse events that appear in more than X% of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in 62economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

For the documentation of health-related quality of life (HRQoL), data from the EORTC QLQ-C30 and EuroQol EQ-5D-5L have been presented in the following sections.

Table 22 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	DB06	Comparative analysis of T-DXd and ICC

Measuring instrument	Source	Utilization
EQ-5D-5L and EQ VAS	DB06	Clinical effectiveness and utilities for the cost-effectiveness model

10.1 Presentation of the health-related quality of life of EORTC QLQ-30

10.1.1 Study design and measuring instrument

In the DB06 trial, difference in symptoms, functioning, and HRQoL in patients treated with T-DXd and ICC was captured using the EORTC QLQ-30. Change from baseline and time to deterioration in the EORTC QLQ-30 were included as secondary endpoints, with change from baseline presented below. The data was analyzed for the ITT population and the HER2-low population, with the results for the ITT population presented below.

The EORTC QLQ-C30 data were summarised descriptively with respect to change from baseline and clinically relevant changes (≥10 points from baseline). Mixed models for repeated measures (MMRM) were used to estimate changes from baseline in each patient reported outcome (PRO) symptom score.

The following patient-reported outcome (PRO) questionnaires were used to assess health-related quality of life (HRQoL) as well as symptoms, tolerability, and functioning in DESTINY-Breast06: EORTC QLQ-C30, EORTC QLQBR45, EQ-5D-5L, PRO-CTCAE, PGIS, PGIC, PGI-TT and PGI-BR.

10.1.2 Data collection

PRO questionnaires were self-administered by patients using a handheld electronic device before infusion on Cycle 1 Day 1 (up to -3 days) as well as every 3 weeks (Q3W) relative to Cycle 1 Day 1 dosing until PFS2. Questionnaires were also administered at End of Treatment (EOT) and disease progression unless the questionnaire was already completed the same day.

The overall compliance rates for completion of the EORTC QLQ-C30 questionnaires at baseline were higher in the chemotherapy arm than the T-DXd arm (74.4% and 66.5%, respectively), but were then generally higher for the T-DXd arm (70% until Week 31) compared to the chemotherapy arm (52% until Week 31) during the trial. The overall compliance rate at the end of follow-up was similar between treatment arms (65.8% for T-DXd and 69.8% for ICC. For a full breakdown of missing data and compliance over time see Table 23. A display of the missing data can be found under appendix K.6.

Table 23 Pattern of missing data and completion EORTC QLQ-C30

Time point	HRQoL population	Missing	Expected to complete	Completion
	N	N (%)	N	N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 4, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 7, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 10, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 13, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 16, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 19, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 22, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 25, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 28, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 31, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 34, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 37, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 40, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 43, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 46, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 49, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 52, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 55, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 58, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 61, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 64, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 67, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 70, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 73, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 76, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 79, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 82, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 85, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]

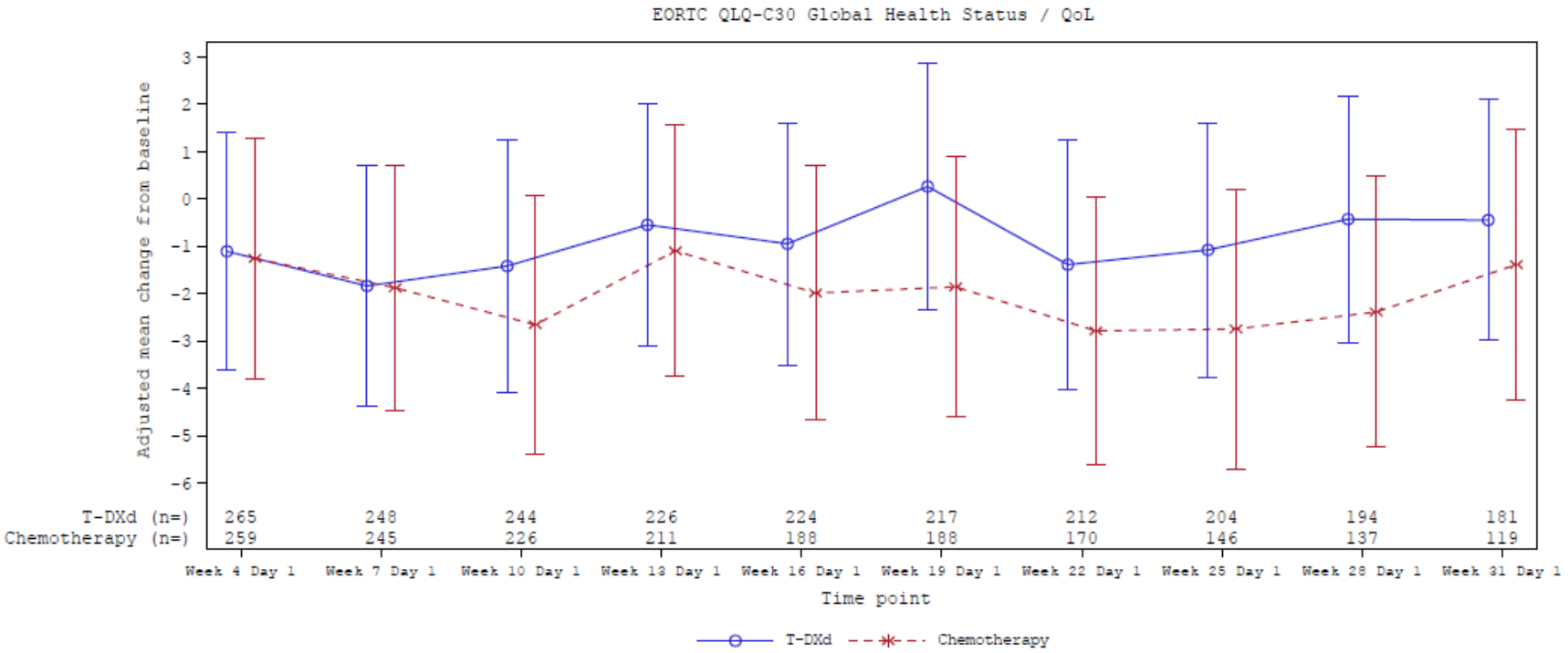
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 88, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 91, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 94, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 97, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 100, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 103, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 106, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 109, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 112, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 115, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 118, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 121, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 124, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 127, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 130, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 133, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 136, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 139, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 142, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 145, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 148, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 151, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 154, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 157, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 160, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 163, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 166, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 169, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 172, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]

10.1.3 HRQoL results

Overall, the mean change from baseline analyses (MMRM) over time showed no differences between treatment arms in the EORTC QLQ-C30 GHS/QoL between week 4 and Week 31 (Figure 15).

Figure 15 EORTC QLQ-C30 change from baseline of scales/items, MMRM, ITT population



Bars represent 95% confidence interval.
Baseline is defined as the last assessment on or prior to randomization, or before the first dose if assessment only available after randomization.

Table 24 HRQoL EORTC QLQ-C30 GHS / QoL summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Week 4, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 7, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 10, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 19, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 22, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 31, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

There was no treatment difference in mean GHS/QOL scores over the analyzed period, that is, until PD or 31 weeks after randomization [adjusted mean difference 1.1 (95% CI 1.2 to 3.4); nominal P = 0.3506]. There was also no difference between T-DXd and TPC in average scores for physical functioning, role functioning, or any other functioning subscales. In symptom scales, T-DXd was associated with lower average scores over time for pain compared with TPC [adjusted mean difference 7.2 (95% CI 9.9 to 4.5); nominal P < 0.0001], with a clinically meaningful (defined as a change in the score from a baseline of 10 points for scales/items) improvement at weeks 25 and 28. A clinically meaningful deterioration in nausea/vomiting symptoms was seen with T-DXd in the first 3 months (up to week 13). Similarly, a clinically meaningful worsening of appetite loss was observed on weeks 10 and 13 in the T-DXd group. T-DXd was associated with higher average scores for nausea/vomiting, appetite loss and constipation symptoms when compared with TPC. Scores for other symptom scales/items (fatigue, dyspnea, insomnia, and diarrhea) were similar across treatment groups (35).

10.2 Presentation of the health-related quality of life EQ-5D-5L + EQ-VAS

10.2.1 Study design and measuring instrument

The EuroQoL 5 Dimensions 5 levels (EQ-5D-5L) and EuroQoL visual analogue scale (EQ-VAS) measurements were also collected in DB06 at the same time points as EORTC QLQ-C30. The data were collected for the ITT population, which is presented here.

10.2.2 Data collection

The overall patterns of missing data and compliance rates for the EQ-5D-5L and EQ-VAS were similar to that observed for the EORTC QLQ-C30 (Table 25). A display of the missing data can be found under appendix K.6.

Table 25. Pattern of missing data and completion EQ-5D-5L

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 4, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 7, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 10, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 13, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 16, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 19, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 22, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 25, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 28, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 31, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 34, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 37, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]

Week 40, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 43, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 46, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 49, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 52, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 55, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 58, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 61, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 64, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 67, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 70, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 73, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 76, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 79, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 82, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 85, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 88, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]

Week 91, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 94, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 97, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 100, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 103, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 106, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 109, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 112, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 115, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 118, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 121, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 124, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 127, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 130, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 133, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 136, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 139, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]

Week 142, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 145, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 148, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 151, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 154, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 157, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 160, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 163, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 166, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 169, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]
Week 172, Day 1	T-DXd: 436, ICC: 430	[redacted]	[redacted]	[redacted]

10.2.3 HRQoL results

The trial-based EQ-5D-5L health state index scores by timepoint were only available based on the UK preference weights (noting that the utilities derived for the model are based on Danish preference weights). For the EQ-5D-5L health state index score at baseline, T-DXd patients (n=267) presented with a mean score of 0.78 (SD=0.21) compared to 0.77 (SD=0.21) for chemotherapy patients (n=310), indicating similar initial health states. Over time, patients on T-DXd generally maintains slightly higher average scores, suggesting some improvement or stability in HRQoL relative to baseline, with the differences between treatment groups statistically significant at multiple follow-up timepoints (Table 26 and Figure 56).

Table 26 EQ-5D-5L Heath State Index Score / Summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
EQ-5D Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 7, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 10, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 19, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 22, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 31, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 34, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 37, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 43, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 46, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 49, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 55, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 58, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 61, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 67, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 70, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 73, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 76, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 79, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 82, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 85, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 91, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 94, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 97, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week 100, Day 1					
Week 103, Day 1					
Week 106, Day 1					
Week 109, Day 1					
Week 112, Day 1					
Week 115, Day 1					
Week 118, Day 1					

At baseline, the average VAS scores for patients treated with T-DXd (n=264) and ICC (n=308) were closely aligned, with mean scores of 72.0 (SD=19.40) and 70.2 (SD=19.46), respectively, indicating comparable initial HRQoL states between the two groups. Over the course of treatment, T-DXd patients exhibited a generally stable trend in VAS scores, with mean scores significantly higher at multiple timepoints than for patients on ICC during the first 46 weeks on treatment (Table 27 and Figure 57).

Table 27 EQ-5D VAS at baseline and over time

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
EQ-5D VAS Baseline					
Week 4, Day 1					
Week 7, Day 1					
Week 10, Day 1					
Week 13, Day 1					
Week 16, Day 1					
Week 19, Day 1					
Week 22, Day 1					
Week 25, Day 1					
Week 28, Day 1					
Week 31, Day 1					
Week 34, Day 1					
Week 37, Day 1					
Week 40, Day 1					
Week 43, Day 1					
Week 46, Day 1					
Week 49, Day 1					
Week 52, Day 1					

Week 55, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 58, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 61, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 67, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 70, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 73, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 76, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 79, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 82, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 85, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 91, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 94, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 97, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 100, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 103, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 106, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 109, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 112, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 115, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 118, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.3 Health state utility values (HSUVs) used in the health economic model

Trial-based utilities collected in the DB06 study via the EQ-5D-5L and mapped to the Danish preference weight set were used throughout the model. The baseline utility values used in the model were adjusted for age over time using the age- and sex-matched general population utility values, following DMC guidelines.

It is expected that the main driver for utility gain is associated with whether a patient is progression-free or not, which was a significant parameter in the utility estimation. Given there are multiple T-DXd clinical studies as well as clinician support for the rationale for using treatment-specific health state utility values, these were deemed appropriate to use in the pre-progression state to capture HRQoL differences between the treatment arms, due to factors 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 utility (43).

For the post-progression health state, even though differences were observed in utility values by treatment arm post-progression, a conservative approach was adopted in the base case analysis, applying the same, pooled utility value to all patients, regardless of treatment. A scenario analysis shows the impact of using treatment specific utility weights also in the progressed health state.

Given the utility weights from DB06 are expected to capture disutility from AEs, no separate AE disutility was included in the base-case. Information about AE disutility for scenario analyses is available in the submitted model.

10.3.1 HSUV calculation

Utility values in the model were obtained from the DB06 trial using the health-state based utility approach and were treatment-specific. The EQ-5D-5L data was initially collected at baseline, and then throughout the treatment period, first at week 4, and then every 3 weeks thereafter up until week 91 for both treatment arms, and until week 118 for those in the T-DXd arm. The total number of observations collected is presented in Table 28.

Table 28 The number of observations for EQ-5D-5L data collected in the DB06 trial

Treatment	Scenario	Patients	Observations
T-DXd	Pre progression	[redacted]	[redacted]
	Post progression	[redacted]	[redacted]
ICC	Pre progression	[redacted]	[redacted]
	Post progression	[redacted]	[redacted]

[a] The total number of patients with an evaluable baseline and at least one evaluable follow-up questionnaire

10.3.1.1 Mapping

EQ-5D-5L utility scores from all available timepoints in the DB06 trial, including baseline, were included in a linear mixed model as a dependent variable. The optimal random effects (subject, timing of questionnaire, or both) were identified based on the lowest AIC and BIC. The model selection was modelled using progression status (progression versus progression-free) at the corresponding visit, progression status at the corresponding visit and planned treatment, time-to-death at the corresponding visit, time-to-death at the corresponding visit and planned treatment, and a fixed set of covariates as independent variables. The stratification factors included prior CDK4/6 treatment (yes, no), HER2 IHC expression, and prior taxane treatment in the non-metastatic setting. Other treatment effect modifiers were age, race, number of prior lines in the metastatic setting (1, 2, or 3 and more), Eastern Cooperative Oncology Group (ECOG) performance status, brain metastases, and the number of metastatic sites.

To model the correlation of random effects, an unstructured correlation matrix was employed. If the statistical model encountered convergence issues, a compound symmetric (CS) covariance structure was used as an alternative. The models provided mean utility values for each health state, along with their corresponding 95% confidence intervals, calculated using least squares means (LSM).

The values from the EQ-5D-5L profiles in DB06 were subsequently mapped using the Danish preference weight set (44). Please refer to Appendix F for further information on the analysis.

10.3.2 Disutility calculation

Disutility due to AEs were not included in the base case health economic analysis, as they were considered to be captured in the treatment-specific utility weights for pre-progression treatment. However the model allows for disutility to be included and can be switched on via the “set_utilities” sheet.

10.3.3 HSUV results

The base case HSUVs are presented below in Table 29, along with HSUVs applied in alternative scenario analyses. The utilities were derived from the trial and mapped using the Danish value set.

The approach applied in this economic assessment is aligned with the approach of the assessment and data used to inform the DB04 assessment evaluated by DMC. It is expected that the main driver for the utility gain is associated with whether the patient is progression-free or not, which was also shown to be a significant parameter in the utility estimation (see Appendix F). For the progression-free health state, treatment-specific utilities were used. For the post-progression health state, even though differences were observed in utility values by treatment arm, the same utility value was assigned to all patients, regardless of treatment. This was considered a more conservative approach for the base case, particularly considering the use of T-DXd in subsequent treatment. A scenario analysis shows the impact of using treatment specific utility weights also in the progressed health state.

Given that there are clinical studies and clinical rationale to use treatment specific health state utility values, these were deemed appropriate to use 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.(43) Clinical experts consulted in the development of this application noted that lack of symptoms is important for HRQoL such as pain, which may be linked to the higher ORR in the T-DXd arm, and anxiety, which may be reduced when patients feel that a treatment is working. In comparison with patients on chemotherapy, initially patients may have more AEs on T-DXd but as the disease progresses slower, they will have less symptoms from the breast cancer and hence report higher HRQoL.

In interviews with clinical experts, it was also noted that taxanes are associated with irreversible adverse events associated with neuro toxicities, that patients will continue to suffer from in subsequent lines. T-DXd and capecitabine, however, have different toxicity

profiles, with toxicities more likely to cease as treatment stops. In conclusion, improved disease control and response rate, in addition to time to definitive deterioration are important aspects of patients' HRQoL, captured in the DB06 trial in the relevant patient population using relevant instruments.

Table 29 Overview of health state utility values used in the model

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Base case				
T-DXd Pre-progression	0.8707 (0.86621, 0.87519)	EQ-5D-5L	DKK	Treatment-specific utility weight
ICC Pre-progression	0.8495 (0.84377, 0.85523)	EQ-5D-5L	DKK	Treatment-specific utility weight
T-DXd and ICC Post progression	0.8216 (0.81164, 0.83156	EQ-5D-5L	DKK	Pooled value for both treatments
Scenario analyses				
T DXd post progression	0.8332 (0.82069, 0.84571)	EQ-5D-5L	DKK	Treatment-specific utility weight
ICC post progression	0.8082 (0.79232, 0.82408)	EQ-5D-5L	DKK	Treatment-specific utility weight

10.4 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

10.4.1 Study design

N/A.

10.4.2 Data collection

N/A.

10.4.3 HRQoL Results

N/A.

10.4.4 HSUV and disutility results

Table 30 Overview of health state utilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A	N/A	N/A	N/A	N/A

Table 31 Overview of literature-based health state disutility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A	N/A	N/A	N/A	N/A

11. Resource use and associated costs

The sum of costs for managing patients with unresectable or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer are described below. Included costs are reported in 2025 Danish kroner (DKK). Costs from previous years were inflated using the subgroup of the consumer price index from Statistics Denmark (2025). The model includes the following costs, which are discussed in detail below:

- Pharmaceutical costs
- Administration costs
- Disease management costs
- Adverse events related costs
- Subsequent treatments costs
- Patient costs
- Other costs

11.1 Medicines - intervention and comparator

The model uses the AIP of T-DXd of DKK 10 856.99 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 DB06 trial ([redacted] mg/kg) was used as the basis for the drug

cost calculation, as this is the basis for the clinical effect used throughout this submission. The mean relative dose intensity in DB06 was [redacted] for T-DXd. To provide more insight on RDI, a comprehensive overview of delays, dose reductions and drug interruptions are added to Appendix K.8.

For the ICC arm, the DB06 trial-based treatment distributions were used to represent the comparator. The comparator treatments included capecitabine (60%), paclitaxel (16%) and Nab-paclitaxel (24%). The RDI[1] differed between treatments: ranging from [redacted] to [redacted], when dose-interruptions and dose-adjustments were taken into consideration. (see Table 78 in Appendix K.8)

The number of vials needed per administration was based on the weight distribution in DB06. According to clinical experts, some 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 applied in the base case of this economic evaluation as broad use of T-DXd started in February 2023 in Denmark.

[1] Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through treatment discontinuation.

Table 32 Medicines used in the model

Medicine	Pack size and form	Units	Price (AIP, DKK)	Dose	Relative dose intensity	Frequency	Vial sharing	Cost per cycle (with RDI, DKK)	Weight in arm
Intervention									
T-DXd	1 vial		10 856.99	5.4 mg/kg	[redacted]	Every 3 weeks	Yes	38,714	100%
Comparator									
Capecitabine	60 tablets	150 mg	616.00	1250 mg/m^2	[redacted]	2 x daily for 14 days	No	487	59.8%
	60 tablets	300 mg	567.00						
	120 tablets	500 mg	540.50						
Paclitaxel	1 vial	100 mg	101.50	175 mg/m^2	[redacted]	Every 3 weeks	Yes	844	15.8%
	1 vial	150 mg	1500.00						
	1 vial	300 mg	201.50						
Nab-paclitaxel	1 vial	100 mg	1,829.67	260 mg/m^2	[redacted]	Every 3 weeks	Yes	8,027	24.4%

11.1.1 Treatment duration

The duration of treatment was based on time-to-discontinuation (TTD) data from the most recent DB06 data cut-off, which were considered mature ([redacted] in the T-DXd arm and [redacted] in the ICC arm had discontinued study treatment). Median TTD in the trial was [redacted] in the T-DXd arm and [redacted] in the ICC arm [redacted]. Given the maturity of the TTD data, the approach taken for modelling long-term TTD was by directly extrapolating the TTD KM curves for both the T-DXd and the ICC arm from DB06.

