Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende trastuzumab deruxtecan til behandling af metastatisk HER2+ brystkræft

Vers. 1.0

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Medicinrådet

Medicinrådets sundhedsøkonomiske afrapportering

Trastuzumab deruxtecan

Metastatisk HER2+ brystkræft efter progression på to HER2-rettede behandlinger

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling, og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter *Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren*.

Dokumentoplysninger	
Godkendelsesdato	27. oktober 2021
Dokumentnummer	117983
Versionsnummer	1.0

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 28. oktober 2021

Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DBCG	Dansk Brystkræft Cancer Gruppe
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
MAIC	*Matching-adjusted indirect comparison*
OS	Samlet overlevelse (*overall survival*)
PFS	Progressionsfri overlevelse
RDI	Relativ dosisintensitet
SAIP	Sygehusapotekernes indkøbspris
T-DXd	Trastuzumab deruxtecan
TTD	Tid til behandlingsophør (*time to treatment discontinuation*)

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for trastuzumab deruxtecan (T-DXd) ca. [redacted] DKK pr. patient sammenlignet med capecitabine i kombination med trastuzumab. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 791.000 DKK pr. patient. De inkrementelle omkostninger er primært drevet af lægemiddelomkostninger for T-DXd. Den forhandlede lægemiddelpris på T-DXd pr. september 2021 er betinget af en anbefaling.

Medicinrådet vurderer, at det foreliggende kliniske datagrundlag ikke er tilstrækkeligt til at dokumentere en effektforskel mellem T-DXd og capecitabine i kombination med trastuzumab. Derfor er der i Medicinrådets hovedanalyse antaget hazard ratioer på 1 mellem T-DXd og komparator vedr. PFS og OS, svarende til at T-DXd og capecitabine er lige effektive. Fagudvalget kan på baggrund af kvalitative sammenligning (jf. vurderingsrapporten) ikke kvantificere den potentielle effektforskel, der måtte være mellem T-DXd og capecitabine i kombination med trastuzumab. På samme vis som for PFS og OS antager Medicinrådet i sin hovedanalyse, at behandlingslængden (TTD) for hhv. T-DXd og komparator er ens. Når MAIC-analysen anvendes til at dokumentere en effektforskel mellem T-DXd og komparator, [redacted] de inkrementelle omkostninger med ca. [redacted] DKK.

Fagudvalget vurderer, at patientkarakteristikaene (herunder vægt og højde) fra DESTINY-Breast01-studiet afviger fra den danske population. Anvendes fagudvalgets estimater for patientkarakteristika, [redacted] de inkrementelle omkostninger isoleret med ca. [redacted] DKK.

Såfremt der antages ikke at være nogen deling mellem T-DXd-pakningerne, [redacted] de inkrementelle omkostninger isoleret med ca. [redacted] DKK.

I Medicinrådets hovedanalyse blev valget af funktion til ekstrapolering af PFS og TTD baseret på fagudvalgets kliniske vurdering. Fagudvalget understreger, at grundlaget for ekstrapoleringen er usikkert, hvorfor Medicinrådet har udarbejdet følsomhedsanalyser. Her ekstrapoleres med de funktioner, som har det bedste statistiske fit på det observerede data. Når PFS- og TTD-kurven samtidig ekstrapoleres med en log-normal funktion fremfor en eksponentiel funktion, [redacted] de inkrementelle omkostninger med [redacted] DKK.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af T-DXd som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 53 mio. DKK i det femte år.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af trastuzumab deruxtecan (T-DXd) som mulig standardbehandling på danske hospitaler til metastatisk HER2+ brystkræft efter progression på to HER2-rettede behandlinger.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Daiichi Sankyo og AstraZeneca. Medicinrådet modtog ansøgningen den 14. juni 2021.

3.1 Patientpopulation

Brystkræft er den hyppigste kræftform hos kvinder verden over og forekommer oftest hos kvinder over 50 år. I Danmark bliver ca. 4.900 patienter årligt diagnosticeret med brystkræft, og ca. 66.000 patienter lever med diagnosen brystkræft [1,2]. Sygdommen opdeles i fire undertyper, afhængigt af om kræftcellerne er hormonfølsomme, dvs. om de udtrykker østrogen receptor (ER) og/eller HER2 [3]. Patienterne testes rutinemæssigt for HER2-status på diagnosetidspunktet ved immunhistokemi og evt. in situ hybridisering (ISH)-analyse [4]. Ca. 10-15 % af patienter med brystkræft er HER2-positive (HER2+).

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af T-DXd på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har trastuzumab deruxtecan (T-DXd) sammenlignet med capecitabine i kombination med trastuzumab for patienter med metastatisk HER2+ brystkræft, som har progredieret på to HER2-rettede behandlinger?

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for T-DXd sammenlignet med capecitabine i kombination med trastuzumab.

Ansøger har i udarbejdelsen af den sundhedsøkonomiske analyse konsulteret sig med to danske kliniske eksperter: [redacted] og [redacted].

Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

4.1.1 Klinisk datagrundlag

Idet der ikke findes nogen studier, der direkte sammenligner T-DXd med capecitabine i kombination med trastuzumab, har ansøger udarbejdet en indirekte sammenligning med brug af den statistiske metode *matching-adjusted indirect comparison* (MAIC). Ansøger har i MAIC-analysen anvendt data fra studierne DESTINY-Breast01 [5,6] og NALA [7] til at generere hazard ratios mellem T-DXd og capecitabine i kombination med trastuzumab for progressionsfri overlevelse (PFS) og samlet overlevelse (OS). DESTINY-Breast01 er et enkeltarms fase II-studie, der undersøgte effekten og sikkerheden af T-DXd hos patienter med ikke-resekterbar eller metastatisk HER2+ brystkræft, som tidligere har modtaget T-DM1. NALA er et fase III-studie, der undersøgte effekt og sikkerhed af neratinib og lapatinib, begge i kombination med capecitabine, hos patienter med metastatisk HER2+ brystkræft, der har modtaget ≥ 2 HER2-rettede behandlinger for deres metastatiske sygdom.

I den sundhedsøkonomiske model er det også muligt at anvende hazard ratios fra MAIC-analyser, der er lavet på baggrund af indirekte sammenligninger mellem DESTINY-Breast01 og hhv. SOPHIA [8] og HER2CLIMB [9]. For yderligere information om MAIC-analyserne, herunder hazard ratios, henvises til Medicinrådets vurderingsrapport vedr. T-DXd.

Ansøger antager, at patientkarakteristikaene for hhv. alder, vægt, højde og kønsfordeling fra DESTINY-Breast01-studiet er repræsentative for den danske patientpopulation.

Medicinrådets vurdering af ansøgers kliniske datagrundlag
Medicinrådet vurderer, at det ikke er metodisk acceptabelt at anvende en omkostningsanalyse, der bygger på kliniske data, som viser en forskel i effekt mellem T-DXd og capecitabine i kombination trastuzumab. Det skyldes, at effektforskellen ikke er

tilstrækkeligt dokumenteret i Medicinrådets vurdering af T-DXd, herunder at MAIC-analyserne ikke kan anvendes som datagrundlag for vurderingen af T-DXd's værdi ift. komparator. Derfor vurderer Medicinrådet, at hazard ratios mellem T-DXd og komparator for både PFS og OS skal justeres til 1. Denne ændring i analysen er baseret på fagudvalgets konklusion: at merværdien af T-DXd sammenlignet med komparator ikke kan kategoriseres.

Vedr. patientkarakteristika vurderer fagudvalget, at de gennemsnitlige værdier fra DESTINY-Breast01-studiet afviger fra den danske population. De gennemsnitlige karakteristika, som er anvendt i Medicinrådets hovedanalyse, fremgår af Tabel 1. Disse ændringer vurderes samlet at have moderat betydning for analysens resultater.

Tabel 1. Patientkarakteristika fra hhv. studiet og fagudvalgets estimater for danske patienter med HER2+ brystkræft

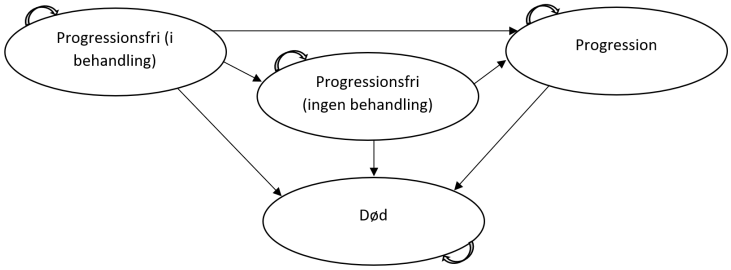
Patientkarakteristika	DESTINY-Breast01	Fagudvalgets estimater
Alder	56 år	59 år[1]
Vægt	62,47 kg	70 kg
Højde	160 cm	166,6 cm[2]
Kønsfordeling (% kvinder)	100 %	99 %

[1] Data fra Dansk Bryst Cancer Gruppe (DBCG).
[2] Gennemsnitlig højde for danske kvinder i år 2017 [10].

Medicinrådet accepterer ikke ansøgers tilgang vedr. anvendelse af hazard ratios fra MAIC-analysen, der viser en effektforskel mellem T-DXd og komparator, og vælger derfor at ændre hazard ratios mellem de to behandlingsarme til 1 for både PFS og OS. Endvidere justerer Medicinrådet patientkarakteristikaene, så de tilnærmelsesvist afspejler den danske population.

4.1.2 Modelstruktur

Ansøger har indsendt en *partitioned-survival*-model til at estimere omkostningerne forbundet med behandlingen med T-DXd. Modellen indeholder en række sygdomsstadier, som patienterne skifter mellem i takt med sygdomsprogression. Ansøgers model består af fire stadier: progressionsfri (i behandling med enten T-DXd eller komparator), progressionsfri (ingen behandling), progression og død. Se Figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem dem.



Figur 1. Strukturen i den sundhedsøkonomiske model

Alle patienter starter i stadiet progressionsfri (i behandling), hvorfra de enten kan forblive i stadiet, ophøre med behandling uden at opleve progression, opleve progression eller dø. Fra stadiet progression kan patienten bevæge sig til det absorberende stadie død. Patienternes bevægelse gennem modellen bestemmes ud fra ekstrapoleret forløbsdata for hhv. PFS, OS og tid til behandlingsophør (TTD) fra DESTINY-Breast01-studiet.

Medicinrådets vurdering af ansøgers modelstruktur
Medicinrådet vurderer, at en *partitioned-survival*-model bestående af de fire stadier progressionsfri (i behandling), progressionsfri (ingen behandling), progression og død er rimelig at anvende til at estimere de omkostninger, der er forbundet med behandling med T-DXd og komparator ved HER2+ brystkræftpatienter.

Medicinrådet accepterer ansøgers tilgang vedr. strukturen af den sundhedsøkonomiske model.

4.1.3 Antagelser vedr. ekstrapoleret forløbsdata

Ansøger modellerer tiden i de forskellige stadier – for de patienter, der behandles med T-DXd – ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for PFS, OS og TTD fra DESTINY-Breast01. Det er nødvendigt at ekstrapolere data, da opfølgningen i studiet er kortere end den anvendte tidshorisont. Ansøger har overvejende udvalgt funktionerne til ekstrapolering af forløbsdata på baggrund af det bedste statistiske fit, jf. AIC- og BIC-værdier.

PFS-KM-data for T-DXd og de ekstrapolerede kurver fremgår af Figur 2. Ansøger har anvendt den log-normale funktion til at ekstrapolere det observerede PFS-data for T-DXd.

Figur 2. Ekstrapolerede PFS-kurver for T-DXd

OS-KM-data for T-DXd og de ekstrapolerede kurver fremgår af Figur 3. Ansøger har anvendt Weibull-funktionen til at ekstrapolere det observerede OS-data for T-DXd.

Figur 3. Ekstrapolerede OS-kurver for T-DXd

Ansøger har benyttet de justerede hazard ratios fra MAIC-analysen til at generere PFS-, OS- og TTD-kurver for capecitabine i kombination med trastuzumab, se Figur 4 og Figur 5. Ved anvendelse af denne tilgang antager ansøger, at der er proportionale hazards over tid mellem T-DXd og komparator for PFS og OS.

Figur 4. PFS-kurve for hhv. T-DXd og capecitabine i kombination med trastuzumab (ekstrapoleret med den log-normale funktion)

Figur 5. OS-kurve for hhv. T-DXd og capecitabine i kombination med trastuzumab (ekstrapoleret med Weibull-funktionen)

Ansøger har estimeret behandlingslængden med T-DXd ved at ekstrapolere TTD-data fra DESTINY-Breast01 med en log-normal funktion. Ansøger vurderer, at denne funktion har det bedste statistiske fit på TTD-KM-data, og at kurven er klinisk plausibel. De ekstrapolerede kurver fremgår af Figur 6, hvor det også ses, at anvendelsen af den log-normale funktion genererer en af de kurver med en gennemsnitlig længere behandlingslængde.

Figur 6. Ekstrapolerede TTD-kurver for T-DXd

For capecitabine i kombination med trastuzumab antager ansøger, at behandlingslængden er lig PFS.

Medicinrådets vurdering af ansøgers antagelser vedr. ekstrapoleret forløbsdata
Fagudvalget understreger, at det er usikkert at konkludere på baggrund af de ekstrapolerede forløbsdata for hhv. T-DXd og capecitabine i kombination med trastuzumab. Fagudvalgets overvejelser skal derfor tolkes som værende bedste bud ift. den kliniske plausibilitet af kurverne fremfor at være en definitiv konklusion. På baggrund af dette suppleres resultaterne fra hovedanalysen med følsomhedsanalyser med udvalgte ekstrapoleringsfunktioner, der baserer sig på det bedste statistiske fit i forhold til det observerede forløbsdata.

Fagudvalget vurderer, at det kan være sandsynligt, at risikoen for progression er konstant over tid. Dette er foreneligt med den eksponentielle funktion. Fagudvalget vurderer, at der både er sandsynlighed for, at risikoen for død er konstant eller varierende over tid, f.eks. hvis patienter udvikler resistens over for den aktive behandling. Medicinrådet anvender derfor den samme funktion som ansøger, Weibull, til at ekstrapolere OS-KM-data i hovedanalysen. Vedr. behandlingslængden for T-DXd vurderer fagudvalget, at der sandsynligvis vil være en kort periode efter behandlingsopstart, hvori nogle patienter vil stoppe behandling med T-DXd grundet bivirkninger. Efter denne korte periode skønner fagudvalget, at hazard for behandlingsophør vil være konstant, hvorfor den eksponentielle funktion, som medfører en konstant hazard, anvendes i Medicinrådets hovedanalyse.

Fagudvalget vurderer, at det som udgangspunkt er rimeligt at antage, at behandlingslængden med capecitabine i kombination med trastuzumab er lig PFS. Idet hazard for progression i Medicinrådets hovedanalyse sættes til 1, vil komparatorarmens PFS-kurve dog være afhængig af PFS-kurven for T-DXd i Medicinrådets hovedanalyse. Det betyder, at behandlingslængden for komparator gennemsnitligt vil være ca. [redacted] end behandlingslængden med T-DXd, hvilket muligvis ikke vil afspejle klinisk

praksis. På baggrund af dette har sekretariatet modelleret muligheden for at sætte behandlingslængden for komparator lig behandlingslængden for T-DXd. Sidstnævnte scenarie anvendes i Medicinrådets hovedanalyse.

De gennemsnitlige estimater, der er anvendt i Medicinrådets hovedanalyse, for behandlingsvarighed, tid til progression og tid til død er præsenteret i Tabel 2. De gennemsnitlige estimater for hhv. tid til progression, behandlingsophør og død antages at være ækvivalente mellem de to behandlingsarme.

Tabel 2. Gennemsnitlig tid i behandling, tid til progression og samlet overlevelse

Behandling	Behandlingsvarighed [år]	PFS [år]	OS [år]
T-DXd	[redacted]	[redacted]	[redacted]
Capecitabine + trastuzumab	[redacted]	[redacted]	[redacted]

*Progressionsfri overlevelse (PFS), samlet overlevelse (OS).

Medicinrådet vælger at ekstrapolere OS-KM-data med Weibull-funktionen og PFS- og TTD-KM-data med den eksponentielle funktion. Endvidere udarbejder Medicinrådet følsomhedsanalyser med øvrige udvalgte funktioner. Medicinrådet justerer behandlingslængden for komparator, så denne er ækvivalent med den gennemsnitlige behandlingslængde for T-DXd.

4.1.4 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 30 år og en cykluslængde på en uge. Ansøger har ikke anvendt *half-cycle correction* grundet den korte cykluslængde.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet vælger at ændre tidshorisonten til 15 år, idet de totale inkrementelle omkostninger mellem T-DXd og komparator, jf. den økonomiske model, ikke ændres efter år 15.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv, men ændrer tidshorisonten til 15 år.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af T-DXd sammenlignet med capecitabine i kombination med trastuzumab. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger. Ansøger har ikke inkluderet

omkostninger forbundet med efterfølgende behandling, idet ansøger vurderer, at en anbefaling af T-DXd ikke betydeligt vil påvirke omkostningerne forbundet med behandling i efterfølgende linjer. Endvidere har ansøger ikke inkluderet kommunale omkostninger i analysen.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. Medicinrådets *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP). Doser anvendt i ansøgers analyse er hentet i de respektive lægemidlers produktresuméer (SPC'er):

- T-DXd: 5,4 mg/kg intravenøst hver tredje uge.
- Capecitabine (1.000 mg/m2 pr. dag oralt i 14 dage efterfulgt af en uges pause) i kombination med trastuzumab (opstartsdosering 8 mg/kg, vedligeholdelsesdosering 6 mg/kg) hver tredje uge.

Ansøger anvender den gennemsnitlige relative dosisintensitet (RDI) fra DESTINY-Breast01 på [redacted] til at estimere doserne af T-DXd i analysen. Desuden antager ansøger, at denne RDI på [redacted] kan anvendes som proxy for den RDI for hhv. capecitabine og trastuzumab. Ansøger vurderer, at der intet spild er forbundet med håndtering af lægemidlerne i analysen.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 3.

Tabel 3. Anvendte lægemiddelpriser, SAIP (juni 2021)

Lægemiddel	Styrke	Mg/dosis	Pakningsstørrelse	Pris [DKK]	Kilde
T-DXd	100 mg	5,4 mg/kg	1 stk.	[redacted]	Amgros
Capecitabine	150 mg	1.000 mg/m^2	60 stk.	[redacted]	Amgros
	500 mg		120 stk.	[redacted]	
Trastuzumab	150 mg	8 mg/kg 6 mg/kg	1 stk.	[redacted]	Amgros

*Den forhandlede SAIP pr. september 2021 er betinget af en anbefaling.

Medicinrådet anvender den gennemsnitlige RDI fra DESTINY-Breast01 som bedste estimat for RDI for T-DXd i dansk klinisk praksis. Det pointeres dog af fagudvalget, at den gennemsnitlige RDI fra DESTINY-Breast01 kan være en anelse for høj, når det tages i betragtning, at man i dansk klinisk praksis også vil behandle patienter med performance status 2 med T-DXd. På trods af at fagudvalget ikke kan kvantificere denne RDI yderligere, vælger Medicinrådet at udarbejde en følsomhedsanalyse, hvor den gennemsnitlige RDI [redacted] til [redacted].

Fagudvalget påpeger, at det fra et klinisk perspektiv ikke er logisk at ekstrapolere en RDI fra lægemiddel til lægemiddel, som ansøger har gjort mellem T-DXd og hhv. capecitabine og trastuzumab. Sekretariatet har undersøgt betydningen af at variere RDI for hhv. capecitabine og trastuzumab. Idet disse ændringer ikke vurderes at have stor betydning for analysens resultat, udføres der ikke følsomhedsanalyser vedr. komparatorens RDI.

Fagudvalget vurderer, at der kun vil være et minimalt eller mindre spild med trastuzumab og capecitabine, mens der sandsynligvis vil være et spild med håndteringen af T-DXd. På baggrund af dette inkluderes spildomkostninger forbundet med T-DXd i Medicinrådets hovedanalyse under antagelsen om at pakningerne ikke deles fuldstændigt mellem patienterne. Denne ændring vurderes at have lille betydning for analysens resultater.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger, men vælger at inkludere lægemiddelspild forbundet med håndtering af T-DXd.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger har inkluderet administrationsomkostninger for T-DXd og trastuzumab i form af en DRG-takst, idet disse lægemidler håndteres intravenøst. Ansøger antager, at der ikke er administrationsomkostninger forbundet med administration af capecitabine, idet lægemidlet administreres oralt som tabletter.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet ekskluderer omkostninger forbundet med administration af T-DXd og trastuzumab, idet administrationsomkostningerne for hhv. T-DXd og trastuzumab vil være ækvivalente og dermed uden betydning for de inkrementelle omkostninger, når det antages, at behandlingslængden for capecitabine i kombination med trastuzumab er lig behandlingslængden for T-DXd (jf. afsnit 4.1.3).

Fagudvalget pointerer, at der vil være administrationsomkostninger forbundet med administration af capecitabine, idet lægemidlet udleveres af sundhedspersonale hver tredje uge. På baggrund af at ansøger har anvendt en DRG-takst, der beskriver de gennemsnitlige omkostninger forbundet med hele DRG-gruppen, vurderer Medicinrådet, at det er rimeligt at antage, at administrationsomkostningerne for begge interventioner er indfanget i denne DRG-takst.

Medicinrådet ekskluderer administrationsomkostninger i analysen.

Monitoreringsomkostninger

Ansøger har inkluderet monitoreringsomkostninger forbundet med, at patienterne befinder sig i stadierne progressionsfri og progression, herunder besøg ved onkolog, blodprøve, ECHO/MUGA-scanning (kardiologisk undersøgelse) og CT-scanning. Ansøger antager den samme frekvens for monitoreringsbesøgene, uanset om patienterne er i præ- eller post-progressionsstadiet. Ansøger har anvendt DRG-takster og Medicinrådets *Katalog for værdisætning af enhedsomkostninger*.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Medicinrådet ekskluderer omkostninger forbundet med monitorering, idet monitoreringsomkostningerne for hhv. T-DXd og komparator vil være ens, når der antages en hazard ratio på 1 mellem de to behandlingsarmes overlevelsesdata (jf. afsnit 4.1.1).

Medicinrådet ekskluderer omkostninger forbundet med monitorering.

Bivirkningsomkostninger

For T-DXd har ansøger inkluderet omkostninger forbundet med håndtering af grad 3+ bivirkninger, hvis ≥ 5% af patienterne oplevede disse, eller hvis bivirkningen var blevet defineret som værende af særlig interesse i den kliniske studierapport for DESTINY-Breast01-studiet eller af et klinisk *advisory board*. For capecitabine i kombination med trastuzumab anvender ansøger data fra HER2CLIMB [9], idet ansøger argumenterer, at de observerede bivirkninger i HER2CLIMB-studiet bedst reflekterer dansk klinisk praksis. Ansøger pointerer, at den komplette bivirkningsprofil for komparator ikke er tilgængelig, hvorfor de inkrementelle omkostninger for T-DXd kan være overestimeret i analysen. Ressourcerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på DRG 2021. Ansøger har ikke inkluderet omkostninger forbundet med håndtering af neutropeni og fald i neutrofiltælling, idet ansøger antager, at disse bivirkninger kun er associeret med et ressourceforbrug, hvis patienten oplever feber eller infektion.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Fagudvalget vurderer, at de observerede bivirkningsfrekvenser fra DESTINY-Breast01 og HER2CLIMB formentlig vil afspejle eller afspejler brugen af hhv. T-DXd og capecitabine i kombination med trastuzumab. Fagudvalget påpeger dog, at der sandsynligvis vil være flere patienter i komparatorarmen, der oplever hånd-fod-syndrom i dansk klinisk praksis, sammenlignet med den rapporterede frekvens fra HER2CLIMB-studiet. På baggrund af dette justerer Medicinrådet frekvensen for denne bivirkning til værende 20 % (i ansøgers analyse er frekvensen 9,14 %). Denne ændring vurderes at have minimal betydning for analysens resultat.

Fagudvalget er blevet konsulteret vedr. anvendelsen af de respektive DRG-takster. I den sammenhæng pointerer fagudvalget, at flere af taksterne sandsynligvis kan være overestimerede kontra det reelle ressourceforbrug i dansk klinisk praksis. Derfor har sekretariatet så vidt muligt opdateret DRG-taksterne på baggrund af relevante diagnose- og procedurekoder, jf. Interaktiv DRG.

Medicinrådet ekskluderer omkostningerne forbundet med de bivirkninger, der er defineret som værende af særlig interesse (< 5 %). Det skyldes, at de anvendte DRG-takster er behæftet med usikkerhed, og at denne gruppe af bivirkningsomkostninger vurderes at have lille betydning for analysens inkrementelle resultater.

Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 4.

Tabel 4. Rapporterede bivirkningsfrekvenser ved behandling med T-DXd og capecitabine i kombination med trastuzumab samt enhedsomkostninger for bivirkningerne

	T-DXd [%]	Capecitabine + trastuzumab [%]	DRG-kode	Takst
Fald i neutrofiltal	20,65	0,00	-	-
Anæmi	15,22	0,00	36.865	09MA08
Neutropeni	20,11	0,00	-	-
Kvalme	8,70	0,00	1.735	09MA98
Fatigue	8,15	0,00	1.735	09MA98
Fald i hvid-blodcelletælling	5,98	0,00	36.865	09MA08
Diarré	0,00	8,63	1.735	09MA98
Hånd-fod-syndrom	0,00	20	1.735	09MA98

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men vælger at ekskludere omkostningerne forbundet med bivirkninger af særlig interesse.

Terminale omkostninger

Ansøger har inkluderet terminale omkostninger baseret på et estimat fra et britisk studie, hvori de terminale omkostninger forbundet med patienter med bl.a. brystkræft blev estimeret i 2015 [11]. Ansøger har omregnet omkostningerne til DKK og fremskrevet disse til 2021.

Medicinrådets vurdering af ansøgers antagelser vedr. terminale omkostninger

Medicinrådet ekskluderer terminale omkostninger, idet de terminale omkostninger forbundet med anvendelse af T-DXd og komparator vil være ens, når der antages en hazard ratio på 1 (jf. afsnit 4.1.1) mellem de to behandlingsarmes overlevelsesdata.

Medicinrådet ekskluderer terminale omkostninger.

4.2.3 DPD-analyse

Fagudvalget har gjort Medicinrådet opmærksom på, at patienterne skal undersøges for mangel på enzymet dihydropyrimidin dehydrogenase (DPD) forud for behandling med capecitabine. Ansøger har ikke inkluderet omkostninger forbundet med denne DPD-analyse i sin analyse. I dansk klinisk praksis testes alle patienter både med en fænotype- og genotypetest, hvor fagudvalgets estimerer, at prisen er hhv. ca. 250 DKK og ca. 1.000 DKK.

Medicinrådet inkluderer en engangsomkostning pr. patient for en samlet DPD-analyse (fænotype- og genotypetest) svarende til 1.250 DKK. Denne ændring vurderes at have minimal betydning for analysens resultater.

4.2.4 Patientomkostninger

Patientomkostningerne er estimeret på baggrund af besøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 3,44 DKK/km, jf. Medicinrådets *Værdisætning af enhedsomkostninger.* Ansøger antager, at patienterne vil have et besøg på hospitalet, hvis de oplever bivirkninger.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet ekskluderer patientomkostninger forbundet med monitorering og administration af T-DXd og komparator, idet disse patientomkostninger vil være ens, når der antages en hazard ratio på 1 (jf. afsnit 4.1.1) mellem de to behandlingsarmes overlevelsesdata. Idet bivirkningsprofilerne af de to interventioner ikke vurderes at være ækvivalente, vil analysens resultater afspejle en mindre forskel i patientomkostninger mellem T-DXd og capecitabine i kombination med trastuzumab, forbundet med besøg på hospitalet forbindelse med bivirkningshåndtering. Denne omkostning vurderes dog at være så minimal, at Medicinrådet ekskluderer alle patientomkostninger i analysen.

Medicinrådet ekskluderer patientomkostninger forbundet med administration, monitorering og bivirkninger af T-DXd og komparator.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere forskellige parameterinputs samt strukturelle og metodiske antagelser.

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges, se Tabel 5.

Tabel 5. Ansøgers følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Diskonteringsrente	Ændres til 0 % og 6 %
Tidshorisont	Ændres til 5, 10 og 20 år
Ekstrapolering af OS-KM-data for T-DXd	Anvendelse af den log-normale funktion
Ekstrapolering af PFS-KM-data for T-DXd	Anvendelse af den eksponentielle funktion

Følsomhedsanalyse	Beskrivelse
Ujusterede hazard ratios for PFS og OS	Anvendelse af de ujusterede hazard ratios mellem T-DXd og komparator fra MAIC-analysen
Kemoterapi	Docetaxel anvendes som kemoterapi i komparatorarm
Spild	Inkluderer 50 % spild

Ansøger har derudover udført en række følsomhedsanalyser, hvor parameterinputs blev varieret med prædefinerede øvre og nedre grænser. Parametrene, som ansøger undersøgte, var bl.a. RDI for interventionerne og ressourceforbruget forbundet med administration og monitorering.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser af tidshorisont, anvendelse af ujusterede hazard ratios og de øvrige følsomhedsanalyser, hvor parametre blev varieret med prædefinerede øvre og nedre grænser. Endvidere præsenterer Medicinrådet ikke følsomhedsanalysen, hvor docetaxel anvendes som kemoterapi-komparator, idet fagudvalget vurderer, at paclitaxel primært anvendes som taxanbaseret kemoterapi i dansk klinisk praksis.

Medicinrådet udarbejder en følsomhedsanalyse, hvor RDI for T-DXd varieres til [redacted], og en følsomhedsanalyse hvor det antages, at der ikke vil være nogen deling af pakninger med T-DXd. Ligeledes præsenteres en scenarioanalyse, hvor funktionen, der anvendes til at ekstrapolere observeret KM-data for PFS og TTD, er blevet valgt på baggrund af statistisk fit. Medicinrådet udfører denne scenarioanalyse, idet fagudvalget har understreget, at det er usikkert at udtale sig eksakt om de forventede forløb af kurverne for forløbsdata mht. klinisk plausibilitet. Medicinrådet præsenterer desuden en scenarioanalyse, hvor effektforskellen mellem T-DXd og komparator modelleres ved brug af MAIC-analysen, og følsomhederanalyser hvor funktionen til ekstrapolering af TTD-data justeres separat.

Medicinrådet vælger at præsentere udvalgte af ansøgers følsomhedsanalyser.

4.4 Opsummering af basisantagelser

I Tabel 6 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 6. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	30 år	15 år
Diskonteringsrente	3,5 %	3,5 %

Basisantagelser	Ansøger	Medicinrådet
Inkluderede omkostninger	Lægemiddelomkostninger Administrationsomkostninger Monitoreringsomkostninger Bivirkningsomkostninger Terminale omkostninger Patientomkostninger	Lægemiddelomkostninger Bivirkningsomkostninger DPD-analyse
Behandlingslinje	3. linje	3. linje eller derefter
Patientkarakteristika		
Alder	56 år	59 år
Vægt	62,47 kg	70 kg
Højde	160 cm	166,6 cm
Køn (% kvinder)	100 %	99 %
Hazard ratios mellem T-DXd og capecitabine + trastuzumab		
PFS:	0,29	1
OS	0,16	1
Parametriske funktioner for TTD	Log-normal	Eksponentiel
Gennemsnitlig behandlingslængde		
T-DXd:	[redacted]	[redacted]
Capecitabine + trastuzumab:	[redacted]	[redacted]
Parametriske funktioner for PFS	Log-normal	Eksponentiel
Gennemsnitlig tid til progression		
T-DXd	[redacted]	[redacted]
Capecitabine + trastuzumab:	[redacted]	[redacted]
Parametriske funktioner for OS	Weibull	Weibull
Gennemsnitlig tid til død		
T-DXd:	[redacted]	[redacted]
Capecitabine + trastuzumab:	[redacted]	[redacted]

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 6.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 791.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 7.

Tabel 7. Resultatet af Medicinrådets hovedanalyse ved sammenligning med capecitabine i kombination med trastuzumab, DKK, diskonterede tal

	T-DXd	Capecitabine + trastuzumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Bivirkningsomkostninger	8.106	620	7.486
DPD-analyse	0	1.250	- 1.250
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 8.

Tabel 8. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
MAIC-analyse anvendes til at estimere effektforskel mellem T-DXd og komparator ved brug af justerede HR	[redacted]
Funktion til ekstrapolering af PFS og TTD Log-normal	[redacted]
Spild: 0 % deling af T-DXd-pakninger	[redacted]
RDI: [redacted]	[redacted]

Scenarie	Inkrementelle omkostninger
Funktion til ekstrapolering af TTD-data (behandlinglængde)	
- Weibull	[redacted]
- Gompertz	[redacted]
- Generaliseret gamma	[redacted]
- Log-logistisk	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at T-DXd vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- T-DXd bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- T-DXd bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Estimat af patientantal og markedsandel

I Medicinrådets protokol vedr. T-DXd fremgår det, at ca. 730 patienter årligt diagnosticeres med HER2+ brystkræft. Ansøger pointerer, at patientantallet sandsynligvis er overestimeret, hvis data fra DBCG tages i betragtning, hvor 13,9 % af patienterne i databasen blev registreret som havende HER2+ brystkræft i 2019 [12]. På baggrund af dette vurderer ansøger, at antallet af patienter, der diagnosticeres med HER+ brystkræft, ca. er 680 patienter årligt. Endvidere antager ansøger, at ca. 102 patienter med HER+-brystkræft vil være kandidater til at modtage tredjelinjebehandling om året. Ud af disse patienter vurderer ansøger, at det kun er [redacted], som kandiderer til behandling med T-DXd, idet patienter med tidligere lungesygdomme, hjernemetastaser og dårlig almentilstand ikke vil være tilstrækkeligt stabile til at modtage behandlingen.

Ansøger antager dermed at der vil være ca. [redacted] patienter om året, der ved anbefaling vil være kandidater til behandling med T-DXd.

Hvis T-DXd anbefales af Medicinrådet, antager ansøger, at markedsoptaget vil være 80 % i år 1-2, 85 % i år 3-4 og 90 % i år 5.

Ansøger har jf. protokollen udarbejdet en budgetkonsekvens-følsomhedsanalyse, hvori det antages, at 20 % af patienterne vil modtage taxanbaseret kemoterapi i kombination med trastuzumab, og 80 % vil modtage capecitabine i kombination med trastuzumab.

Ansøger har i følsomhedsanalysen anvendt docetaxel som den taxanbaserede kemoterapi.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis T-DXd anbefales som mulig standardbehandling, og hvis ikke T-DXd anbefales.

Fagudvalget er umiddelbart enig med ansøger i, at det ikke er alle patienter, der kandiderer til tredjelinjebehandling, som også kandiderer til behandling med T-DXd grundet bl.a. lungesygdom, dårlig performance status og symptomer af fjernmetastaser. Omvendt vurderer fagudvalget, at ansøgers estimat på [redacted] er for [redacted]. Fagudvalget estimerer, at ca. 80-85 % af de patienter, som kandiderer til tredjelinjebehandling eller efterfølgende linjer, vil kandidere til behandling med T-DXd. Fagudvalget understreger, at der er usikkerheder forbundet med at definere patientantallet, der kandiderer til behandling med T-DXd, idet lægemidlet på baggrund af data ikke kan begrænses til tredjelinjebehandling. Fagudvalget estimerer, at ca. 82 patienter årligt forventes at være kandidater til behandling med T-DXd til den pågældende indikation.

Fagudvalget estimerer, at markedsoptaget af T-DXd – hvis lægemidlet bliver anbefalet – vil være 90 % i år 1, 85 % i år 2-3 og 80 % i år 4-5. Patienttallene, som anvendes i Medicinrådets hovedanalyse, fremgår af Tabel 9.

Tabel 9. Medicinrådets estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
T-DXd	74	70	70	66	66
Capecitabine + trastuzumab	8	12	12	16	16
			Anbefales ikke		
T-DXd	0	0	0	0	0
Capecitabine + trastuzumab	82	82	82	82	82

Vedr. budgetkonsekvens-følsomhedsanalysen påpeger fagudvalget, at paclitaxel anvendes i dansk klinisk praksis, hvorfor paclitaxel anvendes som taxanbaseret kemoterapi i følsomhedsanalysen fremfor docetaxel.

