Medicinrådet

Bilag til Medicinrådets vurdering af trastuzumab deruxtecan til behandling af HER2-positiv adenokarcinom i mavesæk eller mavemund

Til patienter med lokalavanceret, ikke-resektabel eller metastatisk adenokarcinom, og som tidligere har fået trastuzumab

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

07.08.2026

Notat vedr. Medicinrådets udkast til vurderingsrapport for Enhertu (trastuzumab deruxtecan, T-DXd) til behandling af HER2-positiv adenokarcinom i mavesæk og mavemund til patienter med lokalavanceret, ikke-resektabel eller metastatisk adenokarcinom og som tidligere har fået trastuzumab.

AZ/DS vil gerne takke Medicinrådets sekretariat for vurderingen af Enhertu (T-DXd) samt muligheden for at kommentere på vurderingsrapporten inden den endelige beslutning i Medicinrådet.

Ansøgningen på T-DXd til behandlingen af kræft i mavesæk og mavemundblev indsendt på opfordring fra medlemmer af Medicinrådet og de regionale lægemiddelkomitéer som reaktion på en obseret stigning i ansøgninger om individuelt tilskud til T-DXd. I alt har [redacted] patienter modtaget behandling med T-DXd til kræft i mavesæk og mavemundsiden 2022 hvor Destiny-gastric02 studiet blev godkendt af EMA. Det er værd at bemærke, at en betydelig andel af disse patienter modtog T-DXd i anden eller en senere behandlingslinje, hvilket indikerer, at klinikere aktivt søgte adgang til T-DXd for udvalgte patienter, , der havde progredieret efter trastuzumab-baseret behandling i første linje. Dette understreger et uafdækkede medicinske behov til denne patientgruppe og bekræfter, at T-DXd anses som klinisk relevant og værdifuld behandling i nuværende dansk klinisk praksis.

AZ/DS bemærker, at vurderingsrapporten konsekvent identificerer en klinisk meningsfuld fordel ved T-DXd på tværs af effektmål, herunder våde progressionsfri overlevelse (PFS) og samlet overlevelse (OS). Endvidere peger behandlingseffektens retning konsistent i samme retning på tværs af alle de analytiske tilgange, som Medicinrådet har undersøgt. Samtidig vurderer vi, at den nuværende vurdering muligvis lægger uforholdsmæssig stor vægt på metodologiske usikkerheder i forhold til deres relevans for beslutningstagning. Dette gælder især for proportional hazards-antagelsen og fortolkningen af den indirekte sammenlignling. Vi vurderer, at scenarie 1 er den mest klinisk plausible analyse for økonomisk beslutningstagning.

Indirekte sammenligning
Medicinrådets sekretariat vurderer, at den indirekte sammenligning mellem Destiny-Gastric04 (DG04) og RAINBOW er behæftet med betydelige usikkerheder, da studierne er gennemført med 10 års mellemrum og adskiller sig med hensyn til tidligere behandling, HER2-selektion samt andre sygdomskarakteristika såsom histologi og tumorlokation. AZ/DS anerkende disse baseline-forskelle mellem DG04 og RAINBOW, men vurderer, at dette ikke udelukker muligheden for en indirekte sammenligning af behandlingseffekten. Den tilgængelige evidens viser ikke, at disse forskelle skævvrider den relative sammenligning til fordel for T-DXd. Tvlrtimod kan visse aspekter få komparatorarmen (PTX-baseret behandling) til at præsentere bedre i den indirekte sammenligning end historisk observeret.

Medicinrådet fremhæver, at resultaterne for patienter, der behandles i nuværende dansk praksis, kan være bedre end dem, der blev observeret i PTX-armen af RAINBOW-studiet. Dette afspejler fremskrift inden for tidligere behandlingslinjer. AZ/DS er enige i, at dette påvirker den absolutte prognose. Vurderingsrapporten bemærker dog også, at disse ændringer ikke nødvendigvis forventes at ændre den relative behandlingseffekt mellem RAM+PTX og PTX. Efter vores opfattelse er denne skelnen vigtig, for selvom de absolutte resultater muligvis kan være forbedret over tid de seneste 10 år, betyder det ikke, at den relative effekt, der anvendes til at udlede komparatoren, er upassende. Den resterende usikkerhed bør derfor primært fortolkes som usikkerhed ved overførbarheden af absolutte resultater fremfor bevis for at komparatorarmen er upålidelig.

Overordnet indikerer overvejelserne ikke, at resultaterne i RAINBOW er uanvendelige i dansk klinisk kontekst. Tværtimod antyder de, at den relative effekt, der anvendes den indirekte sammenligning, fortsat udgør et rimeligt og potentielt konservativt grundlag for sammenling. Komparatoren, der anvendes i Danmark, er desuden hovedsageligt den samme, som da RAINBOW-studiet startede i 2010. Dette indikerer, at behandlingslandskabet for kræft i mavesæk og mavemund ikke nødvendigvis har ændret sig væsentligt, og understreger tværtimod det fortsatte, udækkede medicinske behov for nye og mere effektive behandlingsmuligheder.

Det er vigtigt at bemærke, at vurderingsrapporten konkluderer, at ingen alternativ tilgang kan betragtes som entydigt mere valid end den metode, der er anvendt i ansøgningen. Selvom antagelserne bag den indirekte sammenligning bør

anerkendes, medfører alene eksistensen af usikkerhed ikke, at alternative metoder ville give mere pålidelige estimater af komparativ effektivitet.

Antagelse om proportional hazard
Medicinrådet anser PH-antagelsen for at være usikker, især i RAINBOW, baseret på Schoenfeld residual- og log-kumulative hazard-vurderinger og argumenterer for, at dette svækker tilliden til den hazard ratio-baserede (HR) indirekte sammenligning og tilføjer væsentlig usikkerhed til den modellerede sammenligning af T-DXd versus paclitaxel.

AZ/DS er generelt enige i, at PH-antagelsen var usikker baseret på de præsenterede grafer, men vil præcisere, at PH ikke var en central modelleringsantagelse for sammenligningen af T-DXd versus SoC i den indsendte økonomiske model. Her blev T-DXd og SoC nemlig modelleret separat snarere end gennem en konstant HR-tilgang. For RAM+PTX versus PTX blev PH-antagelsen kun anvendt for PFS og TTD som en pragmatisk modelleringsmetode. For disse endepunkter blev de valgte ekstrapolationer samlet set anset for passende og havde begrænset indflydelse på resultaterne. Dette er også i overensstemmelse med Medicinrådets vurdering, der angiver, at de resulterende kurver ikke blev anset for væsentligt at påvirke resultaterne. For OS blev PH ikke antaget for hele tidsperioden; i stedet blev en hazard-justering anvendt således, at hazarder for RAM+PTX og PTX blev antaget at være ens fra uge 96 og fremefter. Denne tilgang blev også anvendt af Medicinrådet i rapporten. På dette grundlag anser AZ/DS ikke usikkerhed omkring PH for at være en central, resterende usikkerhed i det omfang, der er antydet i vurderingen.

Ekstrapolering af samlet overlevelse
AZ/DS bemærker, at de indsende OS-ekstrapoleringer udelukkende blev vurderet for klinisk plausibilitet i ansøgningen, herunder forholdet mellem PFS, OS og tid brugt i post-progressive stadie. Selvom Medicinrådet angiver at dets foretrukne fremskrivninger er klinisk plausible, beskrives det ikke klart det specifikke kliniske rationale, der gør disse fremskrivninger mere plausible end de indsendte. Medicinrådet konkluderer at både den generaliserede gamma og gamma fremskrivning kan betragtes som klinisk plausible og præsenterer derfor to scenarier i vurderingsrapporten.

Af de to scenarer vurderer AZ/DS, at scenarie 1 fremstår som værende mere klinisk plausibelt. Den generaliserede gamma fremskrivning følger en hazard-form, der ligner den log-normale (AZ/DS reference case) fremskrivning og er mere konsistent med både det observerede sygdomsforløb og behandlingseffekten af T-DXd. Den generaliserede gamma fremskrivning er tilstrækkelig fleksibel til at fange det observerede OS-mønster for T-DXd, nemlig den startende høje risiko efterfuldt af en udfladende hazard over tid, hvilket antyder, at nogle patienter kan opleve en længerevarig fordel ved brug af T-DXd. Derimod anses gamma fremskrivningen i scenarie 2 som mindre kliniske plausibel givet den stigende hazard over tid. I kombination med gamma fremskrivningen for komparatorarmen kan denne tilgang undervurdere OS-forskellen mellem T-DXd og komparator ved at påtvinge en hurtigere faldende langtidsoverlevelse for T-DXd. Fra et klinisk perspektiv er det tvivlsomt, at scenarie 2 antager en mere begrænset forskel i post-progressions overlevelse mellem behandlingsarmene, fordi den ikke kun påvirkes af den initiale behandlingseffekt, men også af tilgængeligheden og brugen af efterfølgende behandling. Patienter, der modtager T-DXd, kan opnå fordele ud over behandlingsophør, og der er større sandsynlighed for at de kvalificerer sig til efterfølgende behandling. Dette stemmer godt overens med Medicinrådets vurdering af at andelen af patienter, der modtager efterfølgende behandling, kan variere mellem behandlingsarmene og kan være lavere for komparator, da disse patienter hyppigere er påvirket af deres behandling og er mindre tilbøjelige til at modtage behandling i senere linjer. Desuden bemærker Medicinrådet, at behandlingsresultater i anden linje er forbedret de seneste år på grund af nye behandlingsmuligheder i tidligere linjer. Samlet set understøtter det forventningen om at T-DXd resulterer i fordelen ud over progression og forbedret post-progression overlevelse, hvilket gør scenarie 2 mindre klinisk plausibelt og afspejler en mere konservativ analysetilgang.

Afslutningsvis vil AZ/DS gerne fremhæve det betydelige udækkede medicinske behov til behandling af HER2-positiv kræft i mavesæk og mavemund samt den kliniske fordel ved brug af T-DXd, hvilken demonstreres af den store interesse fra klinikere for at behandling patienter med T-DXd siden 2022. Derudover er det værd at bemærke, at T-DXd til denne indikation har fået en national anbefaling i Sverige og Norge.

Med Venlig Hilsen,

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16.10.2026

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	28.10.2026
Leverandør	AstraZeneca
Lægemiddel	Enhertu (trastuzumab deruxtecan)
Ansøgt indikation	Behandling af voksne patienter med fremskreden ikke småcellet lungekræft (NSCLC), hvis tumorer har en aktiverende HER2 (ERBB2)-mutation, og som har behov for systemisk behandling efter platinbaseret kemoterapi med eller uden immunterapi. + Behandling af voksne patienter med fremskredent HER2- positivt adenokarcinom i ventriklen eller den gastroøsofageale overgang (GEJ), som tidligere har fået et trastuzumab-baseret regime
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Enhertu (trastuzumab deruxtecan):

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakning)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Enhertu	100 mg (1 stk.)	10.628,99	[redacted]	[redacted]

Aftaleforhold

Amgros har en eksisterende aftale på Enhertu som gælder til den 31.03.2027. Ved anbefaling af disse to indikationer, vil der blive indgået en ny aftale med start [redacted].

[redacted]

Information fra forhandling

[redacted]

Konkurrencesituationen – lungekræft

Førstelinjebehandling af patienter med ikke-planocellulær NSCLC er enten en PD-(L)1-hæmmer som monoterapi eller i kombination med platinbaseret kemoterapi. Efterfølgende tilbydes platinbaseret kemoterapi og/eller docetaxel afhængigt af førstelinjebehandlingen. På nuværende tidspunkt er der ingen godkendt standardbehandling målrettet patienter med HER2-muteret NSCLC.

Enhertu er anbefalet af Medicinrådet til andenlinjebehandling af metastatisk HER2+ brystkræft.

Tabel 2 viser lægemiddeludgifter til behandling med Enhertu for et gennemsnitlig behandlingsforløb på ca. 47 uger svarende til 0,9 år, jf. Medicinrådets vurdering af trastuzumab deruxtecan til behandling af fremskreden HER2-muteret NSCLC efter platinbaseret kemoterapi med eller uden immunterapi.

Tabel 2: Lægemiddeludgifter pr. patient – lungekræft

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 47 uger (SAIP, DKK)
Enhertu	100 mg (1 stk.)	5,4 mg/kg* hver 3. uge, i.v.	[redacted]	[redacted]

*Kropsvægt for gennemsnitspatient er 74,2 kg jf. Medicinrådets vurdering af trastuzumab deruxtecan til behandling af fremskreden HER2-muteret NSCLC efter platinbaseret kemoterapi med eller uden immunterapi.

Konkurrencesituationen – kræft i mavesæk eller mavemund

Den nuværende behandling er kemoterapi – enten et taxan (paclitaxel eller docetaxel) eller irinotecan. Enhertu er tidligere anbefalet til flere indikationer indenfor brystkræft.

Tabel 3 viser lægemiddeludgiften ved behandling med Enhertu for et gennemsnitligt behandlingsforløb på [redacted]. Lægemiddeludgifter til kemoterapi er ikke medtaget i beregningen nedenfor, da den udgør mindre end 10.000 DKK for et års behandling.

Tabel 3: Lægemiddeludgifter pr. patient – kræft i mavesæk eller mavemund

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsforløb (SAIP, DKK)
Enhertu	100 mg (1 stk.)	6,4 mg/kg* hver 3. uge, i.v.	[redacted]	[redacted]

*Patientvægt 67,7 kg. Jf. Medicinrådets vurdering af trastuzumab deruxtecan til behandling af HER2-positiv adenokarcinom i mavesæk eller mavemund

[redacted]

[redacted]

[redacted]

[redacted]

Status fra andre lande – lungekræft

Tabel 5: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til vurdering
England	Under vurdering	Link til status
Sverige	Anbefalet	Link til vurdering

Status fra andre lande – kræft i mavesæk og mavemund

Tabel 6: Status fra andre lande

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

Opsummering

Amgros har en eksisterende aftale på Enhertu. Anbefales Enhertu til lungekræft på baggrund af den foreslåede alternative aftale, kan aftalen tidligst starte den [redacted]

[redacted]

Application for assessment of Enhertu® (trastuzumab deruxtecan) for the treatment of HER2-positive gastric cancer or gastro-oesophageal junction cancer in patients who have previously received trastuzumab

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[redacted]

Abbreviations

Table 1. Abbreviation list

Abbreviation	Description
AE	Adverse event
AESI	Adverse event of special interest
AIP	Pharmacy purchasing price (Apotekernes indkøbspris)
ALP	Alkaline phosphatase
ASCO	American Society of Clinical Oncology
BCA	Bias-corrected and accelerated
BIC	Bayesian information criterion
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CPS	Combined positive score
CR	Complete response
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DCO	Data cut-off
DCR	Disease control rate
DEGC	Dansk EsophagoGastrisk Cancer Gruppe
DG01	DESTINY-Gastric01 study
DG02	DESTINY-Gastric02 study
DG04	DESTINY-Gastric04 study
DKK	Danish Kroner
DNA	Deoxyribonucleic acid
DMC	Danish Medicines council
DRG	Diagnosis-related group
DSU	Decision Support Unit
DTX	Docetaxel
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
EQ-VAS	EuroQol visual analogue scale
ESMO	European Society for Medical Oncology
FACT-Ga	Functional Assessment of Cancer Therapy – Gastric
FAS	Full analysis set
FE	Fixed effect
FOLFIRI	folinic acid (leucovorin/calcium folinate) + fluorouracil (5-FU) + irinotecan
GC	Gastric cancer
GEJ	Gastroesophageal junction
GEJC	Gastroesophageal junction cancer
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment

Abbreviation	Description
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IPD	Individual patient data
IQR	Interquartile range
ISH	In situ hybridization
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
JCA	Joint European assessment
JNHB	Joint Nordic assessment
KM	Kaplan-Meier
LMM	Linear mixed model
LSM	Least-squares mean
LV	Left ventricle
mBC	Metastatic breast cancer
MMR	Mismatch repair
MSI-H	Microsatellite instability-high
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not estimated
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reached or not reported
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressed disease
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PGI-C	Patient global impression of change
PGI-S	Patient global impression of severity
PH	Proportional hazards
PICO(S)	Population, intervention, comparator, outcomes, (study design)
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient Reported outcomes
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PTX	Paclitaxel
QALY	Quality-adjusted life year
QoL	Quality of life
RAM	Ramucirumab
RCT	Randomized controlled trial
RDI	Relative dose intensity

Abbreviation	Description
RECIST	Response Evaluation Criteria in Solid Tumors
RPSFTM	Rank-preserving structural failure time model
RWE	Real-world evidence
SAE	Serious adverse event
SAS	Safety analysis set
SD	Stable disease
SE	Standard error
SG	Standard gamble
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment-emergent adverse event
TNM	Tumour-Node-Metastasis
TSD	Technical support document
TTD	Time to treatment discontinuation
UICC / AJCC	Union for International Cancer Control / American Joint Committee on Cancer
VAS	Visual analogue scale

1. Information on the drug

Table 2. Information about Enhertu®

Drug information	
Trade name	Enhertu
Generic name	Trastuzumab deruxtecan
Indication as formulated by the European Medicines Agency (EMA)	Enhertu as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive GC/GEJ cancer who have received a prior trastuzumab based regimen.
Marketing Authorization Holder in Denmark	Daiichi Sankyo Europe GmbH Zielstattstrasse 48 81379 München Tyskland.
ATC code	L01FD04
Combination therapy and/or concurrent treatment	No
Expected date of EU approval (marketing authorisation)	Positive opinion issued 10 November 2022 and EMA approval was granted 12 December 2022 based on DESTINY-Gastric02 supported by DESTINY-Gastric01 (renewal 21 November 2025 based on DESTINY-Gastric04)
Has the drug received a conditional marketing authorisation?	No
Has the drug been in 'accelerated' assessment' at EMA?	No
Does the drug have orphan drug designation?	No
Other indications approved by the EMA	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/ultralow breast cancer HR-positive, HER2-low/ultralow: after ≥1 endocrine therapy in metastatic setting and not suitable for further endocrine therapy. HER2-low: after prior metastatic chemotherapy or recurrence during/within 6 months of adjuvant chemotherapy. Non-small cell lung cancer (NSCLC) Enhertu monotherapy for adults with advanced NSCLC with activating HER2 (ERBB2) mutation, requiring systemic therapy after platinum-based chemotherapy ± immunotherapy.
Other indications that have been evaluated by the Danish Medicines Council	Yes: All breast cancer indications Ongoing assessments: NSCLC
Joint Nordic Assessment (JNHB): Is current treatment practice comparable across the Nordic countries (DK, FI, IS, NO, SE)?	No—joint JNHB is not appropriate because treatment practices differ between countries.
Joint Nordic Assessment (JNHB): Is the drug suitable for a joint Nordic assessment?	No, treatment practices differ between countries. T-DXd is recommended for the treatment of HER2-positive metastatic gastric and GEJ cancer in Sweden and HTA already ongoing in Norway.
Has a joint European assessment (JCA) been carried out via the EU HTA Regulation?	No
Delivery	BEGR
Packaging – types, sizes/number of units and concentrations	Strength: 100 mg Pack size: 1 vial of powder for concentrate

Abbreviations are defined in the list of Abbreviations

2. Summary table

Table 3. Summary table

Overview	
Indication relevant to the assessment	Enhertu as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive GC/GEJ cancer who have received a prior trastuzumab based regimen.
Dosage regimen and administration route	The recommended dose of T-DXd is 6.4 mg/kg body weight given as an IV infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity (1).
Comparator selection	Selected comparator for this assessment is SoC (2, 3). Second-line options in Denmark include irinotecan or taxane-based chemotherapy (DTX and PTX monotherapy, refer to section 3.2.1).
Prognosis with current standard treatment (comparator(s))	Patients with advanced or metastatic GC/GEJC have limited targeted treatment options beyond first line and prognosis remains poor. For patients diagnosed with metastatic disease, disease progression is rapid following first-line treatment: second-line median OS, 4–11 months; median PFS, 1.5–3.5 months; third-line median OS, 3–6 months; median PFS, 1.6–3.7 months (4-7). Danish real-world evidence data shows that the proportion of patients with cancer of the oesophagus, stomach, or gastric cardia who initiated an oncological, palliative treatment course and were alive 1 year after the first systemic treatment was 45.6% (95% CI: 39.5–51.7) nationwide in 2024 (8).
Type of documentation for the clinical evaluation	Simplified indirect treatment comparison
Main outcomes including at least one outcome for health-related quality of life (difference/improvement compared to comparator(s))	OS: - DG04: OS was significantly longer with T-DXd than with RAM+PTX (median, 14.7 vs. 11.0 months; HR for death (with crossover adjustment), [redacted]; 95% CI, [redacted] p value= 0.0006) (9). - RAINBOW: Median OS was significantly longer in the RAM+PTX group than in the placebo plus PTX group (median 9.6 months [95% CI 8.5–10.8] vs 7.4 months [95% CI 6.3–8.4], HR 0.807 [95% CI 0.678–0.962]; p=0.017) (10). PFS: - DG04: PFS results were also significant. T-DXd improved PFS vs RAM+PTX, with a median PFS of 6.7 months (95% CI 5.6–7.1) compared to 5.6 months (95% CI 4.9–5.8) for RAM+PTX (HR for disease progression or death, 0.74; 95% CI, 0.59 to 0.92, p= 0.0074) (11). - RAINBOW: RAM+PTX improved PFS versus PTX alone, with a median of 4.4 months (95% CI 4.2–5.3) versus 2.9 months (95% CI 2.8–3.0), yielding a HR of 0.64 (95% CI 0.54–0.75) (10). ORR: - DG04: ORR was 44.3% (95% CI 37.8–50.9) for T-DXd and 29.1% (95% CI 23.4–35.3) for the RAM+PTX (11).

	- RAINBOW: The confirmed ORR was 27.9% (95% CI 23.3–33.0) for RAM+PTX and 16.1% (95% CI 12.5–20.6) for placebo+PTX (10). HRQoL: DG04: Overall, the results of the subjects with a post-baseline EQ-5D-5L score showed that quality of life in the T-DXd arm was maintained over the course of treatment and did not deteriorate through [redacted] after which the number of subjects was too low to allow for meaningful interpretation (11).
Serious adverse events for the intervention and comparator	The three most frequent TEAEs in the T-DXd arm (DG04) were anaemia (4.9%), pneumonia (4.1%), and vomiting (3.7%); for the SoC, the three most frequent TEAEs (not specified as serious, weighted average based on the SoC treatment regimens) were neutrophil count decreased (14.09%), diarrhoea (10.16%), and anaemia (8.74%).
Type of health economic analysis	Cost-utility analysis
Health economic model	Partitioned survival model
Outcomes and sources for extrapolating patient transitions	DG04 (OS, PFS, TTD for T-DXd, HRQoL for T-DXd and SoC, the RAM+PTX arm used as reference arm for SoC, refer to section 9). RAINBOW (HR for OS and PFS: applying the HRs for RAM+PTX versus PTX from the RAINBOW study and applying them to the RAM+PTX arm in DG04 to derive PTX outcomes (a proxy for SoC))
Instrument and sources for health-related quality of life	EQ-5D-5L sourced from DG04, disutilities linked to AEs sourced from literature.
Life years gained (discounted, corrected for half-cycle and background mortality)	0.87 life years
QALYs gained (discounted, corrected for half-cycle and background mortality)	0.70 QALY
ICER (DKK/QALY) (discounted, corrected for half-cycle and background mortality)	755,582 DKK/QALY
Company's assessment of uncertainty	• Relying on an ITC is linked to uncertainty. • Based on the sensitivity analyses, variation in the utilities for the progression-free and progressed health states is a key driver of the ICER. • Scenario analyses showed that the RDI of T-DXd materially influences the ICER.

Abbreviations are defined in the list of Abbreviations

3. Patient population, intervention, choice of comparator(s) and outcome(s)

3.1 Patient population

3.1.1 The disease

Gastric and GEJ cancer

Gastric and gastroesophageal junction cancer (GC/GEJC) are classified in squamous cell carcinoma and adenocarcinoma, with adenocarcinomas being the most prevalent (12). Gastric and GEJ adenocarcinomas are aggressive cancers that represent a significant global health burden. Taken as a group, they are the fifth most common cancer and fourth leading cause of cancer deaths worldwide, with approximately 1,7 million new cases and over 769,000 deaths in 2020, accounting for 7.7% of all cancer-related deaths (13) (14). Advanced Human Epidermal Growth Factor receptor 2 (HER2)-positive GC/GEJC is a progressive disease leading to premature death and reduced quality of life (QoL) (15).

Approximately 30% of GC/GEJCs are detected at an early stage and are often asymptomatic or present with nonspecific symptoms; consequently, roughly 70% are diagnosed at an advanced stage, typically with dyspepsia, epigastric pain, early satiety, weight loss, anorexia, iron deficiency anaemia, nausea or vomiting, bleeding, gastric outlet obstruction (particularly antral/pyloric), and—specifically for GEJC—dysphagia (12, 16-20).

Risk profiles differ by anatomical site, with non-cardia- GC primarily linked to Helicobacter pylori infection and GEJC associated with obesity, high fat diets, and -gastroesophageal- reflux disease (12, 21); tobacco use, high salt intake, and heavy alcohol consumption further increase the risk (21). Similar to other Western European (WE) countries, Denmark's comparatively low H. pylori prevalence corresponds to a relatively higher incidence of GEJC (22).

Disease heterogeneity across anatomical location (GC vs GEJC), histology (e.g., Laurén intestinal/diffuse), and molecular subtype (e.g., Epstein-Barr virus-positive, microsatellite instability-high (MSI-H), chromosomal instability) necessitates accurate classification to support diagnosis, staging, outcome prediction, and treatment selection. Danish national guidelines classify upper gastrointestinal tumours per World Health Organisation classification of Digestive System Tumours and stage using Union for International Cancer Control (UICC) / American Joint Committee on Cancer (AJCC) Tumour–Node–Metastasis (TNM) (8th edition), staged as GC or oesophageal cancer based on tumour epicentre relative to the cardia (Siewert I-III) (23).

Diagnosis

Diagnosis typically involves endoscopy with biopsy, followed by imaging studies such as computed tomography (CT); positron emission tomography (PET) scans are also recommended for staging (24).

HER2 testing is recommended for all patients with inoperable locally advanced, recurrent, or metastatic GC/GEJC to determine eligibility for first-line HER2-targeted therapy. This is typically done through immunohistochemistry (IHC) and/or in situ hybridization (ISH) on tumour biopsy samples (24). Between 10% and 20% of metastatic gastric/GEJ tumours exhibit HER2 overexpression, with higher prevalence in GEJC and intestinal GC type (25). Other prognostic biomarkers that are recommended to be tested include programmed death-ligand 1 (PD-L1) expression, MSI-H/mismatch repair proteins (MMR) (15, 24), and Claudin18.2 (26). Both HER2 testing, PDL-1 and MSI-H/MMR testing is established in Denmark (15).

Prognosis

Outcomes in GC/GEJCs are heterogeneous, with stage at diagnosis being a key determinant of prognosis. Among patients treated with curative intent, 1-year survival after initiation of preoperative oncologic therapy was 81.2% (8). However, in Denmark, only approximately 30% of GC/GEJC patients receive curative intent surgery (8).

Prognosis for metastatic GC/GEJC remains poor and treatment is often palliative (15). Among patients with cancer of the oesophagus, stomach, or gastric cardia who initiated a palliative oncological treatment course, 45.6% (95% confidence interval (CI), 39.5–51.7) were alive 1 year after first systemic therapy (8). Within this population, outcomes differ by disease stage please see figure: OS for the GC patients; intestinal (A) and diffuse (B) in Kempf et al. (27): among patients treated with palliative intent, overall survival (OS) declines with advancing stage for both intestinal and diffuse histological subtypes (27).

Among patients receiving palliative care (chemotherapy or best supportive care (BSC)), chemotherapy was associated with a significantly lower hazard of death compared with no chemotherapy (hazard ratio [HR] 0.36; 95% CI 0.31–0.41; p<0.001) (27). While patients receiving chemotherapy showed better OS as reflected by the HR, observed differences may partly reflect baseline characteristics: individuals eligible for chemotherapy often differ from those receiving BSC in performance status (PS), comorbidities, and tumour features. Thus, although OS remains poor in this setting, outcomes vary across subgroups according to receipt of systemic therapy, which generally requires patients to be sufficiently fit. This pattern is consistent with the relative-survival estimates reported by Hemminki et al (28), which show increases in younger age groups, and a smaller or no increase in the oldest group. Poorer survival among older patients is attributable to less intensive diagnostic work-up leading to more advanced stage at presentation, which limits treatment options, compounded by a higher burden of comorbidities (28).

3.1.2 Selected patient population

The Danish patient population eligible for treatment with trastuzumab deruxtecan (T-DXd) is aligned with the European Medicines Agency (EMA)-indication, i.e. for patients with advanced HER2-positive GC/GEJC who have received a prior trastuzumab-based regimen.

No additional restrictions to the EMA-indicated population were applied, as clinical experts confirmed that the EMA label corresponds to Danish clinical practice (refer to section 6.1.3).

Number of patients eligible for treatment with T-DXd

In 2024, 310 new cases of gastric and 643 of GEJ adenocarcinoma were diagnosed in Denmark 2024 (8). Of these cases, approximately 40% were diagnosed with stage IV disease (Table 4). Patient selection for T-DXd relies on HER2 status. Clinical experts confirmed that HER2 testing uptake is effectively 100% in routine practice, ensuring that all potentially eligible patients are identified consistent with Danish clinical practice (2, 3, 23). For this assessment, a HER2-positivity rate of 20% was assumed, in line with the previous statement from the Danish Medicines Council (DMC) (29). Resulting in 75 HER2-positive stage IV cases annually.

In the first-line setting, it was assumed that most HER2-positive patients initiate HER2-targeted therapy (trastuzumab), with fewer than 5% not starting treatment due to ineligibility, in line with clinical expert expectations. This corresponds to 71 patients receiving trastuzumab treatment (2, 3). Following progression on first-line therapy, it was estimated that 53% of patients are eligible for any second-line treatment resulting in 38 patients. This estimate aligns with the range provided by Danish clinical experts, who noted that only patients who remain clinically fit, e.g., with adequate performance status, are considered for second-line therapy (2, 3). Of the patients Danish clinical experts assessed that around 80% would be eligible for treatment with T-DXd (Table 4) (2, 3). Using these inputs, it was estimated that on average 30 patients per year will initiate T-DXd (Table 5).

Danish real-world evidence (RWE) (data on file) shows that since 2022, [redacted] patients in Denmark have received T-DXd in later treatment lines through name-based reimbursement applications ("enkelttilskudsansøgninger") (30) (see Appendix P). Although T-DXd is not part of the current second-line treatment algorithm, these name-based reimbursement cases demonstrate that clinicians actively seek access to T-DXd for selected patients who progress after trastuzumab-based therapy, reflecting a high unmet need for HER2-directed treatment options beyond first line.

Due to generally low patient numbers and low variation anticipated, a stable patient volume for the next 5 years was assumed. The recent introduction of pembrolizumab in first-line HER2-positive metastatic GC/GEJC (DMC recommendation, 2024) (29) may influence future eligibility for second-line T-DXd. However, as pembrolizumab's approval for use is recent and real-world treatment patterns have not yet stabilised, the direction or magnitude of any impact on the second-line population cannot yet be quantified. In this context, maintaining a conservative, stable estimate of the eligible second-line population is considered justified. This also reflects that not all patients progressing after first-line chemo-immunotherapy are expected to be sufficiently fit to receive T-DXd.

For budget impact analysis results, refer to section 13.

Table 4. Patient funnel

Cancer	%	N	References

Gastric	Incidence	Gastric adenocarcinoma incidence 2024		310	DEGC annual report 2025 (8)
	Stage	Stage IV	44.2%	137	
GEJ	Incidence	Gastric-oesophageal junction adenocarcinoma incidence 2024		643	
	Stage	Stage IV	37.30%	240	
GC/GEJ, Metastatic Adenocarcinoma				377	
HER2-testing		HER2-testing Rate	100%	377	Assumption
HER2-positivity		HER2-positivity Rate	20%	75	Previous DMC assessment (29)
1st line treatment initiation		HER2-targeted therapy initiation in 1st line	95%	71	Danish clinical expert input (2, 3)
2nd line eligibility		Eligible for any drug treatment in 2nd line (i.e. fit for treatment)	53%	38	Assumptions and Danish clinical expert input (2, 3)
T-DXd eligibility		Likely treated with T-DXd in 2nd line	80%	30	

Abbreviations are defined in the list of Abbreviations

Table 5. Expected number of patients and patient uptake when implementing T-DXd

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Expected number of patients	30	30	30	30	30
Patient uptake	*100%*	*100%*	*100%*	*100%*	*100%*

3.2 Intervention

An overview of T-DXd, according to the indication, is provided in Table 6. An overview of the dose distribution for T-DXd is provided in Table 7.

Table 6. Overview of the intervention: T-DXd

Therapeutic indication relevant to the assessment	T-DXd as monotherapy for the treatment of adult patients with advanced HER2-positive GC/GEJ who have received a prior trastuzumab-based regimen (1).
Generic name	Trastuzumab deruxtecan
ATC code	L01FD04
Mechanism of action	T-DXd is a next-generation HER2-targeted antibody–drug conjugate. It couples a humanized anti-HER2 antibody (trastuzumab sequence) to a topoisomerase I inhibitor (DXd) via a cleavable tetrapeptide linker. After binding HER2, the conjugate is internalized and the linker is cleaved by lysosomal enzymes, releasing DXd to exert cytotoxicity (31). DXd can diffuse into adjacent tumour cells, producing a bystander effect that helps target HER2 heterogeneous or low expressing tumours (31). Design features include a plasma stable, tumour selective cleavable linker, a high drug to antibody ratio of approximately 8 to 1, and a short systemic half-life aim to enhance tumour specificity and efficacy.
Administration method	Intravenous infusion

Packaging type, pack sizes, shelf life and strengths	Packaging type: powder for concentrate for solution for infusion Pack sizes: vial volumes of 1 vial containing 1 ml Shelf life: Shelf life: 4 years (unopened; 2–8°C, do not freeze). After reconstitution: use immediately; otherwise up to 24 hours at 2–8°C (chemical/physical stable to 48 h), protected from light. After dilution (5% glucose): use immediately; otherwise ≤4 hours at ≤30°C (incl. prep + infusion) or up to 24 hours at 2–8°C, protected from light. Strengths: 100 mg
Package size(s)	Strength: 100 mg Pack size: 1 vial of concentrate for solution for infusion
If vials: Can these be shared?	Yes
Pre-medication: Should pre-medication be administered? Which one?	T-DXd is emetogenic: premedication to prevent nausea and/or vomiting. .
Co-administration: Should the drug be administered with other drugs? Which ones?	No
Need for diagnostics, monitoring or other tests (e.g., companion diagnostics)	T-DXd has some restrictions of use. These include warnings about the risk of ILD, severe neutropenia, and Left ventricular ejection fraction decrease (2, 3)(47). Appropriate monitoring and management strategies are recommended to mitigate these risks. Patients treated with T-DXd for advanced GC/GEJC should have documented HER2-positive tumour status, defined as a score of 3+ by IHC or IHC2+/FISH or ISH positive(1) (11)

Abbreviations are defined in the list of Abbreviations

Table 7. Dose distribution in DG04 (11)

	T-DXd (n= 244)	RAM (n= 233)	PTX (n= 233)
Dose reduction: Yes	[redacted]		
Starting dose			
First dose reduction			
Second dose reduction			
Third dose reduction			
Fourth dose reduction			
Fifth dose reduction			
Dose interruption: Yes			

Abbreviations are defined in the list of Abbreviations

Notes: [a] Units: Trastuzumab deruxtecan (T-DXd) and Ramucirumab (RAM) = mg/kg; paclitaxel (PTX) = mg/m2; [b] Cumulative dose level is the sum of dose level at each infusion; [c] the starting dose for T-DXd is 6.4 mg/mg, for RAM is 8 mg/kg, and for PTX is 80 mg/m² * Despite three recorded dose reductions, the patient's final administered dose was 4.4 mg/kg in line with the study protocol.

Relative dose intensity

The DESTINY-Gastric04 (DG04) study reported a mean relative dose intensity (RDI) of [redacted] (average delivered dose [redacted] mg/kg) (11), which was applied in the base case cost calculations (refer to drug cost calculations in Appendix L). In Danish clinical practice, lower average dosing may occur in some patients due to individual tolerance and management of adverse events (AE), potentially leading to a lower RDI than observed in the study (2, 3). Differences in dose intensity in Danish clinical practice may influence both drug acquisition costs and the efficacy and safety profile of T-DXd. Such differences are

anticipated in patient subgroups who are unable to tolerate the recommended 6.4 mg/kg dose and require dose reductions or interruptions. For the broader patient population, treatment effects observed in DG04 are considered representative of expected outcomes under routine use. A scenario analysis using an RDI of 80% was performed showing the impact of a lower RDI on the incremental costs (refer to Table 63).

Dosage, treatment duration and dose adjustments for T-DXD observed in DG04 and assumed in the health economic assessment are summarised in Table 8.

Table 8. The intervention in the study and the health economic model

	Study	Health economic model
Dosage and frequency [if weight-based, please state weight in brackets and any criteria for transition to flat-dose]	6.4 mg/kg (IV) once every 3 weeks Mean weight: 67.7 kg DG04, data on file (11). Transition to a flat dose is not applicable	6.4 mg/kg (IV) once every 3 weeks Mean weight: 67.7 kg (DG04, data on file (11). Transition to a flat dose is not applicable
Average dose	The mean RDI was [redacted] corresponding to an average dose of [redacted] mg/kg (11).	Average dose of [redacted] mg/kg translates into a total dose of 394 mg based on weight distribution (refer to Appendix L).
Criteria for treatment discontinuation	Until treatment progression, or unacceptable toxicity.	Until progression, or unacceptable toxicity.
Treatment duration	Median TTD: [redacted] months (DG04, ITT set, data on file) (11).	Median TTD: [redacted] months (extrapolations based on DG04 ITT analysis set; refer to Table 41).
Dose adjustment: Report if/how dose adjustment is made*	The starting dose of T-DXd was 6.4 mg/kg every three weeks (Q3W), with dose reduction to 5.4 mg/kg or 4.4 mg/kg permitted due to the occurrence of clinically significant and/or unacceptable toxicity. A relative dose intensity of [redacted] was observed	RDI from DG04 was applied in the health economic model: [redacted] (11).
Dose pause: Specify if/how pause (treatment interruption) is performed*	Permanently discontinue for severe infusion reactions. Discontinue treatment if requirement for further dose reduction beyond second dose reduction.	N/A

Abbreviations are defined in the list of Abbreviations
Notes: Dose intensity = total cumulative dose level / treatment duration * cycle length. Dose intensity units: T-DXd = mg/kg/21 days; RDI (%) = (Dose intensity/ PDI) × 100. PDI = 6.4 mg/kg per cycle (21 days) for T-DXd

3.2.1 The intervention in the context of Danish clinical practice

Management of non-curable GC/GEJC in Denmark is guided by national clinical recommendations coordinated through the Danish Esophago-Gastric Cancer Group (DEGC) (23) and monitored via national registries. Diagnosis typically involves endoscopy

with biopsy, followed by CT/PET imaging to assess local and distant spread. Prior to systemic therapy, biomarker testing includes HER2, PD-L1, MSI-H/MMR (further detail is provided in section 3.1.1). All required biomarkers, including HER2, are routinely tested in Danish practice, and introduction of T-DXd does not require new or non-standard diagnostic methods.

According to the DEGC multidisciplinary working group, which develops the Danish treatment guidelines for oesophageal/GC/GEJC, treatment recommendations align with international guidance (European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO)) but are adapted to Danish approvals and cost-effectiveness assessments by DMC. Treatment selection is driven by histology (adenocarcinoma vs squamous), molecular markers (HER2, PD-L1, MSI/MMR), PS (typically PS 0–2), comorbidities, and patient preferences, refer to section 3.1.1.

Current standard of care

Complete resection is the only treatment with curative intent and can be offered to some patients with localized disease. In cases of non-curable disease, palliative resection may be indicated if the patient has mechanical obstruction, bleeding, or perforation (23). First-line treatment of non-curable or advanced disease is systemic chemotherapy. According to DEGCs clinical guideline from February 2025, DEGC recommends that all treatment-eligible patients should have determination of PD-L1 score (CPS), MMR/MSI status, and HER2 status before treatment (23).

<u>First line treatment for HER2-positive metastatic disease</u>

The following treatments are recommended for patients with HER2-positive adenocarcinomas who are suitable for chemotherapy (23):

- Trastuzumab and platinum- and fluoropyrimidine-based chemotherapy, with addition of pembrolizumab for PD-L1 CPS ≥1.

This is currently the only HER2-targeted therapy routinely used in Denmark, meaning that most HER2-positive patients do not receive a HER2-directed agent beyond first line under current practice.

<u>Second-line treatment for HER2-positive metastatic disease</u>

Upon progression during or after first-line treatment, Danish guidelines recommend offering further systemic therapy to patients in good PS. Recommended second-line regimens include (23):

- Irinotecan monotherapy
- Taxane monotherapy (docetaxel (DTX) or paclitaxel (PTX)).

Choice of second-line cytotoxic agent should avoid repeating the same class used in first line and should account for toxicity history (e.g., neuropathy with taxanes, diarrhoea risk with irinotecan) (23).

Ramucirumab (RAM) (alone or with PTX) has phase III evidence internationally but is not part of Danish standard practice, as its previous conditional approval (recommended by

Koordineringsrådet for Ibrugtagning af Sygehusmedicin (KRIS) in 2016) was withdrawn following national follow-up (32).

Table 9 shows the most commonly used and recommended treatments (standard of care (SoC)) in the second-line setting for this patient population in Denmark. For this assessment, the treatments were weighted based on Danish clinical expert input (2, 3).

Table 9. Second-line treatments – SoC

Comparator	Danish SoC
Taxanes	83%
Irinotecan	17%

Abbreviations are defined in the list of Abbreviations

Notes: While Table 9 summarises the use of taxanes (pooled) and irinotecan to reflect clinical practice, Table 50 provides the treatment-specific proportions for PTX, DTX, and irinotecan, which were required for modelling because each treatment has distinct costs and safety data, and hence used for modelling purposes.

Third line treatment for HER2-positive metastatic disease

For patients with good PS and acceptable organ function who progress after first- and second-line therapy, third line options in Denmark include single-agent cytotoxic chemotherapy (taxanes or irinotecan). Participation in clinical studies and continued symptom-directed palliative measures should be considered (23).

T-DXd position in the treatment algorithm

In line with the EMA label, T-DXd is expected to be positioned as a second-line option for patients with HER2-positive advanced GC/GEJC who have progressed on or after trastuzumab-based therapy. This positioning is fully supported by the DG04 study results, which demonstrated significant improvements in objective response rate (ORR) and OS (33). The introduction of T-DXd is expected to primarily displace current non-targeted second-line treatment options.

As noted above, T-DXd has been used in this patient population in Denmark through name-based reimbursement applications for [redacted] patients since 2022. This highlights the unmet need in this setting and the added clinical benefit, which has been recognized by Danish oncologists.

3.2.2 Advanced Therapy Medical Products

N/A

3.3 Choice of comparator(s)

The comparator for this submission is Danish SoC in the second-line setting. In line with national guidelines (23), this comprises irinotecan or taxane based monotherapy (PTX or DTX) (section 3.2.1). For the comparison of efficacy, PTX was used as a proxy for Danish SoC. This assumption was supported by Danish clinical expert validation of current practice, but also by the available empirical evidence on the regimens relevant in Denmark: PTX, DTX, and irinotecan. In Denmark, second-line treatment after trastuzumab-based first-line therapy for advanced HER2-positive GC/GEJC consists of taxane monotherapy or irinotecan monotherapy, with treatment choice primarily driven by

toxicity profile, residual neuropathy, gastrointestinal tolerability, performance status, and clinician judgement rather than clear evidence of materially different efficacy between these cytotoxic options. This is consistent with national guidelines and the treatment mix applied in the model (PTX 44%, DTX 39%, irinotecan 17%).

From an efficacy perspective, the available evidence supports PTX as a reasonable, and likely conservative, anchor for the SoC basket. In the supplementary network meta-analysis (NMA) submitted in the dossier, the estimated hazard ratios for T-DXd versus PTX, DTX, and irinotecan were [redacted], and [redacted] for PFS, and [redacted], [redacted] and [redacted] for OS, respectively. These estimates do not suggest that DTX or irinotecan provide better outcomes than PTX; if anything, they appear numerically less favourable. Consequently, using PTX as the single efficacy anchor is likely to favour the comparator basket and may therefore underestimate the incremental benefit of T-DXd versus the full Danish SoC basket.

This interpretation is also consistent with the published trial literature. PTX, although off-label, is a well-established second-line regimen in advanced gastric cancer and has been evaluated in a large international randomized phase III study, RAINBOW, in which the control backbone was weekly PTX. In that study, median OS with PTX was 7.4 months and median PFS was 2.9 months ((10). DTX and irinotecan are also accepted second-line monotherapies, but the published evidence does not show consistent superiority over PTX. In COUGAR-02, second-line DTX improved survival versus active symptom control, confirming clinical activity, but not superiority versus PTX (34). Similarly, irinotecan improved survival versus best supportive care in the AIO trial, again demonstrating efficacy as a second-line option, but not superiority versus PTX (35). In addition, randomized evidence comparing weekly PTX and irinotecan in advanced gastric cancer has shown broadly similar efficacy, supporting the view that these cytotoxic monotherapies are reasonable alternatives selected mainly on tolerability and patient factors rather than major expected efficacy differences (36). Accordingly, using PTX as the representative efficacy profile for the SoC basket is not intended to assert strict equivalence, but rather to provide a pragmatic and conservative approximation grounded in the available comparative evidence.

With respect to treatment duration, the empirical evidence similarly supports PTX as a reasonable proxy. In the model, the median time on treatment / TTD for SoC was 3.68 months, derived by applying the RAINBOW relative effect to the DG04 RAM+PTX reference arm. This is broadly consistent with treatment durations reported for the individual regimens in the literature. In RAINBOW, median treatment duration for PTX was 12.0 weeks (approximately 2.8 months) (10). For DTX, published studies report treatment exposure of a similar order of magnitude: in Roy et al., mean exposure was 4.7 cycles every 3 weeks (around 3.2 months), while COUGAR-02 allowed treatment for up to six 3-weekly cycles (34); (37). For irinotecan, treatment duration was also broadly comparable, for example mean 4.6 cycles every 3 weeks in Roy et al., and median numbers of administrations or cycles in other studies corresponding approximately to 2–3 months, depending on schedule (Roy, 2013 #39; Thuss-Patience, 2011 #46; (36). Overall, these data suggest that PTX, DTX, and irinotecan have broadly similar treatment duration in second

line, and there is no evidence that PTX materially misrepresents comparator exposure in the SoC basket.

Regarding safety, the regimens differ in their toxicity profiles, but not in a way that undermines the use of PTX as an efficacy proxy. Importantly, in the health economic analysis, it is not assumed that PTX safety represented the full SoC basket. Instead, adverse event rates and costs were weighted across PTX, DTX, and irinotecan using the expected Danish treatment mix.

In summary, the use of PTX as a proxy for the Danish second-line SoC basket is supported by four empirical considerations. First, PTX is a major component of Danish SoC, and taxanes overall account for the majority of use. Second, the available comparative evidence, including the submitted NMA, does not indicate that DTX or irinotecan are more effective than PTX; if anything, they appear numerically less effective, making PTX a conservative comparator anchor. Third, treatment duration across PTX, DTX, and irinotecan is broadly similar in the identified studies. Fourth, although toxicity profiles differ, the model did not rely on PTX alone for safety, since AE inputs were weighted across all relevant SoC regimens. For these reasons, PTX was considered an appropriate and pragmatic proxy for the SoC basket in the base case, while uncertainty around this assumption was explicitly explored in supplementary and scenario analyses, including analyses using regimen-specific NMA estimates and weighted SoC comparisons.

In this assessment, comparative efficacy (section 7) is informed by a simple indirect treatment comparison (ITC) that conservatively uses PTX monotherapy as a proxy for the Danish basket of second-line SoC regimens. Given that, in the ITC (described in Appendix D), lower PFS and OS HRs for DTX and irinotecan correspond to shorter survival and worse outcomes relative to PTX, using PTX as the reference comparator should be considered a conservative choice.

Dose distributions included in the SoC basket (refer to Table 50 for overview of included treatment regimens) were based on clinical expert statements reflecting routine Danish clinical practice (2, 3) and used to estimate drug costs in the health economic model. For information on efficacy refer to section 7.

Table 10, Table 12, and Table 14 below provide the overview of treatments included in the SoC basket. As described above, information on posology for SoC is sourced from clinical experts. In addition, and in line with DMC guidelines, the posology and dose distributions reported in the individual clinical studies (identified in the SLR and included in the network meta-analysis [NMA]) are presented in Appendix O. Dosage, treatment duration and dose adjustments of the SoC basket in the clinical studies and the health economic model are summarised in Table 11, Table 13, and Table 15. Further details on RDI are provided in Appendix O.3.

Table 10. Overview of the comparator: PTX

Therapeutic indication relevant to the assessment	Off label
Generic name	Paclitaxel
ATC code	L01CD01

Mechanism of action	PTX is an antimicrotubular agent that stabilizes microtubules by promoting their assembly and preventing depolymerization. By blocking normal microtubule dynamics, it disrupts essential interphase and mitotic functions, producing abnormal microtubule bundles and multiple mitotic asters that inhibit cell division.
Administration method	IV
Packaging type, pack sizes, shelf life and strengths	Packaging type: Concentrate for solution for infusion Pack sizes: vial volumes of 16.7 and 50.0 ml Shelf life: 3 years unopened. Single use; up to 24 hours at 2–8°C protected from light (vial or bag), with the bag optionally held a further 4 hours at 15–25°. Strengths: 6 mg
Package size(s)	Pack sizes: vial volumes of 16.7 and 50.0 ml
If vials: Can these be shared?	Yes
Pre-medication: Should pre-medication be administered? Which one?	N/A
Co-administration: Should the drug be administered with other drugs? Which ones?	No. PTX monotherapy
Need for diagnostics, monitoring or other tests (e.g., companion diagnostics)	N/A

Abbreviations are defined in the list of Abbreviations

Table 11. Comparator in the clinical study and in the health economic model: PTX

	Study	Health economic model
Dosage and frequency [if weight-based, please state weight in brackets and any criteria for transition to flat-dose]	80 mg/m2 (IV) on days 1, 8, and 15 of a 28-day cycle (10). Transition to a flat dose is not applicable	80 mg/m^2 (IV) every week. BSA: 1.8 (11) Transition to a flat dose is not applicable
Average dose	80 mg/m2 with mean RDI of 90% (10).	BSA from DG04 and dosing results in a dose of 141.9 mg, with a mean RDI of 90% (10), the average dose results in 127 mg
Criteria for treatment discontinuation	Until treatment progression, or unacceptable toxicity.	Until progression
Treatment duration	Median duration of treatment was 12.0 weeks (6.4–20.0) with placebo in the placebo plus PTX group (10).	3.68 months (extrapolations based on RAINBOW HR applied to RAM+PTX (DG04) arm; refer to Table 41).
Dose adjustment: Report if/how dose adjustment is made*	Between cycles: Reduce by 10 mg/m^2 for the next cycle if prior cycle had Grade 4 hematologic toxicity or Grade 3 PTX-related non-hematologic toxicity (except alopecia). No re-escalation. Discontinue if	90% RDI (mean) as reported for the PTX + placebo arm in RAINBOW (see also Table 139) (10).

	Study	Health economic model
	reduction would go below 60 mg/m² or for any life-threatening PTX-related event (10).	
Dose pause: Specify if/how pause (treatment interruption) is performed*	Day 1: If criteria are not met (labs/toxicities), delay cycle start; repeat weekly until recovery. Days 8/15: If criteria not met or PTX-related toxicity, skip PTX on that day (no within-cycle dose reduction). >28 days unable to treat: Permanently discontinue PTX (10).	N/A

Abbreviations are defined in the list of Abbreviations

Table 12. Overview of the comparator: DTX

Overview of comparator	
Therapeutic indication relevant to the assessment	Metastatic gastric adenocarcinoma in patients who have not yet received any treatment for metastatic cancer. Docetaxel Accord is used with cisplatin and fluorouracil (other cancer medicines) (38). For this analysis, DTX monotherapy was considered.
Generic name	Docetaxel
ATC code	L01CD02
Mechanism of action	DTX is an anticancer drug that stabilizes microtubes, blocking their disassembly and reducing free tubulin, without changing protofilament number. This disrupts the microtubule network needed for cell division and interphase (38).
Administration method	IV
Packaging type, pack sizes, shelf life and strengths	Packaging type: Concentrate for solution for infusion Pack sizes: vial volumes of 1.0, 4.0, and 8.0 ml Shelf life: 2 years unopened. Single use; use immediately after opening. Prepare dilution aseptically and use it promptly. If stored <25°C, infusion solution is stable up to 6 hours total, including the ~1-hour IV infusion. Strengths: 20 mg, 80mg, and 160 mg
Package size(s)	Pack sizes: vial volumes of 1.0, 4.0, and 8.0 ml
If vials: Can these be shared?	Yes
Pre-medication: Should pre-medication be administered? Which one?	Due to the significant risk of hypersensitivity reactions and fluid retention, all patients must receive premedication with an oral corticosteroid. Not included in the health economic analysis.
Co-administration: Should the drug be administered with other drugs? Which ones?	No
Need for diagnostics, monitoring or other tests (e.g., companion diagnostics)	N/A

Abbreviations are defined in the list of Abbreviations

Table 13. Comparator in the clinical study and in the health economic model: DTX

	Study	Health economic model
Dosage and frequency [if weight-based, please state weight in brackets and any criteria for transition to flat-dose]	75 mg/m² (IV) once every 21-day cycle (34) (37). Transition to a flat dose is not applicable	75 mg/m² (IV) every 3 weeks BSA: 1.8 (11) Transition to a flat dose is not applicable
Average dose	75 mg/m2 with median RDI of >90% (37).	BSA from DG04 and dosing results in a dose of 133.05 mg, with a median RDI of 90% (37), resulting in an average dose of 119.75 mg
Criteria for treatment discontinuation	Until treatment progression, or unacceptable toxicity (or patient request) (37).	Until progression
Treatment duration	By Roy et al: DTX given every three weeks, mean 4.7 cycles (range 1–12); COUGAR-02: DTX planned for up to six 3-weekly cycles, discontinued at six cycles or earlier for >21-day delay, progression, unacceptable toxicity, or patient request (34) (37).	PTX as proxy for SoC basket 3.68 months (extrapolations based on simplified ITC, refer to Table 41).
Dose adjustment: Report if/how dose adjustment is made*	DTX 75 mg/m2 was reduced to 55 mg/m2 after recovery from any of the following: prolonged grade 4 neutropenia (>7 days) or febrile neutropenia; platelets <50×10^9/L; hepatic toxicity above protocol thresholds (bilirubin > ULN; ALT/AST >1.5× ULN; ALP >2.5× ULN without liver metastasis or >5× ULN with liver metastasis); grade 3–4 non-hematologic toxicity (skin grade 3–4 resumed at 55 mg/m2; grade 2 skin resumed at full dose). Treatment was permanently stopped for grade 3–4 peripheral neuropathy (34).	RDI > 90% (see also Table 139) (37).

	Study	Health economic model
Dose pause: Specify if/how pause (treatment interruption) is performed*	Cycles were held for ANC <1.5×10^9/L, platelets <100×10^9/L, qualifying hepatic toxicity, or grade ≥2 significant non-hematologic toxicity until recovery. If ANC/platelets recovered within 14 days (ANC >1.5×10^9/L; platelets >100×10^9/L), treatment resumed with dose per criteria above. Therapy was discontinued for >21-day delay, completion of six cycles, progression, unacceptable toxicity, or patient request (34).	Not applicable

Abbreviations are defined in the list of Abbreviations

Table 14. Overview of the comparator: Irinotecan

Overview of comparator	
Therapeutic indication relevant to the assessment	Off label
Generic name	Irinotecan
ATC code	L01CE02
Mechanism of action	Irinotecan inhibits the enzyme topoisomerase I. Causes single strand breaks in DNA and blocks DNA repair. This leads to inhibition of cell division and subsequent cell death (39).
Administration method	Intravenous infusion
Packaging type, pack sizes, shelf life and strengths	Packaging type: Concentrate for solution for infusion Pack sizes: vial volumes of 5.0, 15.0, and 25.0 ml Shelf life: Store protected from light. Do not freeze. The ready-to-use infusion solution should be used immediately after preparation. Strengths: 20 mg
Package size(s)	Pack sizes: vial volumes of 5.0, 15.0, and 25.0 ml
If vials: Can these be shared?	Yes
Pre-medication: Should pre-medication be administered? Which one?	Not applicable
Co-administration: Should the drug be administered with other drugs? Which ones?	No
Need for diagnostics, monitoring or other tests (e.g., *companion diagnostics*)	Treatment should be carried out under close monitoring of leukocyte and platelet counts, with dose reduction in cases of leukopenia and thrombocytopenia.

Table 15. Comparator in the clinical study and in the health economic model: Irinotecan

	Study	Health economic model
Dosage and frequency [if weight-based, please state weight in brackets and any criteria for transition to flat-dose]	150 mg/m2 of irinotecan (40) (36, 41-43) or 300 mg/m2 of irinotecan (IV) every three weeks (37). Transition to a flat dose is not applicable	250 mg/m^2 every 3 weeks BSA: 1.8 (11) Transition to a flat dose is not applicable
Average dose	300 mg/m2 with median RDI of 90% (37). Other studies not specified	BSA from DG04 and dosing results in a dose of 443.5 mg, with a median RDI of 90% (37), resulting in an average dose of 399.15 mg
Criteria for treatment discontinuation	Until treatment progression, or unacceptable toxicity (or patient request).	Until progression
Treatment duration	Median of 4.5 administrations (range 1–39), with dosing once every three weeks (36). Mean number of treatment cycles was 4.6 in the irinotecan arm (range 1–12), with administrations scheduled every three weeks (37). Median treatment duration of 6.2 weeks (range 0–138.3) (42). Median number of treatment courses was 4.0 (range 1–12) (43). Median number of treatment cycles per patient was 2 (range 0–9) (35).	PTX as proxy for SoC basket 3.68 months (extrapolations based on simplified ITC, refer to Table 41).
Dose adjustment: Report if/how dose adjustment is made*	Dose reduction was permitted according to predefined toxicity criteria (36) (37) (42) (43). Starting irinotecan 250 mg/m2, routinely increased to 350 mg/m2 from cycle 2 unless first-cycle toxicities occurred (hematologic grade 3/4 or any other toxicity grade ≥2); if toxicity-related dose delay >2 weeks, or CTC grade 4 leukopenia/neutropenia/thrombocytopenia, or any other grade 3/4 toxicity, reduce irinotecan by 50 mg/m2 (35).	RDI > 90% (see also Table 139) (37).
Dose pause: Specify if/how pause (treatment interruption) is performed*	Cycle delays were permitted per predefined toxicity criteria, treatment continued until progression/unacceptable toxicity/refusal.	N/A

Abbreviations are defined in the list of Abbreviations

3.4 Subsequent treatment

In Danish clinical practice, a proportion of patients who experience disease progression after the intervention and/or comparator are expected to receive a subsequent line of therapy. Based on input from Danish clinical experts (2, 3), the percentage of patients who receive subsequent therapy among those who progress on second-line treatment is uncertain and estimated to range from approximately 20% to 50%. This variation reflects real-world constraints, including clinical deterioration, discontinuation of therapy due to AEs, reduced fitness for further therapy, and limited availability of suitable regimens at later lines of treatment (2, 3).

In the DG04 study, among patients who experienced disease progression, [redacted] and [redacted] received subsequent drug therapy in the T-DXd and RAM+PTX arms, respectively (44). Subsequent regimens observed in DG04 were guideline-aligned third line and later therapies. Appendix C shows the distribution of subsequent treatments in the DG04 study. For completeness, post-discontinuation treatment data from the RAINBOW study are also presented in Appendix C.

In the RAM+PTX arm (total population), 64 patients (25.8%) of patients received subsequent anti-HER2 antibody-drug conjugate therapy (T-DXd 21% or disitamab vedotin/RC48 4.8%). Although within-trial crossover prior to progression was neither permitted nor observed (11), use of later-line anti-HER2 ADCs following progression was anticipated and allowed per protocol and reflects local clinical practice. To account for post-progression anti-HER2 ADC use in the comparator arm, rank-preserving structural failure time models (RPSFTM) were implemented following National Institute for Health and Care Excellence (NICE) Decision Support Unit Technical Support Document 24 (DSU TSD 24)(45), with and without re-censoring. This adjustment improves interpretability for settings where later line ADC access is limited (e.g. Denmark). For more information on the crossover analysis, refer to Appendix N.

In the base case, crossover adjustment without re-censoring was applied to the RAM+PTX arm to maximize data, with a scenario analysis exploring the crossover analysis with re-censoring (refer to Table 63).

For the base case, it was assumed that 50% of patients who initiate second-line treatment and subsequently progress receive subsequent therapy. This reflects the upper bound of estimates from Danish clinical experts (2, 3). The distribution of subsequent therapies by second-line treatment, as included in the health economic analysis, is based on Danish clinical expert opinion and is presented in Table 16. These subsequent regimens reflect guideline-aligned third- and later-line therapy options, and the table summarises the assumptions applied in the model.

Table 16. Assumptions regarding subsequent treatment in the health economic analysis

Subsequent treatment	T-DXd (%)	SoC (%)	Average treatment duration including source	Dosage (Dose, frequency and form of administration including source)	Any assumptions regarding dose adjustment and pause including source
Proportion of patients receiving a subsequent line of therapy following disease progression	50%	50%			
Taxanes (PTX)	73%	17%	9.37 weeks (11)	80 mg/m2 (IV) every week	Refer to Table 11
Irinotecan	27%	83%	13.29 weeks (11)	250 mg/m^2 (IV) every 3rd week	Refer to Table 15

Abbreviations are defined in the list of Abbreviations

3.5 Relevant outcomes

3.5.1 Definition of outcomes

All efficacy and safety outcome measures included in the application are defined in Table 17.

OS, progression-free survival (PFS), and European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L) data were selected based on their clinical relevance and alignment with the decision problem for patients with HER2-positive, locally advanced or metastatic GC/GEJC who have progressed after first-line trastuzumab-containing therapy.

OS and PFS were first analysed using Kaplan–Meier (KM) estimates in DG04, providing the core evidence of T-DXd' clinical efficacy. OS and PFS were subsequently used as anchor outcomes in a simplified indirect comparison linking DG04 with RAINBOW to estimate the relative effect of T-DXd versus PTX, used as the proxy for Danish SoC.

The definitions of OS and PFS are consistent across DG04 and RAINBOW. Both studies collected patient-reported outcomes, including the EQ-5D. However, in this assessment, health-related quality of life (HRQoL) data was included only from DG04, and between-study differences were not evaluated.

In both studies, AEs were collected using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), but different NCI CTCAE versions were applied. Version differences can affect both the identification and grading of events, which may influence the reported incidence of Grade ≥3 AEs (relevant for the cost-effectiveness analysis). Because patient-level data for RAINBOW are unavailable, regrading and harmonizing definitions is not feasible; thus, observed differences in Grade ≥3 AE rates may partly reflect measurement differences. These version-related reporting differences do not affect efficacy endpoints, and any impact on the conclusions of this assessment is expected to be limited.

Table 17. Outcomes in DG04 (11) and RAINBOW (10)

Outcome	Study	Follow-up time	Definition
Overall survival	DG04	T-DXd: Median follow-up: 16.8 months (95% CI 14.0–20.0) RAM+PTX: 14.4 months (95% CI 13.1–19.7)	OS is defined as the time from randomization to death from any cause.
	RAINBOW	Median follow-up: 7.9 months (IQR 4.2–13.0).	OS is defined as the time from randomization to death from any cause.
Progression-free survival	DG04	T-DXd: Median follow-up: 13.7 months (95% CI 10.9–19.6) RAM+PTX: 8.5 months (95% CI 7.0–13.9)	Time from randomization to first radiographically documented progressive disease based on Investigator assessment using RECIST v1.1.
	RAINBOW	NR	Time from randomization to first radiographically documented progressive disease based on Investigator assessment using RECIST v1.1.
HRQoL/ EQ-5D-5L	DG04	See section 10	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.
	RAINBOW	Not available	Not available
Safety	DG04	Not available	AEs were graded according to NCI-CTCAE v5.0.
	RAINBOW	NR	AEs were graded according to NCI-CTCAE v4.02.

Abbreviations are defined in the list of Abbreviations

3.5.2 Relevance of outcomes

OS represents the gold standard endpoint in oncology and directly captures the primary clinical objective of extending survival. PFS reflects time without objective disease progression or death and is clinically relevant as a surrogate of disease control and is frequently used in clinical decision-making for metastatic GC/GEJC. EQ-5D-5L is the

preferred measure of HRQoL for health economic evaluation and is required for quality-adjusted life year (QALY) estimation in the cost-effectiveness model.

3.5.3 The validity of outcomes

All outcome measures are standard, internationally used and valid measures for assessing the efficacy of treatment in oncology studies. There have been numerous assessments by the DMC using these endpoints, also for other GC treatments (46, 47).

4. Health economic analysis

4.1 Reference-case Assumptions

Table 18 shows the key assumptions in the health economic analysis.