The statistical test for proportionality indicated that the PH assumption does not hold hence independent parametric curves for each treatment group could be used for modelling TTD. The methods for the analysis and curve selection are described in detail in Appendix D.

Figure 16 and Figure 17 show the extrapolations with all the distributions alongside the KM curve from the DB06 trial for both the ICC and T-DXd arm in the ITT population.

Figure 16 All distributions ICC TTD with KM curve of DB06

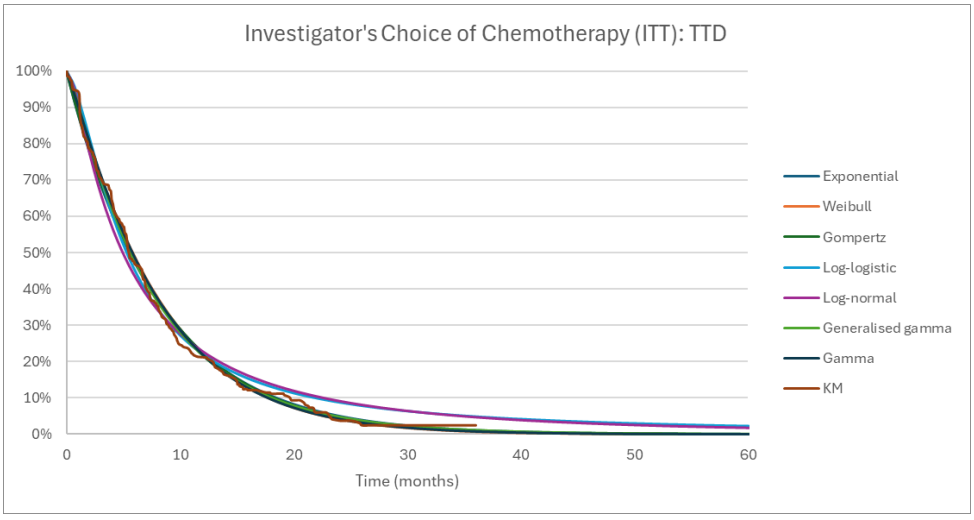
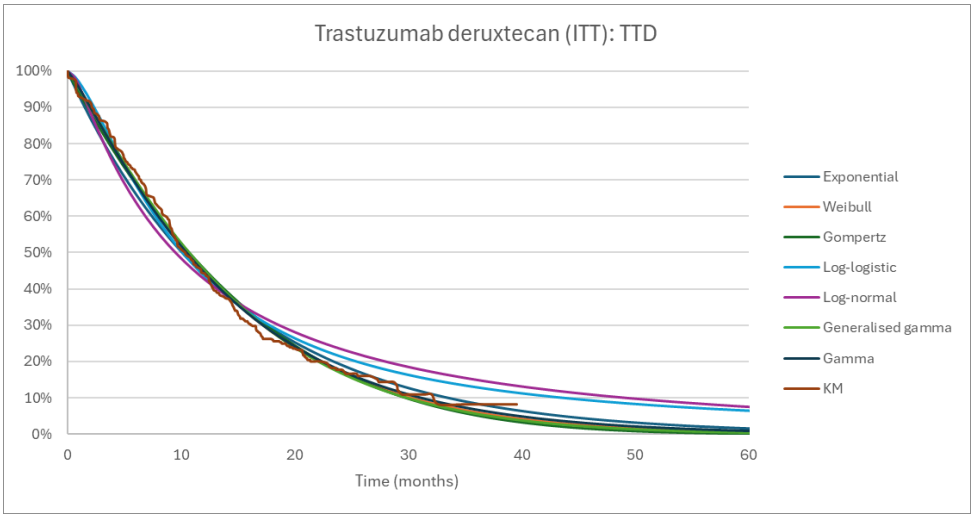


Figure 17 All distributions T-DXd TTD with KM curve of DB06



The Gamma distribution was chosen to extrapolate the TTD data from both arms. In addition to displaying a good statistical fit, the Gamma curve provided a strong visual fit for both arms and produced the most clinically plausible results (see Appendix D for details). The modelled median TTD is 10.35 months in the T-DXd arm and 5.52 months in the ICC arm, which matches the DB06 data (10.4 months and 5.5 months, respectively).

11.2 Medicines– co-administration

N/A

11.3 Administration costs

The cost of administration was included for all drugs given via IV infusion (in primary and subsequent treatment) and has been sourced from the Danish DRG list for 2025 (45). No administration cost was applied for oral treatments (i.e. capecitabine in the ICC arm).

Table 33 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion	T-DXd, Paclitaxel and Nab-paclitaxel: Every 3rd week	1578	DRG 09MA98: MDC09 1-dagsgruppe, patienter på mindst 7 år	DRG 2025 (45)

11.4 Disease management 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 the same regardless of progression status. The types and frequencies of medical resource use were the same as those preferred by the DMC in the DB04 T-DXd submission and were validated by Danish clinical experts. Table 34 summarizes the resource use, frequency and costs associated with disease management (45).

Table 34 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Specialist/Oncologist visit	Every 3 months	1578	09MA98	DRG 2025 (45)
Blood tests	Every month	0* Assumed to be captured by administration visit	N/A	N/A
ECHO/MUGA-scanning, cardiological examination	Every 3 months	2111	05PR04 "Kardiologisk undersøgelse, udvidet "	DRG 2025 (45)
CT-Scan	Every 3 months	2401	30PR07 "CT-scanning, ukompliceret"	DRG 2025 (45)

11.5 Costs associated with management of adverse events

In the health economic model, AEs were included when they were Grade 3 and higher and with an incidence rate of at least 2% in one or both arms in DB06. Further, all AEs of special interest (ILD + LVEF decrease) were included in the analysis. The majority of AEs were minor and would be managed during routine visits. Others can be handled in outpatient care and would only require an additional medical visit, while some of the more sever AEs (e.g. ILD) would require inpatient care. Costs associated with the management of AEs were sourced from the Danish DRG list 2025 (45) and are aligned with the previous DMC evaluations of T-DXd and the DMC Guidelines.

AEs were entered in the model as one-off events. This means that the incidence data used are for the whole treatment period and the unit costs are per event and assumes that patients only experience the consequences of AEs once, regardless of the length of time they are on treatment. The probability of experiencing an AE and the cost per event is summed across all AEs to calculate an average AE cost per patient. The AE cost was 1,445 DKK for patients on T-DXd and 721 DKK for patients on ICC.

Table 35 Cost associated with management of adverse events

AE	DRG code	Unit cost/DRG tariff	Source/Assumption
Neutrophil count decreased	-	0	Managed at administration visit as per DMC assessment of T-DXd (DB04)
Anaemia	16MA98 MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis code: HDD649 Anæmi UNS	2208	DRG Taksliste 2025 (45)
White blood cell decrease	-	0	Managed at administration visit as per DMC assessment of T-DXd (DB04)
Platelet count decreased	-	0	Managed at administration visit as per DMC assessment of T-DXd (DB04)
Palmar-Plantar Erythrodysesthesia	09MA98: MDC09 1-dagsgruppe, patienter på mindst 7 år	1578	DRG Taksliste 2025 (45)
Nausea	-	0	Managed at administration visit as per DMC assessment of T-DXd (DB04)
Diarrhoea	06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.	4977	DRG Taksliste 2025 (45)
Fatigue	-	0	Managed at administration visit as per DMC assessment of T-DXd (DB04)
Asthenia	-	0	Managed at administration visit as per DMC assessment of T-DXd (DB04)
Hypertension	-	0	Managed at administration visit as per DMC assessment of T-DXd (DB04)

AE	DRG code	Unit cost/DRG tariff	Source/Assumption
Gamma-glutamyltransferase increased	-	0	Managed at administration visit as per DMC assessment of T-DXd (DB04)
Lymphocyte count decreased	-	0	Managed at administration visit as per DMC assessment of T-DXd (DB04)
Neutropenia	16MA98 MDC16 1-dagsgruppe, pat. mindst 7 år	2208	DRG Taksliste 2025 (45)
Hypokalaemia	MDC17 1-dagsgruppe, pat. mindst 7 år	2136	DRG Taksliste 2025 (45)
Interstitial lung disease	04MA17: Interstitielle lungesygdomme	48957	DRG Taksliste 2025 (45)
Left ventricular ejection fraction decreased	05MP42 Hjertesvigt, herunder kardiogent shock, proceduregrp. A	24111	DRG Taksliste 2025 (45)

11.6 Subsequent treatment costs

Upon discontinuation of the primary treatment, a proportion of patients can switch to a subsequent active treatment, modelled as a single basket of treatments for a mean treatment duration upon entry to the post progression health state. These treatments were assumed to affect costs only, as the survival impact was expected to be captured within the OS curve. This reflects the DB06 trial, where patients who progressed on their primary treatment could switch to a subsequent treatment.

This reflects current Danish practice, where the majority of patients who progress on chemotherapy are eligible for further treatment, with T-DXd being the most frequently used treatment for patients, as per the DB04 T-DXd indication and recommended in Danish guidelines. In the DB06 trial based on IA2, [redacted]% of patients who progressed in the ICC arm received another line of treatment, which Danish experts confirmed would be reasonable to assume in local clinical practice. (7, 25)

However, as the DB06 trial was initiated before T-DXd was standard of care in later lines, significantly more patients in the ICC arm would receive T-DXd in Danish clinical practice than what was observed in the DB06 trial. Danish clinical experts suggest that most patients eligible for treatment would receive T-DXd (in any subsequent line), as per its current approval (25). This is further supported by the national guidelines which recommend T-DXd after ET and one line of chemotherapy (10). That is compared to only

[redacted] % of patients who received T-DXd following chemotherapy in the DB06 trial, based on IA2. Other subsequent treatments included capecitabine ([redacted] %), eribulin ([redacted] %), paclitaxel ([redacted] %) and vinorelbine ([redacted] %). (7)

Given this difference, the subsequent treatment mix in the cost-effectiveness analysis has been adjusted to align with Danish clinical practice and the use of T-DXd as a subsequent treatment following chemotherapy. In the base case analysis, an assumption was made that of those patients receiving a subsequent therapy, [redacted] % of patients would receive T-DXd in a (any) subsequent treatment line. Patients with HER2 ultralow expression (11.2%) would not be eligible for T-DXd as it is not currently approved for this patient group and would receive other treatments (Table 36).

In the T-DXd arm of the DB06 trial IA2, [redacted] % of patients received a subsequent therapy. This was considered generalizable to Danish clinical practice. Subsequent treatments in the T-DXd arm of DB06 are expected to be aligned to Danish clinical practice, with [redacted] % receiving capecitabine, [redacted] % paclitaxel, [redacted] % eribulin, and [redacted] % vinorelbine in a subsequent treatment line. (7, 25). In Danish clinical practice, no patient is assumed to be rechallenged with T-DXd or another ADC such as sacituzumab govitecan in later treatment lines.

In the subsequent treatment analysis it is assumed that multiple treatment options can be used by one patient sequentially, causing the total percentage of treatments used to exceed 100% (see the tab 'Set_Costs' in the model). This is important to consider in the DB06 setting, which is directly following ET, as the majority of patients are likely to receive an ADC and several different chemotherapy treatment options.

In the calculations on subsequent treatments vial sharing of 50% was assumed and an administration cost of DKK 1 578 per dose.

Table 36 Proportion of subsequent treatments in each treatment arm

Medicine	T-DXd arm	ICC arm
Capecitabine	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]

11.6.1 Duration of subsequent treatments

The duration of subsequent treatments was derived from published EMA data sources for non T-DXd treatments and from the modelled average treatment duration from the DB04 trial for T-DXd, and is assumed to be the same in both treatment arms (see the tab 'Set_Costs' in the CEM) (Table 37). (33, 46, 47)

Please note that costs associated with subsequent treatment can be calculated in two ways in the CEM: either utilizing the duration of treatment, as described above, to

calculate an average one-off cost of treating patients post-progression or treating patients until death.

Table 37 Treatment duration of subsequent treatments

Treatments	Duration of treatment (cycles)	Duration of treatment data and source
Capecitabine	5	Median time to progression: 93 and 98 days; EMA SPC (46)
Eribulin	6	4.1 months PFS; EMA SPC (47)
Paclitaxel	8	Median time to progression: 5.3 months EMA SPC (33)
Vinorelbine	4	PFS and median time to progression: 12 weeks; (48)
T-DXd	[redacted]	DB04 modelled mean time on treatment (based on the DMC base case)

Table 38 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency (doses per cycle)	Vial sharing
Capecitabine	1250.00 mg/m^2	[redacted]	28	No
Eribulin	0.88 mg/m^2	[redacted]	2	Yes
Paclitaxel	175.0 mg/m^2	[redacted]	1	Yes
Vinorelbine	60.0 mg/m^2	[redacted]	3	Yes
T-DXd	5.4 mg/m^2	[redacted]	1	Yes

11.7 Patient costs

Patient costs were included in the health economic analysis. The assumption is that each oncology outpatient visit will have a 30-minute duration on average. With walking and waiting times at the hospital the total patient time will be around 1 hour per visit. CT scan and cardiac ECHO assessment are also estimated to take around one hour in total (the procedures in themselves are shorter, but there are also walking and waiting times for patients at the hospital).

For T-DXd and chemotherapy infusions, both time costs and transport costs were included. The time required for the IV administration was obtained from the EMA Summary of Product Characteristics (SPC) or from pro.medicin.dk for each medicine. The transport costs are associated with the IV administration visits every third week. It is assumed that medical visits, diagnostics and tests (CT scan, blood tests and cardiac ECHO

assessment) are performed on the same days as medical treatments are administered and will therefore not incur separate travel costs. For transport costs, it was assumed that patients needed to drive 40 km to hospital and did so once per cycle. The unit costs for patient time and transport were sourced from the unit cost list provided by the DMC (49). No patient costs have been included for the management of adverse events, as the impact of these was deemed negligible. Another simplifying assumption is that we did not differentiate time costs for subsequent therapy by arm.

Table 39 Patient costs used in the model

Activity	Time spent [minutes, hours, days]	Unit cost	Cost per cycle progression-free	Cost per cycle, post-progression
Time costs, health states	1 hour lost per medical visit, CT, or cardiac ECHO assessment	188 kr / h	129.8 kr	223.8 kr
Time costs, IV admin	IV treatment duration according to EMA SPC	188 kr/h	T-DXd: 94.00 kr ICC: 112.05 kr	Subsequent therapy: 94.00 kr
Transport costs	40 km per trip (once per cycle)	3.79 per km	151.6 kr	151.6 kr
Total cost*			281.4 kr	375.4 kr

*Excluding time costs for IV administration of T-DXd and ICC, as these costs only apply to the progression-free state and differ by treatment arm.

Abbreviations: EMA: European Medicines Agency, ICC: Investigator's Choice of Chemotherapy, IV: Intravenous, SPC: Summary of Product Characteristics, T-DXd: Trastuzumab deruxtecan.

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A. Not included by DMC is the DB04 assessment (29).

12. Results

12.1 Base case overview

Table 40 Base case overview

Feature	Description
Comparator	ICC
Type of model	PSM
Time horizon	30 years (life time)
Treatment line	Patients who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for ET as the next line of treatment.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in DB06. Danish population weights were used to estimate health-state utility values.
Costs included	Medicine costs Administration costs Costs of adverse events Disease management costs Subsequent treatment costs Patient costs
Dosage of medicine	Based on weight
Average time on treatment	Intervention: 14.20 months Comparator: 8.18 months
Parametric function for PFS	Intervention: Log logistic Comparator: Log logistic
Parametric function for OS	Intervention: Log logistic Comparator: Log logistic
Inclusion of waste	Yes
Average time in model health state	
Progression-free:	T-DXd: 24.70 months ; ICC: 16.53 months [#]
Post-progression:	T-DXd: 22.46 months ; ICC: 23.92 months [#]

Half cycle correction and discounting applied.

12.1.1 Base case results

In the base case, the incremental QALYs with the use of T-DXd vs. ICC were 0.45 and the incremental cost was DKK 297 985, with the base case ICER of DKK 661 992 per QALY.

Table 41 Base case results, discounted estimates

	T-DXd	ICC	Difference
Medicine costs	785 583	27 251	758 332
Medicine costs – co-administration	N/A	N/A	N/A
Administration	32 565	7 769	24 796
Disease management costs	87 501	75 764	11 737
Costs associated with management of adverse events	1 445	721	724
Subsequent treatment costs	34 435	534 777	-500 342
Patient costs	22 325	19 586	2 739
Palliative care costs	N/A	N/A	N/A
Total costs	**963 853**	**665 868**	**297 985**
Life years gained (Progression-free)	1.87	1.27	0.595
Life years gained (Post-progression)	1.72	1.84	-0.113
Total life years	**3.59**	**3.11**	**0.48**
QALYs (Progression-free)	1.62	1.08	0.544
QALYs (Post progression)	1.41	1.51	-0.094
QALYs (adverse reactions)	N/A	N/A	N/A

	T-DXd	ICC	Difference
Total QALYs	**3.04**	**2.58**	**0.45**
Incremental costs per life year gained		**618 881**	
Incremental cost per QALY gained (ICER)		**661 992**	

12.2 Sensitivity and scenario analyses

12.2.1 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. Table 42 presents a summary of the most influential parameters with corresponding ICERs, showing that utility values are the parameters most likely to generate significant changes in the ICER. A more detailed table with all varied parameters is available in the model in the sheet 'OSA' and 'OSA_Calc'.

Figure 18 Tornado diagram of ICER: T-DXd vs. ICC

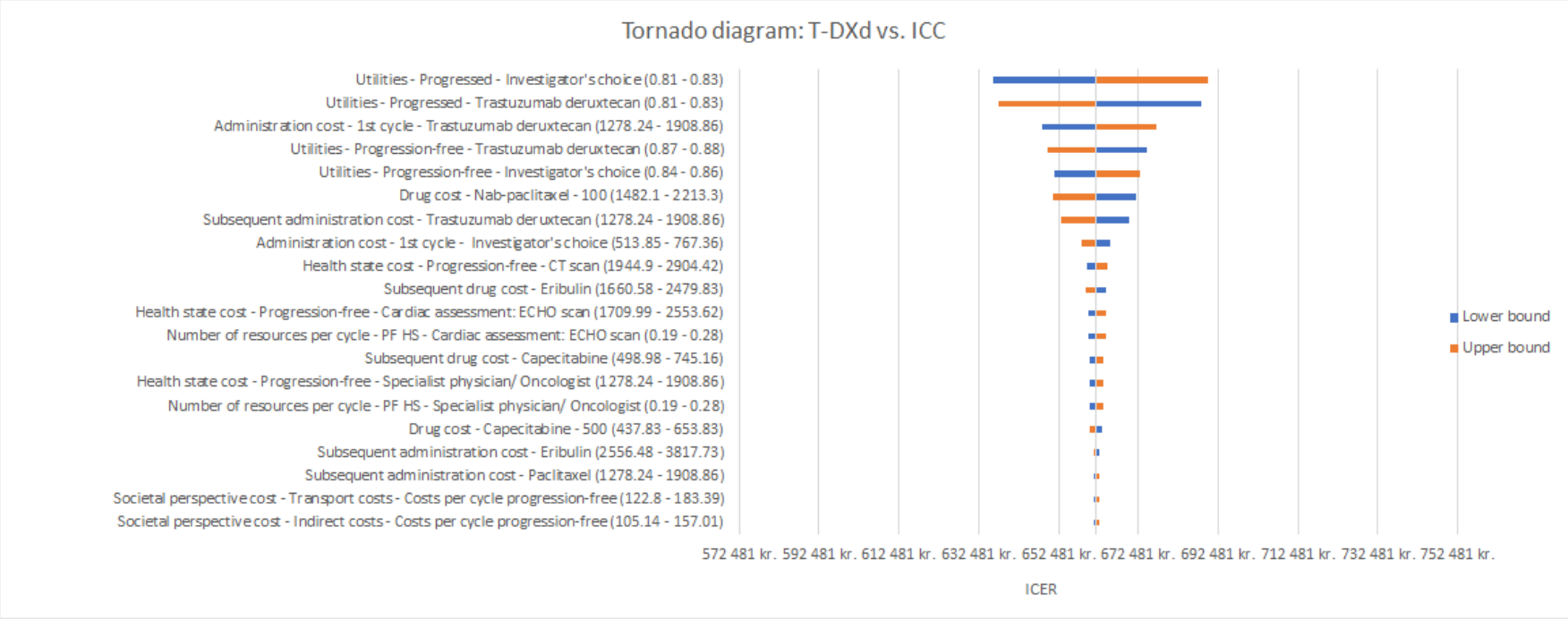


Table 42 One-way sensitivity analyses results

Base case (value)	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	297 985	0.45	661 992
Utilities – Progressed – ICC (0.82)	Lower bound: 0.81	Assumption	297 985	0.47	636 090
	Upper bound: 0.83	Assumption	297 985	0.43	690 094
Utilities - Progressed – TDXd (0.82)	Lower bound: 0.81	Assumption	297 985	0.43	688 278
	Upper bound: 0.83	Assumption	297 985	0.47	637 640
Administration cost – T-DXd (BC: 1578.00)	Lower bound:1278 .24	Assumption	291 799	0.45	648 250
	Upper bound: 1908.86	Assumption	304 813	0.45	677 161
Utilities – Progression free – T-DXd (0.87)	Lower bound: 0.866	Assumption	297 985	0.44	674 531
	Upper bound: 0.875	Assumption	297 985	0.46	649 912
Utilities – Progression free – ICC (0.85)	Lower bound: 0.84	Assumption	297 985	0.46	651 460
	Upper bound: 0.86	Assumption	297 985	0.44	672 871
Drug cost - Nab-paclitaxel -100 (1829.7)	Lower bound: 1482.10	Assumption	302 446	0.45	671 903
	Upper bound: 2213.30	Assumption	293 062	0.45	651 054

Base case (value)	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Subsequent administration cost – T-DXd (1578)	Lower bound: 1278.24	Assumption	301 611	0.45	670 048
	Upper bound: 1908.86	Assumption	293 983	0.45	653 101

12.2.2 Scenario analyses

The scenario analyses that were deemed relevant to the decision problem are shown in Table 43.