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor andelen af patienter, der kandiderer til behandling med T-DXd (ud af den samlede population, som kandiderer til 3. linjebehandling), er 80 %. Desuden justerer Medicinrådet markedsoptaget for T-DXd ved en anbefaling, så markedsoptaget er højt kort efter anbefalingen, hvorefter det falder og opnår steady state efter nogle år.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- Andelen af patienter, der kandiderer til tredjelinjebehandling med T-DXd, er 80 % ud af den samlede population, som kandiderer til tredjelinjebehandling.
- Markedsoptaget ændres til 90 % i år 1, 85 % i år 2-3 og 80 % i år 4-5.
- I budgetkonsekvens-følsomhedsanalysen udskiftes docetaxel med paclitaxel.

Medicinrådet estimerer, at anvendelse af T-DXd vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 10.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 53 mio. DKK i år 5.

Tabel 10. Medicinrådets analyse af totale budgetkonsekvenser, [redacted] DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1 Resultat af følsomhedsanalyser for budgetkonsekvensanalysen

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men med ændret fordeling af komparator, hvor patienterne modtager enten capecitabine eller paclitaxel (begge kemoterapier i kombination med trastuzumab) fordelt på hhv. 80 % og 20 %, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 11.

Tabel 11. Medicinrådets analyse af totale budgetkonsekvenser, hvor både capecitabine og paclitaxel (begge kemoterapier i kombination med trastuzumab) anvendes som komparator, [redacted] DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

Behandling med T-DXd er forbundet med inkrementelle omkostninger på ca. [redacted] DKK pr. patient sammenlignet med behandling med capecitabine i kombination med trastuzumab. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for T-DXd.

Medicinrådet vurderer, at det foreliggende kliniske datagrundlag ikke er tilstrækkeligt til at dokumentere en effektforskel mellem T-DXd og capecitabine i kombination med trastuzumab. Derfor er der i Medicinrådets hovedanalyse antaget hazard ratios på 1 mellem T-DXd og komparator vedr. PFS og OS. Fagudvalget kan på baggrund af den narrative sammenligning (jf. vurderingsrapporten) ikke kvantificere den potentielle effektforskel, der muligvis måtte være mellem T-DXd og capecitabine i kombination med trastuzumab. På samme vis som for PFS og OS antager Medicinrådet i sin hovedanalyse, at behandlingslængden (TTD) for hhv. T-DXd og komparator er ens. Når MAIC-analysen anvendes til at dokumentere en effektforskel mellem T-DXd og komparator, [redacted] de inkrementelle omkostninger med ca. [redacted] DKK.

Fagudvalget vurderer, at patientkarakteristikaene fra DESTINY-Breast01-studiet afviger fra den danske population. Med fagudvalgets antagelser for patientkarakteristikaene, herunder vægt og højde, [redacted] de inkrementelle omkostninger isoleret med ca. [redacted] DKK. Hvis der antages ikke at være nogen deling mellem T-DXd-pakningerne, [redacted] de inkrementelle omkostninger isoleret med ca. [redacted] DKK.

I Medicinrådets hovedanalyse blev valget af funktion til ekstrapolering af PFS og TTD baseret på fagudvalgets bedste bud på baggrund af klinisk plausibilitet af kurvernes forløb. Fagudvalget understreger, at disse antagelser er usikre, hvorfor Medicinrådet har udarbejdet følsomhedsanalyser med de funktioner, som har det bedste statistiske fit på det observerede data. Når PFS- og TTD-kurven samtidig ekstrapoleres med den log-normale funktion fremfor den eksponentielle funktion, [redacted] de inkrementelle omkostninger isoleret med [redacted] DKK. I både ansøgers og Medicinrådets hovedanalyse blev OS-KM-data ekstrapoleret med Weibull-funktionen, der havde det bedste statistiske fit på det observerede forløbsdata, hvorfor der ikke er blevet udarbejdet følsomhedsanalyser for OS-data.

I analysen estimeres omkostningerne på baggrund af PFS-, OS- og TTD-kurverne for det ekstrapolerede forløbsdata. I og med at der i Medicinrådets hovedanalyse ikke antages at være forskel i effekt mellem T-DXd og komparator, vil kurvernes forløb for de to interventioner være identiske. Idet det i analysen samtidig antages, at frekvenserne af ressourceforbruget er identiske mellem de to behandlingsarme, vil omkostningerne forbundet med administration, monitorering, terminal pleje og patienternes effektive tid derfor overordnet også være ækvivalente. Disse omkostningsgrupper er derfor ekskluderet i Medicinrådets hovedanalyse. Det betyder ikke, at der i dansk klinisk praksis ikke vil kunne observeres forskelle i f.eks. hospitalsomkostninger mellem T-DXd og capecitabine i kombination med trastuzumab, som vil kunne opfanges ved brug af en *micro-costing*-tilgang til estimering af ressourceforbruget.

Analysen er behæftet med stor usikkerhed, hvorfor fortolkningen af analysens resultater skal ske med forsigtighed.

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	27. oktober 2021	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 30 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 12.

Tabel 12. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	T-DXd	Capecitabine + trastuzumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administrationsomkostninger	40.366	14.377	25.989
Monitoreringsomkostninger	76.566	37.859	38.707
Bivirkningsomkostninger	10.500	1.963	8.537
Terminale omkostninger	59.690	62.510	-2.820
Patientomkostninger	20.078	9.940	10.137
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af T-DXd vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 13.

Tabel 13. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	29.09.2021
Leverandør	Daiichi-Sankyo i samarbejde med AstraZeneca
Lægemiddel	Trastuzumab deruxtecan, T-DXd (Enhertu)
Ansøgt indikation	Til behandling af metastatisk HER2+ brystkræft efter progression på to HER2-rettede behandlinger

Forhandlingsresultat

Amgros har forhandlet følgende pris på T-DXd. Prisen er betinget af, at Medicinrådet anbefaler T-DXd.

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
T-DXd	100 mg	Pulver til konc.	12.234	[redacted]	[redacted]	[redacted]

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi på nuværende tidspunkt har opnået den bedst mulige pris. Denne vurdering baserer vi på følgende punkter:

- Leverandøren mener, at denne behandling opfylder et uopfyldt medicinsk behov som 3. linje behandling, og lægger vægt på, at det er det første lægemiddel, der har fået EMA godkendelse til denne patientpopulation.
- [redacted]

[redacted]

Konklusion

[redacted]

Relation til markedet

Der er i dag ingen 3. linje behandling til disse patienter, derfor sammenlignes T-DXd med den nuværende 2. linje behandling:

Lægemiddel	Dosis*	Frekvens	SAIP (DKK) pr. behandling	Antal behandlinger (51 uger)	Samlet pris SAIP (DKK)
Enhertu (Trastuzumab deruxtecan)	5,4 mg/mg 3,78 pakning pr beh.	IV Hver 3 uge	[redacted]	[redacted]	[redacted]
Kadcyla (Transtuzumab emtansin)	3,6 mg/kg 1,58 pakning pr beh.	IV Hver 3 uge	[redacted]	[redacted]	[redacted]

*Vægt 70 kg
** Kadcyla gives maksimalt 14 gange

Andre lande:

Norge og Sverige er under evaluering[1].

UK har givet en "betinget anbefaling" 26.5.2021, se citat: ***"More evidence on trastuzumab deruxtecan is being collected, until there is sufficient data to address the uncertainties. After this NICE will decide whether or not to recommend it for use on the NHS and update the guidance. It will be available through the Cancer Drugs Fund until then"***[2]

[1] Enhertu (trastuzumab deruxtekan) vid HER-2-positiv bröstcancer (janusinfo.se)
Trastuzumab derukstekan (Enhertu) (nyemetoder.no)
[2] Overview | Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies | Guidance | NICE

Daiichi-Sankyo | AstraZeneca

Att: Danish Medicine Council

We hereby include our comments based on the draft added-benefit evaluation of Enhertu (T-DXd) received August 27th 2021.

AstraZeneca and Daiichi-Sankyo look forward to receiving your feedback.

1 Summary

AstraZeneca and Daiichi-Sankyo (the company) are thankful for the Danish Medicines Council's (DMC) assessment of trastuzumab deruxtecan (T-DXd, Enhertu) and appreciate the opportunity to comment on the added-benefit evaluation.

As stated in the submission, we acknowledge that the comparative effectiveness estimates are surrounded with some uncertainty due to single arm study design of DESTINY- Breast01 (DB01) (1). While it is difficult to estimate an exact treatment effect due to the lack of comparator arm, the uncertainty in the results versus current clinical practice is overstated.

Leading Danish clinical expert ([redacted]) have confirmed that the data from DB01 are unprecedented. The additional follow-up data from DESTINY-Breast01 further confirms our conclusion and means that it is highly unlikely that T-DXd do not meet the threshold for added value. This given the more than:

- [redacted] months longer median OS than in Danish clinical practice ([redacted] vs 18.5)
- 3 times longer median PFS than in Danish clinical practice (19.4 vs 5.5)
- doubling response rates versus Danish clinical practice (61.4 vs 10-25%)

The naïve and covariate adjusted hazard ratios used as indirect comparisons versus the similar randomized controlled trials (RCTs) in the published literature are all pointing in a same direction and show individually and combined considerable and significant treatment effects above the DMC threshold for minimum clinically relevant difference even when adjusting for between-study differences. This was seen both before and after the matching of covariates.

[redacted]

Trial data and Danish clinical expert feedback has suggested that the unprecedented results observed for T-DXd are unlikely to be due to patient selection.

The company would like to continue to work with the DMC/Amgros to reduce the uncertainty in their decision problem. This to ensure that Danish breast cancer patients with an high unmet need get access to this innovative treatment in an economically sustainable way.

In the next sections we provide more detailed statements around the data limitations presented by DMC. [redacted]

2 General comments

2.1 Treatment effect

While the company acknowledge that the comparative effectiveness estimates are surrounded with some uncertainty due to single arm study design of DB01, we believe that this uncertainty is overestimated by DMC and that the company's view have regulatory, statistical, real-world data and clinical expert support:

Summary of regulatory/authority support of the data

Due to the strong efficacy outcomes, and patient unmet medical need, where no official standard of care exists after 2L mBC, T-DXd has received regulatory approval based on data from DESTINY-Breast01 by all authorities that has assessed the drug:

- The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on the 10th December 2020, and a conditional marketing authorization was granted by the European Commission on 18th January 2021 (7). **European Commission stated that T-DXd offer clinically meaningful benefits compared with the current standard of care (7).**
- The Medicines and Healthcare products Regulatory Agency (MHRA) granted a conditional marketing authorization for T-DXd on 12th February 2021 (9).
- T-DXd has been approved in the United States (US) and in Japan, where it was assessed under the US Food and Drug Administration's (FDA) Breakthrough Therapy and Priority Review programme and Japan's conditional early approval system (10, 11).

Further, NICE have recently recommended T-DXd for advanced HER2-positive breast cancer through cancer drugs fund as it was assessed to be cost-effective (12).

Summary of statistical support of the data

Indirect treatment comparisons are the only way to generate comparative effectiveness data in order to answer the decision problem stated by DMC.

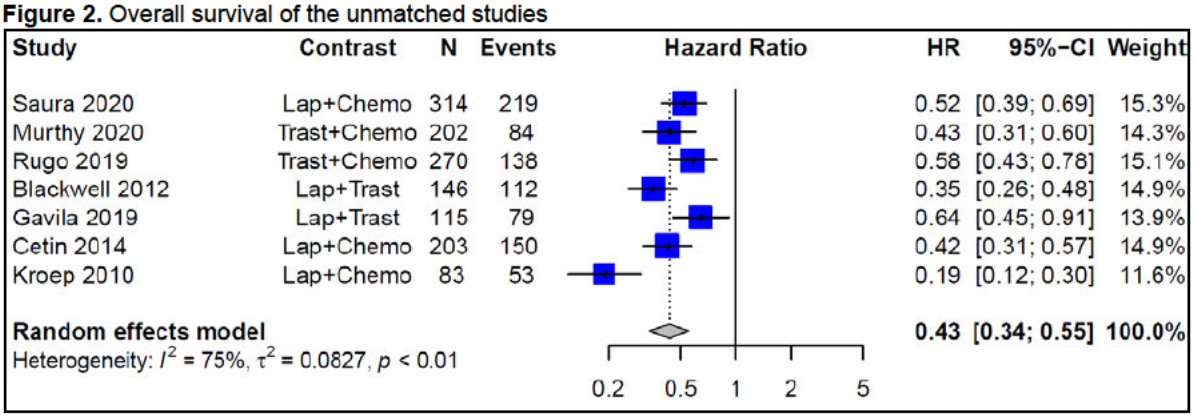
The naïve and covariate adjusted hazard ratios used as indirect comparisons versus the similar randomized controlled trials (RCTs) in the published literature are all pointing in a same direction and show individually and combined considerable and significant treatment effects. The effective sample size is relatively small in some of the covariate-adjusted comparisons but there are more than 275 patients in the effective sample for matched T-DXd arm in the meta-analysis, which show a clear and consistent reduction in the risk of death. Hence, there is a considerable treatment effect above the DMC threshold for minimum clinically relevant difference even when adjusting for between-study differences.

Figure 1 presents the hazard ratio in overall survival when all of the performed covariate-adjusted indirect comparisons are meta-analysed.

[redacted]

Figure 2 present the results of the meta-analysis, before the matching. As shown in the figure, while the matching had an expected effect on the hazard ratios in each of the individual trials, it had a minor effect on the overall HR (0.43→0.40), which indicate that the treatment effect is stable regardless if between study differences are considered or not.

Figure 2. Overall survival of the unmatched studies



Key: ESS: Effective sample size, HR: Hazard ratio, CI: Confidence interval

A new data cut with [redacted] additional months of follow-up also showed that the median OS [redacted] which means that T-DXd further distanced itself from treatments used in current clinical practice. Both the new and old data cut show that even the median PFS of T-DXd (19.4 months) is longer than mOS reported for most comparator therapies (2-4, 6).

Randomized phase III data from DESTINYBreast02 is currently not expected to be available before [redacted]

Summary of real-world evidence support

The results from the indirect comparisons of RCTs are furthermore confirmed by a recently conducted real-world study, which showed similar results:

Table 1. Summary of the reported patient characteristics in relevant studies

	Danish clinical practice, DBCG data (13)	DESTINY-Breast01 (1, 6)	NALA (2)	SOPHIA (3)	HER2CLIMB (4)
Intervention of interest	[redacted]	Trastuzumab deruxtecan	Lapatinib + capecitabine	Trastuzumab + chemotherapy	Trastuzumab + capecitabine
Study design	[redacted]	Single-armed multicentre study	RCT multicentre study	RCT multicentre study	RCT multicentre study
Phase	[redacted]	Phase II	Phase III	Phase III	Phase II
Patients number, n	[redacted]	184	314	270	160/202
Median age (range)	[redacted]	55 (28-96)	54	56 (27-86)	54
Median prior lines (range)	[redacted]	6 (2-27)	2	-	3 (1–13)
Prior lines ≥3		90.8	31.5	33.0	-
Prior T-DM1 (%)	[redacted]	100	~54.3	91.5	100
Prior pertuzumab in the metastatic setting (%)	[redacted]	65.8	NR	99.6	99.4
HR+ (%)	[redacted]	52.7	59.2	63.0	44.4
Metastatic sites					
bone (%)	[redacted]	28.8	47.1	57.4	53.1
lung (%)	[redacted]	57.1	55.4	46.7	51.2
liver (%)	[redacted]	30.4	47.1	35.2	40.0
CNS (%)	[redacted]	13.0	15.9	12.6	44.4
Visceral (%)		91.8	86.0		
Top line results					
PFS, month (95%, CI)	[redacted]	19.4 (14.1 – [redacted])	5.5 (4.3 – 5.6)	4.4 (4.1 – 5.5)	5.6 (4.2 – 7.1)
OS, month (95%, CI)	[redacted]	24.6 (23.1 – [redacted])	18.7 (15.5 – 21.2)	19.8 (17.5 – 22.3)	17.4 (13.6 – 19.9)

Key: CI: confidence interval, N/A: not applicable, NE: not estimable, PFS: progression-free survival, OS: Overall survival.*Mean.**New data cut.

We ran the covariate-adjusted indirect comparisons that was outlined in the submission also on the Danish RWE. The DESTINY-Breast01 and the Danish RWE had a relatively large overlap with an effective sample size of 85 patients. The covariate adjusted indirect comparison predicted an HR for OS of 0.33 and a HR for PFS of 0.22 versus current standard of care.

Clinical expert support

Median OS in the June 2020 data cut of DESTINY-BREAST01 was 24.6 months (95% CI: 23.1, not evaluable) (6) [redacted] Danish clinical expert opinions provided to the company confirmed that this results are unprecedented in this setting and highlighted the unmet need with current treatments. Further, nine Nordic (two Danish) leading clinical experts

confirmed that the modelled survival of the comparators was reflective of the survival in their clinical practice.

2.2 Generalizability of DB01 versus comparator studies

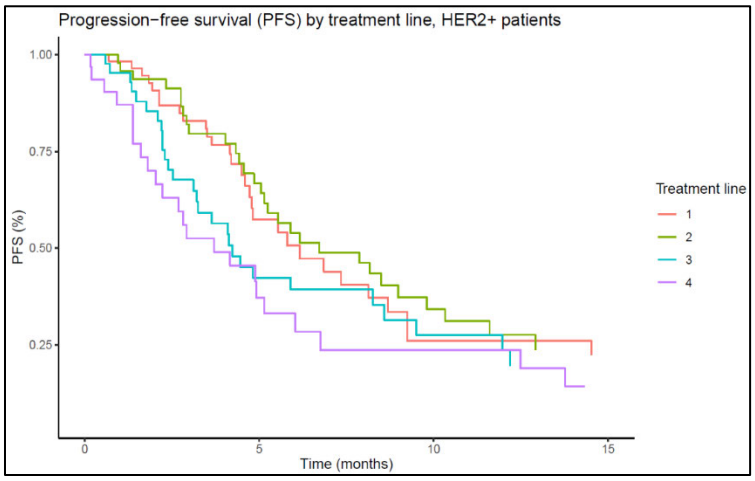
There are no evidence showing that the patients in DB01 are significantly more fit than patients in recent studies of treatments currently used in 3L+ clinical practice (see the NALA, SOPHIA and DBCG study).

- The patient population in DB01 is more pre-treated than other populations included in the submission. Subgroup analyses show that patients with less prior treatment line had longer progression-free survival in DB01.

Figure 3. Progression free survival depending on number of prior lines

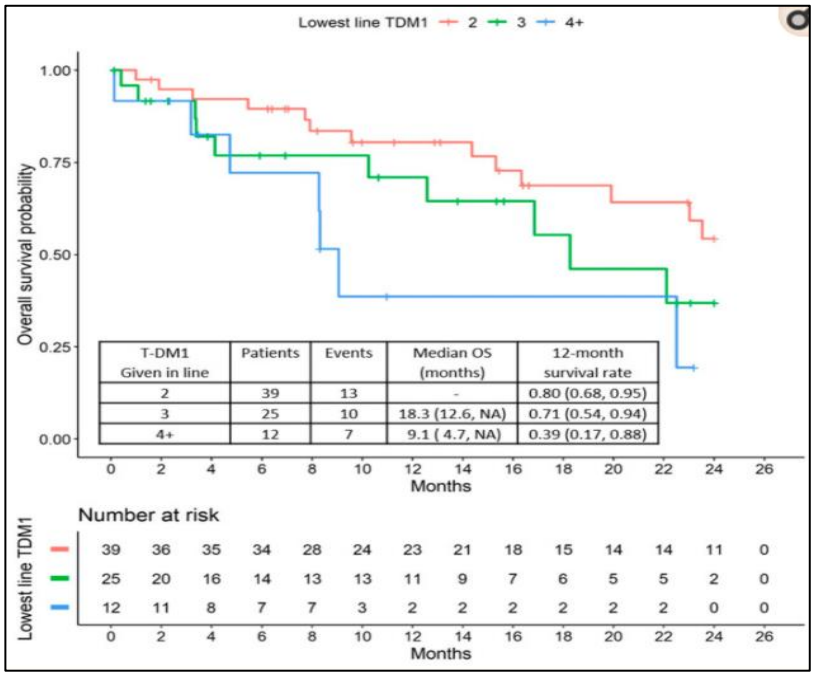
- Data from DB01 shows that outcomes in patients who had received exactly two prior lines of therapy was improved compared with those who had received more prior lines:
    - Overall response rate was higher in this subgroup of DB01 (76%; 95% confidence interval: 50% to 93%) compared with those with greater than two prior therapies (59%; 95% confidence interval: 51% to 67%).
    - You can also argue that the response rate, which is less correlated with the expected survival in the population, is unprecedented and indicate that they get a benefit from the treatment and not patient selection.
- Danish clinical opinion provided to the company has confirmed that prognosis worsens with each subsequent line of therapy (with the possible exception of very late lines of therapy).
- This is consistent with data from 63 patients treated in Uppsala, Sweden (Figure 4).

Figure 4. Progression free survival depending on number of prior lines



- This is also consistent with the findings of Michel et al, who report OS by lowest line of trastuzumab emtansine (T-DM1) use and observe later therapy lines appeared to have a poorer prognosis than patients with T-DM1 treatment in earlier therapy lines (Figure 5) (14).

Figure 5: OS relative to T-DM1 treatment line, reproduced from Michel et al (14)



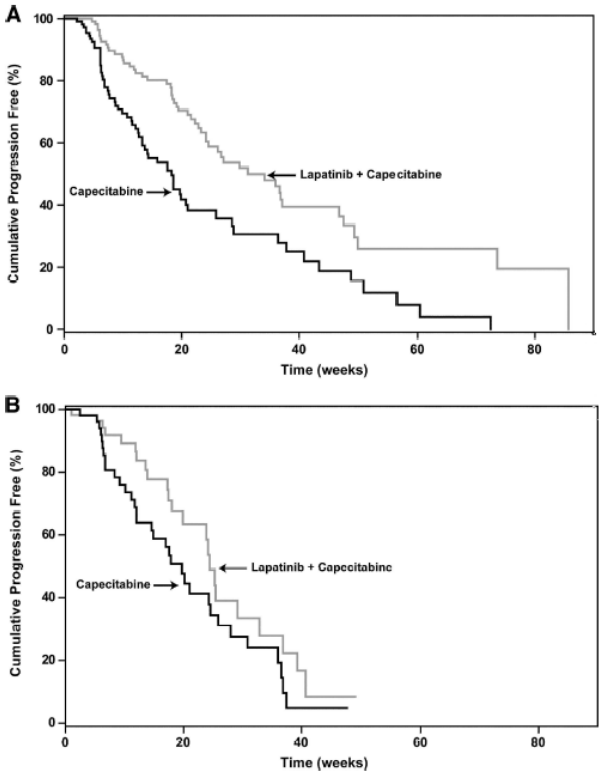
Abbreviations: OS, overall survival; T-DM1, trastuzumab emtansine.

- This is also consistent with results presented by Cameron et al (15), in which time to progression (TTP) at earlier lines of HER2-targeted therapy appears to be longer than at later lines of therapy in a HER2-positive metastatic breast cancer population treated with capecitabine or lapatinib + capecitabine(Figure 6)
    - Median TTP was improved in the group of lapatinib + capecitabine patients who had received one prior metastatic trastuzumab-based regimen vs. those that had received more than one (31.3 weeks vs. 24.4 weeks); median TTP in the capecitabine arm was similar between the two groups (18.6 weeks vs. 19.7 weeks).

- Only 9.2% of patients had received exactly two prior lines of therapy in DB01 (the population expected to receive T-DXd in clinical practice).

    - Since outcomes are expected to be worse at fourth and later lines, the results of DB01 represent a conservative estimate of efficacy for patients at third line.

Figure 6: Reproduced from Cameron et al, 2010.



KM estimates of TTP in patients receiving: one prior metastatic trastuzumab-based regimen (A) or more than one prior metastatic trastuzumab-based regimen (B)

Clinical expert feedback has suggested that the unprecedented results observed for T-DXd are unlikely to be due to patient selection. In patients enrolled in DESTINY-Breast01, complete or partial response was experienced in 21.7% of patients when exposed to T-DM1 (16). In the DB01 trial the numbers were 6.0% (complete) and 54.9% (partial), respectively, post T-DM1 exposure.

3 Detailed comments

We have below listed our comments to specific subjects in the document from DMC

Subject	Company comment
Added-value report	
On page 7, it is reported that T-DXd is not approved in other indications.	FDA approved T-DXd for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen. **ACTION: Please clarify that it is not approved by EMA in other indications.**
On page 10, an average OS of 22 months for Danish patients is reported.	The company have provided DMC with Danish RWE data directly from DBCG that show that the survival in the relevant population is 18.5 month. The 18.5 month is in line with relevant and recent studies that show that the OS is between 18 and 20 months. Scientific evidence is hence supporting OS below 20 months for Danish patient **ACTION: We believe this should be changed or removed.**
On page 14, CNS (%) is reported as 13%.	According to an updated report from DBCG, this number should be [redacted] when the number of patients screened are taken into consideration. **ACTION: We would appreciate if this number is updated.**
On page 15, Fagudvalget state that there is some uncertainty with a comparison between DB01 and HER2CLIMB as patients with brain metastases often receive dose reductions.	We agree with the assessment of AEs by DMC. In addition to possible dose reductions in patients with brain metastases, it should also be noted that the patients in the control arm of the HER2CLIMB study are treated much shorter than the patients in DB01, which likely should lead to lower AE rates.
DMC comment that most of the patients in Destiny have not received pertuzumab in 1 L	It should be noted that prior pertuzumab use was associated with better outcomes in DB01. Hence, based on that, even better outcomes could be expected if more patients where treated with pertuzumab before T-DXd.
On page 16, the maturity of the data was 35%/38% with the 20.5 m follow-up for OS/PFS.	The company have provided DMC with updated data that showed an improved and almost fully mature median OS/PFS. **ACTION:** This sentence is hence not relevant anymore and should hence be removed or updated with the new numbers.
Page 18, the median OS for T-DXd is reported as 24.6.	New data was provided to DMC during the assessment that will be presented as ESMO 18 of September. **ACTION:** We would appreciate if a note is added to the table outlining that the median OS is [redacted].

On page 25, it is stated that “median follow-up er ikke opgjort for DBCG-data”.	This was not requested by DMC, but can most likely be supplied when published by DBCG
Cost-analysis report	
The company accept all changes done by DMC. The suggested mark-up of confidential data is appropriate.	

We hope DMC will include our comments/feedback in the added-benefit assessment and also for the final evaluation of Enhertu.

Kind Regards

Søren Clausen and Mattias Aronsson — AstraZeneca

Katja Lundberg Rand — Daiichi-Sankyo

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Medicinrådet

Medicinrådets vurdering vedrørende trastuzumab deruxtecan til behandling af metastatisk HER2+ brystkræft efter progression på to HER2-rettede behandlinger

Version 1.1

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	1. september 2021
Dokumentnummer	121925
Versionsnummer	1.1

Indholdsfortegnelse

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 1. september 2021

1. Medicinrådets konklusion

Medicinrådet vurderer, at værdien af T-DXd sammenlignet med trastuzumab + capecitabin til patienter med metastatisk her2+ brystkræft efter progression på to HER2-rettede behandlinger, ikke kan kategoriseres efter Medicinrådets metoder. Datagrundlaget er et igangværende todelt, ublindet, enkeltarms fase II studie, som er sammenlignet med trastuzumab + capecitabin, trastuzumab + kemoterapi eller capecitabin + lapatinib. Der er lavet en kvalitativ sammenligning af de inkluderede studier, men forskelle på baselinekarakteristika mellem studierne har gjort vurderingen svær, og datagrundlaget meget usikkert.

På baggrund af den kvalitative sammenligning af T-DXd og komparator, finder Medicinrådet, at den samlede værdi af T-DXd sammenlignet med trastuzumab + capecitabin ikke kan kategoriseres. Rådet vurderer dog, at T-DXd samlet set ikke har dårligere effekt eller sikkerhedsprofil end trastuzumab + capecitabin.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (f.eks. på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET), I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

CI:	Konfidensinterval
DBCG:	*Danish Breast Cancer Group*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
ER:	*Estrogen receptor* (østrogen receptor)
EUnetHTA:	*European Network for Health Technology Assessment*
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HER2:	Human epidermal vækstfaktorreceptor 2
HR:	*Hazard ratio*
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
ISH:	In situ-hybridisering
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention-to-treat*
MKRF:	Mindste klinisk relevante forskel
NICE:	*The National Institute for Health and Care Excellence*
OR:	*Odds ratio*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP:	*Per Protocol*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR:	Relativ risiko
SMD	*Standardized Mean Difference*
T-DM1	Trastuzumab emtansin
T-DXd	Trastuzumab deruxtecan

3. Introduktion

Formålet med Medicinrådets vurdering af trastuzumab deruxtecan (T-DXd) til patienter med metastatisk human epidermal vækstfaktorreceptor 2 positiv (HER2+) brystkræft, som tidligere har modtaget to eller flere HER2-rettede behandlinger, er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra AstraZeneca og Daiichi Sankyo. Medicinrådet modtog ansøgningen den 14. juni 2021.

Det kliniske spørgsmål er:

Hvilken værdi har trastuzumab deruxtecan (T-DXd) sammenlignet med capecitabin i kombination med trastuzumab for patienter med metastatisk HER2+ brystkræft, som har progredieret på to HER2-rettede behandlinger?

3.1 Metastatisk HER2+ brystkræft

Brystkræft er den hyppigste kræftform hos kvinder verden over og forekommer oftest hos kvinder over 50 år. I Danmark bliver ca. 4.900 patienter årligt diagnosticeret med brystkræft, og ca. 66.000 patienter lever med diagnosen brystkræft [1,2]. Af de 4.900 patienter, som årligt diagnosticeres med brystkræft i Danmark, vil ca. 4.400 have tidlig brystkræft, dvs. at de ikke har fjernmetastaser. Ca. 10 %, dvs. ca. 490 patienter, har på diagnosetidspunktet derimod enten lokalt fremskreden (inoperabel) eller metastatisk sygdom (primært dissemineret), der ikke behandles med kurativt sigte.

HER2+ brystkræft
Sygdommen kan opdeles i fire undertyper, afhængigt af om kræftcellerne er hormonfølsomme, dvs. om de udtrykker østrogen receptor (ER) og/eller HER2 [3].

Patienterne testes rutinemæssigt for HER2-status på diagnosetidspunktet ved immunhistokemi og evt. in situ-hybridisering (ISH)-analyse [4]. Ca. 10-15 % af patienterne med brystkræft er HER2-positive (HER2+). Således bliver op til ca. 660 patienter årligt diagnosticeret med tidlig HER2+ brystkræft, mens ca. 70 patienter årligt bliver diagnosticeret med lokalt fremskreden inoperabel eller primær metastatisk HER2+ brystkræft [5]. De fleste af patienterne med inoperabel sygdom (ca. 30) vil blive behandlet med kurativt sigte, mens ca. 40 patienter med primær metastatisk sygdom vil modtage behandling for metastatisk sygdom (se figur 1).

Der har i de seneste år været en del udvikling ift. (neo)adjuverende behandling af HER2+ brystkræft med bl.a. indførelsen af pertuzumab neoadjuverende behandling og trastuzumab emtansin (T-DM1) adjuverende behandling [6,7] . Fagudvalget har ikke kendskab til opgørelser eller kliniske studier, der belyser, hvor mange patienter som får metastatisk tilbagefald med den nuværende danske behandlingsstrategi. Fagudvalget skønner ud fra klinisk erfaring, at ca. 20 % af de 660 patienter med tidlig HER2+ brystkræft (dvs. op til ca. 130 patienter), som behandles med kurativt sigte med (neo)adjuverende systemisk onkologisk behandling, operation og evt. strålebehandling,

årligt vil få metastatisk tilbagefald. Dette er en smule lavere, end hvad eksempelvis RADS angav i behandlingsvejledningen vedr. HER2+-rettet behandling [8], hvilket skyldes, at den nuværende behandlingsstrategi er mere effektiv, hvormed færre patienter får tilbagefald.
Samlet set estimerer fagudvalget således, at de 40 patienter, der har metastatisk sygdom på diagnosetidspunktet og ikke er kandidater til behandling med kurativt sigte, og at de 130 patienter med tidlig brystkræft, der får metastatisk tilbagefald, årligt er kandidater til 1. linje metastatisk behandling, dvs. ca. 170 patienter (se yderligere beskrivelse vedr. tredjelinjebehandling i afsnit 3.3).

3.2 Trastuzumab deruxtecan (T-DXd)

T-DXd har fået følgende indikation af EMA: *Enhertu som monoterapi er indiceret til behandling af voksne patienter med ikke-resekterbar eller metastatisk HER2-positiv brystcancer, som har fået to eller flere tidligere anti-HER2-baserede regimer.*

Fagudvalget fremhæver, at T-DXd således har indikation til at behandle patienter i tredje eller senere linjer.

T-DXd gives intravenøst, 5,4 mg/kg én gang hver tredje uge. EMA har vurderet T-DXd i en accelereret proces.

T-DXd er en sammenkobling af deruxtecan, som er en topoisomerase-1-hæmmer (dvs. en type af kemoterapi), og trastuzumab, som er et antistof rettet mod HER2. T-DXd virker ved, at trastuzumab genkender HER2, som er overudtrykt på overfladen af brystkræftcellerne. Når T-DXd binder til HER2-proteiner, transporteres det ind i cellen, hvor kemoterapien frigives og slår cellen ihjel. Deruxtecan kan bevæge sig hen over cellemembraner og kan dermed slå nærliggende celler ihjel. T-DXd har et højere antal molekyler af kemoterapi koblet til hvert antistof sammenlignet med tidligere konjugerede antistoffer.

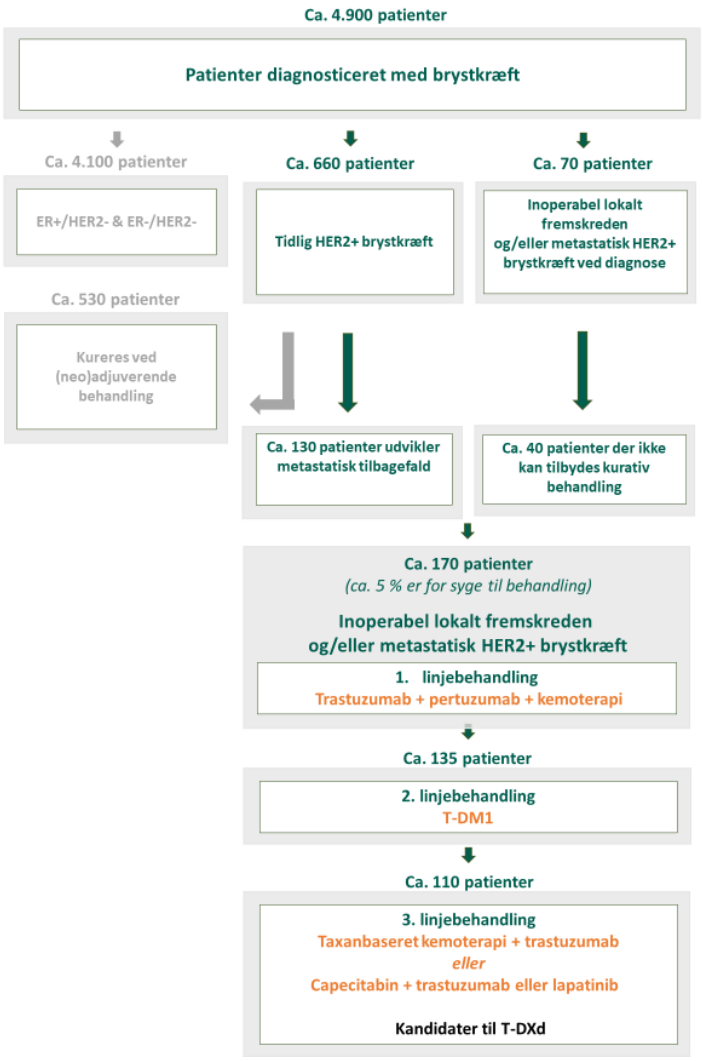
T-DXd er ikke godkendt til andre indikationer.

3.3 Nuværende behandling

3.3.1 Nuværende behandlingsrækkefølge

Patienter med HER2+ brystkræft med metastatisk sygdom modtager som udgangspunkt (under hensyntagen til tidligere givet (neo)adjuverende behandling) vinorelbine i kombination med pertuzumab og trastuzumab i første linje og T-DM1 i anden linje, se figur 1. Fagudvalget forventer, at ca. 5 % ikke får førstelinjebehandling, da de er for syge. 15 % dør eller ophører behandlingen i perioden fra første- til andenlinjebehandling, mens det er tilfældet for 20 % i perioden fra anden- til tredjelinjebehandling. Dermed er der årligt ca. 110 patienter med metastatisk HER2+ brystkræft, som kan komme i betragtning til behandling i tredje linje, se figur 1.