Table 18. Reference-case assumptions in the health economic analysis

Assumption regarding	Assumption	Justification
Patient population	Patients with advanced HER2-positive GC/GEJC who have received a prior trastuzumab-based regimen.	T-DXd is expected to be used in the second line setting (according to EMA label (1)).
Intervention	T-DXd 6.4 mg/kg (IV) once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.	According to EMA label (1).
Comparator(s)	SoC	According to national treatment guidelines (23). Validated by Danish clinical expert (2, 3). The basket of SoC is anchoring efficacy to PTX, assuming similar efficacy across treatments. This approach was discussed and validated by Danish clinical experts (2, 3). An overview of treatments in the 'SoC' basket can be found in Table 50.
Clinical outcomes	OS, PFS, TTD, HRQoL, safety	Primary and secondary endpoints in DG04 reflecting the course of the disease.
Analysis type	Cost-utility analysis	T-DXd is a new treatment option that offers additional clinical benefit over the current SoC.
Model type	Partitioned survival model	Consistent with prior accepted HTA submissions in metastatic GC (47, 48) this approach reflects established practice.
Average age at entry into the model	[redacted] years	Based on DG04 data (11). Alignment with Danish RWE data (data on file). Refer to section 6.1.3 and Appendix P.
Time horizon	Lifetime (10 years)	A patient's lifetime horizon (10 years) was adopted to capture all potential differences

Assumption regarding	Assumption	Justification
		in costs and outcomes associated with the assessed interventions.
Cycle length	1 week	To capture the costs and events associated with the rapid progression of the disease and to account for different treatment schedules.
Half-cycle correction	No	According to DMC preference

Abbreviations are defined in the list of Abbreviations

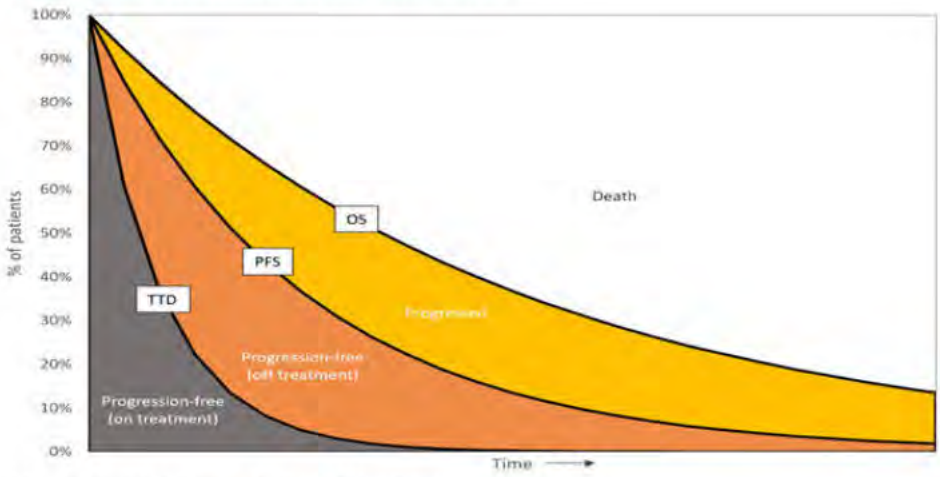
Additionally, a discount rate of 3.5% was used for both costs and benefits. The base case analysis takes limited societal perspective in line with the DMC preference (49).

4.2 Model type and model structure

A three-state cohort-based partitioned survival model (PSM) with health states for progression-free (PF), progressed disease (PD), and death was developed in Microsoft Excel® (Figure 1). These health states are mutually exclusive and exhaustive, meaning each patient occupies only one state at any time.

In addition, the model accounts for the time to treatment discontinuation (TTD) to reflect the fact that some patients discontinue treatment prior to progression and more accurately reflect the corresponding treatment related costs.

Figure 1. Schematic overview of the model structure



Abbreviations are defined in the list of Abbreviations

The PFS curve shows the proportion of patients remaining in the PF health state over time. Based on the TTD curve, patients can be on or off treatment while in the PF health state. The OS curve provides insight into the survival of all patients still alive (i.e., the sum of patients in the PF and PD health states) as well as information about the membership in the death state. For the PD health state, state membership is derived from the difference between the OS curve and the PFS curve at each time point; this provides the proportion of patients who are alive but not PF. Patients cannot return to the PF state.

For T-DXd, the PSM was informed by the outcomes of the DG04 study with a median follow-up time of 16.8 months for OS and 13.7 months for PFS (11). For the base case analysis, HRs reported in the RAINBOW study (NCT01170663 (10)) were used to estimate OS, PFS, and TTD for the SoC currently available in Denmark. This approach was assessed to be the most robust method to estimate OS and other outcomes for the SoC. The RAM+PTX arm in DG04 was used as a reference arm to obtain the health state occupancy for patients treated with SoC. For more information see section 9.

The choice of health economic analysis type, model type, and overall model structure is summarised in Table 19 below.

Table 19. Choice of health economic analysis, model and model structure

Health economic analysis	Model type	Model structure	Assumptions
Cost utility analysis	Partitioned survival model	Three health states: progression-free, post-progression, and death.	T-DXd was modelled independently, using data from DG04; SoC was modelled by applying HRs for PTX vs RAM+PTX to the RAM+PTX arm in DG04. PTX was used as a proxy for Danish SoC in terms of OS, PFS and TTD. Hazard adjustment applied to the SoC arm (OS), refer to section 9.

Abbreviations are defined in the list of Abbreviations

5. Literature overview

As there is no head-to-head evidence comparing T-DXd with the Danish SoC basket as described in section 3.5, a simplified ITC is used for the base case in this assessment. DG04 (T-DXd vs RAM+PTX) was combined with RAINBOW (RAM+PTX vs PTX) to derive effects versus relevant Danish SoC regimens; RAINBOW was identified via the systematic literature review (SLR). Furthermore, the SLR was used to identify AE incidence rates, AE disutilities, and economic parameters identification (refer to the following tables in the section). The assessment also includes a supplementary analysis based on a NMA using studies identified in the SLR which supported the supplementary analysis (refer to section 12.2.1.

5.1 Literature Used to Assess Clinical Effectiveness and Safety

The literature used for the assessment of clinical efficacy and safety is presented in Table 20.

Table 20. Relevant literature included in the assessment of effectiveness and safety

Reference	Study name	NCT-number	Study dates (Start date and expected end date, data cut-off and expected data cut-offs)	Used when comparing*
Shitara, Kohei, Eric Van Cutsem, Mahmut Gümüş, Sara Lonardi, Christelle de la Fouchardière, Clélia Coutzac, Jeroen Dekervel et al. "Trastuzumab deruxtecan or ramucirumab plus paclitaxel in gastric cancer." New England Journal of Medicine (2025) (33). Data on file: DG04 Clinical study report (11)	DESTINY-Gastric04	NCT04704934	Start: 21/05/2021 Completion: Event driven Data cut-off 24/10/2024 Future data cut-offs: Not expected	OS, PFS, TTD, and safety for T-DXd vs RAM+PTX vs PTX (reference arm for simplified ITC)
Wilke, Hansjochen, Kei Muro, Eric Van Cutsem, Sang-Cheul Oh, György Bodoky, Yasuhiro Shimada, Shuichi Hironaka et al. "Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomized phase 3 trial." The lancet oncology 15, no. 11 (2014): 1224-1235 (10).	RAINBOW	NCT01170663	Start: N/A/12/2010 Data cut-off N/A/07/2013 Completion: N/A/02/2017	OS and PFS RAM+PTX vs PTX Safety data for PTX (refer to section 8).
Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014;15(1):78-86 (34).	COUGAR-02	NCT00978549	Start: N/A/04/2008 Data cut-off: N/A Completion: 28/02/2012	AEs for DTX (refer to section 8).
Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as	AIO-trial	NCT00144378	Start: NA/10/2002 Data cut-off: N/A Completion: N/A/2010	AEs for irinotecan (refer to section 8).

Reference	Study name	NCT-number	Study dates (Start date and expected end date, data cut-off and expected data cut-offs)	Used when comparing*
second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer. 2011;47(15):2306-14.				

Abbreviations are defined in the list of Abbreviations

5.2 Literature Used to Assess Health-Related Quality of Life

The literature used for the assessment of HRQoL is presented in Table 21.

Table 21. Relevant literature included in the assessment of health-related quality of life

Reference	Instrument and purpose	Identification method (documented in appendix)	Used in paragraph
Shitara, Kohei, Eric Van Cutsem, Mahmut Gümüş, Sara Lonardi, Christelle de la Fouchardière, Clélia Coutzac, Jeroen Dekervel et al. "Trastuzumab deruxtecan or ramucirumab plus paclitaxel in gastric cancer." New England Journal of Medicine (2025) (33).	EQ-5D-5L data for health state utility values	Clinical trial	Section 10; section 10.3
Swinburn, Paul, Andrew Lloyd, Paul Nathan, Toni K. Choueiri, David Cella, and Maureen P. Neary. "Elicitation of health state utilities in metastatic renal cell carcinoma." *Current Medical Research and Opinion* 26, no. 5 (2010): 1091-1096 (50).	EQ-5D-5L (UK) AE disutility for anaemia	Utility decrements were identified from previous TAs and literature in GC or other diseases, including NSCLC and mBC, when unavailable for metastatic GC.	Section 10.3.3
Nafees, Beenish, Megan Stafford, Sonia Gavriel, Shkun Bhalla, and Jessamy Watkins. "Health state utilities for non small cell lung cancer." Health and quality of life outcomes 6, no. 1 (2008): 84 (51).	SG; EQ-5D; VAS scores (UK) AE disutility for nausea, leukopenia, neutrophil count decreased, fatigue, diarrhoea, vomiting, and infection		

Reference	Instrument and purpose	Identification method (documented in appendix)	Used in paragraph
Doyle, Scott, Andrew Lloyd, and Mark Davis. "Public perception of atrial fibrillation and treatment-related adverse events in the UK." British Journal of Cardiology 18 (2011): 88-93 (52).	EQ-5D (UK) AE disutility for ILD and pain		
Sandhu, Alexander T., Jeremy D. Goldhaber-Fiebert, Douglas K. Owens, Mintu P. Turakhia, Daniel W. Kaiser, and Paul A. Heidenreich. "Cost-effectiveness of implantable pulmonary artery pressure monitoring in chronic heart failure." *JACC: Heart Failure* 4, no. 5 (2016): 368-375 (53).	Instrument not specified AE disutility for left ventricular dysfunction		
Lloyd, A., B. Nafees, J. Narewska, Sarah Dewilde, and J. Watkins. "Health state utilities for metastatic breast cancer." *British journal of cancer* 95, no. 6 (2006): 683-690 (54).	SG, EQ-5D and interviews AE disutility for febrile neutropenia		

Abbreviations are defined in the list of Abbreviations

5.3 Literature Used as Input in the Health Economic Model

Literature used for the health economic model are presented in Table 22.

Table 22. Relevant literature used in the health economic model

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in paragraph
Shitara, Kohei, Eric Van Cutsem, Mahmut Gümüş, Sara Lonardi, Christelle de la Fouchardière, Clélia Coutzac, Jeroen Dekervel et al. "Trastuzumab deruxtecan or ramucirumab plus paclitaxel in gastric cancer." New England Journal of Medicine (2025) (33). Data on file (11)	Overall survival for T-DXd and reference arm for SoC Progression-free survival for T-DXd and reference arm for SoC Time-to-treatment discontinuation for T-DXd and reference arm for SoC AEs for T-DXd	Clinical study	See mainly sections 6, 7, 8 and 9

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in paragraph
	Patient characteristics for T-DXd and SoC RDI for T-DXd		
Wilke, Hansjochen, Kei Muro, Eric Van Cutsem, Sang-Cheul Oh, György Bodoky, Yasuhiro Shimada, Shuichi Hironaka et al. "Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial." The lancet oncology 15, no. 11 (2014): 1224-1235 (10).	Overall survival HR for PTX Progression-free survival HR for PTX AEs for PTX RDI for PTX	Simplified ITC (including the SLR, see Appendix H)	See mainly sections 6, 7, 8 and 9
Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014;15(1):78-86 (34).	AEs for DTX RDI for DTX	Identified in SLR (see Appendix H)	See sections 8
Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer. 2011;47(15):2306-14.	AEs for irinotecan RDI for irinotecan	Identified in SLR (see Appendix H)	See sections 8
EMA. Summary of Product Characteristics: Enhertu® from: https://www.ema.europa.eu/en/medicines/human/EPAR/enhertu (1).	Dosing for T-DXd	Targeted search (refer to Appendix J.2) and Danish clinical expert interview	See section 11.1
EMA. Summary of Product Characteristics: Docetaxel Accord from: https://www.ema.europa.eu/en/medicines/human/EPAR/docetaxel-accord (38) Medicin.dk. Docetaxel "Accord" from: Docetaxel "Accord" – information til sundhedsfaglige – Medicin.dk) (55)	Dosing for DTX	Targeted search (refer to Appendix J.2) and Danish clinical expert interview	See section 11.1
EMA. Summary of Product Characteristics: Paclitaxel from: Pazenir | European Medicines Agency (EMA) (56) Medicin.dk. Paclitaxel "Accord" from: Paclitaxel "Accord" - information til sundhedsfaglige - Medicin.dk) (57)	Dosing for PTX	Targeted search (refer to Appendix J.2) and Danish clinical expert interview	See section 11.1

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in paragraph
Medicin.dk. Irinotecan “Accord” from: Irinotecan "Accord" - information til sundhedsfaglige - Medicin.dk) (39)	Dosing for irinotecan	Targeted search (refer to Appendix J.2) and Danish clinical expert interview	See section 11.1
Sundhedsdatastyrelsen; Danish Diagnosis-Related Group tariffs 2026 via InteraktivDRG. Available from: https://casemix360.solutions.iqvia.com/InteractiveProd (58)	Disease management costs – unit costs IV administration costs – unit costs AEs management costs – unit costs	Targeted search (refer to Appendix J.2)	See section 11.2
Danish Medicines Council (Medicinrådet). Costs calculations - Guideline, version 1.0. 2026. Available from: https://medicinraadet.dk/ansogning/ansogningsskema (59)	Patient time and transportation costs – unit costs	Targeted search (refer to Appendix J.2)	See section 11.3
Lægemiddelstyrelsen. Medicinpriser.dk – officielle danske medicinpriser. Available from: https://medicinpriser.dk/ (60)	Medicine costs	Targeted search (refer to Appendix J.2)	See section 11.1

Abbreviations are defined in the list of Abbreviations

6. Clinical studies

6.1 Trastuzumab deruxtecan compared with standard of care for patients with human epidermal growth factor receptor 2-positive gastric cancer or gastro-oesophageal junction cancer

6.1.1 Relevant Studies

Both DG04 and RAINBOW were used to inform the comparative analysis (Table 23). A CONSORT diagram for each study is included in Appendix A.

Overall, both DG04 and RAINBOW show treatment-discontinuation rates driven primarily by disease progression, which is expected in a late-line metastatic GC/GEJC setting. DG04 reported fewer patients discontinuing treatment compared to RAINBOW, likely reflecting differences in effect and tolerability (see section 8). Rates of patients not receiving assigned treatment were low across all studies, suggesting good adherence to study protocols. Study drop-out in DG04 was modest, while limited information was available for RAINBOW.

For DG04, the population used for this assessment corresponds to the full protocol-defined HER2-positive metastatic gastric/GEJ adenocarcinoma population, and no subpopulation restriction has been applied. The DG04 analysis uses the 24 Oct 2024 predefined data cut off (DCO), with a median OS follow-up of 16.8 months for T-DXd and 14.4 months for RAM+PTX (11). For RAINBOW the full intention-to-treat (ITT) population was used without subpopulation restriction and is based on the predefined July 2013 DCO, with a median OS follow-up of 7.9 months (10).

Treatment exposure and patients not receiving assigned treatment

In the DG04 safety/treated population, 2/246 (0.8%) patients in the T-DXd arm and 15/248 (6%) in the RAM+PTX arm did not receive the assigned treatment (33).

In RAINBOW, 4/330 (1.2%) patients in the RAM+PTX did not receive treatment, resulting in a treated population of 327; in the placebo + PTX arm, 5/335 (1.5%) did not receive treatment (treated population 329) (10).

Treatment discontinuation

In DG04, treatment was discontinued in 198/244 (81.1%) patients receiving T-DXd and 190/233 (81.5%) receiving RAM+PTX. The primary reasons for treatment discontinuation in the T-DXd arm included progressive disease (139; 57.0%), AEs (26; 10.7%), clinical progression (14; 5.7%), patient withdrawal (5; 2.0%), physician decision (2; 0.8%) and death (13; 5.3%). In the RAM+PTX arm, reasons included progressive disease (126; 53.6%), AEs (16; 6.9%), clinical progression (10; 4.3%), patient withdrawal (16; 6.9%), physician decision (4; 1.7%) and death (19; 8.2%) (33).

For RAINBOW, treatment discontinuation occurred in 313/327 (95%) patients in the RAM+PTX and 323/329 (96%) in the placebo+PTX arm. Primary reasons for discontinuation

in the RAM+PTX arm included progressive disease (236; 72%), AEs (39; 12%), death (12; 4%), withdrawal of consent (23; 7%), and other causes (<1%). In the placebo + PTX arm, reasons included progressive disease (255; 76%), AEs (38; 11%), death (13; 4%), withdrawal of consent (13; 4%), other (3; <1%) and lost to follow-up (1; <1%) (10).

Study discontinuation (drop out)

In DG04, 10/246 (4.1%) patients in the T-DXd arm and 24/248 (9.7%) in the RAM+PTX arm discontinued the study. Reasons for study discontinuation in the T-DXd arm were withdrawal by subject (8; 3.3%) and lost to follow-up (2; 0.8%). In the RAM+PTX arm, reasons included withdrawal by subject (22; 8.9%), lost to follow-up (1; 0.4%), and other (1; 0.4%) (33).

RAINBOW contains no available information on study discontinuation beyond the treatment-discontinuation figures already provided.

Internal and external validity

Randomized controlled clinical trials generally provide strong internal validity because randomization balances known and unknown confounders, outcomes are prospectively defined, and assessments follow a standardized protocol with ITT analysis. Both DG04 and RAINBOW are randomized controlled trials and therefore support causal inference. Blinding further reduces performance and assessment bias: RAINBOW's double-blind design offers an additional safeguard against such biases. DG04 is open-label, which can introduce bias in subjective outcomes and management decisions; however, its randomized design, protocolized assessments, and use of objective endpoints help preserve internal validity. The external validity, including the applicability of the study populations to the Danish clinical setting, is discussed in section 6.1.3.

Table 23. Overview of study characteristics for all studies included in the comparison

Study name, NCT number (reference)	Studio design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
DG04, NCT04704934 (33)	A phase 3, multicenter, 2-arm randomized, open-label study of trastuzumab deruxtecan in subjects with HER2-positive metastatic and/or unresectable gastric or GEJ adenocarcinoma who have progressed on or after a trastuzumab-containing regimen.	Data cut-off: 24 Oct 2024 (event-driven)	• Pathologically documented, inoperable, locally advanced, recurrent, or metastatic GC or GEJC • Progressed on or after first-line therapy with a trastuzumab-containing regimen • HER2-positive status (defined as IHC 3+ or IHC 2+/ISH+) • ECOG PS 0 or 1	T-DXd by IV at a dose of 6.4mg/kg Q3W until progression	RAM 8mg/kg on days 1 and 15 of every 28-day cycle PTX 80 mg/m2 by IV on days 1, 8 and 15 of every 28-day cycle	Primary: OS Secondary: PFS, safety, PROs Follow-up: Median OS follow-up 16.8 months (T-DXd) vs 14.4 months (RAM+PTX); Median PFS follow-up 13.7 months (T-DXd) vs 8.5 months (RAM+PTX); Median EQ-5D-5L follow-up 4.8 months
RAINBOW, NCT02898077 (10)	A randomized, multicenter, double-blind, placebo-controlled, phase 3 study of weekly paclitaxel with or without ramucirumab (imc-1121b) in patients with advanced gastric or GEJ adenocarcinoma, refractory to or progressive after first-line therapy with platinum and fluoropyrimidine.	Data cut-off: July 2013, study completion Feb 2017	• Patients aged 18 years or older with advanced GC or GEJC • Disease progression on or within 4 months after first-line chemotherapy (platinum plus fluoropyrimidine with or without an anthracycline)	RAM 8 mg/kg IV on days 1 & 15 + PTX 80 mg/m² IV on days 1, 8, 15 of each 28-day cycle	Placebo IV on days 1 & 15 + PTX 80 mg/m² IV on days 1, 8, 15 of each 28-day cycle	Primary: OS Secondary: PFS, safety, PROs (EORTC QLQ-C30; EQ-5D) Follow-up: Median OS follow-up 7.9 months (IQR 4.2–13.0)

6.1.2 Comparability of studies

For the base case analysis, the DG04 and RAINBOW studies were used to inform treatment outcomes and the relative effect of T-DXd versus Danish SoC. This section examines the comparability of the two studies, covering patient characteristics, prognostic factors, and potential treatment effect modifiers, and assesses the generalizability of the evidence to the Danish setting. In particular, prognostic factors were discussed in relation to the patient characteristics presented in DG04 and/or RAINBOW, and treatment effect modifiers were explicitly considered in line with subgroup analyses conducted in DG04 and RAINBOW. Sources of heterogeneity, i.e., study differences relevant to the comparison, are outlined in Table 24 below.

Table 24. Assessment of comparability – DG04 and RAINBOW

Category	Description of study difference	Expected impact on comparison
HER2-positivity	DG04 enrolled only HER2-positive participants; RAINBOW is not restricted to HER2-positive. HER2-positivity is a treatment-effect modifier for T-DXd but not anticipated for PTX.	Unlikely to bias the ITC meaningfully, given the target population for future T-DXd use is HER2-positive GC/GEJC.
Other patient characteristics	Overall, characteristics broadly similar across studies; detailed imbalances and potential effect modifiers discussed in section 6.1.2.1.	Aggregate heterogeneity is not expected to bias results materially; residual bias from unreported/unobserved confounders cannot be fully excluded.
First-line therapy	DG04: progressed on/after trastuzumab-containing regimen; RAINBOW: progressed on/after fluoropyrimidine-containing regimen. RAINBOW likely aligned with ESMO/NCCN (platinum–fluoropyrimidine ± trastuzumab for HER2- positive).	Relative treatment effects expected to generalize to clinical practice; any bias from first-line differences expected to be small.
Study design (blinding)	DG04: open-label. RAINBOW: double-blinded Blinding can influence persistence and OS/PFS.	The randomized design, protocolized assessments, and use of objective endpoints helps reduce bias. Evidence (Lord-Bessen et al.) (61) found comparable discontinuation, PRO completion, and OS in blinded vs open-label trials (melanoma, NSCLC). Thus, blinding-related bias is possible, but likely small in magnitude.

Abbreviations are defined in the list of Abbreviations

For more information, refer to section 7.

6.1.2.1 Comparability of Patients Across Studies

The key baseline demographic and disease characteristics of patients in the ITT population for the DG04 and RAINBOW are presented in Table 25. Patient characteristics for the relevant studies included in the NMA (scenario analysis) are presented in Appendix O.1.

The DG04 cohort (N=494) was older and included more men than RAINBOW (N=665), with a median age of 63.8 vs 59.5 years and 79.4% vs 71.0% male, respectively. In DG04, race/ethnicity was predominantly White (49.8%) and Asian (40.1%); RAINBOW did not report race in this layout. Geographically, both studies were largely Western-centric (DG04 56.4% vs RAINBOW 60.0%), with substantial Asian enrolment in both studies (23.7% vs 33.5%); rest-of-world was higher in DG04 (19.8% vs 6.5%). PS was similar: Eastern Cooperative Oncology Group (ECOG) 0–1 constituted nearly all patients (DG04 99.4% vs RAINBOW 100%), with ECOG 0 at ~37–39% and ECOG 1 at ~61–62%; ECOG 2 was rare and only reported in DG04 (0.4%).

Table 25. Patients' baseline characteristics in included studies used in the comparative analysis of effectiveness and safety

Study	DG04 (33)		RAINBOW (10)	
	T-DXd (N=246)	Ram+PTX (N=248)	Ram+PTX (N=330)	Placebo+PTX (N=335)
Sample size (N)	246	248	330	335
Male %	76.0%	82.7%	69%	73%
Median age	63.2	64.3	61	61
Mean body weight (kg)	67.7	67.7	NR	NR
Ethnicity %**				
Asian	41.1%	39.1%	33%	36%
White	47.2%	52.4%	63%	59%
Black	0%	0.8%	NR	NR
Black or other	NR	NR	4%	4%
Other	11.4%	7.7%	NR	NR
Geography %				
Western	56.90%	56.00%	60%*	60%*
Asia	23.2%	24.2%	33%	34%
Rest of the world	19.9%	19.8%	7%	6%
ECOG %				
ECOG PS 0	39.40%	35.50%	35%	43%
ECOG PS 1	60.20%	63.70%	65%	57%
ECOG PS 0 or 1	99.60%	99.2%†	100%	100%
ECOG PS 2	0.40%	0.40%	0%	0%
Histological subtype %				
Intestinal	28	26.60	44%	40%
Diffuse	10.20	7.70	35%	40%
Mixed	2.40	4	6%	4%
Not reported	58.90	61.70	15%‡	16%‡
Location of tumour %				
Gastric	62.20%	60.10%	80%	79%
GEJ	37.80%	39.90%	20%	21%

Presence of primary				
Present	NR	NR	63%	62%
Not present	NR	NR	37%	38%
Time to progressive disease on first-line				
<6 months	24.80%	24.60%	76%	76%
≥6 months	75.20%	75.40%	24%	24%
Disease measurability				
Measurable	NR	NR	81%	81%
Non-measurable	NR	NR	19%	19%
Presence of ascites				
Yes	NR	NR	39%	32%
No	NR	NR	61%	68%
Peritoneal metastases				
Yes	NR	NR	49%	45%
No	NR	NR	51%	55%
Number of metastatic				
0-1	29.70%	30.20%	NR	NR
1	NR	NR	NR	NR
1-2	NR	NR	NR	NR
0-2	NR	NR	63%	69%
2	NR	NR	NR	NR
≥2	70.30%	69.80%	NR	NR
≥3	NR	NR	37%	31%
Previous gastrectomy %				
Partial gastrectomy	8.5%	5.6%	24%	18%
Total gastrectomy	7.7%	7.7%	16%	19%
Other	10.2%	10.9%	<1%	<1%

Abbreviations are defined in the list of Abbreviations * For RAINBOW, Western corresponds to Region 1 (Europe, Israel, Australia, and the USA). † In DESTINY-Gastric04, ECOG PS 0 or 1 in the ramucirumab + paclitaxel arm is 99.2% because 0.4% of patients had ECOG PS 2 and 0.4% had missing ECOG data. ‡ For RAINBOW, Not reported under histological subtype corresponds to the trial categories "unknown or not available". ** For RAINBOW, ethnicity was defined based on "Ethnic origin" by self-report

6.1.2.1.1 Prognostic factors

Hand searches of published literature were conducted to identify prognostic factors in advanced or metastatic GC/GEJC that may or may not have been previously identified as treatment effect modifying factors. From these searches, five publications were identified and reviewed. These studies were a simulated treatment comparison assessing the comparative efficacy of nivolumab versus RWE datasets (50), an SLR and meta-analysis on the prognostic value of histological subtype (51), a retrospective cohort study of patients diagnosed with stage IV GC in Canada identifying factors predictive of survival (52), and two studies assessing differences in survival outcomes for patients of different ethnicities in the United States (53,54).

The identified simulated treatment comparison reported by Chau et al. included prognostic factors identified from an SLR which identified 22 studies of interest (50). The prognostic factors presented in the study were age, ECOG PS, prior gastrectomy, the

presence of GEJC, sex, and some laboratory measurements (haemoglobin > 10.5 g/dL, lactate dehydrogenase > 250 IU/L, alkaline phosphatase (ALP) > 100 U/L). Dixon et al. found that age, sex, tumour location, presence of ascites, number of metastatic sites, prior gastrectomy, and prior treatment with chemotherapy or radiotherapy were independent predictors of survival based on a multivariable analysis of Canadian healthcare data (52). Petrelli et al. conducted an SLR, and meta-analysis of studies reporting the association between histological subtype and survival outcomes and concluded that patients with a diffuse subtype had a poorer prognosis (51). Kim et al. and Jin et al. (62, 63) both reported the relationship between patient ethnicity and survival in GC, with both studies concluding that Asian patients had an improved prognosis in comparison with white patients. A list of relevant prognostic factors is presented in Table 26.

Table 26. Simplified list of prognostic factors in GC

Prognostic factor	Subgroup with better prognosis	Subgroup with worse prognosis
Age (64, 65)	Younger	Older
Sex (64, 65)	Female	Male
Ethnicity (62, 63,)	Asian	White
Geography (10) (62, 63, 66, 67)	Asian	Western
ECOG performance status (64)	ECOG 0	ECOG ≥1
Histological subtype (68)	Intestinal	Diffuse
Primary tumour location (64, 65)	Gastric (non-cardia)	GEJ (cardia)
Presence of primary tumour (64)	No	Yes
Previous gastrectomy (64, 65)	Yes	No
Presence of ascites (64, 65)	No	Yes
Presence of peritoneal metastases (64)	No	Yes
Number of metastatic sites (64, 65)	Low	High

Abbreviations are defined in the list of Abbreviations

DG04 and RAINBOW studies

In both studies, most patients were men, with DG04 showing a higher male proportion than RAINBOW (79.4% vs 71.0%). Ethnicity was reported differently in RAINBOW; however, based on geographic distribution, similar representation can be inferred. RAINBOW had a larger share of patients living in Asia, while DG04 included more patients from the rest of the world, but overall, the regional overlap was substantial.

ECOG PS was aligned, with approximately 100% of patients in ECOG 0–1 across both studies. Histology was incompletely reported in DG04 (not reported in 60.5%), with lower diffuse subtype representation compared to RAINBOW, which had higher intestinal (42.0%) and diffuse (37.5%) proportions.

A notable difference was observed in primary tumour location: DG04 included a higher proportion of GEJ tumours (gastric 61.1%, GEJ 38.9%) compared with RAINBOW (gastric 79.5%, GEJ 20.5%). As primary tumour location was identified as a potential treatment effect modifier, this difference was considered further below.

Regarding metastatic burden, DG04 reported ≥2 sites in 70% of patients, whereas RAINBOW reported 0–2 sites in 66% and ≥3 sites in 34%. Although categorization differs between the studies, both indicate substantial metastatic burden. This factor was not

identified as a potential treatment effect modifier and was therefore not expected to impact the relative effect, acknowledging limited comparability due to reporting formats.

6.1.2.1.2 Treatment effect modifiers

Potential treatment effect modifiers were identified based on subgroup analyses from DG04 (33) and RAINBOW (10). Factors where the point estimate for the HR of one subgroup fell outside the CI of the complementary subgroup were considered as a potential treatment effect modifying factors. The relevant factors are presented in Table 27.

For each potential treatment effect modifier identified, the subgroup reported first corresponds to the group with the best response to the treatment for the outcome reported in the outcome column.

HER2 status

HER2 overexpression was identified as a potential treatment effect modifier for T-DXd for OS only. Given its mechanism of action, HER2 status is not expected to modify the treatment effect of PTX. T-DXd was modelled independently in this analysis (see section 9). Therefore, HER2 status was not considered to introduce bias to this assessment.

Time to progressive disease on first-line therapy

For time to progressive disease on first-line therapy, patients with ≥6 months on first-line treatment demonstrated better OS outcomes. In DG04, 75% of patients remained on first-line therapy for six months or longer until PD, whereas in RAINBOW this proportion was 24%. Given the direction of treatment effect modification, longer time on first-line treatment until progression being more favourable for RAM+PTX, this imbalance may yield an optimistic estimate for PTX (and SoC) when applying the observed HR from RAINBOW to the RAM+PTX data in DG04. If the percentage of patients with ≥6 months on first-line therapy in RAINBOW had been similar to DG04, the HR could plausibly be lower, further favouring RAM+PTX than observed. Consequently, the relative effect of RAM+PTX versus PTX may be underestimated when anchored to DG04 data, potentially leading to overestimation of PTX treatment outcomes. Given that DG04 was assessed to be largely reflective of Danish clinical practice in terms of patient characteristics, the analysis can be characterized as conservative.

Primary tumour location

A similar consideration applies to primary tumour location. This variable was identified as a treatment effect modifier in both studies, with patients having GEJC demonstrating improved relative outcomes (lower HR) compared to patients with GC. Because DG04 includes a higher proportion of GEJ cases than RAINBOW, applying the RAINBOW HR to the RAM+PTX arm in DG04 may lead to underestimation of the relative effect of RAM+PTX versus PTX and, consequently, potentially overestimation of PTX treatment outcomes.

Disease measurability

Disease measurability, defined per Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1, was identified as a treatment effect modifier in RAINBOW: patients with

measurable disease (81%) had improved outcomes compared with those without measurable disease (19%). In DG04, eligibility required at least one measurable lesion per RECIST v1.1; thus, it is reasonable to assume all DG04 patients had measurable disease. Applying the RAINBOW HR (which reflects a mixed population including non-measurable disease) to the RAM+PTX arm in DG04 (all measurable) may therefore underestimate the relative effect of RAM+PTX versus PTX and, consequently, overestimate PTX/SoC treatment outcomes. In line with other treatment effect modifiers discussed, this supports characterizing the analysis as potentially conservative.

6.1.2.1.3 Potential impact on relative effect

Potential within-study treatment-effect modification is expected to be limited. If present, it would likely attenuate the difference between PTX vs RAM+PTX when applied to DG04, leading to potential overestimation of PTX outcomes and yielding conservative relative effect estimates for PTX vs T-DXd in this assessment. On balance, applying the RAINBOW HR to DG04 RAM+PTX data was assessed as appropriate for estimating PTX outcomes.

Table 27. Potential treatment effect modifying factors

Treatment effect modifier	Treatment	Outcome	Potential impact on relative effect of PTX vs. RAM+PTX if matched to DG04 patient characteristics	Study
HER2-positive status	T-DXd (IHC 2+/ISH+ vs ICH 3+)	OS	Not expected to modify the treatment effect of PTX or RAM+PTX.	DG04 (11)
Time to progressive disease on 1st-line therapy	RAM+PTX (≥6 months vs <6 months)	OS	Potential overestimation of PTX due to greater number of patients with >6 months on 1L therapy in DG04.	RAINBOW (10)
Disease measurability	RAM+PTX (measurable vs non-measurable)	OS	Potential overestimation of PTX due to greater disease measurability in DG04.	RAINBOW (10)
Primary tumour location	RAM+PTX (GEJC vs GC)	OS and PFS	Potential overestimation of PTX due to increased proportion of patients with GEJC in DG04.	RAINBOW (10)
	T-DXd (GEJC vs GC)	OS and PFS		DG04 (11)

Abbreviations are defined in the list of Abbreviations

6.1.3 Comparability of Study Population(s) with Danish Patients Eligible for Treatment

Patient characteristics in Danish clinical practice were discussed with Danish clinical experts (2, 3). Since 2022, [redacted] patients have been treated with T-DXd through name-based reimbursement applications. When discussing DG04's external validity with Danish clinical experts, the consensus was that the DG04 cohort is broadly generalisable to eligible Danish patients.

Age distribution

Danish registry data indicate a relatively high age at diagnosis, median 71 years for GEJC and 70 years for GC (8). A substantial share of patients receives no active systemic treatment, reflecting the sizable older or frail subgroup for whom therapy may be challenging; in the 2024 DEGC annual report, 35.5% of patients with GC and 29.4% with GEJC did not receive systemic therapy (8). Consistent with this, Danish clinical experts and Danish RWE (data on file, refer also to Appendix P) indicate that patients fit for active treatment, and particularly those who proceed to second-line therapy, are generally younger than the overall patient population (2, 3, 30). Danish RWE (data on file) shows a mean age of [redacted] years at first-line trastuzumab initiation (30), a few years younger than the average age at diagnosis. Given that eligibility for T-DXd requires a certain level of patient fitness, the patients who receive T-DXd are likely to be even younger on average than the general patient with HER2-positive metastatic GC/GEJC following trastuzumab treatment. Given that Danish clinical experts expect second-line HER2-positive patients to be younger than the patient population at diagnosis, the age of patients in DG04 [redacted] (11) is considered representative of the Danish population and provides a clinically relevant estimate for this assessment.

Gender distribution

Both GC/GEJC show male predominance. The incidence of GEJC is approximately four times higher in men than in women, while the incidence of GC is 1.6 times higher in men compared with women (8). This is reflected in Danish registry data from DEGC (approximately 61-81% male) (8) and Danish RWE (data on file) (30) for trastuzumab-treated patients [redacted] male). These patterns are consistent with the DG04 population (see Table 28) (11). Danish clinical experts therefore considered gender distribution in DG04 appropriate for Danish practice.

Body weight

As confirmed by Danish clinical experts, patients with metastatic GC/GEJC eligible for second-line therapy typically present with lower body weight than sex- and age-matched individuals in the general population, due to cumulative disease- and treatment-related weight loss. Consistent with Danish clinical expert input, patients initiating second-line therapy typically present with substantial weight loss compared with their usual baseline weight before disease progression (2, 3). Consequently, the body weight of the ITT study population in DG04 was viewed as representative relative to Danish clinical practice.

Disease characteristics

While the PS distribution in Danish clinical practice is essentially identical to that observed in DG04, some differences exist between the study population and Danish practice. Denmark has a higher proportion of GEJC relative to GC than the study cohort in DG04, and race/ethnicity differs; however, HER2 expression (IHC 2+ vs IHC 3+) is comparable, and a larger proportion of Danish patients will have received prior immune checkpoint inhibitors. Based on clinical expert experience treating Danish GC/GEJC with T-DXd, these differences are not expected to materially affect the anticipated treatment effect in Denmark (2, 3).

Table 28 presents patient characteristics relevant for the health economic assessment. Patient characteristics from DG04 were assumed to be representative of the Danish patient population and used as the primary reference for the health economic analysis.

Table 28. Characteristics of the relevant Danish population and input parameters in the health economic model

	Danish population	Study population	Health economic model
Age	[redacted]		
Sex (male, %)			
Weight			

Abbreviations are defined in the list of Abbreviations

Geography

The DG04 trial included patients stratified by three regions – Asia, Western Europe, and Rest of the World, with 279 (56.5%) being WE (11). Subgroup analysis results based on the Western geography, which are likely the most representative of Danish patients, have been included for completeness and are presented in Appendix B.1.2. Similarly for the RAINBOW study, PFS and OS for the regional subgroups have been presented.

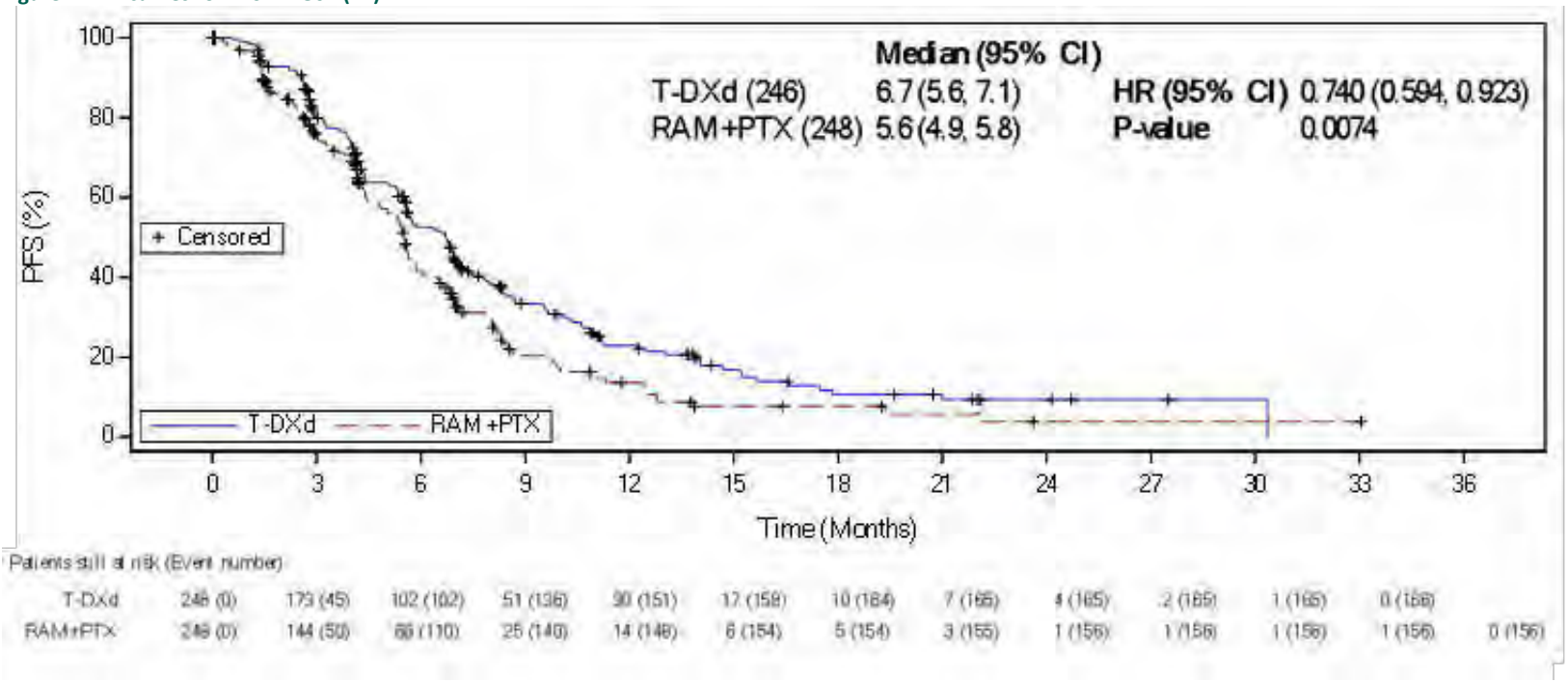
6.1.4 Analysis method

All analyses were conducted in accordance with the ITT principle. Details of the statistical methods are provided in Appendix B. Graphical assessments of the proportional hazard assumption are provided in Appendix E.

6.1.5 Effect – Results per Study: DESTINY-Gastric04

Figure 2 shows the KM plot for PFS in the ITT population in DG04. In DG04, T-DXd improved PFS versus RAM+PTX, with a median PFS of 6.7 months (95% CI 5.6–7.1) compared with 5.6 months (95% CI 4.9–5.8), corresponding to a HR of 0.74 (95% CI 0.59–0.92); landmark PFS was 52.6% at 6 months and 22.9% at 12 months for T-DXd versus 41.5% and 13.6% for RAM+PTX (33). This is a clinically meaningful difference in PFS.

Figure 2. KM curves for PFS – DG04 (11)



Abbreviations are defined in the list of Abbreviations

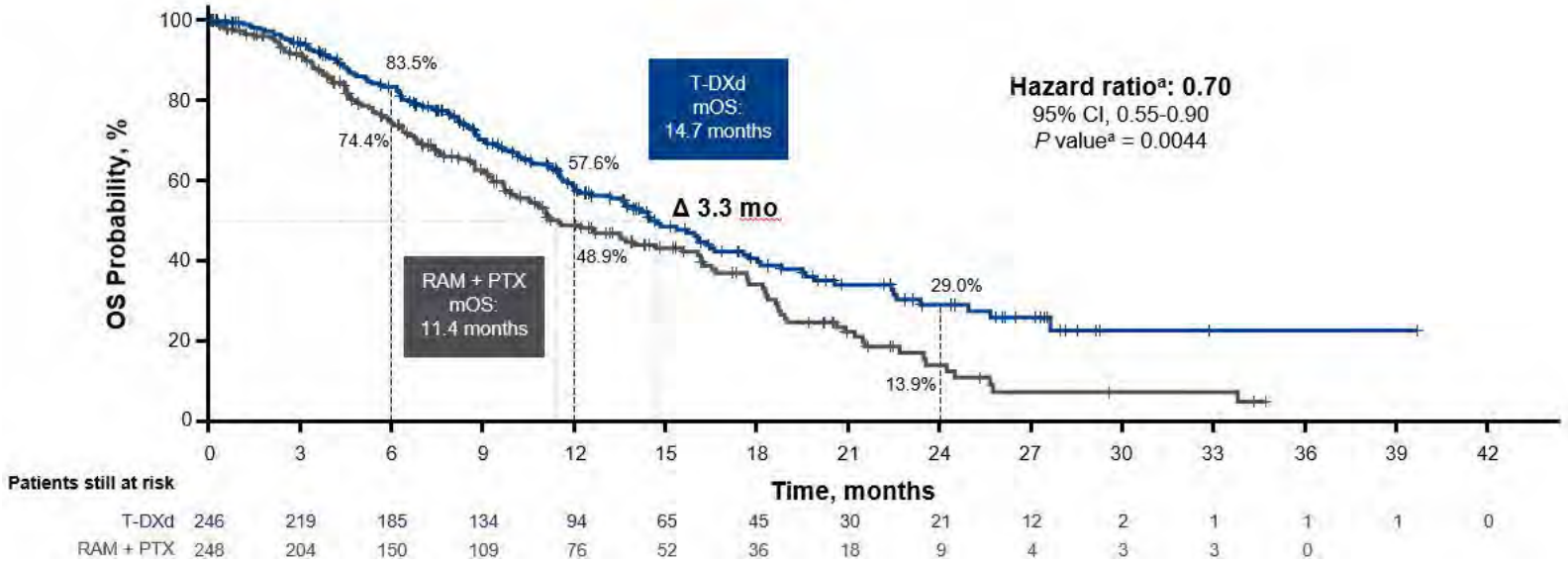
Figure 3 shows the KM plot for OS in the ITT population (DG04). Median OS was 14.7 months (95% CI 12.1-16.6) in the T-DXd arm, compared to 11.4 months (95% CI 9.9-15.5) in the RAM+PTX arm (11). The OS HR was 0.70 (95% CI 0.55–0.90, p=0.004), corresponding to a 30% relative reduction in the risk of death with T-DXd, a clinically meaningful difference. Half of the patients had an event (50.4%) in the T-DXd group at the DCO, whilst for those treated with RAM+PTX, 57.3% patients had an event.

Landmark survival rates indicate a sustained benefit with T-DXd over time. At 12 months, 57.6% of patients were alive in the T-DXd group versus 48.9% in the comparator. At 24 months, survival was 29.0% versus 13.9%, respectively, suggesting not only prolongation of survival but also a greater likelihood of longer-term benefit with T-DXd, a clinically important outcome.

In DG04, 64 (25.8%) of patients randomised to the RAM+PTX received subsequent treatment with an anti-HER2 ADC (refer to section 3.4 and Appendix N for more information). A RPSFTM was used to adjust for treatment crossover both with and without re-censoring. The crossover-adjusted analysis without re-censoring is presented in Figure 4. The median OS for RAM+PTX was [redacted] months ([redacted] when adjusted for crossover (9). Further details on the crossover methods are provided in Appendix N.

The median TTD were [redacted] months and [redacted] months for T-DXd and RAM+PTX, respectively (11). The TTD KM curve is presented in Figure 5. The main reason for discontinuation was disease progression.

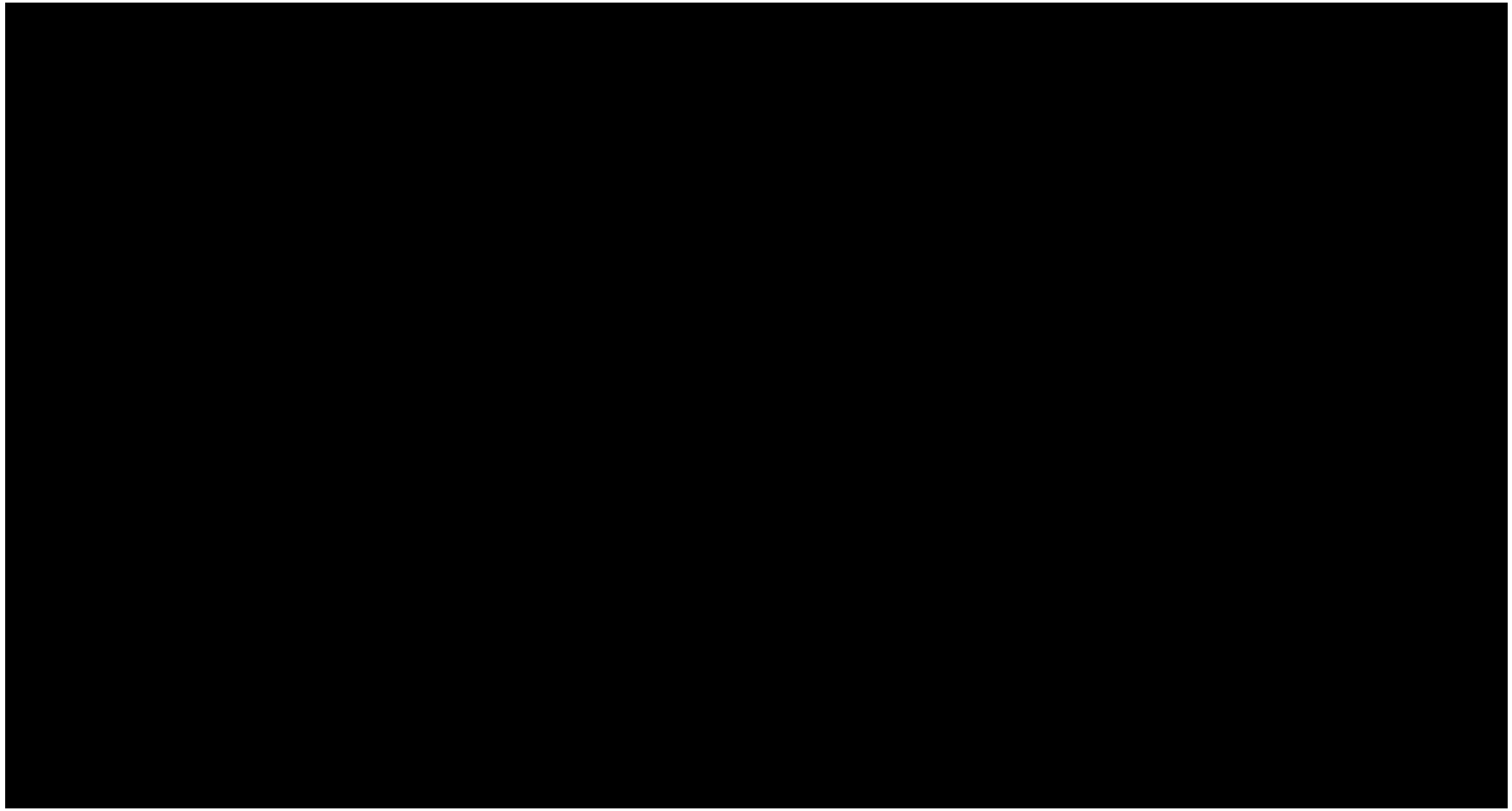
Figure 3. KM curves for OS– DG04 (33)



Abbreviations are defined in the list of Abbreviations

Notes: At DCO (October 24, 2024), the median duration of OS follow-up was 16.8 months for T-DXd and 14.4 months for RAM+PTX. Boundary for superiority: 2-sided P < 0.0228.

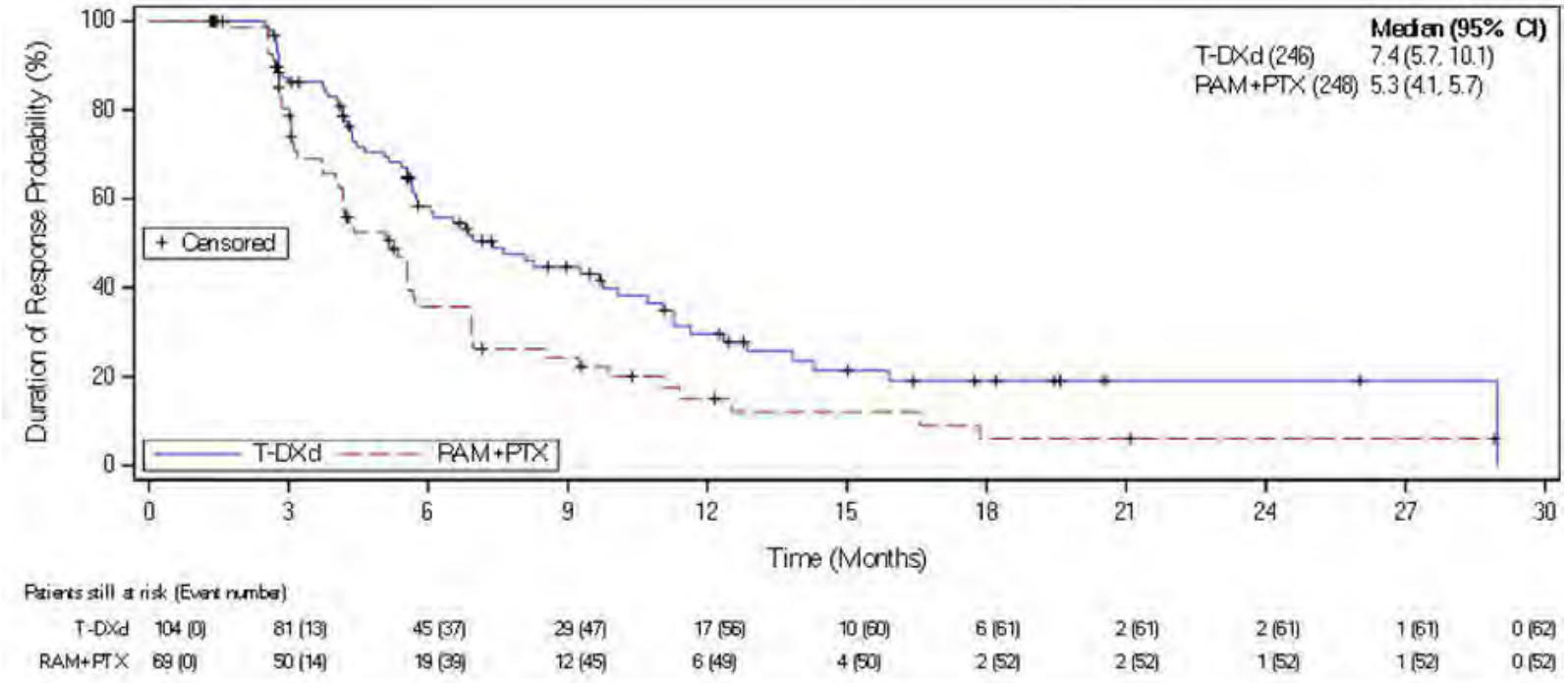
aTwo-sided P value from stratified log-rank test and stratified Cox proportional hazards model adjusted for stratification factor: HER2 status (IHC 3+ or IHC 2+/ISH+).





The confirmed ORR was 44.3% (95% CI 37.8–50.9) for T-DXd and 29.1% (95% CI 23.4–35.3) for RAM+PTX. The complete response (CR) rate was 3.0% with T-DXd compared to 1.3% with RAM+PTX (11). The disease control rate (DCR)—including CR, partial response (PR), and stable disease (SD)—was 91.9% for T-DXd and 75.9% for RAM+PTX. The duration of confirmed CR or PR was 7.4 months (95% CI 5.7–10.1) for T-DXd and 5.3 months (95% CI 4.1–5.7) for RAM+PTX. The higher response and DCRs observed with T-DXd indicate greater tumour shrinkage and more upfront disease control, which is particularly relevant for symptom relief and may contribute to prolonged survival. The duration of response is presented in Figure 6 and Table 29 includes an overview of treatment response estimates observed in DG04.

Figure 6. KM curves for DoR by investigator assessment - DG04 (33)



Abbreviations are defined in the list of Abbreviations

Table 29. Overview of treatment response – DG04 (11)

	T-DXd n = 246	RAM+PTX n = 248
Confirmed ORR (95% CI)[a] %	**44.3 (37.8-50.9)**	**29.1 (23.4-35.3)**
P value	0.0006	
Difference (95% CI)[b] %	15.1 (6.1-24.2)	
DoR. median (95% CI), months	**7.4 (5.7-10.1)**	**5.3 (4.1-5.7)**
DCR (95% CI) %	**91.9 (87.7-95.1)**	**75.9 (70.0-81.2)**
Confirmed BOR, n (%)		
CR[c]	7 (3.0)	3 (1.3)
PR	97 (41.3)	66 (27.8)
SD[d]	112 (47.7)	111 (46.8)
PD	13 (5.5)	22 (9.3)
NE	6 (2.6)	35 (14.8)

Abbreviations are defined in the list of Abbreviations

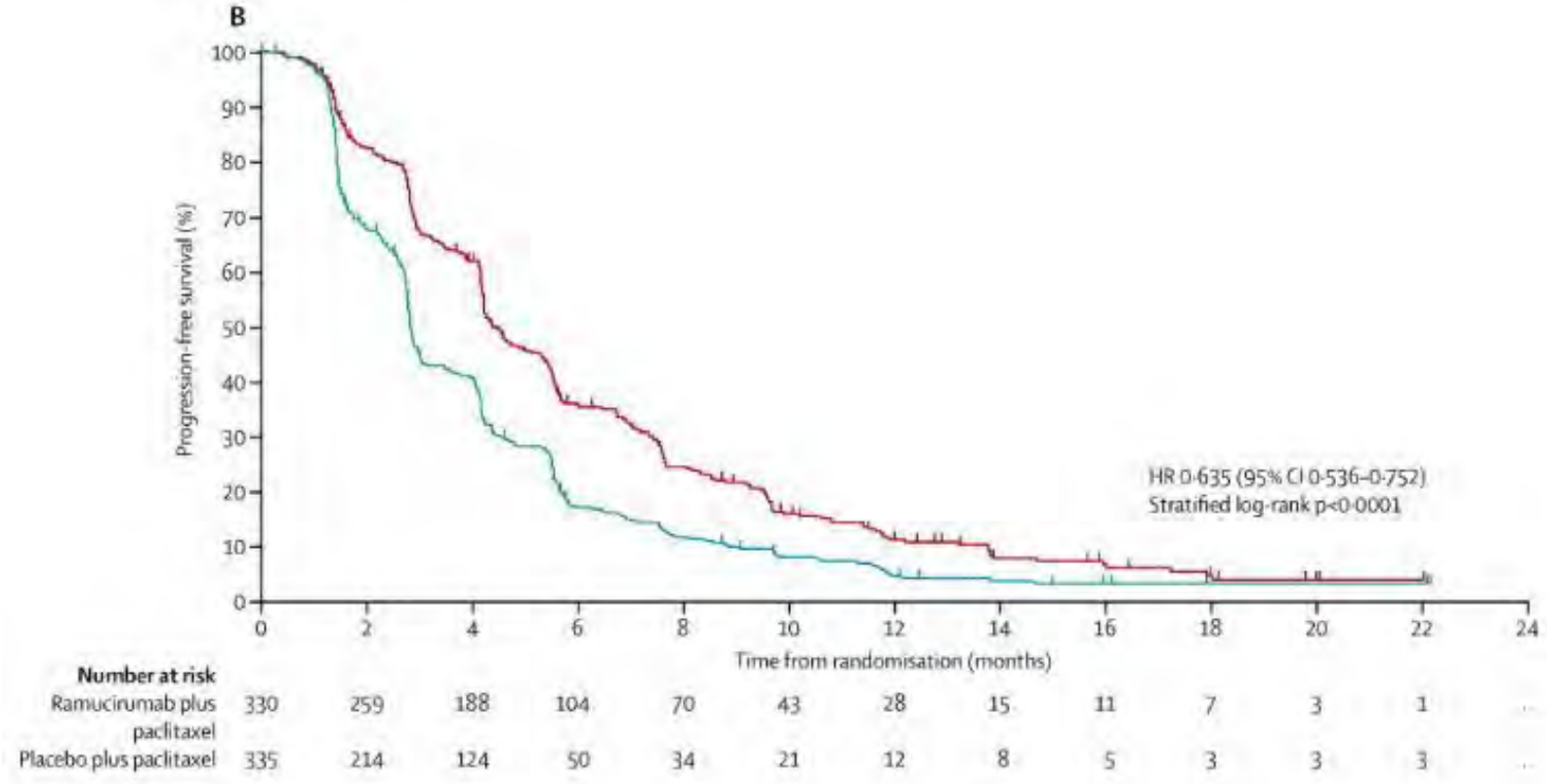
[a]Based on Clopper-Pearson method for single proportion. [b]2-sided 95% CI for the difference in ORR is based on Wald method using continuity correction. [c]CR patients without target lesions at baseline were included. [d]Non-CR/non-PD patients without target lesions at baseline were included.

6.1.6 Effect – Results per study: RAINBOW

In RAINBOW (10), RAM+PTX improved PFS versus PTX alone, with a median of 4.4 months (95% CI 4.2–5.3) versus 2.9 months (95% CI 2.8–3.0), yielding a HR of 0.64 (95% CI 0.54–0.75). Six-month PFS was 36% with RAM+PTX versus 17% with PTX, and nine-month PFS was 22% versus 10%, respectively. Figure 7 shows the KM plot for PFS in the RAINBOW study.

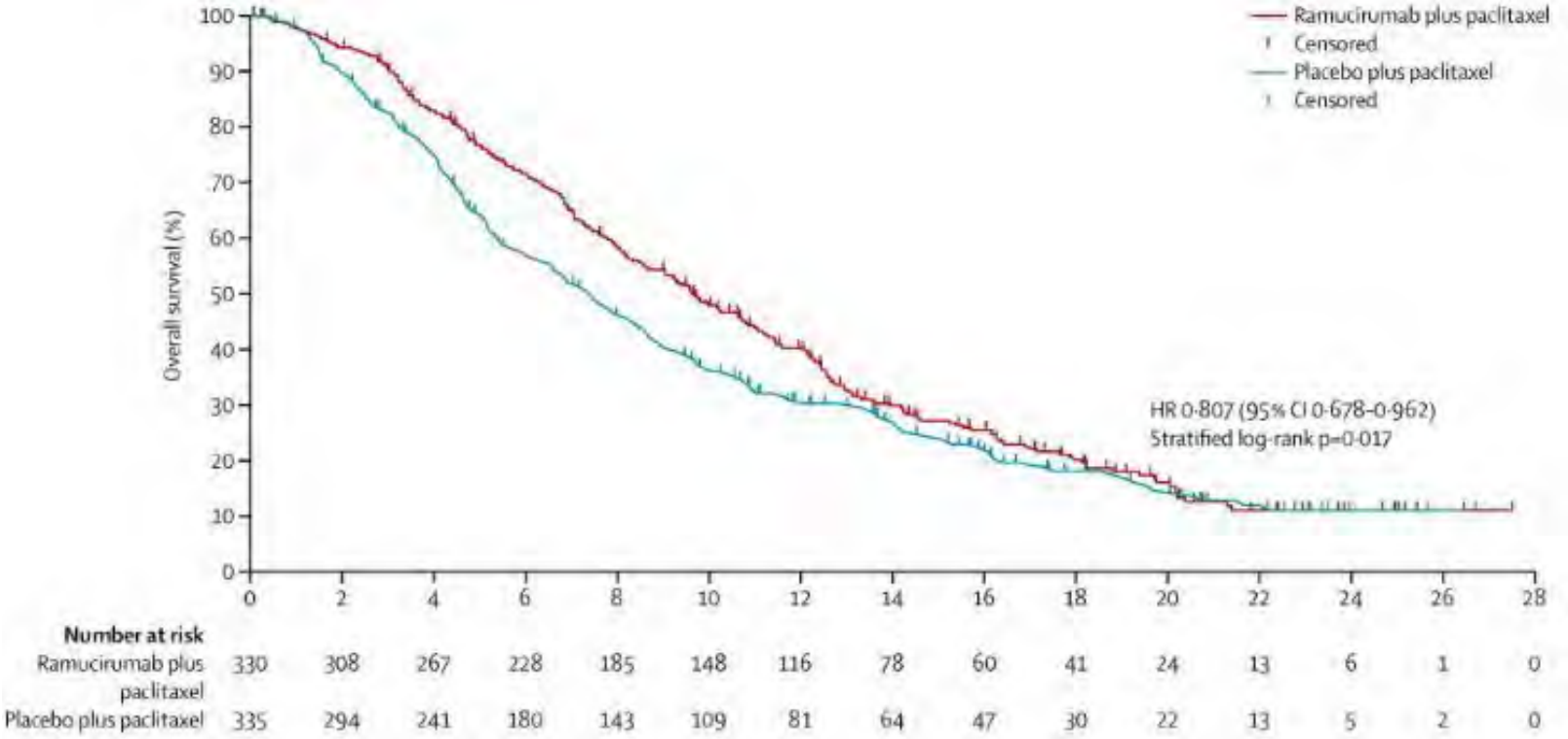
The observed OS for RAM+PTX and PTX in RAINBOW is presented in Figure 8.

Figure 7. KM curves for PFS – RAINBOW (10)



Abbreviations are defined in the list of Abbreviations

Figure 8. KM curves for OS – RAINBOW (10)



Abbreviations are defined in the list of Abbreviations

No TTD data are available from RAINBOW; consequently, the RAINBOW PFS HR (PTX vs RAM+PTX) was applied to the DG04 RAM+PTX TTD data to estimate TTD for SoC.

The confirmed ORR was 27.9% (95% CI 23.3–33.0) for RAM+PTX and 16.1% (95% CI 12.5–20.6) for placebo+PTX (10). The CR rate was 0.6% with RAM+PTX compared to 0.3% with placebo+PTX. The DCR—including CR, PR, and SD —was 80.0% (95% CI 75–84) for RAM+PTX and 63.6% (95% CI 58–69) for placebo+PTX. The median duration of confirmed CR or PR was 4.4 months (interquartile range (IQR): 2.8–7.5) for RAM+PTX and 2.8 months (IQR: 1.4–4.4) for placebo+PTX.

7. Comparative analyses of efficacy

The treatment for advanced HER2-positive GC/GEJC is individualized and depends on various factors, including toxicities from previous treatments, PS, and comorbidities. RAM+PTX, the comparator treatment in DG04, is neither reimbursed nor used in Denmark. Therefore, an ITC was required to estimate the efficacy, costs and QALY of the current SoC for patients with advanced HER2-positive GC/GEJC who have previously received a trastuzumab-based regimen in Denmark.

7.1 Analysis Method

An ITC was implemented by applying the HRs for RAM+PTX versus PTX from the RAINBOW study to the RAM+PTX arm in DG04 to derive PTX (i.e. SoC) outcomes; T-DXd was modelled independently (Figure 9). The approach resembles a Bucher analysis, using a single external source (RAINBOW) and a common anchor (RAM+PTX). The RAINBOW study was identified in the SLR (Appendix H).

This simplified approach using RAINBOW data, anchored to the DG04 RAM+PTX arm, was judged to be most robust and straightforward for estimating the efficacy of SoC by focusing solely on the two relevant treatments (RAM+PTX and PTX), thereby avoiding additional variability that can arise from larger evidence networks. The full method description is included in Appendix D.