Alternative curves for extrapolation of OS data were considered for the scenario analyses. Extrapolation using Gamma is included as it provided the best fit considering the statistical fit of the data and 5-year estimate which is above the range identified as a lower bound (see discussion on this in the section on Overall survival). A scenario was also explored in which independent curves were used for the OS extrapolation.

With regards to vial sharing, scenarios were explored in which the assumption was set to 25% and 75%, as it is known that vial sharing is conducted but unknown to what extent. DMC included a scenario analysis in which vial sharing was assumed to be 50% in the economic evaluation of DB04.

The assumption on the proportion of patients receiving T-DXd as a subsequent treatment in the ICC arm was shown in scenario analyses reducing this by 5%. HRQoL data sourced from the DB06 trial show differences in utility weights also in the progressed disease health state between the treatment arms (see section 10.3), the impact of applying these weights in the model was also explored in a scenario. A healthcare payer perspective without patient time and transport cost was also included.

Table 43 Scenario analyses

#	Scenario name	ICER (DKK)
	Base-case	[redacted]
1	OS: Log-normal	[redacted]
2	OS: Gamma	[redacted]
3	OS: indep curves, Log-logistic	[redacted]
4	75% vial sharing for all IV treatments	[redacted]
5	25% vial sharing for all IV treatments	[redacted]
6	Proportion of patients in the ICC arm receiving T-DXd as a subsequent treatment 2L+: -5%	[redacted]
7	Treatment specific utility estimates for both health states	[redacted]
8	Healthcare-payer perspective (no time and transport costs)	[redacted]

12.2.3 Probabilistic sensitivity analyses

In the probabilistic sensitivity analysis (PSA), all parameters that were subject to uncertainty in the model were randomly sampled from their assigned probability distribution around a point estimate of that parameter. For a complete list of the parameters used in the probabilistic analysis see the model sheet: 'Parameters' (these can be included or excluded by the user).

A PSA using 10 000 iterations was run for T-DXd compared to ICC using the base-case settings as detailed above. The average results of all PSA iterations showed similar results (<2% difference) as the base case deterministic results, with an ICER of DKK 650 569.

The probability of cost-effectiveness for the treatment arms are presented in the scatter plot and cost effectiveness acceptability curves, show in Figure 19 and Figure 20, respectively. In the majority of iterations, the incremental costs were between 200,000-400,000 DKK, with the incremental QALYs between 0.2 and 0.6. In the CEAC, based on the current list price for T-DXd, there is a 71% chance of T-DXd being cost-effective at a threshold of 1,000,000 DKK.

Figure 19 Scatter plot showing incremental costs and QALYs based on PSA

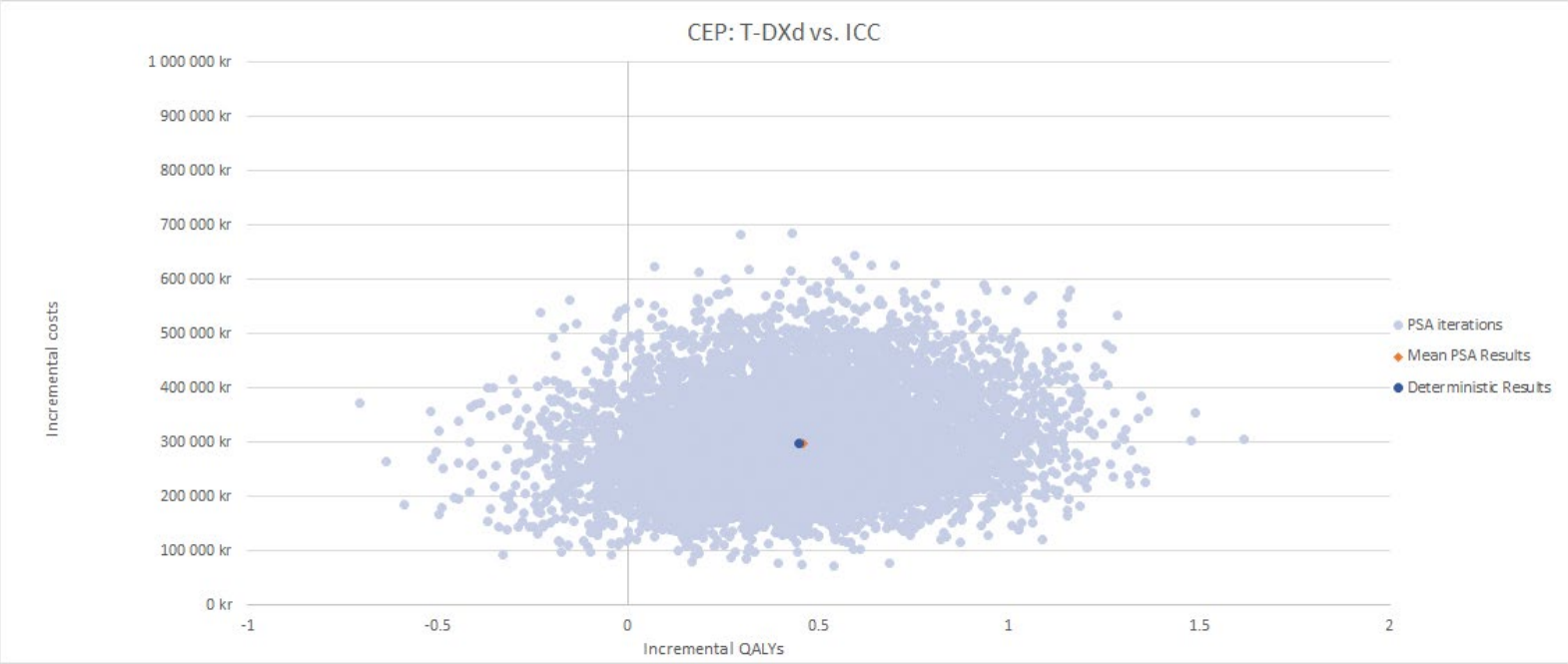
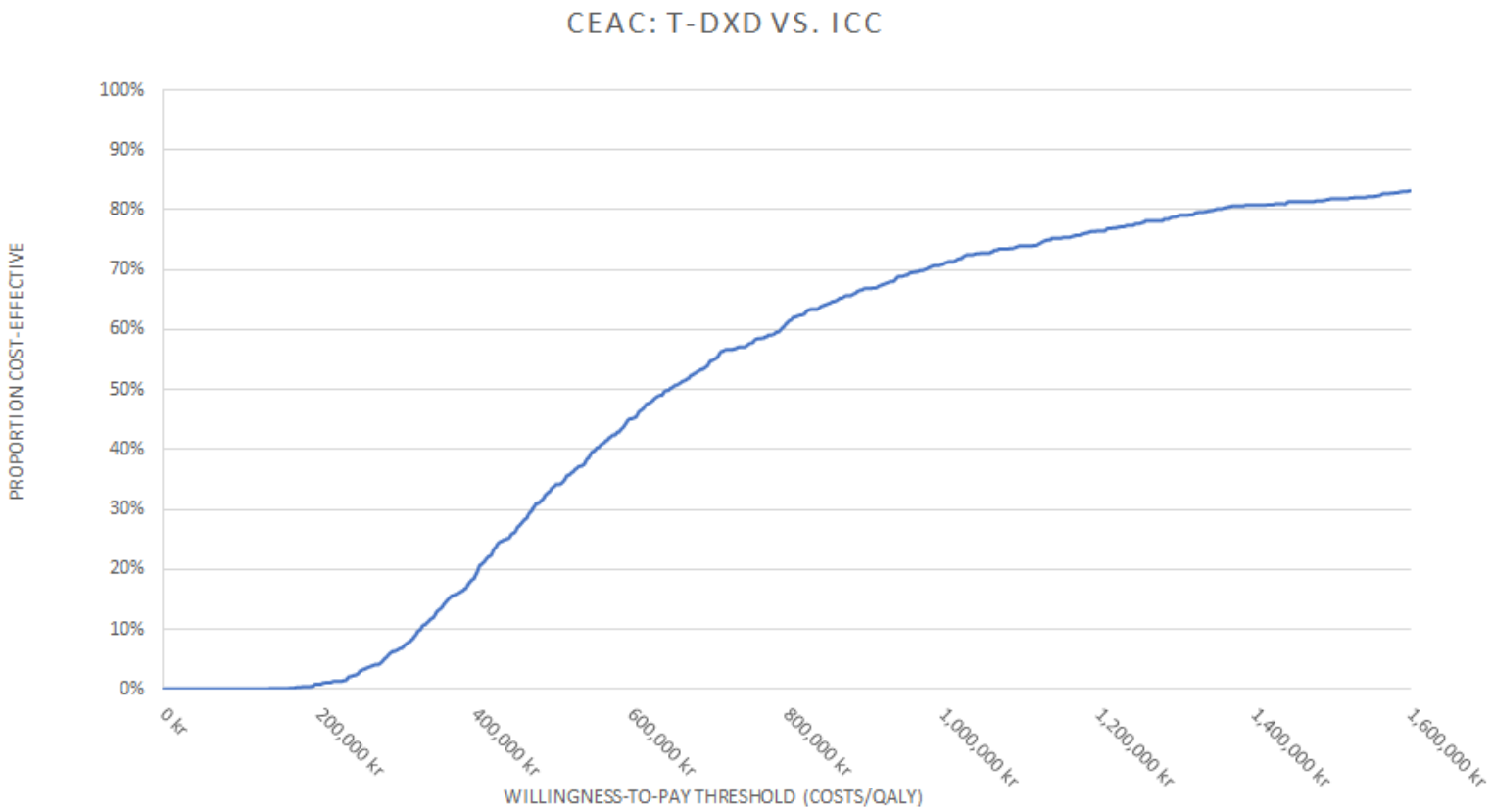


Figure 20 Cost-effectiveness acceptability curves for T-DXd versus ICC



13. Budget impact analysis

The number of eligible patients in year 1 is 196, it is assumed that 45% of these patients will receive T-DXd in year 1 and an increase in market uptake of 5% is assumed for the following years. This equates to 88 patients receiving T-DXd in year one, leading to 130 patients receiving T-DXd in year 5. Note that the majority of these patients would have been treated as per the DB04 indication but would now receive treatment one line earlier.

Number of patients (including assumptions of market share)

Table 44 Number of patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			DB06 Recommendation		
T-DXd	88	98	109	119	130
ICC	108	98	89	79	70
			Non-recommendation		
T-DXd	0	0	0	0	0
ICC	196	197	198	199	200

Budget impact

The budget impact is obtained by comparing the total cost in a world with and world without T-DXd, as per the DB06 indication. The estimated total budget impact in year 1 is approximately DKK 11.6 million, and DKK 53.0 million in year 5 (Table 45).

Table 45 Expected budget impact of recommending the medicine for the indication (million)

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	91 321 026	115 573 089	129 509 354	138 519 634	145 772 586
The medicine under consideration is NOT recommended	79 677 800	85 730 956	89 089 250	91 170 246	92 723 074
Budget impact of the recommendation	11 643 225	29 842 134	40 420 104	47 349 388	53 049 512

14. List of experts

In this application, the following experts have been consulted.

[redacted]

[redacted]

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Appendix A. Main characteristics of studies included

Table 46 Main characteristic of studies included (2, 34)

Trial name: DESTINY-Breast06	**NCT number: NCT04494425**
Objective	This study will evaluate the efficacy, safety and tolerability of trastuzumab deruxtecan compared with investigator's choice chemotherapy in human epidermal growth factor receptor (HER)2-low, hormone receptor (HR) positive breast cancer patients whose disease has progressed on ET in the metastatic setting.
Publications – title, author, journal, year	Trastuzumab Deruxtecan after ET in Metastatic Breast Cancer. Bardia A, Hu X, Dent R, et al. N Engl J Med. 2024 Dec 5;391(22):2110-2122. doi: 10.1056/NEJMoa2407086. Epub 2024 Sep 15.
Study type and design	A Phase 3, Randomized, Multi-center, Open-label Study. Enrolled patients were randomly assigned 1:1 using interactive response technology (IRT) to treatment with T-DXd 5.4 mg/kg or Investigator's choice chemotherapy. This study is an open-label study that will be conducted "Sponsor-blind". To maintain the integrity of the study, Sponsor personnel directly involved in study conduct will not undertake or have access to efficacy data aggregated by treatment group prior to final data readout for the primary endpoint.
Sample size (n), ITT	A total of 866 patients were randomly assigned to the T-DXd group (436 patients) or the chemotherapy group (430 patients).
Main inclusion criteria	• Patients must be ≥18 years of age • Pathologically documented breast cancer that: 1. is advanced or metastatic 2. has a history of HER2-low or negative expression by local test, defined as IHC 2+/ISH- or IHC 1+ (ISH- or untested) or HER2 IHC 0 (ISH- or untested) 3. has HER2-low or HER2 IHC >0 <1+ expression as determined by the central laboratory result established on a tissue sample taken in the metastatic setting 4. was never previously HER2-positive 5. is documented HR+ disease in the metastatic setting. • No prior chemotherapy for advanced or metastatic breast cancer. • Has adequate tumor samples for assessment of HER2 status

Trial name: DESTINY-Breast06		NCT number: NCT04494425
	• Must have either: 1. disease progression within 6 months of starting first line metastatic treatment with an ET combined with a CDK4/6 inhibitor or 2. disease progression on at least 2 previous lines of ET with or without a targeted therapy in the metastatic setting. Of note with regards to the ≥2 lines of previous ET requirement: disease recurrence while on the first 24 months of starting adjuvant ET, will be considered a line of therapy; these patients will only require 1 line of ET in the metastatic setting. • Has protocol-defined adequate organ and bone marrow function	
Main exclusion criteria	• Ineligible for all options in the investigator's choice chemotherapy arm • Lung-specific intercurrent clinically significant illnesses • Uncontrolled or significant cardiovascular disease or infection • Prior documented interstitial lung disease (ILD)/ pneumonitis that required steroids, current ILD/ pneumonitis, or suspected ILD/ pneumonitis that cannot be ruled out by imaging at screening. • Patients with spinal cord compression or clinically active central nervous system metastases • Prior randomization or treatment in a previous trastuzumab deruxtecan study regardless of treatment arm assignment • Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study during the follow up period of a prior interventional study (prescreening for this study while a patient is on treatment in another clinical study is acceptable)	
Intervention	T-DXd (5.4 mg/kg) administered as an IV infusion once every 3 weeks. N=436	
Comparator(s)	Investigators choice chemotherapy: Paclitaxel 175 mg/m^2 administered as an IV infusion once every 3 weeks Or Capecitabine 1250 mg/m^2 administered orally twice daily 2 weeks on/1 week off in 3-week cycles Or	

Trial name: DESTINY-Breast06	NCT number: NCT04494425
	Nab-paclitaxel 260 mg/m² administered as an IV infusion once every 3 week
Follow-up time	The used data cut-off date for study DB06 was 18 March 2024. Median (range) duration of follow-up of censored patients in the ITT population was 15.3 months in the T-DXd and 7.2 months in the chemotherapy arm. At the time of the OS IA2 (DCO: 24 March 2025), the OS data were [redacted]56.8% mature [redacted] Median duration of follow-up was [redacted] in the T-DXd arm [redacted] in the chemotherapy arm.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was progression-Free Survival (PFS) in HR+, HER2-low population by BICR Secondary endpoints were progression Free Survival (PFS) - in intent to treat (ITT) population (HER2-Low and HER2 IHC >0<1+ [HER2-Ultralow]) Overall Survival - in intent to treat (ITT) population (HER2-Low and HER2 IHC >0<1+ [HER2-Ultralow]) Overall Survival (OS) - in HR+, HER2-low population Objective response rate and health related quality of life (HRQoL) **Other endpoints:** • PFS by Investigator assessment according to RECIST 1.1 in the hormone receptor-positive, HER2-low population • ORR and DoR by BICR and by Investigator assessment according to RECIST 1.1 in the hormone receptor-positive, HER2-low population • ORR and DoR by BICR and by Investigator assessment in the ITT population (HER2 IHC > 0 < 1+ and HER2-low) • PFS2 in the hormone receptor-positive, HER2-low population and the ITT population • TFST in the hormone receptor-positive, HER2-low population and the ITT population • TSST in the hormone receptor-positive, HER2-low population and the ITT population • AEs, changes from baseline in laboratory findings, ECHO/MUGA scans, ECGs, and vital signs

Trial name: DESTINY-Breast06		NCT number: NCT04494425
	• T-DXd total anti-HER2 antibody and MAAA-1181a concentrations in serum • Change from baseline in EORTC QLQ-C30 and EORTC QLQ-BR45 scale scores • Time to deterioration in EORTC QLQ-C30 scale scores • Number and percentage of patients who develop ADAs for T-DXd	
Method of analysis	Efficacy analysis of the primary endpoint, PFS was conducted on the HER2+ population. Efficacy analysis of the secondary outcomes was conducted on intention-to-treat (ITT) basis. • Kaplan-Meier Method: Used to estimate rates of progression-free survival (PFS) and overall survival (OS). • Log-rank test: Used for treatment comparisons between T-DXd and chemotherapy, stratified by factors such as prior treatment and HER2 IHC expression. • Cox proportional Hazard regression: Used to estimate HR and CI for T-DXd and comparator, based on the same stratification variables as for the log-rank test.	
Subgroup analyses	N/A	
Other relevant information	N/A	

Appendix B. Efficacy results per study

Table 47 Results per study

Results of DB06											
				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**		
PFS by BICR, HER2-low	T-DXd	359	13.2 (11.4, 15.2) months	5.1	N/A	N/A	HR: 0.62	0.52, 0.75	<0.0001	PFS distribution was compared between T-DXd and Investigator's choice chemotherapy using a stratified log-rank test adjusting for prior CDK4/6 inhibitor use (yes vs. no), and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-). The HR (T-DXd vs. Investigator's choice chemotherapy) and its CI were estimated from a stratified Cox proportional hazards model, based on the same stratification variables as for the log-rank test.	EPAR (2)
	ICC	354	8.1 (7.0, 9.0) months								
	T-DXd	436	13.2 (12.0, 15.2) months	5.1	N/A	N/A	HR: 0.63	0.53, 0.75	0.0001	PFS distribution was compared between T-DXd and	EPAR (2)

Results of DB06											
				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		
PFS by BICR, ITT population	ICC	430	8.1 (7.0, 9.0) months							Investigator's choice chemotherapy using a stratified log-rank test adjusting for prior CDK4/6 inhibitor use (yes vs. no), and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-). The HR (T-DXd vs. Investigator's choice chemotherapy) and its CI were estimated from a stratified Cox proportional hazards model, based on the same stratification variables as for the log-rank test.	
OS – ITT, DCO March 2024	T-DXd	436	28.9 (26.4, 32.7) months	1.5	N/A	N/A	HR: 0.81	0.65, 1.00	N/A	Analysis of OS is similar to analysis of PFS. The final OS analysis will be performed when approximately 489 OS events have been observed in the HER2-low population (70% maturity), which was expected to occur approximately 57 months after the first patient	EPAR (2)
	ICC	400	27.4 (23.9, 29.9) months								

Results of DB06											
				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		
										was randomized. At that time, it was estimated that 594 OS events will be observed in the ITT population.	
OS – ITT, DCO March 24th 2025	T-DXd	[redacted]	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICC	[redacted]	[redacted]							[redacted]	
PFS2	T-DXd	436	20.3 (18.9, 23.8) months	5.6	N/A	N/A	HR: 0.61	0.51, 0.73	0.0001	PFS distribution was compared between T-DXd and	EPAR (2)

Results of DB06											
				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		
	ICC	430	14.7 (13.5, 15.9) months							Investigator's choice chemotherapy using a stratified log-rank test adjusting for prior CDK4/6 inhibitor use (yes vs. no), and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-). The HR (T-DXd vs. Investigator's choice chemotherapy) and its CI were estimated from a stratified Cox proportional hazards model, based on the same stratification variables as for the log-rank test.	
DoR	T-DXd	268	13.7 (11.8, 15.4) months	6.4	N/A	N/A	N/A	N/A	N/A	ORR was defined as the percentage of patients with at least one visit response of complete or partial response (using RECIST 1.1). Data obtained up until progression, or last evaluable assessment in the absence of progression, was to be included in the assessment of ORR. However,	EPAR (2)
	ICC	158	7.3 (6.0, 10.8) months								

Results of DB06											
				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		
										patients who receive subsequent anticancer therapy (note that for this analysis radiotherapy is not considered a subsequent anticancer therapy) after discontinuing study treatment without progression and then respond were not included as responders in the ORR.	