Figur 1. Oversigt over nuværende behandlingsrækkefølge*



*Der kan i klinisk praksis være afvigelser fra behandlingsrækkefølgen, bl.a. grundet hensyntagen til, hvilken behandling der er givet (neo)adjuverende, da man ikke genbehandler i metastatisk setting.

Hvis patienterne progredierer på andenlinjebehandling, tilbydes de en af følgende behandlinger, jf. Danish Breast Cancer Group's (DBCG) retningslinjer [9]:

- capecitabin i kombination med enten trastuzumab eller lapatinib
- taxanbaseret kemoterapi (typisk paclitaxel) i kombination med trastuzumab.

Valget imellem disse to behandlingskombinationer afhænger af, hvilken type kemoterapi patienten tidligere har modtaget, om patienten er progredieret på den pågældende behandling, og hvilke bivirkninger patienten er villig til at acceptere.

F.eks. vil en patient, som tidligere er progredieret på taxanbaseret kemoterapi, blive tilbudt capecitabin.

Fagudvalget vurderer, at ca. 80 % af patienterne modtager capecitabin i kombination med trastuzumab i tredje linje. Som nævnt er det muligt at kombinere capecitabin med

lapatinib fremfor trastuzumab. Fagudvalget vurderer, at dette sker relativt sjældent grundet mere toksicitet forbundet med lapatinib i forhold til trastuzumab. Fagudvalget vurderer, at effekten af capecitabin i kombination med hhv. trastuzumab og lapatinib er sammenlignelig [10,11]. Derfor konkluderer fagudvalget, at capecitabin i kombination med trastuzumab er den mest relevante komparator for sammenligningen med T-DXd.

3.3.2 Patienternes almene tilstand og behandlingsmålet med den nuværende behandling

Patienter, der har progredieret på andenlinjebehandling og dermed er kandidater til tredjelinjebehandling, kan være præget af deres brystkræftsygdom. Dette er dog meget forskelligt fra patient til patient og afhænger i høj grad af metastasernes udbredelse og beliggenhed. Fagudvalget vurderer, at ca. 35-40 % af patienter med HER2+ brystkræft vil udvikle hjernemetastaser. Hjernemetastaser medfører ofte svære symptomer og kan være vanskelige at behandle, men også metastaser i lunger og lever samt lungehinde og bughule kan medføre symptomatisk sygdom.

Patienter kan desuden være præget af bivirkninger fra tidligere behandlinger. I dansk klinisk praksis behandles patienter med performance status 0, 1 og 2 [9]. Nogle patienter er således oppegående, men hviler sig en betragtelig del af dagen, mens andre stadig kan opretholde et arbejde.

Behandlingsmålet med den nuværende tredjelinjebehandling er både symptomlindring og livsforlængelse. Behandlingen har således ikke kurativt sigte.

3.3.3 Prognose ved nuværende behandling

Fagudvalget gør opmærksom på, at det er vanskeligt at estimere patienternes samlede overlevelse ved tredjelinjebehandling. I dette afsnit gennemgår fagudvalget derfor flere forskellige randomiserede forsøg for at give et retvisende billede af den heterogenitet i studieresultater, som gør det udfordrende at estimere prognosen for patientgruppen.

- Patienter med metastatisk HER2+ brystkræft, som modtager trastuzumab + pertuzumab + kemoterapi i første linje, har en median samlet overlevelse på ca. 56 måneder [12].
- Den senest publicerede artikel for andenlinjebehandling af metastatisk HER2+ brystkræft viser, at patienter, som modtager T-DM1, har en median samlet overlevelse på 29,9 måneder [13].
- Der foreligger forskellige studier for tredjelinjebehandling, hvoraf ingen dog afspejler den danske patientpopulation fuldstændigt. Et studie viste en median samlet overlevelse på ca. 17 måneder for patienter, som modtog capecitabin + trastuzumab [14]. Dette reflekterer dog ikke danske patienters prognose, da patienterne i studiet havde modtaget imellem 2-14 forskellige behandlinger for metastatisk sygdom. Det betyder, at en del patienter i studiet har dårligere prognose end danske patienter. Et andet studie viste en median samlet overlevelse på ca. 27 måneder for patienter, som modtog capecitabin + trastuzumab [15]. Dette studie overestimerer dog prognosen, da der ikke var inkluderet patienter med hjernemetastaser, og 44 % af patienterne modtog behandlingen i første linje. Dermed er der selekteret for patienter med den bedste prognose. Et tredje studie viste en median samlet

overlevelse på ca. 19 måneder (gennemsnitlig overlevelse er opgjort til 22 måneder) for patienter, som modtog capecitabin + lapatinib, hvilket fagudvalget forventer har samme effekt som capecitabin + trastuzumab [16]. Samlet set vurderer fagudvalget, at en median samlet overlevelse på ca. 22 måneder er forventelig for danske patienter, men understreger, at der er usikkerheder forbundet med estimatet.

4. Metode

Medicinrådets protokol for vurdering vedrørende trastuzumab deruxtecan til tredjelinjebehandling af metastatisk HER2+ brystkræft beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Der findes ikke studier, hvor T-DXd er sammenlignet direkte med capecitabin i kombination med trastuzumab, da den primære publikation vedr. T-DXd er et enkeltarms fase II-studie. Derfor har Medicinrådet angivet en søgestreng i protokollen, så ansøger kunne finde studier til en indirekte sammenligning. Ansøger har søgt litteratur med søgestrengen og udvalgt fire fuldtekstartikler samt en poster. Dertil har ansøger indsendt fortroligt data fra et observationsstudie af danske patienter udarbejdet på baggrund af data fra DBCG. Publikationerne fremgår af nedenstående tabel 1.

Tabel 1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Relevant intervention/komparator
Modi et al. 2020 Modi et al. 2020 (poster/abstract)	DESTINY-Breast01	NCT03248492	Trastuzumab deruxtecan (T-DXd)

Publikationer	Klinisk forsøg	NCT-nummer	Relevant intervention/komparator
Rugo et al. 2021	SOPHIA	NCT03248492	Trastuzumab i kombination med kemoterapi
Murthy et al. 2020	HER2CLIMB	NCT02614794	Trastuzumab i kombination med capecitabin
Saura et al. 2020	NALA	NCT01808573	Lapatinib i kombination med capecitabin
Upublicerede, fortrolige data, AstraZeneca/DBCG	[redacted]	[redacted]	[redacted]

Udover studierne i tabellen fandt ansøger to publikationer, som blev vurderet ikke at være relevante for det kliniske studie:

- J101: Et fase I-studie af T-DXd. Studiet er ekskluderet, idet der et fase II-studie af T-DXd.
- CEREBEL: Et fase III-studie af lapatinib i kombination med capecitabin sammenlignet med trastuzumab i kombination med capecitabin. Studiet er ekskluderet, da mange af patienterne i studiet er behandlet i 1. linje, og da antallet af patienter behandlet i 3. linje ikke er rapporteret. Desuden er patienter med hjernemetastaser ekskluderet i studiet, og 65 % af patienterne i studiet havde ikke modtaget trastuzumab for metastatisk sygdom.

Fagudvalget er enig med ansøger i at ekskludere de to studier.

De fire studier, som ansøger har identificeret, og som i udgangspunktet kan anvendes til at besvare det kliniske spørgsmål, er beskrevet nedenfor. Det fortrolige observationsstudie med data fra dansk klinisk praksis er ligeledes beskrevet nedenfor.

DESTINY-Breast01

Dette er et igangværende todelt, ublindet, enkeltarms fase II-studie, der undersøgte hhv. farmakokinetik og valg af dosis samt effekten og sikkerheden af T-DXd hos patienter med ikke-resekterbar eller metastatisk HER2+ brystkræft, som tidligere har modtaget T-DM1-behandling [17].

Studiets første del: Denne del af studiet omhandlede farmakokinetik samt valg af dosis og var opdelt i to faser. I fase 1 blev patienterne randomiseret 1:1:1 til 7,4 mg/kg (n = 21), 6,4 mg/kg (n = 22) og 5,4 mg/kg (n = 22) hver 3. uge. I fase 2 blev patienterne

randomiseret 1:1 til hhv. 5,4 mg/kg (n = 28) og 6,4 mg/kg (n = 26) hver 3. uge. Således modtog 50 patienter (22 + 28) de 5,4 mg/kg T-DXd hver 3. uge i studiets første del.

Studiets anden del: Denne del af studiet undersøgte effekten og sikkerheden af T-DXd 5,4 mg/kg hver 3 uge. I studiet indgik de 50 patienter, der i studiets første del havde modtaget denne dosis, yderligere 130 patienter, der havde haft tumorprogression under eller efter tidligere behandling med T-DM1, samt 4 patienter, der havde stoppet behandling med T-DM1 af andre grunde end sygdomsprogression. Der er således i alt 184 patienter, der har modtaget T-DXd 5,4 mg/kg hver 3. uge. Studiets primære effektmål er objektiv respons rate (ORR). Sekundære effektmål af relevans er samlet overlevelse (OS), progressionsfri overlevelse (PFS) og sikkerhed.

SOPHIA

Dette er et randomiseret, ublindet fase III-studie, der undersøgte effekt og sikkerhed af margetuximab sammenlignet med trastuzumab, begge i kombination med kemoterapi, hos patienter med fremskreden HER2+ brystkræft [18]. Patienterne skulle have haft sygdomsprogression på mindst to tidligere anti-HER2-rettede behandlinger og have modtaget 1-3 behandlingslinjer for metastatisk sygdom. Valget af kemoterapi var op til investigator og bestod af hhv. capecitabin, eribulin, gemcitabine eller vinorelbine. Patienterne var randomiseret 1:1 til margetuximab i kombination med kemoterapi (n = 266) eller trastuzumab 6 mg/kg hver 3. uge i kombination med kemoterapi (n = 270). Randomiseringen var stratificeret efter antal tumorsteder, antal behandlingslinjer og valget af kemoterapi. Studiets primære effektmål er PFS efterfulgt af OS. Sekundære effektmål af relevans er sikkerhed.

HER2CLIMB

Dette er et randomiseret, dobbeltblindet fase II-studie, der undersøgte effekt og sikkerhed af tucatinib og placebo, begge i kombination med capecitabin og trastuzumab, hos patienter med ikke-resekterbar lokalt avanceret eller metastatisk HER2+ brystkræft, som tidligere var behandlet med trastuzumab, pertuzumab og T-DM1 [14]. Patienterne var randomiseret 2:1 til tucatinib (n = 410/320) eller placebo (n = 202/160), begge i kombination med trastuzumab 6 mg/kg hver 3. uge og capecitabin 1.000 mg/m^2 legemsoverflade 2 gange i døgnet i 14 dage efterfulgt af 1 uges pause. Randomiseringen var stratificeret efter, om patienterne havde hjernemetastaser, ECOG-performance status (0 eller 1) og geografisk region. Studiets primære effektmål er PFS. Sekundære effektmål af relevans er OS og sikkerhed.

NALA

Dette er et randomiseret, ublindet fase III-studie, der undersøgte effekt og sikkerhed af neratinib og lapatinib, begge i kombination med capecitabin, hos patienter med metastatisk HER2+ brystkræft, der har modtaget ≥ 2 HER2-rettede behandlinger for deres metastatiske sygdom [16]. Patienterne var randomiseret 1:1 til neratinib i kombination med capecitabin (n = 307) eller lapatinib 1.250 mg/m^2 legemsoverflade 1 gang i døgnet i kombination med capecitabin 1.000 mg/m^2 legemsoverflade 2 gange i døgnet i 14 dage efterfulgt af 1 uges pause (n = 314). Randomiseringen var stratificeret efter hormonreceptor-status, antal tidligere HER2-rettede behandlinger for metastatisk sygdom (2 eller ≥ 3), geografisk region, og om patienten havde visceral sygdom. Studiets

primære effektmål er PFS og OS. Sekundære effektmål af relevans er livskvalitet og sikkerhed.

Af nedenstående tabel fremgår baselinekarakteristika for den interventions- eller komparatorarm fra de fire studier, der er relevant for besvarelsen af klinisk spørgsmål 1.

Observationsstudie, data fra DBCG

[redacted]

Tabel 2. Baselinekarakteristika for DESTINY-Breast01, SOPHIA, HER2CLIMB og NALA

	DESTINY-Breast01 T-DXd N = 184	Observations-studie [redacted]	NALA Capecitabin + lapatinib N = 314	SOPHIA Trastuzumab + kemoterapi N = 270	HER2CLIMB Trastuzumab + capecitabin N = 160/202
Median alder	55 (28-96)	[redacted]	54	56 (27-86)	54
Median antal tidligere behandlinger	6 (2-27)	[redacted]	2	-	3 (1–13)
Tidligere behandlinger ≥ 3 (%)	90,8	[redacted]	31,5	33,0	-
Tidligere T-DM1-behandling (%)	100	[redacted]	36**	91,5	100
Tidligere pertuzumab i metastatisk setting (%)	65,8	[redacted]	41,7	99,6	99,4

	DESTINY-Breast01 T-DXd N = 184	Observations-studie [redacted]	NALA Capecitabin + lapatinib N = 314	SOPHIA Trastuzumab + kemoterapi N = 270	HER2CLIMB Trastuzumab + capecitabin N = 160/202
ECOG Performance score = 0 (%)	55,4	[redacted]	52,2	59,6	47,5
Hormon-receptor positiv (%)	52,7	[redacted]	59,2	63,0	61,9
Metastaser					
Knogle (%)	28,8	[redacted]	47.1	57,4	53,1
Lunge (%)	57,1	[redacted]	55,4	46,7	51,2
Lever (%)	30,4	[redacted]	47,1	35,2	40,0
CNS (%)	13,0	[redacted]	15,9	12,6	44,4
Visceral (%)	91,8	[redacted]	86,0	-	

*Gennemsnit.
**Har modtaget trastuzumab, pertuzumab og T-DM1.

Fagudvalget finder, at der er flere relevante forskelle på tværs af studierne ift. DESTINY-Breast01:

- I NALA, SOPHIA og HER2CLIMB er det mediane antal tidligere behandlinger, og andelen, der har modtaget ≥ 3 tidligere behandlinger, lavere end i DESTINY-Breast01.
- Andelen af patienter, der har modtaget T-DM1, er betydeligt mindre i NALA end i DESTINY-Breast01, da det ikke var et inklusionskrav i NALA.
- I SOPHIA og HER2CLIMB har næsten alle patienter tidligere modtaget pertuzumab for metastatisk sygdom, hvilket ikke er tilfældet i DESTINY-Breast01. I dansk klinisk praksis vil patienterne netop modtage pertuzumab inden eventuel behandling med T-DXd.
- I NALA, SOPHIA og HER2CLIMB er andelen af patienter med knoglemetastaser højere end i DESTINY-Breast01.
- I NALA er andelen af patienter med levermetastaser højere end i DESTINY-Breast01.
- I HER2CLIMB er andelen af patienter med hjernemetastaser (CNS) betydeligt højere end i DESTINY-Breast01.

[redacted] Fagudvalget anslår, at det reelt er ca. 30 % af patienterne i dansk klinisk praksis, der har hjernemetastaser.

Dertil pointerer fagudvalget, at der mangler flere relevante informationer om baselinekarakteristika i flere af studierne, hvilket kan betyde, at der er flere relevante forskelle i baselinekarakteristika på tværs af studierne end de oplistede.

Valg af komparator til at belyse effekt

Jf. det kliniske spørgsmål er den efterspurgte komparator capecitabin i kombination med trastuzumab. Af protokollen fremgår det dog, at det ligeledes er muligt at kombinere capecitabin med lapatinib fremfor trastuzumab, men at dette sker relativt sjældent i dansk klinisk praksis grundet mere toksicitet forbundet med lapatinib i forhold til trastuzumab. Fagudvalget vurderer dog, at effekten af capecitabin i kombination med hhv. trastuzumab og lapatinib er sammenlignelig. Derudover fremgår det af protokollen, at sammenligningen mellem T-DXd og komparator kan overføres til patienter, som modtager taxanbaseret kemoterapi i kombination med trastuzumab.

Med afsæt i ovenstående argumenterer ansøger for, at komparatorarmen fra NALA-studiet (capecitabin + lapatinib) er den rette komparator i klinisk spørgsmål 1 fremfor komparatorarmen i hhv. SOPHIA (trastuzumab + kemoterapi) eller HER2CLIMB (trastuzumab + capecitabin). Ansøgers argumenter er som følger:

- NALA er sandsynligvis det studie, der bedst afspejler den danske patientpopulation, og hvor PFS og OS i komparatorarmen bedst reflekterer patienternes PFS og OS ved standardbehandling i Danmark.
- SOPHIA inkluderer patienter med mindre end 2 tidligere behandlingslinjer for metastatisk sygdom og ekskluderer patienter, hvis de har fået mere end 3 (dvs. inkluderer kun patienter, der har fået 1-3 behandlingslinjer for metastatisk sygdom). Dette kommer til udtryk ved den lange overlevelse efter progression i komparatorarmen sammenlignet med de andre studier. Studiet er derfor mindre repræsentativt for dansk klinisk praksis.
- HER2CLIMB inkluderer et stort antal patienter med hjernemetastaser, hvilket formentligt er årsagen til den kortere overlevelse efter progression sammenlignet med, hvad man ser hos patienter i dansk klinisk praksis.

Fagudvalget er ikke enig i, at NALA afspejler den danske patientpopulation bedst. Kun 36 % af patienterne har modtaget trastuzumab, pertuzumab og T-DM1, mens det i dansk klinisk praksis vil være over 90 %. Fagudvalget er imidlertid enig i ansøgers argumenter for, hvorfor SOPHIA og HER2CLIMB ikke afspejler den danske patientpopulation tilstrækkeligt.

På baggrund heraf samt gennemgangen af baselinekarakteristika i tabel 2 finder fagudvalget, at en sammenligning af DESTINY-Breast01 med alle de identificerede studier giver det bedste datagrundlag for vurdering af T-DXd's effekt.

Valg af komparator til at belyse sikkerhed

Ansøger argumenterer derudover for, at effektmålet bivirkninger bør belyses ved en sammenligning med data fra HER2CLIMB, da komparatorarmen i NALA (capecitabin + lapatinib) er mere toksisk end den reelle komparator i det kliniske spørgsmål og dansk klinisk praksis (capecitabin + trastuzumab). Komparatorarmen i HER2CLIMB er netop den relevante komparator. Fagudvalget er enig heri og finder, at forskellen i studiepopulationen i hhv. DESTINY-Breast01 og HER2CLIMB (større antal patienter med hjernemetastaser) ikke er nær så problematisk ift. belysning af sikkerhed som ved belysning af effekt. Fagudvalget er dog opmærksom på, at man oftere dosisreducerer patienter med hjernemetastaser.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Ansøgers analyse

Som beskrevet i afsnit 5.1.1. er den primære publikation vedr. T-DXd et enkeltarmsstudie, og der foreligger således ikke en direkte sammenligning med komparator. Ansøger har derfor lavet indirekte komparative analyser af DESTINY-Breast01 og hhv. NALA, SOPHIA og HER2CLIMB ved Matching Adjusted Indirect Comparison (MAIC)-analyse. MAIC er en metode, der bruges til indirekte sammenligninger af lægemidler, der er evalueret i forskellige, men lignende populationer. Idet DESTINy-Breast01 er et enarmet studie uden komparator er MAIC-analysen unanchored (uforankret) hvilket betyder, at analysen har stærke antagelser, der generelt antages at være svære at leve op til [19]. MAIC-sammenligninger kan bruges i situationen, hvor man har individuelle patientdata til rådighed for ét lægemiddel (her T-DXd), og man kun har aggregerede data til rådighed for et andet (her capecitabin + lapatinib). Ved brug af metoden vægtes patienter i den ene population, så valgte patientkarakteristika ligner dem i studiet med aggregerede data, efter vægtningen er udført. Vægtene er patienternes odds for at være inkluderet i det ene studie mod det andet studie og udregnes ved brug af en logistisk regressions-model.

Den indirekte sammenligning er foretaget i henhold til Medicinrådets metoder, men da MAIC-analysen medfører, at patientpopulationens størrelse i DESTINY-Breast01 reduceres markant (fra 184 til hhv. 24,6, 7,5 og 27,9 for sammenligningen med hhv. NALA, HER2CLIMB og SOPHIA) finder Medicinrådet, at MAIC-analyserne ikke kan anvendes som datagrundlag for vurderingen af T-DXd's værdi ift. komparator. Data fra MAIC-analysen er præsenteret til perspektivering.

Med afsæt i ovenstående vurderer fagudvalget i stedet T-DXd ved en kvalitativ sammenligning på tværs af de inkluderede studier sammenholdt med DESTINY-Breast01. Medicinrådet understreger, at en sådan analyse er lavere i evidenshierarkiet end en direkte eller indirekte kvalitativ sammenligning.

Medicinrådet har følgende bemærkninger til datagrundlaget:

- Datagrundlaget består af en række studier (hvoraf et er et single-arm studie (DESTINY-Breast01)) med forskellig opfølgningstid (fra 2,8 til 29,9 måneder for PFS og fra 14 til 29,9 måneder for OS) og betydningsfulde forskelle i patientpopulationerne (se afsnit 5.1.1).
- I DESTINY-Breast01 er median OS estimeret på et tidspunkt hvor 64,7 % af patienterne (n = 119) er censureret) ved en median follow-up på 20,5 måneder. Estimatet er dermed behæftet med en vis usikkerhed.
- I DESTINY-Breast01 er median PFS estimeret på et tidspunkt hvor 62 % af patienterne (n = 114) er censureret) ved en median follow-up på 20,5 måneder. Estimatet er dermed behæftet med en vis usikkerhed.
- Effektmålet livskvalitet er ikke opgjort i DESTINY-Breast01, og det er derfor ikke muligt at lave en kvalitativ sammenligning med de andre studier for dette effektmål.
- Ansøger har ikke opgjort de nyeste data for ≥ grad 3 uønskede hændelser i DESTINY-Breast01. Medicinrådet har derfor tilføjet dette i den kvalitative sammenligning.

5.1.3 Evidensens kvalitet

Der er primært tale om en kvalitativ sammenligning uden kvantitative sammenligninger på baggrund af et ukontrolleret studie for interventionen. Der findes ikke velvaliderede værktøjer til at vurdere evidensens kvalitet for non-komparative studier. Der er derfor hverken udarbejdet en Risk of Bias profil eller en GRADE-profil.

Samlet vurderer Medicinrådet, at evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.1.4 Effektestimater og kategorier

Datagrundlaget tillader ikke, at effekten af T-DXd kategoriseres efter Medicinrådets metoder. Fagudvalget sammenligner T-DXd og komparator i en kvalitativ sammenligning. Nedenfor ses effektestimater, som indgår i den kvalitative sammenligning, de aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 3. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	T-DXd (DESTINY-Breast01)	Capecitabin + lapatinib (NALA)	Trastuzumab + kemoterapi (SOPHIA)	Trastuzumab + capecitabin (HER2CLIMB)	[redacted]	Aggregeret værdi for effektmålet
Samlet overlevelse (OS)	Median OS (MKRF: 5 måneder)	Kritisk	24,6 (23,1;NE)	18,7 (15,5;21,2)	19,8 (17,5;22,3)	17,4 (13,6;19,9)	[redacted]	Kan ikke kategoriseres
Livskvalitet	Gennemsnitlig ændring over tid	Kritisk	Ingen data	-	-	-	-	Kan ikke kategoriseres
Bivirkninger	Andel patienter, der oplever en eller flere grad 3-4 bivirkninger (MKRF: 5 %-point)	Vigtigt	Uønskede hændelser ≥ grad 3: 61,4 %	-	-	Uønskede hændelser ≥ grad 3: 48,7 %	-	Kan ikke kategoriseres
	Gennemgang af bivirkningsprofil		Se afsnit 5.1.4 Gennemgang af bivirkningsprofil					
Stabilisering eller forbedring af symptomer	Median progressionsfri overlevelse (PFS) (MKRF: 3 måneder)	Vigtigt	19,4 (14,1;NE)	5,5 (4,3;5,6)	4,4 (4,1;5,5)	5,6 (4,2;7,1)	[redacted]	Kan ikke kategoriseres
Konklusion								
Samlet kategori for lægemidlets værdi			Kan ikke kategoriseres efter Medicinrådets metoder					
Kvalitet af den samlede evidens			Meget lav					

CI = Konfidensinterval, NE = Not evaluated, * = Hovedsageligt.

Samlet overlevelse (OS)
Som beskrevet i protokollen er effektmålet OS kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det er afgørende for patienterne, om behandlingen forlænger deres liv. Fagudvalget ønskede effektmålet opgjort som median OS. Fagudvalget vurderede, at en forskel ift. median OS på 5 måneder er klinisk relevant.

Data for OS er opgjort i alle de inkluderede studier. I DESTINY-Breast01 er median OS estimeret ved kun ca. 35 % modenhed (64,7 % af patienterne (n = 119) er censureret) ved en median follow-up på 20,5 måneder. I hhv. NALA, SOPHIA og HER2CLIMB er den mediane follow-up på 29,9, 15,6 og 14 måneder.
[redacted]

For patienter behandlet med T-DXd er den mediane OS 24,6 måneder (23,1;NE). For behandling med capecitabin + lapatinib (NALA), trastuzumab + kemoterapi (SOPHIA), trastuzumab + capecitabin (HER2CLIMB og DBCG) er den mediane OS hhv. 18,7, 19,8, 17,4 måneder [redacted](se tabel 3). Fagudvalget finder, at de tilgængelige effektestimater indikerer, at overlevelsen er længere for patienter behandlet med T-DXd end ved de andre behandlingskombinationer. Fagudvalget understreger, at de store forskelle på tværs af studierne medfører, at den kvalitative sammenligning er behæftet med stor usikkerhed.

Fagudvalget vurderer, at T-DXd aggregeret har en **værdi, der ikke kan kategoriseres** efter Medicinrådets metoder vedr. effektmålet OS. Fagudvalget kan ikke vurdere eventuelle forskelle mellem T-DXd og de forskellige komparatorer grundet usikkerhederne forbundet med data. Med afsæt i den kvalitative sammenligning finder fagudvalget imidlertid, at der ikke er noget, der taler for, at T-DXd er dårligere end komparator.

Til perspektivering inddrager fagudvalget MAIC-analyserne for DESTINY-Breast01 og hhv. NALA, SOPHIA og HER2CLIMB. Resultatet af MAIC-analyserne fremgår af nedenstående tabel.

Tabel 4. Resultater for MAIC-analysen vedr. effektmålet OS

Studie	Behandlingsarm	Patientantal	Absolut effektforskel	Relativ effektforskel
NALA	Capecitabin + lapatinib	314	5,9 måneder	HR: 0,29 (0,14;0,60)
DESTINY-Breast01 (justeret)	T-DXd	24,6		
HER2CLIMB	Trastuzumab + capecitabin	202	7,2 måneder	HR: 0,51 (0,20;1,32)
DESTINY-Breast01 (justeret)	T-DXd	7,5		
SOPHIA	Trastuzumab + kemoterapi	270	> 11 måneder	HR: 0,27 (0,14;0,50)
DESTINY-Breast01 (justeret)	T-DXd	27,9		

I alle MAIC-analyserne er den absolutte forskel større end den mindste klinisk relevante forskel på 5 måneder. Tilsvarende indikerer de relative effektforskelle, at T-DXd har en stor merværdi sammenlignet med komparator. Der gælder dog for samtlige analyser, at pga. manglende ligheder mellem komparator-populationen og T-DXd-behandlingsarmen er patientantallet for T-DXd reduceret betydeligt ved MAIC-analysen.

Fagudvalget bruger derfor udelukkende MAIC-analyserne til perspektivering, da de er forbundet med stor usikkerhed og dermed bør anvendes med store forbehold. Fagudvalget finder, at MAIC-analyserne understøtter den ovenstående konklusion vedr. effektmålet OS.

Livskvalitet
Som beskrevet i protokollen anser fagudvalget livskvalitet som et kritisk effektmål, da det er et patientrelevant effektmål, som ud over at give indblik i sygdomsbyrden kan indikere, om bivirkningerne ved lægemidlet påvirker patienternes livskvalitet. Fagudvalget ønsker, jf. protokollen, effektmålet belyst ved et valideret spørgeskema og finder, at den mindste klinisk relevante forskel er forskellen i ændring svarende til den validerede mindste klinisk relevante forskel for det involverede livskvalitetsspørgeskema.

Da patienternes livskvalitet ikke er undersøgt i DESTINY-Breast01, er det ikke muligt at foretage en komparativ analyse med livskvalitetsdata.

Fagudvalget vurderer på den baggrund, at T-DXd aggregeret har en **værdi, der ikke kan kategoriseres** vedr. effektmålet livskvalitet. Baseret på nedenstående gennemgang af effektmålene PFS og bivirkninger vurderer fagudvalget imidlertid, at det er sandsynligt, at T-DXd ikke fører til forringet livskvalitet sammenlignet med komparator.

Bivirkninger
Som beskrevet i protokollen er behandlingsmålet med T-DXd at forlænge patienternes liv. Fagudvalget finder, at bivirkninger er et vigtigt effektmål, da det belyser, hvor godt patienterne tolererer T-DXd sammenlignet med komparator. Effektmålet er vigtigt, da det er fagudvalgets vurdering, at patienterne er relativt villige til at risikere bivirkninger for at kunne opnå en eventuel forlængelse i overlevelse. Fagudvalget ønsker, jf. protokollen, effektmålet belyst ved forskellen i andelen af grad 3-4 bivirkninger, hvor den mindste klinisk relevante forskel er 5 %-point, og ved en kvalitativ sammenligning af bivirkningsprofilen.

Jf. afsnit 5.1.1 er effektmålet bivirkninger belyst ved en sammenligning med data fra HER2CLIMB (capecitabin + trastuzumab), da dette er den behandling, man anvender i dansk klinisk praksis.

Bivirkninger grad 3-4

I DESTINY-Breast01 oplever 105 (61,4 %) af patienterne behandlet med T-DXd en grad ≥ 3 uønsket hændelse. I HER2CLIMB er der 96 (48,7 %) af patienterne, der oplever en grad ≥ 3 uønsket hændelse i løbet af opfølgningstiden.

Dermed er der flere patienter, der oplever uønskede hændelser ved behandling med T-DXd i DESTINY-Breast01 end ved behandling med trastuzumab i kombination med capecitabin i HER2CLIMB. Dertil skal der tages forbehold for forskellen i median opfølgningstid på hhv. 20,5 og 14 måneder DESTINY-Breast01 og HER2CLIMB. Dvs. at med en ca. 6 måneder længere opfølgningstid kan andelen, der oplever uønskede hændelser ved T-DXd-behandling, være overestimeret ved sammenligning med HER2CLIMB-studiet.

Fagudvalget kan med afsæt i ovenstående kvalitative sammenligning ikke vurdere, om T-DXd medfører flere eller færre bivirkninger af grad 3-4. Ud fra de tilgængelige data tyder det på, at T-DXd medfører flere grad ≥ 3 uønskede hændelser end trastuzumab + capecitabin. Fagudvalget understreger, at det kan skyldes forskel i opfølgningstid. Dertil tager fagudvalget forbehold for, at sammenligningen er foretaget på baggrund af en kvalitativ sammenligning.

Kvalitativ gennemgang af bivirkningsprofil

Fagudvalget har kvalitativt gennemgået bivirkningsprofilerne for T-DXd og trastuzumab i kombination med capecitabin med henblik på at vurdere bivirkningernes type og reversibilitet som supplement til den kvantitative opgørelse over bivirkninger.

T-DXd's sikkerhed er blevet evalueret i en puljet analyse af patienter (fra fase I-studiet J101 og fase II-studiet DESTINY-Breast01) med ikke-resekterbar eller metastatisk HER2-positiv brystkræft, som fik mindst én dosis T-DXd 5,4 mg/kg i de kliniske studier. Da der ikke er nogen kontrolgruppe til T-DXd-armen i DESTINY-Breast01, er opgørelsen af bivirkninger behæftet med usikkerhed. Bivirkningsdata på trastuzumab i kombination med capecitabin kommer fra HER2CLIMB-studiet. Den mediane opfølgningstid i DESTINY-Breast01 og HER2CLIMB var henholdsvis 11,1 måneder og 14 måneder.

Oversigt over de hyppigste bivirkninger ved behandling af T-DXd fremgår nedenfor.

Tabel 5. Hyppigste bivirkninger ved behandling med TDXd

MedDRA Preferred Term/ Grouped Term	HER2-positive BC 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Subjects with Any TEAE	233 (99.6)	233 (99.6)	50 (100.0)	50 (100.0)	183 (99.5)	183 (99.5)
Nausea	79,1 %	79,9 %	86,0 %	88,0 %	77,2 %	77,7 %
Fatigue	47,9 %	49,1 %	48,0 %	48,0 %	47,8 %	49,5 %
Vomiting	47,4 %	48,7 %	56,0 %	60,0 %	45,1 %	45,7 %
Alopecia	45,7 %	46,2 %	38,0 %	38,0 %	47,8 %	48,4 %
Constipation	34,6 %	35,9 %	36,0 %	36,0 %	34,2 %	35,9 %
Decreased appetite	32,5 %	34,6 %	46,0 %	48,0 %	28,8 %	31,0 %
Anaemia	30,8 %	33,8 %	48,0 %	48,0 %	26,1 %	29,9 %
Neutrophil count decrease	29,5 %	32,5 %	24,0 %	24,0 %	31,0 %	34,8 %
Diarrhoea	28,6 %	30,8 %	36,0 %	36,0 %	26,6 %	29,3 %
Platelet count decrease	20,1 %	23,1 %	30,0 %	30,0 %	17,4 %	21,2 %
Cough	19,7 %	21,4 %	28,0 %	30,0 %	17,4 %	19,0 %
White blood cell count decreasw	19,2 %	20,5 %	18,0 %	18,0 %	19,6 %	21,2 %
Abdominal pain	17,9 %	18,8 %	26,0 %	26,0 %	15,8 %	16,8 %
Headache	17,9 %	18,8 %	16,0 %	16,0 %	18,5 %	19,6 %
Dizziness	10,3 %	10,7 %	16,0 %	16,0 %	8,7 %	9,2 %
Oedema peripheral	8,5 %	10,7 %	20,0 %	22,0 %	5,4 %	7,6 %
Pyrexia	9,8 %	10,7 %	20,0 %	22,0 %	7,1 %	7,6 %

De mest almindelige bivirkninger var kvalme (79,9 %), træthed (60,3 %), opkast (48,7 %), alopeci (46,2 %), forstoppelse (35,9 %), nedsat appetit (34,6 %), anæmi (33,8 %), neutropeni (32,5 %), diarré (30,8 %), trombocytopeni (23,1 %), hoste (21,4 %), leukopeni (20,5 %) og hovedpine (20,1 %).

Fagudvalget vurderer, at de hyppigste bivirkninger ved behandling med T-DXd generelt er reversible, håndterbare for lægen og tolerable for patienten.

Bivirkninger grad ≥ 3

Grad ≥ 3 bivirkninger ved behandling med hhv. T-DXd og trastuzumab + capecitabin.

De mest almindelige **grad ≥ 3** bivirkninger var ved behandling med T-DXd: neutropeni (18,8 %), anæmi (9,0 %), kvalme (6,8 %), træthed (6,4 %), leukopeni (5,6 %), lymfopeni (5,1 %), opkastning (4,3 %), trombocytopeni (4,3 %), hypokaliæmi (3,4 %), interstitiel lungesygdom (ILD, 3,0 %), diarré (2,6 %), febril neutropeni (1,7 %), dyspnø (1,7 %), abdominalsmerter (1,3 %), nedsat appetit (1,3 %) og forhøjet alaninaminotransferase (1,3 %). Hos 2,6 % af patienterne førte ILD til døden.

Ved behandling med trastuzumab i kombination med capecitabin i HER2CLIMB-studiet var almindelige **grad ≥ 3** bivirkninger (sorteret på interventionsarmen i HER2CLIMB) palmar-plantar erythrodysesthesia (PPE-syndrom)[1] (9,1 %), diarré (8,6 %), dyspnø (5,1 %), hypokaliæmi (5,1 %), neutropeni (4,6 %), træthed (4,1 %) og opkastning (3,6 %).

Alvorlige uønskede hændelser blev observeret for 22,8 % i DESTINY-Breast01-studiet, hvor 4,9 % af disse førte til døden. Hæmatologisk toksicitet er tidligere set med andre antibody-drug conjugater, og i DESTINY-Breast01 så man ligeledes anæmi og neutropeni hos ca. en tredjedel af patienterne. Da der ikke foreligger en EPAR for trastuzumab + capecitabin, og alvorlige uønskede hændelser ikke er opgjort i HER2CLIMB, kan fagudvalget ikke vurdere eventuelle forskelle i typen og andelen af alvorlige uønskede hændelser ved behandling med hhv. T-DXd og trastuzumab + capecitabin.