An NMA can leverage broader direct and indirect evidence, potentially increase precision and enable comparative ranking across multiple options; however, it relies on stronger assumptions of homogeneity, transitivity, and consistency, and clinical applicability may be reduced if less relevant regimens or populations are included. In contrast, the simplified ITC applied here focuses on the most relevant anchor (RAM+PTX) and studies, limiting heterogeneity from unrelated regimens and minimizing global assumptions.

The definition of outcomes was aligned across the two studies (see section 3.5.1). OS and PFS outcomes from DG04 and RAINBOW are presented in section 6.1.5 and section 6.1.6, respectively, and are therefore not repeated here. No formal definition of TTD was provided in RAINBOW, and no estimate was reported. For this analysis, it was assumed that the PFS HR reported in RAINBOW is representative of TTD as well.



7.2 Results of the Comparative Analysis

HRs describing the relative effect of RAM+PTX vs PTX and RAM+PTX vs T-DXd are presented in Table 30.

In the absence of head-to-head data in the relevant patient population, anchoring the relative effect of RAM+PTX vs PTX observed in RAINBOW to DG04 RAM+PTX data was assessed as appropriate. This approach, however, likely generates optimistic clinical effect estimates for PTX, given the difference in study populations and direction of treatment effect modifiers discussed in section 6.1.2.1.3. The comparative analysis should therefore be considered conservative, with potential for a larger clinical benefit of T-DXd vs PTX in practice.

Although no HR for T-DXd versus PTX was applied in the simplified ITC (T-DXd was modelled independently), the observed OS difference corresponds to a HR of approximately [redacted] PFS HR: [redacted] for T-DXd vs PTX when conducting a Bucher analysis, underscoring T-DXd's effectiveness and clinical relevance for this patient population.

Table 30. Results from the comparative analysis (simplified ITC) of T-DXd vs. RAM+PTX/PTX in patients with HER2-positive GC or GEJC

Outcome	**T-DXd (n=246)** Months, median (95%)	**RAM+PTX (n=248)** Months, median (95% CI)	**Observed** hazard ratio (95% CI)*
DG04 (9, 33)			
Progression-free survival	6.7 (5.6–7.1)	5.6 (4.9–5.8)	0.74 (0.59–0.92)
Overall survival	14.7 (12.1–16.6)	[redacted]	[redacted]
Outcome	**RAM+PTX** (n=330) Months, median (95%)	**PTX (n=335)** Months, median (95% CI)	**Observed** hazard ratio (95% CI)
RAINBOW (10)			

Progression-free survival	4.4 (4.2–5.3)	2.9 (2.8–3.0)	0.64 (0.54–0.75)
Overall survival	9.6 (8.5–10.8)	7.4 (6.3–8.4)	0.80 (0.68–0.96)

Simplified ITC*(10)		Hazard ratio (95% CI)
Progression-free survival	RAM +PTX vs PTX	0.64 (0.54–0.75)
Overall survival	RAM +PTX vs PTX	0.80 (0.68–0.96)

Abbreviations are defined in the list of Abbreviations

† Because a proportion of patients in the RAM+PTX arm in DG04 received post-progression anti-HER2 ADC therapy (T-DXd 21% and disitamab vedotin/RC48 4.8%), a crossover adjustment was applied to the RAM+PTX OS using RPSFTM per NICE DSU TSD 24 to mitigate treatment-switching bias. For more information on the crossover adjustment, refer to Appendix O. * Note that T-DXd was modelled independently of RAM+PTX and PTX in this assessment

A summary of efficacy estimates for the DG04, and RAINBOW studies is provided in Table 31.

Table 31. Comparative efficacy for DG04 and RAINBOW studies

Study	Arm	Endpoint	DCO	Events, n (%)	Median, months (95% CI)	Fixed time rate estimates (6, 9, 12 and 24 months) (%)
DG04	T-DXd	OS	24 Oct 2024	124 /246 50.4%	14.7 (12.1–16.6)	6: NR 9: NR 12: 57.6% 24: 29.0%
DG04	RAM+PTX	OS	24 Oct 2024	142 / 248 57.3%	11.4 (9.9–15.5)	6: NR 9: NR 12: 48.9% 24: 13.9%
RAINBOW	RAM+PTX	OS	12 Jul 2013	256 / 330 (77.6%)	9.6 (8.5–10.8)	6: 72% 9: NR 12: 40% 24: NR
RAINBOW	Placebo +PTX	OS	12 Jul 2013	260/335 (77.6%)	7.4 (6.3–8.4)	6: 57% 9: NR 12: 30% 24: NR
DG04	T-DXd	PFS	24 Oct 2024	NR	6.7 (5.6–7.1)	6: 52.6% 9: NR 12: 22.9% 24: NR
DG04	RAM+PTX	PFS	24 Oct 2024	NR	5.6 (4.9–5.8)	6: 41.5% 9: NR

						12: 13.6% 24: NR
RAINBOW	RAM+PTX	PFS	12 Jul 2013	NR	4.4 (4.2–5.3)	6: 36% 9: 22% 12: NR 24: NR
RAINBOW	Placebo +PTX	PFS	12 Jul 2013	NR	2.9 (2.8–3.0)	6: 17% 9: 10% 12: NR 24: NR

7.3 Supplementary analysis

Relative efficacy based on NMA

To supplement the simplified ITC, a NMA was conducted (described in more detail in Appendix D). The treatment of patients with advanced HER2-positive GC/GEJC who have received a prior trastuzumab-based regimen depends on multiple factors, and therefore several comparator therapies must be considered when assessing the cost-effectiveness of T-DXd in Denmark. This is reflected in the base case (refer to section 12.1.1) by using a basket of SoC treatments and anchoring efficacy to PTX (RAINBOW), assuming similar efficacy across treatments (a simplified and conservative approach).

However, a NMA suggests there may be differences in outcomes across comparator therapies, with both DTX and irinotecan having lower PFS and OS HRs than PTX, indicating poorer outcomes (Table 32). To address uncertainty in SoC efficacy, supplementary analyses were conducted in which incremental cost-effectiveness ratios (ICERs) were estimated separately for T-DXd versus PTX, DTX, and irinotecan, individually. The efficacy of PTX, DTX, and irinotecan was estimated by applying the NMA derived HRs to the T-DXd arm (T-DXd as reference arm). In addition, a weighted ICER was presented, accounting for all relevant SoC treatments separately based on the NMA (as opposed to the simplified ITC used in the base case) (refer to section 12.1.2).

Table 32. HRs based on NMA (69)

	Hazard ratio (95% CrI)**		
Outcome T-DXd vs.	PTX	DTX	Irinotecan
Progression-free survival	[redacted]	[redacted]	[redacted]
Overall survival†	[redacted]	[redacted]	[redacted]

Abbreviations are defined in the list of Abbreviations

† Because a proportion of patients in the RAM+PTX arm in DG04 received post-progression anti-HER2 ADC therapy (T-DXd 21% and disitamab vedotin/RC48 4.8%), a crossover adjustment was applied to the RAM+PTX OS using RPSFTM per NICE DSU TSD 24 to mitigate treatment-switching bias. For more information on the crossover adjustment, refer to Appendix O. **fixed-effects

Western European subgroup

In both the DG04 and RAINBOW study, the relative treatment effect was examined for Western subgroups. For DG04, this included WE patients (56.5% of the total population)

(11) and for the RAINBOW study this included the USA, Europe, Israel and Australia (60% of the total population (10)).

A supplementary analysis was conducted using these Western subgroups to better reflect the Danish patient population in terms of the relative efficacy of T-DXd vs SoC. Hazard ratios for PFS and OS were estimated using the Bucher indirect comparison based on subgroup analyses reported in Appendix B.1.2. The HRs of T-DXd vs PTX (i.e. SoC) for the Western subgroup are 0.49 (95% CI 0.30 – 0.70) for PFS/ TTD and 0.45 (95% CI 0.30 – 0.67) for OS with the Bucher approach (10, 33). Consistent with the supplementary analysis using the NMA to generate SoC outcomes, for the Western subgroup the derived HRs were applied to the T-DXd arm (ITT) to estimate SoC outcomes. Cross-over was not considered for this analysis. The Western subgroup analysis can be seletected in the "Survival inputs sheet" in the cost-effectiveness model, using the drop down menu for the model population. The ICER for this subgroup is presented in section 12.1.2.

7.4 Effect – PFS

Refer to section 6.1.5 (DG04) and section 6.1.6 (RAINBOW).

7.5 Effect – OS

Refer to section 6.1.5 (DG04) and section 6.1.6 (RAINBOW).

8. Safety

The incidence of treatment-emergent adverse events (TEAEs) for T-DXd was informed by DG04. For Danish SoC, not investigated in DG04, incidence of TEAEs were sourced from pivotal studies identified through the SLR (Appendix H). The clinical documentation of DG04 and for SoC is described below: *intervention* and *comparator*.

The AE frequencies applied in the model are used for two purposes: to estimate resource use due to AE management (11.2.4) and to quantify QALY loss associated with AEs (10.3.3). AE frequencies applied in the model are presented in Table 58.

Safety data from the clinical documentation

Intervention

The safety profile of T-DXd in the DG04 study was 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. The safety analysis in DG04 included all patients who received at least one dose of the study drug (n=244 in the T-DXd group). Median treatment duration (treatment exposure for the safety analysis set [SAS]) for T-DXd was 5.4 months (11). In DG04, AEs were graded according to NCI-CTCAE v5.0. Table 33 presents the overall safety summary for DG04, based on the SAS population (11).

Table 33. Overview of adverse events [DG04; SAS population (DCO date: 24 Oct 2024) (11)]

	T-DXd (n=244) (11)	RAM+PTX (n=233) (11)	Difference, %-points	Difference, RR (95 % CI)
All adverse events (AE), n (%)	244 (100)	228 (97.9)	0.021 (-0.001, 0.044)	1.02 [1.00, 1.04]

	T-DXd (n=244) (11)	RAM+PTX (n=233) (11)	Difference, %-points	Difference, RR (95 % CI)
Serious AE (SAE), n (%)	100 (41.0)	104 (44.6)	-0.037 (-0.129, 0.056)	0.92 [0.75, 1.13]
AE grade ≥ 3, n (%) [2]	167 (68.4)	172 (73.8)	-0.054 (-0.139, 0.032)	0.93 [0.83, 1.04]
Dose reduction due to AE, n (%)	77 (31.6)	87 (37.3)	-0.058 (-0.147, 0.032)	0.85 [0.66, 1.08]
Treatment discontinuation due to AE, n (%)	35 (14.3)	40 (17.2)	-0.028 (-0.098, 0.041)	0.84 [0.55, 1.27]

Abbreviations are defined in the list of Abbreviations
Notes: TEAEs were defined as any AE that emerged or worsened following the first dose of study treatment up to 47 days after the last dose; SAEs with onset ≥48 days after the last dose were also considered TEAEs if judged related to study treatment.

Table 34 presents AEs occurring at a frequency of at least 10% in any treatment arm, irrespective of grade or severity, together with AEs of grade ≥3 that occurred in ≥3% of patients in any arm. The most frequently reported treatment-emergent serious adverse events (SAE) reported in ≥1% of subjects in either treatment group (SAS population) is shown in Appendix F.

Table 34. Proportion of patients with adverse events [DG04 DCO date: 24 Oct 2024) (11)]

	T-DXd (n=244) (11)		RAM+PTX (n=233) (11)	
	All	**Grade ≥ 3**	**All**	**Grade ≥ 3**
Subjects with any TEAE	244 (100)	166 (68.0)	228 (97.9)	172 (73.8)
Fatigue	141 (57.8)	20 (8.2)	114 (48.9)	13 (5.6)
Nausea	129 (52.9)	13 (5.3)	47 (20.2)	0
Neutropenia	121 (49.6)	72 (29.5)	117 (50.2)	84 (36.1)
Anaemia	120 (49.2)	56 (23.0)	104 (44.6)	48 (20.6)
Decreased appetite	98 (40.2)	8 (3.3)	70 (30.0)	5 (2.1)
Diarrhoea	86 (35.2)	-	66 (28.3)	-
Transaminases increased	69 (28.3)	-	37 (15.9)	-
Leukopenia	67 (27.5)	19 (7.8)	52 (22.3)	29 (12.4)
Thrombocytopenia	67 (27.5)	22 (9.0)	37 (15.9)	8 (3.4)
Constipation	66 (27.0)	-	43 (18.5)	-
Vomiting	64 (26.2)	10 (4.1)	33 (14.2)	3 (1.3)
Alopecia	61 (25.0)	-	62 (26.6)	-
Abdominal pain	56 (23.0)	8 (3.3)	50 (21.5)	7 (3.0)
Weight decreased	53 (21.7)	-	26 (11.2)	-
Hypokalaemia	40 (16.4)	20 (8.2)	21 (9.0)	8 (3.4)
Hypalbuminaemia	39 (16.0)	-	23 (9.9)	-
Pyrexia	39 (16.0)	-	34 (14.6)	-
Adjudicated drug-related ILD	34 (13.9)	-	3 (1.3)	-
Cough	31 (12.7)	-	34 (14.6)	-
Lymphopenia	29 (11.9)	8 (3.3)	18 (7.7)	6 (2.6)
Musculoskeletal pain	28 (11.5)	-	48 (20.6)	-
Blood alkaline phosphatase increased	25 (10.2)	-	16 (6.9)	-
Oedema peripheral	25 (10.2)	-	30 (12.9)	-
Stomatitis	17 (7.0)	-	35 (15.0)	-
Peripheral sensory neuropathy	8 (3.3)	-	35 (15.0)	-
Neuropathy peripheral	7 (2.9)	-	24 (10.3)	-

	T-DXd (n=244) (11)		RAM+PTX (n=233) (11)	
Hypertension	6 (2.5)	1 (0.4)	44 (18.9)	25 (10.7)
Epistaxis	-	-	-	-
Pneumonia	-	12 (4.9)	-	7 (3.0)
Disease progression	-	8 (3.3)	-	18 (7.7)
Febrile neutropenia	-	7 (2.9)	-	11 (4.7)
Ascites	-	5 (2.0)	-	9 (3.9)

Abbreviations are defined in the list of Abbreviations
Notes: AEs were coded using MedDRA v27.1 and graded according to NCI-CTCAE v5.0.

Comparator

AE incidences for SoC were combined using a weighted average based on the proportional distribution of SoC regimens used in Danish clinical practice (Table 50) ensuring that the composite safety profile reflects the expected real-world SoC mix.
For the comparator studies, AE grading was based on earlier common terminology criteria for adverse events CTCAE/CTC versions: NCI-CTCAE v4.02 in RAINBOW (PTX) (10), NCI-CTCAE v3.0 in COUGAR-02 (DTX) (34), and NCI CTC v2.0 in Thuss-Patience et al. (irinotecan) (35).

An overview of AE as per the DMC application form is provided in Appendix M (per treatment regimen: Table 127, Table 130, and Table 133). Furthermore, Appendix M shows all AEs with a frequency of ≥ 10%, regardless of grade/severity recorded in RAINBOW, COUGAR-02 and by Thuss-Patience et al, as well as all AEs grade ≥ 3, which occurred in ≥ 3% in neither of the treatment arm (where available) (Table 128, Table 131, and Table 134). SAE data were not available for PTX, DTX, or irinotecan in the published studies, and therefore Appendix F only contains SAE data from the DG04 study.

Adverse event of special interest

Interstitial lung disease (ILD)/pneumonitis and left ventricular (LV) dysfunction are adverse events of special interest (AESIs) in the DG04 study. In the T-DXd arm, 13.9% of patients experienced drug-related ILD/pneumonitis (2.9% grade 1, 10.7% grade 2, 0.4% grade 3), with no grade 4 or fatal events. LV dysfunction was reported in 2.5% of patients receiving T-DXd (33).

9. Extrapolation of patient transitions

9.1 Clinical Data Used for Extrapolation of Patient Transitions

Time-to-event data for T-DXd were obtained from the DG04 study. For Danish SoC, including PTX, DTX, and irinotecan (Table 50), treatments were assumed to be interchangeable in terms of efficacy and PTX was used as the proxy to estimate SoC outcomes.

An overview of data sources for clinical outcome is presented in Table 35. Although RAM+PTX is not used in Denmark, it was retained as a reference arm to reflect relative efficacy of SoC versus T-DXd, with RAM+PTX linked to PTX via the RAINBOW study. HRs from RAINBOW (used in the simplified ITC) and the NMA are presented in (Table 30).

Extrapolated OS and PFS using parametric survival models then informed health-state occupancy over a lifetime horizon.

Because no relevant TTD HR was reported in RAINBOW, the PFS HR from RAINBOW was used as a proxy for the TTD HR.

Table 35. Overview of data sources for clinical endpoints

Outcome	Data source for extrapolation	
	T-DXd	Standard of care
PFS	DG04 - T-DXd arm; ITT population	RAINBOW (RAM+PTX vs PTX) PFS HR applied to DG04 RAM+PTX arm (reference arm)
OS	DG04 - T-DXd arm; ITT population	RAINBOW (RAM+PTX vs PTX) OS HR applied to DG04 RAM+PTX arm (reference arm)
TTD	DG04 - T-DXd arm; ITT population	RAINBOW (RAM+PTX vs PTX) PFS HR applied to DG04 RAM+PTX arm (reference arm)

Abbreviations are defined in the list of Abbreviations

9.2 Extrapolation Using Parametric Extrapolation Models

9.2.1 Extrapolation of progression-free survival

Table 36. Overview of assumptions regarding extrapolation of PFS

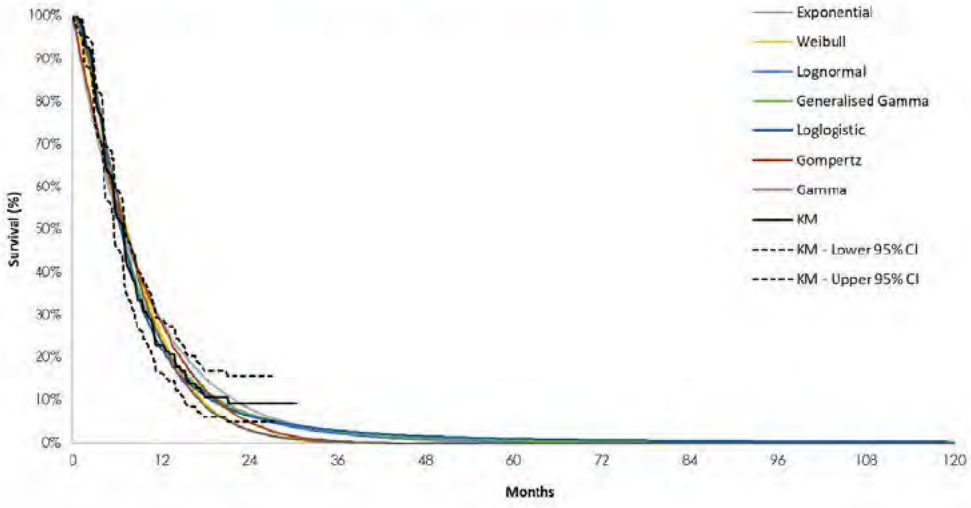
Method	Description
Data	DG04 (registrational study for T-DXd) and RAINBOW (RAM+PTX vs PTX) PFS HR used to generate PFS for SoC
Selected distribution	**T-DXd:** Generalized gamma **SoC:** Generalized gamma (HR applied to DG04 RAM+PTX arm)
Models investigated	Distributions explored: exponential, Weibull, lognormal, loglogistic, gamma, Gompertz, generalized gamma; independent fit
Assumptions	
Proportional hazards between intervention and comparator	T-DXd was modelled independently of SoC. For the SoC comparator, PH were assumed between RAM+PTX and PTX.
Flexible parametric models	No
Cure point and/or share	No
Treatment waning	No
Any other assumptions	Given limited follow-up in RAINBOW and DG04 and the absence of suitable external data to inform late tails, T-DXd, RAM+PTX, and SoC were assumed to share the same functional-form hazard for PFS
Internal validity	
Distribution with best AIC fit	**T-DXd:** Lognormal, Loglogistic, Generalized gamma **SoC**: Loglogistic (for RAM+PTX reference arm, not considered in the analysis)

Method	Description
Distribution with best BIC fit	**T-DXd:** Lognormal, Loglogistic **SoC**: Loglogistic (for RAM+PTX reference arm, not considered in the analysis)
Distribution(s) with best visual fit on probability scale (e.g., Kaplan-Meier data)	**T-DXd:** Lognormal, Loglogistic, Generalized gamma (best alignment with KM) **SoC**: not assessed
Distribution(s) with best visual fit according to evaluation of smoothed hazards	**T-DXd:** Generalized gamma **SoC:** Generalized gamma
External validity	
References for validating external validity	Not assessed
Distribution with highest external validity	Not assessed

Abbreviations are defined in the list of Abbreviations

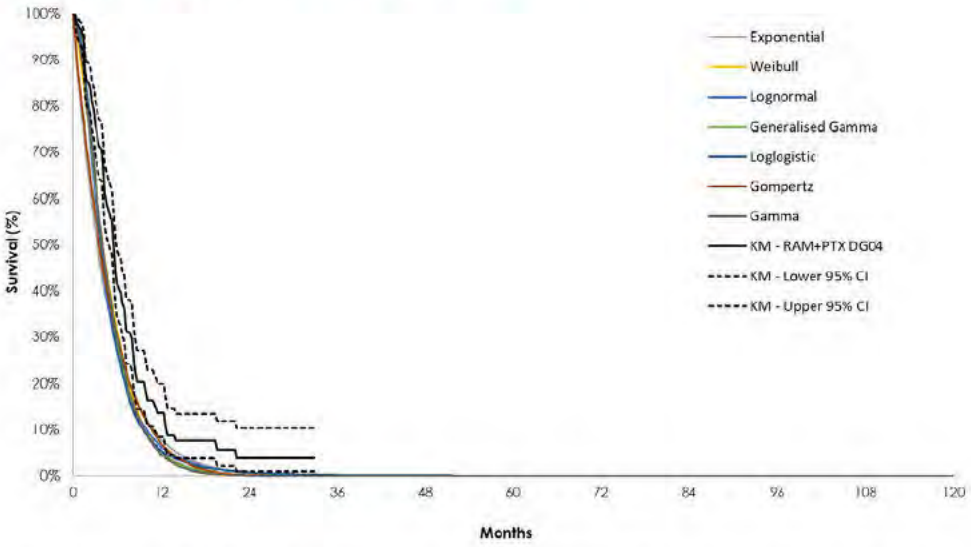
Figure 10 and Figure 11 present all parametric models explored for PFS for T-DXd and SoC. Figure 12 shows the observed data alongside the selected extrapolation models for both treatment arms.

Figure 10. PFS – all parametric models explored for T-DXd



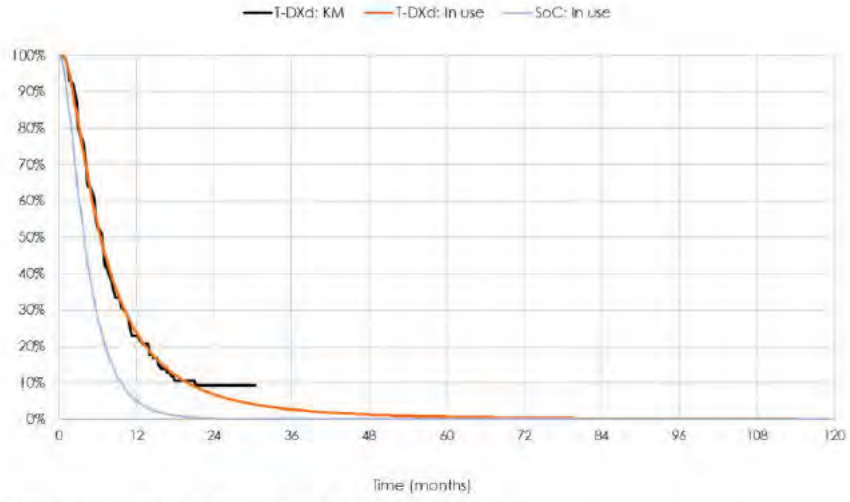
Abbreviations are defined in the list of Abbreviations

Figure 11. PFS – all parametric models explored for SoC*



Abbreviations are defined in the list of Abbreviations *RAM+PTX DG04 KM data presented for completeness

Figure 12. Base case extrapolation – PFS (both arms)



Abbreviations are defined in the list of Abbreviations
Notes: KM data not available for the SoC arm

9.2.2 Extrapolation of overall survival

Table 37. Overview of assumptions regarding extrapolation of OS

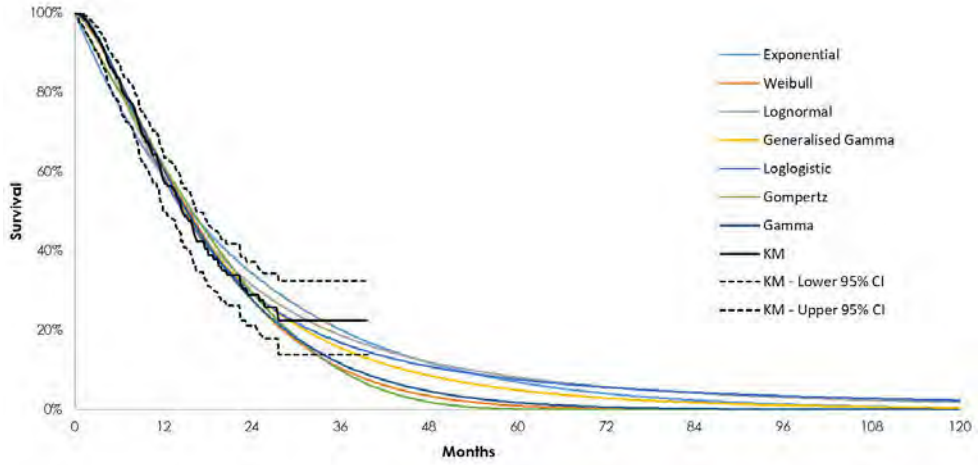
Method/approach	Description/assumption
Data	DG04 as registrational study for T-DXd; RAINBOW (RAM+PTX vs PTX) OS HR used to generate OS for SoC
Selected distribution	**T-DXd:** Lognormal **SoC**: Gamma (HR applied to DG04 RAM+PTX arm)
Models investigated	Distributions explored: exponential, Weibull, lognormal, loglogistic, gamma, Gompertz, generalized gamma; independent fit

Method/approach	Description/assumption
Assumptions	
Proportional hazards between intervention and comparator	T-DXd was modelled independently of SoC. For the SoC comparator, the analysis incorporated a hazard adjustment to reflect potential non-proportional hazards between RAM+PTX and PTX.
Flexible parametric models	No
Cure point and/or share	No
Treatment waning	No
Any other assumptions	**Crossover adjustment for OS for reference arm** Crossover adjustment was considered because subsequent anti HER2 ADC use occurred in the DG04 RAM+PTX arm. In DG04, 64 patients (25.8%) receiving RAM+PTX had post progression anti HER2 ADC therapy (T-DXd 21% or disitamab vedotin/RC48 4.8%). As T-DXd and RC48 are not routinely available in the Danish third line/later setting, this subsequent ADC use could lead to underestimation of the relative OS benefit of T-DXd compared with RAM+PTX in DG04. Following NICE DSU TSD 24 (45), RPSFTM were implemented with and without re censoring. For model fitting, crossover adjustment without re censoring was used for the RAM+PTX arm in the base case to maximize data. Appendix N reports crossover methods and treatment specific estimates.
Internal validity	
Distribution with best AIC fit	**T-DXd:** Lognormal, Loglogistic, Generalized gamma, gamma **SoC**: Weibull, Gamma, generalized gamma (for RAM+PTX reference arm, not considered in the analysis)
Distribution with best BIC fit	**T-DXd:** Lognormal, Loglogistic, gamma **SoC**: Weibull, Gamma (for RAM+PTX reference arm, not considered in the analysis)
Distribution(s) with best visual fit on probability scale (e.g., Kaplan-Meier data)	**T-DXd:** Lognormal, Loglogistic, Generalized gamma (best alignment with KM) **SoC**: not assessed
Distribution(s) with best visual fit according to evaluation of smoothed hazards	**T-DXd:** Lognormal, Loglogistic, Generalized gamma (best alignment with hazard plots) **SoC**: Gamma
External validity	
References for validating external validity	Published gastric cancer survival literature, hazard patterns from Destiny-gastric 02 (DG02) and RAINBOW, real-world OS for patients with HER2-positive metastatic gastric cancer, and clinical expert judgement on long-term plausibility
Distribution with highest external validity	**T-DXd:** Lognormal **SoC**: Gamma

Abbreviations are defined in the list of Abbreviations

Figure 13 and Figure 14 show all parametric models explored for OS for T-DXd and SoC. Figure 15 shows the observed data alongside the selected parametric models for both T-DXd and SoC.

Figure 13. OS – all parametric models explored for T-DXd



Abbreviations are defined in the list of Abbreviations

[redacted]



9.2.3 Extrapolation of time-to-treatment discontinuation

Table 38. Overview of assumptions regarding extrapolation of TTD

Method/approach	Description/assumption
Data	DG04 TTD data, RAINBOW (RAM+PTX vs PTX) – PFS HR used to generate TTD for SoC
Selected distribution	**T-DXd:** Generalized gamma **SoC**: Generalized gamma (HR applied to DG04 RAM+PTX arm)
Models investigated	Distributions explored: exponential, Weibull, lognormal, loglogistic, gamma, Gompertz, generalized gamma; independent fit
Assumptions	
Proportional hazards between intervention and comparator	T-DXd was modelled independently of SoC. For the SoC comparator, a proportional hazards relationship was assumed between RAM+PTX and PTX.
Flexible parametric models	No
Cure point and/or share	N/A
Treatment waning	N/A
Other assumptions	Model selection for TTD combined statistical fit, visual inspection, and clinical plausibility, with explicit consideration of alignment with PFS; both endpoints were expected to follow a similar trend. PTX TTD was derived by applying the RAINBOW PFS HR to the DG04 RAM+PTX TTD curve, and the resulting PTX TTD extrapolation was checked for coherence with the modelled PTX PFS profile.
Internal validity	
Distribution with best AIC fit	**T-DXd:** Lognormal, Loglogistic, Generalized gamma **SoC**: Loglogistic, generalized gamma, gamma (for RAM+PTX reference arm, not considered in the analysis)
Distribution with best BIC fit	**T-DXd:** Lognormal, Loglogistic, Generalized gamma

Method/approach	Description/assumption
	SoC: Loglogistic, gamma (for RAM+PTX reference arm, not considered in the analysis)
Distribution(s) with best visual fit on probability scale (e.g., Kaplan-Meier data)	**T-DXd:** Lognormal, Loglogistic, Generalized gamma **SoC**: not assessed
Distribution(s) with best visual fit according to evaluation of smoothed hazards	**T-DXd:** Generalized gamma **SoC**: Generalized gamma
External validity	
References for validating external validity	Clinical study data, anticipated alignment with PFS
Distribution with highest external validity	**T-DXd:** Generalized gamma **SoC**: Generalized gamma

Abbreviations are defined in the list of Abbreviations

Figure 16 and Figure 17 show all parametric models explored for TTD for T-DXd and SoC. Figure 18 shows the observed data alongside the selected extrapolation models for both treatment arms.







Refer to Appendix E for more information on extrapolation of PFS, OS and TTD, and selected distributions explored in scenario analyses (refer to Table 87 in Appendix E and to Table 63).

9.3 Extrapolation Using Transition Probabilities

Health state occupancy and transitions between health states were derived from PFS and OS data from DG04 and RAINBOW, as detailed in Section 9.1.

Table 39. Transition probabilities in the health economic model

From health state	To health state	Transition probability, including calculation	Assumption	Reference
Progression-free	Post-progression	OS – PFS	N/A	DG04, RAINBOW
Post-progression	Death	1 – OS	N/A	DG04, RAINBOW

Abbreviations are defined in the list of Abbreviations

Table 40. Transition matrix for [intervention/comparator]

Off/On	State A		State B	State C	...
N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations are defined in the list of Abbreviations

9.4 Summary and Validity of Extrapolated Patient Transitions

The time spent in the progression-free and progressed health states as well as the distribution of patients across health states over the analysis time horizon are presented below (Table 41, Figure 19, and Figure 20).

The state occupancy results appear reasonable and support logical and clinically plausible transitions over time, both during and beyond the observation period, across health states and treatment arms.

For T-DXd and SoC, patients spend approximately 55% and 59%, respectively, of total survival time in the post-progression health state, based on the modelled median estimates. This is broadly consistent with the clinical trial data used to inform the model.

In DG04, patients treated with T-DXd had a median PFS of 6.7 months and a median OS of 14.7 months, implying that approximately 54% of total survival time was spent in the post-progression state, based on medians. Similarly, in RAINBOW, patients receiving paclitaxel spent approximately 61% of total survival time in the post-progression state, again based on median estimates.

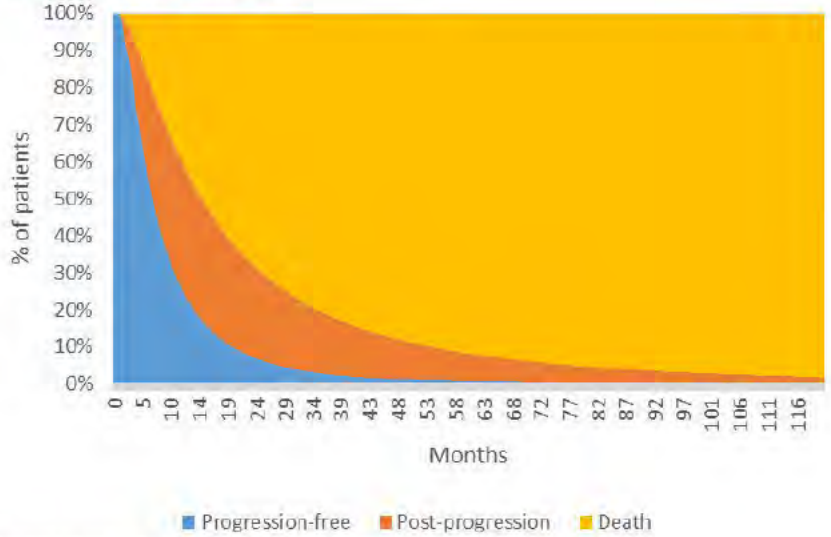
Post-progression survival is influenced not only by the effect of initial treatment but also by the availability and use of sometimes multiple subsequent treatments. The short PFS and poor OS observed with PTX (i.e., SoC) further highlight the high unmet need in this patient population. Given that the introduction of T-DXd into the treatment algorithm may increase access to subsequent treatment options for these patients, a longer post-progression OS could reasonably be expected compared with SoC. Against this background, the assumption of similar post-progression survival for both treatment strategies further underscores the conservative nature of the analysis.

Table 41. Modelled means in years, undiscounted estimates, half-cycle corrected and adjusted for background mortality

	T-DXd	SoC	Difference
Total life years	**1.93**	**0.98**	**0.96**
Life years in progression-free	0.79	0.40	0.39
Life years in progressed disease	1.14	0.58	0.56
Duration of treatment	0.68	0.35	0.33

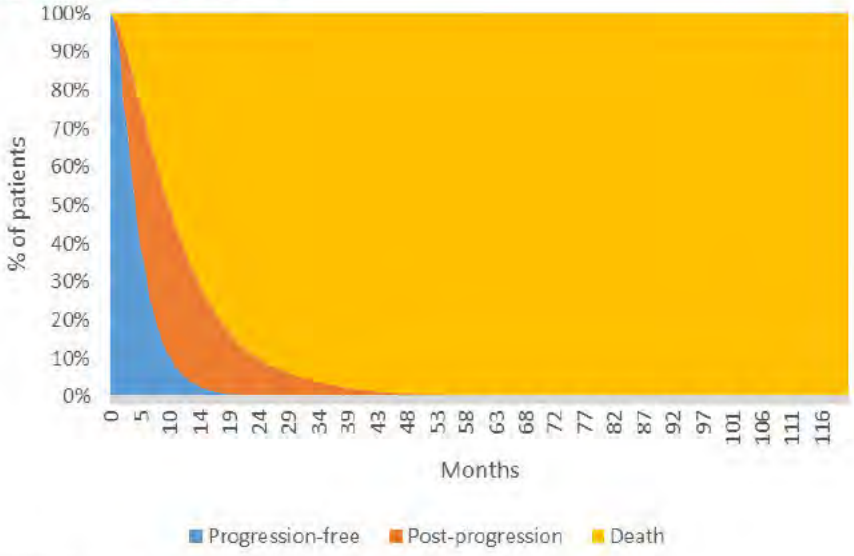
Abbreviations are defined in the list of Abbreviations

Figure 19. Markov trace – T-DXd



Abbreviations are defined in the list of Abbreviations

Figure 20. Markov trace – SoC



Abbreviations are defined in the list of Abbreviations

10. Health-related quality of life

10.1 Overview

Table 42 summarizes all instruments measuring HRQoL in DG04. HRQoL was captured using EQ-5D-5L; visual analogue scale (VAS, EQ-VAS); Functional Assessment of Cancer Therapy–Gastric (FACT-Ga); Patient global impression of severity (PGI-S); and Patient global impression of change (PGI-C) (11).

The following sections present the EQ-5D-5L and EQ-VAS. EQ-5D-5L index scores were estimated to generate utility inputs applied in the health economic assessment. EQ-VAS results are presented alongside these in accordance with DMC requirements (49) (see section 10.2.1.3). The use of EQ-5D-5L follows the DMC method guide for HRQoL reporting (49) and is consistent with previous DMC assessments for GC/GEJC (47, 70).

Table 42. Overview of included instruments for measuring health-related quality of life

Instrument	Median follow-up time and data cut	Application	Source	Reference to description
EQ-5D-5L	Median follow-up time [redacted]	HSUVs	DG04	Section
EQ-VAS	months*	Clinical effectiveness	(71)	10.2.1
	DCO: 2024-OCT-24			
	Expected future DCO: N/A			
EORTC	N/A	Clinical effectiveness		N/A
FACT-Ga	N/A	Clinical effectiveness		N/A
PGI-S	N/A	Clinical effectiveness		N/A
PGI-C	N/A	Clinical effectiveness		N/A

Abbreviations are defined in the list of Abbreviations
Notes: [*] Median follow-up time (months): [redacted] for T-DXd and RAM+PTX, respectively, [redacted] months in total (n=494)

Table 43. Basis for estimating utility values

Instrument	Preference weights	Source	Short description
EQ-5D-5L	DK	DG04 (71)	EQ-5D-5L data from pivotal study was used to inform the economic model

Abbreviations are defined in the list of Abbreviations

10.2 Instruments

10.2.1 EuroQol 5 Dimensions 5 Levels and EuroQol visual analogue scale

10.2.1.1 Study Design and Instrument

EQ-5D-5L was selected because it is a generic, preference-based instrument that facilitates the calculation of utility values using Danish preference weights, as required by the DMC (49). As mentioned above, EQ-VAS is reported alongside EQ-5D-5L index scores for completeness and in line with the requirements of section 10.2.1.3.

The data used to inform the utility analysis came from the ITT population (DG04) (6). No direct comparative PTX-specific data were available to estimate QoL for patients receiving

SoC. Although patients might experience better QoL with a more efficacious treatment such as T-DXd, in the absence of relevant data it was assumed that SoC patients do not have better QoL than that captured in the DG04 study.

10.2.1.2 Data Collection

In the DG04 study, EQ-5D-5L questionnaires were completed by patients at the following times:

- Cycle 1, Day 1 before infusion and before the completion of any other study-related procedures (including blood collection).
- Every 3 weeks (±3 days) until Day 64 (i.e. Day 22, 43, 64), and then every 6 weeks (±3 days) until the 40 Day follow-up visit (i.e. Days 106 and 148), regardless of delays in dosing.
- Disease progression visit, unless already completed on the same day.
- End of treatment unless already completed on the same day.

The DG04 clinical documentation does not report a prespecified statistical approach to handling missing EQ-5D-5L data. Therefore, the utility analysis was performed using observed data only (complete-case analysis). The number of evaluable patients at baseline was similar between arms (244 and 248 patients (T-DXd vs RAM+PTX), respectively). The EQ-5D-5L compliance data from the DG04 study is reported in Appendix G (Table 102 and Table 103). An overview of responses by health states is provided in Table 44.

Table 44. Overview of responses by health state (71)

Health state	Number of responses in health state N	Number of patients who have provided at least one response in the health state N
T-DXd		
Progression-free	1421	236
Progressed	137	109
RAM+PTX		
Progression-free	1047	220
Progressed	120	82

Abbreviations are defined in the list of Abbreviations

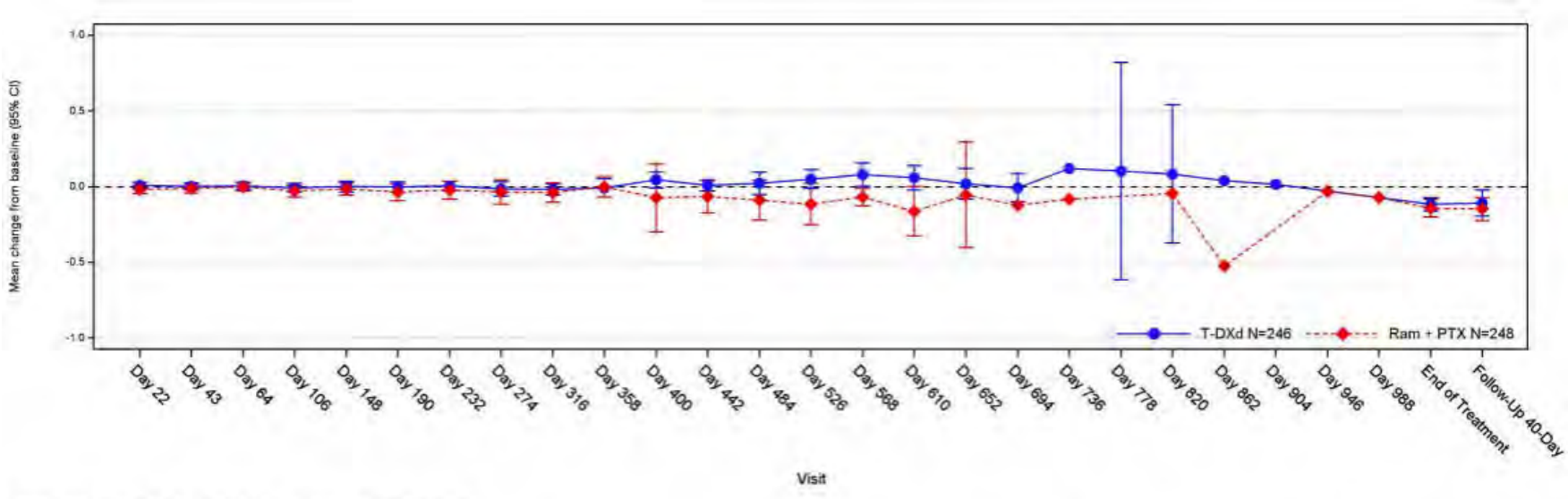
10.2.1.3 Results

Overall, the results of the subjects with a post-baseline EQ-5D-5L score showed that QoL in the T-DXd arm was maintained over the course of treatment and did not deteriorate compared to the RAM+PTX arm through Day 274, after which the number of subjects was too low to allow for meaningful interpretation (71).

The mean change from baseline across all measure time points, together with 95% CI for both treatment arms, is presented in Figure 21. Summary statistics for the Danish-weighted EQ-5D-5L scores at each scheduled assessment time point are provided in Table 45. Results for individual domains (EQ-5D-5L) are provided in Appendix G.2.

EQ-VAS results are reported for completeness in line with the DMC template (refer to Figure 22 and Table 46).

Figure 21. Plot of change from baseline in utility values over time (EQ-5D-5L): Denmark - FAS (DCO date: 24 Oct 2024) (71)

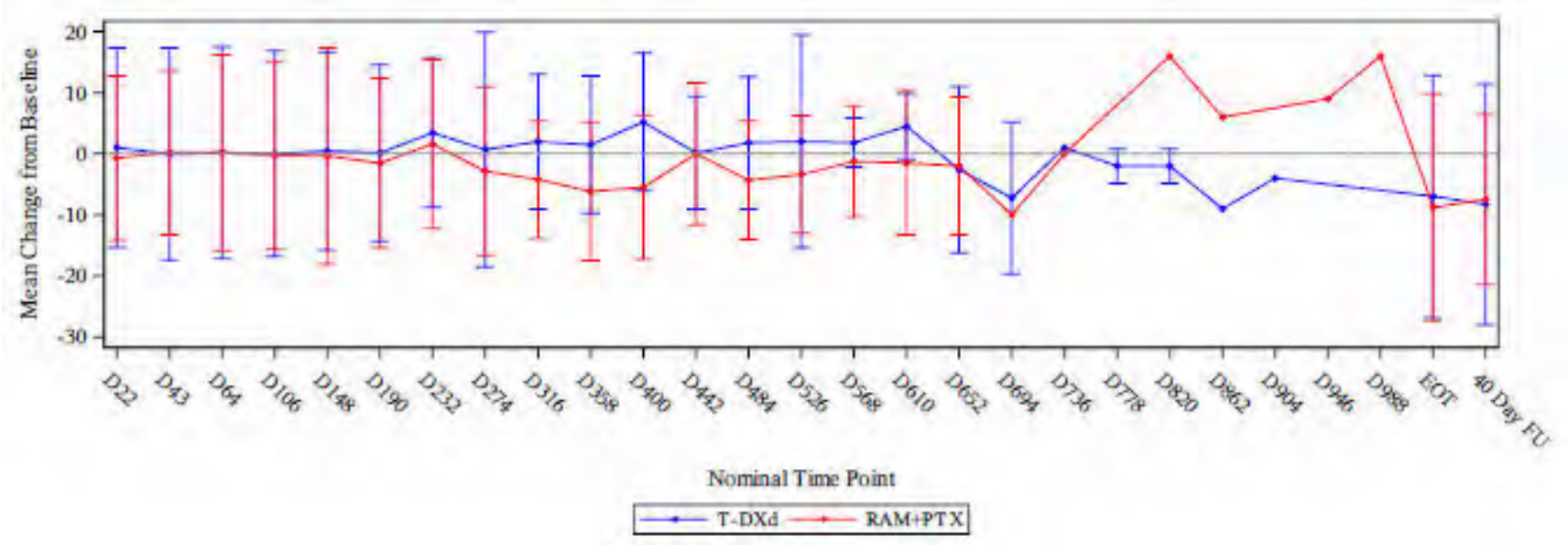


Number of subjects with available change from baseline record

T-DXd	192	185	173	128	96	85	52	44	35	29	21	13	9	7	5	6	5	4	1	2	2	1	1	0	0	112	32
Ram + PTX	149	121	139	115	79	54	34	22	17	12	8	7	6	5	4	4	2	1	1	0	1	1	0	1	1	86	36

Abbreviations are defined in the list of Abbreviations

Figure 22. Plot of change from baseline in utility values over time (EQ-VAS): FAS (DCO date: 24 Oct 2024) (71)



Abbreviations are defined in the list of Abbreviations

Table 45. Results for EQ-5D-5L summary statistics (DCO date: 24 Oct 2024) (71)

Time point	T-DXd (n=246)	RAM+PTX (n=248)	Difference
	Average (SE)	Average (SE)	Difference (95%CI)
Baseline	0.86861 (0.012488)	0.86607 (0.011606)	0.00253 (-0.03112, 0.03619)
Day 22	0.88528 (0.012464)	0.86033 (0.012978)	0.02494 (-0.01077, 0.06066)
Day 43	0.88788 (0.012044)	0.87598 (0.012975)	0.01190 (-0.02390, 0.04769)
Day 64	0.88910 (0.011717)	0.87294 (0.011339)	0.01616 (-0.01643, 0.04876)
Day 106	0.88579 (0.013712)	0.84743 (0.018953)	0.03836 (-0.00692, 0.08364)
Day 148	0.89646 (0.013296)	0.86194 (0.017299)	0.03452 (-0.00780, 0.07685)
Day 190	0.90747 (0.014025)	0.86428 (0.023812)	0.04320 (-0.00789, 0.09428)
Day 232	0.92882 (0.010303)	0.86750 (0.022264)	0.06132 (0.01781, 0.10484)
Day 274	0.90731 (0.018966)	0.84813 (0.035309)	0.05919 (-0.01379, 0.13217)
Day 316	0.90069 (0.018218)	0.86478 (0.025435)	0.03591 (-0.02804, 0.09987)
Day 358	0.91855 (0.020304)	0.88875 (0.026982)	0.02980 (-0.04445, 0.10405)
Day 400	0.95270 (0.016354)	0.81175 (0.120352)	0.14095 (-0.01071, 0.29260)
Day 442	0.95480 (0.010727)	0.85171 (0.037433)	0.10309 (0.04157,0.16460)
Day 484	0.95760 (0.018006)	0.83817 (0.086070)	0.11943 (-0.02899, 0.26786)
Day 526	0.97325 (0.018719)	0.78560 (0.091334)	0.18765 (0.02429, 0.35101)
Day 568	0.97300 (0.021100)	0.84000 (0.061432)	0.13300 (0.00556, 0.26044)
Day 610	0.97757 (0.011489)	0.71350 (0.061379)	0.26407 (0.15760, 0.37055)
Day 652	0.95600 (0.021970)	0.84300 (0.004000)	0.11300 (0.01834, 0.20766)
Day 694	0.93250 (0.032518)	0.80600 (NE)	0.12650 (-0.10490, 0.35790)
Day 736	0.95900 (NE)	0.84700 (NE)	0.11200 (NE, NE)
Day 778	0.98900 (0.011000)	NE (NE)	NE (NE, NE)
Day 820	0.95933 (0.004333)	0.81900 (NE)	0.14033 (0.10304,0.17762)
Day 862	0.87800 (NE)	0.34100 (NE)	0.53700 (NE, NE)
Day 904	0.85400 (NE)	NE (NE)	NE (NE, NE)
Day 946	NE (NE)	0.83200 (NE)	NE (NE, NE)
Day 988	NE (NE)	0.79300 (NE)	NE (NE, NE)
End of Treatment	0.76649 (0.024302)	0.75272 (0.030026)	0.01376 (-0.06159, 0.08912)
Follow-up 40-Day	0.81488 (0.040544)	0.78403 (0.038741)	0.03086 (-0.08126, 0.14297)

Abbreviations are defined in the list of Abbreviations

Table 46. Results for EQ-VAS summary statistics (DCO date: 24 Oct 2024) (71)

Time point	T-DXd (n=246)	RAM+PTX (n=248)	Difference
	Average (SE)	Average (SE)	Difference (95%CI)
Baseline	75.6 (1.23)	72.9 (1.33)	2.7 (N/A)
Day 22	76.9 (1.20)	73.2 (1.29)	3.7 (N/A)
Day 43	77.1 (1.24)	75.6 (1.37)	1.5 (N/A)
Day 64	77.3 (1.27)	73.7 (1.32)	3.6 (N/A)
Day 106	78.3 (1.35)	74.4 (1.58)	3.9 (N/A)
Day 148	79.3 (1.28)	75.4 (1.67)	3.9 (N/A)
Day 190	79.8 (1.54)	75.6 (1.84)	4.2 (N/A)
Day 232	84.2 (1.49)	77.2 (1.87)	7.0 (N/A)
Day 274	79.3 (2.69)	73.7 (3.00)	5.6 (N/A)
Day 316	79.2 (2.86)	74.1 (3.23)	5.1 (N/A)
Day 358	82.6 (1.95)	72.1 (4.38)	10.5 (N/A)
Day 400	85.2 (1.85)	68.6 (6.53)	16.6 (N/A)
Day 442	84.0 (1.92)	75.9 (5.21)	8.1 (N/A)
Day 484	83.0 (2.91)	72.7 (6.76)	10.3 (N/A)
Day 526	80.9 (4.26)	68.8 (9.16)	12.1 (N/A)

Time point	T-DXd (n=246)	RAM+PTX (n=248)	Difference
Day 568	80.3 (1.05)	71.8 (8.82)	8.5 (N/A)
Day 610	83.6 (2.40)	65.0 (10.21)	18.6 (N/A)
Day 652	79.0 (3.62)	72.5 (2.50)	6.5 (N/A)
Day 694	76.0 (2.62)	70.0 (N/A)	6.0 (N/A)
Day 736	90.0 (N/A)	80.0 (N/A)	10.0 (N/A)
Day 778	85.0 (2.89)	N/A (N/A)	0.0 (N/A)
Day 820	85.3 (3.18)	85.0 (N/A)	0.3 (N/A)
Day 862	80.0 (N/A)	75.0 (N/A)	5.0 (N/A)
Day 904	85.0 (N/A)	N/A (N/A)	0.0 (N/A)
Day 946	N/A (N/A)	78.0 (N/A)	0.0 (N/A)
Day 988	N/A (N/A)	85.0 (N/A)	0.0 (N/A)
End of Treatment	68.5 (1.91)	68.4 (2.02)	0.1 (N/A)
Follow-Up 40-Day	72.2 (3.05)	70.8 (2.74)	1.4 (N/A)

Abbreviations are defined in the list of Abbreviations

10.2.2 Summary when reporting multiple instruments

Utility inputs were based on EQ-5D-5L index scores. No additional HRQoL instruments were included for this assessment.

10.3 Utility values

10.3.1 Data Sources

Health state utility values (HSUVs) derived from EQ-5D-5L data in DG04 (ITT population) informed the base case, with separate estimates for the progression-free and post-progression states. HSUVs were assumed to be identical for T-DXd and SoC.

Age-adjustment

HSUVs were age-adjusted according to the methods described in the DMC guidelines (49) (the "Standard sheets (Excel)" was included in the cost-effectiveness model.

10.3.2 Calculation of Utility Values

The DG04 clinical documentation did not prespecify a statistical approach for handling missing EQ-5D-5L data; therefore, the utility analysis applied a complete-case approach using all observed EQ-5D-5L assessments from the ITT population.

Utility values were estimated using linear mixed models (LMM), with utility scores from all available time points (including baseline) included as the dependent variable. Two models were fitted:

- Model 1 (base case model): Progression status at each visit (progression-free vs progressed) as a time-varying covariate
- Model 2: Progression status at each visit and planned treatment as covariates

Both models included subject-level random effects (intercept and slope) to account for repeated measurements within individuals and used an unstructured correlation matrix. Least square means (LSM) were used to derive mean utility values and 95% CIs.

Progression-free and post progression health statue utilities

Regression results for both models are presented in Table 47. In both models, disease progression was associated with a statistically significant reduction in utility (Model 1: 0.1052 (-0.1235, -0.0869), p-value<0.0001; Model 2: -0.1052 (-0.1235, -0.0869), p-value<0.0001). The treatment covariate in Model 2 was not statistically significant (p= 0.2061) and did not improve model fit. Full model details, equations and output tables are available in Appendix G.

Model 1 represents the preferred model to estimate utility weights to inform the health economic model. Utilities are primarily driven by disease status (progression-free vs progressed) rather than by treatment assignment. The EQ-5D-5L utility estimates show a clear decline following progression (0.8647 pre-progression vs. 0.7595 post-progression). This conclusion is further supported by the model fit statistics, with both Akaike information criterion and Bayesian information criterion (BIC) favouring Model 1 over Model 2. Table 47 shows the regression results.

This approach models HRQoL as a function of disease burden rather than specific treatments, which is appropriate given that the health economic analysis relies on an external comparator (SoC) and lacks treatment-specific utility data for the latter. HSUV derived from DG04 were therefore assumed to be representative of SoC. This assumption is supported by evidence from RAINBOW, where EQ-5D scores were comparable between treatment arms, remained stable during treatment, and worsened at discontinuation (72). Hence, no treatment-specific differences in HRQoL are expected between RAM+PTX and PTX, further supporting the use of DG04-derived utility estimates across treatments.

Table 47. LMM regression coefficients of mapped EQ-5D-5L utility values from DG04 (71)

	Model 1*†	Model 2*†
Intercept (95% CI) p - value	0.8647 (0.8502, 0.8793) <0.0001	0.8548 (0.8337, 0.8759) <0.0001
Treatment arm (T-DXd vs RAM+PTX) (95% CI) p - value		0.0187 (-0.0103, 0.0478) 0.2061
Progression status (progression vs progression-free) (95% CI) p - value	-0.1052 (-0.1235, -0.0869) <0.0001	-0.1052 (-0.1235, -0.0869) <0.0001
AIC	-2830.29	-2825.30
BIC	-2812.82	-2808.84

Abbreviations are defined in the list of Abbreviations

* Unstructured covariance matrix was used to model the random effects correlation; † The mixed model included a random intercept and slope.

10.3.3 Adverse Events, Comorbidity and Other State-Specific Adjustments to the Utility Values

AE-related utility decrements were calculated by summing, across AE, the product of AE frequency, the corresponding utility decrement, and AE duration. The sum of decrements was applied as a one-off decrement in the first model cycle.

For T-DXd, grade ≥3 AEs observed in DG04 were included in the analysis; for SoC, weighted AE rates were sourced from the literature (Table 58; section 11.2.4, and Appendix M). Mean AE durations (days) were obtained from DG04 using grade ≥3 AEs in the safety population (Table 48).

Utility decrements were sourced from the literature and are presented in Table 49. When values specific for metastatic GC were unavailable, disutilities were taken from previous technical appraisals (TAs) and studies in related cancers (e.g. non-small cell lung cancer (NSCLC), metastatic breast cancer (mBC)) (73-75). Despite differences in patient populations, it was assumed that a given AE has a comparable marginal impact on HRQoL across cancer types. These values are based on UK value sets rather than the Danish value set.

Table 48. AE – duration (days) (11)

Adverse event	Duration (days)
Anaemia	8.8
Leukopenia	5.7
Nausea	8.4
Neutrophil count decreased	10.0
ILD (any grade) *	15.8
Fatigue	9.9
Febrile neutropenia	6.6
Pain	17.0
Diarrhoea	4.8
Vomiting	15.3
Infection	15.1
Left ventricular dysfunction (any grade) *	36.0

10.3.4 Results for Utility Values

Table 49 presents the utility values by health state included in the cost-effectiveness model for the ITT population, based on the LSM (Model 1), refer to section above (section 10.3.2). The AE-related disutilities and respective sources are also presented in Table 49 below.

Table 49. Utility values used in the health economic model

	Utility value [95% CI]	Instrument, preference weight	Source and reference
Main analysis			
Progression-free	0.8647 (0.8502, 0.8793)	EQ-5D-5L, DK	DG04 EQ-5D-5L data with Danish population-based EQ-5D-5L tariff - data on file (71)
Progressive disease	0.7595 (0.7361, 0.7829)	EQ-5D-5L, DK	DG04 EQ-5D-5L data with Danish population-based EQ-5D-5L tariff - data on file (71)

	Utility value [95% CI]	Instrument, preference weight	Source and reference
Decrease in HRQoL (disutility[1])			
Anaemia	-0.1190 (73)	EQ-5D (level not known), UK	Original sourced from Swinburn et al 2010 (50)
Leukopenia	-0.0900 (76)	SG; EQ-5D (level not known); VAS scores, UK	Original sourced from Nafees et al 2008 (51)
Nausea	-0.0480 (76)	SG; EQ-5D (level not known); VAS scores, UK	Refer to "Leukopenia"
Neutrophil count decreased	-0.0900 (76)	SG; EQ-5D (level not known); VAS scores, UK	Refer to "Leukopenia"
ILD (any grade)	-0.1700 (74)	EQ-5D (level not known), UK	Original source: Doyle et al 2011 (52)
Fatigue	-0.0735 (76)	SG; EQ-5D (level not known); VAS scores, UK	Refer to "Leukopenia"
Febrile neutropenia	-0.1500 (73)	SG; EQ-5D (level not known); and interviews, UK	Original source: Lloyd et al 2006 (54)
Pain	-0.0690 (77)	EQ-5D (level not known), UK	Original source: Doyle et al 2011 (52)
Diarrhoea	-0.0480 (76)	SG; EQ-5D (level not known); VAS scores, UK	Refer to "Leukopenia"
Vomiting	-0.0480 (76)	SG; EQ-5D (level not known); VAS scores, UK	Refer to "Leukopenia"
Infection	-0.0900 (76)	SG; EQ-5D (level not known); VAS scores, UK	Refer to "Leukopenia"
Left ventricular dysfunction (any grade)	-0.0590 (74)	6-month Minnesota Living with Heart Failure questionnaire mapped to EQ-5D (level not known); (preference weight N/A)	As reported by Sandhu et al 2017 (53)

Abbreviations are defined in the list of Abbreviations

11. Calculation of Costs

The health economic analysis includes medicine acquisition and administration costs, costs associated with disease management, and AEs, as well as non-medical costs (patient time and transportation costs). Included costs are reported in 2026 Danish kroner (DKK).

[1] All disutilities in Table 48 are based on UK value sets, and the EQ-5D version (3L vs. 5L) was not reported for the underlying studies. As a result, conversion to Danish weights was not feasible due to lack of necessary data. These values were therefore used as proxies, with a minimal impact on model outcomes.

11.1 Drug Costs

11.1.1 Drug Costs for Intervention and Comparator

The health economic model used the pharmacy retail price (AIP) of T-DXd of DKK 10,628.99 per 100 mg vial. Drug acquisition costs for intervention and SoC were sourced from the Danish drug cost database Medicinpriser.dk (60).

Dosing was based on the DG04 study for T-DXd (6.4 mg/kg), refer to Table 8. Weight-based dosing was applied for T-DXd, and a method of moments approach was used to estimate the mean administered dose based on the body weight distribution of the ITT population from DG04 (Appendix L).

SoC was modelled as a basket of component regimens. The health economic model includes the most commonly used SoC treatments in this setting (refer to section 3.2.1). In the base case, the relative distribution of these regimens is shown in Table 50. The composition of the SoC basket was explored through scenario analyses. The scenarios include an equal distribution (33% PTX / 33% DTX / 33% irinotecan) and single-comparator scenarios (100% PTX, 100% DTX, 100% irinotecan) (refer to Table 63).

For each SoC component, dosing followed its respective summary of product characteristics (SmPC) with posology detailed in Table 51.

Table 50. Second-line treatments – SoC: proportions used for modelling purposes

Comparator	Expected Danish SoC
Taxanes	83%
PTX	44%
DTX	39%
Irinotecan	17%

Drug costs were applied for each cycle in the model in line with the extrapolated TTD for T-DXd and SoC (section 9). The mean RDI in DG04 was [redacted] for T-DXd, which was used in the base case analysis (11). For SoC, an RDI of 90% was applied for each regimen (PTX; DTX, and irinotecan), consistent with reported RDIs across clinical studies (see Table 139).

For the base case analysis, 100% vial sharing was applied, in line with a previous DMC T-DXd assessment (78). According to clinical experts, clinics try to minimize wastage by coordinating specific treatment days for T-DXd patients or rounding doses to a specific number of vials. Alternative vial sharing assumptions were explored as part of the scenario analyses (refer to Table 63).

Table 51 presents the drug acquisition costs.

Table 51. Medicines used in the model. (prices from April 17th, 2026)

Medicine	Strength	Units	Pack size and form	Price (AIP) (60)	Dose	RDI	Frequency	Vial sharing
Intervention								
T-DXd	100 mg	mg/ml	1 ml vial	10,628.99	6.4 mg/kg	[redacted]	Every 3 weeks	Yes
SoC								
PTX	6 mg	mg/ml	50 ml vial	2,200.00	80 mg/m^2	90.0%	Every week	Yes
	6 mg	mg/ml	16.7 ml vial	1,002.00				
	6 mg	mg/ml	50 ml vial	1,890.00				
	6 mg	mg/ml	16.7 ml vial	891.00				
	6 mg	mg/ml	25 ml vial	1,500.00				
DTX	160 mg	mg/ml	8 ml vial	309.00	75 mg/m^2	90.0%	Every 3 weeks	Yes
	80 mg	mg/ml	4 ml vial	140.00				
	20 mg	mg/ml	1 ml vial	35.00				
	160 mg	mg/ml	8 ml vial	300.00				
	80 mg	mg/ml	4 ml vial	150.00				
	20 mg	mg/ml	1 ml vial	71.90				
Irinotecan	20 mg	mg/ml	5 ml vial	125.00	250 mg/m^2	90.0%	Every 3 weeks	Yes
	1.5 mg	mg/ml	180 ml vial	356.00				
	20 mg	mg/ml	25 ml vial	350.00				
	20 mg	mg/ml	15 ml vial	3,050.00				
	1.5 mg	mg/ml	240 ml vial	470.00				
	20 mg	mg/ml	5 ml vial	100.00				
	20 mg	mg/ml	25 ml vial	300.00				
	1.5 mg	mg/ml	200 ml vial	395.00				
	1.5 mg	mg/ml	220 ml vial	435.00				

Abbreviations are defined in the list of Abbreviations

11.1.2 Drug costs for Subsequent Treatment

As outlined in section 3.4, Danish clinical expert input supports the assumption that 20-50% of patients receive any subsequent treatment following second line treatment (2, 3). A proportion of 50% was used in the base case analysis to provide a conservative estimate and reflect the upper bound of anticipated Danish clinical practice.

Table 52 presents the third-line treatment options based on Danish clinical expert estimates, capturing the most relevant treatments in the Danish setting. Rechallenge of second-line treatments was not assumed. Subsequent treatment costs were estimated based on dosing schedule, treatment duration and the unit cost for each drug used in subsequent treatment lines. Table 53 shows the dosing and duration of each treatment regimen.

The drug costs were sourced from the Danish drug cost data base Medicinpriser.dk (60) (refer to Table 51 for drug acquisition costs and RDI) and administration costs were aligned with second-line administration costs, and doses per cycle were sourced from the respective SmPC or from Danish clinical expert input. Where a treatment was included in both second and subsequent lines, the same dosing and administration assumptions were used.

The drug cost for each subsequent regimen was calculated from the dosing schedule and unit prices, then multiplied by mean treatment duration for total course cost. These costs were weighted by the distribution and proportion of patients receiving each regimen by second-line treatment. The total weighted subsequent treatment acquisition and administration costs were applied as a one-off cost to the proportion of patients who progressed in each model cycle.