Appendix C. Comparative analysis of efficacy

N/A. The application is based on a H2H vs. current standard treatment.

Table 48 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the lysis	Difference	CI	P value	Difference	CI	P value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix D. Extrapolation

Extrapolated survival curves were used to inform health state occupancy over a lifetime horizon in the model using an area under the curve (AUC) approach. Time-to-event data used to model the T-DXd and ICC arms were taken from DB06 (PSF: IA1; OS and TTD: IA2). In the CEM, PFS, OS and TTD data were used on the ITT population. Parametric models were fitted to extrapolate the survival data from the DB06 trial to inform the CEM. The following parametric curves were fitted, based on the DMC guidelines:

- Exponential
- Weibull
- Gompertz
- Log-logistic
- Log-normal
- Generalised gamma
- Gamma

The following approach was used to select the best fitting model. First, the proportional hazards assumption was tested for each outcome by visual inspection and statistical testing using log(-log) plots and Schoenfeld residuals to see whether the distributions should be modelled dependently or independently. Then, the curves were assessed based on a visual inspection of their fit to the data, their statistical goodness-of-fit (assessed by, among others, the Akaike information criterion [AIC] and Bayesian information criterion [BIC] statistics), and their clinical plausibility.

The proportional hazard (PH) assumption was assessed to determine whether these models could be fitted to the entire dataset with the treatment group included as a covariate in the analysis (PH/AFT models). The PH assessment was performed using log-cumulative hazard plots and Schoenfeld residuals. Log-cumulative hazard plots were generated for each outcome, and these plots allow an assessment of whether the PH assumption is reasonable (55). If the plots for the treatment groups are (approximately) parallel, the PH assumption could be considered reasonable, and PH models with the treatment group included as a covariate can be used. Schoenfeld residuals were also assessed to determine the validity of the PH assumption. These residuals should be independent of the time when the PH assumption holds. In addition, the accelerated failure time (AFT) assumption was tested using quantile-quantile plots. A central assumption of AFT models is that treatments have a multiplicative effect on survival time that is consistent over time. When treatment effects are consistent, the plot should approximate a straight line, i.e., if these plots do not show a straight line the AFT assumption does not hold. Results of these assessments are outlined separately for PFS, OS, and TTD in the ITT population.

In dependent modelling, the parametric models were fitted with the treatment indicator included as an independent variable. Consequently, the models are fitted jointly to both

the T-DXd and ICC arm and assume a particular form on the shape of the treatment effect. For the exponential, Weibull and Gompertz models, a PH shape is assumed, whilst, for the log-logistic, log-normal, Gamma and Generalised gamma, an AFT effect is inherently assumed.

When modelling the survival curves independently, the parametric models are fitted individually to the T-DXd and ICC arms. When the model is set to independent, the parameters of the distributions are varied between both treatment arms and produce different outcomes. Therefore, distribution selection can subsequently be done stratified per treatment arm. It is possible, however, that with selecting different distributions for both arms, the curves for a given survival outcome may cross. In such cases, attention is required to ensure realistic survival in the model.

In a PSM, OS and PFS are modelled separately and therefore it is inherently assumed that both clinical endpoints are independent. To avoid unrealistic estimates, however, a cap was implemented to ensure that PFS is always less than or equal to OS. Additionally, time to treatment discontinuation (TTD) data from the DB06 trial was used to calculate treatment costs by separating the progression-free patients into patients on and off treatment. A similar cap was implemented to ensure that TTD is always less than or equal to PFS.

D.1 Extrapolation of PFS

D.1.1 Data input

Data from the DB06 trial is used to inform the extrapolation of PFS beyond the follow-up in the clinical trial.

D.1.2 Model

Standard parametric models were used to extrapolate PFS from the DB06 data, the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-logistic
- Log-normal
- Generalised gamma
- Gamma

D.1.3 Proportional hazards

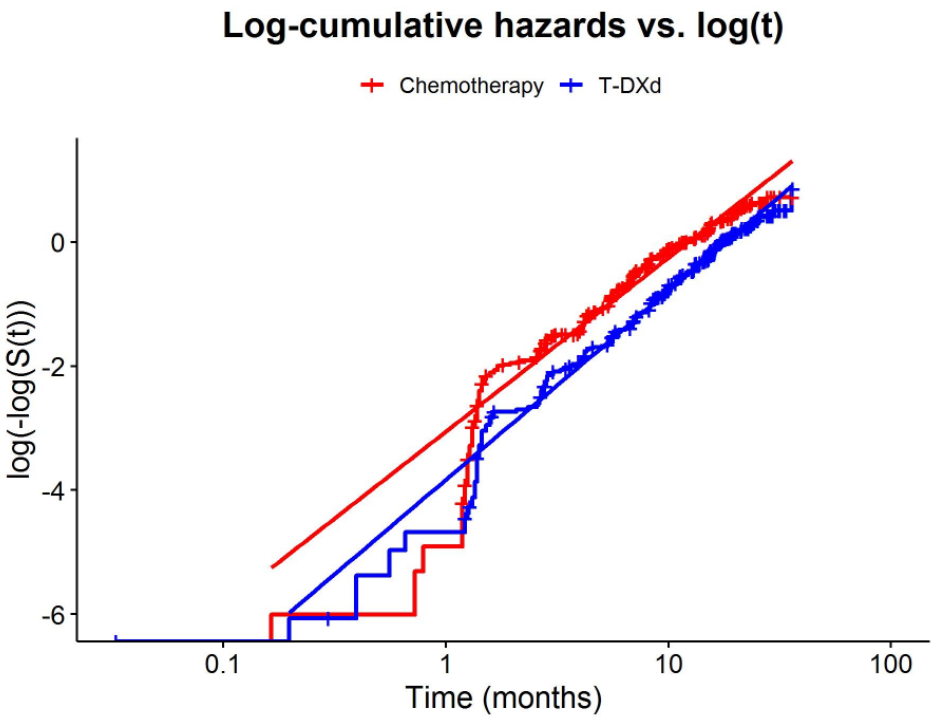
Figure 21 shows the log-cumulative hazard plot for T-DXd and ICC and Figure 22 shows the Schoenfeld residuals for PFS.

The log-cumulative hazards plot, displays relatively straight and parallel lines for most time points but deviations are observable at earlier time points, approximately up until

two months. This suggests that the proportional hazard models may not be completely appropriate.

The time-dependent hazard ratio in the Schoenfeld residuals shows some variability, with the hazard ratio increasing over time. The p-value from the Grambsch-Therneau test of non-proportionality (p-value = 0.004) indicates that the proportional hazards assumption may not hold.

Figure 21 Log-cumulative hazard plot of PFS in the ITT population



Abbreviations: ITT, intention-to-treat; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

Figure 22 Schoenfeld residuals for PFS in the ITT population

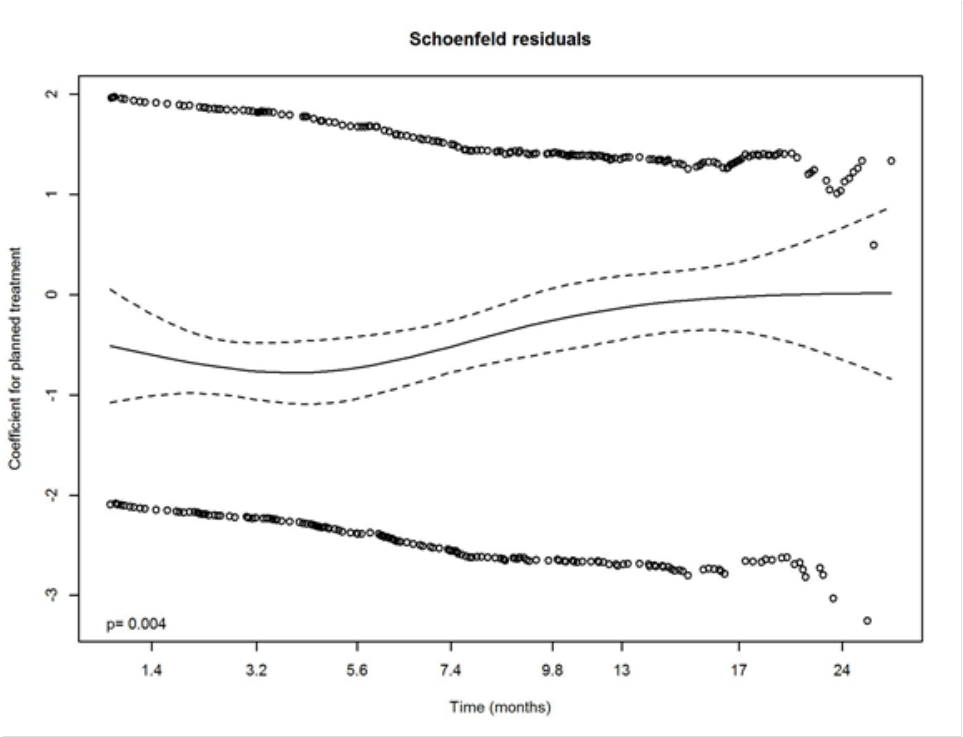
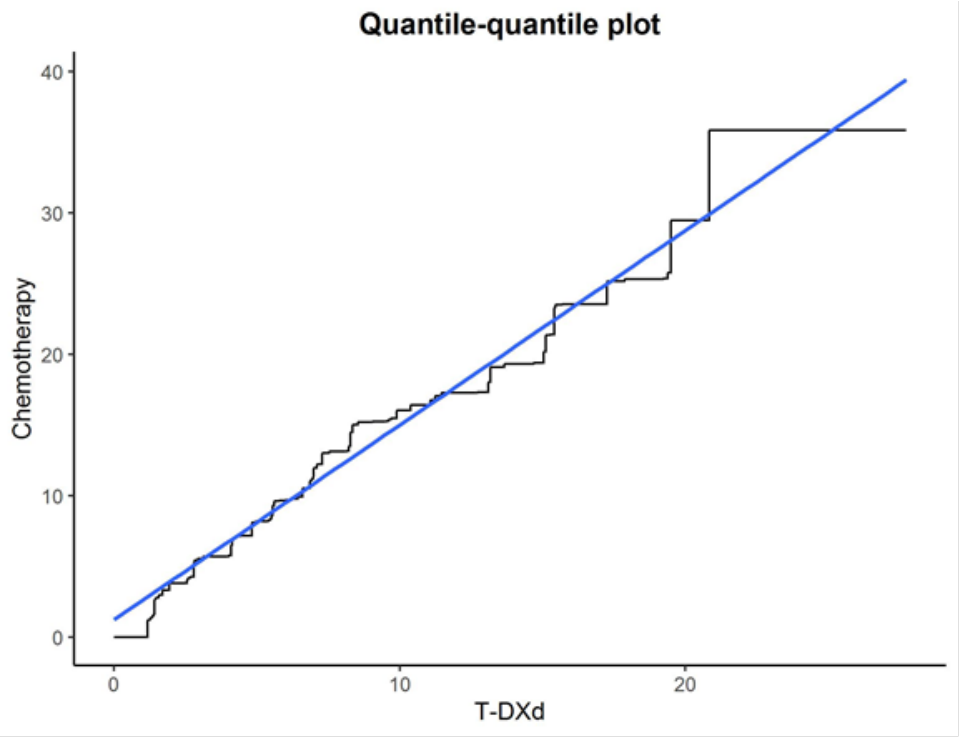


Figure 23 shows the quantile-quantile plot for PFS, which was used as a tool to evaluate whether an AFT model is appropriate for survival extrapolations. The quantile-quantile plot is relatively straight through the origin but exhibits some slight departures, indicating that the AFT assumption does not hold.

Taken together, the quantile-quantile plot, the plots by treatment group of log(S(t)/ (1-S(t))) vs. log(t), and the lines of the inverse normal(S(t)) vs. log(t)) plots suggest that the proportional hazard and AFT assumptions may not hold. As such, only independent models on the ITT set are presented.

Figure 23 Quantile-quantile plot for PFS in the ITT population



D.1.4 Evaluation of statistical fit (AIC and BIC)

Given that PFS is modelled independently, the statistical goodness of fit is assessed separately for both treatment arms. Based on the AIC and BIC values, the log-logistic, log-normal, and generalised gamma are the best-fitting distributions for the PFS data from the ICC arm in the DB06 trial (Table 49).

Table 49 Goodness-of-fit for ICC to the DB06 PFS data according to the AIC and BIC values

Distribution	AIC	BIC
Exponential	1924.578	1928.642
Weibull	1919.332	1927.459
Gompertz	1926.577	1934.705
Log-logistic	**1899.817**	**1907.945**
Log-normal	**1894.951**	**1903.079**
Generalised gamma	**1896.949**	**1909.140**
Gamma	1914.564	1922.691

Notes: The distributions highlighted in green had the best statistical fit to the KM data based on the lowest AIC and BIC scores.

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Based on the AIC and BIC values, the Weibull, log-logistic, generalised gamma, and gamma are the best-fitting distributions for the PFS data from the T-DXd arm in the DB06 trial (Table 50).

Table 50 Goodness-of-fit for T-DXd to the DB06 PFS data according to the AIC and BIC values

Distribution	AIC	BIC
Exponential	2133.379	2137.457
Weibull	**2116.199**	**2124.355**
Gompertz	2127.095	2135.250
Log-logistic	**2115.466**	**2123.622**
Log-normal	2123.044	2131.199
Generalised gamma	**2115.049**	**2127.282**
Gamma	**2114.110**	**2122.265**

Notes: The distributions highlighted in green had the best statistical fit to the KM data based on the lowest AIC and BIC scores.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

D.1.5 Evaluation of visual fit

The statistically best-fitting curves were subsequently plotted along the KM curve of the DB06 trial for visual inspection. For the ICC arm, the log-logistic, log-normal, and generalised gamma were displayed a good fit to the trial data (Figure 24 and Figure 25).

Figure 24 All distributions ICC PFS with KM curve of DB06

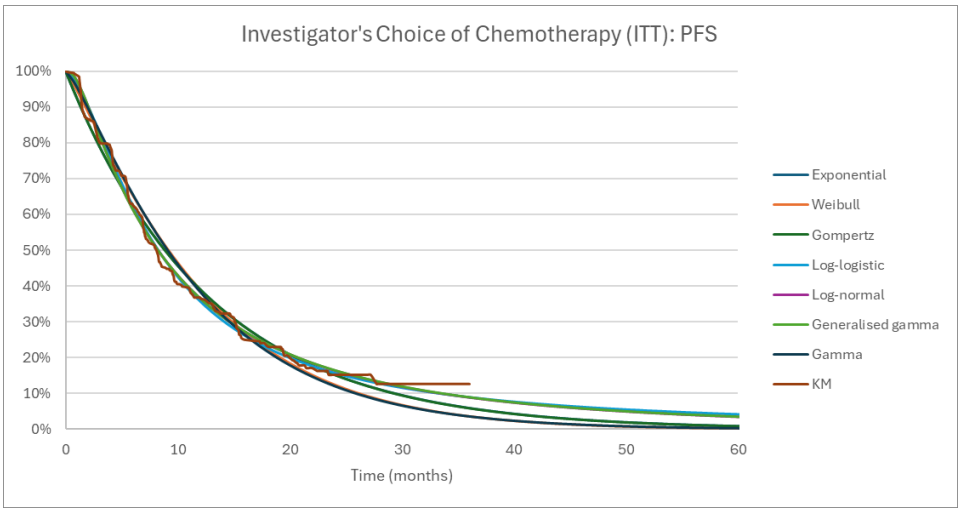
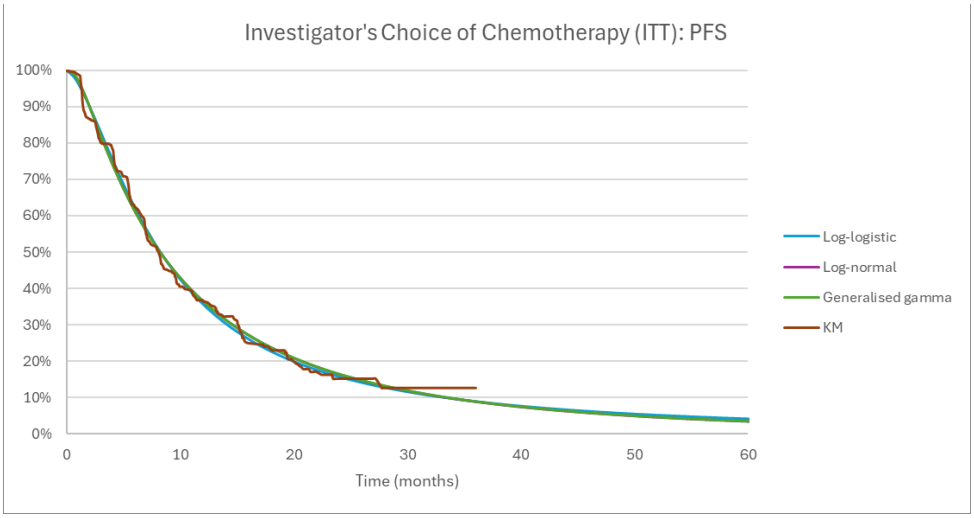


Figure 25 Best fitting curves plotted against the KM curve of DB06 – ICC arm



For the T-DXd arm (Figure 26 and Figure 27), all extrapolations closely follow the trend of the KM curve up until approximately 25 months, after which the log-logistic curve seems to approximate the tail end of the KM curve better than the other distributions.