Til sammenligning medførte 2,5 % af de uønskede hændelser døden i trastuzumab + capecitabin-behandlingsarmen i HER2CLIMB-studiet. Årsagerne hertil var henholdsvis multiorgansvigt, myokardieinfarkt, sepsis og systemisk inflammatorisk respons syndrom. Behandlingsophør som følge af bivirkninger forekom i 15,2 % af patienterne behandlet med T-DXd og i 3 % behandlet med trastuzumab + capecitabin i HER2CLIMB-studiet.

Uønskede hændelser af særlig interesse ved behandling med T-DXd:

- Interstitiel lungesygdom (ILD): ILD var ved studiestart identificeret som en alvorlig potentiel risiko ved T-DXd-behandling. Tilfælde med ILD blev graderet som grad 1 (3,0 %), grad 2 (8,5 %) eller grad 3 (0,4 %), mens grad 5-hændelser opstod hos 3,0 % af patienterne.
- Neutropeni: Der blev rapporteret et fald i neutrofiltallet hos 32,5 % af patienterne, hvor 18,8 var grad 3 eller 4. Der blev rapporteret 1,7 % med febril neutropeni.
- Hjertesvigt: Der blev rapporteret få tilfælde af hjertesvigt, og disse var ikke associeret med et nedsat left ventricular ejection fraction (LVEF). Patienter med i forvejen nedsat LVEF (< 50 % normal LVEF) var dog i forvejen udelukket fra at

[1]Palmar-plantar erythrodysesthesia (også kaldet hånd og fod-syndrom) er forbundet med rødme, smerte og hævelse i hænder og fødder. Det er en hyppig årsag til dosisreduktion ved behandling med capecitabine.

deltage i studiet. Hjertepåvirkning anses som en klasse-effekt ved HER2-rettede lægemidler.

Sikkerhedsstudie-populationen for T-DXd havde generelt god performance status og med relativt få symptomer på deres underliggende metastatiske brystkræftssygdom på trods af at have modtaget mange tidligere behandlinger. Den gode performance status kan medvirke til en underestimering af bivirkningerne i samme population. Overordnet vurderer fagudvalget, at risikoen for ILD er den mest alvorlige risiko ved T-DXd-behandling. Det stemmer også overens med, at andre HER2-rettede behandlinger såsom trastuzumab, trastuzumab emtansin (TDM-1) samt topoisomerasehæmmere har vist lungetoksicitet [20,21].

Fagudvalget vurderer på den baggrund, at det er vigtigt at have skærpet opmærksomhed omkring lungetoksicitet ved behandling med T-DXd.

Samlet vurdering af bivirkningsprofiler
Fagudvalget bemærker på baggrund af ovenstående gennemgang af bivirkningsprofilerne for hhv. T-DXd og trastuzumab + capecitabin, at bivirkningsprofilerne er forskellige, hvor begge lægemidler kan medføre en række uønskede hændelser. Særligt er fagudvalget opmærksom på risikoen for lunge- og hjertetoksicitet ved behandling med T-DXd, men hvor hjertetoksicitet er en kendt bivirkning ved HER2-rettet behandling. Fagudvalget understreger, at særligt ILD er en alvorlig og potentielt dødelig bivirkning, der kræver øget opmærksomhed og tidlig behandling. Fagudvalget finder, at lægemidlerne overordnet set er sammenlignelige, hvad angår byrden af bivirkninger, reversibilitet og håndterbarhed for læge og patient.

Samlet vurdering for effektmålet bivirkninger

Baseret på ovenstående gennemgang af effektmålets to delmål vurderer fagudvalget, at T-DXd aggregeret har **en værdi, som ikke kan kategoriseres** vedr. effektmålet bivirkninger. Der er ikke data til en formel sammenligning af delmålet grad 3-4 bivirkninger, som derfor ikke kan kategoriseres efter Medicinrådets metoder. Ud fra den kvalitative gennemgang af bivirkningsprofiler finder fagudvalget, at bivirkningsprofilerne er forskellige, men at lægemidlerne er sammenlignelige, hvad angår bivirkningernes sværhedsgrad. Fagudvalget bemærker dog, at kvaliteten af data er meget begrænset, og at vurderingen derfor er behæftet med stor usikkerhed.

Stabilisering eller forbedring af symptomer
Som beskrevet i protokollen ønsker fagudvalget at belyse forskellen i andel patienter, som opnår stabilisering eller forbedring af symptomer vha. PFS. PFS bliver anvendt til at vurdere, hvor lang tid der går, inden patienternes sygdom udvikler sig. Tredjelinjebehandling er den sidste mulige standardbehandling for patienter med metastatisk HER2+ brystkræft. Fagudvalget vurderer derfor, at det er af stor værdi for patienterne at modtage en behandling, som stabiliserer deres sygdom og forlænger tiden til progression, og fagudvalget anser derfor effektmålet som vigtigt. Stabilisering af sygdommen betyder ofte, at patienterne undgår forværring af deres symptomer for en tid. Fagudvalget fremhæver, at det har særlig betydning for patienterne at forblive i en

effektiv behandling så længe som muligt. Den mindste klinisk relevante forskel er sat til 3 måneder for median PFS.

Data for PFS er opgjort i alle de inkluderede studier. I DESTINY-Breast01 er median PFS estimeret ved kun 38 % modenhed (62 % af patienterne (n = 114) er censureret) ved en median follow-up på 20,5 måneder. I hhv. NALA, SOPHIA og HER2CLIMB er den mediane follow-up på 29,9, 2,8 og 14 måneder.
[redacted]

For patienter behandlet med T-DXd er den mediane PFS 19,4 måneder (14,1;NE). For behandling med capecitabin + lapatinib (NALA), trastuzumab + kemoterapi (SOPHIA), trastuzumab + capecitabin (HER2CLIMB og DBCG) er den mediane PFS hhv. 5,5, 5,6, 4,4 og [redacted] (se tabel 3). Fagudvalget finder, at de tilgængelige effektestimater indikerer, at stabilisering eller forbedring af symptomer målt ved PFS er markant længere for patienter behandlet med T-DXd end ved de andre behandlingskombinationer. Fagudvalget understreger, at de store forskelle på tværs af studierne medfører, at den kvalitative sammenligning er behæftet med stor usikkerhed.

Fagudvalget vurderer, at T-DXd aggregeret har en **værdi, der ikke kan kategoriseres** vedr. effektmålet stabilisering eller forbedring af symptomer, da fagudvalget ikke kan vurdere eventuelle forskelle mellem T-DXd og de forskellige komparatorer grundet usikkerhederne forbundet med data. Med afsæt i den kvalitative sammenligning finder fagudvalget imidlertid, at der ikke er noget, der taler for, at T-DXd er dårligere end komparator.

Til perspektivering inddrager fagudvalget MAIC-analyserne for DESTINY-Breast01 og hhv. NALA, SOPHIA og HER2CLIMB. Resultatet af MAIC-analyserne fremgår af nedenstående tabel.

Tabel 6. Resultater for MAIC-analysen vedr. effektmålet PFS

Studie	Behandlingsarm	Patientantal	Absolut effektforskel	Relativ effektforskel
NALA	Capecitabin + lapatinib	314	16,7 måneder	HR: 0,16 (0,08;0,29)
DESTINY-Breast01 (justeret)	T-DXd	24,6		
HER2CLIMB	Trastuzumab + capecitabin	202	>16,6 måneder	HR: 0,09 (0,03;0,22)
DESTINY-Breast01 (justeret)	T-DXd	7,5		
SOPHIA	Trastuzumab + kemoterapi	270	18,5 måneder	HR: 0,12 (0,06;0,21)
DESTINY-Breast01 (justeret)	T-DXd	27,9		

I alle MAIC-analyserne er den absolutte forskel større end den mindste klinisk relevante forskel på 3 måneder. Tilsvarende indikerer de relative effektforskelle, at T-DXd har en stor merværdi sammenlignet med komparator. Der gælder dog for samtlige analyser, at pga. manglende ligheder mellem komparator-populationen og T-DXd-behandlingsarmen er patientantallet for T-DXd reduceret betydeligt ved MAIC-analysen.

Fagudvalget bruger derfor udelukkende MAIC-analyserne til perspektivering, da de er forbundet med stor usikkerhed og dermed bør anvendes med store forbehold. Fagudvalget finder, at MAIC-analyserne understøtter den ovenstående konklusion vedr. effektmålet PFS.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at T-DXd til patienter med metastatisk HER2+ brystkræft, som har progredieret på to HER2-rettede behandlinger, giver en **værdi, der ikke kan kategoriseres** efter Medicinrådets metoder sammenlignet med komparator.

Datagrundlaget har ikke tilladt, at effekten af T-DXd kunne kategoriseres efter Medicinrådets metoder. Derfor har fagudvalget sammenlignet T-DXd og komparator i en kvalitativ sammenligning. Den kvalitative sammenligning er behæftet med stor usikkerhed, da særligt studiepopulationerne er meget forskellige på tværs af studierne og i sammenligning med DESTINY-Breast01. For samtlige effektmål har fagudvalget derfor ikke kunnet vurdere, om der er eventuelle forskelle mellem T-DXd og de forskellige komparatorer.

Fagudvalget fremhæver, at T-DXd formentlig forlænger overlevelsen og ikke mindst tid til progression, sammenlignet med trastuzumab + capecitabin og at dette sker efter behandling med T-DM1. Det lader således til, at T-DXd er et virksomt stof, som er

gavnligt efter behandling med T-DM1. Fagudvalget understreger dog, at analyserne er behæftet med stor usikkerhed. Fagudvalget finder derudover, at T-DXd's sikkerhedsprofil ikke er dårligere end ved nuværende standardbehandling, og at der er en risiko for en alvorlig bivirkning i form af ILD.

Fagudvalget understreger på baggrund af ovenstående, at T-DXd formentlig er et virksomt stof efter behandling med T-DM1, men at det med afsæt i det foreliggende data ikke er muligt at vurdere, om T-DXd er bedre – og i givet fald hvor meget – sammenlignet med standardbehandling.

Fagudvalget understreger yderligere, at nye studier med en direkte sammenligning af T-DXd med standardbehandling formentligt kan ændre den samlede vurdering.

6. Andre overvejelser

Antal tidligere behandlinger
Fagudvalget har i protokollen for T-DXd efterspurgt en redegørelse for antallet af behandlingslinjer, som patienter modtager i det kliniske studie, og en beskrivelse af, hvad en eventuel forskel kan have af betydning for effekt af behandling med T-DXd i hhv. studiet og i dansk klinisk praksis.

Ansøger har ikke besvaret dette punkt direkte, men henviser til besvarelsen af klinisk spørgsmål 1 i den endelige ansøgning. Her fremgår det, at der er forskel i antallet af tidligere behandlinger i de inkluderede studier, og at antallet af behandlinger er en stærk negativ prognostisk faktor.

Fagudvalget konstaterer, at der er væsentlige forskelle i antallet af tidligere modtagende behandlinger i de forskellige studiepopulationer, og at det vanskeliggør sammenligninger (se afsnit 5.1.1 og 5.1.2 for uddybning heraf).

Performance status
Fagudvalget konstaterer, at det kun er patienter med ECOG-performance status 0 og 1, der er inkluderet i DESTINY-Breast01 og NALA, og at dette afviger fra en forventet dansk klinisk praksis, hvor patienter med HER2-positiv brystkræft med performance status 0, 1 og 2 tilbydes behandling i tredje linje.

Efterfølgende behandling
Medicinrådet har efterspurgt informationer, der kan belyse, om og hvordan indførelsen af T-DXd i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer, hvad angår type, varighed og forventet effekt.

Ansøger svarer, at de ikke forventer stor påvirkning af behandlingstype, varighed eller effekt, idet overlevelse efter progression ikke forventes at blive påvirket. I nogle tilfælde vil nuværende tredjelinjebehandling blive rykket til fjerdelinjebehandling, men pga. en forventet dårlig effekt af en eventuel fjerdelinjebehandling og en kort forventet overlevelse vurderes det ikke at have stor betydning.

Fagudvalget konstaterer, at der er store usikkerheder om effekten af T-DXd og i endnu højere grad effekten af eventuelle behandlingslinjer efter T-DXd.

En anden overvejelse fra fagudvalget er, om T-DM1 i samme grad fremover vil kunne gives som andenlinjebehandling, da det er standard som adjuverende behandling ved non-pCR og dermed vil påvirke rækkefølgen af den metastatiske behandling.

Data med længere opfølgningstid

Virksomheden har undervejs i processen indleveret data efter længere opfølgningstid, som ikke indgår direkte i vurderingsrapporten. Fagudvalget har gennemgået det fremsendte data og vurderet, at resultaterne ikke afviger fra resultaterne efter kortere opfølgningstid, som ligger til grund for vurderingen. Fagudvalget finder således, at de nye data understøtter fagudvalgets initiale vurdering og ikke medfører behov for ændringer i konklusionerne i vurderingsrapporten.

7. Relation til behandlingsvejledning

Medicinrådet har ikke foretaget en gennemgang af hele terapiområdet og har derfor ikke taget stilling til det øvrige kliniske grundlag i RADS' baggrundsnotat (se https://rads.dk/media/2121/bgn-anti-her2-feb-2016.pdf), herunder placering af trastuzumab emtansin (TDM-1) og lapatinib ved metastatisk sygdom i andenlinjebehandling og metastatisk sygdom *treatment beyond progression*.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende brystkræft

Sammensætning af fagudvalg	
Formand	**Indstillet af**
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Julia Kenholm *Overlæge*	Region Midtjylland
Jeanette Dupont Jensen *Overlæge*	Region Syddanmark
Alexey Lodin *Afdelingslæge*	Region Sjælland
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Eva Balslev *Overlæge*	Inviteret af formanden
Guri Spiegelhauer *Sygeplejerske*	Dansk Sygepleje Selskab
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Patient/patientrepræsentant	Danske Patienter

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.1	29. september	På baggrund af et nyt datacut har fagudvalget præciseret ordlyden i deres konklusion samt indsat et afsnit under 'andre overvejelser' Fagudvalgets kategorisering og Medicinrådets konklusion er ikke ændret
1.0	1. september 2021	Godkendt af Medicinrådet.

Medicinrådet

Application for the assessment of Enhertu (Trastuzumab Deruxtecan) for human epidermal receptor 2 (HER2) positive advanced breast cancer after two or more prior anti-HER2-based regimens.

INCLUDE CONFIDENTIAL DATA HIGHLIGHTED IN YELLOW.

[redacted]

Contents

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Overview of the pharmaceutical	
Proprietary name	Enhertu
Generic name	Trastuzumab Deruxtecan (T-DXd)/DS-8201a
Marketing authorization holder in Denmark	Daiichi Sankyo Europe GmbH, Zielstattstr. 48, 81379 Munich, Germany
ATC code	L01XC41
Pharmacotherapeutic group	Monoclonal antibody specifically targeting HER2,
Active substance(s)	Trastuzumab deruxtecan
Pharmaceutical form(s)	Intravenous (IV) every 3 weeks, 5.4 mg/kg, powder for concentrate for solution for infusion 100 mg/vial. T-DXd will be administered at room temperature by controlled infusion into a peripheral or central vein. Standard infusion time ~90 min ± 10 min for first infusion. If the first infusion is well tolerated, with no infusion-related reaction(s), then the minimum infusion time for subsequent cycles is 30 min. If there are interruptions during infusion, the total allowed infusion time should not exceed 3 hours at room temperature.
Mechanism of action	T-DXd is a novel next generation HER2-targeted ADC designed to deliver optimal antitumor effect. T-DXd is composed of a humanised mAb specifically targeting HER2, with the same amino acid sequence as trastuzumab, covalently linked to a camptothecin analogue (known as a topoisomerase I inhibitor) via a tetrapeptide-based cleavable linker. Specifically, deruxtecan is composed of the linker and the cytotoxic topoisomerase I inhibitor payload (a water-soluble exatecan derivative [DXd]).
Dosage regimen	5.4 mg/kg IV every 3 weeks
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	EMA's approval Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti HER2 based regimens
Other approved therapeutic indications	HER2 positive unresectable or metastatic breast cancer is the first indication for the product in Denmark
Will dispensing be restricted to hospitals?	Yes. Labelled BEGR
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	100 mg vial. Powder. Reconstitute each 100 mg vial using a sterile syringe to slowly inject 5 mL of water for injection into each vial to obtain a final concentration of 20 mg/mL. Dilute the calculated volume of reconstituted Enhertu in an infusion bag containing 100 mL of 5% glucose solution. Enhertu was launched in medicinpriser.dk on April 5th
Orphan drug designation	No
Is the drug evaluated in an accelerated process at EMA?	Yes

2. Abbreviations

3L	Third line
3L+	Third line and beyond
ADC	Antibody drug conjugate
AE	Adverse event
ATC	Anatomic Therapeutic Chemical classification system
AZ	AstraZeneca
CBR	Clinical benefit rate
CI	Confidence interval
CR	Complete response
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DB01	DESTINY-Breast01 study
DBCG	Danish Breast Cancer Group
DCR	Disease control rate
DoR	Duration of response
DS	Daiichi Sankyo
DXd	The payload of T-DXd, a potent topoisomerase I inhibitor
ESMO	European Society for Medical Oncology
HER2	Human Epidermal Growth Factor receptor 2
HR	Hormone Receptor
HR	Hazard ratio
HRQoL	Health-Related Quality-of-Life
ILD	Interstitial lung disease
ISH	in-situ hybridisation
ITT	Intention to treat
IV	intravenous
LOT	Line of treatment
LY	Life years

MAIC	Matched adjusted indirect comparison
mBC	Metastatic Breast Cancer
mCRM	modified continuous reassessment method
N/A	Not available
NE	Not evaluated
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Q3W	Every three weeks
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
SC	Subcutaneous
SD	Stable Disease
SD	Standard deviation
SLR	Systematic literature research
SoC	Standard of Care
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment emergent adverse event
TTD	Time to treatment discontinuation
TTR	Time to response
vs	Versus

3. Summary

Background

Breast cancer is the most common cancer in women worldwide (1, 2). In Denmark, about 4.900 women are diagnosed with breast cancer yearly (3, 4). Of these approximately 13.9 % are characterized by overexpression or gene amplification of HER2 (5), a protein that function as a receptor on breast cells (5). This mean that 680 Danish patients will get HER2+ breast cancer every year, which is slightly lower than the number estimated by Medicinrådet (DMC) (4).

When it comes to HER2-positive metastatic breast cancer, no obvious standard of care has been defined after the administration of pertuzumab + trastuzumab + vinorelbine and trastuzumab emtansine (T-DM1) (6). A recent registry study conducted by Danish Breast Cancer Group (DBCG) showed that the overall and progression-free survival post T-DM1 is [redacted] and [redacted] months, respectively (2). Further, the currently available options have limited benefit, with objective response rates of approximately 9 to 31% (7-10). This highlights the need for additional effective treatment options.

Enhertu(Trastuzumab deruxtecan)

Trastuzumab deruxtecan (T-DXd) is a novel next generation HER2-targeted antibody-drug conjugate designed to deliver optimal antitumor effect. T-DXd is composed of a humanized monoclonal antibody specifically targeting HER2, with the same amino acid sequence as trastuzumab, covalently linked to a camptothecin analogue (known as a topoisomerase I inhibitor) via a tetrapeptide-based cleavable linker. T-DXd was designed to overcome the efficacy and toxicity limitations of earlier antibody drug conjugates (such as TDM-1)(11-13).

T-DXd is indicated and approved by EMA as a monotherapy of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens (14) based on evidence from the DESTINY-Breast01 study. Since 20 April 2021, T-DXd is also considered cost-effective and recommended by the National Institute for Health and Care Excellence (NICE) in the UK (15).

DESTINY-Breast01 study

DESTINY-Breast01 is a phase II, multicenter study of T-DXd in patients with HER2+, unresectable, and/or metastatic breast cancer who were previously treated with T-DM1. In an updated analysis from June 2020, patients experienced a median progression-free survival of 19.4 months (95% CI: 14.1 - NE), 74% of the patients were estimated to be alive after 18 months, 61.4 % achieved an objective response with a median duration of response of 20.8 months and a disease control rate of 97.3% (16).

Comparative evidence

Data from DESTINY-Breast01 is the backbone of this application. The study is single-armed but we have been able to compare the results from the T-DXd study with the comparator selected in the protocol and Danish clinical practice in a treatment line that is not well-described in guidelines etc. Based on indirect comparisons, all relevant endpoints greatly exceed what is previously reported for this patient population in recent studies, which was also the reason T-DXd was granted an accelerated assessment and approval by EMA. The endpoints in the study also significantly exceeds what is observed in Danish clinical practice (2).

Outcome	DESTINY-Breast01 (16, 17)	The NALA study (7)	Danish clinical practice (2)
Median OS, months (95% CI)	24.6 (23.1 – NE)	18.7 (15.5 – 21.2)	[redacted]
Median PFS, months (95% CI)	19.4 (14.1 – NE)	5.5 (4.3 – 5.6)	[redacted]
ORR, % (95% CI)	61.4 (54.0 – 68.5)	26.7 (21.5 – 32.4)	N/A

Despite being significantly more pre-treated, the patients in DESTINY-Breast01 lived ~6 months longer than patients in the most relevant comparator study (the NALA study) and in Danish clinical practice. Further, the PFS and ORR reported in DESTINY-Breast01 exceeded any reported results in this population with more than 13 months for PFS and more than 34% for objective response rate (ORR). All outcomes exceeds the threshold for minimal clinically relevant difference.

While the quality of life in breast cancer patients are often connected to disease progression (18) and a positive impact of T-DXd therefore should be expected, there is currently no data available on this outcome that can be used for a DMC assessment. The AE profile of T-DXd is similar to trastuzumab in combination with capecitabine but interstitial lung disease (ILD) should be monitored by the treating clinicians. Phase III studies are ongoing and we will submit updates on the progress of these as part of a recommendation of T-DXd by Medicine Council.

4. Literature search

The search strategy to identify the relevant literature was conducted on PubMed and CENTRAL and was in line with the strategy outlined in the DMC protocol (4). The search strings are provided in Table 1 and Table 2.

Table 1. PubMed search string

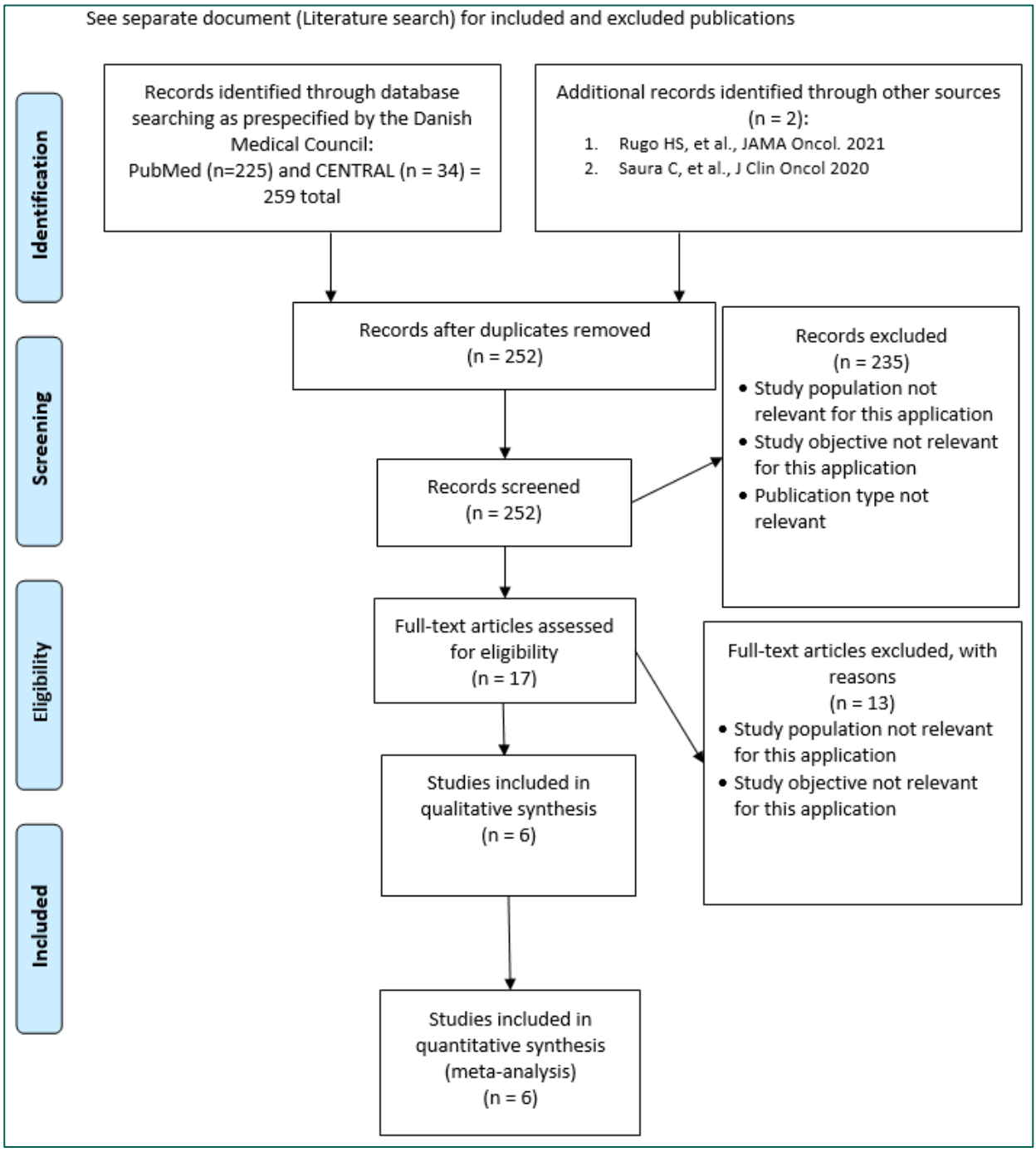
Search	Query	Results
#12	Search: #10 NOT #11	225
#11	Search: Case Reports [pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report [ti]	6,759,749
#10	Search:#5 and #9	462
#9	Search: #6 OR (#7 AND #8)	703
#8	Search:Trastuzumab[mh] OR trastuzumab [tiab] OR Herceptin*[tiab]	12,535
#7	Search:Capecitabine[mh] OR capecitabine[tiab] OR Xeloda*[tiab]	7,575
#6	Search: trastuzumab deruxtecan[nm] OR (trastuzumab[tiab] AND deruxtecan[tiab]) OR Enhertu*[tiab] OR T-DXd[tiab]	82
#5	Search:#3 AND #4	129,247
#4	Search:advanced[tiab] OR inperable[tiab] OR "non resectable" [tiab] OR "not resectable" [tiab] OR unresectable[tiab] OR relaps*[tiab] OR metasta*[tw] OR recurren*[tw]	1,696,459
#3	Search: #1 OR #2	425,609
#2	Search: (breast[tiab] OR mammary[tiab]) AND (cancer[tiab] OR carcinoma[tiab])	359,910
#1	Search: Breast Neoplasms[mh]	301,312

Table 2. Central search string

Search	Query	Results
#1	((breast or mammary) near/2 (cancer og carcinoma)):ti,ab,kw	35,659
#2	(advanced or metasta* or unresectable or un-resectable or non-resectable or inoperable) :ti,ab,kw	88,775
#3	#1 AND #2	12,896
#4	(trastuzumab next deruxtecan or Enhertu* or T-DXd) :ti,ab,kw	36
#5	(capecitabine or Xeloda*):ti,ab,kw	3,972
#6	(trastuzumab or Herceptin*):ti,ab,kw	2,858
#7	#4 OR (#5 AND #6)	394
#8	#3 AND #7	270
#9	("conference abstract" or review) :ti,pt	192,338
#10	(clinicaltrials.gov or trialsearch):so	356,147
#11	NCT*:au	204,358
#12	(abstract or conference or meeting or proceeding*):so	44,807
#13	#9 or #10 or #11 or #12	578,202
#14	#8 not #13	93
#15	#14 not pubmed:an	34

The PRISMA flow diagram in Figure 1 show the number of references identified and the number of included and excluded references. A list of references excluded after full-text screening is provided, as Appendix B including the reasons for exclusion of each reference (separate file).

Figure 1. Prisma diagram of literature review for trastuzumab deruxtecan



***Source**: Figure adapted from Moher et al. (2009). (19)*

4.1.Relevant studies

The relevant studies identified in the SLR is summarized in

Table 3.

Table 3. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question 1
Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer S. Modi et al.N Engl J Med 2020; 382:610-621, February 13, 2020 (16, 17)	DESTINY-Breast01	NCT03248492	Inclusion between October 2017 and September 2018.	Yes
Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. Tamura K. et al. Lancet Oncol. 2019 Jun;20(6):816-826 (20)	J101	NCT02564900	August 28th 2015, and August 10th 2018	No
Efficacy of Margetuximab vs Trastuzumab in Patients with Pretreated ERBB2-Positive Advanced Breast Cancer.A Phase 3 Randomized Clinical Trial Rugo HS. JAMA Oncol. 2021;7(4):573-584 (8)	SOPHIA	NCT0249271	July 2015 to October 2018	Yes
Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. Murthy et al. N Engl J Med 2020; 382:597-609 (9)	HER2CLIMB	NCT02614794.	February 23rd 2016, and May 3rd 2019.	Yes
Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated with ≥ 2 HER2-Directed Regimens: Phase III NALA Trial Saura C et al. N Engl J Med 2020; 382:597-609 (7)	NALA	NCT01808573	Between May 29, 2013 and July 21, 2017	Yes
A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients with Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Pivot et al. J Clin Oncol.2015 May 10;33(14):1564-73 (21)	CEREBEL	NCT00820222	First patient in April 14th 2009, and the study was terminated on June 11, 2012, on recommendation of the IDMC, after analysis of interim safety and efficacy data from 475 randomly assigned patients.	No

As described in the table, not all studies were deemed relevant for the clinical question 1. The studies were assessed qualitatively on an individual basis, and in collaboration with Danish clinical experts. Five main criteria, as listed below, were used in the assessment to make sure they are in line with the PICO reported in the DMC protocol (4):

1. Treatment in the study should be of relevance with respect to clinical practice in Denmark. For this application DMC has included capecitabine in combination with trastuzumab as comparator. However, as stated by DMC, the clinical outcome of chemotherapy combined with either trastuzumab or lapatinib is expected to result in similar outcomes (22) and can also be considered to represent Danish clinical practice.

2. Majority of patients should be in third line or later. T-DXd is expected to be used after pertuzumab + trastuzumab + vinorelbine and T-DM1, which is in line with the DMC protocol. Depending on the exact definition of treatment lines and individual patient characteristics, patients relevant for T-DXD treatment will therefore be in third or later line.
3. More than 50% of the patients in the study should have received pertuzumab or T-DM1 in prior lines. Danish clinical experts stated that studies conducted before pertuzumab and T-DM1 was given as standard of care are not fully relevant for Danish clinical practice.
4. The included studies should have a prospective and controlled study design, such as phase II+ trials to avoid selection bias.
5. Studies do not exclude patients with stable brain metastases. These patients are not a negligible part of the patients treated in Danish clinical practice and should be included to be representative.

Three studies in addition to the DESTINY-Breast01 study were considered appropriate for the assessment as they fulfilled criteria 1 - 5:

- Murthy et al., (9); the HER2CLIMB study with a control arm of trastuzumab plus capecitabine
- Rugo et al., (8); the SOPHIA study with a control arm of trastuzumab plus chemotherapy
- Saura et al., (7); the NALA study with a control arm of lapatinib plus capecitabine

These three studies were also the studies that Danish clinical experts deemed most appropriate for an indirect comparison versus DESTINY-Breast01 and the studies EMA selected for their naïve comparison in their assessment of T-DXd (23). The relevance of each of these studies are further discussed in section 5.1.1.

4.1.1. Excluded studies mentioned in the protocol

The CEREBEL study mainly included first-line patients, the number of third line patients are not reported, excluded patients with brain metastases and 65% of the patients had not received trastuzumab for metastatic disease prior to the study. The lack of prior trastuzumab treatment is important as resistance to trastuzumab is an important factor in later treatment lines (21). Real-world data of Danish patients show that the results and the patients characteristics in CEREBEL is not representative of the population relevant for this assessment (2). This make the CEREBEL study irrelevant for a third line population and for Danish clinical practice in general.

J101 was excluded for clinical question 1, as it is a phase I study. While the result in that study is similar to the result of DESTINY-Breast01, DESTINY-Breast01 was the core evidence for the EMA approval and more suitable for DMC decision making.

4.2. Main characteristics of included studies

4.2.1. The DESTINY-Breast01 study

The Phase II DESTINY-Breast01 trial is currently ongoing in adult patients with HER2+, unresectable, and/or metastatic breast cancer, who have breast cancer that is resistant or refractory to T-DM1.

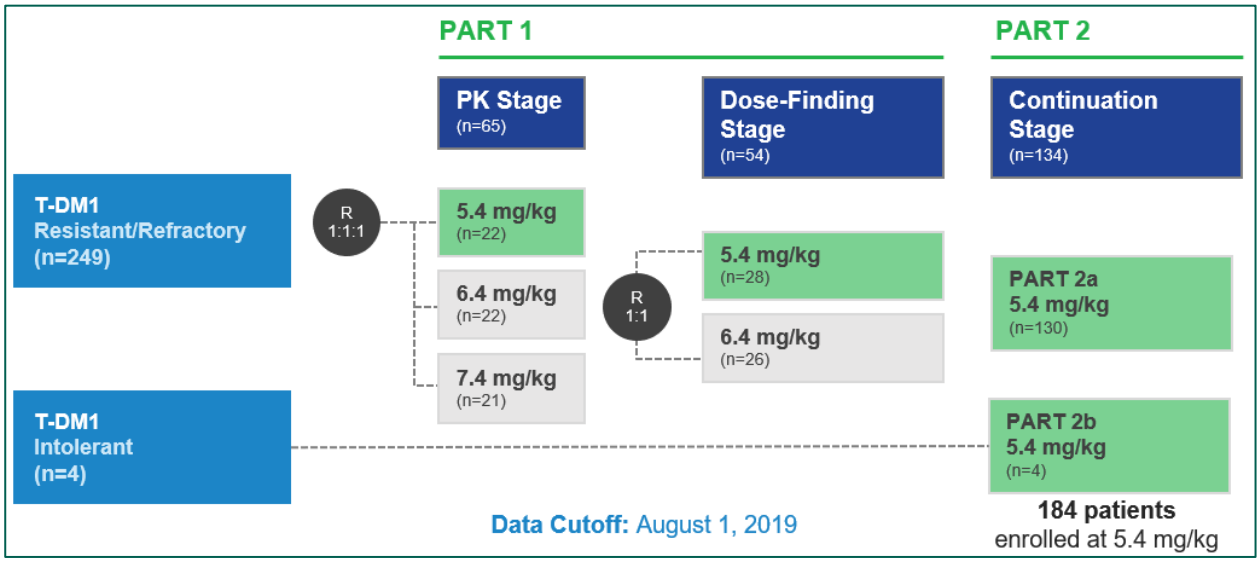
In Part 1 of this study, T-DXd was administered as an (intravenous) IV solution at a dose of 7.4 mg/kg, 6.4 mg/kg, or 5.4 mg/kg every 3 weeks (17). The initial dose of T-DXd was infused for approximately 90 minutes; if there was no infusion-related reaction, after the initial dose, the next doses of T-DXd were infused for approximately 30 minutes.

Figure 2 presents the study design of the two-part Phase II DESTINY-Breast01 trial. Part 1 enrolled 163 patients in a two-stage design (17):

- **Pharmacokinetics stage:** A total of 65 were randomized in a 1:1:1 ratio to receive T-DXd dosing at 7.4 mg/kg (21 patients), 6.4 mg/kg (22 patients), and 5.4 mg/kg (22 patients). The resulting pharmacokinetics profiles were analyzed in conjunction with those reported for the Phase I trial, J101; the doses chosen for the dose-finding stage were 5.4 and 6.4 mg/kg

- **Dose-finding stage:** A total of 54 patients were randomized in a 1:1 ratio to receive 5.4 mg/kg (28 patients) and 6.4 mg/kg (26 patients) of T-DXd. Following a dose selection analysis, the dose of 5.4 mg/kg was selected based on a predicted benefit: risk profile modelled from exposure-response, exposure-safety, and pharmacokinetics analyses, while incorporating observed clinical data from this study and the Phase I trial, J101. The 6.4 mg/kg was projected to have a higher rate of efficacy but also a higher risk of TEAEs, dose reductions, or discontinuations due to TEAEs; as such, 5.4 mg/kg was selected as the most suitable dose for Part 2 (16).