Table 52. Subsequent treatments used after second-line treatments

Third line treatment	After 2nd line T-DXd	After 2nd SoC	Source
Taxanes (PTX)	73%	17%	Danish clinical experts (2, 3)
Irinotecan	27%	83%	

Abbreviations are defined in the list of Abbreviations

Table 53. Subsequent treatment costs, reference treatments, and corresponding prescribing information

Third line treatment	Dose	Relative dose intensity	Frequency	Treatment duration (weeks)(11)	Vial sharing
PTX	80 mg/m^2	90.0%	Every week	9.37	No
Irinotecan	250 mg/m^2	90.0%	Every 3 weeks	13.29	No

Table 54. Drug acquisition costs used in the model: Subsequent treatment costs (60)

Medicine	Strength	Package size	Pharmacy purchase price (DKK)
PTX	Refer to Table 51	Refer to Table 51	Refer to Table 51
Irinotecan	Refer to Table 51	Refer to Table 51	Refer to Table 51

Abbreviations are defined in the list of Abbreviations

11.2 Hospital costs

11.2.1 Administration

Administration costs were applied in line with the administration frequency for each treatment. For oral treatments, no administration cost was assumed. The cost of an intravenous (IV) infusion was sourced from Danish diagnosis-related group (DRG) list 2026 (58) (Table 55). SoC administration costs were calculated based on each regimen's route and frequency (see Table 51). The costs were further weighted by the proportion for each regimen reflecting Danish clinical practice provided in Table 50.

Table 55. Assumptions regarding administrative costs

Route of administration	Diagnosis and procedure codes*	DRG group	Unit cost, DKK
IV infusion	DC169M (A), BWAA62 (P)	06MA98; MDC06 1-dagsgruppe, pat. mindst 7 år	1,729

Abbreviations are defined in the list of Abbreviations

11.2.2 Disease management

Routine care and disease management costs were included in the analysis. The costs were applied according to treatment status (on active treatment and off active treatment). Treatment status was determined using TTD (section 9.4) and the proportion of patients assumed to receive subsequent treatments combined with the corresponding treatment duration. Costs were sourced from Danish DRG list 2026 (58).

Accordingly, costs differ depending on whether patients are receiving active treatment (second or subsequent line) in each model cycle. Table 56 summarises the routine follow-up resource use and costs by treatment status (on treatment and off treatment). The types and frequencies of resource use linked to disease management were informed by previous technology assessments (75) and were validated by Danish clinical experts (2, 3). No differences in disease management between the different treatment options were identified and hence a micro costing approach was not applied.

Table 56. Assumptions regarding disease management costs

Activity/pathway	Frequency (on treatment)	Duration	Frequency (off treatment)	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
CT scan	Every 10th week	Until progression	-	-	DC169M (A), UXCD00 (P)	30PR06, CT-scanning, ukompliceret	2,861
Full blood count	Every 3rd week	Until progression	-	-	-	-	Covered in administration visit
Renal function test	Every 3rd week	Until progression	-	-	-	-	Covered in administration visit
Hepatic function test	Every 3rd week	Until progression	-	-	-	-	Covered in administration visit
Consultation visit	Every 5th week	Until progression	Every 12th week	Until death	DC169M (A), BVAA32 (P); BVAA30 (P)	06MA98, MDC06 1-dagsgruppe, pat. mindst 7 år.	1,729

Abbreviations are defined in the list of Abbreviations

11.2.3 Treatment Monitoring

N/A

Table 57. Assumptions regarding costs for treatment monitoring

Activity/Pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations are defined in the list of Abbreviations

11.2.4 Management of adverse events

Costs associated with the management AEs were sourced from Danish DRG list 2026 (58).

As described in section 8, AE probabilities for T-DXd were taken from DG04, while comparator data were obtained from the literature. Only Grade ≥3 AEs occurring in ≥5% of patients in any treatment arm were included. Additionally, AESIs for T-DXd (ILD and LV dysfunction) of any grade from DG04 were considered.

For each AE, the probability of experiencing the event was multiplied by the unit cost per event, and results were summed across all included AEs to produce an average AE management cost per patient. Table 58 presents the per-patient AE management costs used in the model (cost per event).

Table 58. Assumptions regarding costs for management of adverse events (58)

Adverse event	Proportion		Diagnosis codes	DRG group	Unit cost
	T-DXd	SoC			
Anaemia	23.00%	8.74%	DD649 (A); DC169M (B)	16MA98	2,195.00
Leukopenia	7.00%	6.51%	DD728H (A); DC169M (B)	16MA98	2,195.00
Nausea	5.30%	1.96%			0*
Neutrophil count decreased	20.50%	14.09%			0*
ILD (any grade)	13.90%	0.00%	DJ849 (A); DC169M (B)	04MA17	52,462.00
Fatigue	4.10%	8.67%			0*
Febrile neutropenia	2.90%	6.63%	DT888N (A); DC169M (B)	16MA98	2,195.00
Pain	0.00%	5.00%	DR529 (A); DC169M (B)	23MA03	5,737.00

Adverse event	Proportion T-DXd	SoC	Diagnosis codes	DRG group	Unit cost
Diarrhoea	1.60%	10.16%	DK529 (A); DC169M (B)	06MA98	1,729.00
Vomiting	4.10%	7.55%	DR119C (A); DC169M (B)	06MA98	1,729.00
Infection	0.00%	5.77%	DA449 (A); DC169M (B)	18MA98	2,416.00
Left ventricular dysfunction (any grade)	2.50%	0.00%	DI509 (A); DC169M (B)	05MA04	43,078.00

Abbreviations are defined in the list of Abbreviations
Notes: (*): Assumed to be managed at administration visit as per DMC assessment of T-DXd (DB04) (79)

11.2.5 Other Hospital Costs

NA

11.3 Patient Costs

Patient time and transportation costs for health care visits were included, specifically for IV administrations, CT scans, and consultation visits. The visit frequencies are presented in Table 59. Patient costs were assigned by treatment status (”on or off” second line therapy). TTD was used to define the proportion of patients on T-DXd or SoC treatment during each model cycle. Once treatment was discontinued, patients were classified as ”off treatment”. Patient costs for subsequent therapies were not included.

All outpatient visits were assumed to require one hour of patient time, i.e. 200 DKK per hour. Per visit, 90 minutes transportation time was assigned for a round-trip of 20 km, as recommended by the DMC. Thus, transportation costs include both patient time spent on travel (300 DKK) and the cost of transportation of 150 DKK per round-trip (59).

For IV administrations, administration time was based on the infusion duration specified in the dosing guidance on pro.medicin.dk. Thus, the patient time per administration visit varies by treatment.

For the comparator, SoC, the IV administration-related patient time and transportation costs were derived by constructing separate administration ‘traces’ for PTX, DTX, and irinotecan, each incorporating their treatment-specific infusion duration and administration frequency. The overall SoC estimate was then calculated as a weighted average of these three traces using the proportional regimen weights presented in Table 50.

Assumptions were applied consistently across cycles to estimate total costs.

Table 59. Assumptions regarding patient time

Activity	Frequency of activity	Time spent on activity	Transportation	Patient time spent on transportation	Note
On treatment					
CT scan	Every 10th week	1.0 hour	Separate visit required. Transportation included	90 minutes	Assumption and DMC costing guidance (time spent for transport)
Full blood count Renal function test Hepatic function test	Covered in administration visit	Covered in administration visit	Covered in administration visit	Covered in administration visit	No separate travel time, as it takes place on the same day as IV administration
Consultation visit	Every 5th week	1.0 hour	Separate visit required. Transportation included	90 minutes	Assumption and DMC costing guidance (time spent for transport)
IV administration	Every 3rd week for T-DXd	Irinotecan: 1.5 hours DTX and T-DXd: 1 hour PTX: 3 hours	Separate visit required. Transportation included	90 minutes	Duration of infusion informed by pro.medicin.dk and Enhertu EPAR (refer to Table 25)
Off treatment					
Consultation visit	Every 12th week	1.0 hour	Separate visit required. Transportation included	90 minutes	Assumption and DMC costing guidance (time spent for transport)

Abbreviations are defined in the list of Abbreviations

11.4 Other costs

N/A

12. Results

12.1.1 Reference-case analysis

The results of the cost-effectiveness analysis are presented in Table 60. T-DXd is projected to result in an additional 0.70 QALYs at an incremental cost of DKK 526,770 kr.. This corresponds to an ICER at list price of DKK 752,273 kr.versus SoC. The incremental life-years gained with T-DXd are 0.87, which translates to DKK 604,970 kr.per life-year gained at list price.

The primary cost driver is the drug acquisition cost of T-DXd. Given the low-cost treatments currently used in standard practice, and that subsequent treatment utilization is limited by early mortality, incremental costs of T-DXd dominate, resulting in a higher ICER, despite clinically relevant benefits. Gains in both life-years and QALYs accrue across the progression-free and post-progression health states. In populations with poor prognosis and short survival such as patients with advanced HER2-positive GC/GEJC, the limited time horizon constrains potential health gains; consequently, even clinically meaningful effects yield small QALY gains. Thus, the ICER should be considered in this context, with T-DXd providing significant additional clinical value for patients with a very high unmet need.

The clinical need for T-DXd is supported by Danish data which shows that since 2022, [redacted] patients have received T-DXd in the second-line setting through name-based reimbursement applications ("enkelttilskudsansøgninger") (30) (refer to Appendix P). These cases demonstrate that clinicians actively seek access to T-DXd for selected patients who progress after trastuzumab-based therapy, reflecting a high unmet need for HER2-directed treatment options, as well as a willingness to pay for T-DXd treatment beyond first line.

Table 60. Results, discounted estimates, half-cycle corrected and adjusted for background mortality

	T-DXd	SoC	Difference
Drug costs	505,354 kr.	7,321 kr.	498,033 kr.
Drug costs for subsequent treatment	2,859 kr.	1,076 kr.	1,783 kr.
Administration	27,741 kr.kr.	24,817 kr.kr.	2,924 kr.kr.
Disease management	33,853 kr.	19,553 kr.	14,300 kr.
Management of adverse events	9,190 kr.	1,213 kr.	7,977 kr.
Patient time	18,089 kr.	16,336 kr.	1,753 kr.
Total costs	**597,086 kr.kr.**	**70,316 kr.kr.**	**526,770 kr.kr.**
Life years in progression-free	0.78	0.39	0.38

	T-DXd	SoC	Difference
Life years in progressed disease	1.06	0.57	0.49
Total life years	**1.83**	**0.96**	**0.87**
QALY in progression-free	0.67	0.34	0.33
QALY in progressed disease	0.80	0.43	0.37
QALY decrement	-0.003	-0.002	-0.001
Total QALYs	**1.47**	**0.77**	**0.70**
Incremental costs per life year gained			**604,970 kr.kr.**
Incremental costs per QALY gained (ICER)			**752,273 kr.kr.**

Table 61. Results per drug if combination treatments (more than one drug)

	Drug costs
Intervention: N/A (T-DXd monotherapy)	N/A
SoC basket: N/A (monotherapy not combination treatments)	N/A

Abbreviations are defined in the list of Abbreviations

12.1.2 Supplementary analysis

As discussed in section 7.3, supplementary analyses were conducted to address uncertainty in SoC efficacy vs T-DXd. While the base case assumes similar efficacy across all second-line treatments included in the SoC "basket", the NMA indicates differences between the treatment regimens. A supplementary pairwise analysis was conducted comparing PTX, DTX and irinotecan separately against T-DXd.

In addition, an analysis based on the Western subgroups from DG04 and RAINBOW was included to better reflect the Danish patient population. Table 62 presents the supplementary results, including a weighted ICER that accounts for all relevant SoC treatments separately based on the NMA.

The supplementary analyses yield lower ICERs than the base case. As noted earlier, the base case is considered a conservative estimate of the cost-effectiveness of T-DXd. The NMA-based comparisons of T-DXd vs taxanes/irinotecan provide relevant insights and contribute to a more complete picture of T-DXd's cost effectiveness vs SoC in Denmark. Similarly, when treatments are weighted according to their proportions observed in clinical practice (pragmatic approach), the NMA based weighted ICER remains below the base case ICER derived from the simplified ITC approach, further underscoring the conservatism of the base case.

The inclusion of Western subgroup results further highlights the conservatism of the base case analysis. For subgroups more representative of Danish patients, the ICER is lower than the base case estimate, indicating that cost-effectiveness of T-DXd in Danish clinical practice is likely more favourable than suggested by the base case.

Taken together, these analyses indicate that the plausible ICER is expected to be lower than the base-case estimate and is likely to be between ~ DKK 620,000 and DKK 750,000.

Table 62. Results of supplementary analyses

Scenario	ICER (DKK)

Supplementary analyses – NMA	
PTX as comparator (NMA HR)	723,533
DTX as comparator (NMA HR)	618,831
Irinotecan as comparator (NMA HR)	694,754
SoC basket on weighted average using NMA HRs	677,883.
Supplementary analyses – Western subgroup	
Western subgroup (HRs of T-DXd vs SoC basket based on subgroup analysis applied to T-DXd ITT data)	676,831

Abbreviations are defined in the list of Abbreviations

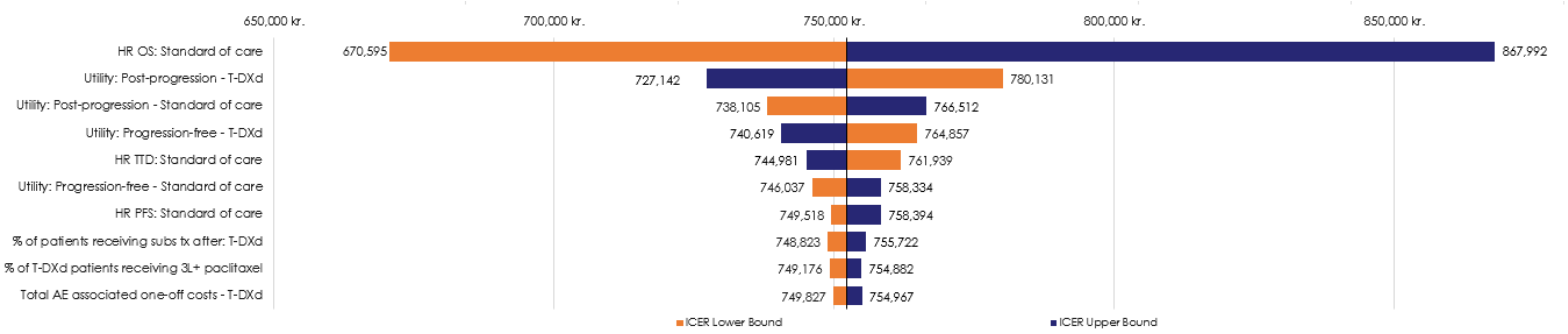
12.2 Sensitivity analyses

12.2.1 Deterministic Sensitivity Analyses

A one-way deterministic sensitivity analysis assessed uncertainty by varying model parameters individually between the upper and lower bounds of their 95% CI. Where available, CIs were sourced from DG04 or the literature; otherwise, they were estimated using suitable distributions, following reliability and recommendations from Briggs et al (80). The 95% CI was derived by using the base case value as the mean of the distribution and the standard error was assumed to be 10% of the mean value.

The most influential parameters driving ICER variations are presented in the tornado diagram below (Figure 23). The analysis identified the [redacted] well as [redacted] as most influential. Variations in these parameters led to substantial differences in the model's outcomes. As previously discussed, demonstrating a significant QALY gain can be challenging in contexts such as metastatic GC, where patients generally face a poor prognosis. Consequently, variations [redacted] can substantially influence the ICER.

Figure 23. Tornado diagram with 10 most sensitive parameters



Abbreviations are defined in the list of Abbreviations

Sensitivity analyses (Table 63) were conducted to assess the impact of key model parameters and assumptions on the estimated cost-effectiveness of T-DXd.

The sensitivity analysis reveals that the ICER varies across different assumptions, ranging from DKK 670,595 to DKK 867,992. Most sensitivity analysis result in an ICER close to the base case ICER of DKK 752,273, suggesting robustness. An RDI of 80% for T-DXd yields the lowest ICER (DKK 469,574). As noted in the results, drug acquisition costs for T-DXd are a key cost driver. Consequently, changes in the RDI materially affect outcomes. Because RDI in clinical practice is expected to be lower than observed in DG04, this analysis is highly relevant. Under a lower real-world RDI, both the ICER and the budget impact linked to T-DXd are likely lower than the base-case estimates, reflecting reduced drug consumption while addressing a high unmet need.

Table 63. Results of deterministic sensitivity analyses

Deterministic sensitivity analysis	Rationale	Incremental costs (DKK)	Incremental QALYs	ICER (DKK)
Base case (T-DXd vs SoC)	-	526,770 kr.	0.70	752,273
PFS both arms: Lognormal	Assess the sensitivity of the model to choice of PFS distribution. Refer to Table 87.	526,718 kr.	0.70	754,987
PFS both arms: Loglogistic		526,177 kr.	0.70	752,733
OS T-DXd: Generalized Gamma	Assess the sensitivity of the model to choice of OS distribution. Refer to Table 87.	525,070 kr.	0.57	920,523
OS T-DXd: Loglogistic		526,396 kr.	0.67	781,793
OS SoC: Generalised Gamma		526,997 kr.	0.72	734,406
OS SoC: Weibull		526,956 kr.	0.71	737,595
TTD both arms: Lognormal	Assess the sensitivity of the model to choice of TTD distribution. Refer to Table 87.	521,558	0.70	744,828
TTD both arms: Loglogistic		531,585	0.70	759,149
OS crossover adjustment with re-censoring	Scenario analysis was undertaken to test how the choice of crossover adjustment (with vs without re-censoring) affects long-term OS. Refer to section 3.4 and section 9.2.2.	526,585 kr.	0.69	767,509
Vial sharing: 0%	Assess the sensitivity of the model to assumptions around treatment wastage. Refer to section 11.1.	589,803 kr.	0.70	842,288
Vial sharing: 50%		558,286 kr.	0.70	797,280
T-DXd RDI: 80%	Assess the sensitivity of the model to the T-DXd dosing (refer to section 3.2).	469,574 kr.	0.70	670,592
SoC treatment basket composition: equal proportions	An equal 33/33/33% distribution and 100% single-comparator scenarios (PTX, DTX, irinotecan) are included to illustrate how different SoC mixes (refer to section 11.1).	531,860 kr.	0.70	759,579
SoC treatment basket composition: 100% PTX		500,076 kr.	0.70	714,627
SoC treatment basket composition: 100% DTX		548,088 kr.	0.70	781,980
SoC treatment basket composition: 100% irinotecan		547,404 kr.	0.70	782,072
Body weight + 10%	This scenario explored the impact of body weight changes on the ICER.	574,491 kr.	0.70	820,421 kr.
Body weight - 10%		481,988 kr.	0.70	688,319 kr.
BSA + 10%	This scenario explored the impact of BSA changes on the ICER.	526,217 kr.	0.70	751,482 kr.
BSA – 10%		527,324 kr.	0.70	753,063 kr.

Abbreviations are defined in the list of Abbreviations

12.2.2 Probabilistic Sensitivity Analyses (PSA)

A probabilistic sensitivity analysis (PSA) was also conducted to account for the joint uncertainty associated with parameter estimates. The distribution for each parameter variation was selected based on reliability and recommendations from Briggs et al (80). Standard errors and 95% CIs were considered when available. When these values were not reported, the standard error was estimated as 10% of the mean value.

A PSA using 1,000 iterations was run for T-DXd versus SoC. The cost-effectiveness plane for the T-DXd and SoC are presented in Figure 24, and the cost-effectiveness acceptability curve (CEAC) is presented in Figure 25. A convergence plot is presented in Figure 26. All PSA runs predict a higher cost and QALYs for T-DXd compared to SoC.

Figure 24. Cost-effectiveness plane (scatterplot)

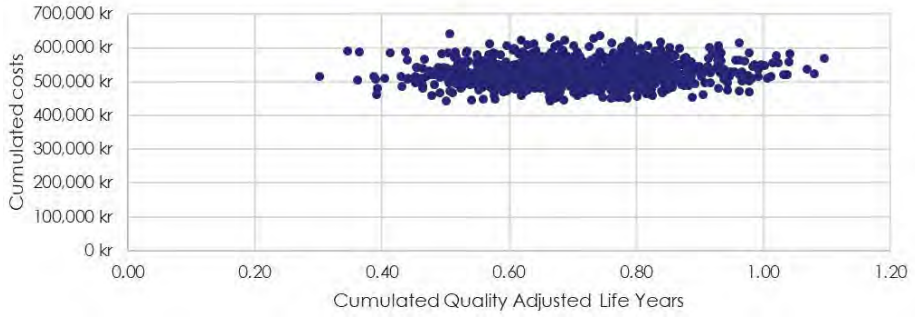
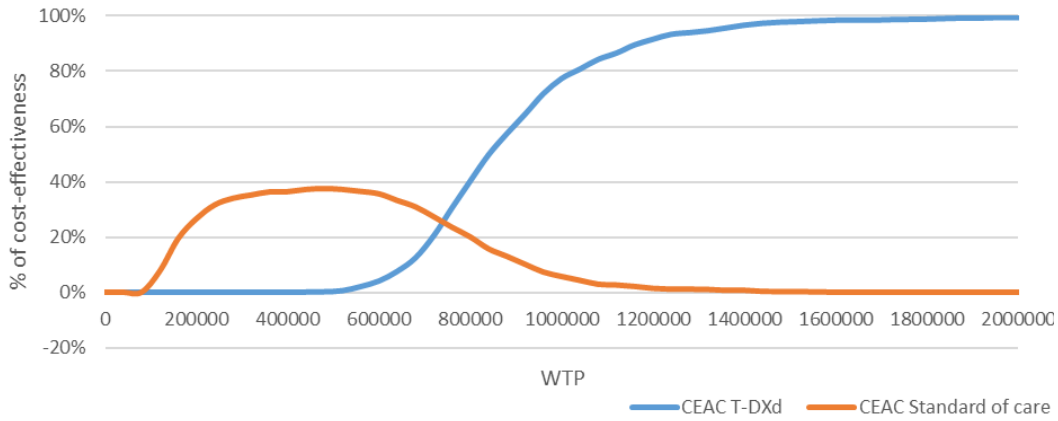
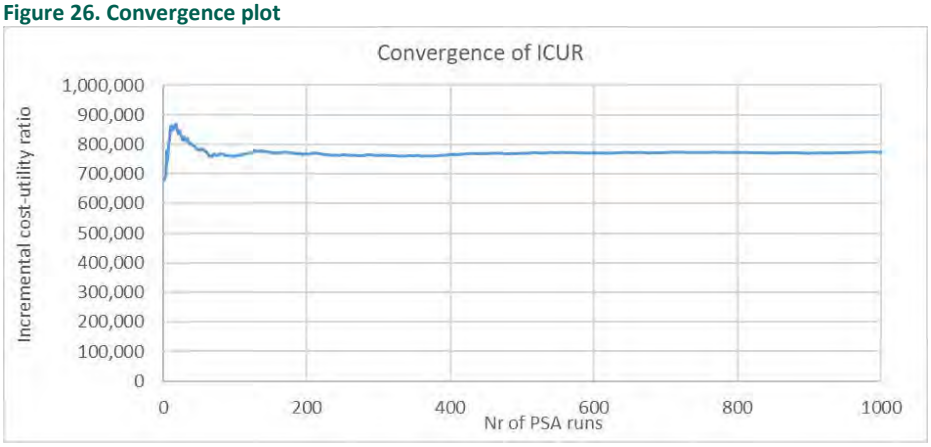


Figure 25. Cost-effectiveness acceptability curve



Abbreviations are defined in the list of Abbreviations

Figure 26. Convergence plot



Abbreviations are defined in the list of Abbreviations

13. Budget Impact Analysis

The key inputs and assumptions for the calculations of the eligible patient population and market share are presented in Table 4 (section 3.1.2). For this budget impact model, 38 patients per year were considered as the "fit for any second-line treatment" cohort. Of these 38 patients, 80% are assumed eligible to receive treatment with T-DXd, yielding an estimated 30 T-DXd initiations annually. Due to low patient numbers and low variation anticipated, the same patient volume was assumed for the next 5 years in the budget impact analysis. Given prior use of T-DXd through name-based reimbursement applications and the substantial unmet need in Denmark, we assume that all eligible patients would receive T-DXd, corresponding to a 100% uptake among eligible patients from year one of reimbursement.

The budget impact is obtained by comparing the total costs under the following two scenarios: 1) with the recommendation of T-DXd, and 2) without the recommendation of T-DXd, as per the DG04 indication. The estimated total budget impact in year 1 is approximately DKK 12,433,104, and DKK 15,799,709 in year 5 (Table 64).

The budget impact is driven primarily by drug acquisition costs, and secondarily by costs that accrue from improved OS with T-DXd relative to SoC. Longer survival increases resource use in follow-up, and administration, increasing total healthcare resource use cost for patients on T-DXd alongside the cost of treatment.

Table 64. Budget impact (undiscounted estimates), DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Regional costs of recommendation					
Drug costs	12,334,207	14,542,164	15,056,990	15,237,320	15,315,795
Other regional hospital costs	1,608,745	1,920,729	2,026,818	2,077,990	2,107,410
Total by recommendation	13,942,952	16,462,893	17,083,808	17,315,311	17,423,205
Regional costs of non-recommendation					
Drug costs	243,449	251,931	252,175	252,184	252,185
Other regional hospital costs	1,266,399	1,352,356	1,366,410	1,370,239	1,371,312
Total for non-recommendation	1,509,849	1,604,287	1,618,585	1,622,423	1,623,496
Total budget impact	**12,433,104**	**14,858,606**	**15,465,223**	**15,692,888**	**15,799,709**

14. List of experts

In this application, the following experts have been consulted.

[redacted]

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Appendix A. Study Characteristics

CONSORT diagrams showing the flow of participants through the DG04 and RAINBOW trials are provided in Figure 1 and Figure 2.

Figure 1: CONSORT diagram from the DG04 study

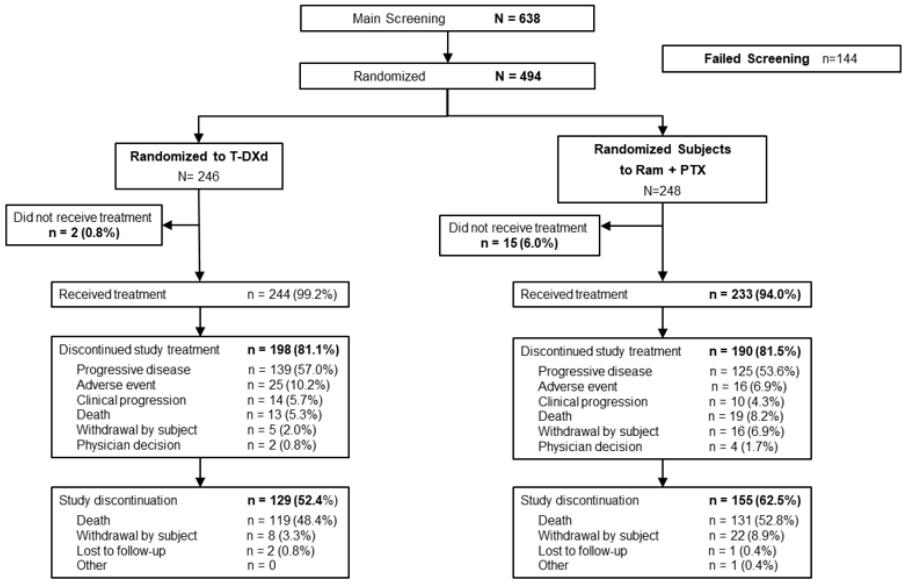


Figure 2 CONSORT diagram from the RAINBOW study

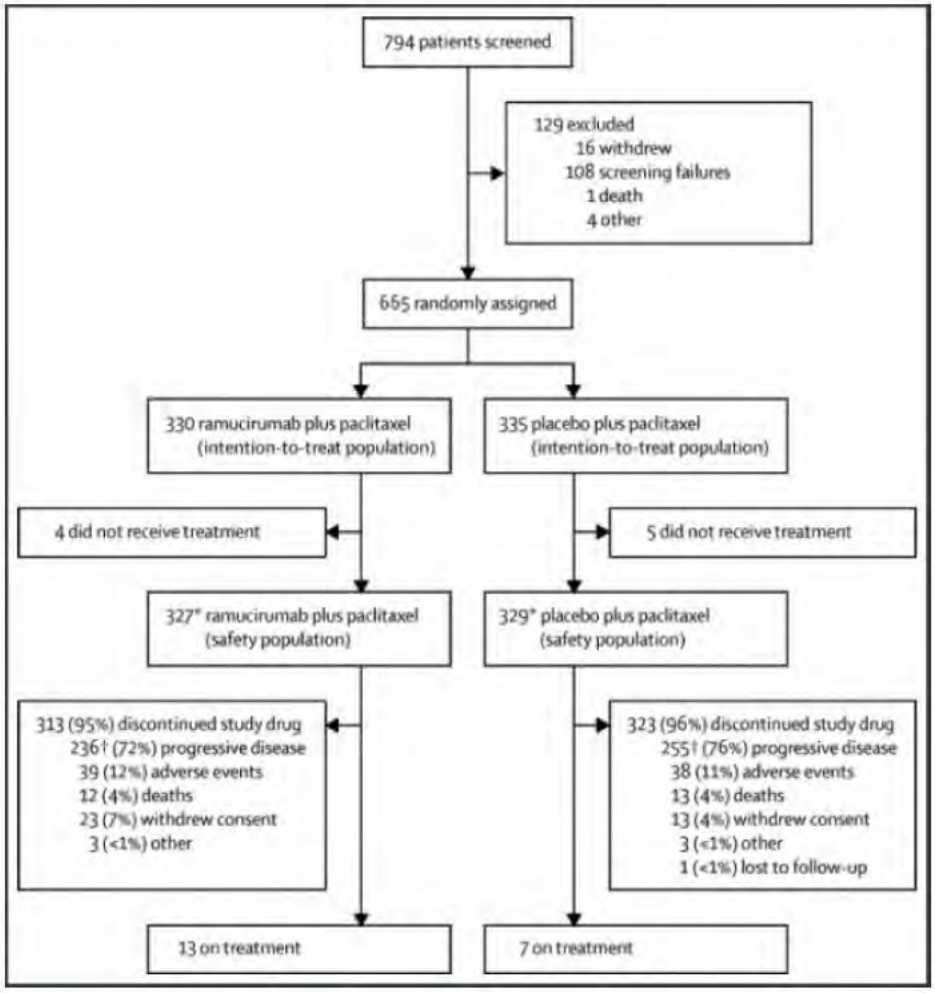


Table 65. Main characteristics of included studies: DG04

Study name: DESTINY-Gastric04	**NCT-number: NCT04704934**
Purpose	To evaluate efficacy and safety of **T-DXd** versus **RAM+PTX** in adult patients with unresectable or metastatic **HER2-positive gastric or GEJ cancer** previously treated with trastuzumab-containing therapy.
Publications – title, author, journal, year	Shitara et al; DESTINY-Gastric04 Trial Investigators. Trastuzumab Deruxtecan or Ramucirumab plus Paclitaxel in Gastric Cancer. N Engl J Med. 2025 Jul 24;393(4):336-348. doi: 10.1056/NEJMoa2503119. Epub 2025 May 31. PMID: 40454632.
Study type and design	This was an open-label, randomised phase 3 study enrolling patients with HER2-positive unresectable or metastatic gastric/GEJ adenocarcinoma after progression on trastuzumab-based therapy. Patients were randomly assigned 1:1 using a stratified permuted-block randomisation method. No blinding was implemented, and crossover between treatment arms was not permitted. The study is ongoing.
Number of trial participants (N)	n=494 (T-DXd n=246; RAM+PTX n=248).
Primary inclusion criteria	Adults (according to local regulation) and able to provide informed consent for study participation. Pathologically documented gastric and GEJ adenocarcinoma that has been previously treated in the metastatic setting (unresectable, locally advanced, or metastatic disease).

Study name: DESTINY-Gastric04	NCT-number: NCT04704934
	Progression on or after first-line therapy with a trastuzumab or approved trastuzumab biosimilar-containing regimen. Note: Prior neoadjuvant or adjuvant therapy with a trastuzumab-containing regimen can be counted as a line of therapy if the subject progressed on or within 6 months of completing neoadjuvant or adjuvant therapy. Prior neoadjuvant or adjuvant therapy that does not include trastuzumab will not be counted as a line of therapy regardless of the progression status of the subject. Locally or centrally confirmed HER2-positive (IHC 3+ or IHC 2+ and evidence of HER2 amplification by ISH) as classified by ASCO-CAP on a tumour biopsy obtained after progression on or after a first-line trastuzumab or approved trastuzumab biosimilar-containing regimen. Eastern Cooperative Oncology Group performance status of 0 or 1 at Screening. Adequate bone marrow, renal, hepatic function, and blood clotting function within 14 days of randomization.
Primary exclusion criteria	Use of anticancer therapy after trastuzumab-containing treatment Medical history of myocardial infarction (MI) within 6 months before randomization/enrolment, symptomatic congestive heart failure (New York Heart Association Class II to IV). Has a history of (non-infectious) interstitial lung disease (ILD/pneumonitis) that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at Screening. Any autoimmune, connective tissue or inflammatory disorders (e.g., rheumatoid arthritis, Sjögren syndrome, sarcoidosis, etc.) where there is documented (or a suspicion of) pulmonary involvement at the time of Screening. Prior complete pneumonectomy. Spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumours curatively treated. History of severe hypersensitivity reactions to either the T-DXd or inactive ingredients in T-DXd. Clinically significant gastrointestinal disorder (e.g., including hepatic disorders, bleeding, inflammation, occlusion, ileus, diarrhoea Grade >1, jaundice, intestinal paralysis, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction) in the opinion of Investigator
Intervention	Trastuzumab deruxtecan was administered at 6.4 mg/kg intravenously on day 1 of each 21-day cycle, and 244 of 246 randomized patients (99.2%) received treatment.
Comparator(s)	RAM+PTX consisted of RAM 8 mg/kg on days 1 and 15 of a 28-day cycle plus PTX 80 mg/m^2 on days 1, 8, and 15, and 233 of 248 randomized patients (94.0%) received treatment.
Follow-up time	Median follow-up time for OS: 16.8 months for T-DXd
Is the study used in the health economic model?	Yes

Study name: DESTINY-Gastric04	NCT-number: NCT04704934
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary end point was overall survival. Secondary and exploratory endpoints included progression-free survival, time-to-treatment discontinuation, HRQoL, and safety. **Other endpoints:** Other secondary endpoints were confirmed objective response (complete or partial response lasting ≥4 weeks), disease control, and duration of response.
Analysis method	All efficacy analyses were intention-to-treat analyses. Kaplan–Meier method was used to estimate rates of PFS and OS. The comparison between the two study groups was conducted on the basis of a stratified log-rank test with the use of the randomization stratification factors at an overall two-sided significance level of 0.05. For predefined sensitivity analyses, a stratified Cox proportional hazards model was used. The proportional hazards assumption was assessed using scaled Schoenfeld residuals (refer to Appendix E).
Subgroup analyses	The DG-04 dataset includes subgroup analyses for the following strata: HER2 status after trastuzumab therapy (IHC 3+ vs IHC 2+ and ISH-positive); geographic region (Asia [excluding mainland China], western Europe, mainland China, and rest of world); and time to progression during first-line therapy. Other clinical factors were explored.
Other relevant information	

Abbreviations are defined in the list of Abbreviations

Table 66 Main characteristics of included studies: RAINBOW

Study name: RAINBOW	NCT-number: NCT01170663
Purpose	To evaluate the efficacy and safety of **RAM+PTX** versus **placebo plus PTX** in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma.
Publications – title, author, journal, year	**Wilke et al.** "Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomized phase 3 trial." *Lancet Oncology*, 2014.
Study type and design	RAINBOW was a double-blind, placebo-controlled, randomised phase 3 study in patients with previously treated metastatic or unresectable gastric or gastro-oesophageal junction adenocarcinoma. Patients were randomly assigned 1:1 to RAM+PTX or placebo plus PTX using a stratified permuted-block randomisation method implemented via a central interactive voice/web-response system. Patients, investigators, study staff, data analysts, and the sponsor were fully blinded to treatment assignment. Crossover was not permitted, and the study has been completed.
Number of trial participants (N)	n=665 (RAM+PTX n=330; Placebo + PTX n=335).
Primary inclusion criteria	Signed informed consent; histologically/cytologically confirmed GC/GEJC; metastatic or locally advanced unresectable disease; progression during or within 4 months after first-line platinum/fluoropyrimidine (± anthracycline); adequate organ function; ECOG PS 0–1.

Study name: RAINBOW	NCT-number: NCT01170663
Primary exclusion criteria	First-line chemo other than platinum/fluoropyrimidine (± anthracycline); prior anti-angiogenic systemic therapy; uncontrolled hypertension; symptomatic/poorly controlled heart disease or MI/stroke within 6 months; baseline central nervous system metastasis
Intervention	RAM+PTX was administered as RAM 8 mg/kg intravenously on days 1 and 15 of each 28-day cycle plus PTX 80 mg/m² on days 1, 8, and 15; 327 of 330 randomized patients (99%) received treatment
Comparator(s)	Placebo plus PTX followed the same PTX dosing schedule with placebo substituted for RAM, and 329 of 335 randomized patients (98%) received treatment.
Follow-up time	Median follow-up for OS: 7.9 months (IQR 4.2–13.0)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary end point was OS. Secondary end points included PFS; safety; PROs (EORTC QLQ-C30; EQ-5D). **Other endpoints:** Other secondary and exploratory endpoints were ORR; DCR; and DoR.
Analysis method	All efficacy analyses were intention-to-treat analyses. Time-to-event outcomes (OS and PFS) were analysed using: • **Kaplan–Meier** methods to estimate survival curves • **Stratified log-rank tests** (stratification factors: geographic region, time to progression on first-line therapy, and disease measurability) • **Stratified Cox proportional hazards models** to estimate HRs and 95% CIs A **pre-planned multivariate stepwise Cox regression** was conducted to adjust for significant baseline prognostic factors and to further explore treatment effects on OS and PFS.
Subgroup analyses	RAINBOW included subgroup analyses for the following strata: geographic region, time to progression on first-line therapy, and disease measurability. Other clinical factors were explored.
Other relevant information	

Abbreviations are defined in the list of Abbreviations

Table 67 Main characteristics of included studies: DG02

Study name: DESTINY-Gastric02	NCT-number: NCT04014075
Purpose	To evaluate the **efficacy and safety of T-DXd** in adult patients with **HER2-positive unresectable or metastatic gastric or GEJ adenocarcinoma** who had **progressed on or after a trastuzumab-containing regimen**.
Publications – title, author, journal, year	Van Cutsem et al. Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study. Lancet Oncol. 2023 Jul;24(7):744-756. doi: 10.1016/S1470-2045(23)00215-2. Epub 2023 Jun 14. PMID: 37329891; PMCID: PMC11298287.

Study name: DESTINY-Gastric02	NCT-number: NCT04014075
Study type and design	DESTINY-Gastric02 was a multicentre (North America and Europe), single-arm, open-label phase 2 study enrolling patients with HER2-positive unresectable or metastatic gastric or gastro-oesophageal junction cancer who had progressed on first-line trastuzumab-containing therapy. All patients received trastuzumab deruxtecan and there was no randomisation or blinding, as this was a single-arm study. The study has been completed
Number of trial participants (N)	n=79
Primary inclusion criteria	Men or women ≥18 years old (local regulatory guidelines apply) Has pathologically documented HER2-positive gastric or GEJC that is unresectable or metastatic, and that progressed during or after treatment regimen containing trastuzumab Has at least one measurable lesion per RECIST v1.1, as confirmed by investigator review
Primary exclusion criteria	Has had anticancer therapy after first-line treatment regimen containing trastuzumab Has uncontrolled cardiovascular disease, including any of the following: history of myocardial infarction (MI) within 6 months of first dose or symptomatic congestive heart failure (New York Heart Association Class II to IV), troponin levels consistent with MI as defined according to the manufacturer within 28 days of first dose, or corrected QT interval prolongation to >470 ms (females) or >450 ms (male) based on screening triplicate 12-lead electrocardiogram (ECG) Has history of non-infectious interstitial lung disease (ILD)/pneumonitis that required corticosteroid therapy, or current ILD/pneumonitis that cannot be ruled out at screening Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (i.e., pulmonary emboli within 3 months of the first dose, severe asthma, severe chronic obstructive pulmonary disease (COPD), restrictive lung disease, pleural effusion, etc.), and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (i.e., rheumatoid arthritis, Sjogren's, sarcoidosis, etc.), or prior pneumonectomy. Has pleural effusion, ascites, or pericardial effusion that requires drainage, peritoneal shunt, or Cell-free and Concentrated Ascites Reinfusion Therapy (CART) Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms (Note: participants with clinically inactive brain metastases may be included in the study as well as participants with treated brain metastases who are no longer symptomatic and no longer require treatment with corticosteroids or anticonvulsants.
Intervention	Trastuzumab deruxtecan (6.4 mg/kg intravenously every three weeks). 79 enrolled in study and received study treatment.
Comparator(s)	-
Follow-up time	10.2 months (IQR 5.6–12.9 months)
Is the study used in the health economic model?	No; it is solely used to inform the selection of parametric model for OS extrapolation.

Study name: DESTINY-Gastric02	NCT-number: NCT04014075
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was confirmed ORR, defined as the proportion of patients who achieved a best overall response of confirmed complete response (CR) or partial response (PR), by ICR using RECIST v1.1. **Other endpoints:** Secondary endpoints were PFS, defined as the time interval from the date of first dose of study drug to the date of disease progression or death due to any cause, OS (defined as the time interval from the date of first dose of study drug to the date of death due to any cause), PFS by investigator, ORR by investigator, DOR defined as the time from the date of first documentation of objective response to the date of the first documentation of disease progression) by ICR and investigator, and safety.
Analysis method	Primary and secondary efficacy analyses were performed in the FAS. The primary endpoint was calculated using the Clopper–Pearson method. **Kaplan–Meier** methods was used for estimation and graphical presentation of PFS, OS, DOR and other time-to-event endpoints.
Subgroup analyses	-
Other relevant information	-

Abbreviations are defined in the list of Abbreviations

Appendix B. Results for Clinical Effectiveness per Study

B.1.1 Results for clinical effectiveness per study

Table 68. Results per study: DG04 (9, 33)

Results of DESTINY-Gastric04 (NCT04704934)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
PFS	T-DXd	246	Median PFS: 6.7 months (95% CI 5.6–7.1)	+1.1 months vs RAM+PTX	-	-	HR 0.740	0.594–0.923	0.0074	PFS was aligned with RECIST v1.1. Median PFS and PFS rates were estimated using Kaplan–Meier survival analysis. 95% CIs for median PFS were computed using the Brookmeyer–Crowley method. The HR was estimated with the two-sided p-value from stratified log-rank test and stratified Cox proportional hazards model adjusted for IRT stratification factor: HER2 status.	DG04, data on file (9, 33)
	RAM+PTX	248	Median PFS: 5.6 months (95% CI 4.9–5.8)								
OS	T-DXd	246	Median OS: 14.7 months (95% CI 12.1–16.6)	+ 3.7 months	-	-	HR [redacted]	[redacted]	0.0006	OS estimated using a (RPSFTM without re-censoring to account for	

Results of DESTINY-Gastric04 (NCT04704934)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
	RAM+PTX	248	Median OS: [redacted] months (95% CI [redacted]							crossover from RAM+PTX to T-DXd or disitamab vedotin. Counterfactual event times based on the RPSFTM were used for RAM+PTX arm, and the observed event times and censoring were used for T-DXd arm. Median OS is from Kaplan-Meier estimate. CIs are respectively computed using the Brookmeyer-Crowley method for T-DXd and bootstrap for RAM+PTX and the Brookmeyer-Crowley method for both T-DXd and RAM+PTX. Adjusted HR is from stratified Cox proportional hazards model, stratified by the randomization stratification factors as recorded by the IRT: HER2 status. P-value is based on stratified log-rank test from overall survival	

Results of DESTINY-Gastric04 (NCT04704934)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
										analysis adjusting for crossover.	
ORR	T-DXd	246	44.3% (95% CI 37.8–50.9)	+15.1% vs RAM+PTX	6.1-24.2	0.0006	-	-	-	Confirmed ORR was defined as the proportion of patients who achieved a best overall response of confirmed CR or PR by investigator assessment. Eligible Subjects are those who were randomized at least 77 days (i.e., 2 x 6 weeks - 1 week) before date of data cut-off. ORR was assessed by investigator based on RECIST version 1.1. ORR %: 95% exact binomial CI, based on Clopper-Pearson method for single proportion. Difference in ORR %: Two-sided 95% CI for the difference in ORR is based on Wald method using continuity correction.	
	RAM+PTX	248	29.1% (95% CI 23.4–35.3)								

Abbreviations are defined in the list of Abbreviations

Table 69. Results per study: RAINBOW (10)

Results of RAINBOW (NCT01170663)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
PFS	RAM+PTX	330	Median PFS: 4.4 months (95% CI 4.2–5.3)	+1.5 months vs placebo	-	-	HR 0.635	0.536–0.752	<0.0001	Survival curves were estimated by the Kaplan–Meier method. A log-rank test, stratified by geographic region, time to progression on first-line therapy, and disease measurability, was used to assess PFS. The HR was estimated with a stratified Cox proportional hazards model.	RAINBOW (10)
	Placebo+PTX	335	Median PFS: 2.9 months (95% CI 2.8–3.0)								
OS	RAM+PTX	330	Median OS: 9.6 months (95% CI 8.5–10.8)	+2.2 months vs placebo	-	-	HR 0.807	0.678–0.962	0.017	Survival curves were estimated by the Kaplan–Meier method. A log-rank test, stratified by geographic region, time to progression on first-line therapy, and disease measurability, was used to assess OS. The HR was estimated with a stratified Cox proportional hazards model.	
	Placebo+PTX	335	Median OS: 7.4 months (95% CI 6.3–8.4)								

Results of RAINBOW (NCT01170663)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
ORR	RAM+PTX	330	28% (95% CI 23–33)	+12% vs placebo	NR	0.0001	-	-	-	The proportion of patients achieving an objective response and disease control were compared between treatment groups with the Cochran-Mantel-Haenszel test, with adjustment for the randomization strata.	
	Placebo+PTX	335	16% (95% CI 13–20)								

Abbreviations are defined in the list of Abbreviations

Table 70. Results per study: COUGAR-02 (34)

Results of COUGAR-02 (NCT00978549)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
PFS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
	NR	NR	NR								
OS	DTX 75mg/m²	84	5.2 (4.1, 5.9)							Analyses used an intention-to-treat approach. OS was measured from randomisation to death, with censoring at the last known date alive. Survival curves were estimated by the Kaplan–Meier method. Survival differences were assessed using a Cox proportional hazards model, reporting hazard ratios with 95% CIs. A planned multivariable Cox regression for overall survival adjusted the treatment effect for stratification variables.	
	Active symptom control	84	3.6 (3.3, 4.4)	-	-	-	0.67	0.49-0.92	0.01		

Results of COUGAR-02 (NCT00978549)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
										Hazard ratios were also estimated for prognostic subgroups and displayed in a hazard ratio plot.	

Abbreviations are defined in the list of Abbreviations

Table 71. Results per study: TCOG GI-0801/BIRIP (40)

Results of TCOG GI-0801/BIRIP (NCT: N/A)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
PFS	Irinotecan 60mg/m²	64	3.8 (3.0–4.7)	-	-	-	0.68	0.47- 0.98	0.0398	N/A	
	Irinotecan 60mg/m² + cisplatin 30mg/m²	66	2.8 (2.1, 3.3)								
OS	Irinotecan 60mg/m²	64	10.7 (8.9, 13.8)				1	0.69 - 1.44	0.9823	N/A	
	Irinotecan 60mg/m² + cisplatin 30mg/m²	66	10.1 (7.2, 12.1)	-	-	-					

Abbreviations are defined in the list of Abbreviations

Table 72. Results per study: KCSG ST10-01 (42)

Results of KCSG ST10-01 (NCT01224652)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
PFS	PTX 70mg/m2	54	3.5 (NR)	-	-	-	1.27	0.86–1.88	0.234	Analyses used an intention-to-treat approach. Survival curves were estimated by the Kaplan–Meier method. The HR of irinotecan compared with PTX in PFS and OS analyses was calculated using the Cox proportional hazards regression model.	
	Irinotecan 150mg/m2	58	2.1 (NR)								
OS	PTX 70mg/m2	54	8.6 (NR)				1.39	0.91 - 2.11	0.126		
	Irinotecan 150mg/m2	58	7.0 (NR)								
				-	-	-					

Abbreviations are defined in the list of Abbreviations

Table 73. Results per study: RAMIRIS (81)

Results of RAMIRIS (NCT03081143)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
PFS	RAM 8mg/kg + PTX 80mg/m²	72	3.7	-	-	-	0.73	0.48-1.11	NR	N/A	
	RAM 8mg/kg + FOLFIRI	38	3.9								
OS	RAM 8mg/kg + PTX 80mg/m²	72	7.6 (NR)	-	-	-	0.97	0.62 - 1.52	NR		
	RAM 8mg/kg + FOLFIRI	38	6.8 (NR)								

Abbreviations are defined in the list of Abbreviations

Table 74. Results per study: Roy 2013 (37)

Results of Roy 2013 (NCT00813072)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
PFS	Irinotecan 300 mg/m² Q3W	43	2.6 (1.5, 4.3)	-	-	-				Analyses used an intention-to-treat approach. Survival curves were estimated by the Kaplan–Meier method. HRs for the Roy (2013) study were estimated from digitised curves published in the journal article.	
	PEP02 (liposomal irinotecan) 120 mg/m² Q3W	41	2.7 (1.5, 3.6)	-	-	-	0.99	0.63- 1.54	NR		
	DTX 75 mg/m² Q3W	40	2.7 (1.4, 5.5)	-	-	-	0.86	0.55-1.35	NR		
OS	Irinotecan 300 mg/m² Q3W	43	7.8 (4.9, 9.2)	-	-	-					
	PEP02 (liposomal irinotecan) 120 mg/m² Q3W	41	7.3 (3.8, 9.2)	-	-	-	1.22	0.74 - 2.03	NR		
	DTX 75 mg/m² Q3W	40	7.7 (5.3, 12.3)				1.14	0.70 - 1.86	NR		

Abbreviations are defined in the list of Abbreviations

Table 75. Results per study: Sym 2013 (43)

Results of Sym 2013 (NCT: N/A)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
PFS	Irinotecan 150mg/m²	29	2.2 (0.2, 4.3)	-	-	-	1.2	0.72 - 2.02	0.481	Descriptive statistics are reported as proportions and medians. PFS was calculated from the day of randomization until disease progression, last day of follow-up or death. OS was measured from the first day of randomization until death or last day of follow-up. Kaplan–Meier estimates were used in the analysis of all time-event variables, and differences between curves were analysed using the log-rank test. Statistical significance was accepted for *P* values of <0.05.	
	FOLFIRI	30	3.0 (2.0, 3.7)								
				-	-	-					
OS	Irinotecan 150mg/m²	29	5.8 (3.0, 8.7)	-	-	-	1.21	0.69 - 2.11	0.514		
	FOLFIRI	30	6.7 (5.3, 8.2)								
				-	-	-					

Abbreviations are defined in the list of Abbreviations

Table 76. Results per study: Thuss-Patience 2011 (35)

Results of Thuss-Patience 2011 (NCT00144378)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
PFS	Irinotecan 250 mg/m² Q3W + BSC	21	2.5 (1.6, 3.9)	-	-	-	NR	NR	NR	The primary endpoint of the study was overall survival in the intention to treat population. The median survival of BSC after tumour progression on first-line therapy was extrapolated from several first-line chemotherapy studies and estimated at 2.5 months. A prolongation of overall survival by irinotecan from 2.5 to 4 months was considered clinically significant. All time to event curves were calculated according to the life-table method described by Kaplan and Meier,	
	BSC	19	NR								
OS	Irinotecan 250 mg/m² Q3W + BSC	21	4 (NR)				0.48	0.25–0.92	NR		
	BSC	19	2.4 (NR)								

Results of Thuss-Patience 2011 (NCT00144378)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
										and compared by a one-sided log rank-test, corresponding to the one-sided study hypothesis.	

Abbreviations are defined in the list of Abbreviations

Table 77. Results per study: TRICS (41)

Results of TRICS (N/A)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
PFS	Irinotecan 150mg/m²	84	4.1 (3.3 - 4.9)	-	-	-	0.86	0.615-1.203	0.376	The primary endpoint of this study was OS, which was defined as the time from the date of random assignment to the date of death as a result of any cause. OS, PFS and	
	Irinotecan 60mg/m² + cisplatin 30mg/m²	84	4.6 (3.4 - 5.9)								

Results of TRICS (N/A)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
OS	Irinotecan 150mg/m²	84	12.7 (10.3, 17.2)	-	-	-	0.83	0.60 - 1.17	0.288	TTF curves were constructed as time-to-event plots using the Kaplan–Meier method. Time-to-event curves were compared using log-rank tests and HR estimated by Cox regression models. The efficacy analysis was performed using intent-to-treat populations, wherein all randomly assigned patients were included.	
	Irinotecan 60mg/m² + cisplatin 30mg/m²	84	13.9 (10.8, 17.6)								

Abbreviations are defined in the list of Abbreviations

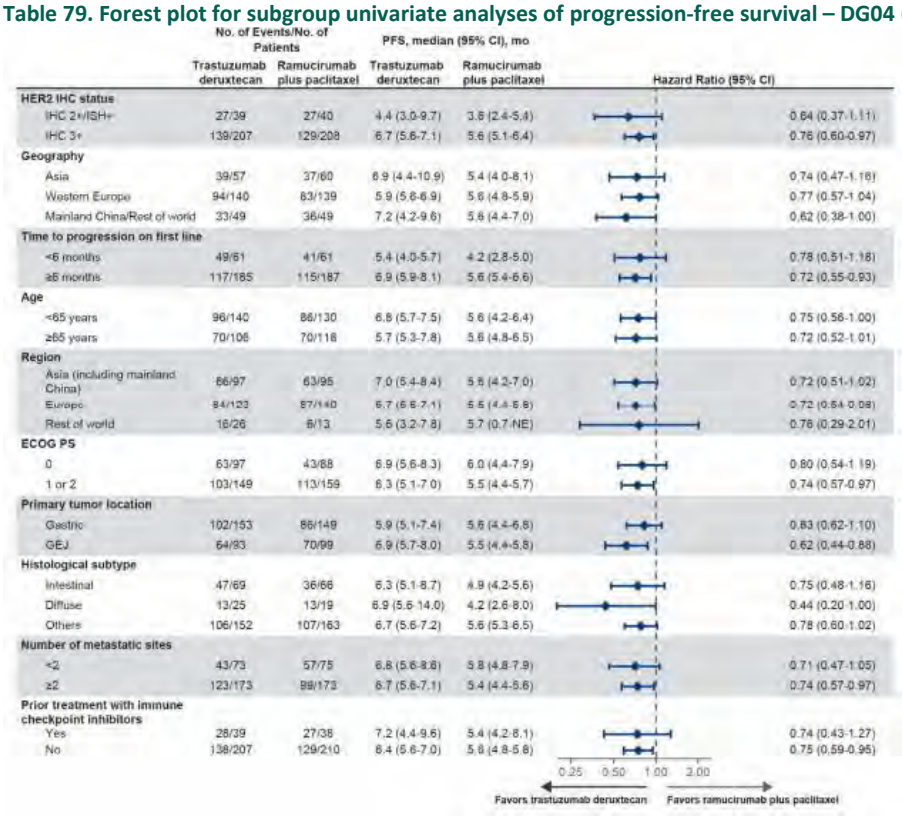
Table 78. Results per study: WJOG4007 (36)

Results of WJOG4007 (N/A)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
PFS	PTX 80mg/m²	108	3.6 (3.3 - 3.8)	-	-	-	1.14	0.88-1.49	0.33	A FAS included all randomly assigned patients who met the eligibility criteria (patients found to be ineligible after random assignment were excluded). OS and PFS were analysed in the FAS and estimated using the Kaplan-Meier method. Cox proportional hazards models were used to calculate HRs and CIs.	
	Irinotecan 150mg/m²	111	2.3 (2.2 - 3.1)								
OS	PTX 80mg/m²	108	9.5 (8.4 - 10.7)	-	-	-	1.13	0.86 - 1.49	0.38		
	Irinotecan 150mg/m²	111	8.4 (7.6 - 9.8)								

Abbreviations are defined in the list of Abbreviations

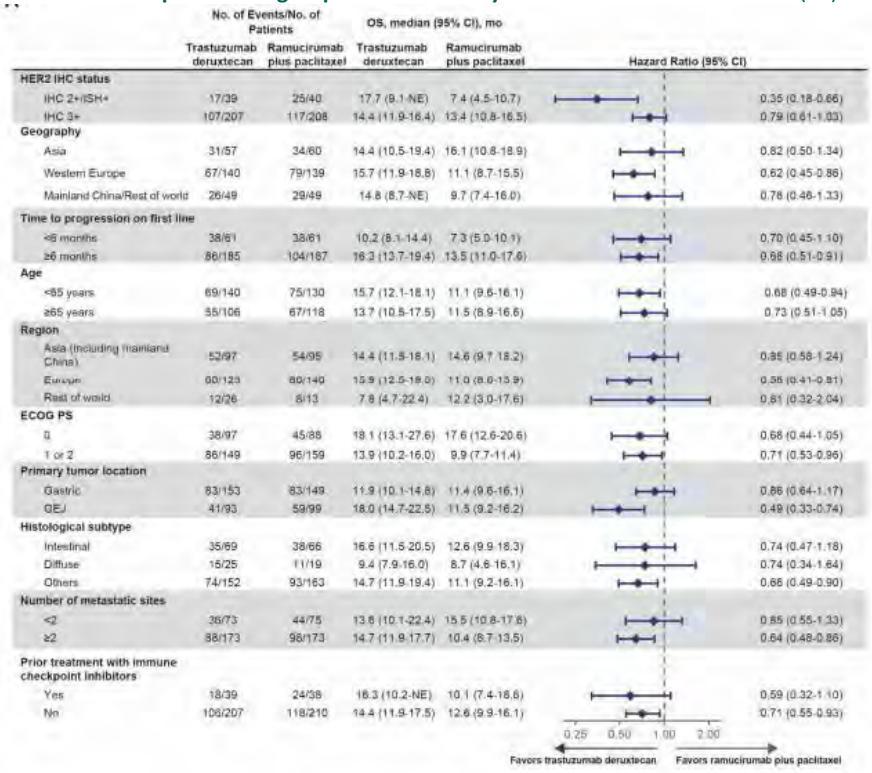
B.1.2 Subgroup analyses

Table 79. Forest plot for subgroup univariate analyses of progression-free survival – DG04 (33)



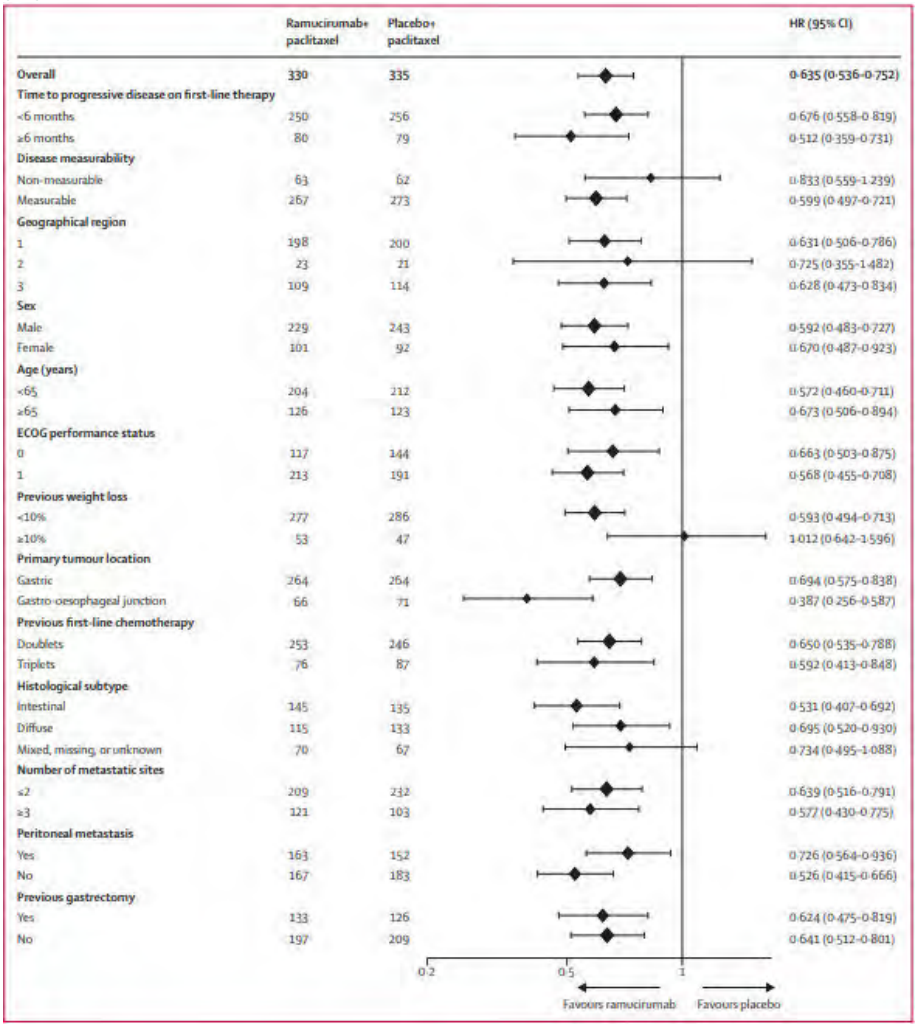
Abbreviations are defined in the list of Abbreviations

Table 80. Forest plot for subgroup univariate analyses of overall survival – DG04 (33)



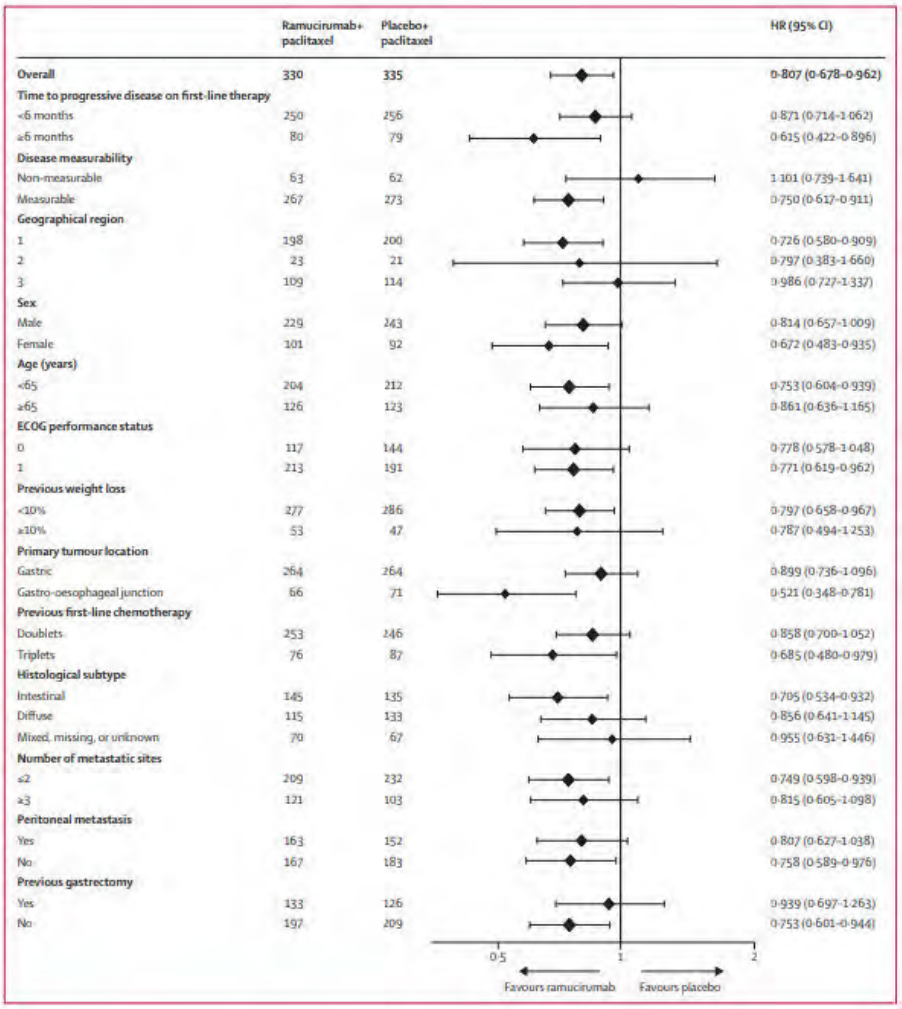
Abbreviations are defined in the list of Abbreviations

Table 81. Forest plot for subgroup univariate analyses of progression-free survival - RAINBOW (10)



Abbreviations are defined in the list of Abbreviations

Table 82. Forest plot for subgroup univariate analyses of overall survival - RAINBOW (10)



Appendix C. Subsequent Treatment

Subsequent therapies included in the model reflect Danish clinical practice and were selected based on clinical expert input (2, 3) for third-line and beyond treatment of advanced/metastatic GC/GEJC. The distribution of subsequent therapies used in the health economic model is presented in Table 52 (section 11.1.2).

Base case analysis

A proportion of 50% was used in the base case analysis for both the T-DXd arm and the SoC arm (refer to section 3.4).

DG04

In the full DG04 study population, 126 patients (51.2%) in the T-DXd group and 118 patients (47.6%) in the RAM+PTX group received subsequent anticancer treatment (refer to Table 83).