Figure 26 All distributions T-DXd PFS with KM curve of DB06

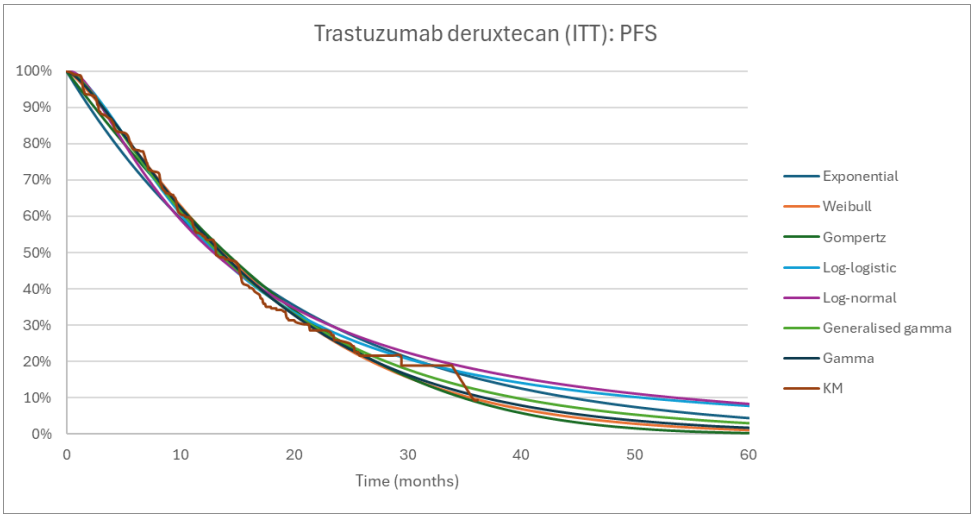
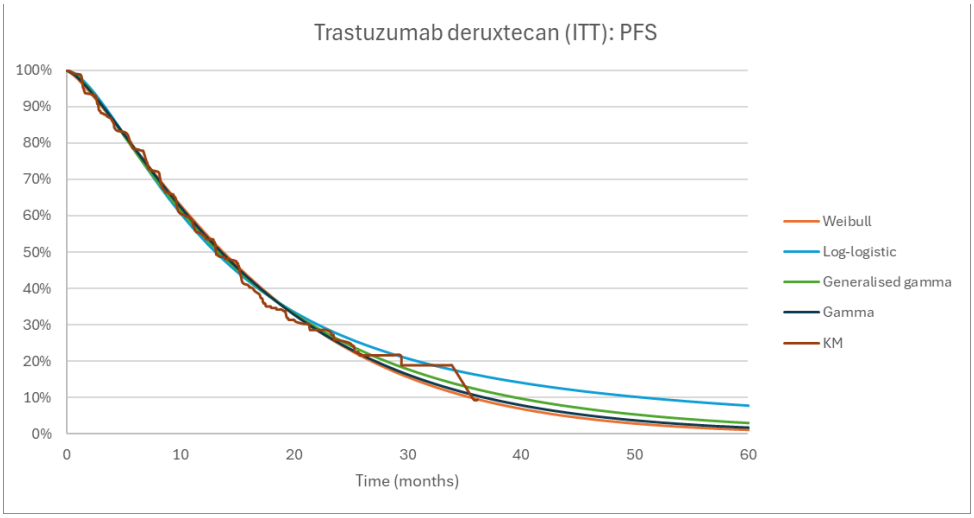


Figure 27 Best fitting curves plotted against the KM curve of DB06 – T-DXd arm



D.1.6 Evaluation of hazard functions

The hazard rate, smoothed and unsmoothed, and by extrapolation model, are shown in Figure 28 and Figure 29.

Figure 28 Hazard rates, smoothed and unsmoothed of PFS

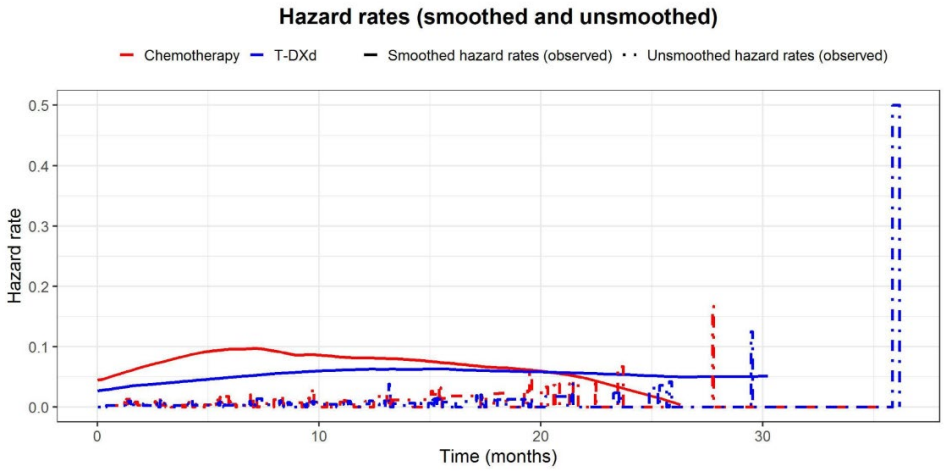
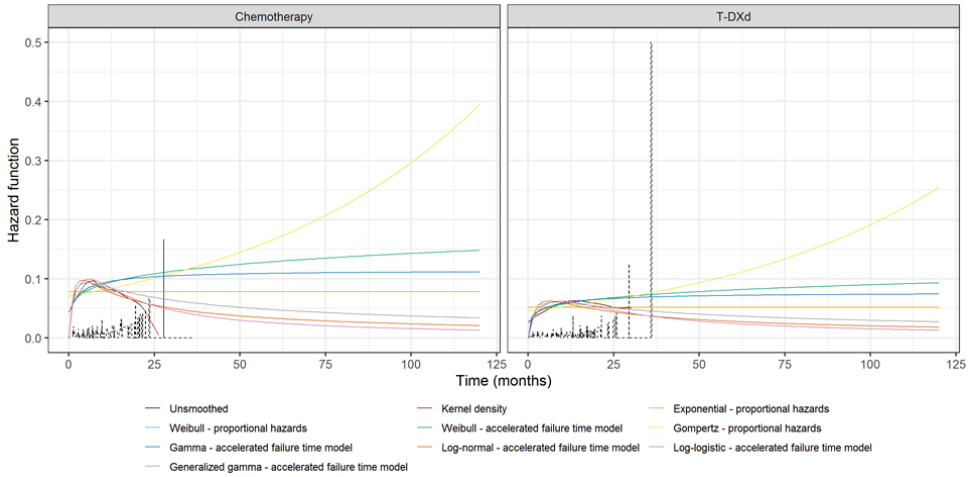


Figure 29 Hazard function, smoothed and by extrapolation model of PFS

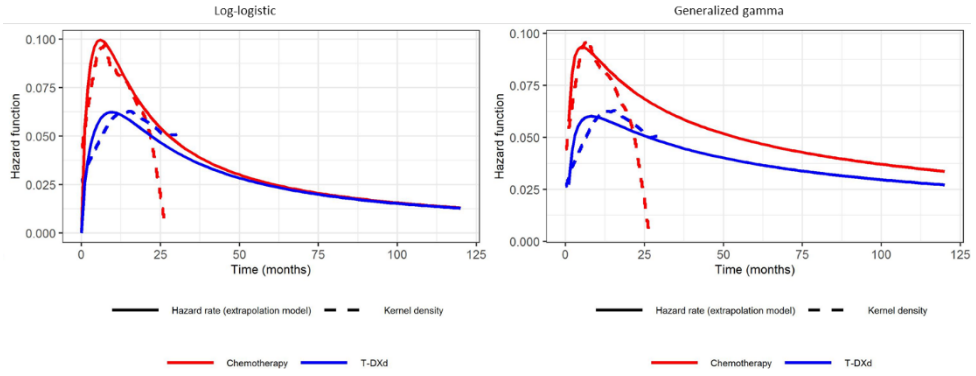


In addition, Figure 30 compares the PFS kernel density curve with the hazard functions of the Log-Logistic and Generalized Gamma distributions for chemotherapy and T-DXd.

For chemotherapy, the Generalized Gamma distribution closely follows the kernel density curve up to approximately 13 months, after which it diverges and predicts a higher hazard rate. The Log-Logistic distribution aligns with the kernel density curve until about 18 months, beyond which it also diverges, predicting a higher hazard function.

For T-DXd, both distributions exhibit a shape similar to the kernel density curve and follow it closely. However, the Log-Logistic distribution aligns slightly better with the kernel density curve up to 12 months, while the Generalized Gamma provides a closer fit after 12 months. Overall, the Log-Logistic distribution offers a better fit for chemotherapy compared to the Generalized Gamma, making it the more clinically plausible choice.

Figure 30 Hazard function of progression-free survival using the Log-logistic and Generalised gamma distributions



D.1.7 Validation and discussion of extrapolated curves

Different distributions displayed a good fit to the trial data for both treatment arms. However, despite modelling being done independently for T-DXd and ICC, the same distribution was chosen to reduce clinical implausibility and enhance comparability. Applying different distributions to each arm can lead to clinically inconsistent or unrealistic extrapolations, especially in long-term projections. By using the same distribution, we ensure that differences in outcomes are attributable to treatment effects rather than characteristics of the distribution choice. The use of the same distribution for both treatment arms was validated in a global advisory board, held in December 2024 (59).

As such, only the log-logistic and generalised gamma were deemed suitable, since these are the only distributions that fit both arms. Figure 31 shows the extrapolations when using the log-logistic and generalised gamma distributions.

Figure 31 Combined figure of PFS extrapolations using the log-logistic and generalised gamma distributions

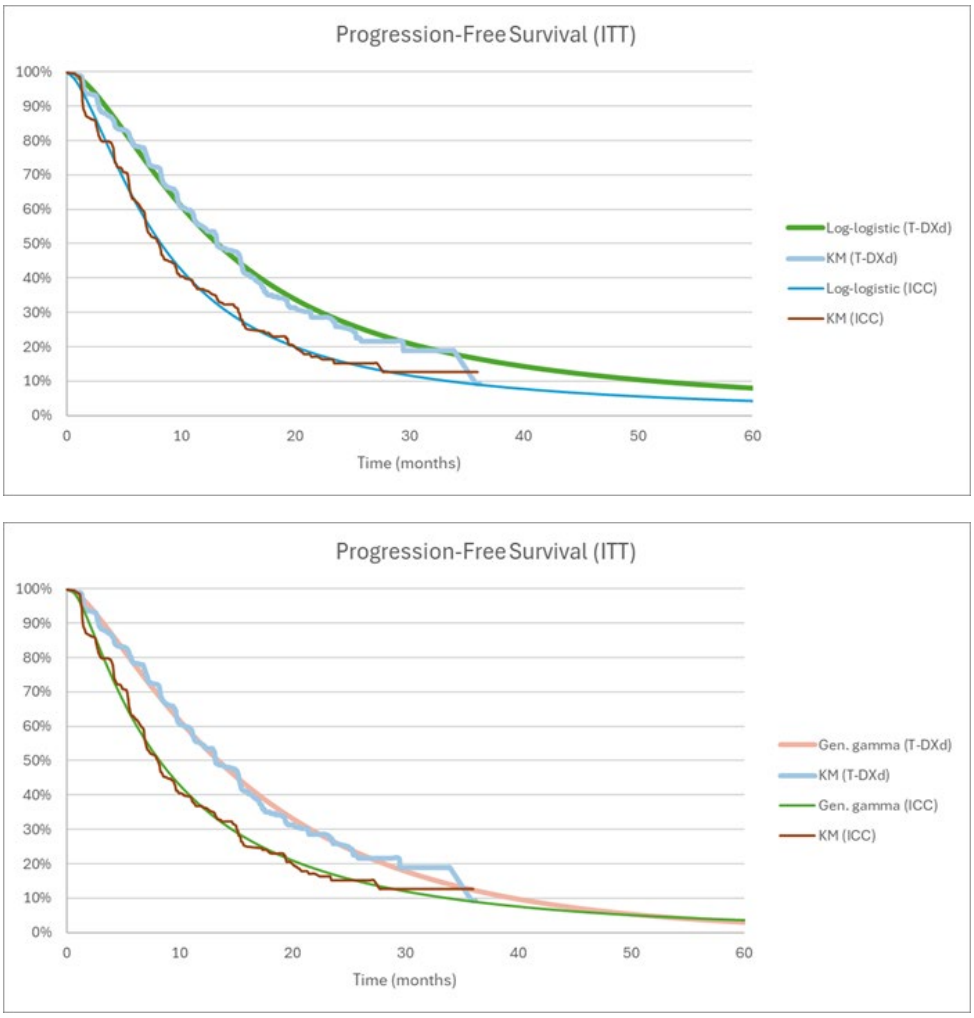


Figure 31 above shows that when using the generalised gamma distributions to extrapolate PFS, the curves cross at around the 50-month mark. This is deemed clinically implausible since a significant PFS benefit was observed in the DB06 trial, and the data is mature. Moreover, the generalised gamma distribution seems to put a heavy emphasis on the sudden drop at the end of the KM curve in the T-DXd arm, which is caused by a small sample size.

The Log-logistic distribution was chosen to extrapolate the PFS data from both arms. Along with displaying a good statistical fit, the Log-logistic curve provided a strong fit for both arms, seemed to have the best visual fit for the T-DXd arm and produced more clinically plausible results than the other well-fitting curve (Generalised gamma) based on the hazard functions comparison. The landmark survival outcomes are presented in Table 51. The median PFS in the T-DXd arm is 13.1 months and the median PFS in the ICC arm is 7.6 months. This is comparable to the DB06 data, where the median PFS in the T-DXd arm was 13.2 months, and 8.1 months with chemotherapy.

Table 51 10-year landmark survival using the log-logistic curve for PFS extrapolations

	Months										
Arm	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**mPFS**
T-DXd	54.6%	27.3%	16.5%	11.1%	7.9%	6.1%	4.8%	3.9%	3.3%	2.8%	13.1
ICC	36.6%	15.7%	9.1%	6.0%	4.3%	3.3%	2.6%	2.1%	1.8%	1.5%	7.6

D.1.8 Adjustment of background mortality

N/A

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

D.2 Extrapolation of OS

D.2.1 Data input

Data from the DB06 trial is used to inform the extrapolation of OS beyond the follow-up in the clinical trial.

D.2.2 Model

Standard parametric models were used to extrapolate OS from the DB06 data, the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-logistic
- Log-normal
- Generalised gamma
- Gamma

D.2.3 Proportional hazards

Figure 32 shows the log-cumulative hazard plot for T-DXd and ICC and Figure 33 shows the Schoenfeld residuals for OS. After deviating in the beginning, the log-cumulative hazard plots remain relatively parallel towards the end of the plot.

Figure 32 Log-cumulative hazard plot of OS in the ITT population

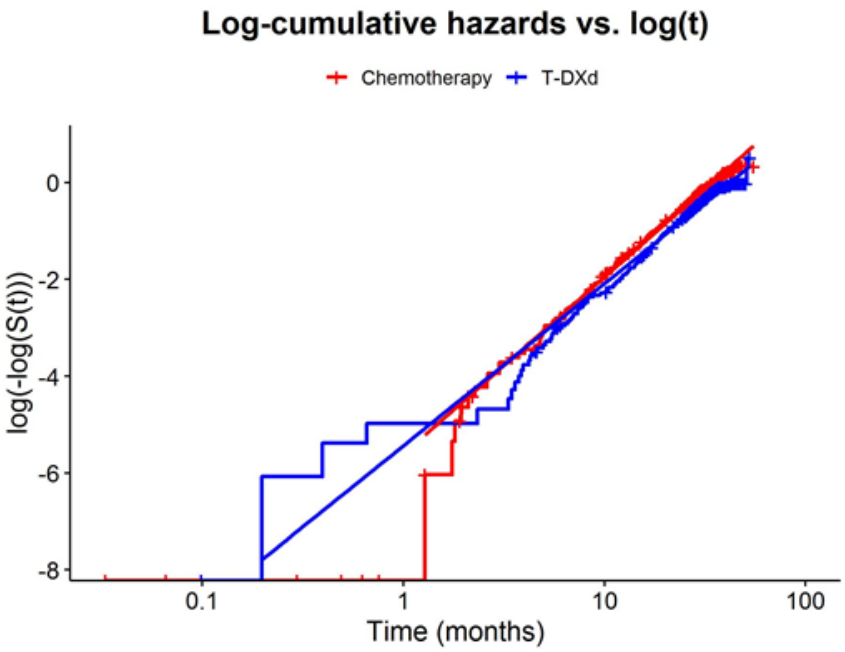
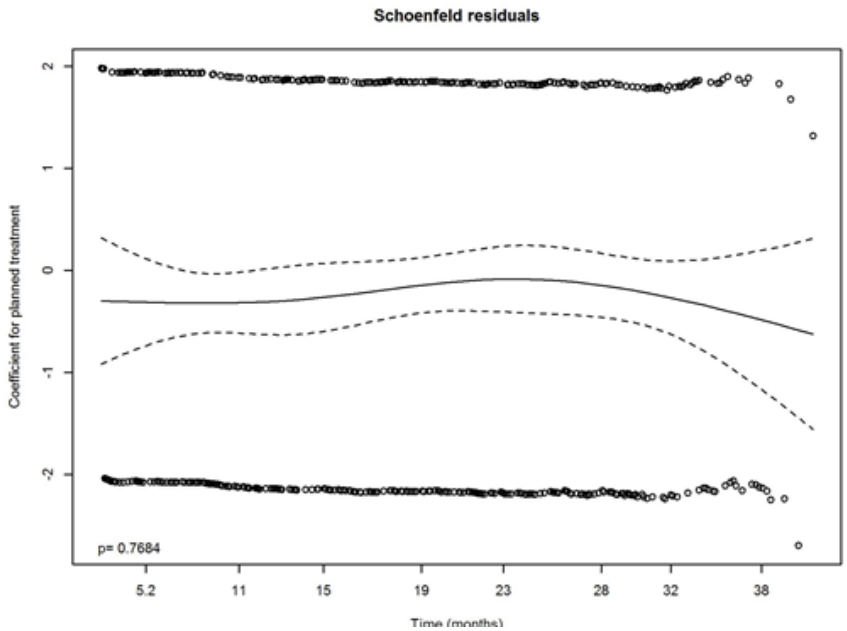


Figure 33 shows the Schoenfeld residuals for OS. If the PH assumption holds, the line in the middle of the graph should be horizontal, indicating independence from time. The Schoenfeld residuals do not show a distinct trend, but the time-dependent hazard ratio shows slight deviations from a straight line. Furthermore, the statistical test of non-proportionality fails to reject the null hypothesis (p-value=0.7684), indicating that the PH assumption may be valid.

Figure 33 Schoenfeld residuals for OS in the ITT population

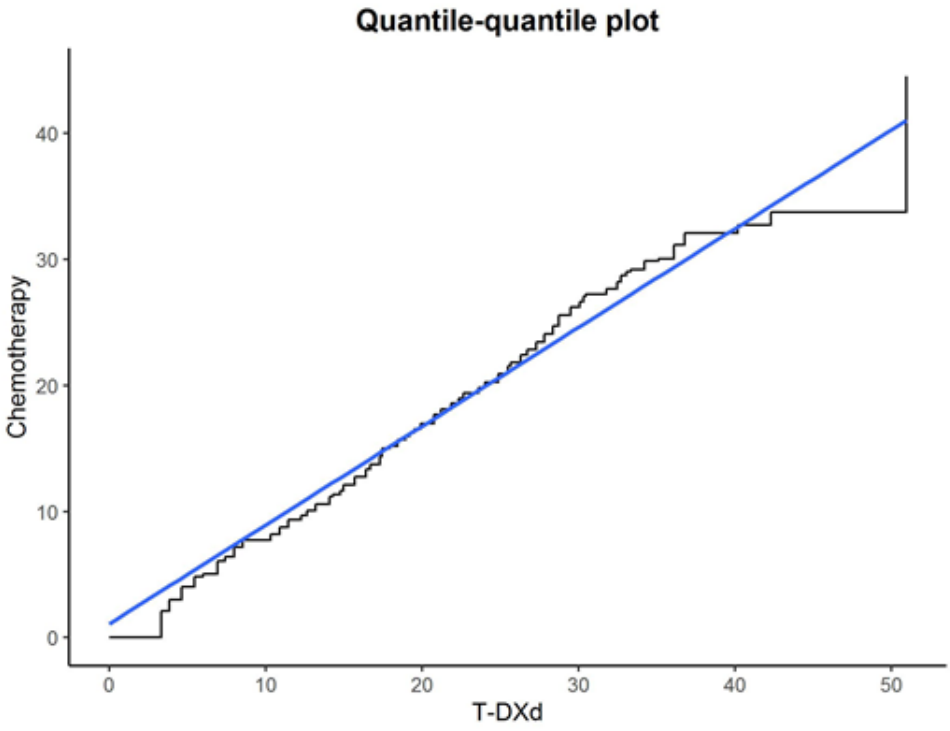


Abbreviations: ITT, intention-to-treat; OS, Overall survival; T-DXd, trastuzumab deruxtecan.