Figure 2: DESTINY-Breast01 study design



***Source**: Modi, Saura (17)*

Part 2 of the study evaluated the safety and efficacy in patients treated at the 5.4 mg/kg dose (17). Consistent with Part 1, Part 2a enrolled patients with mBC that had progressed on or after T-DM1. At data cut-off of 8 June, 2020, Part 2a had enrolled 130 patients (16). Part 2b enrolled an open ended number of patients that were intolerant to T-DM1 and were not eligible for the primary analysis of ORR; these patients must have discontinued T-DM1 treatment for reasons other than resistant or refractory disease. At data cut-off of 8 June, 2020, Part 2b had enrolled 4 patients. (16)

Of relevance for this submission is all patients that received the dose conditionally approved by EMA (5.4 mg/kg). Hence, if nothing else is stated all data reported from DESTINY-Breast01 in this submission concerns the 184 patients receiving 5.4 mg/kg in Part 1, Parts 2a and 2b.

In the study, the primary endpoint is ORR (complete response plus partial response) assessed by independent central imaging facility review according to RECIST Version 1.1 (17).

The secondary efficacy endpoints in the Phase II DESTINY-Breast01 study included (17):

- Overall survival (OS)
- PFS based independent radiologic facility review
- Duration of response (DoR) based on investigator assessment
- Best percent change in the sum of the diameter of measurable tumours
- Disease control rate (DCR) based on investigator assessment
- Clinical benefit rate (CBR) based on investigator assessment
- ORR based on investigator assessment

The DESTINY-Breast01 is summarized in Table 19 in the supplementary materials.

4.2.2. Comparator studies

4.2.2.1. The HER2CLIMB trial

The HER2CLIMB trial is a Phase 2 randomized, international, multi-center, double-blinded study of tucatinib or placebo in combination with capecitabine and trastuzumab in patients with unresectable locally advanced or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab and T-DM1. The control arm of trastuzumab in combination with capecitabine in the HER2CLIMB trial is expected to be reflective of the current standard of care and the study significantly overlaps with the DMC protocol and DESTINY-Breast01 study in terms of study population and design.

Details of the HER2CLIMB trial are summarised in Table 27 in the supplementary materials.

4.2.2.2. The SOPHIA trial

The SOPHIA trial is a phase 3, randomized, open-label, comparator-controlled study comparing margetuximab to trastuzumab, each in combination with chemotherapy, for the treatment of adult patients with advanced HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy in the metastatic setting, or in case of having received (neo)adjuvant pertuzumab, at least 1 prior line of anti-HER2 directed therapy in the metastatic setting, and who have received at least one, and no more than three lines of therapy overall in the metastatic setting. Patients must have progressed on or following the most recent therapy. Eligible patients were assigned to chemotherapy of the investigator's choice to be chosen from capecitabine, eribulin, gemcitabine, or vinorelbine. They received either margetuximab or trastuzumab to be administered in combination with the chosen chemotherapy. Patients were treated until disease progression, death, withdrawal of consent, or request by the treating physician to discontinue treatment.

The control arm of trastuzumab in combination with chemotherapy in the SOPHIA trial is expected to be reflective of the current standard of care and the study significantly overlaps with the DMC protocol and the DESTINY-Breast01 study in terms of study population and design.

Details of the SOPHIA trial are summarised in Table 27 in the supplementary materials.

4.2.2.3. The NALA trial

The NALA trial is a randomized, multi-center, multinational, open-label, active-controlled, parallel design phase III trial comparing capecitabine in combination with neratinib and capecitabine in combination with lapatinib in HER2-positive metastatic breast cancer. Eligible patients were age ≥ 18 years, with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 and ≥ 2 previous HER2-directed therapies for metastatic breast cancer. Patients with brain metastases were eligible unless they had symptomatic or unstable brain metastases. 621 eligible patients were randomly assigned (1:1) to capecitabine in combination with neratinib or capecitabine in combination with lapatinib. The control arm, capecitabine in combination with lapatinib, in the NALA study (7) is expected to be reflective of the current standard of care in Denmark and in line with the DMC protocol.

Details of the NALA trial are summarised in Table 24 in the supplementary materials.

4.2.2.4. [redacted]

[redacted]

5. Clinical questions 1. T-DXd vs capecitabine plus trastuzumab in HER2+ breast cancer

The PICO for clinical question 1 is summarised in Table 4.

Table 4. Summary of clinical question in the DMC protocol

Question	Hvilken værdi har trastuzumab deruxtecan (T-DXd) sammenlignet med capecitabine i kombination med trastuzumab for patienter med metastatisk HER2+ brystkræft, som har progredieret på to HER2-rettede behandlinger?
Population	Patienter med inoperabel lokalt fremskreden og/eller metastatisk HER2+ brystkræft, som har progredieret på to HER2-rettede behandlinger.
Intervention	Trastuzumab deruxtecan (T-DXd), intravenøst, 5,4 mg/kg hver tredje uge.
Komparator	Capecitabine (1.000 mg/m2 pr. dag oralt i 14 dage) i kombination med trastuzumab (opstartsdosering 8mg/kg, vedligeholdelsesdosering 6mg/kg)
Effektmål	OS, HRQoL, AEs og PFS

5.1.T-DXd vs capecitabine plus trastuzumab in HER2+ breast cancer

5.1.1. Presentation of relevant studies

Details of the studies relevant for the assessments are provided in section 4.1 and in the appendix. The studies relevant for assessing clinical question 1 is as outlined in section 4.1:

- The DESTINY-Breast01 study
- The NALA study
- The HER2CLIMB study
- The SOPHIA study

Table 5 present a summary of these trials and the results from a real-world study of Danish patients conducted by the DBCG (2).

In the DBCG study, patients were included on the date of progression leading to subsequent initiation of third line treatment if the patient received T-DM1 in first or second line. If the patient received T-DM1 in third line or later the inclusion was based on the date of progression on T-DM1. Inclusion dates were between 1st of January 2014 and 31st of December 2019. The study population with this study design perfectly matches the population where T-DXd will be used in Denmark. It also represent a population in line with the population described in the DMC protocol. However, as the patients are included on the date of progression on the previous line of treatment rather than the start of treatment, the overall survival is likely slightly overestimated in the DBCG data. This is due to subsequent treatment not always being instantly initiated.

Table 5. Summary of the reported patient characteristics in relevant studies

	Danish clinical practice, DBCG data (2)	DESTINY-Breast01 (16, 17)	NALA (7)	SOPHIA (8)	HER2CLIMB (9)
Intervention of interest		Trastuzumab deruxtecan	Lapatinib + capecitabine	Trastuzumab + chemotherapy	Trastuzumab + capecitabine
Study design	Real-world data	Single-armed multicentre study	RCT multicentre study	RCT multicentre study	RCT multicentre study
Phase	N/A	Phase II	Phase III	Phase III	Phase II
Patients number, n		184	314	270	160/202
Median age (range)		55 (28-96)	54	56 (27-86)	54
Median prior lines (range)		6 (2-27)	2	-	3 (1–13)
Prior lines ≥3		90.8	31.5	33.0	-
Prior T-DM1 (%)		100	56.7**	91.5	100
Prior pertuzumab in the metastatic setting (%)		65.8	41.7	99.6	99.4
ECOG PS = 0 (%)		55.4	52.2	59.6	47.5
HR+ (%)		52.7	59.2	63.0	61.9
Metastatic sites					
bone (%)		28.8	47.1	57.4	53.1
lung (%)		57.1	55.4	46.7	51.2
liver (%)		30.4	47.1	35.2	40.0
CNS (%)		13.0	15.9	12.6	44.4
Visceral (%)		91.8	86.0		
Top line results					
PFS, month (95%, CI)		19.4 (14.1 – NE	5.5 (4.3 – 5.6)	4.4 (4.1 – 5.5)	5.6 (4.2 – 7.1)
OS, month (95%, CI)		24.6 (23.1 – NE)	18.7 (15.5 – 21.2)	19.8 (17.5 – 22.3)	17.4 (13.6 – 19.9)

***Key**: CI: confidence interval, N/A: not applicable, NE: not estimable, PFS: progression-free survival, OS: Overall survival.*Mean, **Calculated based on 20.4% trastuzumab, T-DM1 + 36.3% trastuzumab, pertuzumab, T-DM1.*

The comparator studies and DESTINY-Breast01 reported similar data for most patient characteristics parameters. Two important differences pointed out by Danish clinical experts were, that the number of prior lines was higher in DESTINY-Breast01 than in the other studies and that the proportion of the patients with brain metastases were higher in the HER2CLIMB study (9). Both parameters are associated with shorter expected OS and PFS according to Danish clinical experts.

As shown in Table 5, but also reported in the DMC protocol, the NALA study (5) is likely the study that is most similar to the relevant population in Denmark. The PFS and OS outcomes in this trial are also almost identical to the outcomes in the relevant population in clinical practice in Denmark. The SOPHIA trial, include patients with less than two prior lines of treatment for metastatic disease and excluded patients if they had more than three lines of therapy overall in the metastatic setting. This is indicated by the long survival after progression in that study compared to the other sources and makes the results less representative of the relevant Danish clinical practice and less in line with the DMC protocol. The HER2CLIMB study includes a disproportionally high number of patients with brain metastases, which is likely the reason for the shorter post progression survival compared to patients in Danish clinical practice.

Overall this makes the NALA study the most relevant for answering the clinical questions. However, the OS and PFS results of T-DXd are likely underestimated as the patient population in DESTINY-Breast01 is more heavily pre-treated and line of therapy is a strong negative prognostic factor.

Details of the results selected by DMC as outcomes of interest for the assessments are reported in detail in sections 5.1.2 to 5.1.6.

5.1.2. Results per study

The results for the four studies relevant to this clinical question are described in detail but also briefly described in sections 5.1.2.1 to 5.1.2.4.

5.1.2.1. The DESTINY-Breast01 study

A summary of all the efficacy endpoints as assessed by an independent central review is presented in Table 6.

Table 6: Summary of efficacy endpoints in DESTINY-Breast01

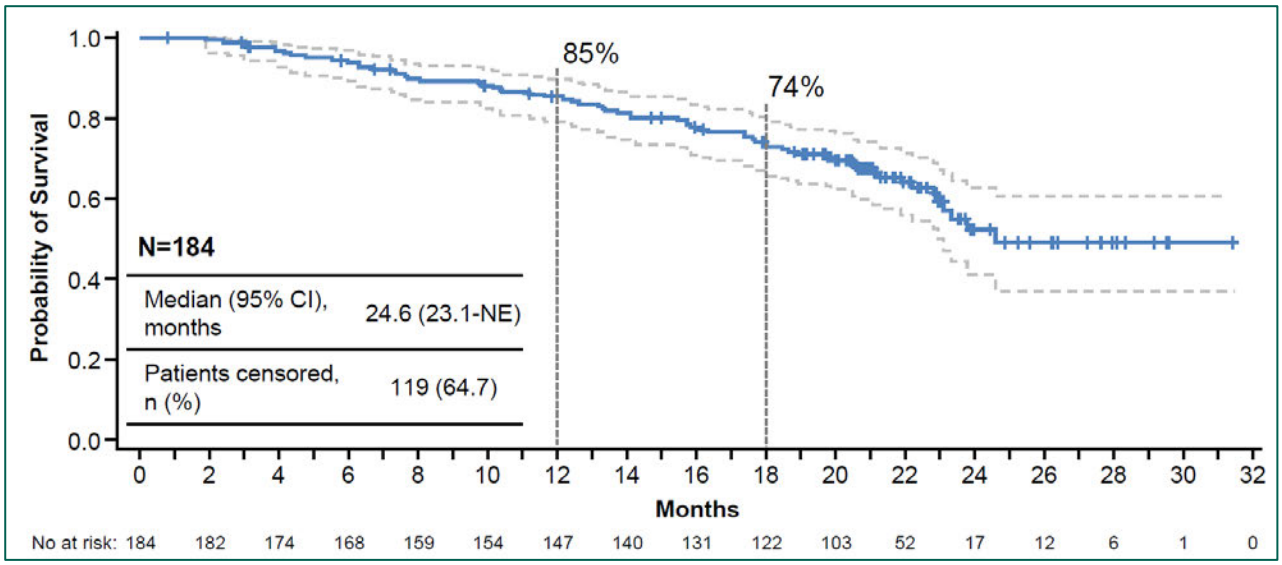
Endpoint	All patients (n=184)
Primary endpoint	
ORR, % [95% CI]	61.4% (54.0%-68.5%)
CR, %	6.5%
PR, %	54.9%
SD, %	35.9%
PD, %	1.6%
NE, %	1.1%
Secondary endpoints	
DCR, n (% [95% CI])	179 (97.3 [93.8, 99.1])
CBR, n (% [95% CI])	140 (76.1 [69.3, 82.1])
Median DOR, months (95% CI)	20.8 (15.0 -NE)
Median TTR, months (95% CI)	1.6 (1.4, 2.6)
Median PFS, months (95% CI)	19.4 (14.1 -NE)
PFS at 6 months (%)	80
PFS at 12 months (%)	66
Median OS, months (95% CI)	24.6 (14.1 -NE)
OS at 12 months (95% CI)	85% (79%-90%)
OS at 18 months (95% CI)	74% (67%-80%)

***Key**: CBR: clinical benefit rate, CI: confidence interval, CR: complete response, DCR: disease control rate, DF: dose finding, DOR: duration of response, NE: not evaluable, ORR: overall response rate, PD: progressive disease, PFS: progression-free survival, PK: pharmacokinetics, PR: partial response, SD: stable disease, TTR: time to response. **Source**: Modi, et al. 2020. (16)*

Overall survival

In the study, the percent of patients alive at 12 and 18 months was 85% (95% CI: 79%-90%) and 74% (95% CI, 67%-80%), respectively (Figure 3) (16). The preliminary median OS was 24.6 months (95% CI: 14.1 months -not estimable). However, median OS was estimated at 35% maturity, with 119 patients censored and only 17 patients at risk after 23 months; additional follow-up is required for more mature OS data.

Figure 3. Kaplan–Meier plot of OS in DESTINY-Breast01

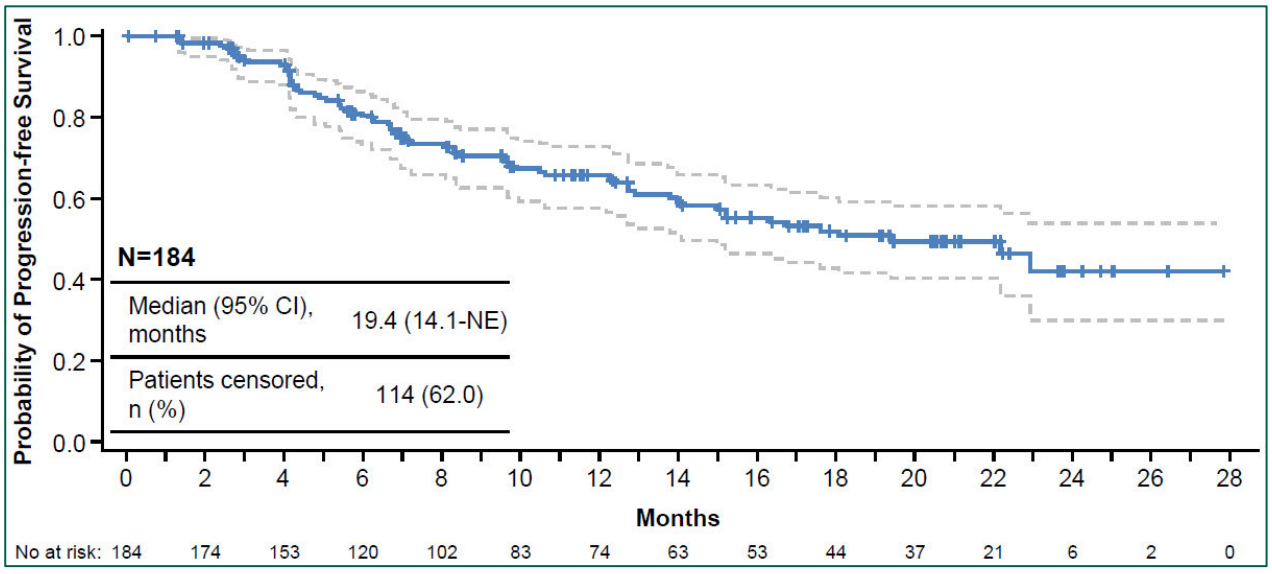


***Note**: June 2020 data cut. **Source:** Modi, et al. 2020. (16)*

Progression-free survival and response to treatment

The median PFS in DESTINY-Breast01 was 19.4 months as shown in Figure 4 (95% CI: 14.1, NE) (16).

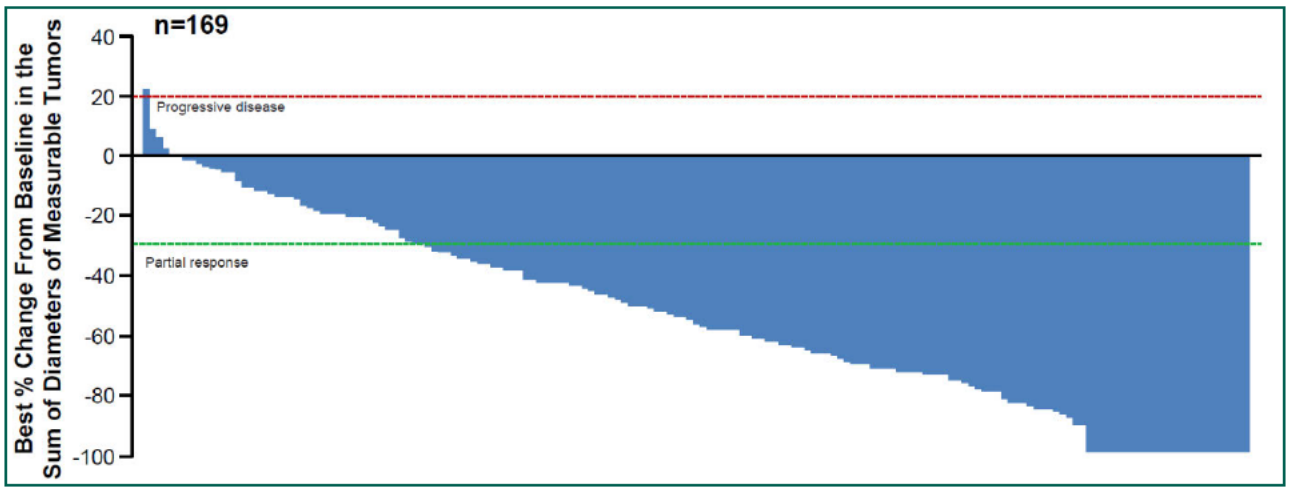
Figure 4. Kaplan–Meier plot of PFS in DESTINY-Breast01



***Note**: June 2020 data cut. **Source**: Modi, et al. 2020. (16)*

The waterfall plot in Figure 5 shows that almost all patients in DESTINY-Breast had an improvement from baseline.

Figure 5. Waterfall plot of change from baseline in tumour size in Destiny-Breast01



Note: *June 2020 data cut.* ***Source:*** *Modi, et al. 2020. (16)*

Safety

A summary of the TEAEs is presented in Table 7, and a more detailed summary of the most common TEAEs is presented in Table 8. The AE data was consistent in the two available cut-offs from DESTINY-Breast01 (16). The august 2019 data-cut has been used for AEs when data was available, as this data cut provide more detailed data.

Table 7. Overall safety summary

Type of Adverse Event	Patients (N = 184) n, (%)
Any TEAEs	183 (99.5)
Drug-related TEAEs	183 (99.5)
TEAEs of CTCAE, Grade ≥ 3	105 (57.1)
Drug-related TEAEs, Grade ≥3	89 (48.4)
serious TEAEs	42 (22.8)
Drug-related serious TEAS	23 (12.5)
TEAEs leading T-DXd discontinuation	28 (15.2)
Drug-related TEAEs leading to T-DXd discontinuation	27 (14.7)
TEAEs leading to dose reduction	43 (23.4)
Drug-related TEAEs leading to dose reduction	40 (21.7)
TEAEs leading to dose interruption	65 (35.3)
Drug-related TEAEs leading to dose interruption	53 (28.8)
TEAEs leading to death	9 (4.9)
Drug-related TEAEs leading to death	2 (1.1)

Note: *August 2019 data cut.* ***Key:*** *CTCAE, common terminology criteria for adverse events; TEAE, treatment-emergent adverse event.*
Source: *Modi, 2020 (17)*

Overall, 99.5% of patients reported at least one TEAE, all of which were considered drug related, and 57.1% with common terminology criteria for adverse events (CTCAE) Grade 3 or higher TEAEs. Serious TEAEs were reported by 22.8% of patients, with drug-related serious TEAEs reported by 12.5% of patients. As a result of a TEAE, 35.3% and 23.4% of patients had a dose interruption or reduction, respectively, and 15.2% discontinued treatment (16). TEAEs that led to discontinuation in ≥2 patients included pneumonitis (n=11) and interstitial lung disease (n=5).

The most commonly reported TEAEs in patients receiving 5.4 mg/kg were: nausea (77.7%), fatigue (49.5%), alopecia (48.4%), vomiting (45.7%), constipation (35.9%), decreased neutrophil count (34.8%) decreased appetite (31.0%), anaemia (29.9%), diarrhoea (29.3%), decreased white blood cell count (21.2%).

Table 8. Summary of TEAEs occurring in ≥15% of patients in DESTINY-Breast01

TEAE (≥ 15%), n (%)	All grades (N=184)	Grade 3	Grade 4
Patients with any TEAE	183 (99.5)	89 (48.4)	7
Nausea	143 (77.7)	14 (7.6)	0
Fatigue	91 (49.5)	11 (6.0)	0
Alopecia	89 (48.4)	1 (0.5)	0
Vomiting	84 (45.7)	8 (4.3)	0
Constipation	66 (35.9)	1 (0.5)	0
Decreased neutrophil count (neutropenia)	64 (34.8)	36 (19.6)	2 (1.1)
Decreased appetite	57 (31.0)	3 (1.6)	0
Anemia	55 (29.9)	15 (8.2)	1 (0.5)
Diarrhea	54 (29.3)	5 (2.7)	0
Decreased white cell count	39 (21.2)	11 (6.0)	1 (0.5)
Thrombocytopenia	39 (21.2)	7 (3.8)	1 (0.5)
Headache	36 (19.6)	0	0
Cough	35 (19.0)	0	0
Abdominal pain	31 (16.8)	2 (1.1)	0
Decreased lymphocyte count	26 (14.1)	11 (6.0)	1 (0.5)

Note: *August 2019 data cut.* ***Key:*** *TEAE, treatment-emergent adverse event.* ***Source:*** *Modi, 2020 (17)*

In addition to the AEs reported in Table 8, only one additional patient experienced a drug-related grade 3-4 AE which was due to interstitial lung disease (ILD), which is a serious AE expected from T-DXd treatment. Otherwise, most ILD events were primarily grade 1 or 2 (22 patients [12%]). However, five patients (2.7%) had a grade 5 event leading to death, see Table 9 below. These ILD events and deaths were judged by an independent ILD adjudication committee in contrast to the AEs in Table 8, which were investigator reported.

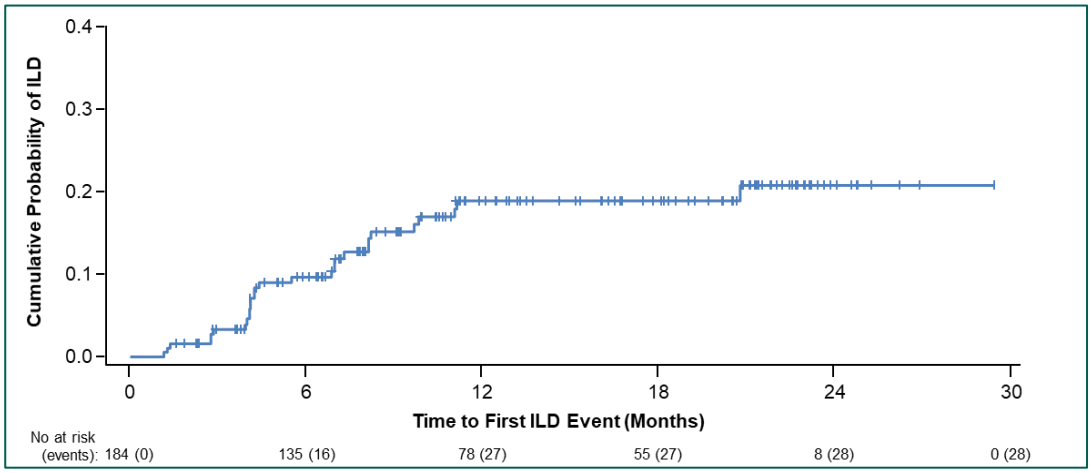
Table 9. Drug-related interstitial lung disease judged by an independent committee

Any Drug-related TEAE, (N=184)*	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)	Any grade ILD, n (%)
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	28 (15.2)
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	25 (13.6)

Note: **As determined by an independent ILD adjudication committee. At data cut-off, one Grade 1 event and one Grade 3 event were pending adjudication.* ***Source:*** *Modi, 2020 (16)*

There was no evidence of cumulative toxicity of T-DXd with a longer duration of therapy. Accordingly, the risk seemed to be highest the first 12 months where after it lowered, see Figure 6 below.

Figure 6. Cumulative probability of adjudicated drug-related any-grade ILD



***Note**: June 2020 data cut. As determined by an independent ILD adjudication committee. At data cut-off, one Grade 1 event and one Grade 3 event were pending adjudication. †In patients with HER2-positive breast cancer (T-DXd 5.4 mg/kg). **Source**: Modi S, et al. (16)*

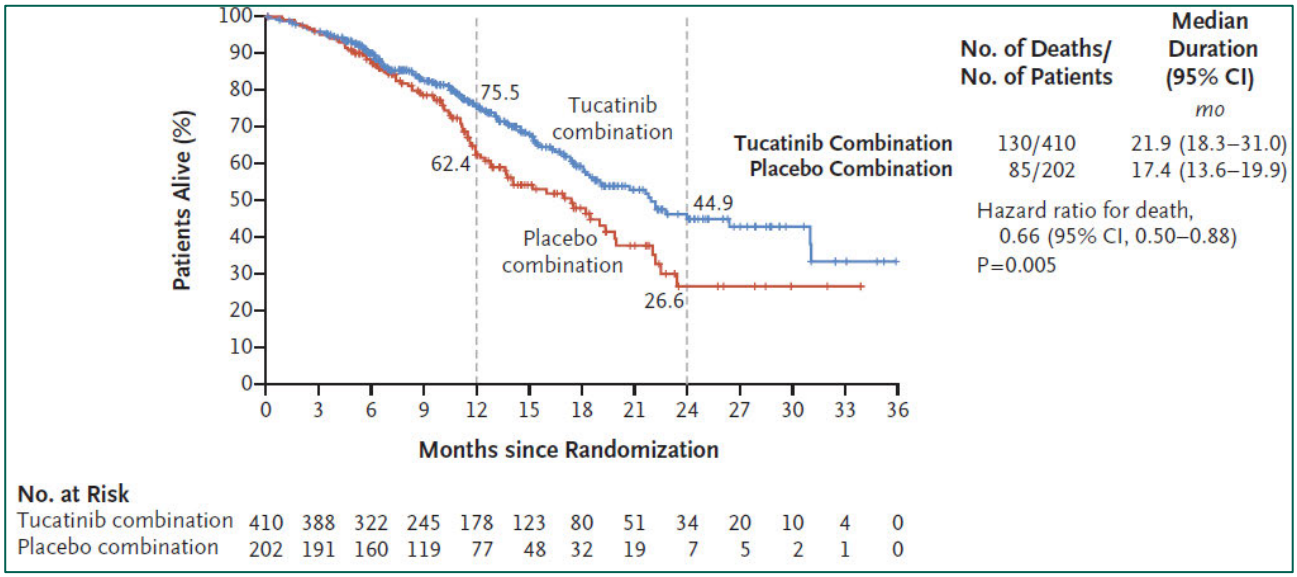
The Danish clinical experts approached during the preparation of this application were largely not concerned about T-DXd-associated ILDs. They had confidence in monitoring for early signs and referred to the positive risk-benefit profile, based on the long OS and PFS that are presented in Figure 3 and Figure 4.

5.1.2.2. The HER2Climb study

Overall survival

In the HER2Climb study, the share of patients alive at 12 and 24 months in the placebo arm relevant for this assessment was 62% and 27%, respectively (Figure 7) (9). The preliminary median OS was reported to be 17.4 months (95% CI: 13.6-19.9).

Figure 7. Kaplan–Meier plot of OS in the HER2CLIMB study

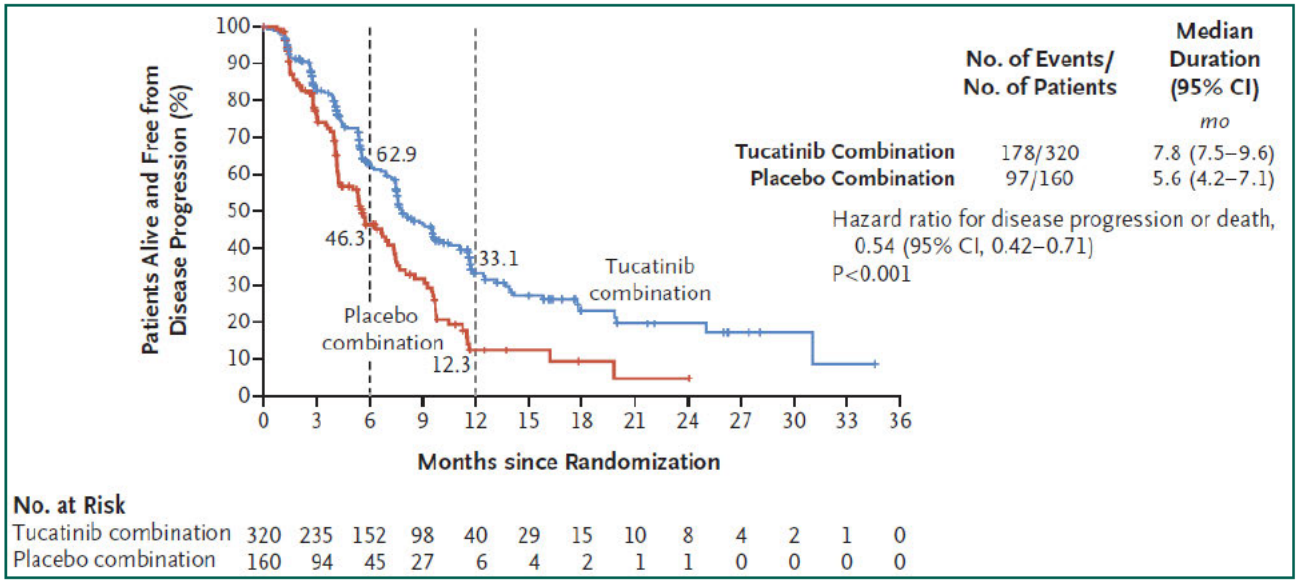


***Source:** Murthy et al., 2020*

Progression-free survival

In the HER2CLIMB study, the share of patients alive and progression-free at 6 and 12 months in the placebo arm relevant for this assessment was 46% and 12%, respectively (Figure 8) (9). The preliminary median PFS was 5.6 months (95% CI:4.2-7.1).

Figure 8. Kaplan–Meier plot of PFS in the HER2CLIMB study



Source: *Murthy et al., 2020 (9)*

Health-related Quality-of-life

No relevant health-related quality-of-life data were identified from the study.

Adverse events

The most common adverse events in the HER2CLIMB study are presented in Table 10.

Table 10. Most Common Adverse Events in HER2CLIMB

	Tucatinib-Combination Group (N = 404)		Placebo-Combination Group (N = 197)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event	401 (99.3)	223 (55.2)	191 (97 0)	96 (48.7)
Diarrhea	327 (80.9)	52 (12.9)	105 (53.3)	17 (8.6)
PPE syndrome	256 (63.4)	53 (13.1)	104 (52.8)	18 (9.1)
Nausea	236 (58.4)	15 43.7)	36 (43.7)	6 (3.0)
Fatigue	182 (45.0)	19 (4.7)	85 (43.1)	8 (4.1)
Vomiting	145 (35.9)	12 (3.0)	50 (25.4	7 (3.6)
Stomatitis	103 (25.5)	10 (2.5)	28 (14.2)	1 (0.5)
Decreased appetite	100 (24.8)	2 (0.5)	39 (19.8)	0
Headache	87 (21.5)	2 (0.5)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	86 (21.3)	18 (4.5)	22 (11.2)	1 (0.5)
Alanine aminotransferase increased	81 (20.0)	22 (5.4)	13 (6.6)	1 (0.5)

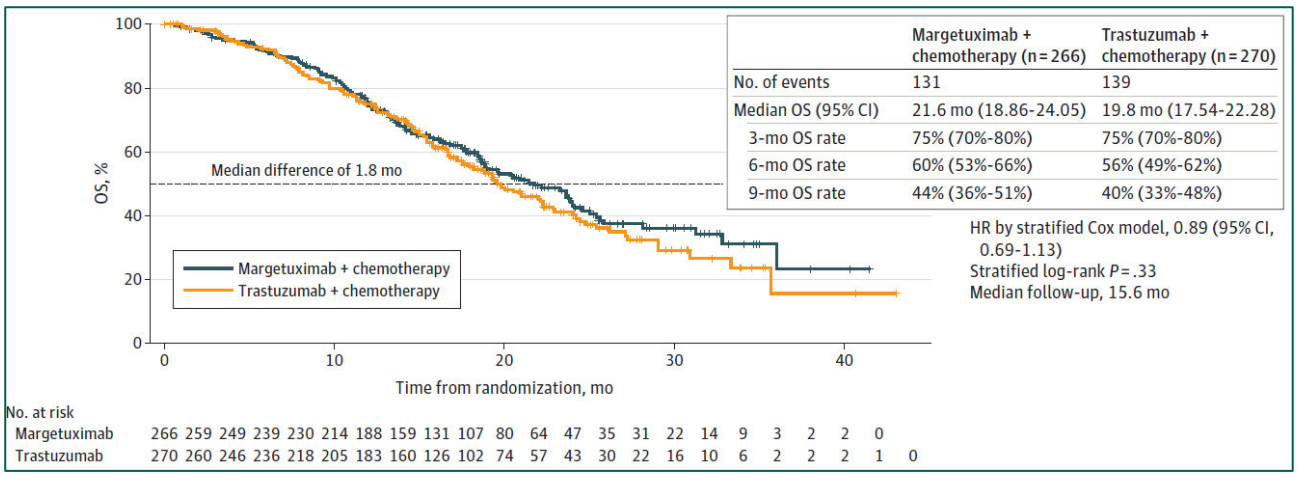
Note: *Listed are adverse events that were reported in at least 20% of the patients in the tucatinib-combination group. Safety analyses included all the patients who received at least one dose of any trial drug or placebo. Data are reported according to preferred terms in the Medical Dictionary for Regulatory Activities, version 22.0. PPE: palmar–plantar erythrodysesthesia.* ***Source:*** *Murthy et al., 2020 (9)*

5.1.2.3. The SOPHIA study

Overall survival

The overall survival in the SOPHIA study is shown in Figure 9 (8). Preliminary median OS was 19.8 months (95% CI, 17.54-22.28).

Figure 9. Kaplan–Meier plot of OS in the SOPHIA study

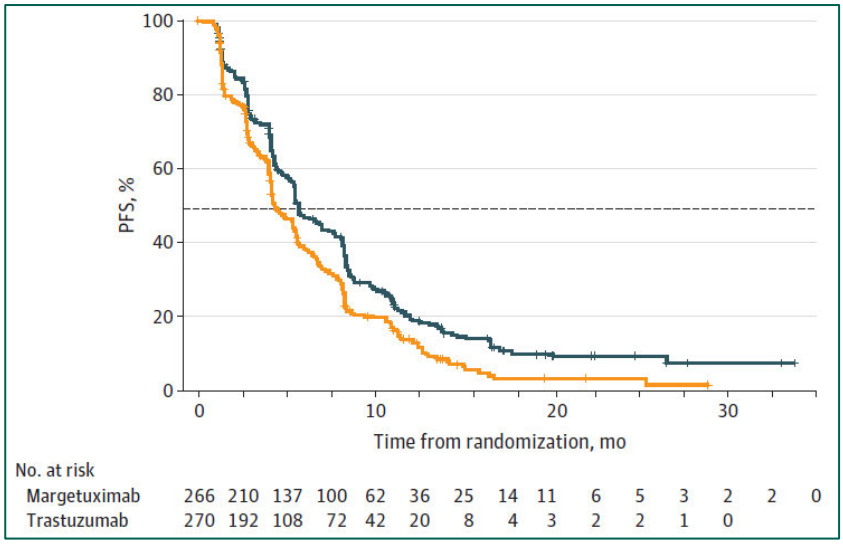


Source: *Rugo et al., 2021 (8)*

Progression-free survival

In the study, the percentare of patients alive and progression-free at 6 and 9 months in the treatment arm relevant for this assessment was 38% (32%-45%) and 20% (16%-26%), respectively (Figure 8) (8). Preliminary median PFS was 4.4 months (95% CI: 4.14-5.45).