Table 83. Subsequent anti-cancer treatment; full population (ITT), DG04 (11)

Subsequent treatment	T-DXd (n=246)	RAM+PTX (n=248)
Subjects receiving any post anti-cancer systemic treatment	126 (51.2)	118 (47.6)
BDC 1001	0	1 (0.4)
Bevacizumab	0	1 (0.4)
Brucea javanica oil	0	1 (0.4)
Calcineurin subunit b	0	1 (0.4)
Calcium folinate	5 (2.0)	2 (0.8)
Calcium folinate; fluorouracil; irinotecan	1 (0.4)	0
Calcium folinate; fluorouracil; irinotecan hydrochloride	11 (4.5)	12 (4.8)
Capecitabine	7 (2.8)	0
Capecitabine; cisplatin	1 (0.4)	0
Capecitabine; irinotecan	0	1 (0.4)
Capecitabine; oxaliplatin	1 (0.4)	1 (0.4)
Carboplatin	1 (0.4)	0
Cisplatin	1 (0.4)	2 (0.8)
Combinations of antineoplastic agents	1 (0.4)	0
Disitamab vedotin	5 (2.0)	12 (4.8)
Docetaxel	4 (1.6)	4 (1.6)
Fluorouracil	10 (4.1)	11 (4.4)
Fluorouracil sodium	1 (0.4)	0
Fluorouracil; folinic acid; oxaliplatin	2 (0.8)	3 (1.2)
Fluorouracil; irinotecan	0	1 (0.4)
Fluorouracil; oxaliplatin	1 (0.4)	0
Folinic acid	2 (0.8)	4 (1.6)
Friquintinib	3 (1.2)	1 (0.4)
Gimeracil; oteracil potassium; tegafur	3 (1.2)	0
GS 181 1	0	1 (0.4)
Immunotherapy	1 (0.4)	1 (0.4)
Investigational drug	5 (2.0)	10 (4.0)

Irinotecan	16 (6.5)	16 (6.5)
Irinotecan hydrochloride	2 (0.8)	7 (2.8)
Irinotecan hydrochloride trihydrate	1 (0.4)	0
Irinotecan hydrochloride trihydrate liposomal	1 (0.4)	0
Levofolinic acid	1 (0.4)	0
Levonorgestrel	0	1 (0.4)
Marsdenia tenacissima stem	0	1 (0.4)
Nivolumab	14 (5.7)	14 (5.6)
Oxaliplatin	10 (4.1)	1 (0.4)
Oxyfedrine hydrochloride	0	1 (0.4)
Paclitaxel	63 (25.6)	8 (3.2)
Paclitaxel nanoparticle albumin-bound	13 (5.3)	0
Paclitaxel; Ramucirumab	13 (5.3)	3 (1.2)
Pembrolizumab	2 (0.8)	2 (0.8)
Pyrotinib maleate	1 (0.4)	1 (0.4)
Ramucirumab	43 (17.5)	8 (3.2)
Regorafenib	0	1 (0.4)
Rivoceranib	1 (0.4)	1 (0.4)
Rivoceranib mesylate	1 (0.4)	2 (0.8)
Runimotamab	0	1 (0.4)
Serplulimab	0	1 (0.4)
Sintilimab	5 (2.0)	2 (0.8)
Sulfasalazine	0	1 (0.4)
Tegafur	0	1 (0.4)
Tipiracil	1 (0.4)	0
Tipiracil hydrochloride; trifluridine	11 (4.5)	11 (4.4)
Tipiracil; trifluridine	2 (0.8)	1 (0.4)
Tislelizumab	0	1 (0.4)
Toripalimab	0	1 (0.4)
Trastuzumab	12 (4.9)	8 (3.2)
Trastuzumab deruxtecan	2 (1.2)	52 (21.0)
Trastuzumab mafodotin	0	1 (0.4)
Trifluridine	2 (0.8)	2 (0.8)
Tumor necrosis factor nos	1 (0.4)	0
Zimberelimab	0	1 (0.4)

Abbreviations are defined in the list of Abbreviations

Notes: 51.2% (T-DXd) and 47.6% (RAM+PTX) are unconditional proportions of all randomized patients who received any subsequent systemic therapy

RAINBOW

In the full RAINBOW study population, 158 patients (48%) in the RAM+PTX group and 154 patients (46%) in the PTX + placebo group received subsequent anticancer treatment (post-discontinuation systemic antineoplastic therapy), refer to Table 84.

Table 84. Post-discontinuation systemic antineoplastic therapy (RAINBOW)

	Ramucirumab plus Paclitaxel	Placebo plus Paclitaxel
All patients	(N=330)	(N=335)
Any treatment	158 (48%)	154 (46%)
Biologic	23 (7%)	18 (5%)
Chemotherapy†	158 (48%)	152 (45%)
Irinotecan	124 (38%)	117 (35%)
Fluorouracil	83 (25%)	74 (22%)
Other chemotherapies‡	125 (38%)	113 (34%)
Other	1 (<1%)	7 (2%)
Regions 1 + 2*	(n=221)	(n=221)
Any treatment	83 (38%)	79 (36%)
Biologic	9 (4%)	6 (3%)
Chemotherapy†	83 (38%)	78 (35%)
Irinotecan	63 (29%)	55 (25%)
Fluorouracil	57 (26%)	51 (23%)
Other chemotherapies‡	64 (29%)	53 (24%)
Other	0	1 (<1%)
Region 1 (Europe, Israel, Australia, United States)	(n=198)	(n=200)
Any treatment	76 (38%)	72 (36%)
Biologic	9 (5%)	5 (3%)
Chemotherapy†	76 (38%)	71 (36%)
Irinotecan	57 (29%)	48 (24%)
Fluorouracil	55 (28%)	47 (24%)
Other chemotherapies‡	60 (30%)	50 (25%)
Other	0	1 (<1%)
Region 2 (Argentina, Brazil, Chile, and Mexico)	(n=23)	(n=21)
Any treatment	7 (30%)	7 (33%)
Biologic	0	1 (5%)
Chemotherapy†	7 (30%)	7 (33%)
Irinotecan	6 (26%)	7 (33%)
Fluorouracil	2 (9%)	4 (19%)
Other chemotherapies‡	4 (17%)	3 (14%)
Other	0	0
Region 3 (Japan, South Korea, Hong Kong, Singapore, and Taiwan)	(n=109)	(n=114)
Any treatment	75 (69%)	75 (66%)
Biologic	14 (13%)	12 (11%)
Chemotherapy	75 (69%)	74 (65%)
Irinotecan	61 (56%)	62 (54%)
Fluorouracil	26 (24%)	23 (20%)
Other chemotherapies‡	61 (56%)	60 (53%)
Other	1 (<1%)	6 (5%)

Data are n (%), unless otherwise indicated. *Europe, Israel, Australia, United States, Argentina, Brazil, Chile, and Mexico. †Patients may be in more than one category; ‡Other chemotherapies include anthracyclines, antineoplastic agents, folic acid analogues, nitrogen mustard analogues, non-steroids, cytotoxic antibiotics, platinum compounds, podophyllotoxin derivatives, pyrimidine analogues, and taxanes.

Source: Wilke et al, supplementary appendix

Appendix D. Comparative Analyses

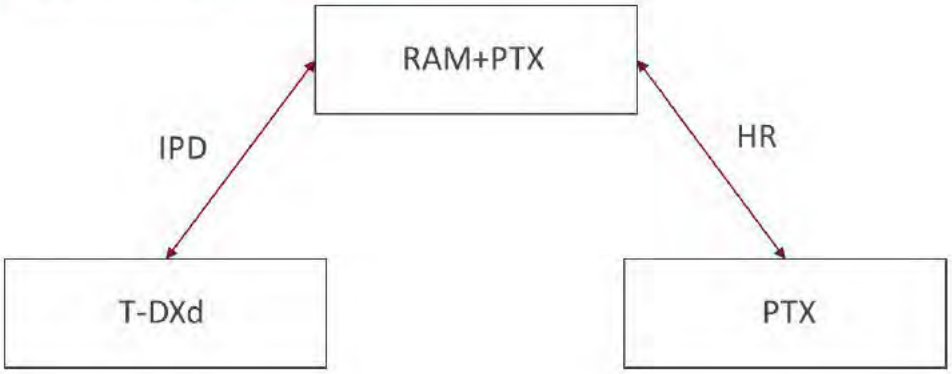
Simplified ITC

For the base case analysis, a simplified ITC was used. The relevant relative efficacy estimates (HRs) are presented in Appendix B.

The simplified ITC was implemented by transporting the HRs for RAM+PTX versus PTX from the RAINBOW study and applying them to the RAM+PTX arm in DG04 to derive PTX outcomes; T-DXd was modelled independently (Figure 9). The approach resembles a Bucher analysis, using a single external source (RAINBOW) and a common anchor (RAM+PTX). The RAINBOW study was identified in the SLR (Appendix H).

The key assumption for the simplified ITC is that the treatment effect of RAM+PTX is similar across studies, with differences in medians or KM curves reflecting population differences in absolute risk rather than changes in the relative effect. This enables applying the HR for RAM+PTX vs PTX to generate PTX outcomes that reflect the relevant patient population, patients with advanced HER2-positive GC/GEJC who have received a prior trastuzumab-based regimen.

Figure 27. Indirect comparison overview



Abbreviations are defined in the list of Abbreviations

OS and PFS outcomes for DG04 and RAINBOW, as required by the DMC template, are provided in Section 6.1.5 and section 6.1.6, respectively. The definition of outcomes was aligned across the two studies (Table 85). No formal definition of TTD was provided in RAINBOW, and no estimate was reported. For this analysis, it was assumed that the PFS HR is representative of TTD as well.

Table 85. Definition of outcomes in DG04 and RAINBOW

Definition of endpoints	DG04	RAINBOW
PFS	Time from randomization to first objective radiographic tumour	Time from randomization to first radiographically documented

	progression or death from any cause, based on Investigator assessment using RECIST v1.1.	progressive disease based on Investigator assessment using RECIST v1.1.
OS	Time from treatment randomization to death from any cause.	Time from treatment randomization to death from any cause.
Treatment response	As per RECIST 1.1	As per RECIST 1.1

Abbreviations are defined in the list of Abbreviations

Proportional hazards (PH) between T-DXd and RAM+PTX and RAM+PTX vs. PTX are inconclusive; therefore, no constant HR was assumed for that comparison. To reflect this, T-DXd and SoC were modelled independently. For SoC, time-varying treatment effects (hazard adjustment) were implemented for OS, and PH were not assumed for RAM+PTX versus PTX (see section 9).

To evaluate treatment outcomes for SoC, PTX alone was considered an appropriate proxy for SoC in this setting. All SoC treatments are expected to be interchangeable for OS and PFS in the target population (2, 3). For DG04, RPSFTM-adjusted OS data was used for RAM+PTX (reference arm).

NMA (for scenario analysis)

To supplement the primary method and evaluate the stability of the findings across a broader evidence base, a Bayesian NMA was performed, drawing on randomised phase II and III trials identified in the SLR presented in Appendix H.

The NMA was conducted to estimate the comparative effectiveness of T-DXd versus guideline-recommended second-line treatments for advanced or metastatic gastric and GEJ adenocarcinoma. The analysis was grounded in an SLR that identified all eligible phase 2 and phase 3 randomized controlled trials reporting OS and/or PFS.

The pivotal DG04 study served as the anchor of the evidence network and provided the key direct comparison between T-DXd and RAM+PTX. As there was crossover from the control arm to T-DXd after disease progression the unadjusted OS estimate would underestimate the true treatment effect. Therefore, OS input for the NMA included the RPSFTM crossover-adjusted HR without re-censoring, which corrects for the impact of treatment switching. This approach produced an adjusted OS HR of [redacted] (95% CI: [redacted]) for T-DXd versus RAM+PTX. PFS was assessed using the same NMA framework applied to OS, ensuring methodological consistency across outcomes. Because disease progression in DG04 occurs before treatment switching, crossover did not affect PFS measurement, allowing the directly observed PFS HR of 0.74 (95% CI: 0.59–0.92) for T-DXd versus RAM+PTX to be incorporated into the base case without any adjustment (69).

A Bayesian NMA framework was used to synthesize evidence across all studies, generating relative treatment effects expressed as Hrs. The analysis applied both fixed-effect (FE) and random-effects (RE) models following NICE DSU Technical Support Document recommendations; however, FE models were prioritized for interpretation due to greater parsimony and narrower credible intervals in the context of a sparsely connected evidence network. All models were estimated using Markov Chain Monte Carlo simulation implemented in 'R' via the BUGSnet package. Vague non-informative priors were selected for treatment effects and heterogeneity parameters to avoid imposing unwarranted

assumptions on the model. Model convergence was verified through visual inspection of Brooks–Gelman–Rubin diagnostics.

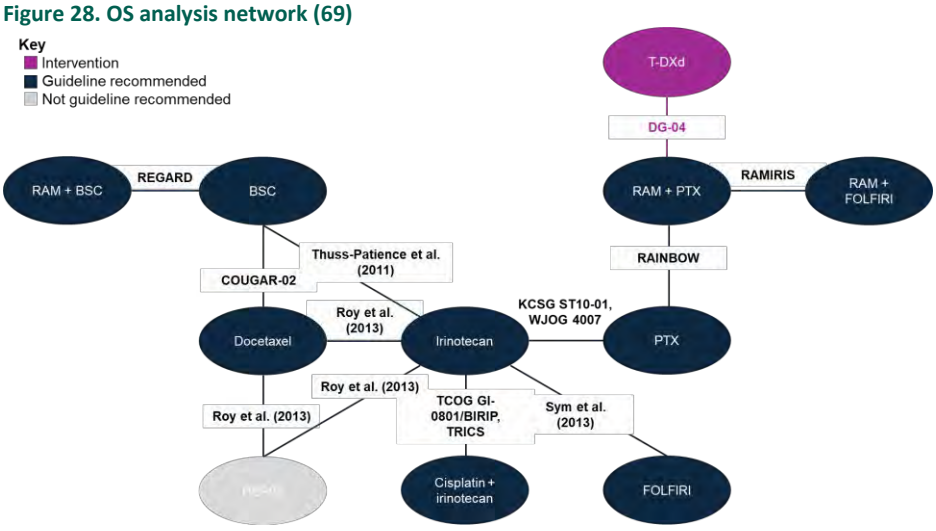
Study-reported HRs and CIs were transformed to their logarithmic equivalents, while studies without reported HRs were reconstructed using pseudo-individual patient data derived from digitized KM curves. The PH assumption was formally assessed across studies using visual inspection of KM curves and log-log plots, supplemented by Schoenfeld residual testing. In general, while statistical analysis suggested that the PH assumption was not maintained across all studies, such as in RAINBOW, Roy et al. (2013) (37) with respect to PFS, and WJOG 4007, there were also no major deviations from proportionality assessed via visual inspection. PH assumptions were typically plausible over the course of the study periods.

Assessment of heterogeneity and inconsistency was performed using multiple approaches. Differences in study populations and potential treatment-effect modifiers were evaluated during a feasibility assessment, confirming that the included studies could be regarded as sufficiently comparable for indirect comparison. Direct comparisons available in more than one study were also pooled separately, and Cochran's Q tests showed no significant heterogeneity, further supporting consistency across studies. Owing to the sparse nature of the network, with many treatment contrasts informed by only a single study, fixed-effect models provided better fit than random-effects models according to the Deviance Information Criterion (DIC).

The final NMA generated posterior distributions for all relative treatment effects, summarized as median HRs with 95% credible intervals. As this analysis was constructed around the crossover-adjusted DG04 OS estimate, all conclusions regarding comparative OS reflect treatment effects corrected for crossover, ensuring that the base case results represent unbiased estimates of the true OS benefit associated with T-DXd.

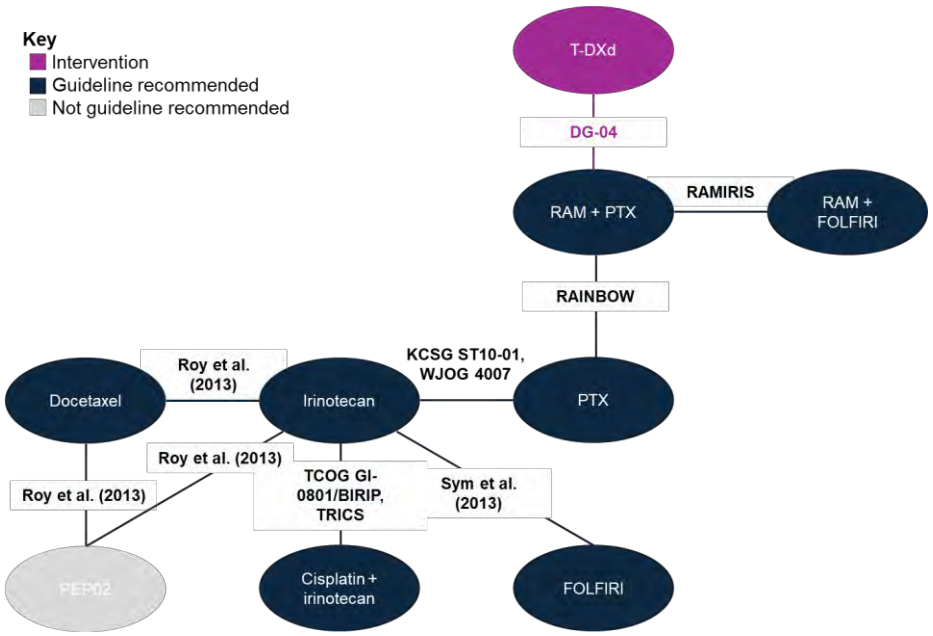
The analysis networks are presented in Figure 28 and Figure 29, respectively.

Figure 28. OS analysis network (69)



Abbreviations are defined in the list of Abbreviations

Figure 29. PFS analysis network (69)



Abbreviations are defined in the list of Abbreviations

The table below summarizes the NMA results for the relevant treatments for this assessment.

Table 86. Comparative analysis of studies comparing T-DXd with SoC for patients with HER2-positive GC/GEJC (69)

Outcome	Studies included in the analysis	Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
		Difference	CI	P-value	Difference	CI	P-value		
PFS									
RAM+PTX	DG-04 (T-DXd vs RAM+PTX) RAINBOW (RAM+PTX vs PTX) RAMIRIS (RAM+FOLFIRI vs RAM+PTX)	-	-	-	[redacted]	[redacted]	-	Bayesian FE NMA	No
PTX	RAINBOW (RAM+PTX vs PTX) WJOG 4007 (PTX vs irinotecan) KCSG ST10-01 (PTX vs irinotecan)	-	-	-	[redacted]	[redacted]	-	Bayesian FE NMA	Scenario analysis
Irinotecan	WJOG 4007 (irinotecan vs PTX) KCSG ST10-01 (irinotecan vs PTX) TCOG GI-0801/BIRIP (irinotecan vs irinotecan+cisplatin) Roy et al. 2013 (PEP02, irinotecan or DTX) TRICS (irinotecan plus cisplatin versus irinotecan) Thuss-Patience et al. (2011) (irinotecan vs BSC) Sym et al. (2013) (Irinotecan vs FOLFIRI)	-	-	-	[redacted]	[redacted]	-	Bayesian FE NMA	Scenario analysis

Outcome	Studies included in the analysis	Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
		Difference	CI	P-value	Difference	CI	P-value		
DTX	Roy et al. 2013 (PEP02, irinotecan or DTX)	-	-	-	[redacted]	[redacted]	-	Bayesian FE NMA The PFS HR for the treatments evaluated in Roy et al. (2013) was estimated using the published study data. The *survival* package in R was used to calculate Cox PH survival curves, based on pseudo-individual patient data generated from digitising the curves in the publication.	Scenario analysis
OS									
RAM+PTX	DG-04 (T-DXd vs RAM+PTX) RAINBOW (RAM+PTX vs PTX) RAMIRIS (RAM+FOLFIRI vs RAM+PTX)	-	-	-	[redacted]	[redacted]	-	Bayesian FE NMA	
PTX	RAINBOW (RAM+PTX vs PTX) WJOG 4007 (PTX vs irinotecan) KCSG ST10-01 (PTX vs irinotecan)	-	-	-	[redacted]	[redacted]	-	Bayesian FE NMA	
Irinotecan	WJOG 4007 (irinotecan vs PTX) KCSG ST10-01 (irinotecan vs PTX) TCOG GI-0801/BIRIP (irinotecan vs irinotecan+cisplatin)	-	-	-	[redacted]	[redacted]	-	Bayesian FE NMA	

Outcome	Studies included in the analysis	Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
		Difference	CI	P-value	Difference	CI	P-value		
	Roy et al. 2013 (PEP02, irinotecan or docetaxel) TRICS (irinotecan plus cisplatin versus irinotecan) Thuss-Patience et al. (2011) (irinotecan vs BSC)								
DTX	COUGAR-02 (DTX vs BSC) Roy et al. 2013 (PEP02, irinotecan or DTX)	-	-	-	[redacted]	[redacted]	-	Bayesian FE NMA The OS HR for the treatments evaluated in Roy et al. (2013) was estimated using the published trial data. The *survival* package in R was used to calculate Cox PH survival curves, based on pseudo-individual patient data generated from digitising the curves in the publication.	

Abbreviations are defined in the list of Abbreviations

Appendix E. Extrapolation of Patient Transitions

E.1 Parametric Extrapolation Models

Parametric models were fitted to extrapolate the survival data from the DG04 study to inform the cost-effectiveness model. The following parametric curves were fitted:

- Exponential
- Weibull
- Gompertz
- Loglogistic
- Lognormal
- Generalised gamma
- Gamma

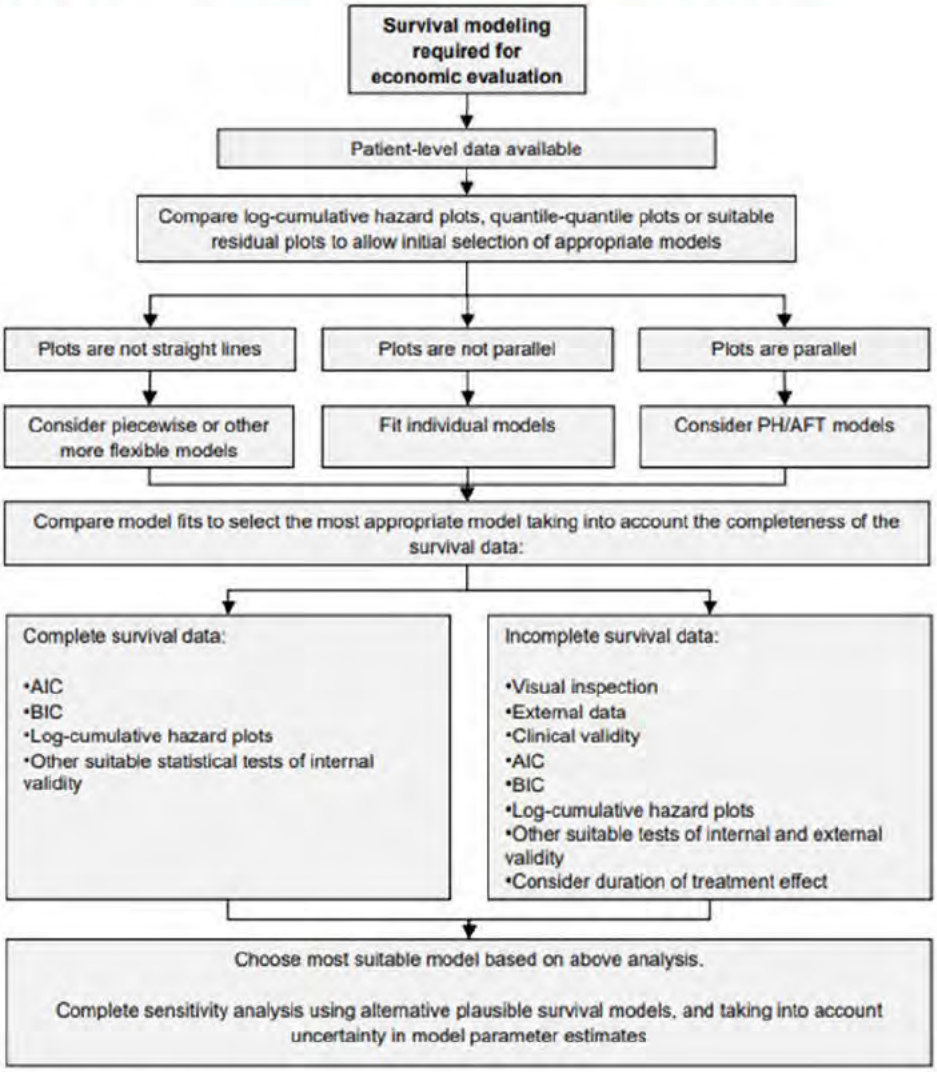
T-DXd and SoC were modelled independently. Model selection followed largely the NICE DSU Technical Support Document 14 algorithm (82). The PH assumption was assessed for T-DXd vs RAM+PTX as well as RAM+PTX vs PTX where data were available. For RAM+PTX vs PTX (OS); a hazard adjustment was implemented to accommodate potential non-proportional hazards for RAM+PTX vs PTX. Specifically, the PH assumption was relaxed by allowing the treatment effect to vary over time. Diagnostic plots were included for completeness for all treatments (this appendix).

For T-DXd, candidate parametric survival functions were evaluated using statistical goodness-of-fit metrics (AIC and BIC), visual fit to observed data, and assessment of clinical plausibility.

For SoC, clinical plausibility based on clinician input and external evidence (clinical expert input and Danish RW data) predominated in model selection, as statistical and visual fit were considered less informative given the indirect evidence structure. Median OS under current SoC is approximately 6–8 months; 1-year survival ~30–40%; 5-year survival is very low. Long-term survivors exist but are rare, highlighting a high unmet need. Table 87 summarizes the selected base-case and scenario extrapolation models. The following section details the rationale for these selections.

As OS and PFS were analysed independently, the cost-effectiveness model enforced a restriction ensuring that PFS never exceeded OS at any time point to prevent inconsistencies. Consistent with the survival ordering constraints, an additional restriction was applied to ensure that TTD never exceeded PFS.

Figure 30. Survival curves selection process as described in the NICE DSU TSD (82)



Abbreviations are defined in the list of Abbreviations

Table 87. Selected models for PFS, OS, and TTD

	Base case	Scenario analysis (Table 63)
PFS		
T-DXd	Generalized gamma	Loglogistic and lognormal
SoC	Generalized gamma	
OS		
T-DXd	Lognormal	Loglogistic and generalized gamma
SoC	Gamma	Weibull and generalised gamma
TTD		
T-DXd	Generalized gamma	Loglogistic and lognormal
SoC	Generalized gamma	

Abbreviations are defined in the list of Abbreviations

E.1.1 Extrapolation of Progression-Free Survival

E.1.1.1 Log-cumulative Hazard Plots and Residual Plots

T-DXd

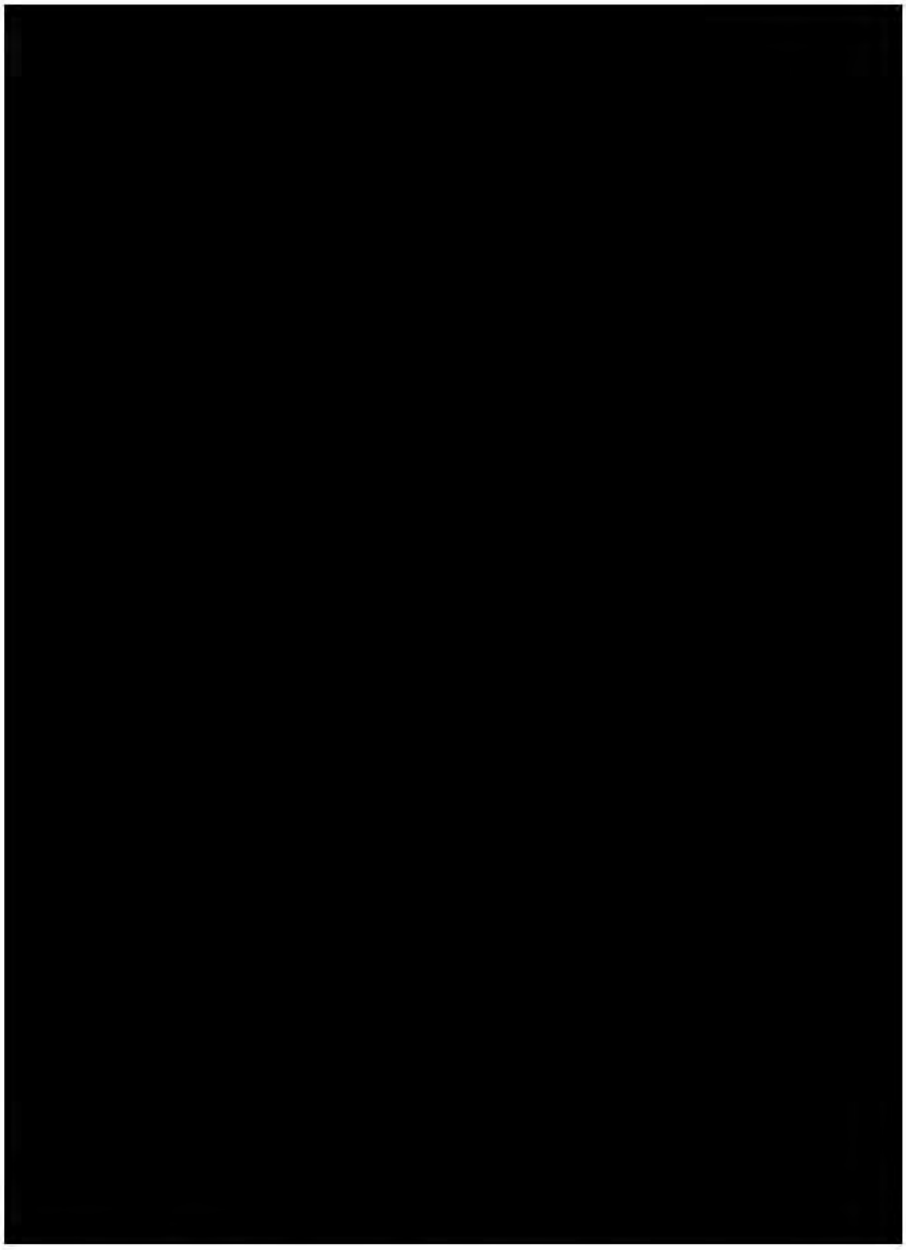
The log-cumulative hazards plot shows the treatment curves converging toward the end of the study period, with similar shapes and no strong evidence against the PH assumption. Analysis of the Schoenfeld residuals displays some variability over time, with a slight increase in the HR, while the Grambsch-Therneau test produced a p-value of [redacted] providing no statistical evidence against the PH assumption (Figure 31).

Although both statistical and visual evidence do not strongly contradict the PH assumption, it remains uncertain whether the assumption fully applies to these data. The quantile-quantile plot for PFS (Figure 33) shows a relatively straight line passing through the origin, with deviations occurring only toward the end of follow-up. This indicates that the observed distribution of survival times matches with the distribution expected under the accelerated failure time assumption. To ensure validity and to appropriately reflect differences in hazard rates between regimens, independent modelling was used for each treatment arm in the analysis of PFS.



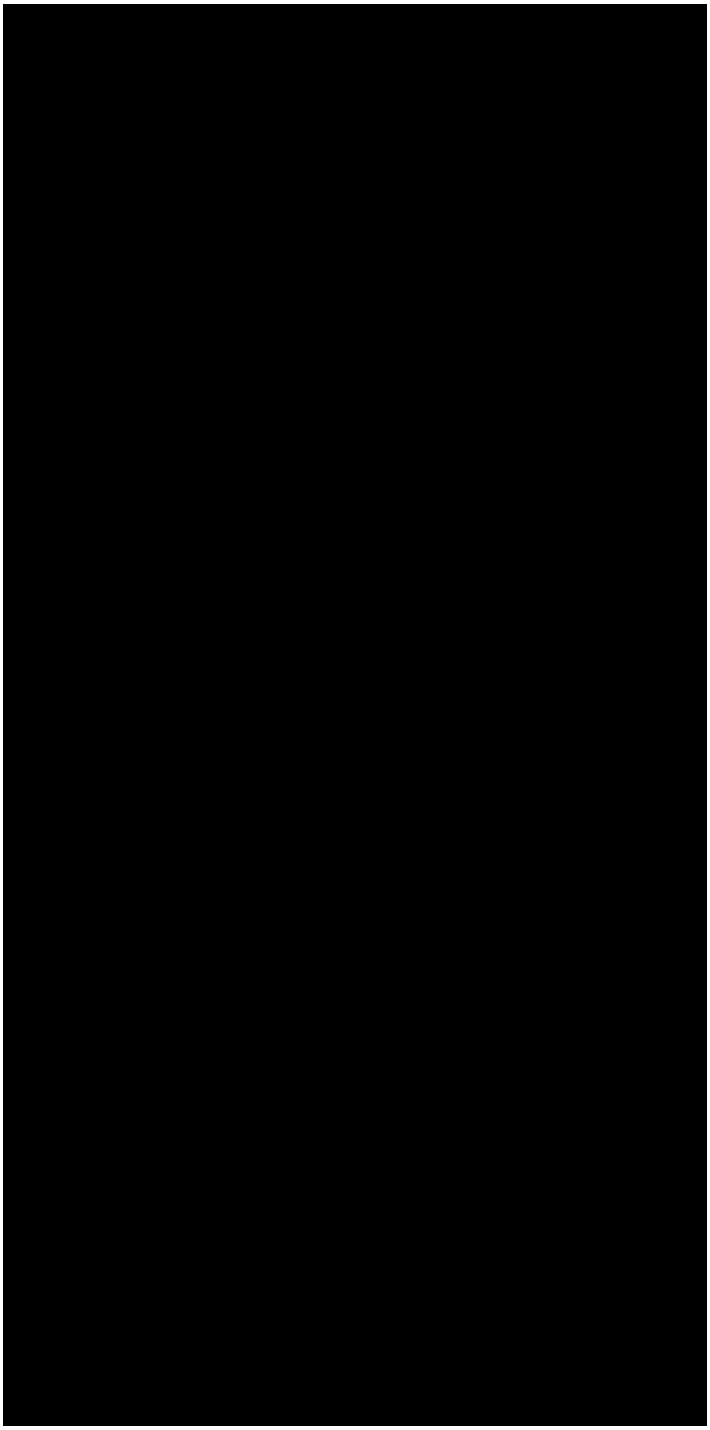






RAINBOW – PTX

In the complementary analyses from RAINBOW (RAM+PTX versus PTX), Schoenfeld residuals (Figure 36) indicated a statistically significant time trend (p-value (p = 0.009), rejecting the null hypothesis of PH. Nonetheless, visual inspection of the KM and log–log plots (Figure 37) suggested approximate proportionality over early to mid-follow up, with emerging non proportionality beyond month 12; from approximately month 10 onward, the PTX arm had few patients at risk, making the late hazard pattern difficult to assess. For the base case analysis, the RAINBOW HR was applied to the DG04 RAM+PTX arm to derive PFS for SoC, assuming PH over time, also beyond 12 months.



E.1.1.2 Internal validity

E.1.1.2.1 Assessment of Statistical and Visual Fit (AIC and BIC)

Given the high level of data maturity for PFS in DG04 (11), the model selection for extrapolating PFS for T-DXd was firstly guided by the statistical fit.

For T-DXd, the loglogistic, lognormal, and generalized gamma models yielded the lowest values for both AIC and BIC, indicating that these models offer the best statistical fit and can be considered essentially equivalent based on these metrics (Table 88).

In contrast, the exponential, Weibull, Gompertz, and gamma models provide a poor statistical fit to the PFS data with AIC and BIC values >30 points higher than the best fitting model for the T-DXd arm. As per Burnham and Andersson's (83) rule of thumb for AIC, there is strong statistical evidence against a given model when AIC is >10 and potentially >3 points higher than the best fitting model. Thus, there is strong statistical evidence for not using these models for extrapolating PFS.

Statistical-goodness-of-fit estimates for RAM+PTX are shown in Table 89.

Table 88. Statistical goodness-of-fit estimates for PFS – T-DXd

Distributions	AIC	BIC
Exponential	1083.3	1086.8
Weibull	1062.1	1069.1
Lognormal	**1037.6**	**1044.7**
Generalised Gamma	**1039.4**	**1050.0**
Loglogistic	**1038.4**	**1045.5**
Gompertz	1081.8	1088.8
Gamma	1052.6	1059.6

Abbreviations are defined in the list of Abbreviations

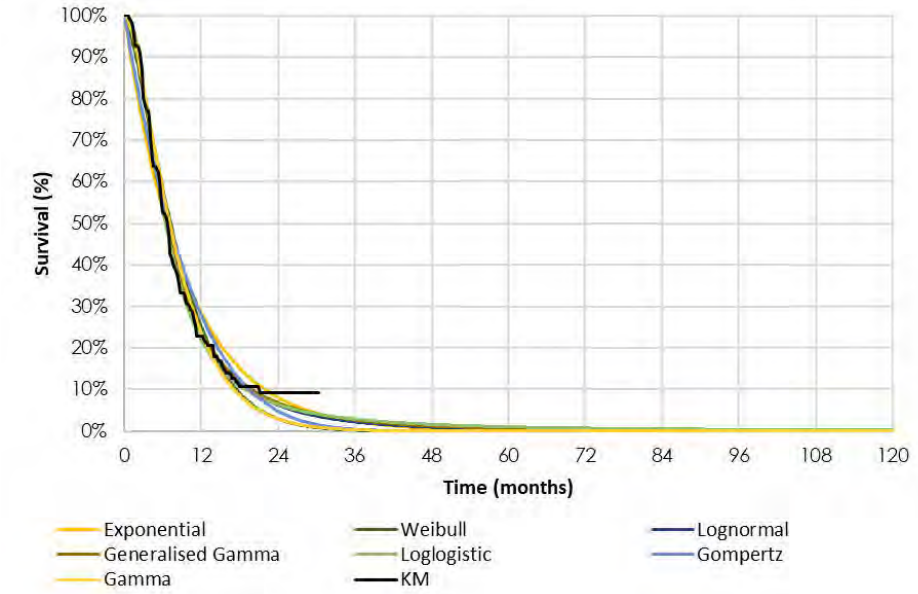
Table 89. Statistical goodness-of-fit estimates for PFS – RAM+PTX

Distributions	AIC	BIC
Exponential	939.7	943.2
Weibull	919.1	926.1
Lognormal	916.6	923.6
Generalised Gamma	912.1	922.7
Loglogistic	907.6	914.6
Gompertz	938.2	945.2
Gamma	912.9	920.0

Abbreviations are defined in the list of Abbreviations

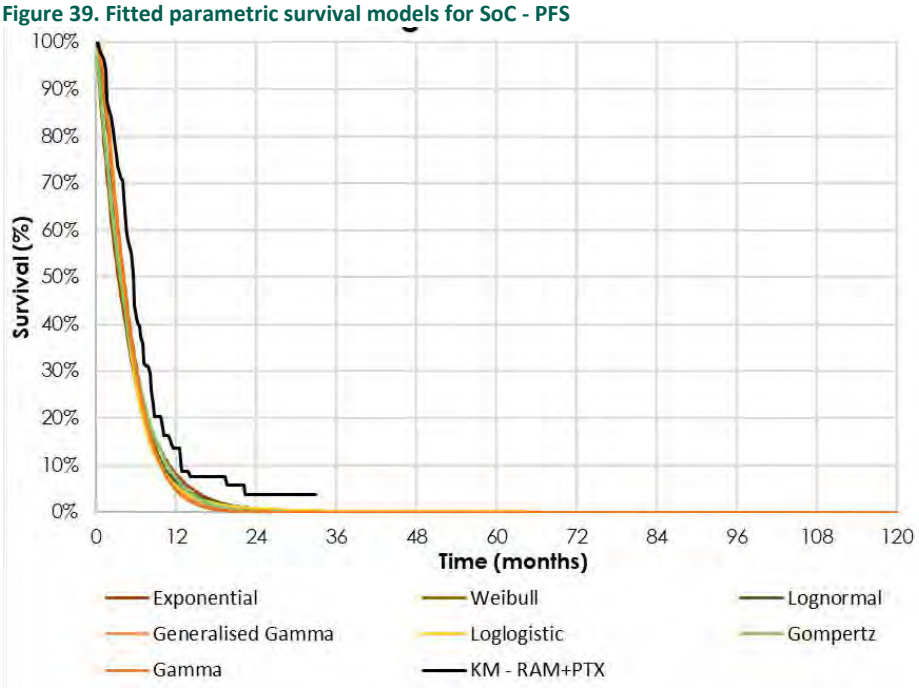
Parametric models were fitted to the T-DXd DG04 PFS. Figure 38 shows the PFS extrapolations with all the distributions alongside the KM curve from the DG04 study for T-DXd. Figure 39 presents the SoC PFS curve generated by applying the RAINBOW HR (RAM+PTX vs PTX) to the RAM+PTX parametric extrapolations. Figure 40 and Figure 41 show parametric survival models in line with the best statistical fit for T-DXd.

Figure 38. Fitted parametric survival models for T-DXd - PFS



Abbreviations are defined in the list of Abbreviations

Figure 39. Fitted parametric survival models for SoC - PFS

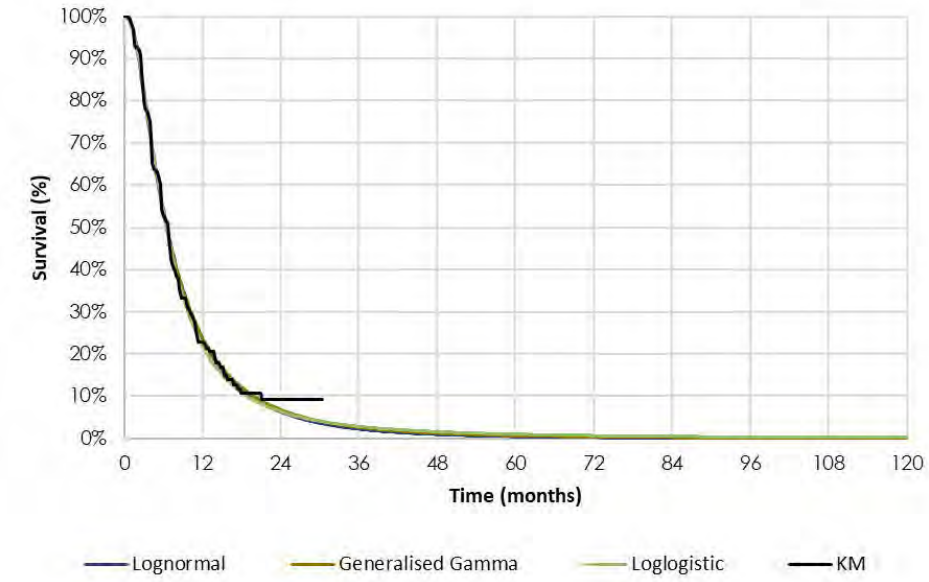


Abbreviations are defined in the list of Abbreviations

For T-DXd, the loglogistic, lognormal and generalized gamma models produce nearly identical trajectories across the observed data (Figure 38). All distributions closely match the observed data up to month 20 but then approach zero on the y-axis rather than capturing the plateau seen in the study results. Given the censoring towards the end of follow-up, this extrapolation may be clinically plausible.

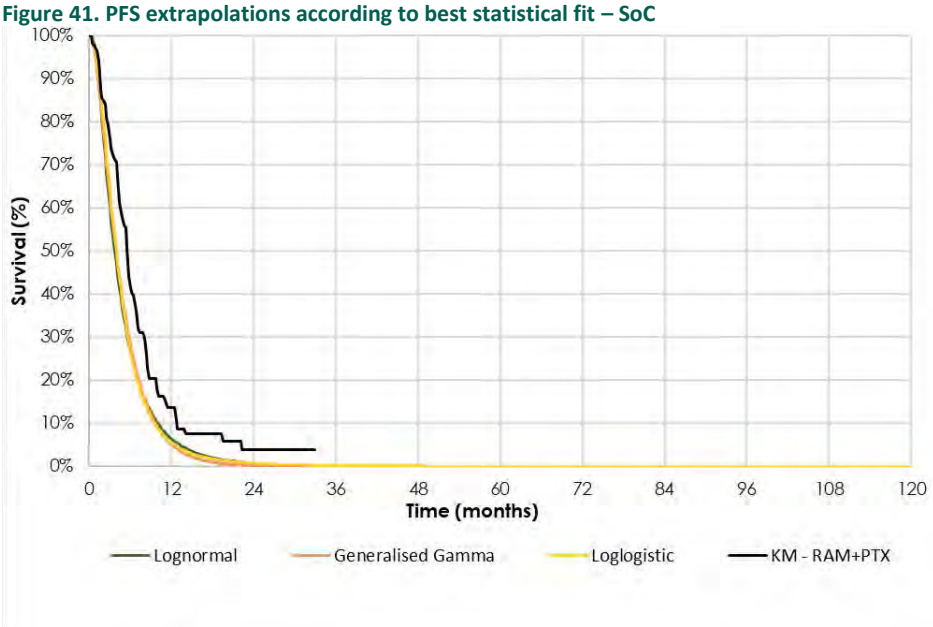
For SoC the three models also produce almost identical PFS estimates (Figure 41).

Figure 40. PFS extrapolations according to best statistical fit - T-DXd



Abbreviations are defined in the list of Abbreviations

Figure 41. PFS extrapolations according to best statistical fit – SoC



Abbreviations are defined in the list of Abbreviations

E.1.1.2.2 Assessment of Smoothed Hazard Functions

Figure 42 presents the PFS hazard rates for T-DXd and RAM+PTX, derived from the DG04 study data. For T-DXd, the hazard for PFS declines over time after an early peak, while the RAM+PTX hazard runs parallel above T-DXd, rising to a peak but then being truncated due to too few patients at risk. A similar pattern is observed in RAINBOW, where hazards rise in parallel followed by a plateau (Figure 43). For both studies, there is a clear separation of the hazards during the study follow-up.

Given limited follow-up in RAINBOW and DG04 and the absence of suitable external data to inform late tails, T-DXd, RAM+PTX, and SoC were assumed to share the same hazard shape for PFS. Accordingly, SoC PFS was derived by applying the HR to the DG04 RAM+PTX comparator arm and using the same parametric distribution as selected for T-DXd. The respective models (loglogistic, lognormal, generalized gamma) were assessed for T-DXd and SoC. Similarly, as for T-DXd, all three models result in similar PFS estimates (Figure 40).

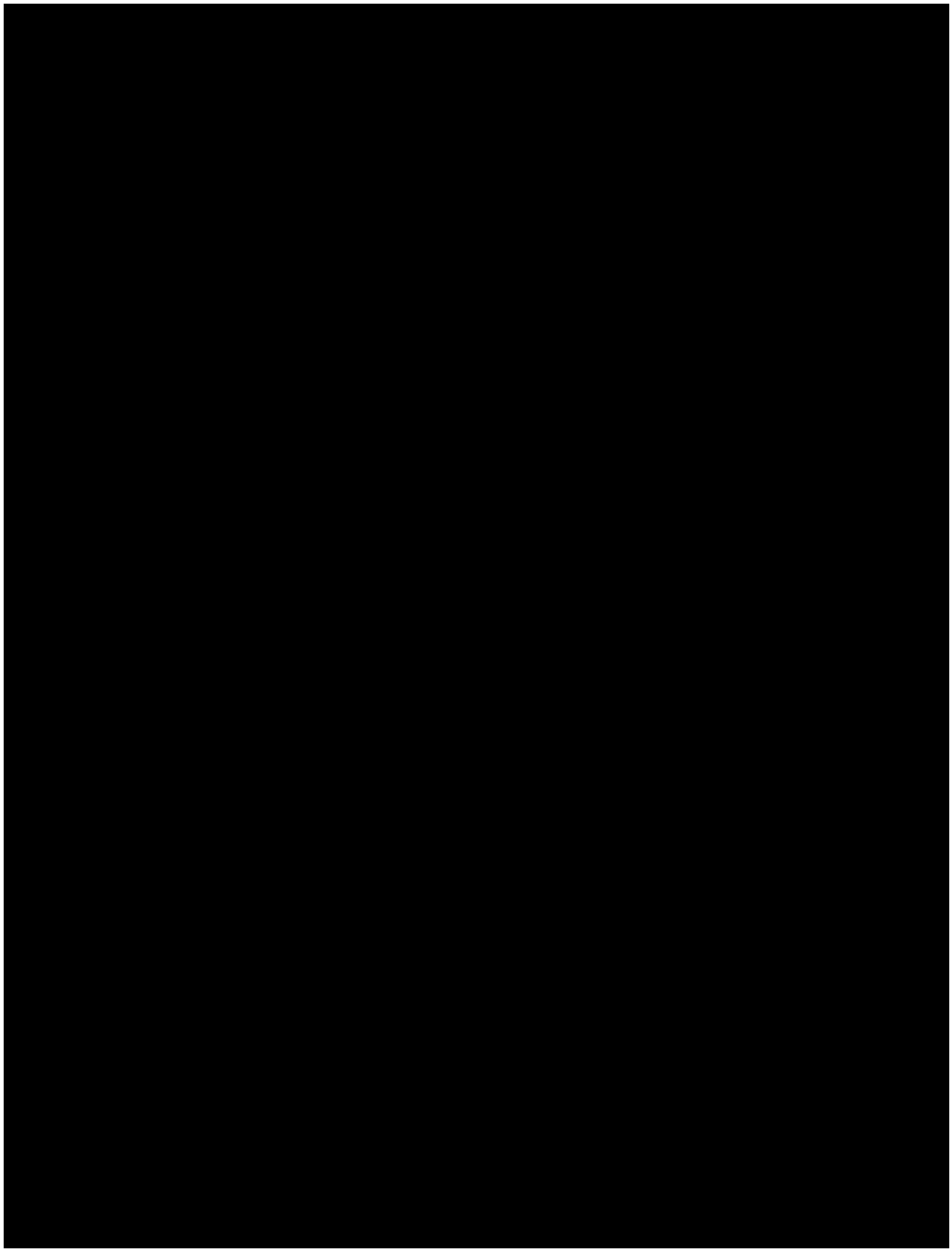
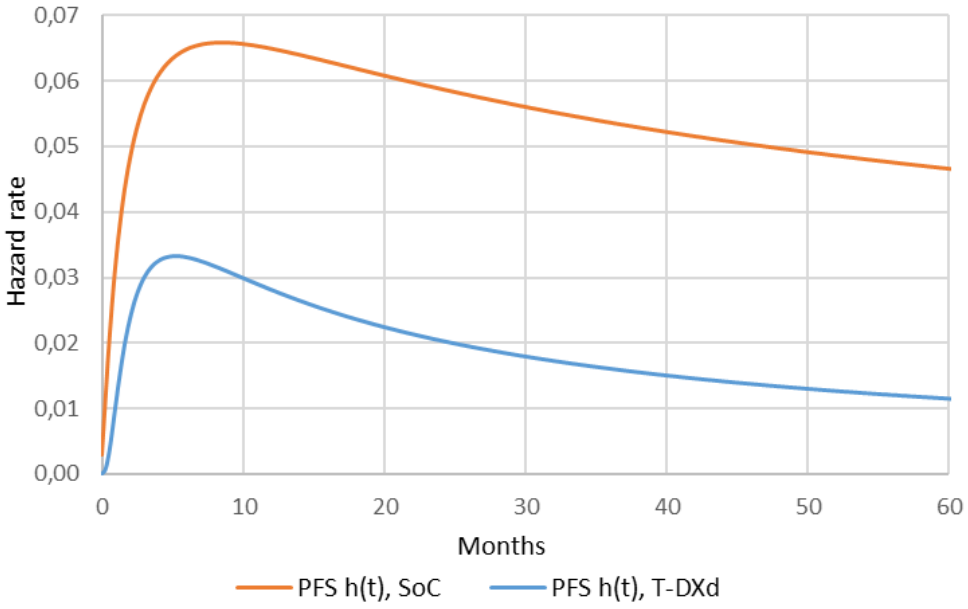


Figure 44 illustrates the modelled hazard functions for the generalized gamma, lognormal and loglogistic distributions. Only the generalized gamma model captures the expected separation of hazards between T-DXd and SoC, as supported by the clinical study data. In contrast, the loglogistic and lognormal models predict that hazards merge over time,

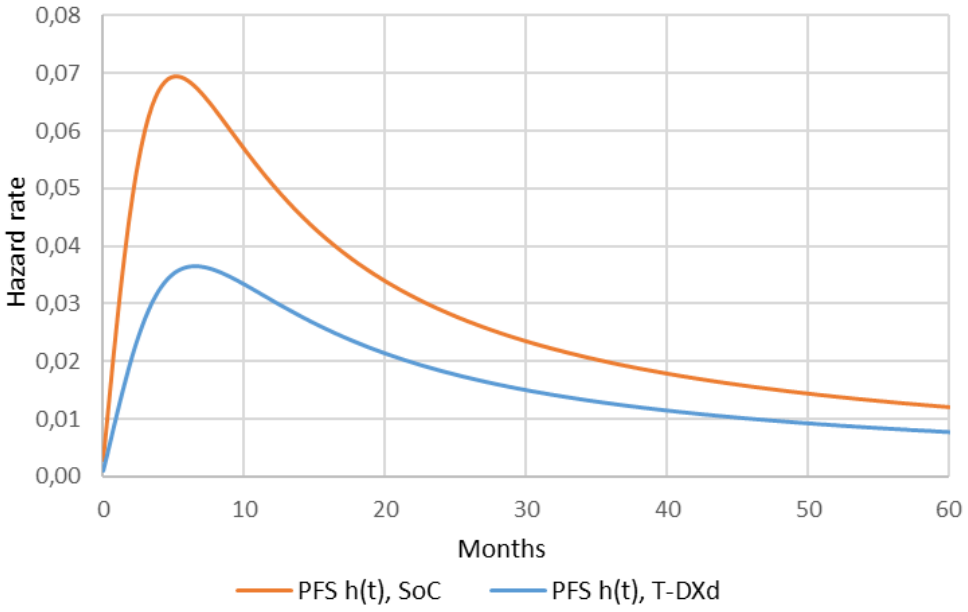
which does not align with observed clinical outcomes in RAINBOW or DG04. Therefore, the generalized gamma model was considered the most appropriate option for both treatments (T-DXd and SoC).

Figure 44. Parametric hazard of death for PFS - T-DXd and SoC

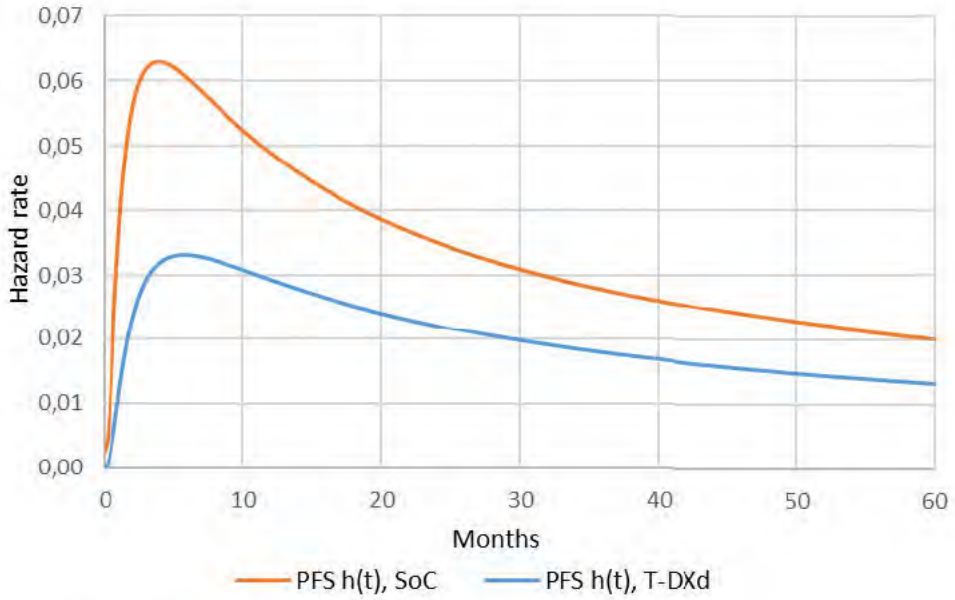
a. Generalized gamma



b. Loglogistic



c. Lognormal



Abbreviations are defined in the list of Abbreviations

E.1.1.3 External Validity

Not assessed

E.1.1.4 Other Assumptions

The extrapolated and observed PFS estimates are presented in Table 90 and Table 91 for T-DXd and SoC, respectively. All three models produce similar estimates overall. The lognormal and loglogistic models yield more optimistic estimates for the SoC, whereas the generalized gamma model provides more conservative estimates from two years onward.

The generalized gamma model was selected for the base case because it provides mid-range projections, neither the highest nor the lowest. The loglogistic and lognormal models were explored in scenario analyses (Table 87).

Table 90. PFS landmarks – extrapolated for T-DXd

Months	Modelled PFS: Generalised Gamma	Modelled PFS: loglogistic	Modelled PFS: lognormal	Observed PFS in DG04
Median PFS, months	6.7	6.7	6.7	6.7
0	100.0%	100.0%	100.0%	100.0%
3	82.0%	83.0%	82.2%	80.3%
6	53.7%	54.1%	54.2%	52.6%
9	35.3%	33.9%	35.5%	33.4%
12	24.0%	22.1%	23.8%	22.9%
15	16.9%	15.2%	16.5%	16.8%
18	12.2%	11.0%	11.7%	10.7%
21	9.1%	8.3%	8.5%	10.7%
24	6.9%	6.4%	6.3%	9.3%
27	5.3%	5.1%	4.8%	9.3%

30	4.2%	4.2%	3.7%	9.3%
60	0.7%	1.0%	0.5%	N/A
72	0.4%	0.7%	0.2%	N/A

Abbreviations are defined in the list of Abbreviations

Table 91. PFS landmarks – extrapolated for SoC

Months	Modelled PFS: Generalised Gamma	Modelled PFS: loglogistic	Modelled PFS: lognormal
Median PFS, months	3.9	4.1	3.7
0	100.0%	100.0%	100.0%
3	63.0%	64.6%	60.3%
6	28.4%	27.0%	26.8%
9	12.1%	11.6%	12.7%
12	5.2%	5.6%	6.5%
15	2.2%	3.0%	3.5%
18	1.0%	1.8%	2.0%
21	0.4%	1.1%	1.2%
24	0.2%	0.8%	0.8%
27	0.1%	0.5%	0.5%
30	0.0%	0.4%	0.3%
60	0.0%	0.0%	0.0%
72	0.0%	0.0%	0.0%

Abbreviations are defined in the list of Abbreviations

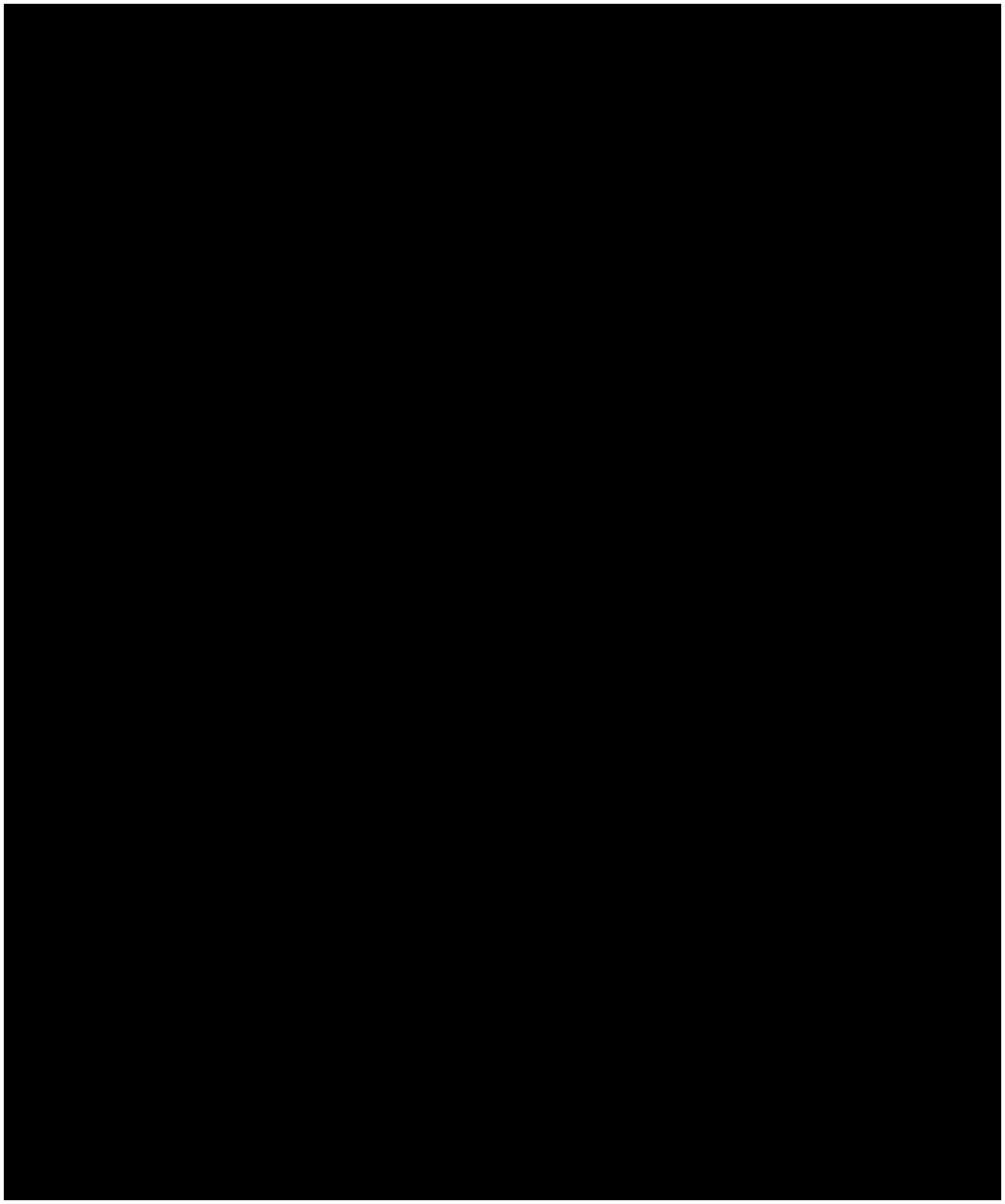
E.1.2 Extrapolation of Overall Survival

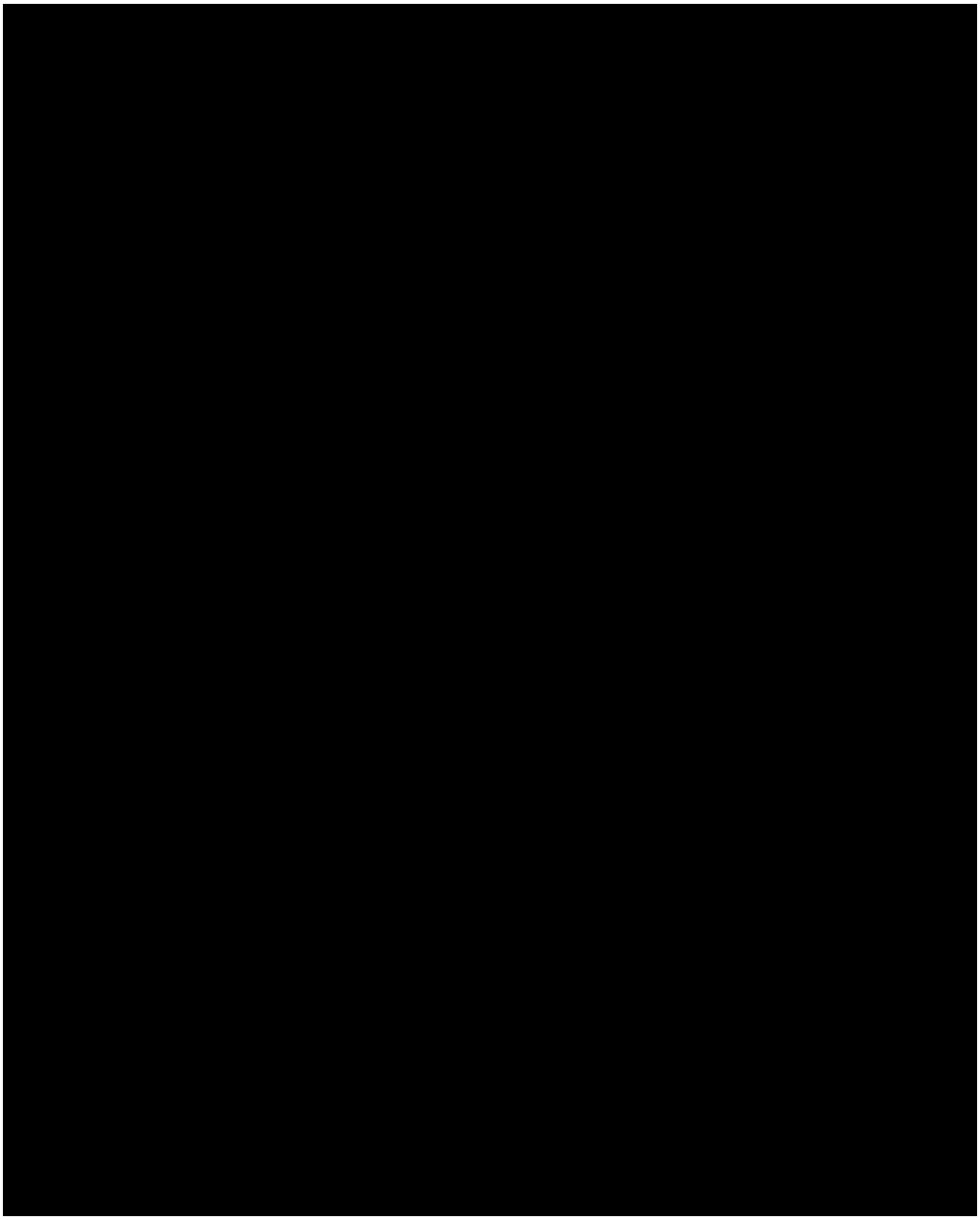
E.1.2.1 Log-cumulative Hazard Plots and Residual Plots

T-DXd and SoC (using DG04 RAM+PTX data as reference arm) were modelled independently and evaluated separately. This approach was deemed most robust for the ITC, particularly given potential treatment-effect modification by HER2-positivity for T-DXd

T-DXd

For OS, the PH assumption was assessed using log-cumulative hazard plots (Figure 46) and Schoenfeld residuals (Figure 45) (crossover adjusted analysis). The log-cumulative hazard plots show approximately straight lines that converge toward the end of the study period, suggesting the PH assumption may not be valid over an extended time horizon. The Schoenfeld residuals plot displays variability in the HR over time without a consistent trend during the study. The Grambsch-Therneau test yielded a p-value of [redacted] not providing any statistical evidence against the PH assumption. The quantile-quantile plot (Figure 47) displays a relatively straight line through the origin, potentially supporting the suitability of AFT models. When assessing the smoothed hazards for OS for both arms and clinical plausibility, it shows that both treatments follow different trends (refer to Appendix E.1.2.2.2). As a result, only independent model fits were considered for each treatment arm, and models were assessed separately.