Altogether, the results of the log-cumulative hazards plot and the Schoenfeld residuals indicate that the PH assumption holds. Therefore, dependent models which include treatment as a covariate are appropriate to use for modelling OS in the ITT population.

Figure 34 shows the quantile-quantile plot for OS. As the plot closely approximates the straight trend line, AFT models are suitable for use when extrapolating OS data.

Figure 34 Quantile-quantile plot for OS in the ITT population



D.2.4 Evaluation of statistical fit (AIC and BIC)

Given that OS is modelled dependently, the statistical goodness of fit is assessed together for both treatment arms. Based on the AIC and BIC values, the Weibull, log-logistic, generalised gamma, and gamma are the best-fitting distributions for the OS data from the DB06 trial (Table 52).

Table 52 Goodness-of-fit for OS data according to the AIC and BIC values

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Notes: The distributions highlighted in green had the best statistical fit to the KM data based on the lowest AIC and BIC scores.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

D.2.5 Evaluation of visual fit

The statistically best-fitting curves were subsequently plotted along the KM curve of the DB06 trial for visual inspection. For both arms, the Weibull, log-logistic, generalised gamma, and gamma distributions were modelled, which all displayed a good fit to the trial data (Figure 35 and Figure 36).

Figure 35 Best fitting curves plotted against the OS KM curve of DB06 – ICC arm

Figure 36 Best fitting curves plotted against the OS KM curve of DB06 – T-DXd arm

D.2.6 Evaluation of hazard functions

The hazard rate, smoothed and unsmoothed, and by extrapolation model, are shown in Figure 37 and Figure 38. The OS hazard functions were not informative due to the relative immaturity of the data.

Figure 37 Hazard rates, smoothed and unsmoothed of OS

Figure 38 Hazard function, smoothed and by extrapolation model of OS

D.2.7 Validation and discussion of extrapolated curves

For PFS, internal validation was performed by comparing the hazard function of the selected distributions with the kernel density curve. However, for OS, this approach was not feasible because the OS data is immature, resulting in none of the distributions fitting the kernel density curve. To clinically validate the extrapolations, external data retrieved from a systematic literature review (SLR) were utilised. Validation was performed through the ICC arm since these patients do not receive a novel treatment in

this setting. Additionally, clinical experts were consulted in a global advisory board held in December 2024 (50) and Danish clinical experts (25) were consulted in the preparation of this dossier. Landmark survival for each distribution is shown as per Table 53, and compared to landmark survival from the literature.

Notably, the studies retrieved in the SLR did not report outcomes specifically on HR-positive/HER2-low or HER2-ultralow patients. However, given that these patients are treated as HER2-negative patients up until now, these studies do contain patients that fall within the indication. The outcomes of the studies were used as a reference to validate the extrapolations presented in the previous section. Studies of interest from the SLR were specifically those that contained a treatment in the ICC arm (capecitabine, paclitaxel, nab-paclitaxel).

Table 53 5-year landmark OS best fitting curves, ICC arm

	Months				
Distribution	**12**	**24**	**36**	**48**	**60**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Studies retrieved in the SLR that reported long-term survival results predominantly reported 5-year survival rates within a range of 15%–25% (39-41). The 5-year survival estimates provided by the Weibull, Gen Gamma and Gamma distributions are not considered clinically plausible, as they fall below the survival rate range observed in the studies obtained in the SLR. As such, the log-logistic seems most plausible.

Interviews with Danish clinical experts (25) and a Global advisory board (50) were held to gather recommendations from clinical experts regarding the expected OS. According to the experts, a 5-year OS rate between 10% and 20% was deemed clinically plausible, with instances of 5-year survival exceeding 20% also being observed. Based on these estimates, the Log-Logistic, Generalised Gamma, and Gamma distributions fall within the expected range.

However, the Gamma and Generalised Gamma distributions predict a 5-year survival rate that is just above the lower boundary of the plausible range, making it an overly conservative choice. The Log-Logistic distribution, by contrast, estimates a 5-year survival rate well within the plausible boundaries, making it the preferred choice for extrapolating the OS data. In interviews with Danish clinical experts, they agreed the landmarks looked reasonable.

While significantly more patients in Denmark would have access to T-DXd in later lines (compared to what is observed in DB06), Danish clinical experts discussed whether the

two intervention arms would have the same risk of dying at some point in time. They concluded that it is reasonable to believe that the curves may never converge over time, as there is a preference to lead with the strongest treatment option and it is challenging to recover the impact on OS by receiving T-DXd in later lines as patients progress.

D.2.8 Adjustment of background mortality

The occupancy of the health states was adjusted to account for Danish background mortality.

D.2.9 Adjustment for treatment switching/cross-over

N/A

D.2.10 Waning effect

N/A

D.2.11 Cure-point

N/A

D.3 Extrapolation of TTD

D.3.1 Data input

Data from the DB06 trial is used to inform the extrapolation of TTD beyond the follow-up in the clinical trial.

D.3.2 Model

Standard parametric models were used to extrapolate TTD from the DB06 data, the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-logistic
- Log-normal
- Generalised gamma
- Gamma

D.3.3 Proportional hazards

Figure 39 shows the log-cumulative hazard plot for T-DXd and chemotherapy. The plots are relatively parallel towards the end of the plot, however, considerable deviations from the parallel trend and multiple crossings of the lines can be seen in the first month.

Figure 39 Log-cumulative hazard plot of TTD in the ITT population

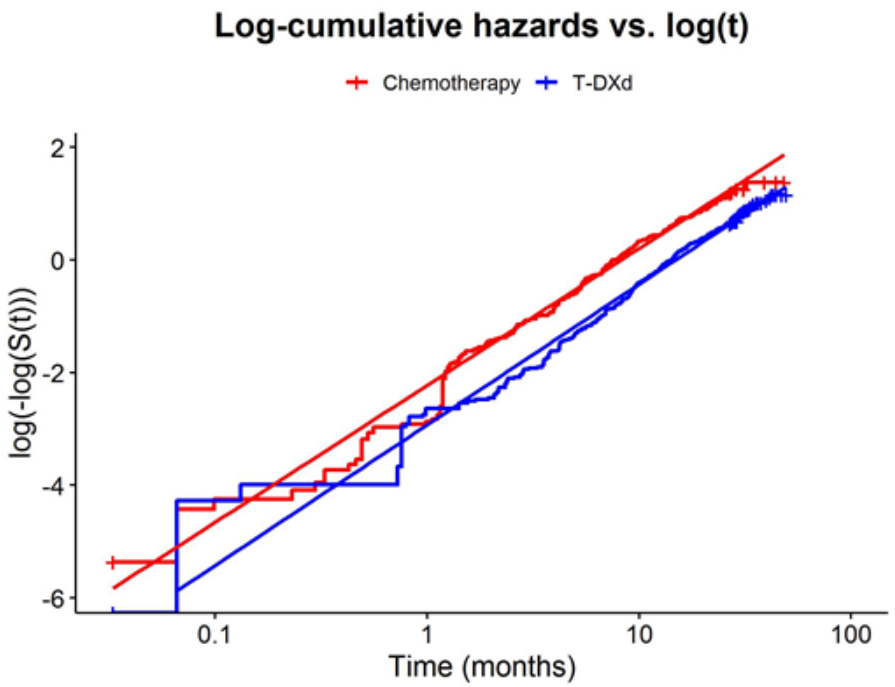
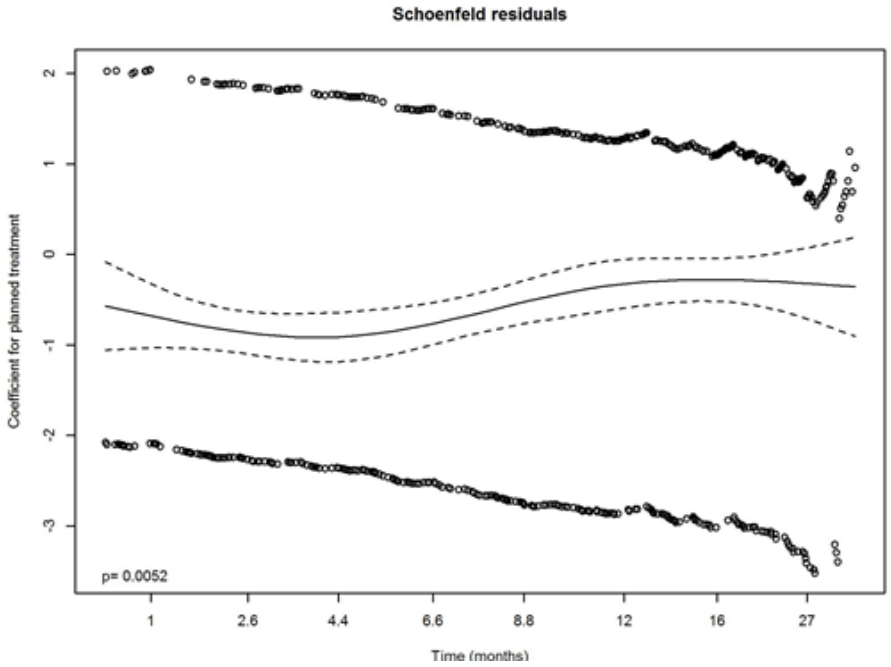


Figure 40 shows the Schoenfeld residuals for TTD. The Schoenfeld residuals do not appear constant over time, and the statistical test for proportionality shows a significant p-value (p=0.036). This indicates that the PH assumption does not hold.

Figure 40 Schoenfeld residuals for TTD in the ITT population

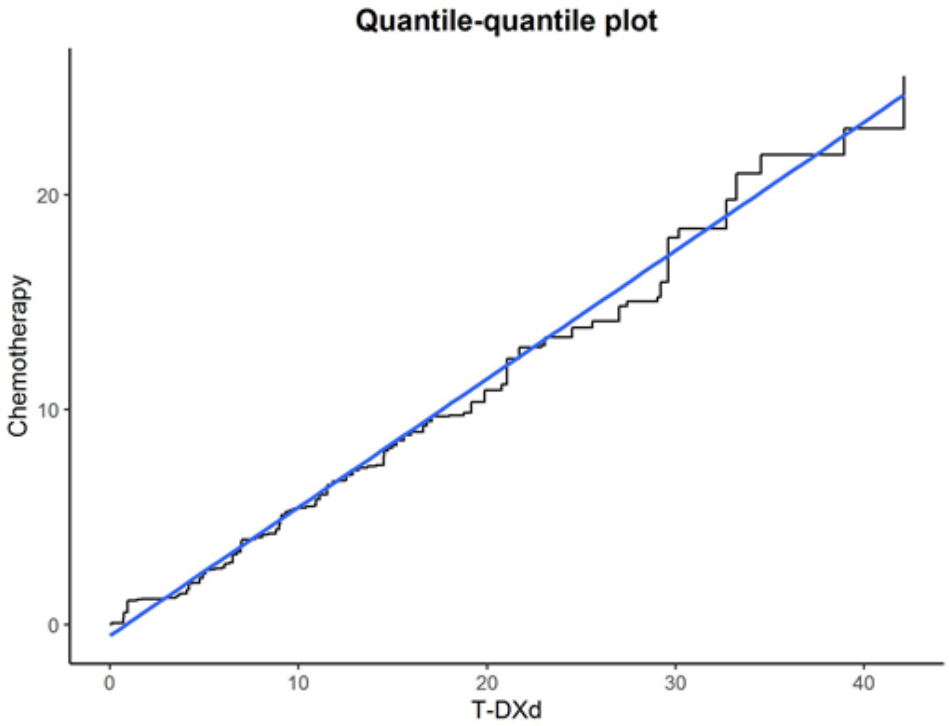


Abbreviations: ITT, intention-to-treat; T-DXd, trastuzumab deruxtecan; TTD: time to discontinuation

Based on the log-cumulative hazards plot and the Schoenfeld residuals, it cannot be concluded with certainty that the PH assumption is valid. The significant p-value shown in the Schoenfeld residuals plot means that the proportionality hypothesis should be rejected. Independent parametric curves for each treatment arm are therefore recommended for use in modelling TTD.

Figure 2 shows the quantile-quantile plot for TTD. As the plot closely approximates the straight trend line, AFT models are suitable for use when extrapolating TTD data.

Figure 41 Quantile-quantile plot for TTD in the ITT population



D.3.4 Evaluation of statistical fit (AIC and BIC)

Given that TTD is modelled independently, the statistical goodness of fit is assessed separately for both treatment arms. Based on the AIC and BIC values, the Exponential, Weibull, Gompertz, Generalised gamma, and Gamma are the best-fitting distributions for the TTD data from the ICC arm in the DB06 trial (Table 54).

Table 54 Goodness-of-fit for ICC to the DB06 TTD data according to the AIC and BIC values

Distribution	AIC	BIC
Exponential	**2527.930**	**2531.994**
Weibull	**2528.907**	**2537.034**
Gompertz	**2528.809**	**2536.937**
Log-logistic	2537.890	2546.017
Log-normal	2562.616	2570.744
Generalised gamma	**2524.332**	**2536.524**
Gamma	**2527.319**	**2535.447**

Notes: The distributions highlighted in green had the best statistical fit to the KM data based on the lowest AIC and BIC scores.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Based on the AIC and BIC values, the Exponential, Weibull, Gompertz, Generalised gamma, and Gamma are the best-fitting distributions for the TTD data from the T-DXd arm in the DB06 trial (see Table 55).

Table 55 Goodness-of-fit for T-DXd to the DB06 TTD data according to the AIC and BIC values

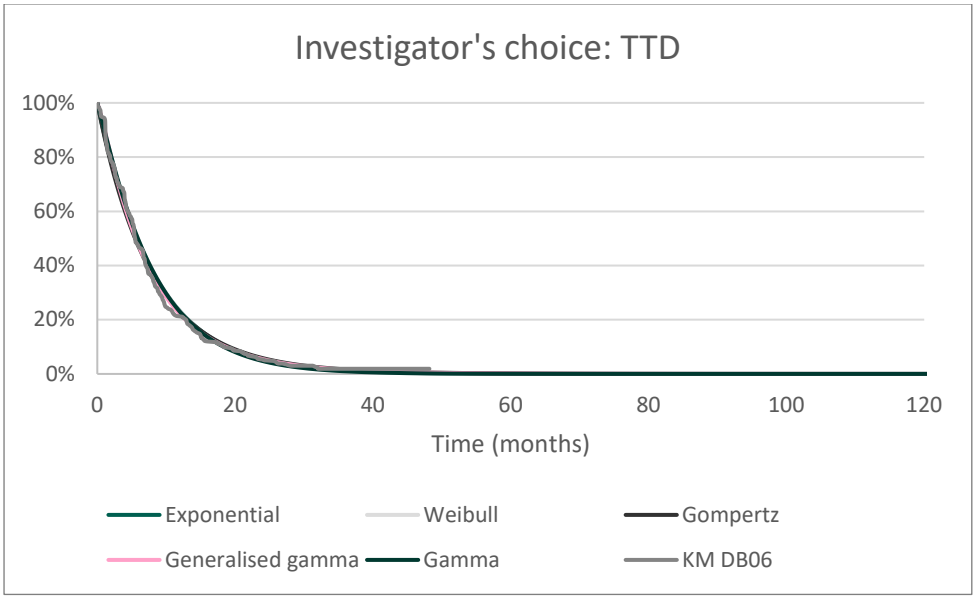
Distribution	AIC	BIC
Exponential	**2926.091**	**2930.169**
Weibull	**2919.789**	**2927.944**
Gompertz	**2924.018**	**2932.174**
Log-logistic	2947.969	2956.124
Log-normal	3000.626	3008.781
Generalised gamma	**2921.777**	**2934.010**
Gamma	**2920.433**	**2928.588**

Notes: The distributions highlighted in green had the best statistical fit to the KM data based on the lowest AIC and BIC scores.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

D.3.5 Evaluation of visual fit

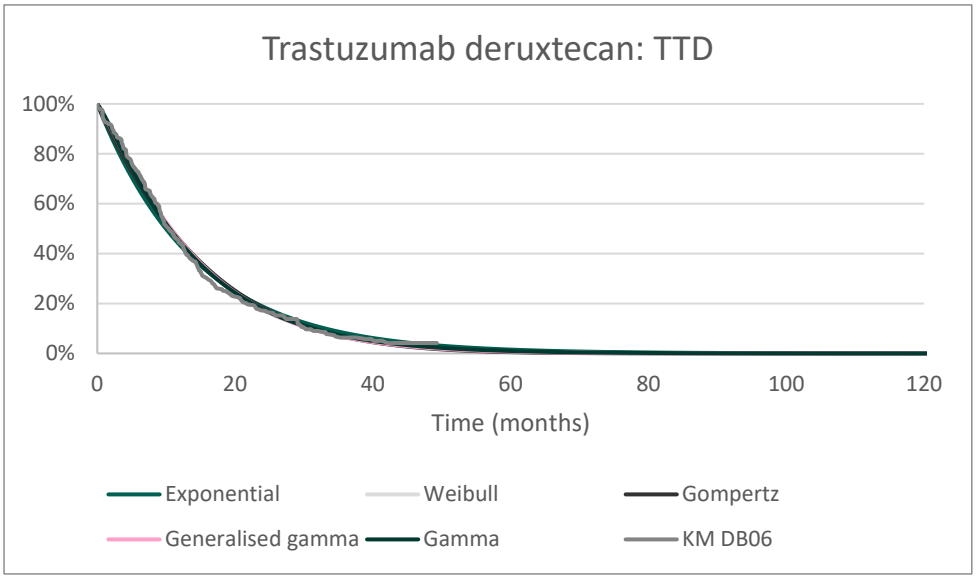
The statistically best-fitting curves were subsequently plotted along the KM curve of the DB06 trial for visual inspection. For the ICC arm, the Exponential, Weibull, Gompertz, Generalised gamma, and Gamma were modelled, which all displayed a good fit to the trial data (Figure 42).

Figure 42 Best fitting curves plotted against the TTD KM curve of DB06 – ICC arm



For the T-DXd arm, the Exponential, Weibull, Gompertz, Generalised gamma, and Gamma distributions were plotted against the TTD data from the DB06 trial. All extrapolations closely follow the trend of the KM curve (Figure 43).