Figure 10. Kaplan–Meier plot of PFS in the SOPHIA study



Source: *Rugo et al., 2021 (8)*

Health-related Quality-of-life

All HRQOL domains, including symptoms and functioning, were maintained in the SOPHIA trial. Changes from baseline were similar between the two treatment groups. Treatment-specific symptoms were consistent with side effects associated with chemotherapy and not antibody study therapy. The findings support similar, acceptable safety profiles for margetuximab and trastuzumab. Detailed results are provided in Appendix 9.1.3 in Table 29.

Adverse events

Adverse events reported in the SOPHIA study are presented in Table 11.

Table 11. Adverse Events in the Safety Population in the SOPHIA trial

	Margetuximab plus chemotherapy (n = 264)		Trastuzumab plus chemotherapy (n = 266)	
	All grade	Grade ≥3	All grade	Grade ≥3
Non-hematologic				
Fatigue	111 (42.0)	13 (4.9)	94 (35.3)	8 (3.0)
Nausea	86 (32.6)	3 (1.1)	86 (32.3)	1 (0.4)
Diarrhea	66 (25.0)	6 (2.3)	67 (25.2)	6 (2.3)
Constipation	51 (19.3)	2 (0.8)	44 (16.5)	2 (0.8)
Vomiting	54 (20.5)	2 (0.8)	38 (14.3)	4 (1.5)
Pyrexia	50 (18.9)	1 (0.4)	37 (13.9)	1 (0.4)
Headache	47 (17.8)	0	42 (15.8)	0
Alopecia	47 (17.8)	0	39 (14.7)	0
Asthenia	47 (17.8)	6 (2.3)	33 (12.4)	5 (1.9)
Decreased appetite	38 (14.4)	1 (0.4)	36 (13.5)	1 (0.4)
Infusion-related reaction••	35 (13.3)	4 (1.5)	9 (3.4)	0
Cough	37 (14.0)	1 (0.4)	31 (11.7)	0
PPE syndrome	33 (12.5)	1 (0.4)	41 (15.4)	8 (3.0)
Dyspnea	34 (12.9)	3 (1.1)	28 (10.5)	6 (2.3)
Pain in extremity	30 (11.4)	2 (0.8)	23 (8.6)	0
Arthralgia	27 (10.2)	0	23 (8.6)	1 (0.4)
Stomatitis	27 (10.2)	2 (0.8)	21 (7.9)	0
Peripheral neuropathy	26 (9.8)	1 (0.4)	28 (10.5)	3 (1.1)
Urinary tract infection	26 (9.8)	2 (0.8)	28 (10.5)	3 (1.1)
Mucosal inflammations	26 (9.8)	0	8 (3.0)	1 (0.4)
Abdominal pain	25 (9.5)	4 (1.5)	37 (13.9)	3 (1.1)
Dizziness	25 (9.5)	1 (0.4)	16 (6.0)	0
Hypokalemia	16 (6.1)	4 (1.5)	19 (7.1)	4 (1.5)
Hypertension	14 (5.3)	5 (1.9)	6 (2.3)	2 (0.8)
Pneumonia	9 (3.4)	5 (1.9)	9 (3.4)	7 (2.6)
Pleural effusion	8 (3.0)	2 (0.8)	14 (5.3)	4 (1.5)
Syncope	4 (1.5)	4 (1.5)	0	0
Hematologic				
Neutropenia	75 (28.4)	52 (19.7)	55 (20.7)	33 (12.4)
Anemia'	49 (18.6)	13 (4.9)	62 (23.3)	17 (6.4)
Neutrophil count decreased	33 (12.5)	23 (8.7)	39 (14.7)	28 (10.5)
ALT increased	24 (9.1)	5 (1.9)	26 (9.8)	4 (1.5)
AST increased	22 (8.3)	7 (2.7)	34 (12.8)	3 (1.1)
WBC decreased	19 (7.2)	5 (1.9)	27 (10.2)	8 (3.0)
Leukopenia	14 (5.3)	4 (IS)	10 (3.8)	1 (0.4)
Syncope	8 (3.0)	8 (3.0)	13 (4.9)	13 (4.9)

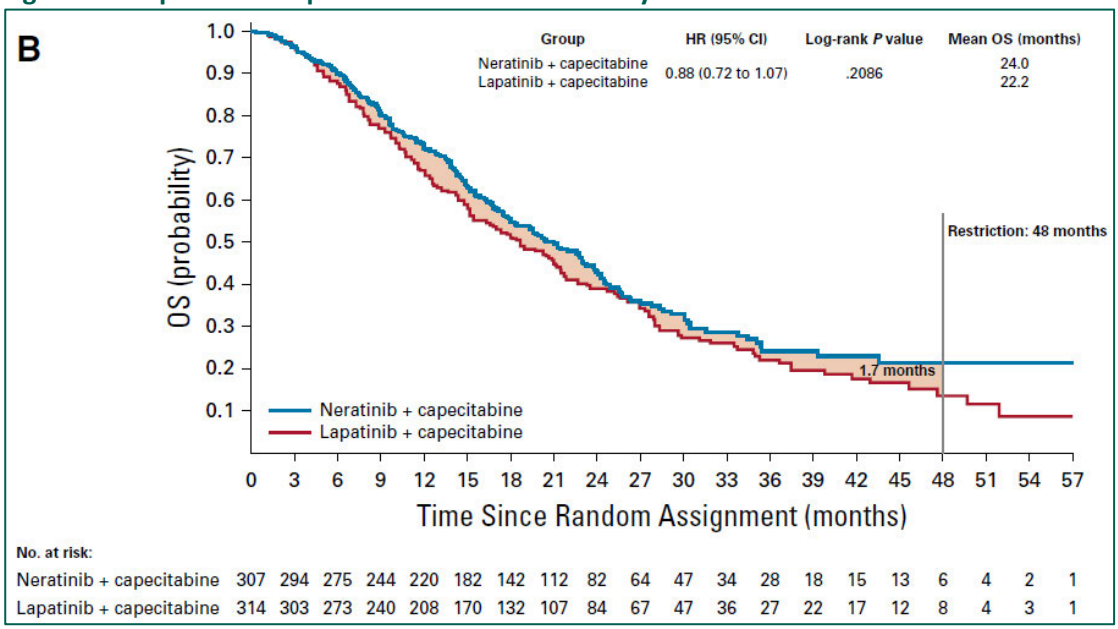
***Note**: Regardless of Causality (April 2019 cut off).*

5.1.2.4. The NALA study

Overall survival

In the NALA study, the percentage of patients alive at 12 and 24 months in the control arm relevant for this assessment was 66.7% (CI 95%, 61.2 - 71.6%) and 39.2% (CI 95%, 33.4 - 45.0%), respectively (Figure 11) (7). Preliminary median OS was 18.7 months (CI: 95%: 15.5 - 21.2).

Figure 11. Kaplan–Meier plot of OS in the NALA study

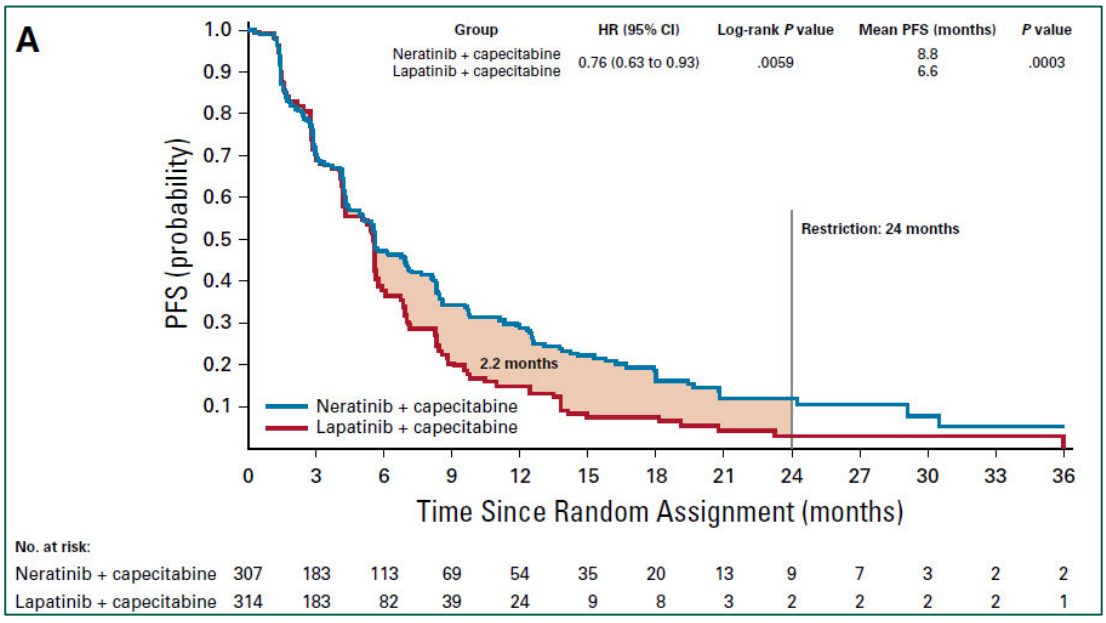


***Source**: Saura et al., (7).*

Progression-free survival

In the NALA study, the proportion of patients alive and progression-free at 6 and 12 months in the treatment arm relevant for this assessment was 38% (32%-44%) and 15% (10% - 20%), respectively (Figure 12) (7). Preliminary median PFS was 5.5 months (CI: 95%: 4.3 – 5.6%).

Figure 12. Kaplan–Meier plot of PFS in the NALA study



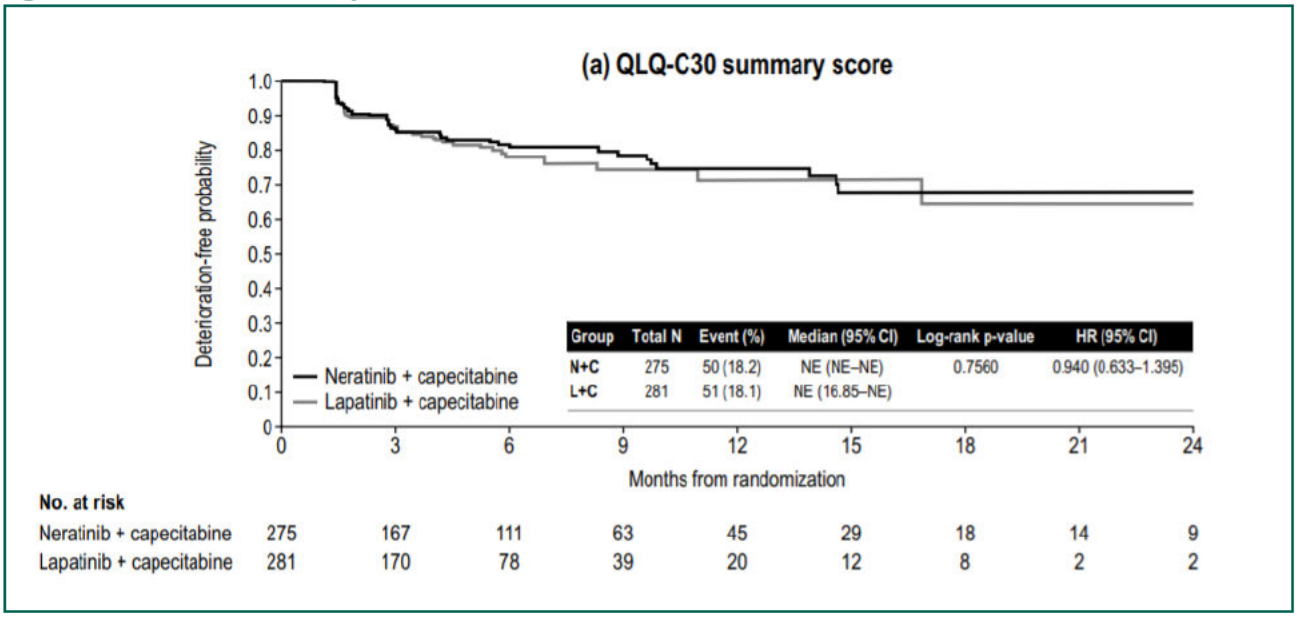
***Source:** Saura et al., (7).*

Health-related Quality-of-life

Patient-reported HRQoL was a secondary endpoint in the NALA study. HRQoL was measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire core module (QLQ-C30; version 3), and the EORTC Quality of Life Questionnaire Breast Cancer-Specifc Module (QLQ-BR23).

EORTC QLQ-C30 questionnaire completion rates were 91% for patients in the HRQoL population. Mean QLQ-C30 summary score and Global Health Status/QoL subscale scores were similar between the arms over time. None of the observed changes over time or between groups at individual time points were greater than the minimum important difference. (24)

Figure 13. QLQ-C30 summary score



Source: *Moy et al., (7). (24)*

Adverse events

Adverse events in the NALA study is presented in Table 12.

Table 12. Treatment-Emergent AEs in the Safety Population in the NALA study

	Neratinib + capecitabine (n= 303)		Lapatinib + capecitabine (n = 311)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Diarrhea	252 (83.2)	74 (24.4)	206 (66.2)	39 (12.5)
Nausea	161 (53.1)	13 (4.3)	132 (42.4)	9 (2.9)
PPE syndrome	139 (45.9)	29 (9.6)	125 (56.3)	35 (11.3)
Vomiting	138 (45.5)	12 (4.0)	97 (31.2)	6 (1.9)
Decreased appetite	107 (35.3)	8 (2.6)	67 (21.5)	7 (2.3)
Fatigue	104 (34.3)	9 (3.0)	97 (31.2)	10 (3.2)
Constipation	94 (31.0)	4 (1.3)	41 (13.2)	1 (0.3)
Stomatitis	62 (20.5)	6 (2.0)	83 (26.7)	8 (2.6)
Weight decreased	60 (19.8)	1 (0.9)	41 (13.2)	2 (0.6)
Rash	30 (9.9)	0	69 (22.2)	2 (0.6)
Anemia	45(14.9)	6 (2.0)	51 (16.4)	11 (3.5)
Dizziness	43 (14.2)	1 (0.3)	31 (10.0)	2 (0.6)
Cough	37 (12.2)	0	34 (10.9)	0

Abdominal pain	36 (11.9)	3 (1.0)	45 (145)	6 (1.9)
Asthenia	36 (11.9)	8 (2.6)	36 (11.6)	5 (1.6)
Hypokalemia	35 (116)	14 (4.6)	44 (14.1)	20 (6.4)
Paronychia	35 (11.6)	2 (0.7)	49 (15.8)	3 (1.0)
Pyrexia	33 (10.9)	0	32 (10.3)	1 (0.3)
Headache	32 (10.6)	1 (0.3)	51 (16.4)	3 (1.0)

Note: *Treatment-Emergent AEs Occurring in ≥10%. Data are presented as No. (%).* ***Abbreviations:*** *AE: adverse event, PPE: palmar-plantar erythrodysesthesia.* ***Source:*** *Saura et al., (7).*

5.1.2.5. [redacted]

[redacted]

5.1.3. Comparative analyses: Overall survival

The OS results from the naïve (unadjusted) indirect comparisons of T-DXd versus the NALA study and the other studies, identified as relevant in section 4.1, are presented in Table 13.

Comparison versus the NALA study

The NALA study is referenced as most relevant for Danish clinical practice by DMC, which we agree with (see section 4.1). The patients in DESTINY-Breast 01 had a 5.9 months longer median OS and met the DMC definition of minimal clinically important difference in comparison with the NALA study. The 5 months minimal clinically important difference in the DMC protocol is based on what is considered a substantial benefit in the ESMO guidelines (4).

It should be noted that the patients in DESTINY-Breast 01 were more heavily pre-treated compared to the patients in the NALA study (7). Thus, the gain of 5.9 months in median OS should be considered as a conservative estimate. Further, despite being more pre-treated, the patients in DESTINY-Breast01 had approximately half the risk of dying when indirectly compared with the patients in the NALA study (HR=0.52). The upper limit of the confidence interval of the hazard ratio was below 0.7. This gives an indication of the significance of the survival in DESTINY-Breat01 even if the statistics from indirect comparisons should be interpreted with caution.

Comparison versus DBCG data

Data on Danish 3L+ patients previously treated with T-DM1 showed that the median overall survival was [redacted] months for the patients relevant to this clinical question. This highlights that the median survival in this population is significantly shorter than the 22 months reported in the DMC protocol. The data from DBCG also show that according to the most suitable available data, T-DXd provides more than 5 additional months of overall survival. Further, as in the indirect comparison with the NALA study, the ~6 months additional survival should be considered as a conservative estimate given that the population in DESTINY-Breast01 is more pretreated than the population in the DBCG study.

Comparison versus other relevant studies

In comparison to other relevant studies identified in the SLR, the gain in median OS was 4.8 and 7.2 months compared with the survival in the SOPHIA study and HER2CLIMB study, respectively. Patients in DESTINY-Breast01 were more pretreated also in comparison to the patients in these studies. Thus, the gain of 4.8 versus the SOPHIA study (8) should be considered as an underestimate of the true effect size, while the result versus the HER2CLIMB study (9) is more inconclusive. This is due to the population, while being less pretreated, had a higher proportion with brain metastases, which could imply that the patients in the HER2CLIMB study had a shorter life expectancy than the T-DXd patients.

Table 13. Summary of unadjusted comparisons of overall survival

Study	Treatment arm	N	Result (95% CI)	Estimated absolute difference in effect		Estimated relative difference in effect			Added clinical value according to ESMO-MSC	Inferential thresholds DMC method guide (5 month)	Methods for estimation of indirect effectiveness
				Difference	95% CI	Difference	95% CI	p-value			
Base-case											Estimates of differences in medians were obtained by bootstrapping from the distribution of medians from the respective studies and subtracting these. The 95% CI were obtained as the 2.5% and 97.5% quantiles in the bootstrap sample of differences. Confidence intervals and p-values for relative differences were based on unadjusted indirect comparisons using patient-level data estimated based on published KM-curves.
DESTINY-Breast01 (16)	T-DXd	184	24.6 (23.1 – NE)								
NALA study (7)	Lapatinib + capecitabine	314	18.7 (15.5 – 21.2)	+5.9	2.4 – 9.4	0.52	0.39 – 0.69	< 0.001	Substantial	High added value	
Additional studies											
HER2CLIMB study (9)	Trastuzumab + capecitabine	202	17.4 (13.6 – 19.9)	+7.2	3.1 – 11.3	0.43	0.31 – 0.60	< 0.001	Substantial	High added value	
SOPHIA study (8)	Trastuzumab + chemotherapy	270	19.8 (17.5 – 22.3)	+4.8	2.1 – 7.5	0.58	0.43 – 0.78	< 0.001	Moderate	High added value	
DBCG data (2)	Mainly Trastuzumab + capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Key: *T-DXd: Trastuzumab deruxtecan, CI: Confidence interval*

Given the uncertainty and likely underestimation of the gain in median OS versus the NALA study (7) and the SOPHIA study (8) the company conducted covariate adjusted indirect comparisons. The most commonly used method for adjusting based on covariates is matching-adjusted indirect comparisons (MAICs). The MAICs were carried out systematically following the guidelines from various HTA authorities (25-30).

The systematic literature review, which was the basis for the inclusion of clinical evidence, and whether the identified studies overlap sufficiently in terms of study design, inclusion criteria, patient characteristics, definition of outcome measures and reporting of data is presented in section 4 and 5.1.1.

Details of the MAICs are provided in Appendix A. Briefly described, the patients from the DESTINY-Breast01 were assigned weights, so that the weighted average patient characteristics equal to what is reported from the comparator studies (Table 5).

Based on covariates reported in the literature and feedback from Danish clinical experts approached during the preparation of this submission, the following patient characteristics were considered for most important for OS and PFS:

- Hormone receptor status (positive/negative)
- Presence of visceral disease at baseline (yes/no)
- Number of lines of prior therapy (</≥3 or mean)
- Brain metastases (yes/no)
- ECOG status
- Age (continuous, where available mean was used; however, if not reported the median taken as a proxy)
- Prior pertuzumab exposure (yes/no)

A summary of the reported patient characteristics from the comparator studies is presented in Table 5.

Table 14 present the results when the covariates in the DESTINY-Breast01 is adjusted so that they matched the populations in the comparator studies.

The gain in median OS remained the same in comparison to the NALA study (7) but the confidence in the results improved. The median OS was not reached in the T-DXd treated population during the ~30 months follow-up when the DESTINY-Breast01 data was adjusted to the less heavily pre-treated population and the SOPHIA study (8). The hazard ratios indicate that the risk of death is significantly lower with T-DXd than in the current Danish clinical practice with a wide margin.

Less than 8 patients could be included in the effective sample size when matching with HER2CLIMB (9). Thus, the estimated comparative effectiveness versus the HER2CLIMB study should be interpreted carefully and is likely not suitable to be a basis for DMCs decisions, as they studies were not similar enough to generate a better matching.

Table 14. Comparative overall survival after covariate matching

Study	Treatment arm	N	Result (95% CI)	Estimated absolute difference in effect	Estimated relative difference in effect			Added clinical value according to ESMO-MSC	Inferential thresholds DMC method guide	Methods for estimation
					Difference	(95% CI)	p-value			
Base-case										Details of the methodology to perform the MAICs are presented in text in section 5.1.3 and additional details in appendix A.
NALA study (7)	Lapatinib + capecitabine	314	18.7 (15.5 – 21.2)	5.9	0.29	0.14, 0.60	<0.001	Substantial	High added value	
Adjusted DESTINY-Breast01 (16)	T-DXd	24.6	24.6 (24.6-NA)							
Additional studies										
HER2CLIMB study (9)	Trastuzumab + capecitabine	202	17.4 (13.6 – 19.9)	7.2	0.51	(0.20, 1.32)	0.17	Not assessable	Not assessable	
Adjusted DESTINY-Breast01 (16)	T-DXd	7.5	24.61 (17.38 – NA)							
SOPHIA study (8)	Trastuzumab + chemotherapy	270	19.8 (17.5 – 22.3)	>+11	0.27	0.14, 0.50	<0.001	Substantial	High added value	
Adjusted DESTINY-Breast01 (16)	T-DXd	27.9	NA (24.61 – NA)							

Key: *T-DXd: Trastuzumab deruxtecan, CI: Confidence interval*

5.1.4. Comparative analysis: HRQoL

A comparative analysis of the health related quality of life could not be performed, as DESTINY-Breast01 or J101 did not include any relevant data on health-related quality of life.

However, a positive impact of T-DXd should be expected as the quality-of-life in breast cancer patients is often connected to disease progression (18). The number of AEs of T-DXd is similar to trastuzumab in combination with capecitabine and should not have a major impact on the quality of life.

5.1.5. Comparative analysis: Grade 3 or 4 AE's

The adverse events reported in the trials are not fully comparable across studies due to different definitions and reporting of the AEs. The HER2CLIMB study is considered as the most suitable comparator for the AE profile of current Danish clinical practice, as that the control arm in that study was in line with the DMC protocol: trastuzumab plus capecitabine. As shown in Table 15, the rate of Grade 3+ events is very similar between T-DXd and the control arm in the HER2CLIMB study.

Table 15. Comparative analysis of adverse events according to CTCAE

Adverse event, n (%)	DESTINY-Breast01 (T-DXd) (N = 184)		HER2CLIMB (Trastuzumab + capecitabine) (N = 197)
	Grade 3	Grade 4	Grade ≥3
Patients with any TEAE	89 (48.4)	7 (3.8)	96 (48.7)
Nausea	14 (7.6)	0	6 (3.0)
Fatigue	11 (6.0)	0	8 (4.1)
Alopecia	1 (0.5)	0	-
Vomiting	8 (4.3)	0	7 (3.6)
Constipation	1 (0.5)	0	-
Decreased neutrophil count (neutropenia)	36 (19.6)	2 (1.1)	-
Decreased appetite	3 (1.6)	0	-
Anemia	15 (8.2)	1 (0.5)	-
Diarrhea	5 (2.7)	0	17 (8.6)
Decreased white cell count	11 (6.0)	1 (0.5)	-
Thrombocytopenia	7 (3.8)	1 (0.5)	-
Headache	0	0	3 (1.5)
Cough	0	0	-
Abdominal pain	2 (1.1)	0	-
Decreased lymphocyte count	11 (6.0)	1 (0.5)	-
PPE syndrome	-	-	18 (9.1)
Aspartate aminotransferase increased	-	-	1 (0.5)
Alanine aminotransferase increased	-	-	1 (0.5)
Stomatitis	-	-	1 (0.5)

Note: *August 2019 data cut for DESTINY-Breast01.* ***Key:*** *CTCAE: common terminology criteria for adverse events; TEAE: treatment-emergent adverse event*

Narrative discussion about AEs

The most common Grade 3/4 AEs in DESTINY-Breast01 were neutropenia and anemia while the most common AEs with trastuzumab + capecitabine in the HER2CLIMB study were palmar-plantar erythrodysesthesia and diarrhea. All of these AEs are common for many oncology drugs and not new to the oncologists.

Five patients (2.7%) had a grade 5 ILD event leading to death, see Table 9. Most first ILD events occurred during the first 12 months of treatment; among the patients who did not have an ILD event for ≥12 months, only 1 subsequently developed ILD; 2 cases were pending adjudication at data cut-off. The risk of adjudicated drug-related ILD appears lower after approximately 12 months on treatment, suggesting that the risk of developing ILD is not related to a cumulative dose of T-DXd. The Danish clinical experts approached during the preparation of this application were largely not concerned about T-DXd-associated ILDs because of confidence in monitoring for early signs and the positive risk-benefit profile based on the long overall and progression-free survival. ILD is managed through discontinuation.

5.1.6. Comparative analyses: Progression-free survival

The PFS results from a naïve indirect comparison of T-DXd versus the NALA study and the other studies identified as relevant in section 4.1 are presented in Table 16.

Comparison versus the NALA study

In comparison with the NALA study, which is referenced by DMC as most relevant for Danish clinical practice, the patients in DESTINY-Breast 01 had a ~13 months longer median progression-free survival. Thus, the absolute and relative difference met the DMC definition of minimal clinical benefit (3 months) with a wide margin. It should be noted that the patients in DESTINY-Breast 01 were more heavily pre-treated compared to the patients in the NALA study (7). The gain (13 months) should therefore be considered as a conservative estimate. Further, despite being more pre-treated, the patients in DESTINY-Breast01 had a 77% lower risk of dying or progressing when indirectly compared with the patients in the NALA study.

Comparison versus DBCG data

Data on Danish patients previously treated with T-DM1 showed that the median PFS was approximately [redacted] months. Thus, this highlight that the median survival in this population is similar to the PFS reported in recently published studies of treatments similar to the Danish clinical practice. It also highlight that the PFS with T-DXd is 3-4 times longer than with the treatments in current Danish clinical practice.

Comparison versus other relevant studies data

In comparison to other relevant studies identified in the SLR, the gain in median PFS was 13.8 and 15.0 months. The gain of 15.0 months versus the SOPHIA study (8) should be considered conservative as the patients in DESTINY-Breast01 were more pre-treated. However, the result versus the HER2CLIMB trial of Murthy et al., (9) is more difficult to assess because while more pretreated, the patients in that study had more brain metastases.

Table 16. Unadjusted comparative analysis of progression-free survival

Study	Treatment arm	N	Result (95% CI)	Estimated absolute difference in effect		Estimated relative difference in effect			Inferential thresholds DMC method guide (3 months)	Methods for estimation
				Difference	(95% CI)	Difference (HR)	(95% CI)	p-value		
Base-case										Estimates of differences in medians were obtained by bootstrapping from the distribution of medians from the respective studies and subtracting these. The 95% CI were obtained as the 2.5% and 97.5% quantiles in the bootstrap sample of differences. Confidence intervals and p-values for relative differences were based on unadjusted indirect comparisons using IPD estimated based on published KM-curves.
DESTINY-Breast01 (16)	T-DXd	184	19.4 (14.1 – NE)							
NALA study (7)	Lapatinib + capecitabine	314	5.5 (4.3 – 5.6)	+13.9	8.4 – 19.4	0.23	0.17 – 0.30	< 0.001	Important added value	
Additional studies										
HER2CLIMB study (9)	Trastuzumab + capecitabine	160	5.6 (4.2 – 7.1)	+13.8	8.3 – 19.3	0.26	0.19 – 0.36	< 0.001	Important added value	
SOPHIA study (8)	Trastuzumab + chemotherapy	270	4.4 (4.1 – 5.5)	+15	9.7 – 20.3	0.20	0.15 – 0.26	< 0.001	Important added value	
DBCG data (2)	Mainly Trastuzumab + capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	

Key: *T-DXd: Trastuzumab deruxtecan, CI: Confidence interval*

In line with the adjustments made for OS, the PFS results were also covariate-adjusted using the same methodology as outlined in section 5.1.3. This adjustment was done to try to correct for differences in the number of prior treatment lines and other covariates.

The results were in line with the unadjusted results and showed that the threshold for minimum clinical benefit was met with a wide margin. As in the case with the MAIC results of OS, it was not possible to accurately predict the relative effectiveness versus the HER2CLIMB study due to the differences in study populations (disproportionally high number of patients with brain metastases in the HER2CLIMB study).

Table 17. Comparative progression-free survival after covariate matching

Study	Treatment arm	N	Result (95% CI)	Estimated absolute difference in effect	Estimated relative difference in effect			Inferential thresholds DMC method guide	Methods for estimation
				Difference	Difference	95% CI	p-value		
Base-case									Details of the methodology to perform the MAICs are presented in section 5.1.3 along with additional details in appendix A.
The NALA study (7)	Lapatinib + capecitabine	314	5.5 (4.3 – 5.6)	+16.7	0.16	0.08 – 0.29	< 0.001	Important added value	
Adjusted DESTINY-Breast01 (16)	T-DXd	24.6	22.2 (18.1 – NA)						
Additional studies									
HER2CLIMB study (9)	Trastuzumab + capecitabine	160	5.6 (4.2 – 7.1)	>+16.6	0.09	0.03 – 0.22	< 0.001	Important added value	
Adjusted DESTINY-Breast01 (16)	T-DXd	7.5	NA (22.2 to NA)						
SOPHIA study (8)	Trastuzumab + chemotherapy	270	4.4 (4.1 – 5.5)	+18.5	0.12	0.06 – 0.21	< 0.001	Important added value	
Adjusted DESTINY-Breast01 (16)	T-DXd	27.9	22.93 (18.1 – NA)						

Key: *T-DXd: Trastuzumab deruxtecan, CI: Confidence interval*

5.1.6.1. Comparative analyses: ORR

Although the PFS results are conclusive and clearly show an added benefit of T-DXd compared to studies representing current Danish clinical practice, an unadjusted comparison of the ORR results from the relevant studies is presented in Table 18. ORR is a useful complement to the PFS results as the ORR results are likely less sensitive to differences in the number of prior treatment lines due to the nature of how it is measured.

As shown in the table, the ORR in DESTINY-Breast01 is significantly higher than the most relevant comparison (the NALA study) but also any other study within the indication.

Table 18. Unadjusted comparative analysis of objective response rate

Study	Treatment arm	N	Result (95% CI)	Estimated absolute difference in effect		Relative difference in effect			Inferential thresholds DMC method guide	Methods for estimation
				Difference (%)	95% CI	Difference RR	95% CI	p-value		
Base-case										
DESTINY-Breast01 (16)	T-DXd	184	61.4% (54.0 – 68.5)							
NALA study (7)	Lapatinib + capecitabine	314	26.7% (21.5 – 32.4)	34.7%	25.5 – 44.0	2.30	1.93 - 2.64	< 0.001	Important added value	Odds ratio was calculated and converted to risk ratios using the formula in appendix 17 in the DMC method guide. The rate of the comparator arm was used for the assumed control group rate based on feedback from DMC.
Additional studies										
HER2CLIMB study (9)	Trastuzumab + capecitabine	202	22.8% (16.7 – 29.8)	38.6%	28.6 – 48.6	2.69	2.19 - 3.14	< 0.001	Important added value	
SOPHIA study (8)	Trastuzumab + chemotherapy	270	16.00% (11.59 – 21.47)	45.4%	36.6 – 54.2	3.84	3.15 - 4.45	< 0.001	Important added value	

Key: *T-DXd: Trastuzumab deruxtecan, CI: Confidence interval, RR: Risk ratio.*

6. Other considerations

The importance of the number of prior treatment lines is presented in section 5.

The DESTINY-Breast01 study only included one patient with ECOG performance status 2. Danish clinicians approach during the preparation of this application stated that, as in most studies, it is likely that more patients will have ECOG PS=2 in Danish clinical practice than in a study setting. However, they still believed that the DESTINY-Breast01 population is reflective of patients in Danish clinical practice

The introduction of T-DXd is not expected to have a major impact on the subsequent treatments as the survival after progression is not expected to be impacted. No subsequent treatment was assumed in the base-case in the cost-analysis as the introduction of T-DXd is not expected to have a relevant impact on the cost for subsequent treatment given that the modelled survival post progression is similar or shorter for T-DXd than for the trastuzumab plus capecitabine according to the economic model. In some cases the treatment currently used in third line will be shifted to fourth line but given the lack of expected efficacy and the short expected survival this is not an important parameter. The cost of trastuzumab plus capecitabine is similar to other third and fourth line options.

Finally given the long survival in DESTINY-Breast01, OS data is still immature and the high degree of censoring leads to data post 20.5 months being more uncertain. OS estimates could be expected to improve with future data cuts given the large improvement in median PFS between the August 2019 data cut (17) and the June 2020 data cut (16). An improvement in future data cuts could also be expected for PFS given that the upper bound of the confidence intervals is currently not estimable.

7. Conclusions

T-DXd is an efficacious treatment when compared to relevant available regimens for the treatment of unresectable or metastatic HER2+ breast cancer in patients previously treated with at least two HER2+ targeted therapies in Denmark. The results in DESTINY-Breast01 are unprecedented, the 19.4 months median PFS in the DESTINY-Breast01 study is in recent comparable patient populations between 5 and 6 months (2) (7-9). As a reference, the CLEOPATRA study, which changed the global SoC with docetaxel, trastuzumab, pertuzumab triple combination for 1L metastatic patients, showed a median PFS of 18.7 months (31). The 13 months longer median PFS met the DMC definition of minimal clinical benefit for PFS with a wide margin (>3 months median PFS).

Further, the patients in DESTINY-Breast 01 had ~6 months longer median OS than trastuzumab + capecitabine and met the DMC definition of minimal clinical benefit for OS (>5 months median OS).

In the currently only published assessment, T-DXd was deemed cost-effective and recommended by NICE in England and Wales as it has the potential to increase the length of time before the disease gets worse and how long people live overall (15).

Based on this, T-DXd should be recommended for use by Medicine Council in Denmark, as it has the potential to significantly improve outcomes for patients that today have a poor prognosis and treatment options with limited efficacy.