RAINBOW – PTX

In complementary analyses from RAINBOW (RAM+PTX versus PTX), Schoenfeld residuals showed a statistically significant time trend (p=0.001), rejecting the null hypothesis of PH, whereas visually, KM curves cross early and again from ~18 months; the log–log plot is approximately parallel between months 2–12, with convergence/crossing thereafter (refer to Figure 50 and Figure 51). Accordingly, PH does not hold overall.





E.1.2.2 Internal Validity

E.1.2.2.1 Assessment of Statistical and Visual Fit (AIC and BIC)

Based on the AIC and BIC values, the lognormal, generalised gamma, gamma, and loglogistic are the best-fitting distributions for the OS data from the T-DXd arm in the DG04 study (<3 points from the lowest AIC/BIC value) (Table 92). The exponential, Gompertz (>10 points from lowest AIC/BIC) and Weibull models (>5 points from lowest AIC/BIC) were not considered suitable or less suitable for T-DXd.

Statistical-goodness-of-fit estimates for RAM+PTX are shown in Table 93.

Table 92. Statistical goodness-of-fit estimates for OS – T-DXd

Distributions	AIC	BIC
Exponential	1022.3	1025.8
Weibull	1006.6	1013.6
Lognormal	1003.1	1010.1
Generalised Gamma	1003.7	1014.3
Loglogistic	1001.8	1008.8
Gompertz	1017.3	1024.3
Gamma	1004.0	1011.0

Abbreviations are defined in the list of Abbreviations

Table 93. Statistical goodness-of-fit estimates for OS – RAM+PTX

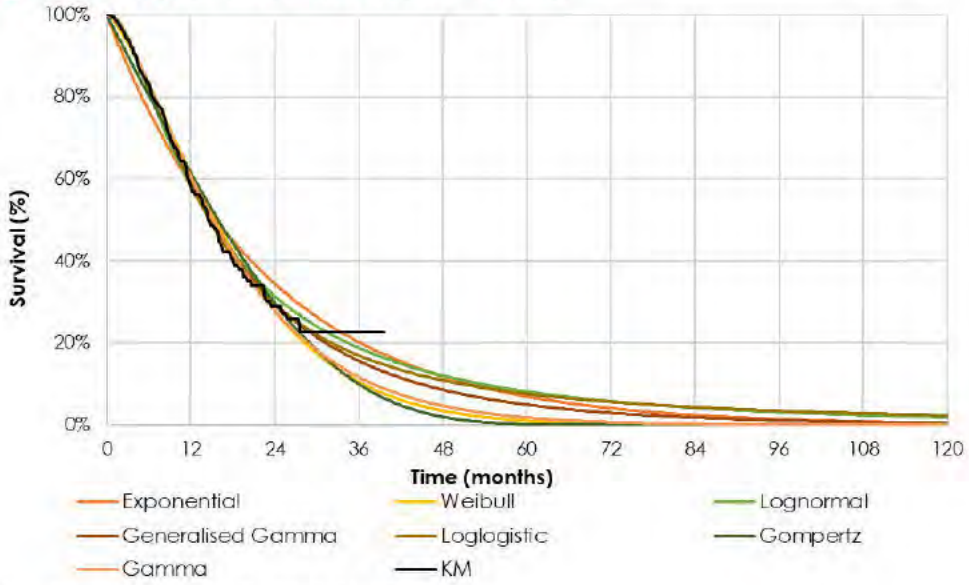
Distributions	AIC	BIC
Exponential	1064.2	1067.7

Distributions	AIC	BIC
Weibull	1045.0	1052.1
Lognormal	1066.5	1073.5
Generalised Gamma	1046.9	1057.5
Loglogistic	1054.3	1061.3
Gompertz	1048.6	1055.7
Gamma	1046.3	1053.3

Abbreviations are defined in the list of Abbreviations

Standard parametric survival models were fitted to the DG04 data (independent fit), including exponential, Weibull, lognormal, generalized gamma, loglogistic, Gompertz, and gamma distributions. Figure 52 shows the OS extrapolations with all the distributions alongside the KM curve from the DG04 study for T-DXd. Figure 53 presents the SoC OS curve generated by applying the RAINBOW HR (RAM+PTX vs PTX) to the RAM+PTX parametric extrapolations. Figure 54 and Figure 55 show the selected parametric extrapolations.

Figure 52. Fitted parametric survival models for T-DXd - OS



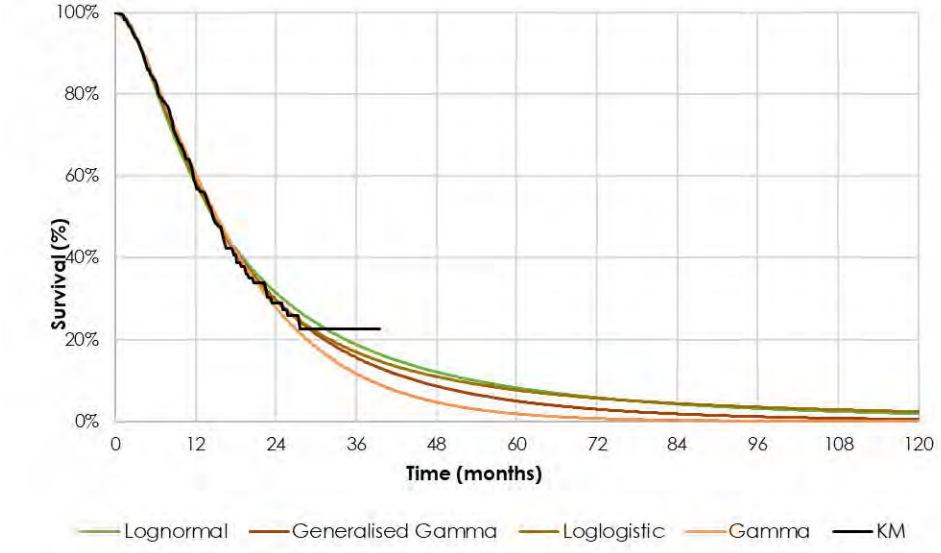
Abbreviations are defined in the list of Abbreviations

[redacted]

The models demonstrating the best statistical fit were compared against the observed OS data from DG04 (Figure 54). The lognormal and loglogistic models follow similar trajectories over time, with a slight divergence from approximately 18 to 50 months. Both models predict a non-zero tail, implying a proportion of patients surviving at the end of the time horizon. The generalized gamma model tracks these two up to roughly 30 months and then diverges, providing more pessimistic estimates and projecting that nearly all patients have died by around 8 years (96 months). The gamma model shows the steepest decline, with survival dropping noticeably from about 18 months and very limited survival beyond 6 years (72 months).

For SoC the three models also produce almost identical OS estimates (Figure 55).

Figure 54. OS extrapolations according to best statistical fit – T-DXd



Abbreviations are defined in the list of Abbreviations



Abbreviations are defined in the list of Abbreviations

E.1.2.2.2 Assessment of Smoothed Hazard Functions

Figure 56 presents smoothed OS hazards from DG04 and Figure 57 shows the smoothed OS hazard for RAM+PTX and PTX in RAINBOW.

For T-DXd, the hazard of death initially increases before decreasing over time. This non-monotonic shape is consistent with AFT models, such as loglogistic, lognormal, and generalized gamma, which also provided the best statistical fit (Figure 60). The shape of the observed hazards for T-DXd indicates that monotonically increasing models, such as the exponential, Weibull, Gompertz, and gamma distributions, are not appropriate for extrapolating OS in this context, as they cannot capture the non-monotonic hazard pattern observed for T-DXd.

For PTX in RAINBOW, the risk of death initially rises then stabilizes (Figure 57), suggesting a plateauing hazard over time. This pattern aligns with gamma distribution or potentially monotonically increasing models like the Weibull model.





To support the visual fit and clinical validity of the model selection for T-DXd, the smoothed hazard function was plotted for T-DXd based on the DG02 study (Figure 58). DG02 is an open-label, single-arm, multicentre phase II study conducted in the USA and Europe to evaluate the efficacy and safety of T-DXd in patients with HER2-positive advanced GC/GEJC who experienced disease progression on or after a trastuzumab-containing regimen (86) (see Table 67). Despite differences between DG02 and DG04, the smoothed hazard of death observed in DG02 reflects both the mechanism of action of T-

DXd and the natural course of the disease, thus supporting its use in model selection for T-DXd. Similarly to the OS hazard observed for T-DXd in the DG04 study (Figure 56), the hazard in DG02 initially increased and then decreased, supporting the choice of an AFT model.



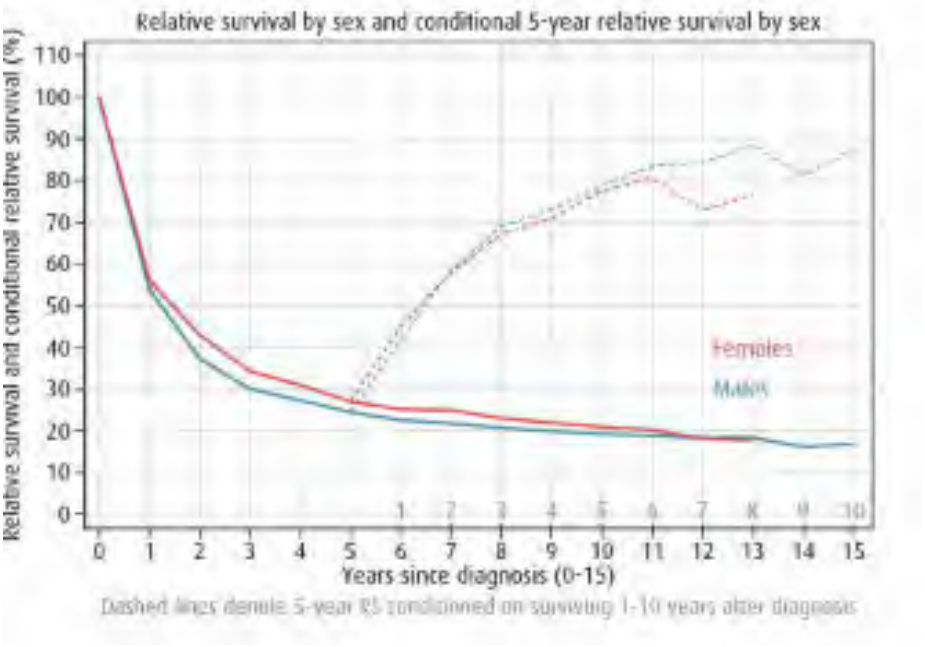
Clinical experts were consulted on disease course and prognostic factors, following the NICE DSU Technical Support Document 26 hazard checklist (87). Factors reported to increase the hazard of death included aggressive tumour biology, rapid progression, poor PS and frailty, comorbidities, and poor treatment response, tolerance or toxicities. Factors that may reduce the hazard include access to active treatments at progression, lower tumour burden and slow-growing disease, good PS, well-controlled comorbidities, and good tolerability and response to treatment, including longer duration of response (2, 3). Response to treatment appears to be a predictor of survival, consistent with published analyses (e.g., Roviello et al. (88)).

The risk of death is expected to stabilize or even decline over time among patients with good treatment response and other favourable factors such as low volume or slow growing disease and good tolerability. Conversely, if treatment response is poor, the risk of death is expected to increase over time.

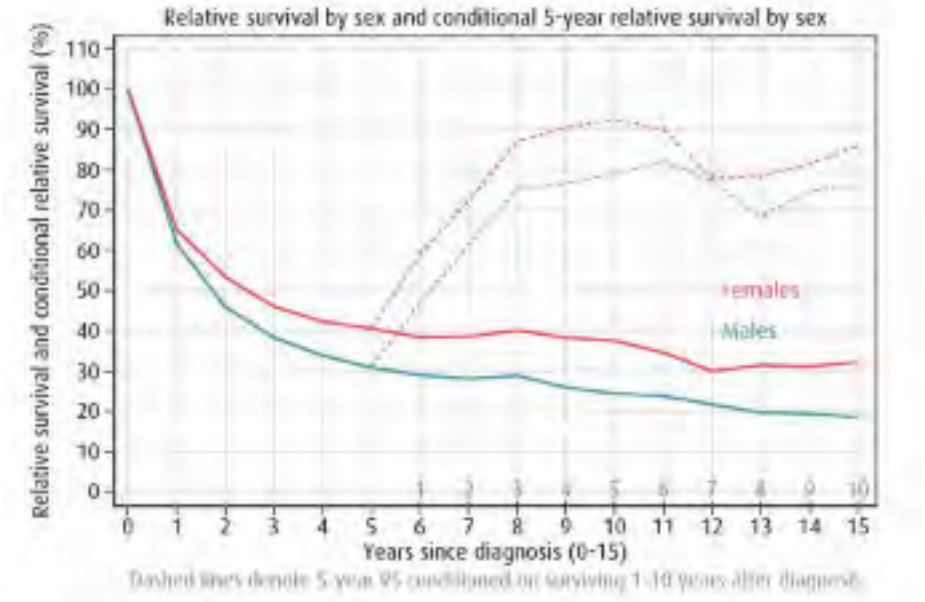
This is reflected in real-world data. Figure 59 presents 5-year relative survival for oesophageal and GC conditional on having already survived an additional 1–10 years post-diagnosis in Norway (i.e., survival measured from 0 years to 5 years, then from 1 to 6 years, 2 to 7 years, … up to 10 to 15 years). The conditional 5-year relative survival increases with each additional year survived from diagnosis, indicating that as patients remain alive longer, reflecting effective treatment response and disease control, their risk of death declines. This observation is believed to be applicable to the Danish setting as well, despite the data originating from Norway.

Figure 59. Relative survival and conditional 5-year relative survival by sex (89)

a) Oesophageal cancer



b) Gastric cancer



Abbreviations are defined in the list of Abbreviations
Source: Kolstad et al (89)

With current SoC for metastatic disease, treatment responses are variable; sustained responses, however, are uncommon according to clinical experts. For example, in RAINBOW, patients receiving PTX achieved an ORR of about 16% (primarily PRs; less than 1% CRs, see section 6.1.6), notably lower than the intervention arm (ORR RAM+PTX: 27.9%), which appears to be reflected in survival outcomes.

In the DG04 study, a greater percentage of patients showed a response and tumour shrinkage in the T-DXd group compared to RAM+PTX (ORR: 44.3% vs. 29.1%, see section 6.1.5). Unlike current Danish SoC, T-DXd targets specifically HER2 on tumour cells. The ToGA study (90) and DG04 supported that HER2 expression serves as a treatment effect modifier for HER2-directed therapies, resulting in improved treatment outcomes for patients with HER2-positive metastatic GC, contributing to the maintained treatment benefit of T-DXd also beyond treatment termination. Additionally, T-DXd enables patients to receive additional lines of therapy following disease progression, which was mentioned as an additional factor potentially resulting in a decreased risk of dying and long-term survival.

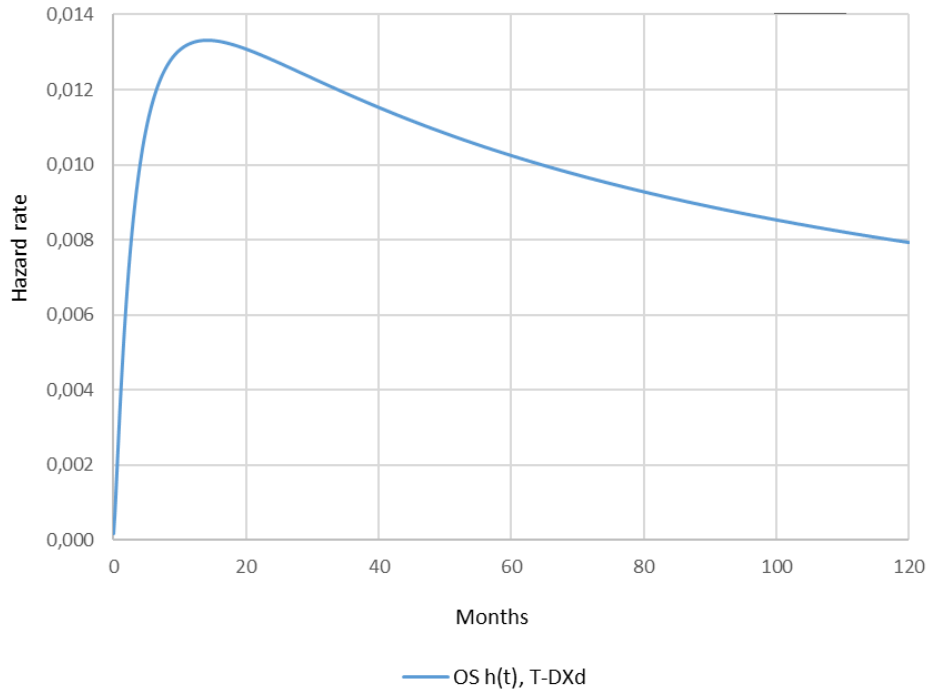
The sustained benefit and potential for additional treatment lines likely results in improved OS and consequently a decreasing risk of dying compared to non-targeted therapies, as evidenced in DG04 and as seen in other studies (91, 92). The generalized gamma, loglogistic and lognormal models reflect that trend (Figure 60).

In routine practice, T-DXd is expected to exhibit a hazard shape similar to DG04 and DG02, indicating a decreasing risk of death over time as patients attain sustained treatment responses. This pattern has been validated by Danish clinical experts (2, 3). For SoC, the hazard of death is anticipated to increase over time, mirroring current clinical practices and highlighting the unmet needs within this patient population. Although a small subset of patients may experience longer survival, the majority tend to succumb within the initial years following second-line treatment. This trend may be represented by a plateauing hazard rather than a continuous increase, indicating that the risk of death stabilizes after a certain period rather than escalating steadily over time. The gamma model provides a clinically plausible fit, with a steep initial increase followed by flattening aligning with the OS hazard pattern in RAINBOW (Figure 61). The generalized gamma and Weibull models may also fit but are more pessimistic predicting a more steeply increasing hazard over time.

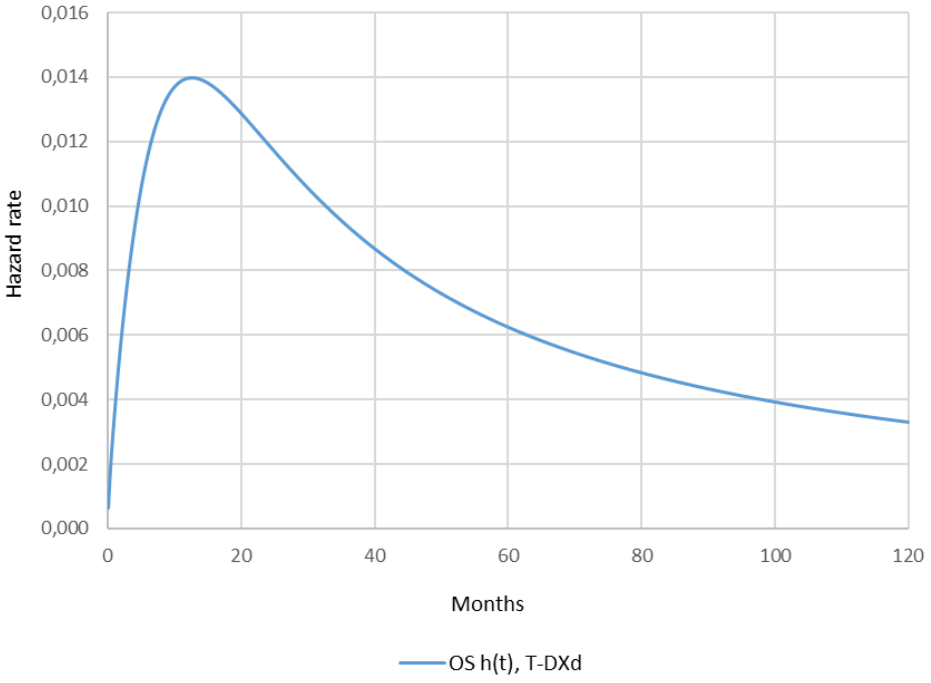
Relevant parametric hazards were plotted for T-DXd and SoC (PTX) (Figure 60 and Figure 61).

Figure 60. Parametric hazard rates for OS – T-DXd

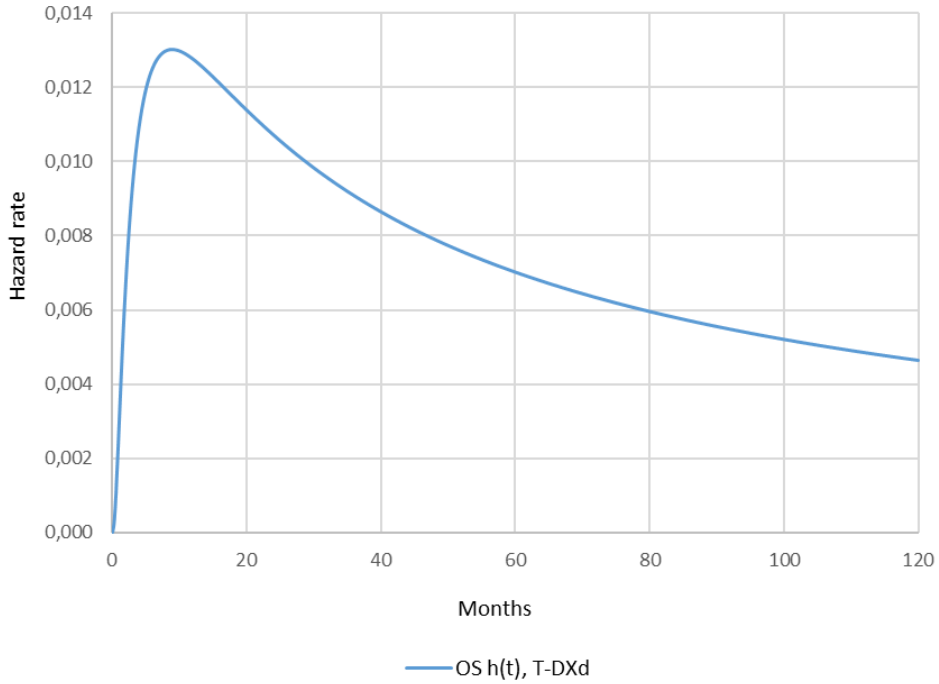
a) Generalized gamma



b) Loglogistic



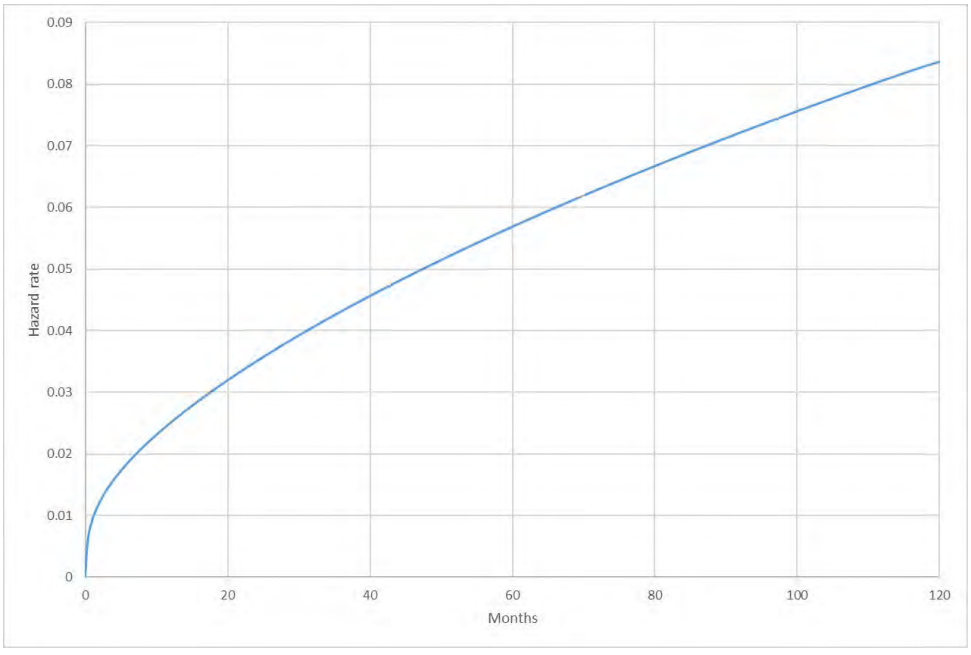
c) Lognormal



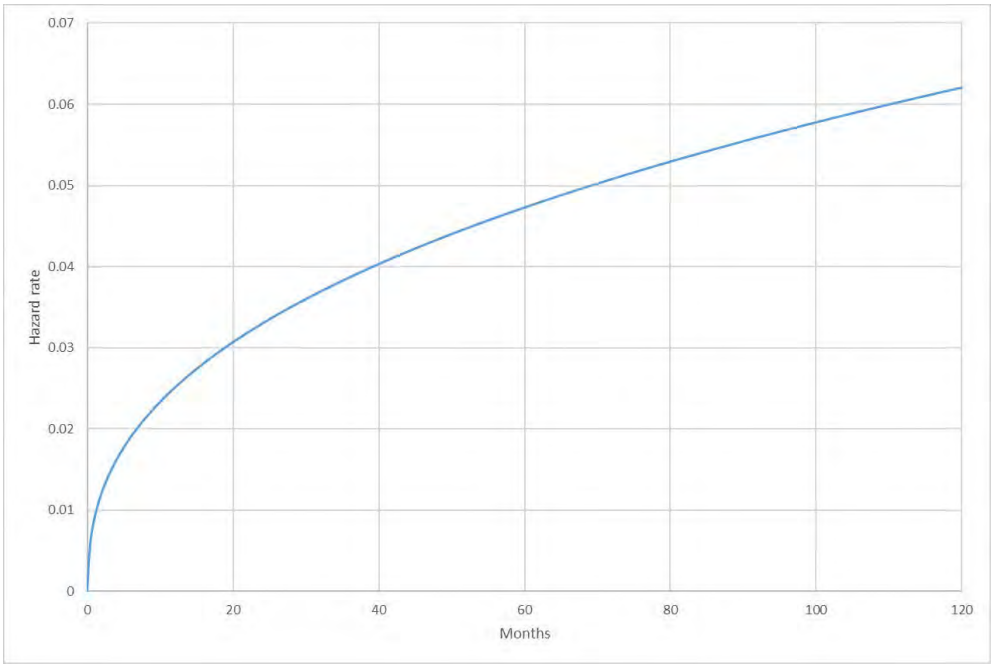
Abbreviations are defined in the list of Abbreviations
Source: DG04 data on file

Figure 61. Parametric hazard of death for OS – SoC

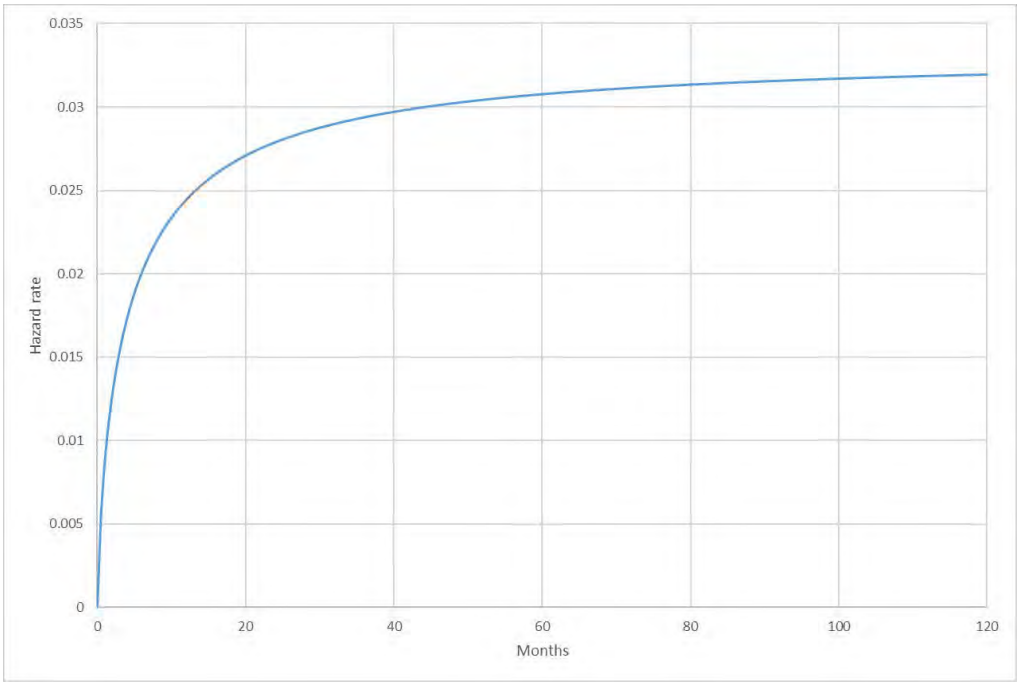
a) Generalized gamma



b) Weibull



c) Gamma



Abbreviations are defined in the list of Abbreviations

E.1.2.3 External Validity

External data and clinician estimates were used to validate long term projections. Experts indicated that with current SoC, 1-year survival is approximately 30–40%, and with a median OS between 6 and 8 months. 5-year survival is low, and while long term survivors exist, they are exceptions, underscoring high unmet need (2, 3).

The longest achievable landmark survival was extracted from the Danish National Cancer Register to determine whether any patients remain alive years after treatment with trastuzumab (Appendix P). This survival estimate reflects a broader patient population than relevant to this assessment, as it includes patients that may not be eligible for T-DXd in second line. A subset of patients [redacted] in the real-world trastuzumab-treated cohort received T-DXd, which is not yet routinely available in Denmark and currently requires name-based reimbursement applications, limiting patient access. In the real-world trastuzumab-treated cohort, [redacted] of patients were alive at six years post-initiation partly reflecting the patients treated with T-DXd.

In routine practice, only patients with a good performance status and who are sufficiently fit are considered for T-DXd in the second-line setting. Consistent with this selection, it was therefore assumed that a share of patients remains alive at six years following initiation of T-DXd. Given the likelihood that models assuming monotonically increasing hazards would underestimate OS for T-DXd, AFT models, specifically loglogistic, lognormal, and generalized gamma, were considered most reasonable for extrapolation, as they better accommodate the expected treatment effect and course of disease for patients with HER2-positive GC/GEJC that receive T-DXd. This validates that the loglogistic, lognormal and generalized gamma model fit the observed OS data well. Additionally, only these three models estimate a median OS close to that observed in the DG04 study (14.7 months), whereas the alternative models appear to overestimate median OS (see Table 94).

The lognormal model was selected for the base case as it produces mid-range projections in terms of long-term OS estimates (Table 94). The generalized gamma and loglogistic models were explored in scenario analyses (Table 87).

Table 94. OS landmarks – extrapolated for T-DXd

Months	Modelled OS: Generalised Gamma	Modelled OS: loglogistic	Modelled OS: lognormal	Observed OS in DG04
Median OS, months	14.9	14.7	14.9	14.7
0	100.0%	100.0%	100.0%	100.0%
3	94.2%	94.4%	94.4%	94.1%
6	82.4%	83.0%	81.5%	83.5%
9	70.2%	70.5%	69.0%	70.3%
12	59.2%	58.9%	58.3%	58.2%
15	49.8%	49.2%	49.5%	48.6%
18	41.9%	41.2%	42.3%	40.6%
21	35.3%	34.8%	36.5%	34.0%
24	29.9%	29.6%	31.6%	29.0%
27	25.3%	25.5%	27.6%	25.8%
30	21.5%	22.1%	24.2%	22.6%
60	5.0%	7.7%	8.2%	N/A
72	3.0%	5.6%	5.8%	N/A
120	0.5%	2.4%	1.9%	N/A

Abbreviations are defined in the list of Abbreviations

External data and clinician opinion were likewise used to validate long-term projects for the comparator, SoC. Danish clinical expert reports that, under current SoC, median OS is approximately 6–8 months, 1-year survival is around ~30–40%, and 5-year survival is very low. While long-term survivors exist, they are rare, underscoring a high unmet need (2, 3).

Across the Weibull, generalized gamma, and gamma models, the estimated median OS is ~10 months, with the gamma model lowest at 9.4 months.

In Danish real-world data, [redacted] of patients were alive at 6 years post-trastuzumab initiation; this proportion includes patients who later received T-DXd. In the absence of T-DXd, long-term survival would likely be below [redacted] Accordingly, modelled OS approaching ~0% by year 5 is plausible for second-line SoC without T-DXd and is consistent with clinical expert opinion that most patients would be deceased by that time (2, 3).

The gamma model best aligns with both the lower median OS and the long-term OS estimates and was therefore considered the most representative of Danish SoC. The Weibull and the generalized gamma models were explored in a scenario analysis (Table 87).

Table 95. OS landmarks – extrapolated for SoC without hazard adjustment

Months	Modelled OS: Gamma	Modelled OS: Weibull	Modelled OS: Generalized gamma
Median OS, months	9.4	9.7	9.9
0	100.0%	100.0%	100.0%
3	87.1%	87.2%	87.1%
6	68.8%	69.9%	70.1%
9	52.0%	53.3%	53.7%
12	38.2%	39.1%	39.5%
15	27.6%	27.7%	28.0%
18	19.6%	19.2%	19.1%
21	13.8%	12.9%	12.7%
24	9.7%	8.5%	8.2%
27	6.7%	5.5%	5.1%
30	4.6%	3.5%	3.1%
60	0.1%	0.0%	0.0%
72	0.0%	0.0%	0.0%
120	0.0%	0.0%	0.0%

Abbreviations are defined in the list of Abbreviations

E.1.2.4 Other Assumptions

For more information on the cross-over adjustment see Appendix N.

In line with the inconclusive PH assumption (Section E.1.2.1) and to accommodate potential non-proportional hazards between RAM+PTX vs PTX, a hazard adjustment was applied by setting the HR to 1, so that the hazard for PTX merges with the hazard for RAM+PTX from the adjustment time point of 22.14 months. This time point corresponds to the last observed PFS event in the PTX arm of the RAINBOW study (see section 6.1.6). By that stage of the study, most patients had progressed, and the OS curves converged.

This approach increases the expected OS for patients receiving PTX by decreasing their hazard of death to the level estimated for RAM+PTX. It was considered a pragmatic approach to address the convergence of OS curves observed in RAINBOW. The respective landmark estimates are presented in Table 96. A scenario analysis was conducted without the hazard adjustment.

Table 96. OS landmarks – extrapolated for SoC with hazard adjustment

Months	Modelled OS: Gamma
Median OS, months	9.4
0	100.0%
3	87.1%
6	68.8%
9	52.0%
12	38.2%
15	27.6%
18	19.6%
21	13.8%
24	10.1%
27	7.5%
30	5.6%
60	0.2%
72	0.1%
120	0.0%

Abbreviations are defined in the list of Abbreviations

E.1.3 Extrapolation of Time-to-Treatment Discontinuation

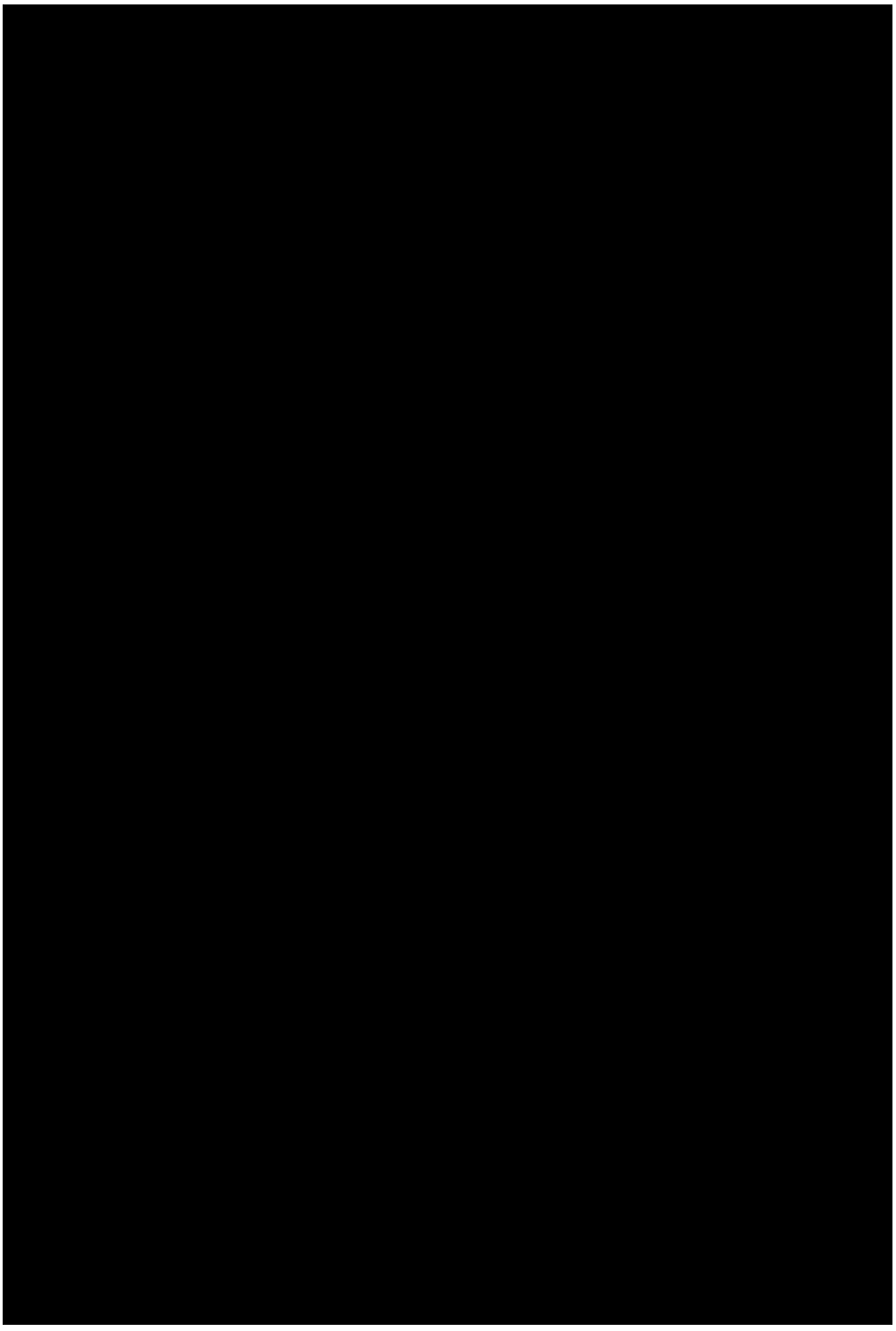
E.1.3.1 Log-cumulative Hazard Plots and Residual Plots

T-DXd

Figures below show the diagnostic plots for TTD data from the DG04 study. For TTD, the PH assumption was evaluated using the log-cumulative hazards (Figure 63) and the Schoenfeld residuals plot (Figure 62). The log-cumulative hazard plot displays non-parallel lines that cross towards the end of the study, which indicates potential violation of the PH assumption. Likewise, the Schoenfeld residuals plot demonstrates time-dependent variability in the HR, with a slight increase over time—resembling what was observed for PFS. Although the Grambsch-Therneau test yielded a p-value of [redacted] suggesting the PH assumption may be acceptable, this evidence is inconclusive overall. The quantile-quantile plot (Figure 64) shows a reasonably straight line through the origin, potentially supporting the suitability of AFT models. Only independent models for each treatment arm were considered in the analysis.









E.1.3.2 Internal Validity

Model selection for TTD combined statistical fit, visual inspection, and clinical plausibility, with explicit consideration of alignment with PFS; both endpoints were expected to follow a similar trend. PTX TTD was derived by applying the RAINBOW PFS HR to the DG04 RAM+PTX TTD curve, and the resulting PTX TTD extrapolation was checked for coherence with the modelled PTX PFS profile. Assessment of statistical and visual fit (AIC and BIC)

Statistical goodness-of-fit for T-DXd is presented in Table 97. Based on the AIC and BIC values, the lognormal, generalised gamma, and loglogistic yielded the best-fitting distributions for the TTD data from the T-DXd arm in the DG04 study (<3 points from lowest AIC/BIC, Table 97). In turn, the exponential, Weibull, Gompertz, and gamma models did not provide a good fit (>10 points from lowest AIC/BIC). Statistical-goodness-of-fit estimates for RAM+PTX is shown in Table 98.

Table 97. Statistical goodness-of-fit estimates for TTD – T-DXd

Distributions	AIC	BIC
Exponential	1241.2	1244.7
Weibull	1207.4	1214.4
Gompertz	1235.6	1242.6
Lognormal	1176.4	1183.4
Loglogistic	1177.7	1184.7
Generalized gamma	1178.2	1188.7
Gamma	1193.7	1200.7

Abbreviations are defined in the list of Abbreviations

Table 98. Statistical goodness-of-fit estimates for TTD – RAM+PTX

Distributions	AIC	BIC
Exponential	1093.2	1096.7
Weibull	1079.2	1086.2

Distributions	AIC	BIC
Lognormal	1095.7	1102.7
Generalised Gamma	1077.0	1087.5
Loglogistic	1077.2	1084.3
Gompertz	1093.2	1100.2
Gamma	1075.7	1082.7

Abbreviations are defined in the list of Abbreviations

Figure 67 shows the TTD extrapolations with all the distributions alongside the KM curve from the DG04 study for T-DXd. [redacted] presents the SoC TTD curve generated by applying the RAINBOW PFS HR (RAM+PTX vs PTX) to the RAM+PTX parametric extrapolations. Figure 69 and [redacted] show the selected parametric extrapolations. For T-DXd, all models follow the same overall trajectory, with potential underestimation from the Gompertz and exponential models at earlier time points, followed by overestimation. All models converge over time, with the loglogistic model being the most optimistic. For SoC, the TTD models are mostly aligned.





The statistically best-fitting curves were subsequently plotted along the KM curve of the DG04 study for visual inspection. The generalized gamma, lognormal and loglogistic models were plotted together with the TTD data for T-DXd from DG04. Similarly to what was observed for PFS, all three distributions produce nearly identical trajectories for T-DXd (Figure 69) and are providing good alignment through the observed follow-up.



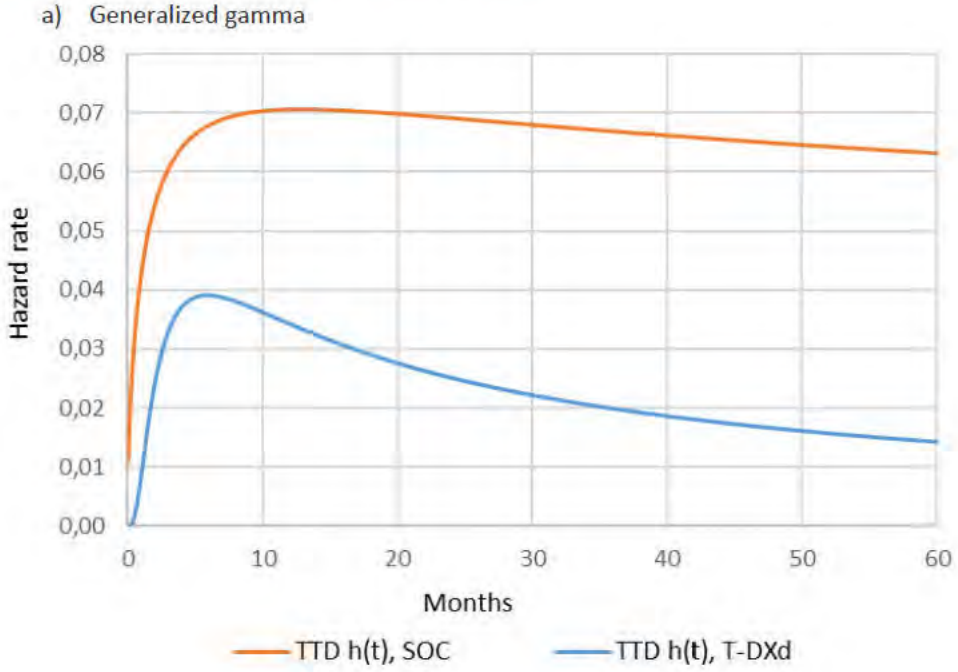


E.1.3.2.1 Assessment of Smoothed Hazard Functions

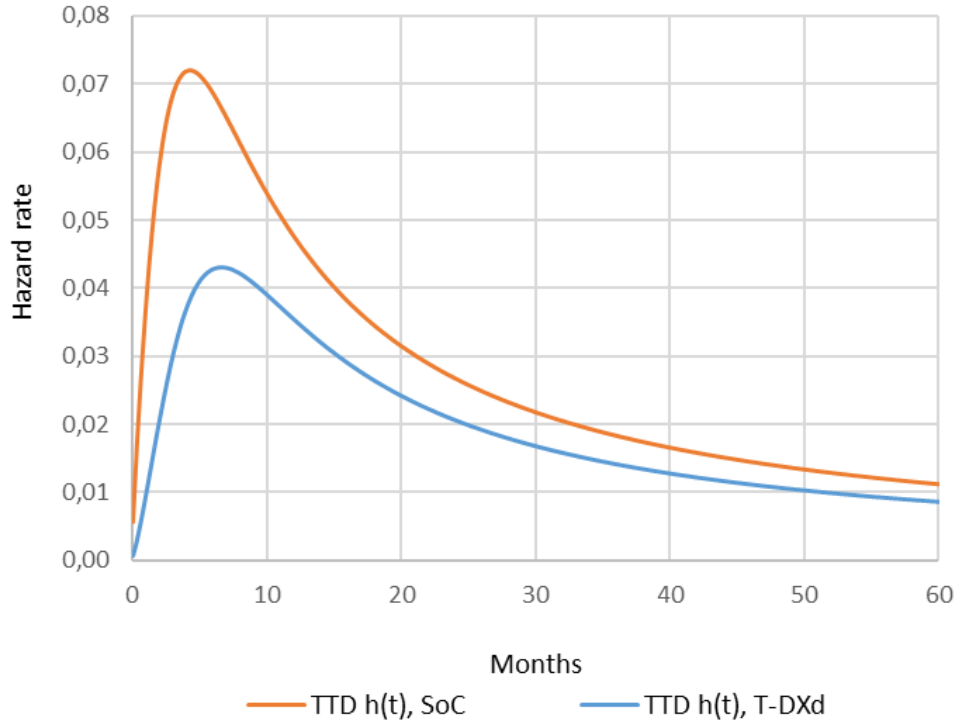
Examination of the observed and smoothed hazards for TTD indicates that the hazard for T-DXd rises initially and then declines (Figure 71). Consistent with the pattern observed for PFS (refer to Appendix E.1.1), there is a separation of both hazard functions, although less pronounced. Figure 72 shows the parametric hazard functions for T-DXd and SoC. Both the loglogistic and lognormal models indicate very small differences between the hazards for the two treatments. This may overestimate TTD for SoC given the expected PFS (see Table 91). Therefore, the generalized gamma model was selected as the base case, reflecting the observed hazard trend, providing plausible TTD estimates for T-DXd (Table 99), and maintaining the anticipated alignment between PFS and TTD.



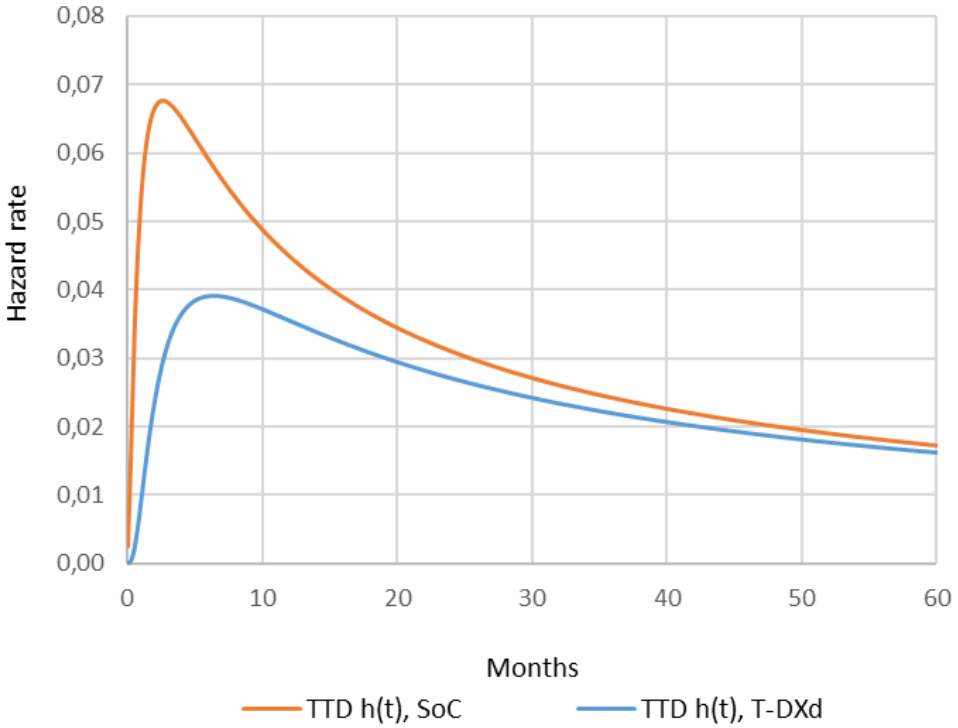
Figure 72. Parametric hazard for TTD – T-DXd and SoC



b) Loglogistic



c) Lognormal



Abbreviations are defined in the list of Abbreviations

E.1.3.3 External Validity

Not assessed

E.1.3.4 Other Assumptions

The extrapolated and observed (T-DXd only) TTD estimates are presented in Table 99 and Table 100 for T-DXd and SoC, respectively.

Based on the landmark estimates for T-DXd below, the generalized gamma provides a good fit, consistent with the PFS extrapolation presented in Section E.1.1.4. The log-logistic model appears overly optimistic relative to observed data. In contrast, the generalized gamma yields mid-range projections, aligning with the PFS pattern and therefore considered reasonable.

For SoC, both log-logistic and log-normal models are optimistic and exceed the PFS landmark estimates (presented in section E.1.1.4). The generalized gamma provides the most plausible extrapolation and is considered the preferred option.

Table 99. TTD landmarks – extrapolated for T-DXd

Months	Modelled TTD: Generalised Gamma	Modelled TTD: loglogistic	Modelled TTD: lognormal	Observed TTD in DG04
Median TTD, months	[redacted]			
0				
3				
6				
9				
12				
15				
18				
21				
24				
27				
30				
60				
72				

Abbreviations are defined in

Table 100. TTD landmarks – extrapolated for SoC

Months	Modelled TTD: Generalised Gamma	Modelled TTD: loglogistic	Modelled TTD: lognormal
Median TTD, months	[redacted]		
0			
3			
6			
9			
12			
15			
18			

21	[redacted]
24	
27	
30	
60	
72	

Abbreviations are defined in [redacted]

E.2 Transition Probabilities

E.2.1 Internal Validity

N/A

E.2.2 External Validity

N/A

E.2.3 Other Assumptions

N/A

Appendix F. Serious Adverse Events

The proportion of subjects with any serious TEAE from the DG04 study is provided in Table 101. SAE data are not available from the included comparator studies and available safety data for the comparator treatments can be found in Appendix M.

Table 101. TEAEs by Preferred Term. SAS population (11) (DG04 DCO date: 24 Oct 2024) (71)

MedDRA Preferred Term or Grouped Terma	Number (%) of subjects	
	T-DXd (n=244) (11)	RAM+PTX (n=233) (11)
Subjects with any serious TEAE	100 (41.0)	101 (43.3)
Anaemia	12 (4.9)	8 (3.4)
Pneumonia	10 (4.1)	8 (3.4)
Vomiting	9 (3.7)	2 (0.9)
Disease progression	8 (3.3)	18 (7.7)
Dysphagia	7 (2.9)	4 (1.7)
Febrile neutropenia	6 (2.5)	6 (2.6)
Adjudicated drug-related ILD	6 (2.5)	6 (2.6)
Dyspnoea	5 (2.0)	2 (0.9)
Haematemesis	4 (1.6)	0
Intestinal obstruction	4 (1.6)	0
Pyrexia	4 (1.6)	1 (0.4)
Upper gastrointestinal haemorrhage	4 (1.6)	6 (2.6)
Abdominal pain	3 (1.2)	3 (1.3)
Ascites	3 (1.2)	8 (3.4)
Death	3 (1.2)	0
Decreased appetite	3 (1.2)	2 (0.9)
Gastrointestinal haemorrhage	3 (1.2)	2 (0.9)
Hypokalaemia	3 (1.2)	0
Nausea	3 (1.2)	1 (0.4)
Neutrophil count decreased	3 (1.2)	6 (2.6)
Respiratory failure	3 (1.2)	1 (0.4)
White blood cell count decreased	3 (1.2)	3 (1.3)
Diarrhoea	2 (0.8)	3 (1.3)
Fatigue	2 (0.8)	3 (1.3)
General physical condition abnormal	2 (0.8)	3 (1.3)
COVID-19	1 (0.4)	5 (2.1)
Gastric perforation	1 (0.4)	5 (2.1)
Sepsis	1 (0.4)	4 (1.7)
Tumour haemorrhage	0	3 (1.3)

Abbreviations are defined in the list of Abbreviations

[b]ILD included all adjudicated study drug-related events by the AC, regardless of whether the events were treatment emergent.

Percentages are calculated using the number of subjects in the Safety Analysis Set as the denominator.

TEAEs are sorted by descending frequency in the T-DXd arm.

If a subject has more than one event per PT or grouped term, the subject is counted once at each level of summation. AEs were coded using MedDRA v27.1.

Appendix G. Health-Related Quality of Life

G.1 Data Collection – Overview of Responses

Table 102 and Table 103 present the results of the completion rates for EQ-5D-5L from the DG04 study. The number of patients at randomization was 246 in the T-DXd arm and 248 in the RAM+PTX arm. Compliance was high, with 93.2% compliance in the T-DXd arm and 86.3% in the RAM+PTX arm (71). Compliance was defined as the total number of patients with an evaluable baseline and at least one evaluable follow-up questionnaire, divided by total number of patients expected to have completed at least a baseline questionnaire. Overall, the results of the subjects with a post-baseline EQ-5D-5L score showed that QoL in the T-DXd arm was maintained over the course of treatment and did not deteriorate compared to the RAM+PTX arm through Day 274, after which the number of subjects was too low to allow for meaningful interpretation.

Table 102. Compliance rates for T-DXd: EQ-5D-5L score (71)

Timepoint	Number of patients "at risk" at time t (expected number of responses)* N	Number of responses at time t N	Response rate out of patients "at risk" at time t %	Response rate out of patients at randomisation %
Baseline	221	219	99.10%	89.0%
Day 22	204	203	99.50%	82.5%
Day 43	194	194	100.00%	78.9%
Day 64	185	184	99.50%	74.8%
Day 106	140	140	100.00%	56.9%
Day 148	107	106	99.10%	43.1%
Day 190	93	93	100.00%	37.8%
Day 232	57	57	100.00%	23.2%
Day 274	49	48	98.00%	19.5%
Day 316	39	39	100.00%	15.9%
Day 358	31	31	100.00%	12.6%
Day 400	23	23	100.00%	9.3%
Day 442	15	15	100.00%	6.1%
Day 484	10	10	100.00%	4.1%
Day 526	8	8	100.00%	3.3%
Day 568	6	6	100.00%	2.4%
Day 610	7	7	100.00%	2.8%
Day 652	5	5	100.00%	2.0%

Timepoint	Number of patients "at risk" at time t (expected number of responses)* N	Number of responses at time t N	Response rate out of patients "at risk" at time t %	Response rate out of patients at randomisation %
Day 694	[redacted]	[redacted]	100.00%	1.6%
Day 736	[redacted]	[redacted]	100.00%	0.4%
Day 778	[redacted]	[redacted]	100.00%	1.2%
Day 820	[redacted]	[redacted]	100.00%	1.2%
Day 862	[redacted]	[redacted]	100.00%	0.4%
Day 904	[redacted]	[redacted]	100.00%	0.4%
Day 946	NE	[redacted]	NE	0.0%
Day 988	NE	[redacted]	NE	0.0%
End of Treatment	124	123	99.20%	50.0%
Follow-Up 40-Day	35	34	97.10%	13.8%

Abbreviations are defined in the list of Abbreviations * The number of patients at risk reflects all patients with an evaluable baseline and at least one evaluable follow-up questionnaire.

Table 103. Compliance rates for RAM+PTX: EQ-5D-5L score (71)

Timepoint	Number of patients "at risk" at time t (expected number of responses) * N	Number of responses at time t N	Response rate out of patients "at risk" at time t %	Response rate out of patients at randomisation %
Baseline	204	203	99.50%	81.9%
Day 22	163	160	98.20%	64.5%
Day 43	129	128	99.20%	51.6%
Day 64	147	147	100.00%	59.3%
Day 106	123	122	99.20%	49.2%
Day 148	86	85	98.80%	34.3%
Day 190	59	58	98.30%	23.4%
Day 232	36	36	100.00%	14.5%
Day 274	25	24	96.00%	9.7%
Day 316	18	18	100.00%	7.3%
Day 358	12	12	100.00%	4.8%
Day 400	8	8	100.00%	3.2%
Day 442	7	7	100.00%	2.8%
Day 484	6	6	100.00%	2.4%
Day 526	[redacted]	[redacted]	100.00%	2.0%
Day 568	[redacted]	[redacted]	100.00%	1.6%
Day 610	[redacted]	[redacted]	100.00%	1.6%
Day 652	[redacted]	[redacted]	100.00%	0.8%
Day 694	[redacted]	[redacted]	100.00%	0.4%
Day 736	[redacted]	[redacted]	100.00%	0.4%
Day 778	[redacted]	[redacted]	NE	0.0%
Day 820	[redacted]	[redacted]	100.00%	0.4%
Day 862	[redacted]	[redacted]	100.00%	0.4%
Day 904	[redacted]	[redacted]	NE	0.0%
Day 946	[redacted]	[redacted]	100.00%	0.4%
Day 988	[redacted]	[redacted]	100.00%	0.4%
End of Treatment	95	94	98.90%	37.9%
Follow-Up 40-Day	40	40	100.00%	16.1%

Abbreviations are defined in the list of Abbreviations

* The number of patients at risk reflects all patients with an evaluable baseline and at least one evaluable follow-up questionnaire.

G.2 Reporting of Domains

The mean change from baseline and the summary statistics of EQ-5D-5L are presented in Figure 21 in section 10.2. An overview of EQ-5D-5L responses by health states (progression-free and progressed) is shown in Table 44 in section 10.2. The EQ-5D-5L summary statistics is presented in Table 45 section 10.2.

Results for individual domains are provided in the following tables below.

Table 104. Summary of EQ-5D-5L health profile: Mobility (71)

Visit	Response	T-DXd (N=246)	RAM+PTX (N=248)
Baseline	n (Completion %)	219 (99.1)	203 (99.5)
	No problems	154 (70.3%)	147 (72.4%)
	Slight problems	44 (20.1%)	41 (20.2%)
	Moderate problems	16 (7.3%)	10 (4.9%)
	Severe problems	[redacted]	[redacted]
	Unable	[redacted]	[redacted]
Day 22	n (Completion %)	203 (99.5)	160 (98.2)
	No problems	144 (70.9%)	111 (69.4%)
	Slight problems	44 (21.7%)	34 (21.3%)
	Moderate problems	8 (3.9%)	10 (6.3%)
	Severe problems	7 (3.4%)	[redacted]
Day 43	n (Completion %)	194 (100)	128 (99.2)
	No problems	137 (70.6%)	84 (65.6%)
	Slight problems	41 (21.1%)	32 (25.0%)
	Moderate problems	13 (6.7%)	11 (8.6%)
	Severe problems	[redacted]	[redacted]
Day 64	n (Completion %)	184 (99.5)	147 (100)
	No problems	133 (72.3%)	92 (62.6%)
	Slight problems	36 (19.6%)	35 (23.8%)
	Moderate problems	10 (5.4%)	17 (11.6%)
	Severe problems	[redacted]	[redacted]
	Unable	[redacted]	[redacted]
Day 106	n (Completion %)	140 (100)	122 (99.2)
	No problems	98 (70.0%)	80 (65.6%)
	Slight problems	30 (21.4%)	24 (19.7%)
	Moderate problems	8 (5.7%)	11 (9.0%)
	Severe problems	[redacted]	6 (4.9%)
	Unable	[redacted]	[redacted]
Day 148	n (Completion %)	106 (99.1)	85 (98.8)
	No problems	78 (73.6%)	51 (60.0%)
	Slight problems	21 (19.8%)	25 (29.4%)
	Moderate problems	[redacted]	9 (10.6%)
	Severe problems	[redacted]	[redacted]
Day 190	n (Completion %)	93 (100)	58 (98.3)

	No problems	71 (76.3%)	38 (65.5%)
	Slight problems	17 (18.3%)	13 (22.4%)
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 232	n (Completion %)	57 (100)	36 (100)
	No problems	45 (78.9%)	25 (69.4%)
	Slight problems	11 (19.3%)	[redacted]
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 274	n (Completion %)	48 (98.0)	24 (96.0)
	No problems	35 (72.9%)	17 (70.8%)
	Slight problems	12 (25.0%)	[redacted]
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 316	n (Completion %)	39 (100)	18 (100)
	No problems	30 (76.9%)	11 (61.1%)
	Slight problems	6 (15.4%)	[redacted]
	Moderate problems	[redacted]	[redacted]
Day 358	n (Completion %)	31 (100)	12 (100)
	No problems	25 (80.6%)	8 (66.7%)
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 400	n (Completion %)	23 (100)	8 (100)
	No problems	20 (87.0%)	6 (75.0%)
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 442	n (Completion %)	15 (100)	7 (100)
	No problems	12 (80.0%)	[redacted]
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
Day 484	n (Completion %)	10 (100)	6 (100)
	No problems	10 (100%)	[redacted]
	Severe problems	[redacted]	[redacted]
Day 526	n (Completion %)	8 (100)	[redacted]
	No problems	7 (87.5%)	[redacted]
	Moderate problems	[redacted]	[redacted]
Day 568	n (Completion %)	6 (100)	[redacted]
	No problems	[redacted]	[redacted]
	Slight problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 610	n (Completion %)	7 (100)	[redacted]
	No problems	6 (85.7%)	[redacted]
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]

	Severe problems		
Day 652	n (Completion %)		
	No problems		
	Slight problems		
Day 694	n (Completion %)		
	No problems		
	Slight problems		
	Moderate problems		
Day 736	n (Completion %)		
	No problems		
	Slight problems		
Day 778	n (Completion %)		
	No problems		
Day 820	n (Completion %)		
	No problems		
	Slight problems		
	Moderate problems		
Day 862	n (Completion %)		
	Slight problems		
	Moderate problems		
Day 904	n (Completion %)		
	Slight problems		
Day 946	n (Completion %)		
	Slight problems		
Day 988	n (Completion %)		
	Moderate problems		
End of Treatment	n (Completion %)	123 (99.2)	94 (98.9)
	No problems	67 (54.5%)	44 (46.8%)
	Slight problems	30 (24.4%)	30 (31.9%)
	Moderate problems	14 (11.4%)	9 (9.6%)
	Severe problems	9 (7.3%)	11 (11.7%)
	Unable		
Follow-Up 40-Day	n (Completion %)	34 (97.1)	40 (100)
	No problems	15 (44.1%)	25 (62.5%)
	Slight problems	14 (41.2%)	
	Moderate problems		6 (15.0%)
	Severe problems		
	Unable		

Abbreviations are defined in the list of Abbreviations

Table 105. Summary of EQ-5D-5L health profile: Self-care (71)

Visit	Response	T-DXd (N=246)	RAM+PTX (N=248)
Baseline	n (Completion %)	219 (99.1)	203 (99.5)
	No problems	187 (85.4%)	177 (87.2%)
	Slight problems	24 (11.0%)	20 (9.9%)
	Moderate problems		
	Severe problems		

	Unable	[redacted]	[redacted]
Day 22	n (Completion %)	203 (99.5)	160 (98.2)
	No problems	175 (86.2%)	135 (84.4%)
	Slight problems	21 (10.3%)	15 (9.4%)
	Moderate problems	6 (3.0%)	7 (4.4%)
	Severe problems	[redacted]	[redacted]
	Unable	[redacted]	[redacted]
Day 43	n (Completion %)	194 (100)	128 (99.2)
	No problems	164 (84.5%)	105 (82.0%)
	Slight problems	20 (10.3%)	17 (13.3%)
	Moderate problems	10 (5.2%)	[redacted]
	Severe problems	[redacted]	[redacted]
Day 64	n (Completion %)	184 (99.5)	147 (100)
	No problems	153 (83.2%)	123 (83.7%)
	Slight problems	20 (10.9%)	18 (12.2%)
	Moderate problems	9 (4.9%)	6 (4.1%)
	Severe problems	[redacted]	[redacted]
Day 106	n (Completion %)	140 (100)	122 (99.2)
	No problems	120 (85.7%)	99 (81.1%)
	Slight problems	13 (9.3%)	12 (9.8%)
	Moderate problems	6 (4.3%)	7 (5.7%)
	Severe problems	[redacted]	[redacted]
	Unable	[redacted]	[redacted]
Day 148	n (Completion %)	106 (99.1)	85 (98.8)
	No problems	94 (88.7%)	73 (85.9%)
	Slight problems	10 (9.4%)	9 (10.6%)
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 190	n (Completion %)	93 (100)	58 (98.3)
	No problems	77 (82.8%)	51 (87.9%)
	Slight problems	13 (14.0%)	[redacted]
	Moderate problems	[redacted]	[redacted]
	Unable	[redacted]	[redacted]
Day 232	n (Completion %)	57 (100)	36 (100)
	No problems	52 (91.2%)	29 (80.6%)
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 274	n (Completion %)	48 (98.0)	24 (96.0)
	No problems	43 (89.6%)	20 (83.3%)
	Slight problems	[redacted]	
	Moderate problems		
	Severe problems		
Day 316	n (Completion %)	39 (100)	18 (100)
	No problems	34 (87.2%)	15 (83.3%)
	Slight problems	[redacted]	[redacted]

	Moderate problems	[redacted]	
	Severe problems		
Day 358	n (Completion %)	31 (100)	12 (100)
	No problems	29 (93.5%)	10 (83.3%)
	Slight problems	[redacted]	
	Moderate problems		
Day 400	n (Completion %)	23 (100)	8 (100)
	No problems	22 (95.7%)	7 (87.5%)
	Slight problems	[redacted]	
	Severe problems		
Day 442	n (Completion %)	15 (100)	7 (100)
	No problems	15 (100%)	6 (85.7%)
	Slight problems	[redacted]	
Day 484	n (Completion %)	10 (100)	6 (100)
	No problems	10 (100%)	6 (100%)
Day 526	n (Completion %)	8 (100)	5 (100)
	No problems	8 (100%)	[redacted]
	Slight problems	[redacted]	
Day 568	n (Completion %)	6 (100)	[redacted]
	No problems	6 (100%)	
	Slight problems	[redacted]	
Day 610	n (Completion %)	7 (100)	
	No problems	6 (85.7%)	
	Slight problems	[redacted]	
	Moderate problems		
Day 652	n (Completion %)		
	No problems		
Day 694	n (Completion %)		
	No problems		
Day 736	n (Completion %)	[redacted]	
	No problems		
Day 778	n (Completion %)		
	No problems		
Day 820	n (Completion %)		
	No problems		
Day 862	n (Completion %)		
	No problems		
Day 904	n (Completion %)		
	No problems		
Day 946	n (Completion %)		
	No problems		
Day 988	n (Completion %)		
	No problems		
End of Treatment	n (Completion %)	123 (99.2)	95 (100)
	No problems	90 (73.2%)	70 (73.7%)
	Slight problems	21 (17.1%)	13 (13.7%)

	Moderate problems	[redacted]	8 (8.4%)
	Severe problems	6 (4.9%)	[redacted]
	Unable	[redacted]	[redacted]
Follow-Up 40-Day	n (Completion %)	35 (100)	40 (100)
	No problems	24 (68.6%)	34 (85.0%)
	Slight problems	8 (22.9%)	[redacted]
	Moderate problems	[redacted]	
	Severe problems		
	Unable		

Abbreviations are defined in the list of Abbreviations

Note: based on item-level completion and include patients who responded to the specific EQ-5D-5L domain shown. The compliance tables (Table 102 and Table 103) reflect completion of the full EQ-5D-5L questionnaire. Consequently, patients with one or more missing items may be included in domain-level summaries but are not counted as full questionnaire completers.