Figure 43 Best fitting curves plotted against the TTD KM curve of DB06 – T-DXd arm



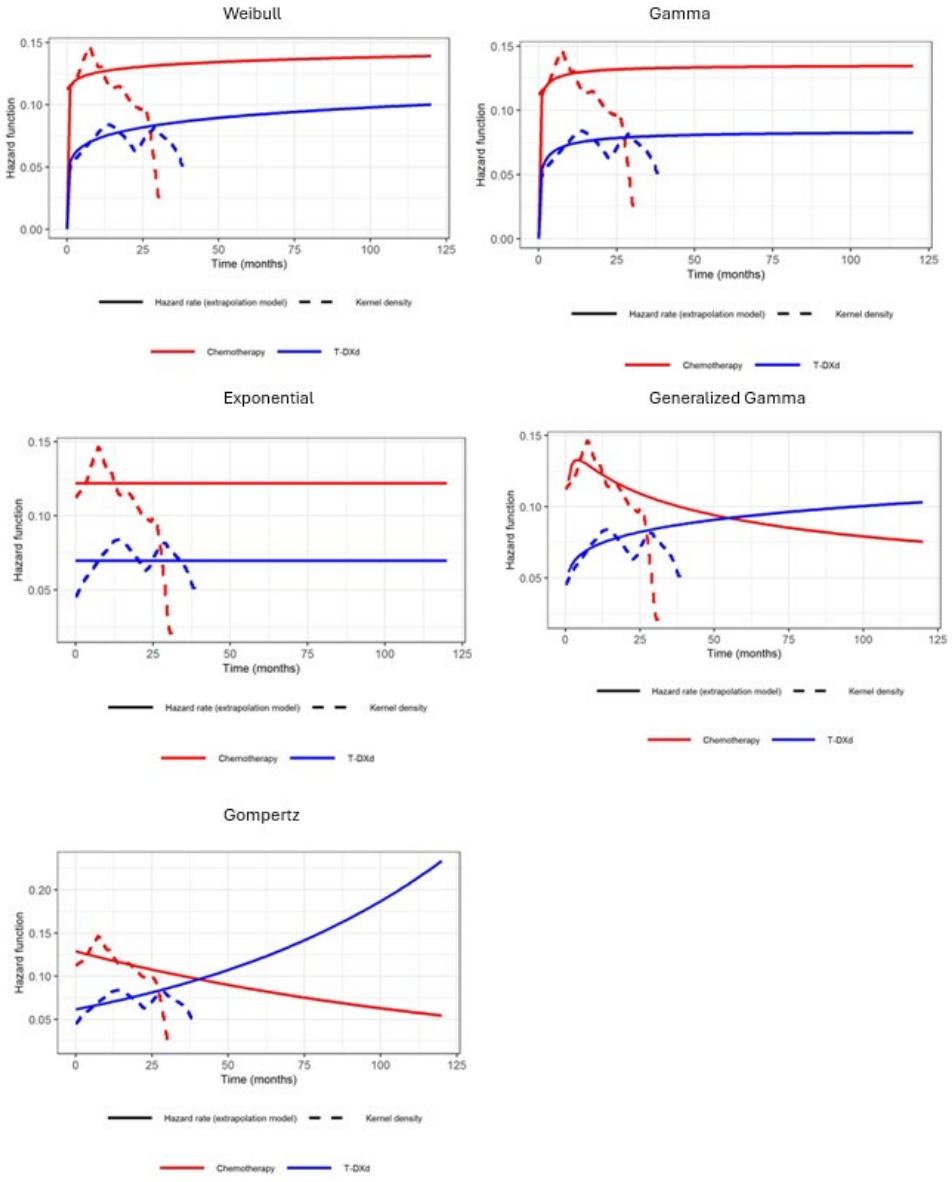
D.3.6 Evaluation of hazard functions

To clinically validate the distributions, internal validation was firstly conducted by comparing the hazard functions of the distributions with the kernel density curves.

Figure 44 compares the kernel density curve of time-to-treatment discontinuation with the Weibull, Gamma, Exponential, Generalised Gamma, and Gompertz distributions for

chemotherapy and T-DXd. All distributions align with the kernel density curve for chemotherapy up to 12 months and for T-DXd up to 25 months. Beyond these points, the distributions diverge from the curve, with the Weibull, Gamma, and Exponential distributions stabilising and showing only minor differences among them. The Generalised Gamma and Gompertz distributions cross around the 50-month mark. Given the shape of the kernel density curves and the maturity of the TTD data, these crossings are considered implausible.

Figure 44 Hazard function of TTD using the Weibull, Gamma, Exponential, Generalised gamma, and Gompertz distributions A



Additionally, the relation between TTD and PFS was assessed by calculating the differences (delta) between the selected PFS distribution and best fitting distributions. As T-DXd is administered up until, or close to, disease progression, the observed difference between PFS and TTD should be minimal.

Table 56 presents the average and maximum differences between the selected PFS distribution and best-fitting TTD distributions. The Gamma distribution provide the lowest average difference between the PFS and TTD curves for T-DXd, apart from the Exponential. Additionally, this distribution also provides the lowest maximum difference between PFS and TTD for T-DXd.

Table 56 Delta PFS-TTD values for the best-fitting curves for T-DXd

Distribution	Average ΔPFS-TTD	Maximum ΔPFS-TTD
Exponential	6.38%	12.16%
Weibull	6.58%	10.13%
Gompertz	6.66%	9.92%
Generalised gamma	6.58%	10.17%
Gamma	**6.50%**	**9.83%**

D.3.7 Validation and discussion of extrapolated curves

The Gamma distribution was chosen to extrapolate the TTD data from both arms. In addition to displaying a good statistical fit, the Gamma curve provided a strong fit for both arms well, seemed to have the best visual fit for the T-DXd arm and produced more clinically plausible results than the other curves that fit both arms well. The landmark survival outcomes are presented in Table 57. The median TTD in the model is 10.35 months in the T-DXd arm and 5.52 months in the ICC arm. This compares well to the DB06 data, where the median TTD in the T-DXd arm was 10.4 months and 5.5 with chemotherapy.

Table 57 10-year landmark survival using the Gamma curve for TTD extrapolations.

	Months										
Arm	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**mTTD**
T-DXd	45.63 %	17.57 %	6.93 %	2.70 %	0.98 %	0.38 %	0.14 %	0.05 %	0.02 %	0.01 %	10.35
ICC	23.71 %	4.67%	0.99 %	0.21 %	0.04 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	5.52

D.3.8 Adjustment of background mortality

N/A

D.3.9 Adjustment for treatment switching/cross-over

N/A

D.3.10 Waning effect

N/A

D.3.11 Cure-point

N/A

Appendix E. Serious adverse events

Tabel 1 Serious adverse events reported in DB06 (2)

	Number (%) of Patients	
	Study DB06	
	T-DXd 5.4 mg/kg (N=434)	Chemotherapy (N=417)
Patients with any TEAE	88 (20.3)	67 (16.1)
Interstitial lung disease	8 (1.8)	0
Pneumonitis	8 (1.8)	0
COVID-19	7 (1.6)	1 (0.2)
Febrile neutropenia	5 (1.2)	2 (0.5)
Hypokalaemia	5 (1.2)	1 (0.2)
Anaemia	3 (0.7)	1 (0.2)
General physical health deterioration	3 (0.7)	0
Nausea	3 (0.7)	1 (0.2)
Pulmonary embolism	3 (0.7)	3 (0.7)
Vomiting	3 (0.7)	1 (0.2)
Sepsis	2 (0.5)	2 (0.5)
Liver injury	2 (0.5)	0
Hypercalcaemia	2 (0.5)	2 (0.5)
Decreased appetite	2 (0.5)	1 (0.2)
Pneumocystis jirovecii pneumonia	2 (0.5)	0
Pneumothorax	2 (0.5)	0
Pyelonephritis	2 (0.5)	1 (0.2)
Constipation	1 (0.2)	2 (0.5)
Cellulitis	1 (0.2)	5 (1.2)
Diarrhoea	1 (0.2)	3 (0.7)

Pneumonia	1 (0.2)	3 (0.7)
Back pain	0	2 (0.5)
Cardiac failure	0	2 (0.5)
Cholangitis	0	3 (0.7)
Colitis	0	3 (0.7)
Femur fracture	0	3 (0.7)
Pleural effusion	0	5 (1.2)
Pyrexia	0	2 (0.5)

Appendix F. Health-related quality of life

F.1 Introduction

This report details the analysis of Danish utility values derived from the EQ-5D-5L profiles in DB06 using the 5L Danish value set by Jensen CE, 2021 (44). The analysis was based on ITT data from DB06. Summarised below are the background, methods and results of the descriptive summary and regression analysis of EQ-5D-5L health state utility data in the DB06 study. (7)

F.2 Background

Quality of life was assessed within DB06 using the EQ5D. The assessment schedule for EQ-5D-5L in DB06 is available from the clinical study protocol.

The EQ-5D is a standardised measure of self-reported health, developed by the EuroQol Group. There are 5 dimensions or domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. In the 5-level ('5L') version of the questionnaire, there are 5 possible levels of response that a subject can give for each dimension: no, mild, moderate, severe, and severe / unable to.

An EQ-5D profile consists of a 5-digit value, with each digit representing a subject's response for each domain. The EQ-5D profiles can be converted to a health state utilities using country-specific value sets that are reflective of the country of interest. The maximum health state utility value is 1, which represents 'full health'. A value of 0 corresponds to a quality of life equivalent to being dead, and negative values are possible which represent a quality of life worse than death.

The results of the utility analysis are intended to provide input data for cost-effectiveness models, which are required in developing cost-utility analysis. Utilities are present in the calculation of quality-adjusted life years (QALYs), which are subsequently used to generate the Incremental Cost Effectiveness Ratio (ICER). These are both used to support health technology assessment and reimbursement submissions.

F.3 Methods

The summary analysis includes estimates of mean, standard deviations, median, and min and max of utility scores in the ITT analysis set of DB06, consisting of all completed EQ-5D-5L measures (excluding EQ-5D-5L with any missing domain responses).

The statistical relationship between EQ-5D-5L health state utility and treatment, and health status was assessed using regression analysis.

Linear mixed models were constructed that included the EQ-5D-5L utility scores from all available timepoints, including baseline, as the dependent variable. The optimal random effects (subject,timing of questionnaire, or both) was identified based on the lowest AIC and BIC. Six models were fitted, including:

1. Progression status (progressed, progression-free) by BICR at the corresponding visit as the independent variable

2. Progression status (progressed, progression-free) by BICR at the corresponding visit and planned treatment as independent variables

3. The following fixed set of covariates as independent variables:

- Stratification factors: Prior CDK4/6 inhibitor use; HER2 IHC expression (excluded for the HER2-ultralow population); prior taxane use in the non-metastatic setting.
- Other potential treatment effect modifiers: Age (< 65 years, ≥ 65 years); race; number of prior lines in metastatic setting (1, 2, ≥ 3); ECOG performance status at baseline; brain metastases at baseline; number of metastatic sites at baseline.

4. The fixed set of covariates above and planned treatment as independent variables.

5. Time-to-death at the corresponding visit as independent variable

6. Time-to-death at the corresponding visit and planned treatment as independent variables

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

The mean utility values, associated 95% CIs, and p-values for the different health states were derived from the model using the regression coefficients. In addition, the covariance matrix from each of the linear mixed models has been extracted. The mean utility values and associated 95% CIs for the different health states were derived from the models using the least square means.

This report presents the results from the regression analysis, performed in R.

F.4 Results - Regression analysis

Table 58 presents the regression coefficients for the linear mixed models on the ITT population for the Danish value set. It includes the regression coefficients for the linear mixed models including only progression status (Model 1) and both planned treatment and progression status (Model 2) as covariates. For both models, progression significantly reduces the utility (Model 1: regression coefficient (95% CI) = -0.045 (-0.055,

-0.036), p-value<0.0001; Model 2: regression coefficient (95% CI): -0.045 (-0.054, -0.035), p-value<0.0001). Additionally, treatment arm was significant in Model 2 (p 0.0014).

Table 58 Regression coefficients of linear mixed model of utility values based on progression status

	Model 1*2 Regression coefficients (95% CI) p-value	Model 2*2 Regression coefficients (95% CI) p-value
Intercept	0.847 (0.836, 0.858) <0.0001	0.828 (0.812, 0.844) <0.0001
Treatment arm (T-DXd vs Chemotherapy)		0.036 (0.014, 0.058) 0.0014
Progression status (progression vs progression-free)	-0.045 (-0.055, -0.036) <0.0001	-0.045 (-0.054, -0.035) <0.0001

* Unstructured covariance matrix was used to model the random effects correlation.
2 The mixed model included a random intercept and slope.
Source: DESTINY-Breast06 Data on file (51).

Table 58 is build on the following:

Model 1: Utility scores based on progression status (progression, progression-free) by BICR at the corresponding visit as an independent variable.

Model 2: Utility scores based on progression status (progressed, progression-free) by BICR at the corresponding visit and planned treatment as independent variables.

Model 1: $Y_{ij}=\beta_0+\beta_1 Progress_{ij}+b_{0i}+b_{1i} date_{ij}+\epsilon_{ij}$, where,

$Progress_{ij}$ is a binary indicator variable for progression status of the ith individual at the jth visit

$date_{ij}$ is measurement time for the ith individual at the jth visit

β_0: fixed intercept term

β_1: fixed effect of having a progression versus not having a progression

b_{0i}: random intercept for the ith individual

b_{1i}: random slope term for date for the ith individual

ϵ_{ij}: residual error term for the ith individual at the jth visit

Model 2: $Y_{ij}=\beta_0+\beta_1 TRT_{ij}+\beta_2 Progress_{ij}+b_{0i}+b_{1i} date_{ij}+\epsilon_{ij}$, where,

$Progress_{ij}$ is a binary indicator variable for progression status of the ith individual at the jth visit

$date_{ij}$ is measurement time for the ith individual at the jth visit

TRT_{ij} is the treatment indicator variable for the ith individual at the jth visit

β_0: fixed intercept term

β_1: fixed effect for the difference in being in the T-DXd arm versus the chemotherapy arm

β_2: fixed effect of having a progression versus not having a progression

b_{0i}: random intercept for the ith individual

b_{1i}: random slope term for date for the ith individual

ϵ_{ij}: residual error term for the ith individual at the jth visit

Table 59 presents the mean utility values by progression status obtained from the regression coefficients, both overall (Model 1) and by treatment group (Model 2).

Table 59 Utility values based on progression status – Least square means of mixed model analysis

	T-DXd (N=436)			Chemotherapy (N=430)			Total (N=866)		
Health State	n [a]	Mean (SD)	Median (Min, Max)	n [a]	Mean (SD)	Median (Min, Max)	n [a]	Mean (SD)	Median (Min, Max)
Progression-free	5810	0.8707 (0.17510)	0.9190 (-0.7580, 1.0000)	3764	0.8495 (0.17906)	0.8800 (-0.5840, 1.0000)	9574	0.8624 (0.17696)	0.9110 (-0.7580, 1.0000)
Progressed	900	0.8332 (0.19142)	0.8800 (-0.2950, 1.0000)	783	0.8082 (0.22681)	0.8780 (-0.5350, 1.0000)	1683	0.8216 (0.20894)	0.8800 (-0.5350, 1.0000)

Appendix G. Probabilistic sensitivity analyses

Table 60. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Patient characteristics				
Mean age (years)	58.2	57.45	58.95	Normal
Average weight (kg)	65.1	65.10	65.10	Log-normal
Average body surface (m2)	1.70	1.36	2.03	Normal
HSUV				
Progression free- T-DXd	0.871	0.866	0.875	Beta
Progression free- ICC	0.850	0.844	0.855	Beta
Progressed – T-DXd and ICC	0.822	0.812	0.832	Beta
AE - Incidence				
Neutrophil count decreased - Trastuzumab deruxtecan	0.14	0.11	0.17	Beta
Anaemia - Trastuzumab deruxtecan	0.09	0.07	0.11	Beta
White blood cell decrease - Trastuzumab deruxtecan	0.06	0.05	0.07	Beta
Platelet count decreased - Trastuzumab deruxtecan	0.04	0.03	0.05	Beta
Nausea - Trastuzumab deruxtecan	0.02	0.02	0.03	Beta
Diarrhoea - Trastuzumab deruxtecan	0.02	0.02	0.03	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Fatigue - Trastuzumab deruxtecan	0.02	0.02	0.03	Beta
Asthenia - Trastuzumab deruxtecan	0.02	0.02	0.03	Beta
Interstitial lung disease (ILD) - Trastuzumab deruxtecan	0.01	0.01	0.02	Beta
Hypertension - Trastuzumab deruxtecan	0.03	0.02	0.03	Beta
LVEF decrease - Trastuzumab deruxtecan	0.01	0.01	0.01	Beta
GGT increased - Trastuzumab deruxtecan	0.02	0.02	0.03	Beta
Lymphocyte count decreased - Trastuzumab deruxtecan	0.02	0.02	0.03	Beta
Neutropenia - Trastuzumab deruxtecan	0.09	0.07	0.10	Beta
Hypokalaemia - Trastuzumab deruxtecan	0.04	0.04	0.05	Beta
Neutrophil count decreased - Investigator's choice	0.09	0.07	0.10	Beta
Anaemia - Investigator's choice	0.04	0.03	0.05	Beta
White blood cell decrease - Investigator's choice	0.05	0.04	0.06	Beta
Palmar-Plantar Erythrodysesthesia - Investigator's choice	0.07	0.06	0.09	Beta
Nausea - Investigator's choice	0.01	0.00	0.01	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Diarrhoea - Investigator's choice	0.03	0.02	0.03	Beta
Fatigue - Investigator's choice	0.01	0.01	0.02	Beta
Asthenia - Investigator's choice	0.01	0.01	0.01	Beta
Hypertension - Investigator's choice	0.03	0.02	0.03	Beta
LVEF decrease - Investigator's choice	0.01	0.01	0.01	Beta
GGT increased - Investigator's choice	0.01	0.00	0.01	Beta
Lymphocyte count decreased - Investigator's choice	0.01	0.00	0.01	Beta
Neutropenia - Investigator's choice	0.08	0.07	0.10	Beta
Hypokalaemia - Investigator's choice	0.01	0.01	0.01	Beta
Resource use				
Number of resources per cycle - PF HS - Specialist physician/ Oncologist	0.23	0.19	0.28	Gamma
Number of resources per cycle - PF HS - Blood tests	1.00	0.81	1.21	Gamma
Number of resources per cycle - PF HS - CT scan	0.23	0.19	0.28	Gamma
Number of resources per cycle - PF HS - Cardiac assessment: ECHO scan	0.23	0.19	0.28	Gamma

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Number of resources per cycle - PP HS - Specialist physician/ Oncologist	0.23	0.19	0.28	Gamma
Number of resources per cycle - PP HS - Blood tests	1.00	0.81	1.21	Gamma
Number of resources per cycle - PP HS - CT scan	0.23	0.19	0.28	Gamma
Number of resources per cycle - PP HS - Cardiac assessment: ECHO scan	0.23	0.19	0.28	Gamma
Number of resources per cycle - EOL - Terminal care cost	1.00	0.81	1.21	Gamma
Subsequent treatments				
Patients receiving subsequent treatment - T-DXd	0.90	0.66	1.00	Beta
Patients receiving subsequent treatment - Comps	0.89	0.66	0.99	Beta
Proportion of Capecitabine as subsequent treatment - T-DXd arm	0.59	0.47	0.70	Beta
Proportion of Eribulin as subsequent treatment - T-DXd arm	0.21	0.17	0.26	Beta
Proportion of Paclitaxel as subsequent treatment - T-DXd arm	0.48	0.38	0.57	Beta
Proportion of Vinorelbine as subsequent treatment - T-DXd arm	0.13	0.10	0.15	Beta
Proportion of Capecitabine as	0.29	0.23	0.35	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
subsequent treatment - Comp arm				
Proportion of Eribulin as subsequent treatment - Comp arm	0.31	0.25	0.37	Beta
Proportion of Paclitaxel as subsequent treatment - Comp arm	0.33	0.26	0.40	Beta
Proportion of Vinorelbine as subsequent treatment - Comp arm	0.14	0.11	0.16	Beta
Proportion of Trastuzumab deruxtecan as subsequent treatment - Comp arm	0.89	0.66	0.99	Beta

*For all distributions: please see the tab 'Parameters' of the CEM, row 1210 to 1293.

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

The clinical assessment is based on the DB06 trial, a head-to-head study of T-DXd versus investigator's choice chemotherapy (ICC), which is the relevant comparator for Danish clinical practice. Even though a systematic literature was not needed to inform the head-to-head (H2H) comparison, a systematic literature search was conducted on September 13, 2023 to confirm that no additional literature would add data to the H2H comparison. As the search was more than 12 months old, the search (of Embase, Medline and Cochrane) was repeated on February 21st, 2025, however no additional studies relevant for the scope of this assessment were identified. Thus, a comprehensive description of the literature searched is not described below.

Table 61 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Abbreviations:

Table 62 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
e.g. EMA website	N/A	N/A	N/A

Abbreviations:

Table 63 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A

H.1.1 Search strategies

Table 64 of search strategy table for [name of database]

No.	Query	Results
#1	N/A	N/A
#2		
#3		
#4		
#5		
#6		
#7		
#8		
#9		
#10		

H.1.2 Systematic selection of studies

Table 65 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	N/A	N/A	N/A
Intervention	N/A	N/A	N/A
Comparators	N/A	N/A	N/A
Outcomes	N/A	N/A	N/A
Study design/publication type	N/A	N/A	N/A
Language restrictions	N/A	N/A	N/A

Table 66 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	N/A	N/A	N/A	N/A	N/A	N/A
Study 2	N/A	N/A	N/A	N/A	N/A	N/A

H.1.3 Excluded full text references

N/A

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

N/A.