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9. Appendices

9.1.1. Literature search

See section 4 and separate document for included and excluded references

9.1.2. Main characteristics of included studies

Table 19. Details of the DESTINY-Breast01 study

Table A2 Main study characteristics DESTINY-breast01	
Trial name	DESTINY-breast01 (16, 17, 32)
NCT number	NCT03248492
Objective	Primary objective is to determine objective response rate (ORR) of T-DXd (DS-8201a) in HER2-positive, unresectable and/or metastatic breast cancer subjects who are resistant or refractory to T-DM1. Secondary to evaluate the duration of response (DOR), best percent change in the sum of the longest diameters (SLD) of measurable tumors, disease control rate (DCR), clinical benefit rate (CBR), progression free survival (PFS), and overall survival (OS). Moreover, to further evaluate the safety and to determine the PK of T-DXd (DS-8201a).
Publications – title, author, journal, year	**Published data:** 1. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop. *N Engl J Med 2020; 382:610-621, February 13, 2020* 2. Modi S, Saura C, Yamashita T, HeePark Y, Sung-Bae Kim, Kenji Tamura, et al. Updated Results From DESTINY-Breast01, a Phase 2 Trial of Trastuzumab Deruxtecan (T-DXd)in HER2-Positive Metastatic Breast Cancer. San Antonio Breast Cancer Symposium® -December 8-11, 2020. 2020.
Study type and design	**DESTINY-Breast01 is a two-part, open-label, single group, multicenter phase II study of T-DXd** in adults with pathologically documented HER2-positive, unresectable or metastatic breast cancer who had received previous treatment with T-DM1. Positivity for HER2 was defined as a score of 3+ on immunohistochemical analysis or as positive results on in situ hybridization, as centrally confirmed on archival tissue. Eligible patients were adults (≥18 years of age in all country sites except for ≥20 years in Japan and South Korea) and had a performance status score of 0 or 1 on the Eastern Cooperative Oncology Group scale (ranging from 0 [no disability] to 5 [death]). Patients were excluded if they had untreated or symptomatic brain metastases or if they had a history of noninfectious interstitial lung disease or pneumonitis resulting in the use of glucocorticoids or current or suspected interstitial lung disease or pneumonitis. **Part 1** of the study was designed to consist of two sequential stages: pharmacokinetics and dose finding, see figure 5 below. In the pharmacokinetics stage, patients were randomly assigned in a 1:1:1 ratio to receive T-Dxd at a dose of 5.4 mg, 6.4 mg, or 7.4 mg per kilogram administered by intravenous infusion every 3 weeks. On the

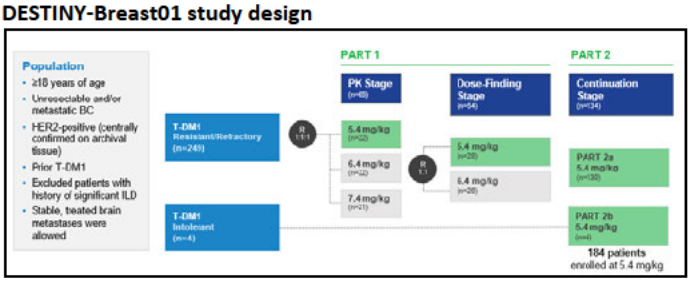
Table A2 Main study characteristics DESTINY-breast01	
	basis of the pharmacokinetics analysis, two doses were identified for evaluation in the dose-finding stage, in which newly enrolled patients were randomly assigned in a 1:1 ratio. The recommended dose was identified using a predicted benefit–risk profile modeled from exposure–response, exposure–safety, and pharmacokinetic analyses as well as clinical data from this study and from a phase 1 DS8201-A-J101 study. (20) **Part 2** of the study evaluated the efficacy and safety of the recommended dose of 5.4 mg/kg of T-DXd in patients confirmed in part 1. Part 2 consisted of two cohorts: one involved patients who had tumor progression during or after the previous administration of T-DM1 and one involved patients who had discontinued T-DM1 for reasons other than progressive disease (e.g., toxicity). Treatment continued until disease progression, the occurrence of unacceptable toxic effects, or withdrawal of consent. **DESTINY-Breast01 study design**  Adapted from Modi S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020;382 610-21; Supplementary Appendix, Figure 1S.(17)
Follow-up time	The primary analysis was performed after all patients - who had received the recommended dose of T-DXd (5.4 mg/kg) - had at least 6 months of follow-up or had discontinued their participation in the study. 128 patients (69.6%) continued to receive T-DXd for more than 6 months. Median duration of follow-up was 11.1 months (range, 0.7 to 19.9) and the median treatment duration was 10.0 months (range, 0.7 to 20.5 months). Updated analysis: Median follow-up was 20.5 months (range, 0.7-31.4 months), representing an additional 9.4 months from the prior analysis.

Table A2 Main study characteristics DESTINY-breast01

Population (inclusion and exclusion criteria)	**Inclusion and exclusion criteria**
	
	Inclusion criteria
	• Men or women ≥20 years old in Japan and South Korea, ≥18 years old in other countries
	• Pathologically documented breast cancer that
	  ▪ Is unresectable or metastatic
	  ▪ Has confirmed HER2+ expression (oestrogen receptor/progesterone receptor positive patients may be enrolled if they are HER2+) according to ASCO-CAP guidelines(68) evaluated at a central laboratory
	• Patient must have breast cancer that is resistant or refractory to T-DM1 with documented clinical or radiographic progression of disease during or after treatment with T-DM1
	• For Part 2b, patients must have discontinued treatment with T-DM1 for reasons other than resistant or refractory disease
	  ▪ Presence of at least one measurable lesion as per RECIST Version 1.1
	• LVEF ≥ 50%
	• ECOG PS 0 or 1
	• Adequate bone marrow function, defined as ANC ≥1.5 × 109/L, platelet count ≥100 × 109/L, and haemoglobin level ≥9.0 g/dL
	• Adequate renal function, defined as creatinine clearance ≥30 mL/min
	• Adequate hepatic function, including mild–moderate hepatic impairment, defined as total bilirubin ≤3 × ULN (including patients with documented Gilbert's Syndrome or liver metastases or other aetiologies) and AST/ALT ≤5 × ULN
	• Adequate blood clotting function, defined as international normalised ratio and activated partial thromboplastin time ≤1.5 × ULN
	
	Exclusion criteria
	• Medical history of myocardial infarction within 6 months before registration, symptomatic CHF (New York Heart Association Class II to IV), unstable angina, or serious cardiac arrhythmia requiring treatment
	• Has a QTc prolongation to >470 msecs (females) or >450 msecs (males) based on average of the screening triplicate12-lead ECG
	• Has a history of non-infectious interstitial lung disease or pneumonitis requiring glucocorticoid treatment, or current/suspected interstitial lung disease or pneumonitis
	• Brain metastases that are untreated, symptomatic, or require therapy to control symptoms
	• Has clinically significant corneal disease in the opinion of the investigator
	• Prior treatment with an ADC which consists of an exatecan derivative that is a topoisomerase I inhibitor
	• Unresolved toxicities from previous anticancer therapy
	• Current treatment with CYP3A4 strong inhibitors (washout period of ≈3 elimination half-lives of the inhibitor is required)

Intervention	**A 2 part single group open labelled study intervention with T-Dxd:** **Part 1** of the study was designed to consist of two sequential stages: pharmacokinetics and dose finding, figure 6) above. In the pharmacokinetics stage, patients were randomly assigned in a 1:1:1 ratio to receive T-DXd at a dose of 5.4 mg, 6.4 mg, or 7.4 mg per kilogram administered by intravenous infusion every 3 weeks. On the basis of the pharmacokinetics analysis, two doses were identified for evaluation in the dose-finding stage, in which newly enrolled patients were randomly assigned in a 1:1 ratio. **Part 2** of the study evaluated the efficacy and safety of the recommended dose of 5.4 mg/kg of T-DXd in patients confirmed in part 1. Part 2 consisted of two cohorts: one involved patients who had tumor progression during or after the previous administration of T-DM1 and one involved patients who had discontinued T-DM1 for reasons other than progressive disease (e.g., toxicity). Treatment continued until disease progression, the occurrence of unacceptable toxic effects, or withdrawal of consent.

Table A2 Main study characteristics DESTINY-breast01

Baseline characteristics

Baseline characteristics

Characteristics	All patients (N=184)
Age, Mean (range)	56.0 (28-96)
Median weight, Kg (range)	60.55 (35.6–121.0)
Mean weight, Kg (range)	62.47 (35.6–121.0)
Female, n (%)	184 (100.0)
Region (%)	
Asia	34.2
North America	28.8
Europe	37.0
ECOG performance status, n (%)	
0	102 (55.4)
1	81 (44.0)
2	1 (0.5)
Hormone receptor status, n (%)	
Positive	97 (52.7)
Negative	83 (45.1)
Unknown	4 (2.2)
HER2 expression (IHC/ISH) by central lab, n (%)	
IHC 3+	154 (83.7)
Time from initial diagnosis to study treatment, months, Median (min, max)	74.17 (1.6, 431.4)
Sum of diameters of target lesions (by ICR), cm	
Median (min, max)	5.40 (1.2, 24.5)
Subjects with following metastases, n (%)	
Yes	172 (93.5)
Brain	24 (13.0)
Bone	53 (28.8)
Lung	105 (57.1)
Liver	56 (30.4)
Visceral	169 (91.8)
Number of prior cancer therapy regimens, n (%),Median (min, max)	6.0 (2, 27)
Prior pertuzumab, n (%)	121 (65.8)
Prior pertuzumab in first or second line in advanced/metastatic BC, n (%)	51 (27.7)
Prior cancer systemic therapy, n (%)	
Trastuzumab	184 (100.0)
T-DM1	184 (100.0)
Pertuzumab	121 (65.8)
Other anti-HER2	100 (54.3)
Hormone therapy	90 (48.9)
Other systemic therapy	183 (99.5)

Source: Modi, Saura (17)

Primary and secondary endpoints

In the study, the **primary endpoint** is ORR assessed by independent central imaging facility review according to RECIST Version 1.1 (17).

The **secondary efficacy** endpoints in the Phase II DESTINY-Breast01 study include (17):

- Overall survival (OS)
- PFS based independent radiologic facility review
- Duration of response (DoR) based on investigator assessment
- Best percent change in the sum of the diameter of measurable tumours
- Disease control rate (DCR) based on investigator assessment
- Clinical benefit rate (CBR) based on investigator assessment
- ORR based on investigator assessment

Method of analysis

We calculated that a sample of approximately 230 patients would result in approximately 150 patients being treated at the recommended part 2 dose of trastuzumab deruxtecan in both parts of the study, which would provide a 95% confidence interval within 10% of the overall response rate. Enrolment was designed to continue until at least 100 patients who had received previous treatment with pertuzumab were enrolled at the recommended dose. With 150 patients, the probability that the lower boundary of the 95% confidence interval would be more than 20% was 0.982, and the probability that the estimated response rate would be 30% or more was 0.916, according to the anticipated response rate of 35%.

Table A2 Main study characteristics DESTINY-breast01	
	We used the Clopper–Pearson method to calculate the two-sided 95% confidence intervals for the response rate. We used the Kaplan–Meier method to estimate the distribution of time-to-event end points of response duration, progression- free survival, and overall survival; corresponding two-sided 95% confidence intervals were calculated with the Brookmeyer and Crowley methods. The primary analysis was per formed after all the patients who had received the recommended dose of trastuzumab deruxtecan had at least 6 months of follow-up or had discontinued their participation in the study.
Subgroup analyses	**Pre-specified subgroup analyses included: (17)** ✓ ERs (positive, negative). ✓ Progesterone receptors (positive, negative). ✓ Lines of prior systemic therapy not including hormone therapy (<3, ≥3). ✓ Prior pertuzumab (yes, no) ✓ Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer (yes, no) ✓ Renal impairment at baseline (within normal range, mild/moderate impairment) ✓ Hepatic impairment at baseline (within normal range, mild-moderate impairment) ✓ Best response to T-DM1 therapy (CR/PR/SD, PD). ✓ Brain metastases (brain metastases, no brain metastases) ✓ Age (<65, ≥ 65 yrs). ✓ Race (Asian, others). ✓ Region (Asia, rest of world). ✓ Ethnicity (Hispanic/Latino, others). ✓ ECOG PS (0, 1). ✓ HER2 expression (IHC 3+, IHC1+/2+/ISH+)

Table 20. Details of the J101 study

Table A2 Main study characteristics DS8201-A-J10123	
Trial name	DS8201-A-J10123
NCT number	NCT02564900
Objective	A phase 1, first-in-human study with the primary objectives of selecting the recommended dose for expansion and evaluating the safety, tolerability, and activity of T-DXd in advanced HER2-expressing or HER2-mutated solid tumours, including breast cancer.
Publications – title, author, journal, year	**Published data:** Tamura K, Tsurutani J, Takahashi S, Iwata H, Krop IE, Redfern C, Sagara Y, Doi T, Park H, Murthy RK, Redman RA, Jikoh T, Lee C, Sugihara M, Shahidi J, Yver A, Modi S. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. Lancet Oncol. 2019 Jun;20(6):816-826. doi: 10.1016/S1470-2045(19)30097-X. Epub 2019 Apr 29. Erratum in: Lancet Oncol. 2019 May 10;: PMID: 31047803.
Study type and design	A multicenter, **single group two part open-label, dose-escalation and dose-expansion** (Multiple Dose First-In-Human Study of DS-8201A) **phase 1 trial** in subjects with advanced solid malignant tumors. **Part 1** is a dose escalation to identify the Maximum Tolerated dose (MTD) or the recommended phase 2 dose of DS-8201a guided by the modified continuous reassessment method using a Bayesian logistic regression model following escalation with overdose control principal. **Part 2** is a dose expansion to examine the safety and efficacy of DS-8201a and it is consist of multiple cohorts: Subjects with T-DM1-treated HER2 overexpressing breast cancer (Part 2a); trastuzumab-treated HER2 overexpressing gastric or gastroesophageal junction adenocarcinoma (Part 2b); HER2 low expressing breast cancer (Part 2c); HER2 expressing other solid malignant tumor (Part 2d) and a pharmacokinetic cohort of patients with HER2-low and overexpressing breast cancer (Part 2e). See figure 6 below.[33] Continuous reassessment method (mCRM) was done by using a Bayesian logistic regression model (BLRM) following escalation with overdose control (EWOC) principle. (20) **Study Design of DS8201-A-J101(33)**

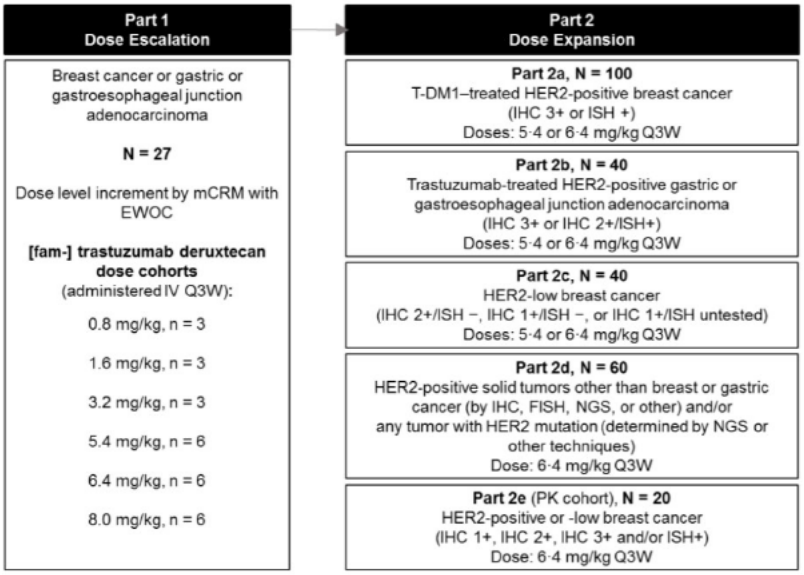
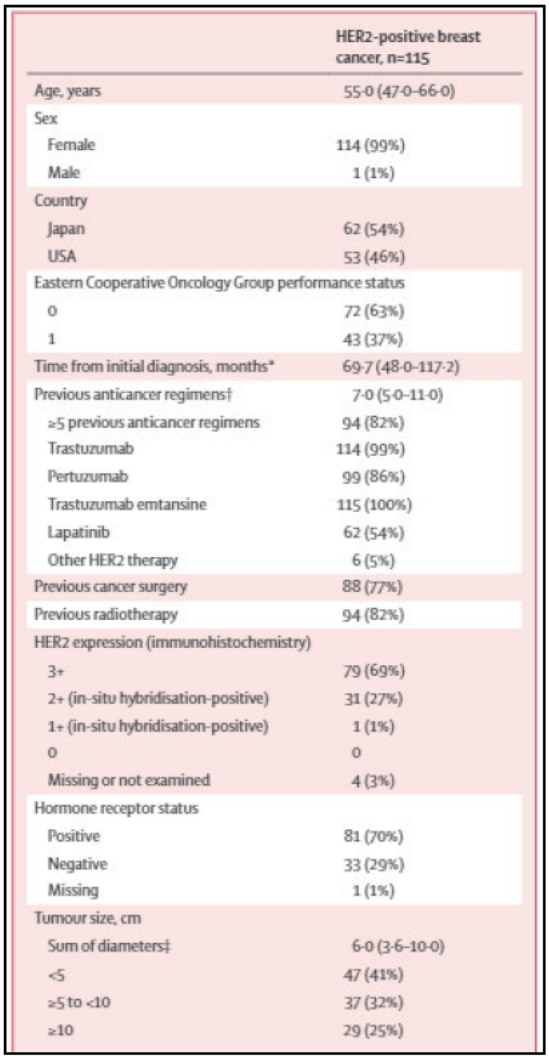
Table A2 Main study characteristics DS8201-A-J10123	
	 ***Key:*** *ISH, In situ hybridization; FISH, fluorescence in situ hybridization; DISH, dual color in situ hybridization; NGS, Next Generation Sequencing; PK, pharmacokinetics; Q3W, every third week.*
Follow-up time	Patients with HER2-positive advanced breast cancer who received T-DXd doses of 5.4 mg/kg or 6.4 mg/kg from parts 1, 2a, and 2e had a median follow-up of 9.9 months. The median time to response was 1.6 months and the median duration of response was 20.7 months. (20)
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** ✓ Age > 20 years in Japan, > 18 years in the United States. ✓ Eastern Cooperative Oncology Group performance status(PS) of 0 or 1. ✓ Left Ventricular Ejection Fraction (LVEF) ≥ 50% - Part 1: ✓ Advanced/unresectable or metastatic breast cancer or gastric or gastroesophageal junction adenocarcinoma that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. - Part 2a: ✓ Advanced breast cancer with HER2 overexpression that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. ✓ Treated with ado-trastuzumab emtansine (T-DM1) - Part 2b: ✓ Advanced gastric or gastroesophageal junction adenocarcinoma with HER2 overexpression that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. ✓ Treated with trastuzumab

Table A2 Main study characteristics DS8201-A-J10123	
	- Part 2c: ✓ Advanced breast cancer with HER2 low expression that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. - Part 2d: ✓ Satisfy at least one of the following criteria 1. Advanced/unresectable or metastatic solid malignant tumor with HER2 expression other than breast cancer and gastric or gastroesophageal junction adenocarcinoma that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. 2. Advanced/unresectable or metastatic tumor with HER2 mutation that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. Part 2e: ✓ Advanced breast cancer with HER2 overexpression that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. Treated with ado-trastuzumab emtansine (T-DM1) (patients with HER2 overexpression only) **Exclusion Criteria:** ✓ Has a medical history of symptomatic Congestive Heart Failure (CHF) (NYHA classes II-IV) or serious cardiac arrhythmia. ✓ Has a medical history of myocardial infarction or unstable angina. ✓ Has a QTc prolongation to > 450 millisecond (ms) in males and > 470 ms in females. ✓ Has a medical history of clinically significant lung diseases Full eligibility criteria can be found in the study appendix (20).
Intervention	**A 2 part single group openlabelled multicenter phase 1 trial with T-Dxd:** **Part 1** enrolled patients with advanced breast or gastric cancer in whom previous therapy had failed. They were treated with doses of 0.8–8.0 mg/kg of T-Dxd intravenously once every 3 weeks. Dose escalation was done using the modified continuous reassessment method to determine the dose-limiting toxicities, maximum tolerated dose, and recommended doses for expansion. **Part 2** was the dose-expansion part of the study where safety, tolerability, and activity of T-Dxd (at the recommended doses for expansion (5.4 mg/kg and 6.4 mg/kg every 3 weeks)) were further assessed in five patient cohorts: advanced, unresectable, or metastatic HER2-positive breast cancer after T-DM1 (defined as immuno histo chemistry 3+ or in-situ hybrid-isation-positive; part 2a), HER2-positive gastric or gastro-oesophageal junction cancer after trastuzumab (defined as immunohisto chemistry 3+ or immunohistochemistry 2+ and in-situ hybridisation-positive; part 2b), HER2-low-expressing breast cancer (defined as immuno histo-chemistry 1+ or 2+, in-situ hybridisation-negative; part 2c), other

Table A2 Main study characteristics DS8201-A-J10123	
	HER2-expressing (defined as immuno-histo chemistry 3+, 2+, or 1+ or amplified) or HER2-mutated solid tumours (as determined by next-generation sequencing or other methods; part 2d), and a pharma-cokinetic cohort that included patients with HER2-expressing advanced, unresectable, or metastatic breast cancer (defined as immunohistochemistry 3+, 2+, 1+, or in-situ hybrid isation-positive; part 2e. (20)
Baseline characteristics	**Patient characteristics** 

	HER2-positive breast cancer, n=115
Age, years	55·0 (47·0–66·0)
Sex	
Female	114 (99%)
Male	1 (1%)
Country	
Japan	62 (54%)
USA	53 (46%)
Eastern Cooperative Oncology Group performance status	
0	72 (63%)
1	43 (37%)
Time from initial diagnosis, months*	69·7 (48·0–117·2)
Previous anticancer regimens†	7·0 (5·0–11·0)
≥5 previous anticancer regimens	94 (82%)
Trastuzumab	114 (99%)
Pertuzumab	99 (86%)
Trastuzumab emtansine	115 (100%)
Lapatinib	62 (54%)
Other HER2 therapy	6 (5%)
Previous cancer surgery	88 (77%)
Previous radiotherapy	94 (82%)
HER2 expression (immunohistochemistry)	
3+	79 (69%)
2+ (in-situ hybridisation-positive)	31 (27%)
1+ (in-situ hybridisation-positive)	1 (1%)
0	0
Missing or not examined	4 (3%)
Hormone receptor status	
Positive	81 (70%)
Negative	33 (29%)
Missing	1 (1%)
Tumour size, cm	
Sum of diameters‡	6·0 (3·6–10·0)
<5	47 (41%)
≥5 to <10	37 (32%)
≥10	29 (25%)

Primary and secondary endpoints	**Primary endpoint** was the ORR (complete response plus partial response) to T-DXd therapy in patients who had tumor progression during or after the administration of T-DM1and who had received the recommended dose of T-DXd in both parts 1 and 2 of the study. The response was confirmed on the basis of an independent central review of imaging with the use of the modified Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. **Secondary endpoints** were the DOR, PFS, OS, ORR according to investigator assessment, best percentage change in the SLD of measurable tumors, DCR

Table A2 Main study characteristics DS8201-A-J10123	
	(response rate plus stable-disease rate), CBR (disease-control rate with stable disease lasting ≥6 months), safety, and pharmacokinetics.
Method of analysis	For dose escalation (part 1), sample size was determined by practical considerations and did not include formal statistical assessments. The planned sample size for dose expansion (part 2a) was 100 patients, providing at least 90% power to exclude a proportion of patients who achieved an objective response of 15% or less at the 5% type I error (one-sided), when the true proportion of patients achieving an objective response was 35%. An objective response of 35% was thought to be clinically meaningful based on historical reports of efficacy in this setting. For part 2e, the planned sample size was 20 patients, which would provide at least 75% power to exclude a proportion of patients who achieved an objective response of 15% or less at the 20% type I error (one-sided), when the true proportion was 30%. The probability values for the sample size were derived from binomial distribution using SAS (version 9.2).
Subgroup analyses	**Pre**-specified subgroup analyses included: (17) ✓ ERs (positive, negative). ✓ Progesterone receptors (positive, negative). ✓ Lines of prior systemic therapy not including hormone therapy (<3, ≥3). ✓ Prior pertuzumab (yes, no) ✓ Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer (yes, no) ✓ Renal impairment at baseline (within normal range, mild/moderate impairment) ✓ Hepatic impairment at baseline (within normal range, mild-moderate impairment) ✓ Best response to T-DM1 therapy (CR/PR/SD, PD). ✓ Brain metastases (brain metastases, no brain metastases) ✓ Age (<65, ≥ 65 yrs). ✓ Race (Asian, others). ✓ Region (Asia, rest of world). ✓ Ethnicity (Hispanic/Latino, others). ✓ ECOG PS (0, 1). ✓ HER2 expression (IHC 3+, IHC1+/2+/ISH+)

Table 21. Details of the CEREBEL study

Table A2 CEREBEL	
Trial name	CEREBEL (EGF111438)
NCT number	NCT00820222

Table A2 CEREBEL	
Objective	CEREBEL compared the incidence of CNS metastases as first site of relapse in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer receiving lapatinib capecitabine or trastuzumab-capecitabine.
Publications – title, author, journal, year	A Phase III, Randomized,Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer.
Study type and design	A Phase III, Randomized,Open-Label Study
Follow-up time	CEREBEL enrolled the first patient on April 14, 2009, and the study was terminated on June 11, 2012.
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • Females at least 18 years old; • ECOG Performance Status 0-2; • Histologically or cytologically confirmed HER2-positive invasive breast cancer, with Stage IV disease; • Prior treatment with taxanes or anthracyclines is required; • Prior treatment with other chemotherapeutic agents, trastuzumab, endocrine and radiation therapy is permitted; • Baseline LVEF ≥ 50% and not lower than the institutional lower limit of normal; • Concurrent treatment with bisphosphonates is permitted, however treatment must be initiated prior to the first dose of study therapy; • Able to swallow and retain oral medications; • Women with potential to have children must be willing to practice acceptable methods of birth control during the study; • Normal organ and marrow function. **Exclusion Criteria:** • History and/or current evidence of CNS metastases. Baseline MRI scan by Independent Reviewer to confirm no brain mets; • Concurrent treatment with an investigational agent or participation in another treatment clinical trial; • Prior therapy with lapatinib or an ErbB2 inhibitor other than trastuzumab (including but not limited to trastuzumab-DM1 and neratinib) and capecitabine; • Known DPD deficiency; • Concurrent chemotherapy, radiation therapy, immunotherapy, biologic therapy, or hormonal therapy for treatment of cancer; • History of allergic reactions attributed to compounds chemically related to lapatinib (quinazolines), capecitabine, fluorouracil or any excipients; • Concomitant use of CYP3A4 inhibitors or inducers; • Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel; • History of immediate or delayed hypersensitivity reaction to gadolinium contrast agents, or other contraindication to gadolinium contrast and other known contraindication to MRI;

Table A2 CEREBEL	
	• Concurrent disease or condition that would make the subject inappropriate for study participation or any serious medical or psychiatric disorder that would interfere with the patient's safety or compliance to study procedures; • have acute or currently active/requiring anti-viral therapy hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease); • Any on-going toxicity from prior anti cancer therapy except alopecia; • Active cardiac disease; • Uncontrolled infection; • History of other malignancy, unless curatively treated with no evidence of disease for at least 5 years, subjects with adequately treated DCIS or LCIS, adequately treated non-melanoma skin cancer or curatively treated in-situ cancer of the cervix are eligible; • Used an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of protocol treatment; • Pregnant or lactating females.
Intervention	**Lapatinib-capecitabine:** Lapatinib 1,250 mg once daily and capecitabine 2,000 mg/m2 per day on days 1 through 14, every 21 days. **Trastuzumab capecitabine:** Trastuzumab infusion of 6 mg/kg every 3 weeks (with possibly a loading dose of 8 mg/kg on day 1) and capecitabine 2,500 mg/m2 per day on days 1 through 14, every 21 days.
Baseline characteristics	

Table A2 CEREBEL

Baseline characteristics

Demographic or Clinical Characteristic	Lapatinib + Capecitabine (n = 271) No. of Patients	%	Trastuzumab + Capecitabine (n = 269) No. of Patients	%	Total (N = 540) No. of Patients	%
Age, years						
Median	53		56		55	
Range	27-83		31-79		27-83	
ECOG performance status at baseline						
0/1	260	96	261	98	521	96
2	9	3	5	2	14	3
Unknown	2	1	3	1	5	1
Race						
White	266	98	261	97	527	98
HER2 status						
IHC 3+	235	87	223	83	458	85
FISH positive	29	11	40	15	69	13
CISH positive	2	< 1	2	< 1	4	< 1
SISH positive	2	< 1	0	0	2	< 1
Not HER2 positive	3	1	4	1	7	1
Estrogen receptor status						
Positive	133	49	122	45	255	47
Negative	135	50	144	54	279	52
Unknown	3	1	3	1	6	1
Progesterone receptor status						
Positive	98	36	80	30	178	33
Negative	158	58	173	64	331	61
Unknown	15	6	16	6	31	6
Visceral disease	173	64	164	61	337	62
No. of involved sites						
≥ 3	77	28	78	29	155	29
< 3	194	72	191	71	385	71
Stage IV at initial diagnosis	52	19	44	16	96	18
Prior treatment						
Prior trastuzumab/no prior met treatment	59	22	58	22	117	22
Prior trastuzumab/≥ 1 prior met treatment	108	40	101	38	209	39
No prior trastuzumab/no prior met treatment	58	21	63	23	121	22
No prior trastuzumab/≥ 1 prior met treatment	46	17	47	17	93	17
Patients who received prior chemotherapy	268	99	268	> 99	536	> 99
Adjuvant	158	58	173	64	331	61
Metastatic	128	47	132	49	260	48
No. of prior treatments for metastatic disease						
0	117	43	121	45	238	44
≥ 1	154	57	148	55	302	56
Patients who received prior trastuzumab	167	62	159	59	326	60
Adjuvant	81	30	70	26	151	28
Metastatic	96	35	93	35	189	35
Duration of prior trastuzumab treatment, months						
Median	11.9		11.8		11.8	
Range	1.0-89.5		0.0-96.1		0.0-96.1	
Duration of prior metastatic trastuzumab treatment, months						
Median	11.8		13.4		12.1	
Range	1.0-89.5		0.0-96.1		0.0-96.1	
Duration of most recent prior metastatic trastuzumab treatment, months						
Median	10.4		10.9		10.6	
Range	0.0-89.5		0.0-96.1		0.0-96.1	
Patients who received prior anthracycline and taxane						
Anthracycline	238	88	234	87	472	87
Adjuvant	138	51	144	54	282	52
Metastatic	56	21	55	20	111	21
Taxane	172	63	180	67	352	65
Adjuvant	47	17	61	23	108	20
Metastatic	97	36	99	37	196	36
Time since initial diagnosis, years	253	93	246	91	499	92
Median	2.6		3.0		2.8	
Range	0-18		0-25		0-25	

Primary and secondary endpoints

Primary endpoint:

1. Number of Participants With Central Nervous System (CNS) Metastases (as Assessed by Independent Review) as the Site of First Relapse

Secondary endpoints:

1. Progression Free Survival (PFS), as Assessed by the Investigator
2. Time to First CNS Progression, Defined as the Time From Randomization Until the Date of Documented CNS Progression as the First Site of Relapse
3. Overall Survival (Cut-off 11-Jun-2012)
4. Number of Participants With Overall Response (OR), as Assessed by the Investigator
5. Number of Participants With Clinical Benefit (CB)
6. Duration of Response
7. Number of Participants With CNS Progression at Any Time
8. Number of Participants With Qualitative and Quantitative Toxicities
9. Number of Participants Expressing Glucocorticoid Receptor, Phosphatase and Tensin Homolog (PTEN), Phosphatidylinositide 3-

Table A2 CEREBEL	
	kinase (PI3K)/AKT, Protein 53 (P53), Insulin-like Growth Factor-1 (IGF-1), and Genes Involved in Cell Cycle Regulation Because the study terminated early, pharmacogenetic and biomarker analyses were not performed. 10. Number of Participants With the Indicated Grade 3 or Grade 4 Adverse Events (AEs) Occurring in >=2% of Participants in Either Treatment Arm.
Method of analysis	A total of 650 patients (325 per arm) were required to achieve 80% power (two-sided a 5 .05) to detect an absolute decrease in the incidence of CNS as site of first relapse of 8%. Safety assessments were conducted in the safety population, which included all randomly assigned patients who received at least one dose of study medication. The primary and CNS end points were analyzed in the modified intent-to-treat (M-ITT) population, comprising all randomly assigned patients without baseline CNS metastases as per independent review committee assessment. Other secondary end points were analyzed in the intent-to-treat (ITT) population. Kaplan-Meier estimates of PFS and OS were compared between treatment arms using a log-rank test, stratified for prior trastuzumab use and prior treatments for metastatic disease, along with the Pike estimator of the hazard ratio (HR) based on the log-rank test.28 Fisher's exact tests were used for the difference in ORR and clinical benefit response between treatment arms. Zelen's tests for homogeneity of the odds ratios across all strata were performed as a measure of validation. A statistical test for the interaction between treatment effect and the baseline stratification factors was performed separately using the Wald x2 test. Post hoc subgroup analyses based on the prespecified stratification factors of prior trastuzumab therapy and lines of prior metastatic therapy for PFS and OS were also performed. The Cox proportional hazards regression model29 was used to assess the heterogeneity of treatment effect among baseline stratification factors.30 All analyses were performed using SAS version 9 or higher (SAS Institute, Cary, NC).
Subgroup analyses	NA

Table 22. Details of the HER2CLIMB study

Table A2 Main study characteristics HER2CLIMB trial	
Trial name	ONT-380-206 (HER2CLIMB)
NCT number	NCT02614794
Objective	Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma (HER2CLIMB)
Publications – title, author, journal, year	**Published data:** Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N Engl J Med*. 2020; 382:597-609. (9)
Study type and design	A Phase 2 randomized, international, multi-center, double-blinded study of tucatinib or placebo in combination with capecitabine and trastuzumab in patients with unresectable locally advanced or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab and T-DM1.
Follow-up time	The median duration of follow-up in the total population was 14.0 months
Population (inclusion and exclusion criteria)	**Inclusion Criteria** • Histologically confirmed HER2+ breast carcinoma, with HER2+ defined by in situ hybridization (ISH), immunohistochemistry (IHC), or fluorescence in situ hybridization (FISH) methodology • Received previous treatment with trastuzumab, pertuzumab, and T-DM1 • Progression of unresectable locally advanced or metastatic breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy • Have measurable or non-measurable disease assessable by RECIST 1.1 • Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 • Adequate hepatic and renal function and hematologic parameters • Left ventricular ejection fraction (LVEF) ≥ 50% • CNS Inclusion - Based on screening brain magnetic resonance imaging (MRI), patients must have one of the following: 1. No evidence of brain metastases 2. Untreated brain metastases not needing immediate local therapy 3. Previously treated brain metastases not needing immediate local therapy a. Brain metastases previously treated with local therapy may either be stable since treatment or may have progressed since prior local CNS therapy b. Patients treated with CNS local therapy for newly identified lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if the following criteria are met: i. Time since whole brain radiation therapy (WBRT) is ≥ 21 days prior to first dose of study treatment, time since stereotactic radiosurgery (SRS) is ≥ 7 days prior to first dose of study treatment, or time since surgical resection is ≥ 28 days. ii. Other sites of disease assessable by RECIST 1.1 are present 4. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions **Exclusion Criteria** • Previously been treated with: 1. lapatinib within 12 months of starting study treatment (except in cases where lapatinib was given for ≤ 21 days and was discontinued for reasons other than disease progression or toxicity) 2. neratinib, afatinib, or other investigational HER2/epidermal growth factor receptor (EGFR) or HER2 tyrosine kinase inhibitor (TKI) at any time previously

	3. capecitabine (or other fluoropyrimidine) for metastatic disease except in cases where capecitabine was given for < 21 days and was discontinued for reasons other than disease progression or toxicity. Patients who have received capecitabine for adjuvant or neoadjuvant treatment at least 12 months prior to starting study treatment are eligible. • Clinically significant cardiopulmonary disease • Carriers of Hepatitis B or Hepatitis C or have other known chronic liver disease • Positive for human immunodeficiency virus (HIV) • Unable for any reason to undergo MRI of the brain • Have used a strong CYP3A4 or CYP2C8 inhibitor within 5 half-lives of the inhibitor, or a strong CYP3A4 or CYP2C8 inducer within 5 days prior to first dose of study treatment • Have known dihydropyrimidine dehydrogenase deficiency (DPD) • CNS Exclusion - Based on screening brain MRI, patients must not have any of the following: 1. Any untreated brain lesions > 2.0 cm in size, unless approved by medical monitor 2. Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of > 2 mg of dexamethasone (or equivalent) 3. Any brain lesion thought to require immediate local therapy. Patients who undergo local treatment for such lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described under CNS inclusion criteria 4. Known or suspected leptomeningeal disease (LMD) 5. Poorly controlled seizures Unblinded Phase Crossover Inclusion Criteria - Participants who were randomized to the control arm (placebo + trastuzumab + capecitabine) must meet the following criteria to be eligible to crossover to the experimental arm. • Have measurable or non-measurable disease assessable by RECIST 1.1 • For patients who were randomized to the control arm and on the long-term follow-up period at the time of crossover screening: have progression of unresectable locally advanced or metastatic breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy. • Have an ECOG Performance Status of 0 or 1 • Have a life expectancy of at least 6 months • Have adequate hepatic and renal function and hematologic parameters • Left ventricular ejection fraction (LVEF) ≥ 50% • CNS Inclusion - Based on screening brain magnetic resonance imaging (MRI), patients must have one of the following: i. No evidence of brain metastases ii. Untreated brain metastases not needing immediate local therapy iii. Previously treated brain metastases not needing immediate local therapy • Brain metastases previously treated with local therapy may either be stable since treatment or may have progressed since prior local CNS therapy • Patients treated with CNS local therapy for newly identified lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if the following criteria are met: 1. Time since whole brain radiation therapy (WBRT) is ≥ 21 days prior to first dose of study treatment, time since stereotactic radiosurgery (SRS) is ≥ 7 days prior to first dose of study treatment, or time since surgical resection is ≥ 28 days. 2. Other sites of disease assessable by RECIST 1.1 are present Unblinded Phase Crossover Exclusion Criteria - Participants who were randomized to the control arm (placebo + trastuzumab + capecitabine) will be excluded from the crossover to the experimental arm for any of the following reasons. • Discontinuation of study treatment due to an adverse event while on the double-blind phase of the study. If the adverse event leading to discontinuation of study treatment has resolved, the patient may be allowed to crossover with approval from the medical monitor.