Table 106. Summary of EQ-5D-5L health profile: Usual activities (71)

Visit	Response	T-DXd (N=246)	RAM+PTX (N=248)
Baseline	n (Completion %)	219 (99.1)	203 (99.5)
	No problems	148 (67.6%)	133 (65.5%)
	Slight problems	51 (23.3%)	49 (24.1%)
	Moderate problems	12 (5.5%)	18 (8.9%)
	Severe problems	7 (3.2%)	[redacted]
	Unable	[redacted]	[redacted]
Day 22	n (Completion %)	203 (99.5)	160 (98.2)
	No problems	130 (64.0%)	92 (57.5%)
	Slight problems	54 (26.6%)	47 (29.4%)
	Moderate problems	11 (5.4%)	13 (8.1%)
	Severe problems	6 (3.0%)	6 (3.8%)
	Unable	[redacted]	[redacted]
Day 43	n (Completion %)	194 (100)	128 (99.2)
	No problems	127 (65.5%)	74 (57.8%)
	Slight problems	47 (24.2%)	38 (29.7%)
	Moderate problems	15 (7.7%)	12 (9.4%)
	Severe problems	[redacted]	[redacted]
	Unable	[redacted]	[redacted]
Day 64	n (Completion %)	184 (99.5)	147 (100)
	No problems	116 (63.0%)	84 (57.1%)
	Slight problems	50 (27.2%)	41 (27.9%)
	Moderate problems	12 (6.5%)	19 (12.9%)
	Severe problems	6 (3.3%)	[redacted]
Day 106	n (Completion %)	140 (100)	122 (99.2)
	No problems	91 (65.0%)	70 (57.4%)
	Slight problems	35 (25.0%)	36 (29.5%)
	Moderate problems	10 (7.1%)	9 (7.4%)
	Severe problems	[redacted]	6 (4.9%)
	Unable	[redacted]	[redacted]
Day 148	n (Completion %)	106 (99.1)	85 (98.8)

	No problems	69 (65.1%)	51 (60.0%)
	Slight problems	29 (27.4%)	24 (28.2%)
	Moderate problems	[redacted]	8 (9.4%)
	Severe problems	[redacted]	[redacted]
	Unable	[redacted]	[redacted]
Day 190	n (Completion %)	93 (100)	58 (98.3)
	No problems	63 (67.7%)	33 (56.9%)
	Slight problems	22 (23.7%)	18 (31.0%)
	Moderate problems	6 (6.5%)	[redacted]
	Severe problems	[redacted]	[redacted]
	Unable	[redacted]	[redacted]
Day 232	n (Completion %)	57 (100)	36 (100)
	No problems	42 (73.7%)	20 (55.6%)
	Slight problems	13 (22.8%)	11 (30.6%)
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 274	n (Completion %)	48 (98.0)	24 (96.0)
	No problems	32 (66.7%)	15 (62.5%)
	Slight problems	13 (27.1%)	[redacted]
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
	Unable	[redacted]	[redacted]
Day 316	n (Completion %)	39 (100)	18 (100)
	No problems	26 (66.7%)	9 (50.0%)
	Slight problems	8 (20.5%)	[redacted]
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 358	n (Completion %)	31 (100)	12 (100)
	No problems	21 (67.7%)	8 (66.7%)
	Slight problems	7 (22.6%)	[redacted]
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 400	n (Completion %)	23 (100)	8 (100)
	No problems	18 (78.3%)	[redacted]
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
	Severe problems	[redacted]	[redacted]
Day 442	n (Completion %)	15 (100)	7 (100)
	No problems	12 (80.0%)	[redacted]
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
Day 484	n (Completion %)	10 (100)	6 (100)
	No problems	8 (80.0%)	[redacted]
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
Day 526	n (Completion %)	8 (100)	[redacted]

	No problems	7 (87.5%)	[redacted]
	Slight problems	[redacted]	
	Moderate problems	[redacted]	
Day 568	n (Completion %)	6 (100)	
	No problems	[redacted]	
	Slight problems	[redacted]	
	Moderate problems	[redacted]	
Day 610	n (Completion %)	7 (100)	
	No problems	[redacted]	
	Slight problems		
	Severe problems		
Day 652	n (Completion %)		
	No problems		
	Slight problems		
Day 694	n (Completion %)		
	No problems		
	Slight problems		
Day 736	n (Completion %)		
	No problems		
	Slight problems		
Day 778	n (Completion %)		
	No problems		
	Slight problems		
Day 820	n (Completion %)		
	No problems		
	Slight problems		
Day 862	n (Completion %)		
	Slight problems		
Day 904	n (Completion %)		
	Slight problems		
Day 946	n (Completion %)		
	Slight problems		
Day 988	n (Completion %)		
	Slight problems		
End of Treatment	n (Completion %)	123 (99.2)	95 (100)
	No problems	57 (46.3%)	43 (45.3%)
	Slight problems	36 (29.3%)	25 (26.3%)
	Moderate problems	15 (12.2%)	15 (15.8%)
	Severe problems	8 (6.5%)	11 (11.6%)
	Unable	7 (5.7%)	[redacted]
Follow-Up 40-Day	n (Completion %)	35 (100)	40 (100)
	No problems	15 (42.9%)	20 (50.0%)
	Slight problems	14 (40.0%)	10 (25.0%)
	Moderate problems	[redacted]	
	Severe problems		
	Unable		

Abbreviations are defined in the list of Abbreviations
Note: based on item-level completion and include patients who responded to the specific EQ-5D-5L domain shown. The compliance tables (Table 102 and Table 103) reflect completion of the full EQ-5D-5L questionnaire. Consequently, patients with one or more missing items may be included in domain-level summaries but are not counted as full questionnaire completers.

Table 107. Summary of EQ-5D-5L health profile: Pain / discomfort (71)

Visit	Response	T-DXd (N=246)	RAM+PTX (N=248)
Baseline	n (Completion %)	219 (99.1)	204 (100)
	No problems	102 (46.6%)	78 (38.2%)
	Slight problems	78 (35.6%)	83 (40.7%)
	Moderate problems	30 (13.7%)	37 (18.1%)
	Severe problems	8 (3.7%)	[redacted]
	Unable	[redacted]	
Day 22	n (Completion %)	203 (99.5)	160 (98.2)
	No problems	107 (52.7%)	64 (40.0%)
	Slight problems	71 (35.0%)	68 (42.5%)
	Moderate problems	21 (10.3%)	25 (15.6%)
	Severe problems	[redacted]	[redacted]
Day 43	n (Completion %)	194 (100)	128 (99.2)
	No problems	105 (54.1%)	55 (43.0%)
	Slight problems	73 (37.6%)	62 (48.4%)
	Moderate problems	10 (5.2%)	9 (7.0%)
	Severe problems	6 (3.1%)	[redacted]
Day 64	n (Completion %)	184 (99.5)	147 (100)
	No problems	93 (50.5%)	64 (43.5%)
	Slight problems	71 (38.6%)	66 (44.9%)
	Moderate problems	18 (9.8%)	14 (9.5%)
	Severe problems	[redacted]	[redacted]
Day 106	n (Completion %)	140 (100)	122 (99.2)
	No problems	70 (50.0%)	56 (45.9%)
	Slight problems	61 (43.6%)	49 (40.2%)
	Moderate problems	8 (5.7%)	12 (9.8%)
	Severe problems	[redacted]	
	Unable		
Day 148	n (Completion %)	106 (99.1)	85 (98.8)
	No problems	52 (49.1%)	31 (36.5%)
	Slight problems	48 (45.3%)	41 (48.2%)
	Moderate problems	[redacted]	11 (12.9%)
	Severe problems	[redacted]	[redacted]
Day 190	n (Completion %)	93 (100)	58 (98.3)
	No problems	51 (54.8%)	24 (41.4%)
	Slight problems	34 (36.6%)	27 (46.6%)
	Moderate problems	8 (8.6%)	6 (10.3%)
	Severe problems	[redacted]	[redacted]
Day 232	n (Completion %)	57 (100)	36 (100)
	No problems	34 (59.6%)	13 (36.1%)
	Slight problems	18 (31.6%)	14 (38.9%)

	Moderate problems	[redacted]	9 (25.0%)
Day 274	n (Completion %)	48 (98.0)	24 (96.0)
	No problems	25 (52.1%)	9 (37.5%)
	Slight problems	20 (41.7%)	8 (33.3%)
	Moderate problems	[redacted]	6 (25.0%)
	Severe problems	[redacted]	[redacted]
Day 316	n (Completion %)	39 (100)	18 (100)
	No problems	21 (53.8%)	5 (27.8%)
	Slight problems	13 (33.3%)	10 (55.6%)
	Moderate problems	[redacted]	[redacted]
Day 358	n (Completion %)	31 (100)	12 (100)
	No problems	17 (54.8%)	[redacted]
	Slight problems	12 (38.7%)	7 (58.3%)
	Moderate problems	[redacted]	[redacted]
Day 400	n (Completion %)	23 (100)	8 (100)
	No problems	18 (78.3%)	[redacted]
	Slight problems	[redacted]	
	Moderate problems		
	Severe problems		
Day 442	n (Completion %)	15 (100)	7 (100)
	No problems	10 (66.7%)	[redacted]
	Slight problems	[redacted]	
	Moderate problems		
Day 484	n (Completion %)	10 (100)	6 (100)
	No problems	8 (80.0%)	[redacted]
	Slight problems	[redacted]	
	Moderate problems		
	Severe problems		
Day 526	n (Completion %)	8 (100)	[redacted]
	No problems	7 (87.5%)	
	Slight problems	[redacted]	
	Severe problems	[redacted]	
Day 568	n (Completion %)	6 (100)	
	No problems	[redacted]	
	Slight problems	[redacted]	
	Moderate problems	[redacted]	
Day 610	n (Completion %)	7 (100)	
	No problems	7 (100%)	
	Slight problems	[redacted]	
	Moderate problems		
Day 652	n (Completion %)		
	No problems		
	Slight problems		
Day 694	n (Completion %)		
	No problems		
	Slight problems		

	Moderate problems	[redacted]	
Day 736	n (Completion %)		
	No problems		
	Slight problems		
Day 778	n (Completion %)		
	No problems		
Day 820	n (Completion %)		
	No problems		
	Slight problems		
	Moderate problems		
Day 862	n (Completion %)		
	Slight problems		
	Severe problems		
Day 904	n (Completion %)		
	No problems		
Day 946	n (Completion %)		
	Moderate problems		
Day 988	n (Completion %)		
	Slight problems		
End of Treatment	n (Completion %)	123 (99.2)	95 (100)
	No problems	40 (32.5%)	35 (36.8%)
	Slight problems	52 (42.3%)	33 (34.7%)
	Moderate problems	22 (17.9%)	18 (18.9%)
	Severe problems	7 (5.7%)	9 (9.5%)
	Unable	[redacted]	[redacted]
Follow-Up 40-Day	n (Completion %)	35 (100)	40 (100)
	No problems	9 (25.7%)	16 (40.0%)
	Slight problems	19 (54.3%)	13 (32.5%)
	Moderate problems	6 (17.1%)	6 (15.0%)
	Severe problems	[redacted]	[redacted]

Abbreviations are defined in the list of Abbreviations

Note: based on item-level completion and include patients who responded to the specific EQ-5D-5L domain shown. The compliance tables (Table 102 and Table 103) reflect completion of the full EQ-5D-5L questionnaire. Consequently, patients with one or more missing items may be included in domain-level summaries but are not counted as full questionnaire completers.

Table 108. Summary of EQ-5D-5L health profile: Anxiety / depression (71)

Visit	Response	T-DXd (N=246)	RAM+PTX (N=248)
Baseline	n (Completion %)	219 (99.1)	204 (100)
	No problems	137 (62.6%)	120 (58.8%)
	Slight problems	61 (27.9%)	63 (30.9%)
	Moderate problems	15 (6.8%)	14 (6.9%)
	Severe problems	[redacted]	7 (3.4%)
	Unable	[redacted]	[redacted]
Day 22	n (Completion %)	203 (99.5)	160 (98.2)
	No problems	133 (65.5%)	88 (55.0%)
	Slight problems	56 (27.6%)	56 (35.0%)
	Moderate problems	9 (4.4%)	13 (8.1%)

	Severe problems	[redacted]	
	Unable		
Day 43	n (Completion %)	194 (100)	128 (99.2)
	No problems	125 (64.4%)	72 (56.3%)
	Slight problems	53 (27.3%)	45 (35.2%)
	Moderate problems	12 (6.2%)	9 (7.0%)
	Severe problems	[redacted]	
	Unable		
Day 64	n (Completion %)	184 (99.5)	147 (100)
	No problems	117 (63.6%)	82 (55.8%)
	Slight problems	56 (30.4%)	50 (34.0%)
	Moderate problems	7 (3.8%)	14 (9.5%)
	Severe problems	[redacted]	
	Unable		
Day 106	n (Completion %)	140 (100)	122 (99.2)
	No problems	86 (61.4%)	70 (57.4%)
	Slight problems	43 (30.7%)	38 (31.1%)
	Moderate problems	7 (5.0%)	10 (8.2%)
	Severe problems	[redacted]	
	Unable		
Day 148	n (Completion %)	106 (99.1)	85 (98.8)
	No problems	67 (63.2%)	44 (51.8%)
	Slight problems	32 (30.2%)	33 (38.8%)
	Moderate problems	[redacted]	6 (7.1%)
	Severe problems	[redacted]	
	Unable		
Day 190	n (Completion %)	93 (100)	58 (98.3)
	No problems	67 (72.0%)	32 (55.2%)
	Slight problems	18 (19.4%)	22 (37.9%)
	Moderate problems	6 (6.5%)	[redacted]
	Severe problems	[redacted]	
	Unable		
Day 232	n (Completion %)	57 (100)	36 (100)
	No problems	39 (68.4%)	21 (58.3%)
	Slight problems	16 (28.1%)	13 (36.1%)
	Moderate problems	[redacted]	[redacted]
Day 274	n (Completion %)	48 (98.0)	24 (96.0)
	No problems	33 (68.8%)	13 (54.2%)
	Slight problems	12 (25.0%)	9 (37.5%)
	Moderate problems	[redacted]	[redacted]
Day 316	n (Completion %)	39 (100)	18 (100)
	No problems	23 (59.0%)	9 (50.0%)
	Slight problems	13 (33.3%)	7 (38.9%)
	Moderate problems	[redacted]	[redacted]
Day 358	n (Completion %)	31 (100)	12 (100)
	No problems	19 (61.3%)	8 (66.7%)

	Slight problems	12 (38.7%)	[redacted]
	Moderate problems	[redacted]	[redacted]
Day 400	n (Completion %)	23 (100)	8 (100)
	No problems	18 (78.3%)	[redacted]
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
Day 442	n (Completion %)	15 (100)	7 (100)
	No problems	12 (80.0%)	[redacted]
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
Day 484	n (Completion %)	10 (100)	6 (100)
	No problems	7 (70.0%)	[redacted]
	Slight problems	[redacted]	[redacted]
Day 526	n (Completion %)	8 (100)	[redacted]
	No problems	7 (87.5%)	[redacted]
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
Day 568	n (Completion %)	6 (100)	[redacted]
	No problems	6 (100%)	[redacted]
	Slight problems	[redacted]	[redacted]
Day 610	n (Completion %)	7 (100)	[redacted]
	No problems	7 (100%)	[redacted]
	Slight problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
Day 652	n (Completion %)	[redacted]	[redacted]
	No problems	[redacted]	[redacted]
	Slight problems	[redacted]	[redacted]
Day 694	n (Completion %)	[redacted]	[redacted]
	No problems	[redacted]	[redacted]
	Slight problems	[redacted]	[redacted]
Day 736	n (Completion %)	[redacted]	[redacted]
	No problems	[redacted]	[redacted]
	Slight problems	[redacted]	[redacted]
Day 778	n (Completion %)	[redacted]	[redacted]
	No problems	[redacted]	[redacted]
Day 820	n (Completion %)	[redacted]	[redacted]
	No problems	[redacted]	[redacted]
Day 862	n (Completion %)	[redacted]	[redacted]
	No problems	[redacted]	[redacted]
	Moderate problems	[redacted]	[redacted]
Day 904	n (Completion %)	[redacted]	[redacted]
	Slight problems	[redacted]	[redacted]
Day 946	n (Completion %)	[redacted]	[redacted]
	No problems	[redacted]	[redacted]
Day 988	n (Completion %)	[redacted]	[redacted]

	Slight problems	[redacted]	[redacted]
End of Treatment	n (Completion %)	123 (99.2)	95 (100)
	No problems	53 (43.1%)	41 (43.2%)
	Slight problems	42 (34.1%)	32 (33.7%)
	Moderate problems	22 (17.9%)	14 (14.7%)
	Severe problems	[redacted]	7 (7.4%)
	Unable	[redacted]	[redacted]
Follow-Up 40-Day	n (Completion %)	35 (100)	40 (100)
	No problems	19 (54.3%)	17 (42.5%)
	Slight problems	11 (31.4%)	18 (45.0%)
	Moderate problems	[redacted]	
	Severe problems		

Abbreviations are defined in the list of Abbreviations

Note: based on item-level completion and include patients who responded to the specific EQ-5D-5L domain shown. The compliance tables (Table 102 and Table 103) reflect completion of the full EQ-5D-5L questionnaire. Consequently, patients with one or more missing items may be included in domain-level summaries but are not counted as full questionnaire completers.

G.3 Mapping

N/A

G.4 Calculations of Utility Values

Utility values were derived from patient-level data collected in DG04 and were estimated using LMMs, in order to account for repeated measures of HRQoL over time within the same patients.

All available utility values from all scheduled time points, including baseline, were included as a dependent variable. Two models were fitted:

- Model 1 (base case model): Progression status (progression-free, progressed) at the corresponding visit as an independent variable.
- Model 2: Progression status (progression-free, progressed) at the corresponding visit and planned treatment (T-DXd or RAM+PTX) as independent variables.

These models included subject as a random effect, to account for repeated measures, with specific intercept and slope. The mean utility values and 95% CI for the different health states from the best fitting model were derived using LSM. An unstructured correlation matrix was used to model the correlation among patients.

In both models:

- Progression status was included as time-varying binary indicator
- Treatment was included as time-invariant binary indicator (Model 2 only)

Model 1 was selected for the base case analysis to inform health-state values for T-DXd and the comparator.

For use in the health economic model, utility values were calculated using the fixed-effect estimates from Model 1. The prediction formula is: $\widehat{U} = \beta_0 + \beta_{PD} \cdot IP_{PD}$

Where:

- $\widehat{U}$= predicted utility value
- β_0= intercept, representing the mean utility in the progression-free (PF) state
- β_{PD}= regression coefficient representing the utility decrement associated with progressed disease
- I_{PD}= indicator for progressed disease

Thus:

- Utility for PF: $\widehat{U}_{PF} = \beta_0$
- Utility for PD: $\widehat{U}_{PD} = \beta_0 + \beta_{PD}$

An overview of the statistical goodness of fit and results of the LMM regression estimates are provided in Table 109. Table 110 presents the HSUV values derived from the regression model for use in the health economic analysis.

Table 109. LMM regression coefficients of EQ-5D-5L utility values from DG04 (71)

	Model 1	Model 2
Intercept (95% CI) p-value	[redacted]	
Treatment arm (T-DXd vs RAM+PTX) (95% CI) p-value		
Progression status (progression vs progression-free) (95% CI) p-value		
AIC		
BIC		

Abbreviations are defined in the list of Abbreviations

Table 110. HSUV based on DG04 (71)

Health states	Utility value (SE) (95% CI)
Pre-progression	[redacted]
Post-progression	

Abbreviations are defined in the list of Abbr

Appendix H. Literature Searches for the Clinical Assessment

H.1 Effect and Safety for Intervention and Comparators

AstraZeneca and Daiichi Sankyo entered into a global development and commercialization collaboration agreement and are investigating the use of T-DXd in patients with HER2-positive metastatic and/or unresectable GC/GEJC. Global SLRs were initially conducted by AstraZeneca and Daiichi Sankyo (2020) in order to gather comprehensive clinical information (efficacy, safety, discontinuation and tolerability) and non-clinical information about T-DXd and SoC therapies for the management of patients with GC/GEJC being treated with second or later line treatment.

Following initial SLR searches, updates followed 2021, 2022 and two additional updates in January and November 2025.

The following outcomes of interest were considered:

- Efficacy and safety (restricted to randomized trials)
- Economic evaluations
- Health state utility values
- Healthcare cost / resource use

Review questions: Clinical

1. What is the efficacy and safety of treatments for second-line locally advanced or metastatic GC/GEJC?
2. Which studies failed to meet their primary endpoints while investigating therapies being used for the treatment of individuals with locally advanced or metastatic GC/GEJC in the second-line setting?

Below a brief description of the SLR is given. Further details are available in the full SLR report: “Enhertu GC+GEJ 2L+ SLR report_200326” (93).

Search methods

Systematic research was conducted utilizing a combination of electronic databases and grey literature to identify records with relevant clinical, cost-effectiveness, cost and resource use, and HSUV evidence for the management and/or treatment of locally advanced or metastatic GC/GEJC, in the second-line and later setting.

The following electronic databases via Ovid were interrogated up to 26th November 2025 (latest search) (Table 111):

Table 111. Bibliographic databases included in the literature search

Database	Platform/source	Date of search completion
Embase	Embase.com	26.11.2025 (latest)
Medline	MEDLINE® In- Process & Other Non-Indexed Citations	
	MEDLINE® ePub Ahead of Print	
	MEDLINE® Daily	
Cochrane Library incorporating all EBM Reviews	Cochrane Database of Systematic Reviews	
	ACP Journal Club	
	Cochrane Clinical Answers	
	Cochrane Methodology Register	
Health Technology Assessment	Health Technology Assessment	
Database of abstracts of reviews of effects (DARE)	Cochrane Central Register of Controlled Trials	
NHS Economic Evaluation Database (NHS EED)	NHS Economic Evaluation Database	

Supplementary searches of secondary databases were also conducted to identify additional, relevant research that might not have been published in peer-reviewed journals indexed in electronic databases, including:

Table 112. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Conference proceedings	American Society of Clinical Oncology (ASCO) Annual meeting	Refer to full SLR report: " Enhertu GC+GEJ 2L+ SLR report_200326" (93).	26.11.2025 (latest)
	ASCO-Gastrointestinal Cancers Symposium Annual Meeting		
	European Society for Medical Oncology (ESMO) Annual Congress		
	ESMO World Congress of Gastrointestinal Cancer		
	ESMO-Asia Annual Meeting		
	Japanese Society of Medical Oncology (JSMO) Annual Meeting		
	World Cancer Congress		
	Academy of Managed Care Pharmacy		
	Health Technology Assessment International (HTAi)		
HTA agency bodies	National Institute for Health and Care Excellence (NICE)		
	Scottish Medicines Consortium (SMC)		
	Canada Drug Agency (CDA) / Pan-Canadian Oncology Drug Review (pCODR)		

Source name	Location/source	Search strategy	Date of search
	Pharmaceutical Benefits Advisory Committee (PBAC)		
	Institute for Clinical and Economic Review (ICER)		
	Haute Autorité de Santé (HAS)		
	Institute für Qualität und Wirschaftlichkeit im Gesundheitswesen (IQWiG) / Federal Joint Committee (G-BA) / Market for Medicinal Products (AMNOG)		
Clinical trial registries (including ClinicalTrials.gov)	Clinical trial registries (including ClinicalTrials.gov)		
Other	International HTA database		
	The Cost Effectiveness Analysis (CEA) Registry		
	EconPapers with Research Papers in Economics (RePEc)		
	The University of Sheffield ScHARR Health Utilities Database		
	International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Presentations Database		
	University of York Centre for Reviews and Disseminations		

In addition to these efforts, the reference lists of all included articles were scanned for articles that met the inclusion criteria (backward tracking), and a citation search was performed to identify articles that cite the included articles (forward tracking).

In the full SLR report: "Enhertu GC+GEJ 2L+ SLR report_200326" (93), Appendix B (Appendix B.1.4. for November 2025 update - clinical) presents the full search strategies used for each electronic database. Biomedical database searches were run in OvidSP® comprising of controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings "MeSH", controlled keywords, text words, Boolean operators, synonyms for the disease and treatment, Scottish Intercollegiate Guidelines Network (SIGN) validated filters for trials, SLRs and meta-analyses, and appropriate limitations specific to each database and review. The main search concept was GC. Retrieval was limited by publication type, i.e., editorial, note, etc, publication date (for updates) and language, i.e., English language. Where possible, retrieval was limited to the human adult population.

H.2 Systematic Selection of Studies and References

Pre-defined search strategies and eligibility criteria were used to identify all relevant literature in response to the clinical and non-clinical review questions. Two independent

reviewers reviewed records based on their title and abstract, with conflicts resolved through discussion or adjudication by a senior reviewer. These steps were repeated when screening full publications. A single reviewer conducted data extraction and quality assessments, with a second reviewer validating 100% of data items. This methodology complies with HTA guidelines for conducting a robust systematic review. For more information, refer to full SLR report: "Enhertu GC+GEJ 2L+ SLR report_200326" (93).

The inclusion and exclusion criteria using the population, interventions, comparators, outcomes, and study design (PICOS) framework for clinical evidence are presented in Table 113 below.

Table 113. Inclusion and exclusion criteria used for assessment of studies: clinical evidence

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Patients with second-line and later locally advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma[a]	Patients with newly diagnosed gastric cancer	No change
Intervention /comparator	Drug interventions recommended for locally advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma, including, but not limited to: • Aclarubicin • Capecitabine • Carboplatin • Cisplatin • Cyclophosphamide • Cytarabine • Docetaxel • Doxifluridine • Doxorubicin • Entrectinib • Epirubicin • Etoposide • Fluorouracil • Folinic Acid • Irinotecan • Lentinan • Leucovorin • Levoleucovorin • Margetuximab • Methotrexate • Mitomycin • Nimustine • Nivolumab • OK-432 • Oxaliplatin • PTX • Pembrolizumab • Picibanil • Pirarubicin	Surgical interventions Complementary/alternative therapies	Drug interventions recommended for locally advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma: • Docetaxel • Paclitaxel • Irinotecan Subsequent treatment: • Docetaxel • Paclitaxel • Irinotecan • Fluorouracil • Folinic Acid • Irinotecan

	• Porfimer • RAM • Regorafenib • Rivoceranib • TAS-118 (S-1 plus leucovorin) • Tegafur • Tipiracil Plus Trifluridine • Trastuzumab including other variants i.e., Herzuma, Kanjinti, Trazimera, Ontruzant, Ogivri • Trastuzumab deruxtecan • TS-1 (Tegafur with Gimeracil plus Oteracil Potassium) • Uft (Tegafur with Uracil)		
Outcomes	Studies reporting at least one outcome of interest on clinical evidence including: • OS • PFS • Recurrence-free survival • Disease-free survival • Mortality, all-cause/cancer-related • Life expectancy • Relative survival/mortality • Objective response rate • Duration of response/time to response • Adverse events (Grade > 3) • Time to discontinuation • HRQoL	Studies not reporting any of the outcomes of interest	No change
Study design	• RCTs[b], pragmatic clinical trials[c] • SLRs and meta-analyses	• Observational studies • Animal/in vitro studies • Case studies and case reports	No change

Publication type	All searches: • All primary publications • SLRs[d]	• Non-SLRs • Editorials • Notes • Letters	No change
Language restrictions	English language publication	N/A	No change
Geographical restrictions	No restrictions	N/A	No change
Other restrictions	Temporal: 2020: No restrictions 2021: 2020 to 9 September 2021 January 2025: September 2021 to 27 January 2025 November 2025: January 2025 to 26 November 2025	N/A	No change

Abbreviations are defined in the list of Abbreviations in the full SLR
Notes: [a]Data regarding stratification/differentiation between Asian and non-Asian populations was noted at full-text review and highlighted in the results section of the report.
[b]Single-arm studies were included during title and abstract screening but deprioritised for full-text screening and data extraction due to RCTs being the gold standard for clinical evidence
[c]Schwartz and Lellouch proposed a distinction between explanatory studies, which confirm a physiological or clinical hypothesis, and pragmatic studies, which inform a clinical or policy decision by providing evidence for adoption of the intervention into real-world clinical practice.(https://www.nejm.org/doi/pdf/10.1056/NEJMra1510059?articleTools=true).
[d]Data was not extracted from SLR articles; however, the reference lists were cross-checked for any relevant sources.

November 2025 SLR update identification of studies

Electronic searches of the databases were conducted on 26th November 2025. The electronic database search identified 1,589 publications. After removal of duplicates, 1,389 records were screened by title and abstract. Of these, 68 records were selected for full-text review, resulting in 10 relevant publications. Supplementary searches identified an additional publication, resulting in a total of 11 publications within the 2L+ scope. Five of these reported trials already included in the review, while the remaining 6 publications reported data from 6 new trials. Following this update, the review comprised a total of 254 publications representing 102 trials.

Of the 11 publications included for the 2L+ scope, 3 specifically reported data for a 2L-only population. This consisted of 2 publications from 2 newly identified trials and 1 publication from a study already included in the review. Altogether, the number of relevant publications within the 2L-only scope increased to 136 studies reporting on 52 trials (refer to full SLR report; Appendix G.1 showing the study flow diagram for this update).

The process of study selection is documented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram provided in Figure 73. Further information is provided in the full SLR report: "Enhertu GC+GEJ 2L+ SLR report_200326" (93).

Studies and references included in the assessment is briefly shown in Table 114. Excluded studies and references can be found in the full SLR report: “Enhertu GC+GEJ 2L+ SLR report_200326” (93). It should be noted that some studies included in the NMA (TRICS (41), WJOG 4007 (36), RAMIRIS (81), Sym et al (43), and KCSG ST10-01 (42)) are not listed in the updated 2025 SLR. These studies were identified during the original 2020 SLR but were not extracted due to failure to meet predefined eligibility criteria, specifically, not meeting the primary endpoint. As these studies were not extracted, they were not retained in subsequent SLR updates, which only carried forward studies meeting the extraction criteria.

For the NMA, a broader evidence base was required to preserve network connectivity and avoid selective exclusion of trials providing relevant OS or PFS data in the second-line setting. Therefore, these earlier identified but non-extracted studies were re-introduced for the purposes of the ITC, despite not being included in the final updated SLR extraction set.

Figure 73. PRISMA flow diagram of study retrieval and selection (November 2025 SLR update, second-line only): clinical evidence

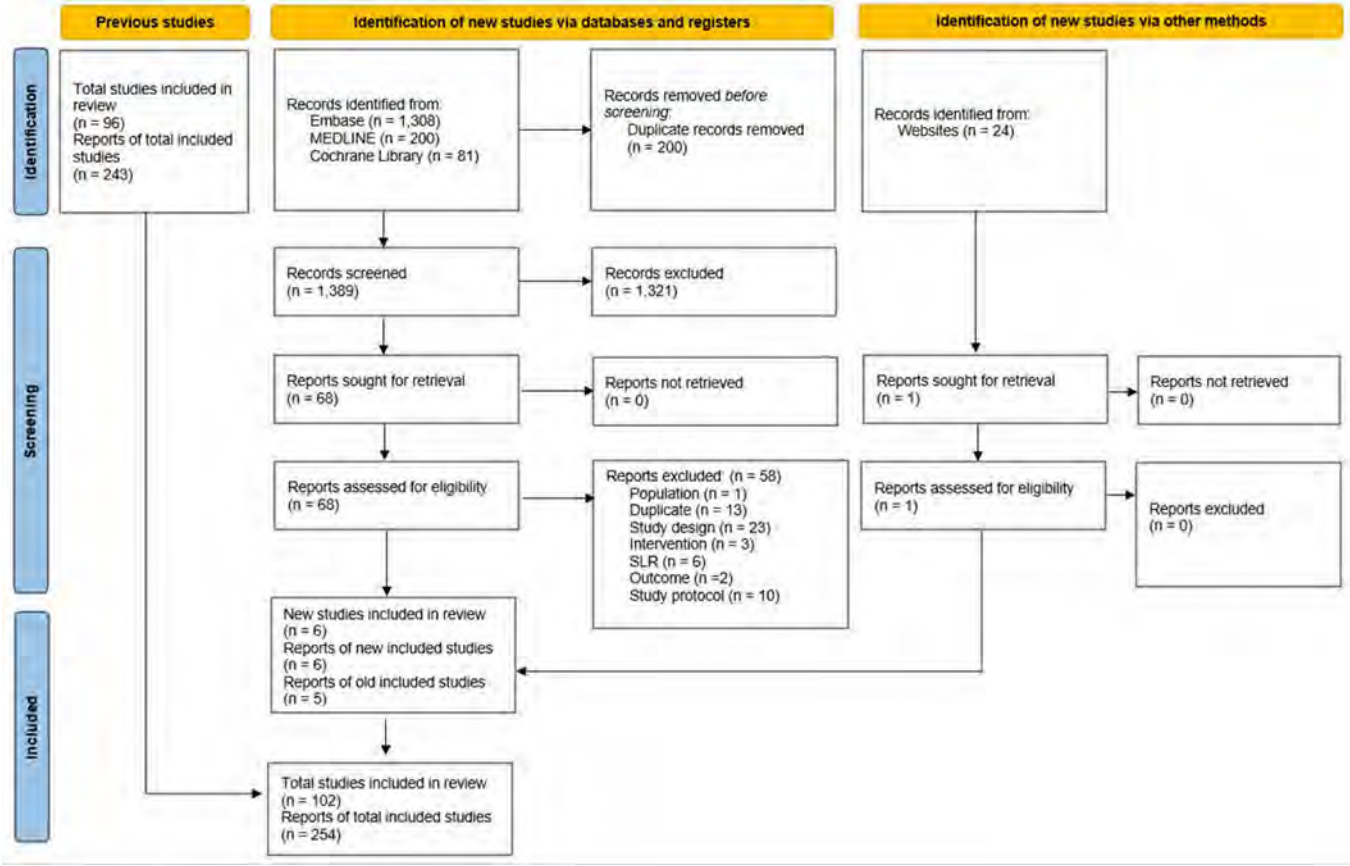


Table 114. Studies / references included in the Danish assessment: Clinical evidence

Study		Reference(s)
DESTINY-Gastric04 NCT04704934		Shitara, Kohei, Eric Van Cutsem, Mahmut Gümüş, Sara Lonardi, Christelle de la Fouchardière, Clélia Coutzac, Jeroen Dekervel et al. "Trastuzumab deruxtecan or ramucirumab plus paclitaxel in gastric cancer." New England Journal of Medicine (2025) (33).
RAINBOW (10) NCT01170663		Wilke, Hansjochen, Kei Muro, Eric Van Cutsem, Sang-Cheul Oh, György Bodoky, Yasuhiro Shimada, Shuichi Hironaka et al. "Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial." The lancet oncology 15, no. 11 (2014): 1224-1235 (10).
Comparators in the NMA		
PTX	RAINBOW (10)	Refer to above
	KCSG-ST10-01 (42)	Lee KW, Maeng CH, Kim TY, Zang DY, Kim YH, Hwang IG, et al. A Phase III Study to Compare the Efficacy and Safety of Paclitaxel Versus Irinotecan in Patients with Metastatic or Recurrent Gastric Cancer Who Failed in First-line Therapy (KCSG ST10-01). Oncologist. 2019 Jan;24(1):18-e24.
	WJOG 4007 (36)	Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol. 2013 Dec 10;31(35):4438–44.
	RAMIRIS	Lorenzen S, Thuss-Patience P, Pauligk C, Gökkurt E, Ettrich T, Lordick F, Stahl M, Reichardt P, Sökler M, Pink D, Probst S, Hinke A, Goetze TO, Al-Batran SE. FOLFIRI plus ramucirumab versus paclitaxel plus ramucirumab as second-line therapy for patients with advanced or metastatic gastroesophageal adenocarcinoma with or without prior docetaxel - results from the phase II RAMIRIS Study of the German Gastric Cancer Study Group at AIO. Eur J Cancer. 2022 Apr;165:48-57. doi: 10.1016/j.ejca.2022.01.015. Epub 2022 Feb 21. PMID: 35202974 (37)
DTX	COUGAR-02 (34)	Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014;15(1):78-86 (34).
	Roy et al. 2013 (37)	Roy AC, Park SR, Cunningham D, et al. A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Ann Oncol 2013; 24: 1567-1573. 2013/02/15. DOI: 10.1093/annonc/mdt002 (37)
Irinotecan	Thuss-Patience et al. 2011 (35)	Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer. 2011;47(15):2306-14.
	TRICS (41)	Nishikawa K, Fujitani K, Inagaki H, Akamaru Y, Tokunaga S, Takagi M, et al. Randomised phase III trial of second-line irinotecan plus cisplatin versus irinotecan alone in patients with advanced gastric

		cancer refractory to S-1 monotherapy: TRICS trial. Eur J Cancer. 2015 May;51(7):808–16.
	WJOG 4007 (36)	Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol. 2013 Dec 10;31(35):4438–44.
	KCSG-ST10-01 (42)	Lee KW, Maeng CH, Kim TY, Zang DY, Kim YH, Hwang IG, et al. A Phase III Study to Compare the Efficacy and Safety of Paclitaxel Versus Irinotecan in Patients with Metastatic or Recurrent Gastric Cancer Who Failed in First-line Therapy (KCSG ST10-01). Oncologist. 2019 Jan;24(1):18-e24.
	TCOG GI-0801/BIRIP (40)	Higuchi K, Tanabe S, Shimada K, Hosaka H, Sasaki E, Nakayama N, et al. Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: a randomised phase III trial (TCOG GI-0801/BIRIP trial). Eur J Cancer. 2014;50(8):1437-45 (40).
	Sym 2013 (43)	Sym SJ, Hong J, Park J, Cho EK, Lee JH, Park YH, Lee WK, Chung M, Kim HS, Park SH, Shin DB. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemother Pharmacol. 2013 Feb;71(2):481-8. doi: 10.1007/s00280-012-2027-3. Epub 2012 Nov 29. PMID: 23192279.

Abbreviations are defined in the list of Abbreviations

Table 115. Excluded studies / references (refer to full SLR report): Clinical evidence

Study	Reference(s)
See full SLR report	See full SLR report: " Enhertu GC+GEJ 2L+ SLR report_200326" (93). In Appendix C.3.1 in the SLR report (November 2025 update)

Abbreviations are defined in the list of Abbreviations in the full SLR

Appendix I. Literature Searches for Health-Related Quality of Life

I.1 Systematic Search

Refer to the description of the search strategy/search method in Appendix H.

Review questions: Non-clinical

1. What economic evidence, including cost-effectiveness analyses, is available for treatments being used in the second-line setting for locally advanced or metastatic GC/GEJC?
2. What are the costs and healthcare resource use associated with treating and/or managing second-line locally advanced or metastatic GC/GEJC?
3. What published literature is available for HSUVs associated with second-line locally advanced or metastatic GC/GEJC?

Systematic selection of studies and references

The inclusion and exclusion criteria using the PICOS framework for non-clinical evidence are presented in Table 116 below.

Table 116. Inclusion and exclusion criteria used for assessment of studies: non-clinical evidence

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Patients with second-line and later locally advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma[a]	Patients with newly diagnosed gastric cancer	No change
Intervention /comparator	Drug interventions recommended for locally advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma, including, but not limited to: • Aclarubicin • Capecitabine • Carboplatin • Cisplatin • Cyclophosphamide • Cytarabine • Docetaxel • Doxifluridine • Doxorubicin • Entrectinib • Epirubicin • Etoposide • Fluorouracil • Folinic Acid • Irinotecan	Surgical interventions Complementary/alternative therapies	Drug interventions recommended for locally advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma: • Docetaxel • Paclitaxel • Irinotecan Subsequent treatment: • Docetaxel • Paclitaxel • Irinotecan • Fluorouracil • Folinic Acid • Irinotecan

	• Lentinan • Leucovorin • Levoleucovorin • Margetuximab • Methotrexate • Mitomycin • Nimustine • Nivolumab • OK-432 • Oxaliplatin • PTX • Pembrolizumab • Picibanil • Pirarubicin • Porfimer • RAM • Regorafenib • Rivoceranib • TAS-118 (S-1 plus leucovorin) • Tegafur • Tipiracil Plus Trifluridine • Trastuzumab including other variants i.e., Herzuma, Kanjinti, Trazimera, Ontruzant, Ogivri • Trastuzumab deruxtecan • TS-1 (Tegafur with Gimeracil plus Oteracil Potassium) • Uft (Tegafur with Uracil)		
Outcomes	Studies reporting at least one outcome of interest on non-clinical evidence including economic, utility and cost/resource use evidence: • Economic evaluations • Quality-adjusted life-years gained • Progression-free life-years gained • Life-years gained • Health state utilities • HRQoL • Mapping algorithms • Treatment cost, including	Studies not reporting any of the outcomes of interest	No change

	healthcare resource use, cost of care, cost of illness		
Study design	• Any	• Observational studies • Animal/in vitro studies • Case studies and case reports	No change
Publication type	All searches: • All primary publications and SLRs[d]	• Non-SLRs • Editorials • Notes • Letters	No change
Language restrictions	English language publication	N/A	No change
Geographical restrictions	No restrictions	N/A	No change
Other restrictions	Temporal: *Cost/resource use evidence* 2020: 2010 to 12 May 2020 2021: 2020 to 9 September 2021 January 2025: September 2021 to 27 January 2025 November 2025: January 2025 to 26 November 2025 Utility/economic evidence 2020: No restrictions 2021: 2020 to 9 September 2021 January 2025: September 2021 to 27 January 2025 November 2025: January 2025 to 26 November 2025	N/A	No change

Abbreviations are defined in the list of Abbreviations in the full SLR
Notes: [a]Data regarding stratification/differentiation between Asian and non-Asian populations was noted at full-text review and reported.[bc]Data was not extracted from SLR articles; however, the reference lists were cross-checked for any relevant sources.

In the full SLR report: "Enhertu GC+GEJ 2L+ SLR report_200326" (93), Appendix B (Appendix B.2.4. for November 2025 update – non-clinical) presents the full search strategies used for each electronic database

November 2025 SLR update identification of studies

Electronic searches of the databases were conducted on 26th November 2025. The electronic database search identified 413 publications. After removal of duplicates, 326

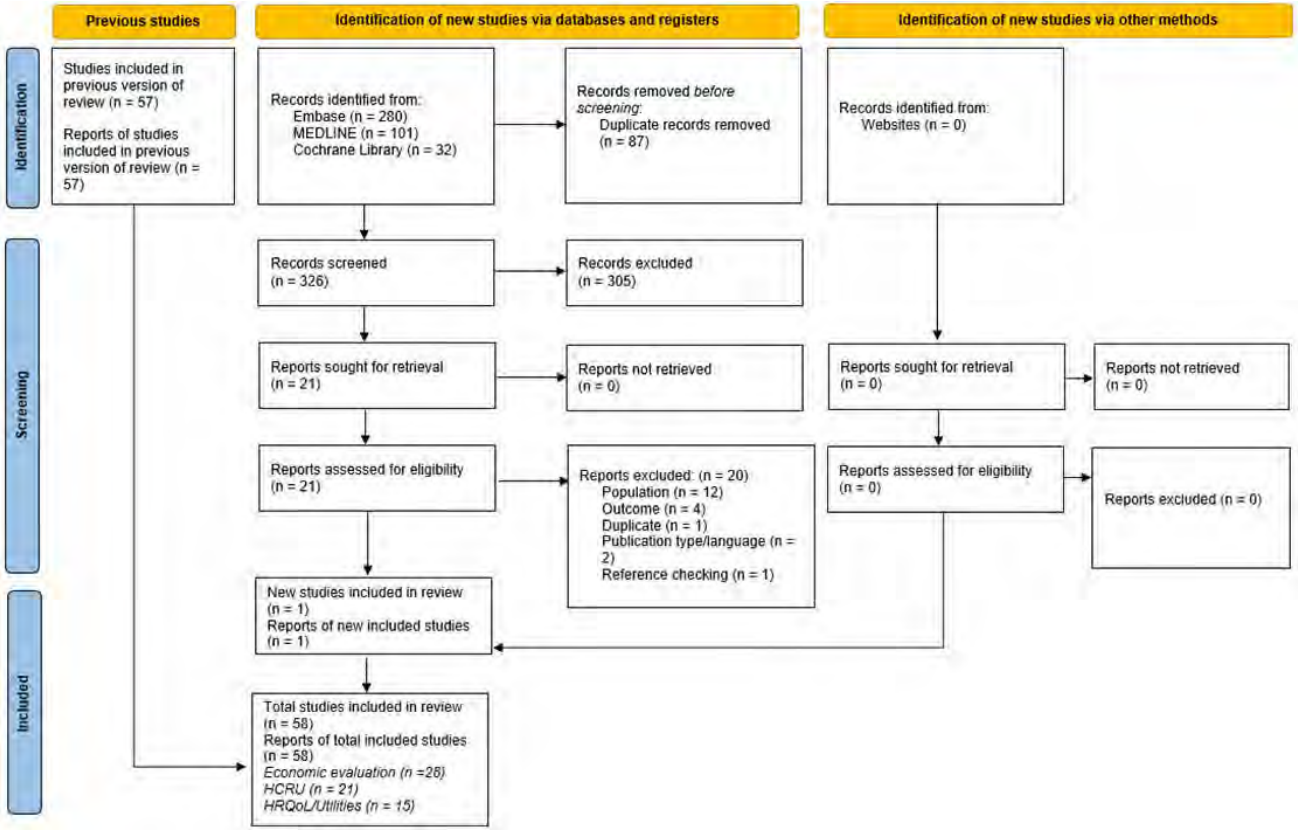
records were screened by title and abstract. Of these, 21 records were selected for full-text review, resulting in one relevant study within the 2L+ scope. Following this update, the review comprised a total of 58 publications representing 58 individual studies.

The newly included publication did not report data for a 2L-only population. Therefore, the number of relevant publications within the 2L-only scope remained as 28 studies (full SLR; Appendix G.2 presents the study flow diagram for this update).

The process of study selection is documented in the PRISMA flow diagram provided in Figure 74. Further information is provided in the full SLR report: “Enhertu GC+GEJ 2L+ SLR report_200326” (93).

Studies and references included in the assessment is briefly shown in Table 117. Excluded studies and references can be found in the full SLR report: “Enhertu GC+GEJ 2L+ SLR report_200326” (93).

Figure 74. PRISMA flow diagram of study retrieval and selection (November 2025 SLR update, second-line only): non-clinical evidence



Abbreviations are defined in the list of Abbreviations in the full SLR

Table 117.Studies / references included in the Danish assessment: Non-clinical evidence

Study	Reference(s)
DESTINY-Gastric04 NCT04704934	Shitara, Kohei, Eric Van Cutsem, Mahmut Gümüş, Sara Lonardi, Christelle de la Fouchardière, Clélia Coutzac, Jeroen Dekervel et al. "Trastuzumab deruxtecan or ramucirumab plus paclitaxel in gastric cancer." New England Journal of Medicine (2025) (33).

Table 118. Excluded studies / references (refer to full SLR report): Non-clinical evidence

Study	Reference(s)
See full SLR report	See full SLR report: " Enhertu GC+GEJ 2L+ SLR report_200326" (93). In Appendix C.3.2 in the SLR report (November 2025 update)

Abbreviations are defined in the list of Abbreviations

I.2 Focused Search

N/A. Refer to section 5.2 for information on method of identification of disutility inputs.

Appendix J. Literature Searches for Additional Input to the Health Economic Model

J.1 Systematic Search

Refer to Appendix I above. For PRISMA flow diagram for the non-clinical SLR, refer to Figure 74.

Inputs for the economic model were not sourced through the SLR (Table 119), but based on a focused search, refer to Appendix J.2 (see also section 5.3).

Excluded studies and references can be found in the full SLR report: "Enhertu GC+GEJ 2L+ SLR report_200326" (93).

Table 119. Studies / references included in the Danish assessment: Non-clinical evidence / economic model

Study	Reference(s)
N/A	N/A; refer to Appendix J.2

Abbreviations are defined in the list of Abbreviations

Table 120. Excluded studies / references (refer to full SLR report): Non-clinical evidence

Study	Reference(s)
See full SLR report	See full SLR report: " Enhertu GC+GEJ 2L+ SLR report_200326" (93). In Appendix C.3.2 in the SLR report (November 2025 update)

Abbreviations are defined in the list of Abbreviations

J.2 Focused Search

A focused literature search was conducted to identify inputs for the health economic model (as described in section 5.3). Inputs such as dosing information, treatment patterns, unit costs required targeted searches in Danish and regulatory sources. Searches were performed in January 2026 using EMA product information, Medicin.dk, Medicinpriser.dk, and Danish DRG tariffs. These searches were based on regimens included as relevant SoC options in Denmark and were used to retrieve locally applicable dosing assumptions and cost inputs (e.g. treatment costs, administration costs, AE management costs etc (refer to section 5.3). The identified references are summarised in Table 121.

Table 121. References from focused search

Item	Reference(s)
Dosing – T-DXd	European Medicines Agency. Summary of Product Characteristics: Enhertu® from: https://www.ema.europa.eu/en/medicines/human/EPAR/enhertu (1).

Dosing – DTX	EMA. Summary of Product Characteristics: Docetaxel Accord from: https://www.ema.europa.eu/en/medicines/human/EPAR/docetaxel-accord (38) Medicin.dk. Docetaxel “Accord” from: Docetaxel “Accord” – information til sundhedsfaglige – Medicin.dk) (55)
Dosing – PTX	EMA. Summary of Product Characteristics: Paclitaxel from: Pazenir | European Medicines Agency (EMA) (56) Medicin.dk. Paclitaxel “Accord” from: Paclitaxel "Accord" - information til sundhedsfaglige - Medicin.dk) (57)
Dosing – Irinotecan	Medicin.dk. Irinotecan “Accord” from: Irinotecan "Accord" - information til sundhedsfaglige - Medicin.dk) (39)
Disease management costs; administration costs; adverse event management costs (unit costs)	Sundhedsdatastyrelsen; Danish Diagnosis-Related Group tariffs 2026 via InteraktivDRG. Available from: https://casemix360.solutions.iqvia.com/InteractiveProd (58)
Patient time and transportation costs (unit costs)	Danish Medicines Council (Medicinrådet). Costs calculations - Guideline, version 1.0. 2026. Available from: https://medicinraadet.dk/ansogning/ansogningsskema (59)
Medicine costs (unit costs	Lægemiddelstyrelsen. Medicinpriser.dk – officielle danske medicinpriser. Available from: https://medicinpriser.dk/ (60)

Abbreviations are defined in the list of Abbreviations

Appendix K. Justification for Confidential Information

The justification for confidentiality is provided in Table 122.

Table 122. Justifications for confidential information

Parameters	Justification
Crossover adjusted RAM+PTX (OS) (section 2, section 6.1.5, section 7.1, section 7.2, section 9.2.2, Appendix B, Appendix E.1.2, and Appendix N)	These data reflect our developed post hoc crossover-adjusted overall survival analysis and therefore reveal internal methodological choices and derived treatment effect estimates beyond the published study results. Disclosure would reveal our internal evidence strategy and comparative efficacy position, which is of substantial commercial importance.
Danish RWE unpublished data (section 3.1.2, section 3.2.1, section 6.1.3, section 12.1.1, Appendix E.1.2, and Appendix P)	The Danish RWE data (data on file) are unpublished and derived from proprietary data sources and analyses commissioned by the company. The results provide market-specific insights into treatment patterns and outcomes that are of strategic value.
Dose reduction data / dose distribution data (section 3.2; Table 7)	These data provide detailed insight into actual treatment exposure and dose management and are relevant to the economic model. Disclosure would allow third parties to more closely reconstruct the cost-effectiveness results and infer aspects of our pricing strategy.
NMA derived estimates/HRs (section 7.1, section 7.2, section 7.3, and Appendix D)	These estimates are derived from our indirect treatment comparison analyses based on methodological choices. Disclosure would reveal our comparative evidence strategy and relative efficacy positioning, which is commercially sensitive.
QoL compliance data (Appendix G)	Disclosed when there is <5 patients in the cohort
QoL domain-level data (Appendix G)	Disclosed when there is <5 patients in the cohort
Danish clinical expert confidentiality (section 14)	Identifying information (name, job title, workplace) is confidential to protect expert anonymity.
Subsequent treatment post-progression (Appendix B.1.2, section 3.4, and section 11.1.2)	These data are important for the interpretation of overall survival, treatment sequencing, and downstream costs in the economic model. Disclosure would assist third parties in reconstructing key aspects of our economic evaluation and value positioning.
Time-to-treatment discontinuation data (section 3.2, section 6.1.5, section 9.2.3, Appendix E.1.3)	TTD data are a key driver of treatment duration and cost in the economic model. Disclosure would enable third parties to reconstruct important model assumptions and more precisely infer our cost-effectiveness results and pricing strategy.
Relative dose intensity (section 3.2, section 11.1.1, and Appendix L)	Relative dose intensity is directly relevant to drug acquisition costs in the economic model. Disclosure would allow third parties to more precisely reproduce the cost-effectiveness outputs and infer key aspects of the our pricing strategy.

Parameters	Justification
Diagnostic plots (extrapolations) (PFS, OS, and TTD) (Appendix E)	These plots reveal internal modelling choices used to generate extrapolated outcomes in the economic model. Disclosure would facilitate reconstruction of the model and of our cost-effectiveness and value strategy.
Visual fit (PFS, OS, and TTD) (Appendix E)	These figures reveal our selected extrapolation approach and model fit judgments. Disclosure would assist third parties in reconstructing key economic model assumptions and hence results

Appendix L. Drug Cost Calculation

T-DXd

Weight-based dosing is recommended for T-DXd, and the method of moments approach was adopted to estimate the mean dose administered to patients, based on the weight data observed in the DG04 study (11).

The weight characteristics from the DG04 study are provided below in Table 123. The estimated body weight distribution is provided in Table 124.

Table 123. Weight characteristics – DG04 (11)

Parameters	Value (kg) ITT population (n= 494)
Mean weight	67.7
Standard deviation weight	15.6
Minimum weight	32.9
Maximum weight	132.1

Abbreviations are defined in the list of Abbreviations

Table 124. Body weight distribution - DG04

ITT population Weight (kg)	Frequency	% of patients
32.90 Kg	0.0021	0.21%
33.89 Kg	0.0025	0.25%
34.88 Kg	0.0028	0.28%
35.88 Kg	0.0032	0.32%
36.87 Kg	0.0036	0.37%
37.86 Kg	0.0041	0.41%
38.85 Kg	0.0046	0.47%
39.84 Kg	0.0052	0.52%
40.84 Kg	0.0058	0.58%
41.83 Kg	0.0065	0.65%
42.82 Kg	0.0072	0.72%
43.81 Kg	0.0079	0.80%
44.80 Kg	0.0087	0.88%
45.80 Kg	0.0096	0.96%
46.79 Kg	0.0104	1.05%
47.78 Kg	0.0113	1.14%
48.77 Kg	0.0123	1.23%
49.76 Kg	0.0132	1.33%
50.76 Kg	0.0142	1.42%
51.75 Kg	0.0152	1.52%
52.74 Kg	0.0161	1.62%
53.73 Kg	0.0171	1.72%
54.72 Kg	0.0181	1.82%
55.72 Kg	0.0190	1.91%
56.71 Kg	0.0199	2.00%
57.70 Kg	0.0208	2.09%

ITT population Weight (kg)	Frequency	% of patients
58.69 Kg	0.0216	2.17%
59.68 Kg	0.0224	2.25%
60.68 Kg	0.0231	2.32%
61.67 Kg	0.0237	2.38%
62.66 Kg	0.0242	2.43%
63.65 Kg	0.0247	2.48%
64.64 Kg	0.0251	2.52%
65.64 Kg	0.0253	2.54%
66.63 Kg	0.0255	2.56%
67.62 Kg	0.0255	2.56%
68.61 Kg	0.0255	2.56%
69.60 Kg	0.0254	2.55%
70.60 Kg	0.0251	2.52%
71.59 Kg	0.0248	2.49%
72.58 Kg	0.0243	2.44%
73.57 Kg	0.0238	2.39%
74.56 Kg	0.0232	2.33%
75.56 Kg	0.0225	2.26%
76.55 Kg	0.0218	2.18%
77.54 Kg	0.0209	2.10%
78.53 Kg	0.0201	2.02%
79.52 Kg	0.0192	1.93%
80.52 Kg	0.0182	1.83%
81.51 Kg	0.0173	1.73%
82.50 Kg	0.0163	1.64%
83.49 Kg	0.0153	1.54%
84.48 Kg	0.0143	1.44%
85.48 Kg	0.0134	1.34%
86.47 Kg	0.0124	1.25%
87.46 Kg	0.0115	1.15%
88.45 Kg	0.0106	1.06%
89.44 Kg	0.0097	0.97%
90.44 Kg	0.0089	0.89%
91.43 Kg	0.0081	0.81%
92.42 Kg	0.0073	0.73%
93.41 Kg	0.0066	0.66%
94.40 Kg	0.0059	0.59%
95.40 Kg	0.0053	0.53%
96.39 Kg	0.0047	0.47%
97.38 Kg	0.0042	0.42%
98.37 Kg	0.0037	0.37%
99.36 Kg	0.0033	0.33%
100.36 Kg	0.0029	0.29%
101.35 Kg	0.0025	0.25%
102.34 Kg	0.0022	0.22%
103.33 Kg	0.0019	0.19%
104.32 Kg	0.0016	0.16%
105.32 Kg	0.0014	0.14%
106.31 Kg	0.0012	0.12%
107.30 Kg	0.0010	0.10%
108.29 Kg	0.0009	0.09%

ITT population Weight (kg)	Frequency	% of patients
109.28 Kg	0.0007	0.07%
110.28 Kg	0.0006	0.06%
111.27 Kg	0.0005	0.05%
112.26 Kg	0.0004	0.04%
113.25 Kg	0.0004	0.04%
114.24 Kg	0.0003	0.03%
115.24 Kg	0.0002	0.02%
116.23 Kg	0.0002	0.02%
117.22 Kg	0.0002	0.02%
118.21 Kg	0.0001	0.01%
119.20 Kg	0.0001	0.01%
120.20 Kg	0.0001	0.01%
121.19 Kg	0.0001	0.01%
122.18 Kg	0.0001	0.01%
123.17 Kg	0.0000	0.005%
124.16 Kg	0.0000	0.004%
125.16 Kg	0.0000	0.003%
126.15 Kg	0.0000	0.002%
127.14 Kg	0.0000	0.002%
128.13 Kg	0.0000	0.001%
129.12 Kg	0.0000	0.001%
130.12 Kg	0.0000	0.001%
132.10 Kg	0.0000	0.001%

Abbreviations are defined in the list of Abbreviations

T-DXd

The method of moments approach was applied as follows:

1. 100 equally spaced weight classes were derived between the minimum and maximum weights observed in the overall cohort of the DG04 study.
2. For each weight class, the weight-adjusted dose was estimated by multiplying the weight by the dose (6.4 kg/mg) and the RDI ([redacted]) (11). For each weight class, the exact fractional number of vials needed for each weight -adjusted dose was calculated and rounded up to the nearest whole number.
3. The cost for both the exact and rounded number of vials for each weight class was estimated by multiplying the number of vials with the vial unit cost.
4. The cost per administration was derived for each weight class by multiplying the number of vials with the vial unit cost.
5. By assuming a normal distribution with mean weight and standard deviation from the DG04 study, the proportion of patients in each weight class was estimated.
6. The total cost per cycle was calculated by applying the sum product function to the proportions of patients within each weight class and their respective per cycle costs.

Standard of care

The posology of included treatments was based on SmPCs or sourced from Danish clinical expert statements ((2, 3). Table 125 summarises the posology of treatments included in the model.

Table 125. Posology of treatments included in the health economic analysis

Treatment regimes	Drug	Initial dose	Subsequent doses	Admin per cycle	Cycle length (weeks)	Duration of treatment (n of cycles)	RDI (%)	Source
T-DXd	T-DXd	6.4 mg/kg	6.4 mg/kg	1	3	Until progression	[redacted]	SmPC
PTX	PTX	80 mg/m^2	80 mg/m^2	1	1	Until progression	90.0%	Danish clinical expert (2, 3)
DTX	DTX	75 mg/m^2	75 mg/m^2	1	3	Until progression	90.0%	
Irinotecan	Irinotecan	250 mg/m^2	250 mg/m^2	1	3	Until progression	90.0%	

Appendix M. Safety Data from the Literature

Table 126 shows the drug-related TEAE sourced from the literature for the health economic model, SoC arm.

Table 126. Summary of drug-related TEAEs (grade ≥3 and in ≥5% of patients) sourced from the literature and used in the health economic model

Event	PTX (%)	DTX (%)	Irinotecan (%)
Anaemia	10.33%	6.17%	10.53%
Leukopenia	6.69%	0.00%	21.05%
Nausea	2.43%	0.00%	5.26%
Neutrophil count decreased	18.84%	14.81%	0.00%
Fatigue	5.47 %	16.05%	0.00%
Febrile neutropenia	2.18%	7.41%	15.79%
Pain	1.52%	11.11%	0.00%
diarrhoea	1.52%	12.96%	26.32%
Vomiting	3.65%	12.96%	5.26%
Infection	0.00%	14.81%	0.00%
Source	RAINBOW (10)	Ford et al (34)	Thuss-Patience et al. 2011 (35)

Abbreviations are defined in the list of Abbreviations
Notes: * Indicates Adverse Events of Special Interest (AESI)

M.1 Paclitaxel

AE rates for PTX was sourced from: RAINBOW (10) by Wilke et al. AEs were graded using NCI-CTCAE v4.02. Most patients discontinued due to disease progression: 72% in the RAM group and 76% in the placebo group. Discontinuation due to AEs was similar (12% vs 11%).

Grade 3 events linked to the vascular endothelial growth factor pathway (hypertension, proteinuria, bleeding) were more frequent with RAM. Grade 4–5 events were rare. SAEs occurred in 47% (RAM) vs 42% (placebo). Deaths due to TEAEs were 12% vs 16%. Drug-related deaths were 6 patients (RAM) and 5 patients (placebo), with causes including sepsis, haemorrhage, and embolism.

An overview of AE as per the DMC application form is provided in Table 127. In addition, SAE data is not available from this study. Table 128 shows all AEs with a frequency of ≥ 10%, regardless of grade/severity recorded in RAINBOW, as well as all AEs grade ≥ 3, which occurred in ≥ 3% in neither of the treatment arm.