Table 67 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Abbreviations:

Table 68 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
e.g. EMA website	N/A	N/A	N/A

Abbreviations:

Table 69 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A

I.1.1 Search strategies

Table 70 of search strategy table for [name of database]

No.	Query	Results
#1	N/A	N/A

No.	Query	Results
#2		
#3		
#4		
#5		
#6		
#7		
#8		
#9		
#10		

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

N/A.

J.1.1 Example: Systematic search for […]

Table 71 Sources included in the search

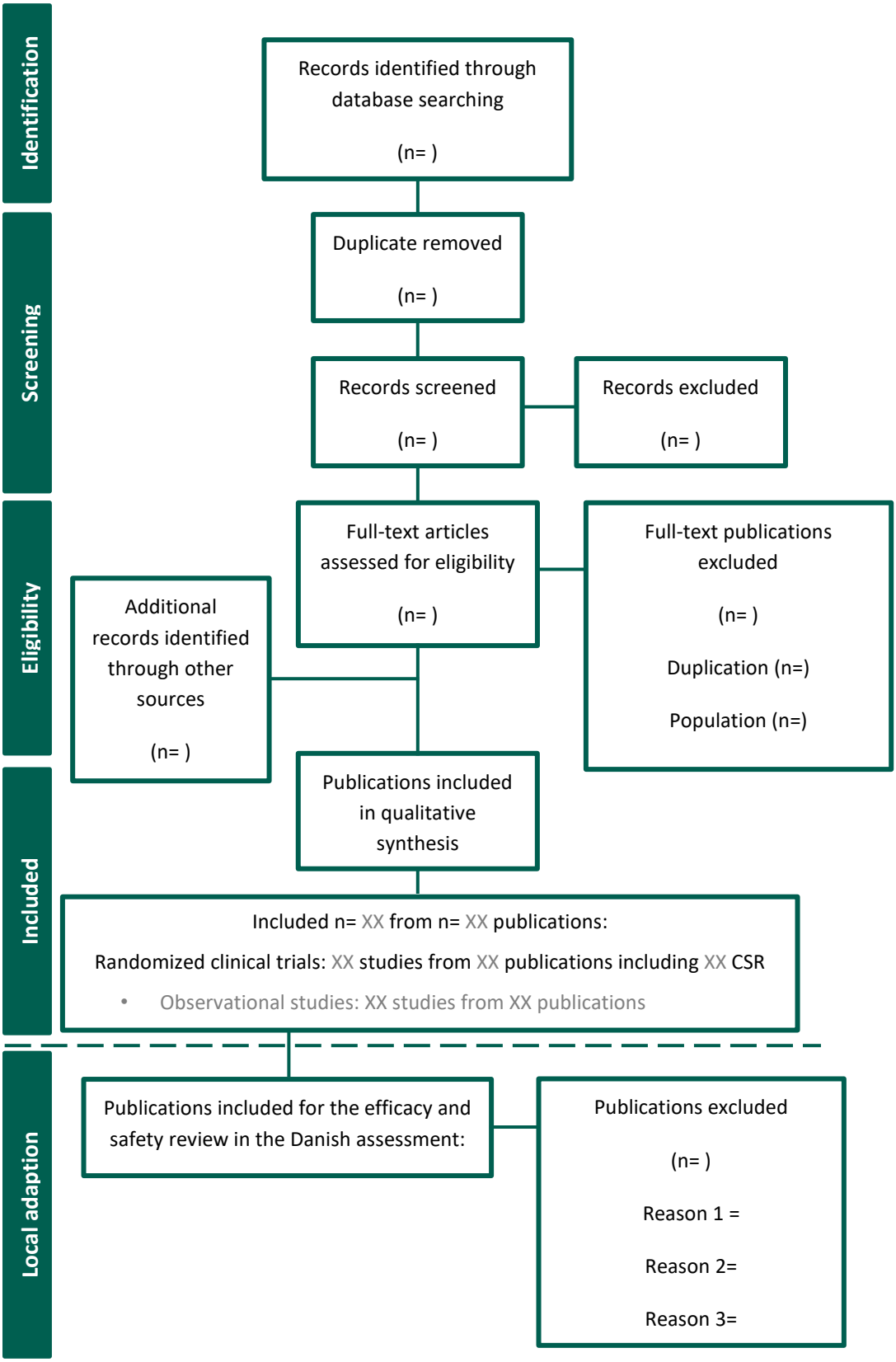
Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A		
Medline	N/A		
CENTRAL	N/A		

J.1.2 Example: Targeted literature search for [estimates]

Table 72 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
N/A			

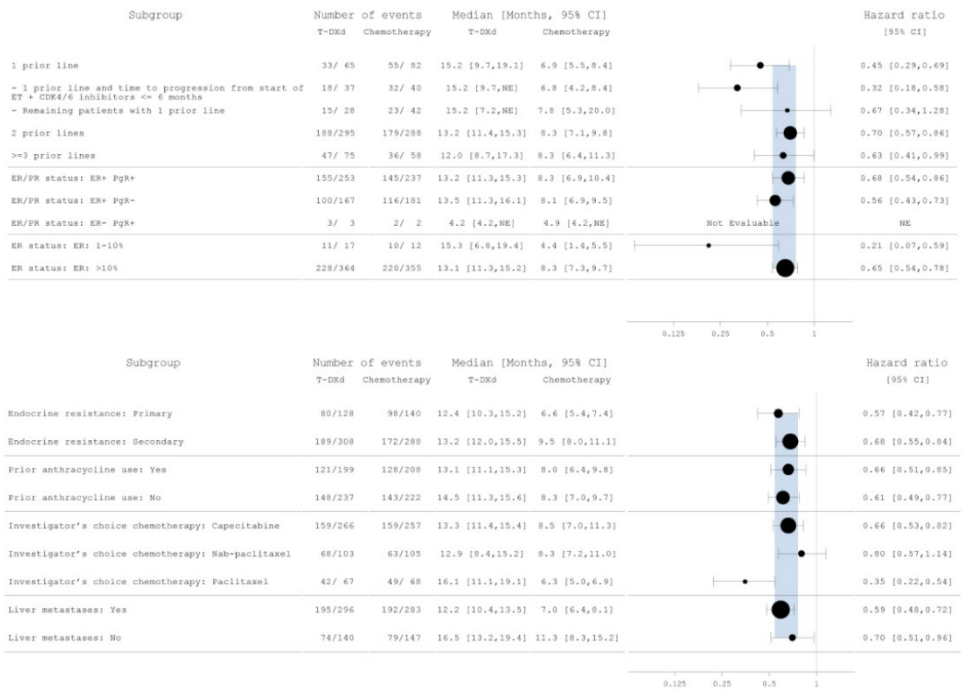
Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



Appendix K. Additional tables and figures to the dossier

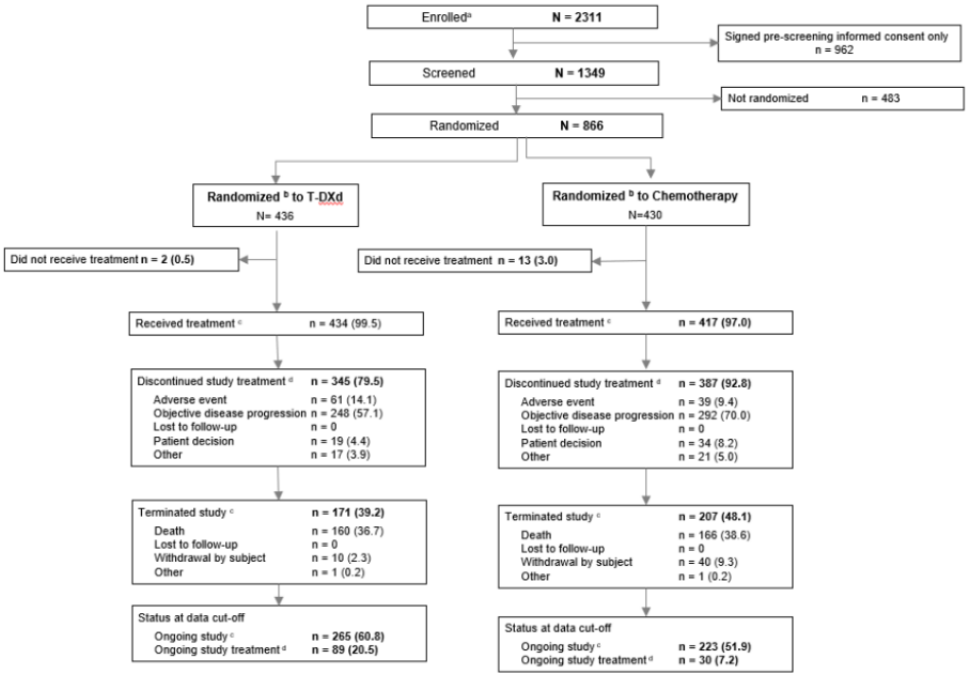
K.1 Forest plots

Figure 45 Forest plot, PFS (BICR), by subgroups related to prior endocrine treatments for mBC (ITT population IA1)



K.2 Consort flow diagram

Figure 46 Consort diagram, patient disposition (IA1).



K.3 PFS and OS at specific time points

The following Figure 47, Figure 48, Figure 49 shows the PFS and OS rated at a specific time point.

Figure 47 Progression-free-survival by BICR at specific time points - Full Analysis Set, DCO 18-MAR-2024

	T-DXd N=436	Chemotherapy N=430
PFS Rate at 3 Months[a]	88.8	80.3
95% CI	[85.4 , 91.4]	[76.1 , 83.9]
PFS Rate at 6 Months[a]	78.4	63.1
95% CI	[74.2 , 82.1]	[58.0 , 67.7]
PFS Rate at 9 Months[a]	66.4	45.1
95% CI	[61.6 , 70.8]	[39.9 , 50.3]
PFS Rate at 12 Months[a]	54.7	36.9
95% CI	[49.6 , 59.4]	[31.7 , 42.0]
PFS Rate at 18 Months[a]	35.1	23.6
95% CI	[30.1 , 40.3]	[18.8 , 28.7]
PFS Rate at 24 Months[a]	26.0	15.3
95% CI	[20.7 , 31.5]	[10.6 , 20.8]
PFS Rate at 36 Months[a]	9.5	12.7
95% CI	[1.3 , 27.6]	[7.3 , 19.7]
PFS Rate at 48 Months[a]	9.5	12.7
95% CI	[1.3 , 27.6]	[7.3 , 19.7]

[a] Estimate and CI for PFS rate at the specified time point are from Kaplan-Meier analysis.

Figure 48 Progression-free survival based on investigator assessment - ITT Analysis Set, DCO 24-MAR-2025

	T-DXd (N=436)	Chemotherapy (N=430)
At 9 months [d]	67.4	38.0
95% CI	[62.7 , 71.6]	[33.1 , 42.8]
At 12 months [d]	52.8	26.8
95% CI	[47.9 , 57.4]	[22.4 , 31.4]
At 18 months [d]	30.8	14.6
95% CI	[26.4 , 35.2]	[11.2 , 18.5]
At 24 months [d]	20.9	6.7
95% CI	[17.1 , 25.0]	[4.4 , 9.7]
At 36 months [d]	9.4	2.8
95% CI	[6.3 , 13.2]	[1.3 , 5.3]

Figure 49 Overall survival - ITT Analysis Set, DCO 24-MAR-2025

K.4 PFS and OS for subpopulations

T-DXd by blinded independent central review (BICR) compared with ICC in HER2-ultralow patients (HR: 0.78; [95% CI: 0.50, 1.21]). Median PFS was 13.2 months (95% CI: 9.8, 17.5) in patients treated with T-DXd and 8.5 months (95% CI: 5.8, 15.2) in patients treated with ICC (Figure 50). Number of events were 44 (57.9%) for the T-DXd arm and 39 (51.3%) for the ICC arm (2).

Table 73 PFS for HER2-ultralow population

	T-DXd (n=76)	ICC (n=354)
N of events (%)	44 (57.9)	39 (51.3%)
Median PFS (m)	13.2 [9.8, 17.5]	8.5 [5.8, 15.2]

The second interim OS analysis (with [redacted] data maturity) for the HER2-low population found that T-DXd-treated patients had a positive OS trend vs the ICC arm (Figure 51). [redacted] ([redacted]) of patients died in the T-DXd arm vs [redacted] of patients died in the ICC arm. Median OS was [redacted] in the T-DXd arm and [redacted] in the ICC arm [redacted] See Table 74 (3).

Table 74 OS in HER2-low population

	T-DXd (n=359)	ICC (n=354)
N of events (%)	[redacted]	[redacted]
Median OS (m)	[redacted]	[redacted]
Median FU (all patients, m)	[redacted]	[redacted]
% alive 12m (95% CI)	[redacted]	[redacted]
% alive 18m (95% CI)	[redacted]	[redacted]

The second interim OS analysis (with [redacted] data maturity) for the HER2-ultralow population found that T-DXd-treated patients had a positive OS trend vs the ICC arm (Figure 52). [redacted] of patients died in the T-DXd arm vs [redacted] of patients died in the ICC arm. Median OS was [redacted] in the T-DXd arm and [redacted] in the ICC arm [redacted] See Table 75 OS in HER2-ultralow population (3).

Table 75 OS in HER2-ultralow population

	T-DXd (n=359)	ICC (n=354)
N of events (%)	[redacted]	[redacted]
Median OS (m)	[redacted]	[redacted]
Median FU (all patients, m)	[redacted]	[redacted]
% alive 12m (95% CI)	[redacted]	[redacted]
% alive 18m (95% CI)	[redacted]	[redacted]

Figure 50 PFS by BICR for T-DXd versus ICC in DB06, Kaplan-Meier plot (HER2-ultralow population) based on IA1 (data cutoff: March 2024)

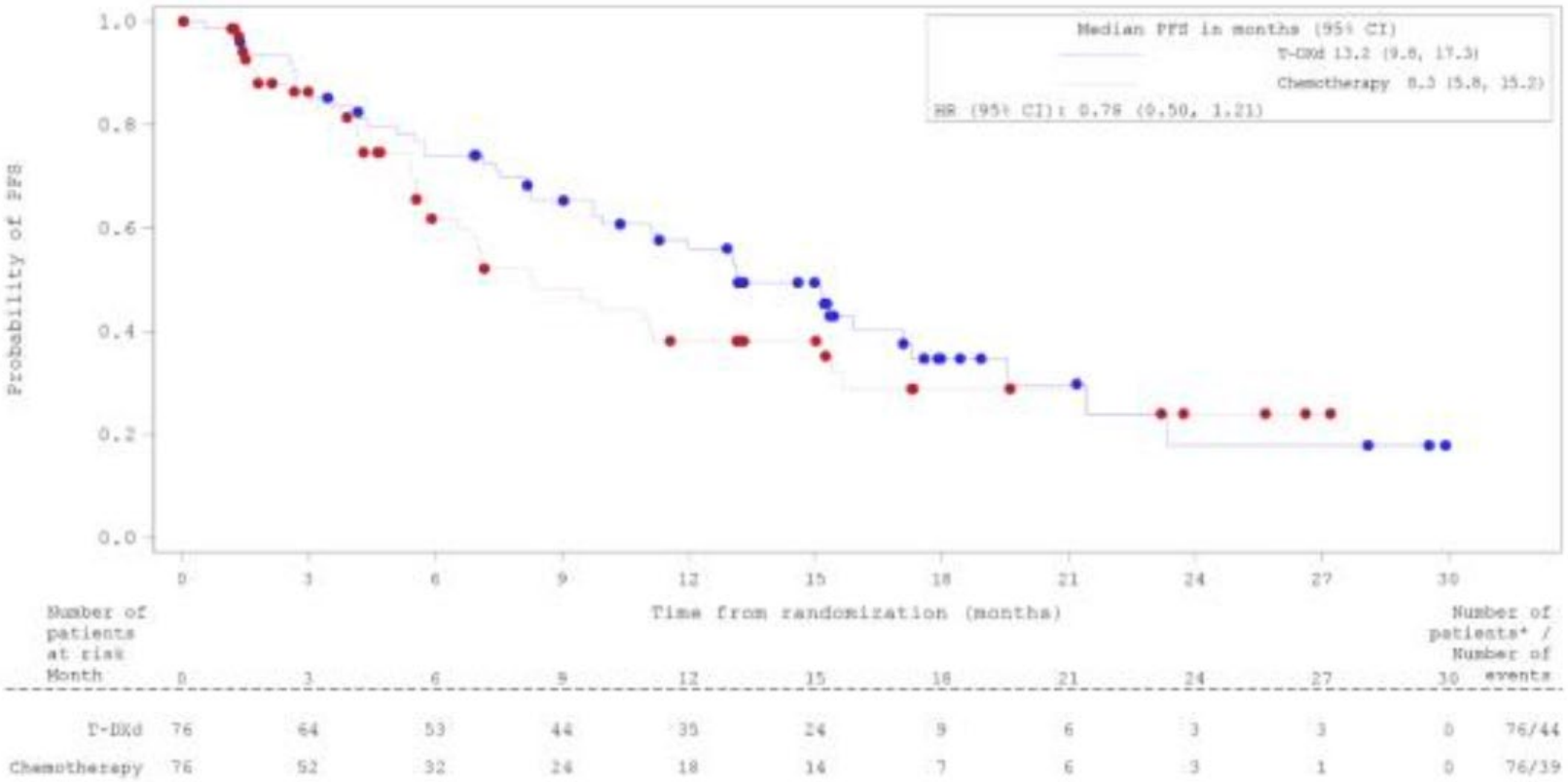


Figure 51 OS for the T-DXd versus ICC in DB06, Kaplan-Meier plot (HER2-low population) based on IA2 (data cutoff: March 2025)

Figure 52 OS for the T-DXd versus ICC in DB06, Kaplan-Meier plot (HER2-ultralowlow population) based on IA2 (data cutoff: March 2025)

K.5 Subsequent treatment

Table 76 The proportion of patients receiving a treatment option in both T-DXd and ICC arm

Reference treatment	Proportion of subsequent treatments – T-DXd arm	Proportion of subsequent treatments – ICC arm
Capacitabine	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]

K.6 Missing data for HRQoL

A display of the missing data pattern per patient and visit for the EORTC QLQ-C30, EORTC QLQ-B45, and EQ-5D-5L questionnaires are presented in Figure 53, Figure 54 and Figure 55. Despite the missing values observed at baseline, we see that the missing data pattern proceeds to be relatively monotone over time, i.e., we observe more missing questionnaires as time into the study progresses. This is to be expected in oncology studies in the palliative setting, as the response rate based on the number of subjects randomized declines over time (e.g., due to the reason of death).

Figure 53 Missing data pattern over time for HRQoL – ITT population, EORTC QLQ-C30

Figure 54 Missing data pattern over time for HRQoL – ITT population, EORTC QLQ-BR45

Figure 55 Missing data pattern over time for HRQoL – ITT population, EQ-5D-5L

K.7 Health state scores over time

Figure 56 EQ-5D-5L UK Health State Index Scores Over Time - Full Analysis Set

Figure 57 EQ-5D VAS score over time - Full Analysis Set

K.8 Relative dose intensity

Table 74 Delays, dose reductions and drug interruptions, Safety analysis set

a: Reasons are not mutually exclusive for patients with multiple delays / reductions / interruptions although will be counted only once percategory.
b: Drug interruptions (evaluated for capecitabine only) exclude any interruptions where the patient forgot to take their dose (only if single non-consecutive missed doses). Two or more consecutive missed dose will be considered a drug interruption.
NA = not applicable. T-DXd = trastuzumab deruxtecan.

Table 75 Dose intensity of study treatments Safety analysis set

[redacted]

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through treatment discontinuation.

Max = maximum. Min = minimum. SD = Standard deviation. Q1 = 1st quartile. Q3 = 3rd quartile. T-DXd = trastuzumab deruxtecan.

K.9 Post anti-cancer systemic treatment

The following Figure 58 shows post anti-cancer systemic treatment after disease progression in the ITT population.

Figure 58 Post anti-cancer systemic treatment after disease progression – ITT

[redacted]

[redacted]

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