Table 127. Overview of AEs RAINBOW - PTX

	RAM+PTX (n=327)	Placebo + PTX (n= 329)	Difference , % points	Difference , RR (95% CI)
All adverse events (AE), n (%)	324 (99%)	322 (98%)	1%	N/A
Serious AE (SAE), n (%)	N/A	N/A	N/A	N/A
AE grade ≥ 3, n (%)	267 (82%)	206 (63%)	19%	N/A
Dose reduction due to AE, n (%)	N/A	N/A	N/A	N/A
Treatment discontinuation due to AE, n (%)	39 (12%)	38 (11%)	1%	N/A

Abbreviations are defined in the list of Abbreviations
Notes: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.02)

Table 128. Proportion of patients with AEs RAINBOW - PTX

	RAM+PTX (n=327)		Placebo + PTX (n= 329)	
	All	**Grade ≥ 3**	**All**	**Grade ≥ 3 or SAE**
Decreased appetite	131 (40.1%)	10 (3.1%)	105 (31.9%)	13 (4.0%)
Nausea	115 (35.2%)	-*	108 (32.8%)	-*
Alopecia	107 (32.7%)	-*	127 (38.6%)	-*
Fatigue	130 (39.8%)	23 (7.0%)	106 (32.2%)	13 (4.0%)
Epistaxis	100 (30.6%)	-*	-*	-*
Diarrhoea	106 (32.4%)	12 (3.7%)	76 (23.1%)	-*
Abdominal pain	101 (30.9%)	18 (5.5%)	67 (20.4%)	11 (3.3%)
Anaemia	111 (33.9%)	30 (9.2%)	117 (35.6%)	34 (10.3%)
Vomiting	88 (26.9%)	10 (3.1%)	68 (20.7%)	12 (3.6%)
Oedema peripheral	82 (25.1%)	-*	45 (13.7%)	-*
Constipation	70 (21.4%)	-*	71 (21.6%)	-*
Stomatitis	64 (19.6%)	-*	-*	-*
Pyrexia	59 (18.0%)	-*	37 (11.2%)	-*
Leukopenia	111 (33.9%)	57 (17.4%)	69 (21.0%)	22 (6.7%)
Asthenia	69 (21.1%)	18 (5.5%)	45 (13.7%)	-*
Peripheral sensory neuropathy	57 (17.4%)	-*	36 (10.9%)	-*

	RAM+PTX (n=327)		Placebo + PTX (n= 329)	
Proteinuria	54 (16.5%)	-*	-*	-*
Neutropenia	178 (54.4%)	133 (40.7%)	102 (31.0%)	62 (18.8%)
Cough	40 (12.2%)	-*	-*	-*
Weight decreased	45 (13.8%)	-*	49 (14.9%)	-*
Thrombocytopenia	43 (13.1%)	-*	-*	-*
Neuropathy peripheral	47 (14.4%)	10 (3.1%)	-*	-*
Back pain	39 (11.9%)	-*	40 (12.2%)	-*
Rash	35 (10.7%)	-*	-*	-*
Myalgia	34 (10.4%)	-*	33 (10.0%)	-*
Dyspnoea	42 (12.8%)	-*	-*	-*
Headache	32 (9.8%)	-*	-*	-*
Hypertension	78 (23.9%)	46 (14.1%)	-*	-*
Abdominal pain upper	32 (9.8%)	-*	35 (10.6%)	-*
Ascites	33 (10.1%)	12 (3.7%)	-*	13 (4.0%)
Hyponatraemia	-*	11 (3.4%)	-*	-*
General physical health deterioration	-*	11 (3.4%)	-*	11 (3.3%)
Dehydration	-*	9 (2.8%)	-*	-*
Malignant neoplasm progression	52 (15.9%)	47 (14.4%)	60 (18.2%)	59 (17.9%)
Febrile neutropenia	-*	10 (3.1%)	-*	-*

Abbreviations are defined in the list of Abbreviations

* If not meeting a frequency of ≥ 10% (all grades column), as well as all AEs grade ≥ 3, which occurred in ≥ 3% (grade 3 or more column)

Table 129. Treatment-emergent AEs of patients on RAM+PTX, irrespective of causality

Preferred term (MedDRA v16.0)	RAM+PTX (n=327)				Placebo + PTX (n= 329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Any patients with TEAE	57 (17%)	155 (47%)	73 (22%)	39 (12%)	116 (35%)	128 (39%)	27 (8%)	51 (16%)
Decreased appetite	121 (37%)	10 (3%)	0	0	92 (28%)	13 (4%)	0	0
Nausea	109 (33%)	5 (2%)	1 (<1%)	0	100 (30%)	8 (2%)	0	0
Alopecia	107 (33%)	0	0	0	126 (38%)	1 (<1%)	0	0
Fatigue	107 (33%)	23 (7%)	0	0	93 (28%)	13 (4%)	0	0
Epistaxis	100 (31%)	0	0	0	23 (7%)	0	0	0
Diarrhoea	94 (29%)	12 (4%)	0	0	71 (22%)	4 (1%)	1 (<1%)	0
Abdominal pain	83 (25%)	18 (6%)	0	0	56 (17%)	10 (3%)	1 (<1%)	0
Anaemia	81 (25%)	30 (9%)	0	0	83 (25%)	31 (9%)	3 (<1%)	0
Vomiting	78 (24%)	9 (3%)	1 (<1%)	0	56 (17%)	12 (4%)	0	0
Oedema peripheral	77 (24%)	5 (2%)	0	0	43 (13%)	2 (<1%)	0	0
Constipation	70 (21%)	0	0	0	69 (21%)	2 (<1%)	0	0
Stomatitis	62 (19%)	2 (<1%)	0	0	22 (7%)	2 (<1%)	0	0

Preferred term (MedDRA v16.0)	RAM+PTX (n=327)				Placebo + PTX (n= 329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Pyrexia	56 (17%)	3 (<1%)	0	0	36 (11%)	1 (<1%)	0	0
Leukopenia	54 (17%)	52 (16%)	5 (2%)	0	47 (14%)	19 (6%)	3 (<1%)	0
Asthenia	51 (16%)	18 (6%)	0	0	39 (12%)	6 (2%)	0	0
Peripheral sensory neuropathy	51 (16%)	6 (2%)	0	0	33 (10%)	3 (<1%)	0	0
Proteinuria	50 (15%)	4 (1%)	0	0	20 (6%)	0	0	0
Neutropenia	45 (14%)	71 (22%)	62 (19%)	0	40 (12%)	51 (16%)	11 (3%)	0
Cough	40 (12%)	0	0	0	25 (8%)	0	0	0
Weight decreased	39 (12%)	6 (2%)	0	0	45 (14%)	4 (1%)	0	0
Thrombocytopenia	38 (12%)	5 (2%)	0	0	14 (4%)	6 (2%)	0	0
Neuropathy peripheral	37 (11%)	10 (3%)	0	0	23 (7%)	7 (2%)	0	0
Back pain	35 (11%)	4 (1%)	0	0	35 (11%)	5 (2%)	0	0
Rash	35 (11%)	0	0	0	26 (8%)	0	0	0
Myalgia	34 (10%)	0	0	0	32 (10%)	1 (<1%)	0	0
Dyspnoea	34 (10%)	8 (2%)	0	0	29 (9%)	2 (<1%)	0	0
Headache	32 (10%)	0	0	0	21 (6%)	1 (<1%)	0	0
Hypertension	32 (10%)	46 (14%)	0	0	8 (2%)	8 (2%)	0	0
Abdominal pain upper	29 (9%)	3 (<1%)	0	0	34 (10%)	1 (<1%)	0	0
Arthralgia	28 (9%)	1 (<1%)	0	0	19 (6%)	1 (<1%)	0	0
Hypoalbuminaemia	27 (8%)	4 (1%)	0	0	11 (3%)	1 (<1%)	0	1 (<1%)
Dry skin	25 (8%)	0	0	0	9 (3%)	1 (<1%)	0	0
Ascites Aspartate	21 (6%)	11 (3%)	1 (<1%)	0	14 (4%)	13 (4%)	0	0
aminotransferase increased	21 (6%)	6 (2%)	0	0	12 (4%)	5 (2%)	0	0
Pruritus	20 (6%)	1 (<1%)	0	0	11 (3%)	0	0	0
Abdominal distension	19 (6%)	2 (<1%)	0	0	16 (5%)	4 (1%)	0	0
Paraesthesia	18 (6%)	6 (2%)	0	0	24 (7%)	1 (<1%)	0	0
Dizziness	18 (6%)	1 (<1%)	0	0	13 (4%)	0	0	0
Urinary tract infection	18 (6%)	1 (<1%)	0	0	10 (3%)	2 (<1%)	0	0

Preferred term (MedDRA v16.0)	RAM+PTX (n=327)				Placebo + PTX (n= 329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	16 (5%)	4 (1%)	0	0	15 (5%)	2 (<1%)	1 (<1%)	0
Dysphonia	16 (5%)	1 (<1%)	0	0	9 (3%)	0	0	0
Polyneuropathy	14 (4%)	4 (1%)	0	0	18 (5%)	4 (1%)	0	0
Upper respiratory tract infection	14 (4%)	1 (<1%)	0	0	10 (3%)	0	0	0
Infusion related reaction	13 (4%)	1 (<1%)	0	0	8 (2%)	0	0	0
Blood bilirubin increased	13 (4%)	3 (<1%)	0	0	6 (2%)	5 (2%)	0	0
Dysphagia	12 (4%)	4 (1%)	0	0	12 (4%)	7 (2%)	0	0
Blood creatinine increased	12 (4%)	1 (<1%)	1 (<1%)	0	6 (2%)	2 (<1%)	0	0
Blood alkaline phosphatase increased	11 (3%)	4 (1%)	0	0	9 (3%)	5 (2%)	1 (<1%)	0
Weight increased	11 (3%)	2 (<1%)	0	0	9 (3%)	2 (<1%)	0	0
Hypocalcaemia	11 (3%)	0	0	0	4 (1%)	1 (<1%)	0	0
Hypoaesthesia	9 (3%)	1 (<1%)	0	0	8 (2%)	0	0	0
Hypomagnesaemia	9 (3%)	1 (<1%)	0	0	6 (2%)	0	0	0
Pleural effusion	9 (3%)	3 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)	2 (<1%)	0
Hypokalaemia	8 (2%)	6 (2%)	0	0	10 (3%)	5 (2%)	0	0
Mucosal inflammation	8 (2%)	2 (<1%)	0	0	6 (2%)	0	0	0
C-reactive protein increased	8 (2%)	2 (<1%)	0	0	5 (2%)	1 (<1%)	0	0
Hyponatraemia	8 (2%)	8 (2%)	3 (<1%)	0	5 (2%)	3 (<1%)	1 (<1%)	0
Leukocytosis	8 (2%)	1 (<1%)	0	0	4 (1%)	2 (<1%)	0	0
Gamma-glutamyltransferase increased	8 (2%)	1 (<1%)	2 (<1%)	0	3 (<1%)	2 (<1%)	1 (<1%)	0
Depression	7 (2%)	1 (<1%)	0	0	7 (2%)	0	0	0
Pain	7 (2%)	3 (<1%)	0	0	3 (<1%)	1 (<1%)	0	0
General physical health deterioration	6 (2%)	8 (2%)	3 (<1%)	0	7 (2%)	7 (2%)	2 (<1%)	2 (<1%)
Hypotension	6 (2%)	4 (1%)	0	0	6 (2%)	2 (<1%)	0	0
Cancer pain	6 (2%)	1 (<1%)	0	0	5 (2%)	2 (<1%)	0	0

Preferred term (MedDRA v16.0)	RAM+PTX (n=327)				Placebo + PTX (n= 329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Dehydration	6 (2%)	7 (2%)	1 (<1%)	1 (<1%)	5 (2%)	8 (2%)	0	0
Hyperbilirubinaemia	6 (2%)	1 (<1%)	0	0	5 (2%)	2 (<1%)	0	0
Erythema	6 (2%)	1 (<1%)	0	0	4 (1%)	0	0	0
Haemoptysis	6 (2%)	1 (<1%)	0	0	3 (<1%)	0	0	0
Neurotoxicity	6 (2%)	3 (<1%)	0	0	3 (<1%)	0	0	0
Mouth ulceration	6 (2%)	1 (<1%)	0	0	2 (<1%)	0	0	0
Hyperkalaemia	5 (2%)	5 (2%)	0	0	9 (3%)	2 (<1%)	0	0
Blood lactate dehydrogenase increased	5 (2%)	1 (<1%)	0	0	6 (2%)	1 (<1%)	0	0
Hyperglycaemia	5 (2%)	3 (<1%)	0	0	5 (2%)	5 (2%)	0	0
Oral candidiasis	5 (2%)	1 (<1%)	0	0	3 (<1%)	0	0	0
Blood albumin decreased	5 (2%)	0	0	0	2 (<1%)	1 (<1%)	0	0
Hydronephrosis	5 (2%)	1 (<1%)	0	0	2 (<1%)	1 (<1%)	0	0
Pneumonia	5 (2%)	5 (2%)	0	0	2 (<1%)	4 (1%)	1 (<1%)	0
Malignant neoplasm progression	5 (2%)	16 (5%)	4 (1%)	27 (8%)	1 (<1%)	24 (7%)	1 (<1%)	34 (10%)
Hyperuricaemia	4 (1%)	1 (<1%)	0	0	5 (2%)	0	0	0
Lethargy	4 (1%)	1 (<1%)	0	0	5 (2%)	0	0	0
Musculoskeletal pain	4 (1%)	1 (<1%)	0	0	5 (2%)	1 (<1%)	0	0
Flank pain	4 (1%)	0	0	0	3 (<1%)	1 (<1%)	0	0
Hypophosphataemia	4 (1%)	4 (1%)	0	0	3 (<1%)	3 (<1%)	1 (<1%)	0
Melaena	4 (1%)	1 (<1%)	1 (<1%)	0	3 (<1%)	0	0	0
Tumour pain	4 (1%)	0	0	0	3 (<1%)	1 (<1%)	0	0
Muscular weakness	4 (1%)	1 (<1%)	0	0	2 (<1%)	3 (<1%)	0	0
Eastern Cooperative Oncology Group performance status worsened	4 (1%)	3 (<1%)	0	0	1 (<1%)	3 (<1%)	0	0
Hypoglycaemia	4 (1%)	0	0	0	1 (<1%)	1 (<1%)	0	0
Lung infection	4 (1%)	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0	0
Vertigo	3 (<1%)	0	0	0	4 (1%)	1 (<1%)	0	0

Preferred term (MedDRA v16.0)	RAM+PTX (n=327)				Placebo + PTX (n= 329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Conjunctivitis	3 (<1%)	1 (<1%)	0	0	3 (<1%)	0	0	0
Device related infection	3 (<1%)	2 (<1%)	0	0	3 (<1%)	4 (1%)	0	0
Drug hypersensitivity	3 (<1%)	1 (<1%)	0	0	3 (<1%)	0	0	0
Lymphopenia	3 (<1%)	2 (<1%)	0	0	3 (<1%)	0	2 (<1%)	0
Blood pressure increased	3 (<1%)	2 (<1%)	0	0	2 (<1%)	0	0	0
Ejection fraction decreased	3 (<1%)	2 (<1%)	0	0	2 (<1%)	1 (<1%)	0	0
Pneumonitis	3 (<1%)	1 (<1%)	0	0	2 (<1%)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	3 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0
Performance status decreased	3 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Lacrimation increased	2 (<1%)	0	1 (<1%)	0	4 (1%)	0	0	0
Deep vein thrombosis	2 (<1%)	3 (<1%)	0	0	2 (<1%)	1 (<1%)	0	0
Herpes zoster	2 (<1%)	0	0	0	2 (<1%)	1 (<1%)	0	0
Jaundice	2 (<1%)	1 (<1%)	0	0	2 (<1%)	1 (<1%)	0	0
Haematemesis	2 (<1%)	2 (<1%)	0	0	1 (<1%)	0	0	0
Neuralgia	2 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Pneumothorax	2 (<1%)	0	0	0	1 (<1%)	1 (<1%)	0	0
Staphylococcal infection	2 (<1%)	0	0	0	1 (<1%)	1 (<1%)	0	0
Blood urea increased	2 (<1%)	0	1 (<1%)	0	0	0	0	0
Lower respiratory tract infection	2 (<1%)	0	0	0	0	0	0	1 (<1%)
Regurgitation	2 (<1%)	1 (<1%)	0	0	0	0	0	0
Cachexia	1 (<1%)	2 (<1%)	0	0	7 (2%)	4 (1%)	0	1 (<1%)
Chest pain	1 (<1%)	2 (<1%)	0	0	4 (1%)	0	0	0
Bronchopneumonia	1 (<1%)	1 (<1%)	0	0	3 (<1%)	0	0	0
Gastric haemorrhage	1 (<1%)	4 (1%)	0	0	3 (<1%)	2 (<1%)	0	0
Ileus	1 (<1%)	0	1 (<1%)	0	3 (<1%)	1 (<1%)	0	0
Urinary retention	1 (<1%)	2 (<1%)	0	0	3 (<1%)	0	0	0
Abdominal infection	1 (<1%)	1 (<1%)	0	0	2 (<1%)	0	0	0

Preferred term (MedDRA v16.0)	RAM+PTX (n=327)				Placebo + PTX (n= 329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Atrial fibrillation	1 (<1%)	2 (<1%)	1 (<1%)	0	2 (<1%)	0	0	0
Gastrointestinal haemorrhage	1 (<1%)	3 (<1%)	0	1 (<1%)	2 (<1%)	0	1 (<1%)	1 (<1%)
Hypercalcaemia	1 (<1%)	1 (<1%)	0	0	2 (<1%)	0	0	0
Infection	1 (<1%)	2 (<1%)	0	0	2 (<1%)	0	0	0
Intestinal obstruction	1 (<1%)	3 (<1%)	2 (<1%)	0	2 (<1%)	3 (<1%)	0	0
Tremor	1 (<1%)	1 (<1%)	0	0	2 (<1%)	0	0	0
Oesophagitis	1 (<1%)	3 (<1%)	0	0	1 (<1%)	0	0	0
Skin exfoliation	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Syncope	1 (<1%)	2 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0
Wound infection	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Angina pectoris	1 (<1%)	0	0	0	0	1 (<1%)	0	0
Cardiac failure	1 (<1%)	0	0	0	0	0	0	1 (<1%)
Cholecystitis	1 (<1%)	2 (<1%)	0	0	0	0	0	0
Depressed level of consciousness	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Hearing impaired	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Hypertransaminasaemia	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Neutrophil count decreased	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Obstruction gastric	1 (<1%)	1 (<1%)	0	0	0	1 (<1%)	0	0
Oesophageal food impaction	1 (<1%)	0	0	0	0	1 (<1%)	0	0
Onycholysis	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Periodontitis	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Peripheral motor neuropathy	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Peritonitis	1 (<1%)	5 (2%)	1 (<1%)	0	0	0	0	0
Upper gastrointestinal haemorrhage	1 (<1%)	0	0	0	0	1 (<1%)	0	0
Spinal pain	0	0	0	0	3 (<1%)	1 (<1%)	0	0
Interstitial lung disease	0	0	0	0	2 (<1%)	2 (<1%)	0	0
Renal failure acute	0	1 (<1%)	0	0	2 (<1%)	0	1 (<1%)	2 (<1%)

Preferred term (MedDRA v16.0)	RAM+PTX (n=327)				Placebo + PTX (n= 329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Acute respiratory distress syndrome	0	1 (<1%)	0	0	1 (<1%)	0	0	0
Arthritis	0	1 (<1%)	0	0	1 (<1%)	0	0	0
Blood pressure decreased	0	1 (<1%)	0	0	1 (<1%)	0	0	0
Convulsion	0	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0
Disease progression	0	0	0	0	1 (<1%)	1 (<1%)	0	0
Feeling abnormal	0	0	0	0	1 (<1%)	1 (<1%)	0	0
Hepatic enzyme increased	0	3 (<1%)	0	0	1 (<1%)	0	0	0
Hypophagia	0	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0
Jaundice cholestatic	0	0	0	0	1 (<1%)	1 (<1%)	0	0
Liver function test abnormal	0	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0	0
Procedural pain	0	0	0	0	1 (<1%)	2 (<1%)	0	0
Pulmonary embolism	0	3 (<1%)	0	1 (<1%)	1 (<1%)	7 (2%)	1 (<1%)	2 (<1%)
Renal failure	0	2 (<1%)	1 (<1%)	0	1 (<1%)	0	0	0
Small intestinal obstruction	0	3 (<1%)	0	0	1 (<1%)	3 (<1%)	0	0
White blood cell count decreased	0	1 (<1%)	0	0	1 (<1%)	0	0	0
Acute coronary syndrome	0	0	0	0	0	1 (<1%)	0	0
Acute prerenal failure	0	0	0	0	0	1 (<1%)	0	0
Akathisia	0	0	0	0	0	1 (<1%)	0	0
Amylase increased	0	0	0	0	0	1 (<1%)	0	0
Anal abscess	0	1 (<1%)	0	0	0	0	0	0
Anticoagulation drug level above therapeutic	0	1 (<1%)	0	0	0	0	0	0
Aphagia	0	1 (<1%)	0	0	0	0	0	0
Aplastic anaemia	0	1 (<1%)	0	0	0	0	0	0
Aspiration	0	0	0	0	0	0	0	1 (<1%)
Atrial thrombosis	0	0	0	0	0	1 (<1%)	0	0
Bile duct obstruction	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Biliary sepsis	0	0	1 (<1%)	0	0	0	0	0

Preferred term (MedDRA v16.0)	RAM+PTX (n=327)				Placebo + PTX (n= 329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Biliary tract infection	0	0	0	0	0	1 (<1%)	0	0
Brain cancer metastatic	0	0	1 (<1%)	0	0	0	0	0
Catheter site infection	0	0	0	0	0	1 (<1%)	0	0
Cellulitis	0	0	0	0	0	1 (<1%)	0	0
Cerebral haemorrhage	0	0	0	0	0	0	0	1 (<1%)
Cerebrovascular accident	0	0	1 (<1%)	0	0	0	0	0
Cholangitis	0	0	0	0	0	1 (<1%)	1 (<1%)	0
Cholecystitis acute	0	1 (<1%)	0	0	0	0	0	0
Clavicle fracture	0	1 (<1%)	0	0	0	0	0	0
Cognitive disorder	0	1 (<1%)	0	0	0	0	0	0
Coma	0	0	1 (<1%)	0	0	0	0	0
Death	0	0	0	1 (<1%)	0	0	0	0
Device dislocation	0	0	0	0	0	0	1 (<1%)	0
Diabetes insipidus	0	0	0	0	0	1 (<1%)	0	0
Diabetes mellitus	0	1 (<1%)	0	0	0	0	0	0
Diarrhoea infectious	0	0	0	0	0	1 (<1%)	0	0
Disseminated intravascular coagulation	0	2 (<1%)	0	0	0	0	1 (<1%)	0
Diverticular perforation	0	0	1 (<1%)	0	0	0	0	0
Drowning	0	0	0	0	0	0	0	1 (<1%)
Endocarditis	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Extrasystoles	0	0	0	0	0	1 (<1%)	0	0
Extremity contracture	0	1 (<1%)	0	0	0	0	0	0
Febrile neutropenia	0	8 (2%)	2 (<1%)	0	0	4 (1%)	3 (<1%)	1 (<1%)
Gallbladder obstruction	0	0	0	0	0	1 (<1%)	0	0
Gastrointestinal perforation	0	1 (<1%)	0	1 (<1%)	0	0	0	0
Generalised oedema	0	0	0	0	0	1 (<1%)	0	0
Hydrocephalus	0	0	0	0	0	0	1 (<1%)	0

Preferred term (MedDRA v16.0)	RAM+PTX (n=327)				Placebo + PTX (n= 329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Hypokinesia	0	0	0	0	0	1 (<1%)	0	0
Hypovolaemic shock	0	0	0	0	0	0	0	1 (<1%)
Hypoxia	0	1 (<1%)	0	0	0	0	0	0
Inappropriate antidiuretic hormone secretion	0	1 (<1%)	0	0	0	0	0	0
Incisional hernia	0	1 (<1%)	0	0	0	0	0	0
Injection site injury	0	1 (<1%)	0	0	0	0	0	0
Intestinal ischaemia	0	0	0	0	0	1 (<1%)	0	0
Intestinal perforation	0	0	1 (<1%)	0	0	0	0	0
Intracranial pressure increased	0	0	0	0	0	0	0	1 (<1%)
Ischaemic stroke	0	0	1 (<1%)	0	0	0	0	0
Laryngitis	0	0	0	0	0	1 (<1%)	0	0
Lobar pneumonia	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Localised infection	0	1 (<1%)	0	0	0	0	0	0
Lung infiltration	0	1 (<1%)	0	0	0	0	0	0
Malabsorption	0	0	0	1 (<1%)	0	0	0	0
Malignant ascites	0	0	0	0	0	2 (<1%)	0	0
Malignant pleural effusion	0	0	0	0	0	1 (<1%)	0	0
Malnutrition	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Metastases to central nervous system	0	0	0	0	0	1 (<1%)	0	0
Metastases to liver	0	0	0	0	0	1 (<1%)	0	0
Metastases to meninges	0	1 (<1%)	0	0	0	2 (<1%)	0	0
Multi-organ failure	0	0	0	0	0	2 (<1%)	0	0
Myocardial infarction	0	1 (<1%)	0	0	0	0	0	1 (<1%)
Neutropenic sepsis	0	0	0	0	0	0	1 (<1%)	0
Obstructive uropathy	0	1 (<1%)	0	0	0	0	0	0
Oesophageal haemorrhage	0	1 (<1%)	0	0	0	0	0	0

Preferred term (MedDRA v16.0)	RAM+PTX (n=327)				Placebo + PTX (n= 329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Oesophageal spasm	0	1 (<1%)	0	0	0	0	0	0
Oesophageal stenosis	0	0	0	0	0	1 (<1%)	0	0
Oliguria	0	0	0	0	0	1 (<1%)	0	0
Pain of skin	0	1 (<1%)	0	0	0	0	0	0
Pancreatitis acute	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Pathological fracture	0	0	0	0	0	1 (<1%)	0	0
Perirectal abscess	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Peritoneal haemorrhage	0	0	0	0	0	1 (<1%)	0	0
Peritonitis bacterial	0	2 (<1%)	1 (<1%)	0	0	2 (<1%)	0	0
Pneumatosis intestinalis	0	1 (<1%)	0	0	0	0	0	0
Portal vein thrombosis	0	2 (<1%)	0	0	0	0	0	0
Procedural hypertension	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Pseudomonas infection	0	1 (<1%)	0	0	0	0	0	0
Pulmonary sepsis	0	0	0	0	0	0	1 (<1%)	0
Pulmonary thrombosis	0	1 (<1%)	0	0	0	0	0	0
Pyloric stenosis	0	0	0	0	0	1 (<1%)	0	0
Respiratory failure	0	0	0	1 (<1%)	0	1 (<1%)	0	0
Sepsis	0	0	3 (<1%)	2 (<1%)	0	0	2 (<1%)	0
Septic shock	0	0	0	3 (<1%)	0	0	0	1 (<1%)
Small intestinal stenosis	0	0	0	0	0	1 (<1%)	0	0
Spinal cord compression	0	0	0	0	0	1 (<1%)	0	0
Splenic rupture	0	1 (<1%)	0	0	0	0	0	0
Staphylococcal sepsis	0	1 (<1%)	0	0	0	0	0	0
Stress cardiomyopathy	0	0	0	0	0	1 (<1%)	0	0
Systolic hypertension	0	1 (<1%)	0	0	0	0	0	0
Thoracic vertebral fracture	0	1 (<1%)	0	0	0	0	0	0
Urinary tract infection bacterial	0	1 (<1%)	0	0	0	0	0	0

Preferred term (MedDRA v16.0)	RAM+PTX (n=327)				Placebo + PTX (n= 329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Vena cava thrombosis	0	0	0	0	0	2 (<1%)	0	0

Abbreviations are defined in the list of Abbreviations
Source: Wilke et al. / RAINBOW (10)

M.2 Docetaxel

AE rates for DTX was sourced from: Ford et al (34). Table 132 shows grade 3–4 treatment-related toxicities. Overall, treatment was well tolerated: 38.6% in the PEP02 arm, 34.1% with irinotecan, and 15.9% with DTX. No treatment-related deaths occurred. Diarrhoea was most common in PEP02 and irinotecan (72.7% vs 68.2%), while alopecia was most frequent with DTX (52.3%). PEP02 had more grade 3–4 diarrhoea and nausea, with similar rates of vomiting, neutropenia, and febrile neutropenia. No major toxicity differences were seen at the 150 mg/m² dose. Six patients in each arm discontinued due to toxicity. AEs were graded using NCI-CTCAE v3.0.

An overview of AE as per the DMC application form (section 8. Safety) cannot be provided. In addition, SAE data is not available from this study. Table 131 shows all AEs with a frequency of ≥ 10%, regardless of grade/severity recorded in COUGAR-02, as well as all AEs grade ≥ 3, which occurred in ≥ 3% in neither of the treatment arm.

Table 130. Overview of AEs COUGAR-02 – DTX

	DTX (n =81)	Active symptom control (n =74)	Difference , % points	Difference , RR (95% CI)
All adverse events (AE), n (%)	N/A	N/A	N/A	N/A
Serious AE (SAE), n (%)	N/A	N/A	N/A	N/A
AE grade ≥ 3, n (%)	N/A	N/A	N/A	N/A
Dose reduction due to AE, n (%)	N/A	N/A	N/A	N/A
Treatment discontinuation due to AE, n (%)	N/A	N/A	N/A	N/A

Abbreviations are defined in the list of Abbreviations

Table 131. Proportion of patients with AEs COUGAR-02 -DTX

	DTX (n =81)		Active symptom control (n =74)	
	All	Grade ≥ 3	All	Grade ≥ 3 or SAE
Neutropenia without fever	13 (16%)	12 (15%)	-*	-*
Anaemia	23 (28%)	5 (6%)	17 (23%)	4 (5%)
Other blood or bone marrow	9 (11%)	-*	-*	2 (3%)
Infection without neutropenia	21 (26%)	12 (15%)	15 (20%)	2 (3%)
Febrile neutropenia	-*	6 (7%)	-*	-*
Constitutional symptoms	55 (68%)	13 (16%)	45 (61%)	10 (14%)
Gastrointestinal	71 (88%)	21 (26%)	60 (81%)	18 (24%)
Haemorrhage or bleeding	8 (10%)	-*	9 (12%)	5 (7%)
Metabolic or laboratory	19 (23%)	5 (6%)	14 (19%)	3 (4%)

	DTX (n =81)		Active symptom control (n =74)	
Musculoskeletal or soft tissue	8 (10%)	4 (5%)	-*	5 (7%)
Neurology	34 (42%)	3 (4%)	14 (19%)	3 (4%)
Pain	45 (56%)	9 (11%)	55 (74%)	15 (20%)
Pulmonary or upper respiratory	23 (28%)	5 (6%)	19 (26%)	5 (7%)
Allergy or immunological	-*	4 (5%)	-*	-*
Lymphatic	-*	-*	-*	-*
Visual	-*	-*	-*	-*
Renal or genitourinary	-*	-*	-*	-*
Vascular	-*	-*	-*	-*
Dermatological	34 (42%)	-*	12 (16%)	-*

Abbreviations are defined in the list of Abbreviations

Source: Ford et al (34)

Notes: toxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0)

* If not meeting a frequency of ≥ 10% (all grades column), as well as all AEs grade ≥ 3, which occurred in ≥ 3% (grade 3 or more column)

Table 132. Most common grade 3–4 AEs sourced from COUGAR 02- DTX

DTX (%) (n = 81)		
	Grade 3	Grade 4
Neutropenia without fewer	4 (5%)	8 (10%)
Anaemia	3 (4.0%)	2 (2.0%)
Other blood or bone marrow	2 (2%)	0
Infection without neutropenia	9 (11%)	3 (4%)
Febrile neutropenia	5 (6%)	1 (1%)
Constitutional symptoms	13 (16%)	0
Gastrointestinal	21 (26%)	0
Haemorrhage or bleeding	0	1 (1%)
Metabolic or laboratory	5 (6%)	0
Musculoskeletal or soft tissue	4 (5%)	0
Neurology	3 (4%)	0
Pain	7 (9%)	2 (2%)
Pulmonary or upper respiratory	3 (4%)	2 (2%)
Allergy or immunological	1 (1%)	1 (1%)
Lymphatic	0	0
Visual	1 (1%)	0

Abbreviations are defined in the list of Abbreviations

Source: Ford et al (34)

Notes: toxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0)

M.3 Irinotecan

AE rates for irinotecan was sourced from: Thuss-Patience et al. 2011 (35). A total of 19 patients who received any dose of irinotecan were evaluable for toxicity (see Table 135).

An overview of AE as per the DMC application form (section 8. Safety) cannot be provided. In addition, SAE data is not available from this study. Table 134 shows all AEs with a frequency of ≥ 10%, regardless of grade/severity recorded by Thuss-Patience et al 2011, as well as all AEs grade ≥ 3, which occurred in ≥ 3% in neither of the treatment arm.

Table 133. Overview of AEs Thuss-Patience et al – Irinotecan (35)

	Irinotecan (n =21)	BSC (n =19)	Difference , % points	Difference , RR (95% CI)
All adverse events (AE), n (%)	N/A	N/A	N/A	N/A
Serious AE (SAE), n (%)	N/A	N/A	N/A	N/A
AE grade ≥ 3, n (%)	N/A	N/A	N/A	N/A
Dose reduction due to AE, n (%)	N/A	N/A	N/A	N/A
Treatment discontinuation due to AE, n (%)	N/A	N/A	N/A	N/A

Abbreviations are defined in the list of Abbreviations

Table 134. Proportion of patients with AEs Thuss-Patience et al – Irinotecan (35)

	Irinotecan (n= 21)		BSC (n= 19)	
	All	**Grade ≥ 3 or SAE**	**All**	**Grade ≥ 3 or SAE**
Nausea	-*	1 (5%)	N/A	N/A
Vomiting	-*	1 (5%)	N/A	N/A
Diarrhoea	5 (26%)	5 (26%)	N/A	N/A
Neutropenic fever	3 (16%)	3 (16%)	N/A	N/A
Leukocytopenia	4 (21%)	4 (21%)	N/A	N/A
Thrombocytopenia Haemoglobin	2 (11%)	2 (11%)	N/A	N/A

Abbreviations are defined in the list of Abbreviations
Notes: only grade 3 and 4 is reported – as per Table 135
* If not meeting a frequency of ≥ 10% (all grades column), as well as all AEs grade ≥ 3, which occurred in ≥ 3% (grade 3 or more column)

Table 135. Toxicity (grade 3/4) in Arm A: Irinotecan as reported from Thuss-Patience et al (35)

Irinotecan (%) - Evaluable pts n= 19		
	CTC Grade 3	CTC Grade 4
Nausea	1 (5%)	
Vomiting	1 (5%)	
Diarrhoea	5 (26%)	
Neutropenic fever	2 (11%)	1 (5%)
Leukocytopenia	3 (16%)	1 (5%)
Thrombocytopenia Haemoglobin	2 (11%)	

Abbreviations are defined in the list of Abbreviations

Appendix N. Crossover Analysis

The full crossover report has been attached: "Enhertu GC+GEJ 2L+ Crossover report_20012026" (9). The RPSFTM is presented below as the chosen approach for crossover adjustment.

N.1 Methods

To account for patients randomized to RAM+ PTX who switched (e.g., after progression) to an ADC, T-DXd or Disitamab Vedotin (RC48), a RPSFTM was fitted (45), consistent with NICE DSU TSD 24 guidance (45) for situations where patients switch between control and experimental treatment. Time spent on either treatment was incorporated, and the common treatment effect was applied, meaning patients received the same treatment effect regardless of when the experimental therapy. By estimating the acceleration factor and accounting for it, counterfactual survival stimes were derived that reflect survival expected had patients not switched. The acceleration factor can be interpreted as the additional survival time achieved on T-DXd (or RC48); correctly estimating this factor and reducing the additional survival benefit generates an accurate counterfactual survival time that would have been observed had patients not received T-DXd after progression on RAM+PTX. The RPSFTM therefore assumes a common treatment effect, meaning that the treatment effect of T-DXd was the same among those who switched from RAM+PTX and those initially randomized to T-DXd.

The RPSFTM can be applied on an 'on treatment' or a 'treatment group' basis. The 'on treatment approach only considers time spent receiving the experimental treatment as time spent on treatment. The 'treatment group' approach considers all time after initiating the experimental treatment as time spent on treatment. The 'treatment group' approach may be useful when a treatment effect beyond treatment discontinuation is expected or when the control treatment is an active therapy (45).

Both re-censoring and not re-censoring approaches are prone to bias, often in opposing directions (45). Re-censoring yields valid estimates of treatment effects up to the maximum re-censored follow-up time but results in loss of information, which increases with larger treatment effect. When extrapolating survival beyond the study period, this loss can impair extrapolation and bias long-term effect estimates. Presenting outcomes from both methods (with / without re-censoring) provides a range in which the true effect is likely to lie (45). Simulation work has shown that adjustment without re-censoring can yield less bias when the switching proportion is low, and the treatment effect is high (94). Given these considerations, the base case OS was adjusted for crossover without re-censoring. OS adjustment with re-censoring was explored in scenario analysis (refer to Table 63).

Rank Preserving Structural Failure Time Model (RPSFTM) adjustment

The RPSFMT model can be formulated as follows. Let T be the observed event time and U the counterfactual event time that would have been observed if crossover had not occurred. Under an AFT model: $U(\psi)=T\text{E}+T\text{E}\ exp(\psi)$

where TE is the observed time on experimental therapy and TC = T− TE.

The treatment-group ("ever treated") approach was applied, whereby all person-time after initiation of T-DXd or RC48 was treated as on-treatment, reflecting the expectation of a treatment effect persistence beyond discontinuation and acknowledging RAM+PTX as an active control.

The treatment parameter ψ was estimated via g-estimation using the log-rank test. If no or multiple roots were identified, the search interval was modified, and alternative g-estimation methods were considered. Because censoring can become informative on the counterfactual time scale, counterfactual event times (U) were re-censored using the minimum censoring time that could have been observed across possible treatment paths, recognizing the associated loss of long-term information. Consistent with NICE DSU TSD 24 (45), RPSFTM results were presented both with and without re-censoring. In simulation work, Latimer et al. (94), RPSFTM implemented without re-censoring generally produced the least bias when the switching proportion was low and the treatment effect was high, although re-censoring can mitigate informative censoring at the cost of reduced long-term information.

As previously describe, the RPSFTM assumes a common treatment effect. In line with NICE DSU TSD 24, sensitivity analyses will relax this assumption by scaling the treatment effect among switchers to a fraction of that among initially treated patients, implemented by multiplying ψ by k (in this case k= 0.5, 0.6, 0.7, 0.8, 0.9): U(ψ) = TC + TE exp (k ψ).

Non-parametric bootstrapping was conducted to quantify uncertainty in the crossover analysis, following the procedure described by Berrar (95), and 95% CIs were estimated for the crossover analysis.

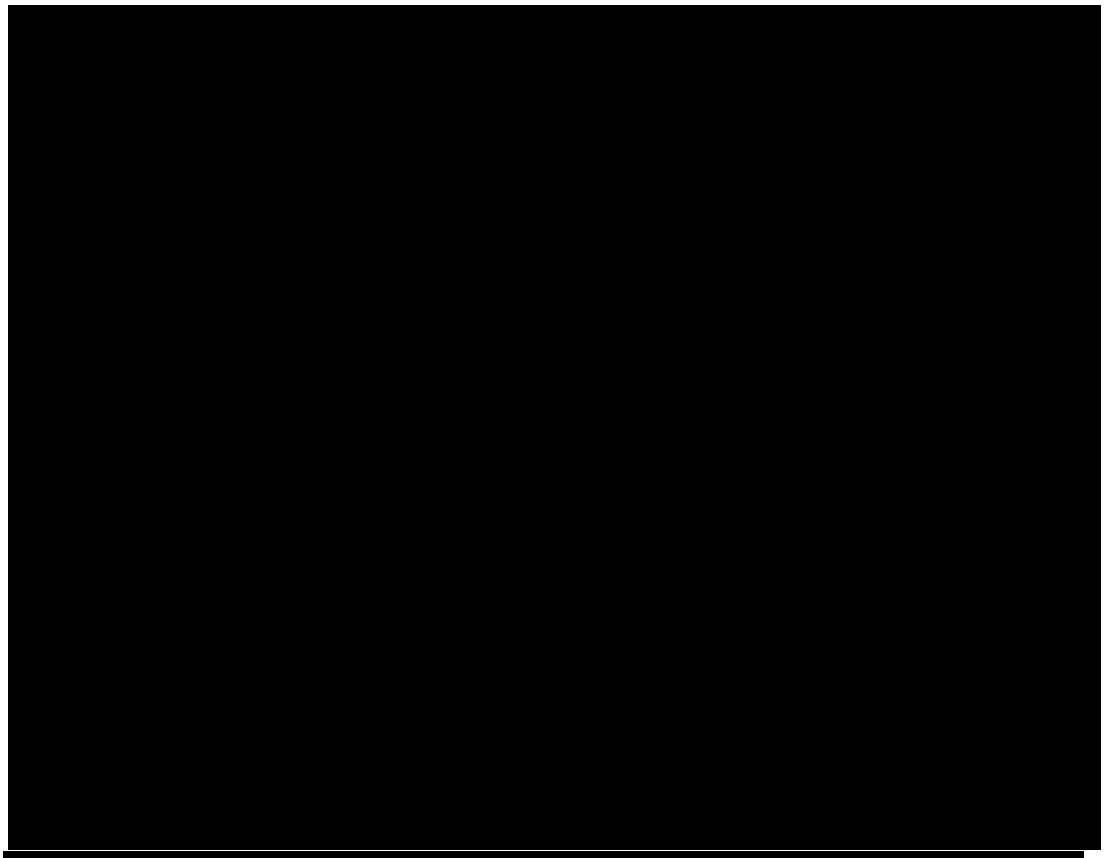
N.2 Results

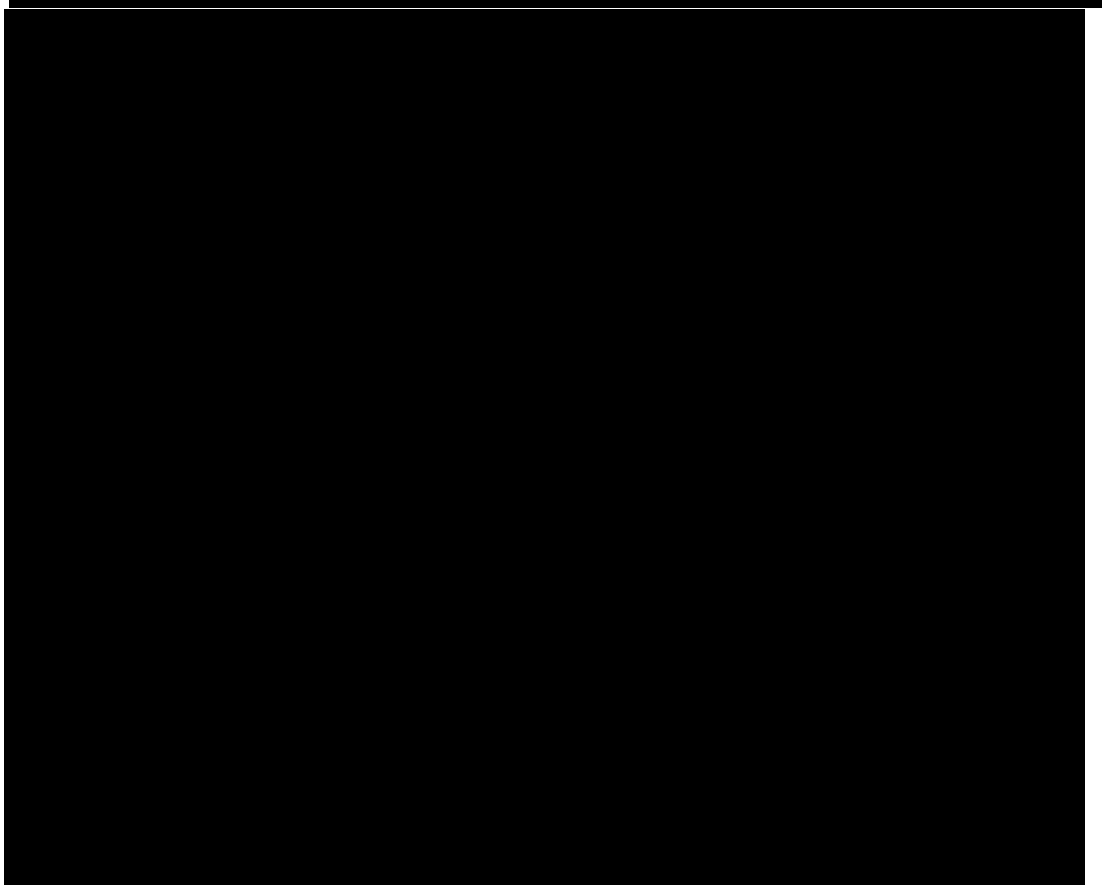
Results below are presented for the following two scenarios:

- With re-censoring adjusting for crossover to either T-DXd or RC48
- Without re-censoring adjusting for crossover to either T-DXd or RC48

N.2.1 G-estimation Diagnostic Plots

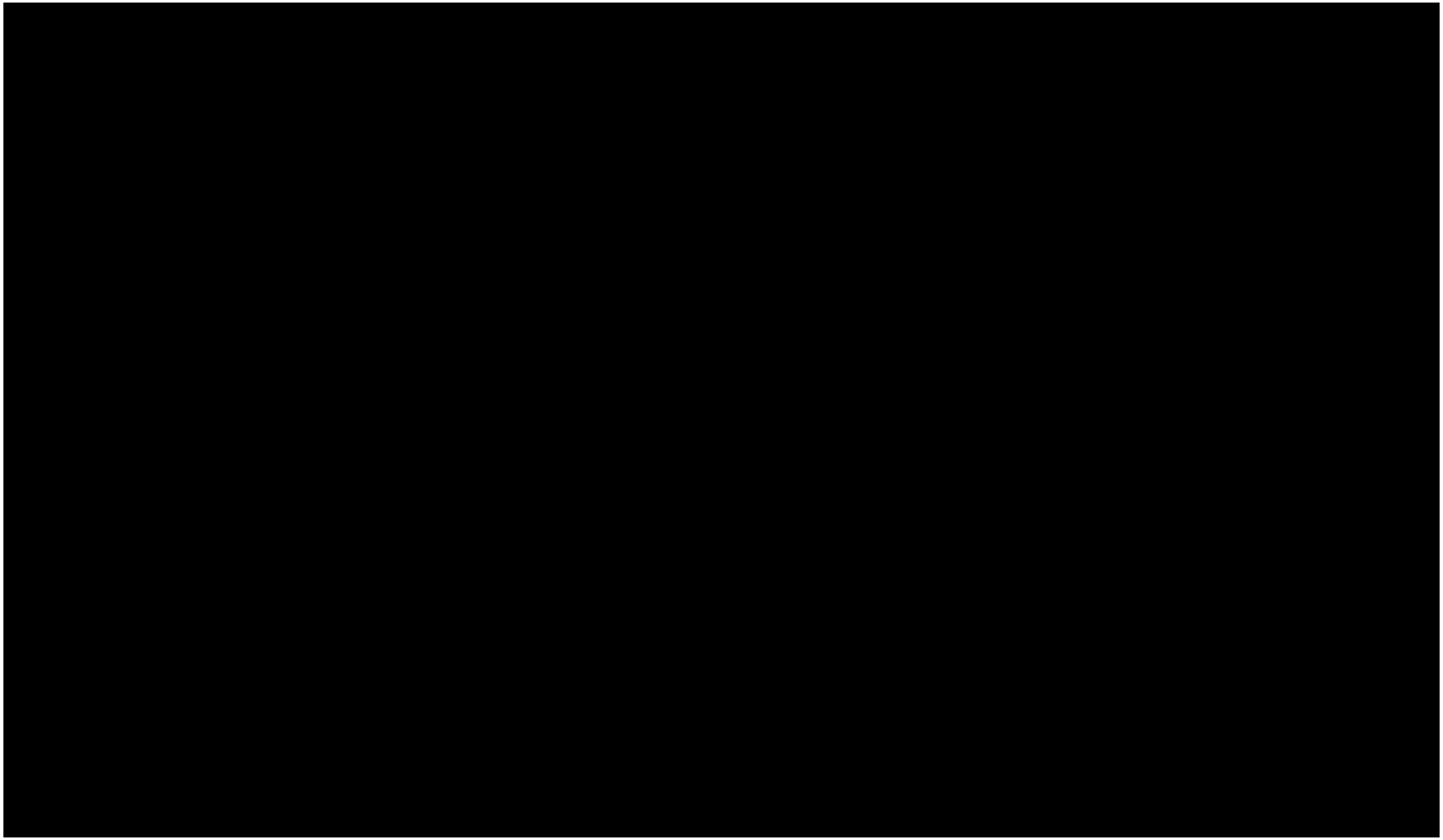
Plots of the g-estimation procedure are presented for the specified scenarios. The estimated treatment parameter ψ is displayed with its 95% CI.





N.2.2 Kaplan-Meier Plots

KM curves for time-to-event endpoints are shown for each treatment group, with monthly numbers at risk displayed beneath each plot. Median survival with two-sided 95% CIs is reported. For T-DXd, CIs was estimated using the Brookmeyer–Crowley method; for the control (RPSFTM-adjusted), CIs was computed using bias-corrected and accelerated (BCA) bootstrap with 1,000 replications. KM survival estimates at fixed time points (3, 6, 9, 12, 18, 24, 36, 48 months) with two-sided 95% CIs are also provided; control-arm CIs used the same bootstrap approach to account for RPSFTM variability.





Adjusted HRs with 95% CIs are compared between the base case and the RPSFTM sensitivity analyses using the treatment-group approach, with and without re-censoring.

Table 136. HR between the base case and the RPSFTM sensitivity analyses

Analysis	Hazard ratio, (95% CI)
No crossover, ITT analysis	0.70, (0.55 – 0.90)
Crossover to T-DXd or disitamab vedotin with re-censoring	[redacted]
Crossover to T-DXd or disitamab vedotin without re-censoring	[redacted]

Abbreviations are defined in the list of Abbreviations

Adjusted HRs were consistent across crossover-adjustment implementations. HR [redacted] with re-censoring and [redacted] without re-censoring, versus 0.70 in the unadjusted ITT analysis. The minimal difference between re-censoring and no re-censoring (absolute Δ=0.01) suggests the choice of re-censoring has negligible impact on the estimated treatment effect in this dataset, while both approaches indicate a stronger effect than the ITT estimate, as expected with control-arm switching.

Appendix O. Clinical Documentation – Standard of Care

O.1 Patient Characteristics

See Table 137.

Table 137. Patient characteristics – SoC

Study	COUGAR-02 (32)	KCSG ST10-01 (33)	RAINBOW (34)	Roy (2013) (38)	Sym (2013) (42)	TCOG GI-0801/BIRIP	Thuss-Patience (2011)	TRICS	WJOG 4007
Sample size (N)	168	112	665	132	59	127	40	168	219
Male %	81.0	69.5	71.0	78.0	57.8	82.0	72.7	78.0	78.0
Median age	65.5	58.5	59.5	58.7	60.5	66.5	56.6	67.5	64.5
Ethnicity %									
Asian	-	-	-	-	-	-	-	-	-
White	-	-	-	-	-	-	-	-	-
Black	-	-	-	-	-	-	-	-	-
Black or other	-	-	-	-	-	-	-	-	-
Other	-	-		-	-	-	-	-	-
Geography %									
Western	100.0	0.0	60.0	54.7	0.0	0.0	100.0	0.0	0.0
Asia	0.0	100.0	33.5	45.3	100.0	100.0	0.0	100.0	100.0
Rest of the world	0.0	0.0	6.5	0.0	0.0	0.0	0.0	0.0	0.0
ECOG %									
ECOG PS 0	27.0	0.0	39.0	-	-	68.5	-	81.0	-
ECOG PS 1	57.5	96.5	61.0	-	-	31.5	-	19.0	-
ECOG PS 0 or 1	84.5	96.5	100.0	92.3	91.5	100.0	77.7	100.0	96.0
ECOG PS 2	15.5	3.5	N/A	7.7	8.5	0.0	22.3	N/A	4.0
Histological subtype %									
Intestinal	-	-	42.0	-	-	50.5	20.2	50.0	49.5
Diffuse	-	-	37.5	-	-	49.5	67.5	50.0	50.5
Mixed	-	-	5.0	-	-	-	-	-	-
Not reported	-	-	15.5	-	-	0.0	12.3	0.0	0.0
Type									
Gastric	45.5	90.9	79.5	77.3	91.5	-	57.5	-	-

Study	COUGAR-02 (32)	KCSG ST10-01 (33)	RAINBOW (34)	Roy (2013) (38)	Sym (2013) (42)	TCOG GI-0801/BIRIP	Thuss-Patience (2011)	TRICS	WJOG 4007
GEJ	35.0	9.1	20.5	22.7	8.5	-	42.5	-	-
Oesophagus	19.5	-	-	-	-	-	-	-	-
Other disease characteristics %									
Primary tumour at entry	-	-	62.5	-	-	-	32.5	17.5	-
Presence of peritoneal metastases	-	54.0	48.0	-	57.0	27.0	-	-	26.5
Presence of ascites	-	-	36.5	-	-	-	-	-	-
Number of metastatic sites %									
0-1	-	-	-	-	52.5	-	-	-	-
1	-	41.1	-	-	-	-	-	60.0	55.5
1-2	-	-	-	-	-	-	70.3	-	-
0-2	-	-	66.0	-	-	-	-	-	-
2	-	-	-	-	30.5	-	-	21.0	-
≥2	-	58.9	-	-	-	-	-	-	44.5
≥3	-	-	34.0	-	17.1	-	29.7	19.0	-
Previous gastrectomy %									
Gastrectomy	-	67.1	-	-	-	36.0	35.7	-	34.5
Partial gastrectomy	-	-	21.0	-	-	-	-	-	-

Study	COUGAR-02 (32)	KCSG ST10-01 (33)	RAINBOW (34)	Roy (2013) (38)	Sym (2013) (42)	TCOG GI-0801/BIRIP	Thuss-Patience (2011)	TRICS	WJOG 4007
Total gastrectomy	-	-	17.5	-	-	-	-	-	-
Other	-	-	1.0	-	-	-	-	-	-

Abbreviations are defined in the list of Abbreviations

O.2 Posology

O.2.1 Docetaxel

DTX monotherapy was evaluated in both COUGAR-02 (34) and the randomised controlled trial (RCT) reported by Roy et al. (37). In both COUGAR-02 and Roy et al. patients were treated with 75 mg/m^2 DTX once every 21-day cycle. This is consistent with the recommended dosing and administration in Danish clinical practice for second-line treatment of advanced or metastatic gastric cancer (2, 3). However, doses between 75 and 100 mg/m2 per 21-day cycle are recommended, and so the dosing considered in COUGAR-02 and Roy et al. is at the lowest end of Danish dosing recommendations for DTX (55). Consequently, patients in real world clinical practice treated with DTX may receive higher doses than those administered in the clinical documentation.

O.2.2 Paclitaxel

PTX monotherapy was evaluated as a treatment in WJOG 4007 (36), KCSG ST10-01 (42), and RAINBOW (10). Both WJOG 4007 and RAINBOW administered 80 mg/m^2 of PTX on days 1, 8, and 15 of each 28-day cycle. In contrast, KCSG ST10-01 administered 70 mg/m^2 on days 1, 8, and 15 of each 28-day cycle. Danish clinical practice recommend administration of 80 mg/m^2 PTX on days 1 of each 7-day cycle with the option to omit every 4th scheduled dose (2, 3).

The dosing of PTX in the RAINBOW study, which informs the relative efficacy of the SoC in this assessment, is aligned with Danish clinical practice. Specifically, RAINBOW's PTX schedule is consistent with the recommended 80 mg/m² weekly administration with omission of every fourth dose, supporting the applicability of RAINBOW efficacy estimates to Danish practice.

O.2.3 Irinotecan

Treatment with irinotecan monotherapy was included in TCOG GI-0801/BIRIP (40), TRICS (41), Roy et al. (37), WJOG 4007 (36), KCSG ST10-01 (42) and Thuss-Patience et al. Treatment with irinotecan monotherapy was included in TCOG GI-0801/BIRIP (40), TRICS (41), Roy et al. (37), WJOG 4007 (36), KCSG ST10-01 (42) and Thuss-Patience et al. (35) studies. In TCOG GI-0801/BIRIP (40), TRICS(41), KCSG ST10-01 (42), WJOG 4007 (36), Sym et al. (43) and Roy et al. (37) patients received 150 mg/m^2 of irinotecan Q2W. In Roy et al. patients received 300 mg/m^2 of irinotecan every three weeks, a larger effective dose than patients treated with irinotecan in the other studies of interest. Danish clinical practice recommend irinotecan is administered at 250 mg/m^2 on day 1 of a 21-day cycle (2, 3). The doses in the studies of interest, although different, may still be representative of the real-world dose of irinotecan under the assumption that patients receive varying doses of drug in clinical practice.

Table 138. Posology of SoC (2, 3)

Treatment regimen	Initial dose	Subsequent doses	Administrations per cycle	Cycle length (weeks)	Duration of treatment
DTX	75.0 mg/m^2	75.0 mg/m^2	1	3	6
PTX	80.0 mg/m^2	80.0 mg/m^2	3	4	Until progression
Irinotecan	250.0 mg/m^2	250.0 mg/m^2	1	3	Until progression

Abbreviations are defined in the list of Abbreviations

O.3 Relative Dose Intensity

Reporting of RDI varied across studies (see Table 139 and Table 140). Wilke et al. (10) reported an mean RDI of 90% for PTX. Roy et al. (37) report a median RDI by cycle of >90% and a proportion of patients requiring dose reduction of 25% (11 of 44) with irinotecan and 22.7% (10 of 44) with DTX (mean RDI values were not reported for DTX and irinotecan).

Table 139. Relative dose intensity – SoC

Treatment regimen	RDI	Source
PTX	Mean: 90%	Wilke et al. (10)
DTX	Median: 90%	Roy et al. RDI > 90% (37)
Irinotecan	Median: 90%	Roy et al. RDI > 90% (37)

Abbreviations are defined in the list of Abbreviations

Table 140. RDI definition - SoC

Study / Source	Treatment(s)	RDI definition	RDI reporting
RAINBOW trial	Ramucirumab + Paclitaxel; Paclitaxel	No formal RDI definition stated	Mean, median, range, by treatment arm
COUGAR-02	Docetaxel	No formal RDI definition stated	No RDI reported
Docetaxel / Irinotecan (Roy et al)	PEP02; Irinotecan; Docetaxel	No formal RDI definition stated	Reported as “>90% dose intensity”
Irinotecan (Thuss-Patience et al.)	Irinotecan	No explicit RDI formula reported	No RDI reported

Abbreviations are defined in the list of Abbreviations

O.4 Treatment Duration

Across studies, treatment duration was reported heterogeneously, differing in metrics and depth of detail (see Table 141).

O.4.1 Docetaxel

In Roy et al. (37) patients in the DTX arm received a mean of 4.7 cycles (range 1–12), with dosing once every three weeks. In COUGAR-02 (34) DTX was planned for up to six cycles and discontinued upon completion of six cycles, a treatment delay exceeding 21 days, disease progression, unacceptable toxicity, or patient request. Among the 84 patients allocated to DTX, 19 (23%) completed all six cycles, 17 (20%) received only one cycle, and 7 (8%) received no DTX.

O.4.2 Paclitaxel

In the WJOG 4007 study (36), the PTX group had a median of 11.5 administrations (range 1–46), with dosing scheduled as three administrations every four weeks. In RAINBOW (10) the placebo plus PTX group had a median treatment duration of 12.0 weeks (IQR 6.4–20.0). In KCSG ST10-01 (42) median treatment duration with PTX was 10.5 weeks (range 0–90.3). In TCOG GI-0801/BIRIP (40), treatment duration was not reported.

O.4.3 Irinotecan

In TCOG GI-0801/BIRIP (40) and TRICS (41), treatment duration was not reported. In the WJOG 4007 study (36), the irinotecan group received a median of 4.5 administrations (range 1–39), with dosing once every three weeks. In Roy et al. (37), the mean number of treatment cycles was 4.6 in the irinotecan arm (range 1–12), with administrations scheduled every three weeks. In KCSG ST10-01 (42), median treatment duration in the irinotecan group was 6.2 weeks (range 0–138.3). In Sym et al. (43) the median number of treatment courses was 4.0 (range 1–12) in the irinotecan monotherapy arm. In Thuss-Patience et al. (35) the median number of treatment cycles per patient was 2 (range 0–9), with a three-week cycle length.

Table 141. Treatment duration – clinical documentation for SoC

Treatment regimen	Study	Dosing schedule	Exposure (cycles/administrations of duration)
DTX	Roy et al.	One administration, every 3 weeks	Mean 4.7 cycles (range 1–12)
	COUGAR-02	One administration, every 3 weeks; planned up to 6 cycles	23% completed 6 cycles; 20% received 1 cycle; 8% received none
PTX	WJOG 4007	Three administrations every 4 weeks	Median 11.5 administrations (range 1–46)
	RAINBOW (placebo + PTX)	Three administrations every 4 weeks	Median 12.0 weeks (IQR 6.4–20.0)
	KCSG ST10-01	Not explicitly stated	Median 10.5 weeks (range 0–90.3)
	TCOG GI-0801/BIRIP	Not reported	Not reported
Irinotecan	TCOG GI-0801/BIRIP	Not reported	Not reported
	TRICS	Not reported	Not reported
	WJOG 4007	One administration, every 3 weeks	Median 4.5 administrations (range 1–39)

Treatment regimen	Study	Dosing schedule	Exposure (cycles/administrations of duration)
	Roy et al.	One administration, every 3 weeks	Mean 4.6 cycles (range 1–12)
	KCSG ST10-01	Not explicitly stated	Median 6.2 weeks (range 0–138.3)
	Sym et al. (mono)	One administration, every 3 weeks	Median 4.0 courses (range 1–12)
	Thuss-Patience et al.	One administration, every 3 weeks	Median 2 cycles (range 0–9)

Abbreviations are defined in the list of Abbreviations

O.5 Subsequent Treatments

Across studies, subsequent treatments were reported heterogeneously, differing in depth of detail (see Table 142).

O.5.1 Docetaxel

In both COUGAR-02 (34) and Roy et al. (37) subsequent treatments were not reported.

O.5.2 Paclitaxel

In the WJOG 4007 study (36), subsequent chemotherapy was not specified, and crossover was allowed. Among patients treated with PTX, third-line chemotherapy was administered to 97 patients (89.8%). In this group, third-line regimens containing irinotecan were used in 81 patients (75.0%). Including later lines, 87 patients (80.6%) in the PTX group received irinotecan. In RAINBOW, (10) it was reported that 70% of patients in Asia received post-study discontinuation treatment and 40% in non-Asian regions, and crossover was not allowed. For KCSG ST10-01 (42) no subsequent treatments were reported.

O.5.3 Irinotecan

TCOG GI-0801/BIRIP (40) and Thuss-Patience et al. (35) allowed crossover. In Thuss-Patience et al. (35) three patients in the irinotecan-arm received a third line therapy after irinotecan (DTX, epirubicin/cisplatin/5-FU and mitomycin C, respectively).

In the WJOG 4007 study (36), subsequent chemotherapy was not specified, and crossover was allowed. Third-line chemotherapy was administered in 80 patients (72.1%) after irinotecan treatment, in the irinotecan group, a taxane-containing regimen was used in 67 patients (60.4%). Including later lines, 75 patients (67.6%) in the irinotecan group received PTX.

For TRICS (41), Roy et al. (37), Sym et al. (43), TCOG GI-0801/BIRIP (40) and KCSG ST10-01 (42) subsequent treatments were not reported.

Table 142. Subsequent treatments – clinical documentation for SoC

Treatment regimen	Study	Subsequent treatment reported	Crossover	Notable subsequent treatments and proportions
DTX	Roy et al.	Not reported	Not specified	—
	COUGAR-02	Not reported	Not specified	—
PTX	WJOG 4007	Partially (subsequent chemotherapy not specified; third-line use reported)	Allowed	Third line given in 97 patients (89.8%); irinotecan-containing regimens in 81 patients (75.0% of group); including later lines. 87 patients (80.6%) received irinotecan
	RAINBOW (placebo + PTX)	Partially	Not allowed	70% of patients in Asia received post-study discontinuation treatment and 40% in non-Asian regions
	KCSG ST10-01	Not reported	Not specified	—
Irinotecan	TCOG GI-0801/BIRIP	Not reported	Allowed	—
	Thuss-Patience et al.	Partially	Allowed	Three patients in irinotecan arm received third line: DTX; epirubicin/cisplatin/5-FU; mitomycin C
	WJOG 4007	Partially (subsequent chemotherapy not specified; third-line use reported)	Allowed	Third-line given in 80 patients (72.1%); taxane-containing regimens in 67 patients (60.4% of group); including later lines. 75 patients (67.6%) received PTX
	TRICS	Not reported	Not specified	—
	Roy et al.	Not reported	Not specified	—
	Sym et al. (mono)	Not reported	Not specified	—
	KCSG ST10-01	Not reported	Not specified	—

Abbreviations are defined in the list of Abbreviations

Appendix P. Danish Real-World Evidence

Background

To support the health economic evaluation of T-DXd within the Danish DG04 assessment, a simple RWE data request was conducted to obtain local patients characteristics and numbers for patients with HER2-positive metastatic GC/GEJC in Denmark. Additionally, the longest achievable landmark survival was extracted to determine whether any patients remained alive years after treatment with trastuzumab.

Methods

The analysis included patients registered in the Danish National Cancer Register with a diagnosis of oesophageal (C15) or gastric (C16) adenocarcinoma (any stage) who had received ≥1 administration of trastuzumab (using the treatment code BOHJ13) following diagnosis. The inclusion window spanned 2018–2024. Descriptive patient characteristics, such as age at trastuzumab initiation, stage at diagnosis, and HER2 status, were summarized, and longest achievable landmark KM estimate of OS was generated from the time of trastuzumab initiation (~6 years OS).

Results

A total of [redacted] patients were identified, with a mean age of [redacted] years at trastuzumab initiation; [redacted] were females and [redacted] males. Tumour location distribution included [redacted] oesophageal cancers, [redacted] cardia GCs, and [redacted] non-cardia GCs. [redacted] patients received T-DXd during follow-up, based on EMA approval of Enhertu (DG02 supported by DESTINY-Gastric01 [DG01]) in 2022.

Table 143. Danish real-world patient characteristics and numbers – data on file (30)

Patients with GC who have received ≥1 administration of trastuzumab	[redacted]
Number of patients (n)	
Average number of patients per year (2019 – 2024)*	
Age at Trastuzumab initiation	
Sex	
Female	
Male	
Location	
Oesophageal (C15)	
Gastric (Cardia) (C16.0)	
Gastric (Non-Cardia) (C16.1-C16.9)	
N receiving trastuzumab deruxtecan during follow-up (2022 - 2025)	

*2018 and 2025 were excluded due to low patient numbers

Table 144. Danish real-world six-year survival

Landmark	OS
Six-year survival	[redacted]

The 6-year OS estimate cannot be considered fully representative of historical SoC in Denmark for HER2-positive GC/GEJC. Because a substantial proportion of patients in the cohort received T-DXd in 2L, the observed OS is likely overestimated relative to a true SoC population without access to T-DXd. With nationwide introduction of T-DXd for this patient population, OS outcomes might reasonably be expected to improve further beyond what is observed in this dataset. Conversely, removing T-DXd as a treatment option would plausibly lead to worse survival outcomes, given the established contribution of T-DXd to improved prognosis in the real-world cohort.

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