	• History of exposure to the following cumulative doses of anthracyclines: 1. Doxorubicin > 360 mg/m^2 2. Epirubicin > 720 mg/m^2 3. Mitoxantrone > 120 mg/m^2 4. Idarubicin > 90 mg/m^2 5. Liposomal doxorubicin > 550 mg/m^2 • History of allergic reactions to trastuzumab, capecitabine, or compounds chemically or biologically similar to tucatinib (exceptions for Grade 1 or 2 infusion related reactions to trastuzumab that were successfully managed, or known allergy to one of the excipients in the study drugs) • Have received treatment with any systemic anti-cancer therapy, non-CNS radiation, or experimental agent within 3 weeks prior to start of crossover therapy • Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions: 1. Alopecia and neuropathy (must have resolved to ≤ Grade 2) 2. CHF (must have been ≤ Grade 1 in severity at the time of occurrence and must have resolved completely) 3. Anemia (must have resolved to ≤ Grade 2) • Have clinically significant cardiopulmonary disease • Have known myocardial infarction or unstable angina within 6 months prior to start of crossover therapy • Require therapy with warfarin or other coumarin derivatives • Inability to swallow pills or significant gastrointestinal disease which would preclude the adequate oral absorption of medications • Have used a strong CYP2C8 inhibitor within 5 half-lives of the inhibitor or have used a strong CYP2C8 or CYP34A inducer within 5 days prior to start of the crossover (tucatinib) treatment. • Known dihydropyrimidine dehydrogenase deficiency • Unable to undergo contract MRI of the brain • Have evidence within 2 years prior to start of crossover therapy of another malignancy that required systemic treatment • CNS Exclusion: • CNS Exclusion - Based on screening brain MRI, patients must not have any of the following: 1. Any untreated brain lesions > 2.0 cm in size, unless approved by medical monitor 2. Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of > 2 mg of dexamethasone (or equivalent) 3. Any brain lesion thought to require immediate local therapy. Patients who undergo local treatment for such lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described under CNS inclusion criteria 4. Known or suspected leptomeningeal disease (LMD) 5. Poorly controlled seizures
Intervention	612 adult Patients were randomly assigned in a 2:1 ratio to receive either tucatinib (300 mg orally twice daily throughout the treatment period) or placebo (orally twice daily), in combination with trastuzumab (6 mg per kilogram of body weight intravenously once every 21 days, with an initial loading dose of 8 mg per kilogram; subcutaneous administration was allowed) and capecitabine (1000 mg per square meter of body-surface area orally twice daily on days 1 to 14 of each 21-day cycle). Patients were stratified according to whether brain metastases were present, ECOG performance-status score (0 or 1), and geographic region (United States, Canada, or the rest of the world).

Baseline characteristics	**Patient characteristics** | Characteristic	Primary End-Point Analysis Population (N=480)		Total Population (N=612)	
	Tucatinib Combination (N=320)	Placebo Combination (N=160)	Tucatinib Combination (N=410)	Placebo Combination (N=202)
Female sex — no. (%)	317 (99.1)	158 (98.8)	407 (99.3)	200 (99.0)
Age — no. (%)				
<65 yr	252 (78.8)	132 (82.5)	328 (80.0)	168 (83.2)
≥65 yr	68 (21.2)	28 (17.5)	82 (20.0)	34 (16.8)
Median age — yr	54.0	54.0	55.0	54.0
Race — no. (%)†				
Asian	17 (5.3)	3 (1.9)	18 (4.4)	5 (2.5)
Black	30 (9.4)	13 (8.1)	41 (10.0)	14 (6.9)
White	225 (70.3)	125 (78.1)	287 (70.0)	157 (77.7)
Unknown or other	48 (15.0)	19 (11.9)	64 (15.6)	26 (12.9)
Geographic region — no. (%)				
United States and Canada	204 (63.8)	103 (64.4)	246 (60.0)	123 (60.9)
Rest of the world	116 (36.2)	57 (35.6)	164 (40.0)	79 (39.1)
Hormone-receptor status — no. (%)				
Positive for ER or PR or both	190 (59.4)	99 (61.9)	243 (59.3)	127 (62.9)
Negative for ER and PR	126 (39.4)	61 (38.1)	161 (39.3)	75 (37.1)
Other	4 (1.2)	0	6 (1.5)	0
ECOG performance-status score — no. (%)‡				
0	159 (49.7)	76 (47.5)	204 (49.8)	94 (46.5)
1	161 (50.3)	84 (52.5)	206 (50.2)	108 (53.5)
Stage IV at initial diagnosis — no. (%)	108 (33.8)	67 (41.9)	143 (34.9)	77 (38.1)
Presence or history of brain metastases — no. (%)	148 (46.2)	71 (44.4)	198 (48.3)	93 (46.0)
Location of other metastases — no. (%)				
Lung	160 (50.0)	82 (51.2)	200 (48.8)	100 (49.5)
Liver	108 (33.8)	64 (40.0)	137 (33.4)	78 (38.6)
Bone	178 (55.6)	85 (53.1)	223 (54.4)	111 (55.0)
Previous lines of therapy, median no. (range)	4 (2–14)	4 (2–17)	4 (2–14)	4 (2–17)
Previous lines of therapy for metastatic cancer, median no. (range)	3 (1–14)	3 (1–13)	3 (1–14)	3 (1–13)
Previous therapies — no. (%)				
Trastuzumab	320 (100)	160 (100)	410 (100)	202 (100)
Pertuzumab	320 (100)	159 (99.4)	409 (99.8)	201 (99.5)
Trastuzumab emtansine	320 (100)	160 (100)	410 (100)	202 (100)
Lapatinib	22 (6.9)	10 (6.2)	24 (5.9)	10 (5.0)	 * The primary end-point analysis population included the first 480 patients who were randomly assigned to the tucatinib-combination group (tucatinib plus trastuzumab and capecitabine) or to the placebo-combination group (placebo plus trastuzumab and capecitabine), and the total population included 612 patients who underwent randomization. Randomization stratification factors included geographic region (United States, Canada, or the rest of the world), presence or history of brain metastases (yes or no), and Eastern Cooperative Oncology Group (ECOG) performance-status score (0 or 1). ER denotes estrogen receptor, and PR progesterone receptor. Data from the patients in the United States and Canada were combined for this analysis. † Race was determined by the local investigator. ‡ ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability.
Primary and secondary endpoints	**Primary Endpoint:** • PFS, defined as the time from randomization to documented disease progression (as determined by BICR per RECIST 1.1), or death from any cause, whichever occurs first **Secondary Endpoints:** • PFS in patients with brain metastases at baseline using RECIST 1.1 based on BICR • OS • PFS, defined as the time from randomization to investigator-assessed documented disease progression (per RECIST 1.1), or death from any cause, whichever occurs first • ORR (RECIST 1.1) as determined by BICR as well as the investigator • DOR (RECIST 1.1) as determined by BICR as well as the investigator • CBR (RECIST 1.1) as determined by BICR as well as the investigator • Safety, Pharmacokinetics, QoL
Method of analysis	The intent-to-treat (ITT) population included all randomized patients and was used for efficacy analyses. Safety analyses included all randomized patients who received at least one dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab). Pharmacokinetic analyses also included all randomized patients who received at least one dose of tucatinib and who had at least one evaluable PK assessment. The primary end point was progression-free survival among the first 480 patients who underwent randomization. Secondary end points, assessed in the total population (612 patients), included overall

	survival, progression free survival among patients with brain metastases, confirmed objective response rate, and safety. The Kaplan Meier method was used to estimate progression-free survival and overall survival time curves, median progression-free survival and overall survival, and 95% confidence intervals for the treatment groups. Cox proportional-hazards models, with stratification factors taken into ac-count, were used to estimate hazard ratios and 95% confidence intervals.
Subgroup analyses	• History of parenchymal brain metastases or brain metastases at baseline (Yes, No): ✓ Patients with target and/or non-target parenchymal brain lesions (per RECIST 1.1) at baseline or who have a history of brain metastases, or with brain lesions of equivocal significance on screening MRI based on screening data collected in eCRF was assigned to the 'Yes' subgroup and referred to as "BM subgroup". Patients not meeting the above criteria was assigned to the 'No' subgroup for this variable. Patients with dural lesions only, i.e. no parenchymal brain lesions, was assigned to the 'No' subgroup. Patients with incomplete screening data and not meeting the criteria for BM subgroup was not evaluable (NE) for this subgroup determination. • Geographic Region: North America, Rest of World • ECOG: 0 vs. 1 as recorded in eCRF at baseline • Age : <65 vs. ≥65 years • Race: White, African-American, others • Hormone Receptor Status (Negative, Positive): Patients 'positive' for either or both estrogen receptor and progesterone receptor was assigned to the 'positive' subgroup. Patients not meeting the above criteria was assigned to the 'negative' subgroup.

Table 23. Details of the SOPHIA study

Table A2 Main study characteristics SOPHIA trial	
Trial name	CP-MGAH22-04
NCT number	NCT02492711
Objective	○ To evaluate margetuximab plus chemotherapy against the current standard of care in third-line HER2-positive metastatic breast cancer. ○ To determine whether patients treated with margetuximab plus chemotherapy have longer progression free survival and overall survival than patients treated with trastuzumab plus chemotherapy. ○ To establish superiority to Trastuzumab. ○ To evaluate margetuximab plus chemotherapy compared to trastuzumab plus chemotherapy in patients with HER2-positive metastatic breast cancer, who have previously been treated with anti-HER2-targeted therapies. ○ To compare the clinical efficacy of margetuximab vs trastuzumab, each with chemotherapy, in patients with pretreated ERBB2-positive advanced breast cancer.
Publications – title, author, journal, year	**Published data:** Rugo HS, Im S, Cardoso F, et al. Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol. Published online January 22, 2021. doi:10.1001/jamaoncol.2020.7932 (8)
Study type and design	A Phase 3, randomized, open-label, comparator-controlled study comparing margetuximab to trastuzumab, each in combination with chemotherapy, for the treatment of adult patients with advanced HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy in the metastatic setting, or in case of having received (neo)adjuvant pertuzumab, at least 1 prior line of anti-HER2 directed therapy in the metastatic setting, and who have received at least one, and no more than three, lines of therapy overall in the metastatic setting. Patients must have progressed on or following the most recent therapy. Eligible patients was assigned to chemotherapy of the investigator's choice to be chosen from capecitabine, eribulin, gemcitabine, or vinorelbine. Randomization of eligible patients were 1:1. They received either margetuximab or trastuzumab to be administered in combination with the chosen chemotherapy. Patients was treated until disease progression, death, withdrawal of consent, or request by the treating physician to discontinue treatment. Following completion of (or discontinuation from) treatment, patients was followed for survival.
Follow-up time	PFS and OS median follow-up time was 2.8 months and 15.6 months, respectively.
Population (inclusion and exclusion criteria)	**Inclusion:** • Histologically-proven metastatic or locally-advanced relapsed/refractory HER2+ breast cancer based on the most recently available tumor biopsy collected from the patient. Tumors may be estrogen receptor (ER)/progesterone receptor (PgR) positive or negative. • Have received at least 2 prior lines of anti-HER2 directed therapy in the metastatic setting, or in case of having received (neo)adjuvant pertuzumab, at least 1 prior line of anti-HER2 directed therapy in the metastatic setting. In either case, patients must have received prior treatment with pertuzumab, in the (neo)adjuvant or metastatic setting. Prior radiotherapy, hormonal therapies, and other anti-HER2 therapies are allowed. • Prior treatment with at least one, and no more than three, lines of therapy overall in the metastatic setting. Patients must have progressed on or following, the most recent line of therapy. • Resolution of all chemotherapy or radiation-related toxicities to ≤ Grade 1 • Life expectancy ≥ 12 weeks • Acceptable laboratory parameters

	• Women of childbearing potential must have negative pregnancy test performed within 14 days of randomization and on the first day of treatment. All subjects must agree to use an effective form of contraception for the duration of study treatment and for 7 months after the last dose of study drug. • Infusion sub-study prior therapy requirements: Same as above, except: ✓ Must have received 4 or more prior lines or therapy in the metastatic setting ✓ Must have received prior trastuzumab, pertuzumab, and T-DM1 **Exclusion:** • Known, untreated brain metastasis. Patients with signs or symptoms of brain metastasis must have a CT or MRI performed within 4 weeks prior to randomization to specifically exclude the presence of radiographically-detected brain metastases • History of uncontrolled seizures within 6 months of randomization • History of prior allogeneic bone marrow, stem-cell, or solid organ transplantation • History of clinically significant cardiovascular disease • Clinically-significant pulmonary compromise, including a requirement for supplemental oxygen use to maintain adequate oxygenation • Any condition that would be a contraindication to receiving trastuzumab as described in the approved local label or a condition that would prevent treatment with the physician's choice of chemotherapy Full inclusion/exclusion criteria are to be found in protocol related to publication.
Intervention	All study patients had previously received trastuzumab, all but one patient had previously received pertuzumab, and 91% had previously received T-DM1. The study enrolled 536 patients who were randomized 1:1 to receive either Margetuximab (n=266) given intravenously at 15 mg/kg every three weeks or trastuzumab (n=270) given intravenously at 6 mg/kg (or 8 mg/kg for loading dose) every three weeks in combination with one of four chemotherapy agents (capecitabine, eribulin, gemcitabine or vinorelbine) given at the standard dose. Intent-to-treat PFS analysis occurred after 265 PFS events. Stratification factors were metastatic sites (2, >2), lines of therapy (2, >2), and chemotherapy choice.
Baseline characteristics	Demographic and Baseline Disease Characteristics in the Intention-to-Treat Population (n = 536)

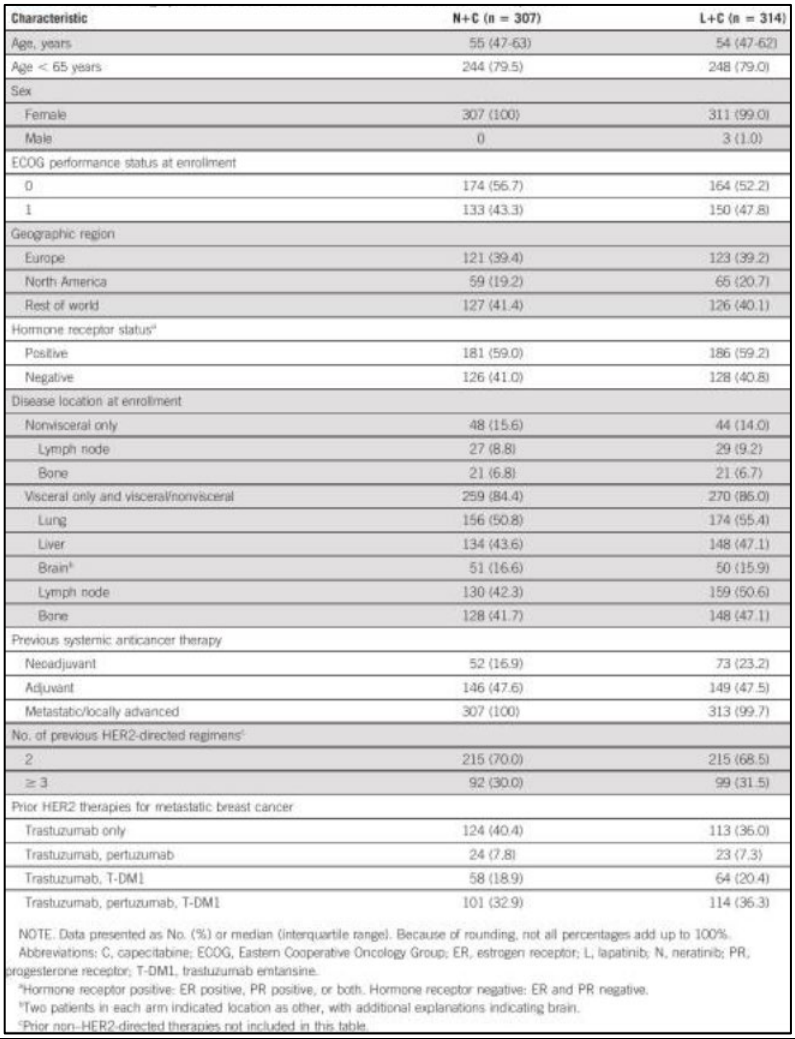
Characteristic	No. (%)	
	Margetuximab plus chemotherapy (n = 266)	Trastuzumab plus chemotherapy (n = 270)
Female sex	266 (100)	267 (98.9)
Age, median (range), y	55.0 (29-83)	56.0 (27-86)
Race		
Asian	20 (7.5)	14 (5.2)
Black or African American	16 (6.0)	12 (4.4)
White	205 (77.1)	222 (82.2)
Other	25 (9.4)	22 (8.1)
Region		
Europe	152 (57.1)	138 (51.1)
North America	85 (32.0)	102 (37.8)
Other	29 (10.9)	30 (11.1)
ECOG performance status		
0	149 (56.0)	161 (59.6)
1	117 (44.0)	109 (40.4)
Disease extent at screening		
Metastatic	260 (97.7)	264 (97.8)
Locally advanced, unresectable	6 (2.3)	6 (2.2)
Measurable disease	262 (98.5)	262 (97.0)
No. of metastatic sites		
≤2	138 (51.9)	144 (53.3)
>2	128 (48.1)	126 (46.7)
Common sites of metastases (≥10% of patients) at study entry		
Bone	153 (57.5)	155 (57.4)
Lymph node	140 (52.6)	151 (55.9)
Lung	124 (46.6)	126 (46.7)
Liver	93 (35.0)	95 (35.2)
Breast	44 (16.5)	37 (13.7)
Skin	41 (15.4)	32 (11.9)
Brain	37 (13.9)	34 (12.6)
Combined ER and PR status		
ER positive, PR positive, or both	164 (61.7)	170 (63.0)
ER negative and PR negative	102 (38.4)	98 (36.3)
Settings of prior systemic/hormonal therapy		
Adjuvant and/or neoadjuvant	158 (59.4)	145 (53.7)
Metastatic only	108 (40.6)	125 (46.3)
No. of prior lines of therapy in the metastatic setting		
≤2	175 (65.8)	180 (66.7)
>2	91 (34.2)	90 (33.3)
Prior systemic therapy in early and metastatic settings		
Chemotherapy		
Taxane	252 (94.7)	249 (92.2)
Anthracycline	118 (44.4)	110 (40.7)
Platinum	34 (12.8)	40 (14.8)
ERBB2-targeted therapy		
Trastuzumab	266 (100)	270 (100)
Pertuzumab	266 (100)	269 (99.6)
Ado-trastuzumab emtansine	242 (91.0)	247 (91.5)
Lapatinib	41 (15.4)	39 (14.4)
Other	6 (2.3)	6 (2.2)
Endocrine therapy	126 (47.4)	133 (49.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor.

Primary and secondary endpoints	The primary endpoints of the study were sequentially-assessed PFS, determined by blinded, centrally-reviewed radiological review, followed by OS. Additional key secondary endpoints are PFS by investigator assessment and ORR. Tertiary endpoints include ORR by investigator assessment and safety. PFS and ORR were assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).
Method of analysis	For 90% power to detect median PFS improvement from 4 to 6 months (hazard ratio [HR], 0.67) at a 2-sided 0.05 significance level, 257 PFS events were needed. Primary PFS by central blinded analysis occurred after 257 PFS events or all patients were randomized, whichever occurred last. The OS was time from randomization to death from any cause and was to be assessed only if PFS was positive. For 80% power to detect a median OS improvement from 12 to 16 months (HR, 0.75) at a 2-sided .05 significance level, 385 OS events were needed. Three OS analyses were planned: first interim coincident with primary PFS analysis, second interim after 270 deaths, and final analysis after 385 events. All α was allocated to PFS, tested at a 2-sided 0.05 significance level. If PFS passed the test, then OS would be tested at the same significance level of 2-sided 0.05. The O'Brien-Fleming type Lan-De Mets α-spending function was applied for α allocation to each interim OS analysis. The PFS and OS were assessed in the randomized, intention-to-treat population. Patients were censored at the last tumor assessment date for PFS and at the last time known to be alive for OS. The ORR and CBR were assessed in randomized patients with baseline measurable disease (response evaluable population). For ORR analysis, if a patient's response was missing, the patient was classified as not available. Safety and antidrug antibodies were assessed in randomized patients after any study treatment (safety population). Kaplan-Meier methods were used to estimate median PFS, OS, and 95% CIs for each treatment group. The stratified log-rank test was used to compare time-to-event end points between groups. A stratified Cox proportional hazards model, with treatment as the only covariate, was used to estimate PFS and OS HRs and 95% Cis. If the primary PFS and OS were each positive, then secondary PFS and ORR end points were to be tested using the Hochberg step-up procedure for multiplicity adjustment. Investigator-assessed PFS was analyzed using the same methods as the primary PFS end point. The ORR was compared between groups by the stratified Mantel-Haenszel test. For the sub-groups, the HRs and 95% CIs for each were assessed using an unstratified Cox proportional hazards model with treatment as the only covariate.
Subgroup analyses	Prespecified PFS and OS subgroup analyses included chemotherapy choice, metastatic sites, lines of prior metastatic therapy, prior ado-trastuzumab emtansine use, hormone receptor status, ERBB2 status, Eastern Cooperative Oncology Group performance status, region, age, and race, as well as FCGR3A (FcγRIIIa/CD16A), FCGR2A (FcγRIIa/CD32A), and FCGR2B (FcγRIIb/CD32B) genotype.

Table 24. Details of the NALA study

Table A2 Main study characteristics NALA trial	
Trial name	PUMA-NER-1301
NCT number	NCT01808573
Objective	The NALA trial (N = 621) was designed to compare neratinib plus capecitabine (N+C) versus lapatinib plus capecitabine (L+C) in patients with HER2-positive metastatic breast cancer (MBC) who received ≥ 2 HER2-directed regimens in the metastatic setting, including those with asymptomatic or stable (treated or untreated) CNS metastases.
Publications – title, author, journal, year	**Published data:** Saura C, Oliveira M, Feng YH, et al. ; NALA Investigators. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol. 2020 Sep 20;38(27):3138-3149. doi: 10.1200/JCO.20.00147. Epub 2020 Jul 17. PMID: 32678716; PMCID: PMC7499616.
Study type and design	The NALA trial is a randomized, multi-center, multinational, open-label, active-controlled, parallel design phase III trial comparing N+C and L+C in HER2-positive metastatic breast cancer. Eligible patients were age ≥ 18 years, with an Eastern Cooperative Oncology Group performance status ≤ 1 and ≥ 2 previous HER2-directed therapies for metastatic breast cancer. Patients with brain metastases were eligible unless they had symptomatic or unstable brain metastases. 621 eligible patients were randomly assigned (1:1) to N+C or L+C. The randomization sequence was stratified by: hormone receptor status (hormone receptor positivity or negative), number of previous HER2-directed therapies for metastatic breast cancer (2 or ≥ 3), geographic region (North America or Europe or rest of world), and visceral disease.
Follow-up time	For PFS, the median follow-up duration was 29.9 months.
Population (inclusion and exclusion criteria)	**Inclusion:** • Aged ≥18 years at signing of informed consent. • Histologically confirmed MBC, current stage IV. • Documented HER2 overexpression or gene-amplified tumor immunohistochemistry 3+ or 2+, with confirmatory fluorescence in situ hybridization (FISH) +. • Prior treatment with at least two (2) HER2-directed regimens for metastatic breast cancer. **Exclusion:** • Received previous therapy with capecitabine, neratinib, lapatinib, or any other HER2 directed tyrosine kinase inhibitor. Full inclusion/exclusion criteria are to be found in protocol related to publication (7).
Intervention	The 621 patients were randomly assigned to N+C (neratinib 240 mg orally once daily continuously in 21-day cycles with no break between cycles, plus capecitabine 1,500 mg/m2 orally daily in 2 evenly spaced doses [750 mg/m2 twice a day] on days 1-14 of 21-day cycles) or L+C (lapatinib 1,250 mg orally once daily continuously, plus capecitabine 2,000 mg/m2 orally daily in 2 evenly spaced doses [1,000 mg/m2 twice a day] on days 1-14 of 21-day cycles). Prophylactic antidiarrheal medication was mandated in N+C for the duration of cycle 1 and in the L+C as per prescribing information. Concurrent endocrine therapy was not permitted. Patients will receive either neratinib plus capecitabine combination or lapatinib plus capecitabine combination until the occurrence of death, disease progression, unacceptable toxicity, or other specified withdrawal criterion.
Baseline characteristics	Demographic and Baseline Disease Characteristics in the Intention-to-Treat Population.

Characteristic	N+C (n = 307)	L+C (n = 314)
Age, years	55 (47-63)	54 (47-62)
Age < 65 years	244 (79.5)	248 (79.0)
Sex		
Female	307 (100)	311 (99.0)
Male	0	3 (1.0)
ECOG performance status at enrollment		
0	174 (56.7)	164 (52.2)
1	133 (43.3)	150 (47.8)
Geographic region		
Europe	121 (39.4)	123 (39.2)
North America	59 (19.2)	65 (20.7)
Rest of world	127 (41.4)	126 (40.1)
Hormone receptor status[a]		
Positive	181 (59.0)	186 (59.2)
Negative	126 (41.0)	128 (40.8)
Disease location at enrollment		
Nonvisceral only	48 (15.6)	44 (14.0)
Lymph node	27 (8.8)	29 (9.2)
Bone	21 (6.8)	21 (6.7)
Visceral only and visceral/nonvisceral	259 (84.4)	270 (86.0)
Lung	156 (50.8)	174 (55.4)
Liver	134 (43.6)	148 (47.1)
Brain[b]	51 (16.6)	50 (15.9)
Lymph node	130 (42.3)	159 (50.6)
Bone	128 (41.7)	148 (47.1)
Previous systemic anticancer therapy		
Neoadjuvant	52 (16.9)	73 (23.2)
Adjuvant	146 (47.6)	149 (47.5)
Metastatic/locally advanced	307 (100)	313 (99.7)
No. of previous HER2-directed regimens[c]		
2	215 (70.0)	215 (68.5)
≥ 3	92 (30.0)	99 (31.5)
Prior HER2 therapies for metastatic breast cancer		
Trastuzumab only	124 (40.4)	113 (36.0)
Trastuzumab, pertuzumab	24 (7.8)	23 (7.3)
Trastuzumab, T-DM1	58 (18.9)	64 (20.4)
Trastuzumab, pertuzumab, T-DM1	101 (32.9)	114 (36.3)

NOTE. Data presented as No. (%) or median (interquartile range). Because of rounding, not all percentages add up to 100%.
Abbreviations: C, capecitabine; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; L, lapatinib; N, neratinib; PR, progesterone receptor; T-DM1, trastuzumab emtansine.
[a]Hormone receptor positive: ER positive, PR positive, or both. Hormone receptor negative: ER and PR negative.
[b]Two patients in each arm indicated location as other, with additional explanations indicating brain.
[c]Prior non-HER2-directed therapies not included in this table.

Primary and secondary endpoints	Primary end points were BIRC assessed PFS [per RECIST; version 1.1] and OS. Secondary end points were time to intervention for metastatic CNS disease (included radiotherapy, surgery, or CNS-directed concomitant medications), investigator-assessed PFS, objective response rate (ORR), duration of response (DoR), and clinical benefit rate (CBR; complete response + partial response + stable disease lasting ≥ 24 weeks). Other secondary end points included safety and health-related quality of life (HRQoL).
Method of analysis	Primary end points were analyzed using an overall type I error rate of 0.01 for PFS and 0.04 for OS. It was estimated that 419 PFS events and 378 OS events were required to obtain 85% power to detect an HR (control v treatment) of 0.70 for PFS and 0.725 for OS. The primary analysis of each end point was event driven. The trial was considered positive if either PFS or OS were statistically significant at the split α level. Approximately 600 patients were to be enrolled and randomly assigned equally between the 2 groups. No interim analyses were performed. Primary efficacy end points were assessed in the intention-to-treat population. Safety analyses were conducted for all patients who received ≥ 1 dose of investigational treatment. The primary analysis method was stratified log-rank test for hypothesis testing and stratified Cox proportional hazards model to estimate HRs and 95% CIs. Differences between treatment groups were examined using a log-rank test statistic stratified by hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, and disease location. If the proportional hazards assumption was not met, a prespecified supportive analysis on the basis of restricted means was added and performed with restrictions at 24 months for PFS and 48 months for OS. The Kaplan-Meier method was used to represent time-to-event end points.

	ORR and CBR were analyzed using Cochran-Mantel-Haenszel tests.
Subgroup analyses	PFS (by BIRC) and OS subgroup analyses included age, race, geographic region, disease location, previous HER2 regimens and hormone receptor status.

[redacted]

9.1.3. Results per study

Table 26. Results of study DESTINY-Breast01

Table A3a Results of study DESTINY-Breast01										
Trial name:	Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop. *N Engl J Med 2020; 382:610-621, February 13, 2020* S. Modi, Saura C, Yamashita T, HeePark Y, Sung-Bae Kim, Kenji Tamura, et al. Updated Results From DESTINY-Breast01, a Phase 2 Trial of Trastuzumab Deruxtecan (T-DXd)in HER2-Positive Metastatic Breast Cancer. San Antonio Breast Cancer Symposium® -December 8-11, 2020. 2020.									
NCT number:	NCT03248492									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
ORR	T-DXd	184	61.4 (54; 68.5)	NA	NA	NA	NA	NA	NA	*Clopper–Pearson method to calculate the two-sided 95% confidence intervals for the response rate. We used the Kaplan–Meier method to estimate the distribution of time-to-event end points of response duration, progression-free survival, and overall survival; corresponding two-sided 95% confidence intervals were calculated with the Brookmeyer and Crowley methods*
	NA	NA	NA							
Median PFS	T-DXd	184	19.4 (14.1 -NE)	NA	NA	NA	NA	NA	NA	*Kaplan–Meier method to estimate the progression-free survival. Corresponding two-sided 95% confidence intervals were calculated with the Brookmeyer and Crowley methods*
	NA	NA	NA							
	T-DXd	184	65%	NA	NA	NA	NA	NA	NA	*Kaplan–Meier method to estimate the progression-free survival.*

Table A3a Results of study DESTINY-Breast01										
PFS at 12 months (%)	NA	NA	NA							
Median OS, months	T-DXd	184	24.6 (14.1 -NE)	NA	NA	NA	NA	NA	NA	*Kaplan–Meier method to estimate overall survival; corresponding two-sided 95% confidence intervals were calculated with the Brookmeyer and Crowley methods*
	NA	NA	NA							
OS at 12 months	T-DXd	184	85% (79%-90%)	NA	NA	NA	NA	NA	NA	*Kaplan–Meier method to estimate overall survival; corresponding two-sided 95% confidence intervals were calculated with the Brookmeyer and Crowley methods*
	NA	NA	NA							
OS at 18 months	T-DXd	184	74% (67%-80%)	NA	NA	NA	NA	NA	NA	
	NA	NA	NA							
HQoL	T-DXd	184	NA	NA	NA	NA	NA	NA	NA	
	NA	NA	NA							

Table 27. Results of the HER2CLIMB study

Table A3a Results ONT-380-206 (HER2CLIMB)										
Trial name	Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma (HER2CLIMB)									
NCT number:	NCT02614794									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
PFS 1-year (BIRC)	tucatinib-combination group	320	33.1%	20.8 %	NA	NA	HR= 0.54	0.42; 0.71	P<0.001	Kaplan–Meier estimates of PFS in the primary end-point analysis population, which included the first 480 patients who underwent randomization.
	placebo-combination group	160	12.3%							
PFS median (BIRC)	tucatinib-combination group	320	7.8 m	2.2 m	NA	NA	HR= 0.54	0.42; 0.71	P<0.001	Kaplan–Meier estimates of PFS in the primary end-point analysis population, which included the first 480 patients who underwent randomization.
	placebo-combination group	160	5.6 m							
OS 2-year	tucatinib-combination group	410	44.9%	18.3%	NA	NA	HR=0.66	0.50; 0.88	P=0.005	Kaplan–Meier estimates of OS in the total population, which included 612 patients who underwent randomization.
	placebo-combination group	202	26.6%							
OS median	tucatinib-combination group	410	21.9 m	4.5 m	NA	NA	HR=0.66	0.50; 0.88	P=0.005	Kaplan–Meier estimates of OS in the total population, which included 612 patients who underwent randomization.
	placebo-combination group	202	17.4 m							
ORR (inv. ass.)	tucatinib-combination group	357	146 (40.9%)		35.8, 46.2	NA	NA	NA	NA	The P value for the between-group comparison of the percent-age of patients who had a confirmed objective response was calculated with the use of a strati-fied Cochran–Mantel–Haenszel test
	placebo-combination group	173	37 (21.4)		15.5, 28.3					
ORR (BIRC)	tucatinib-combination group	340	138 (40.6%)	99 (17,8%)	35.3; 46.0	P=0.00008	NA	NA	NA	

	placebo-combination group	171	39 (22.8%)		16.7; 29.8					The P value for the between group comparison of the percentage of patients who had a confirmed objective response was calculated with the use of a stratified Cochran–Mantel–Haenszel test
AE grade 3 or higher	tucatinib-combination group	404	223 (55.2%)	127 (6.5%)	NA	NA	NA	NA	NA	
	placebo-combination group	197	96 (48.7%)							
Discontinuation due to AE	tucatinib-combination group	404	23 (5.7)	17 (2.7%)	NA	NA	NA	NA	NA	
	placebo-combination group	197	6 (3.0)							
QoL	tucatinib-combination group	NA	NA	NA	NA	NA	NA	NA	NA	
	placebo-combination group	NA	NA							

Table 28. Results of the CEREBEL study

Table A3a Results of study CEREBEL										
Trial name:	Pivot X et al. A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2015 May 10;33(14):1564-73									
NCT number:	NCT00820222.									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
Incidence CNS mets	Lapatinib-capecitabine	251	3 %	−1.6%	(−2%; 5%)	*P* = .360	NA	NA	NA	The CNS end points were analyzed in the modified intent-to-treat (M-ITT) population, comprising all randomly assigned patients without baseline CNS metastases as per independent review committee assessment.
	Trastuzumab-capecitabine	250	5 %							
Median PFS	Lapatinib-capecitabine	271	6.6 m(5.7; 8.1)	- 1.5 m	NA	NA	HR=1.30	(1.04; 1.64)	p=0.021	Kaplan-Meier estimates of PFS were compared between treatment arms using a log-rank test, stratified for prior trastuzumab use and prior treatments for metastatic disease, along with the Pike estimator of the hazard ratio (HR) based on the log-rank test
	Trastuzumab-capecitabine	269	8.1 m (6.1; 8.9)							
PFS no prior trastuzumab	Lapatinib-capecitabine	104	6.3 m(5.6; 8.1)	- 4.6 m			HR=1.70	(1.13; 2.50)		Kaplan-Meier estimates of PFS were compared between treatment arms using a log-rank test, stratified for prior trastuzumab use and prior treatments for metastatic disease, along with the Pike estimator of the hazard ratio (HR) based on the log-rank test
	Trastuzumab-capecitabine	110	10.9 m(8.3; 15.0)							

Table A3a Results of study CEREBEL										
Median PFS prior transtuzumab	Lapatinib-capecitabine	167	6.6m (5.7; 8.3)	0.5 m	NA	NA	HR=1.13	(0.85; 1.50)		Kaplan-Meier estimates of PFS were compared between treatment arms using a log-rank test, stratified for prior trastuzumab use and prior treatments for metastatic disease, along with the Pike estimator of the hazard ratio (HR) based on the log-rank test
	Trastuzumab-capecitabine	159	6.1m (5.7; 8.0)							
Median OS	Lapatinib-capecitabine	271	22.7m(19.5; NR)	- 4.6 m	NA	NA	HR= 1.34	(0.95; 1.90)	p=0.095	Kaplan-Meier estimates of OS were compared between treatment arms using a log-rank test, stratified for prior trastuzumab use and prior treatments for metastatic disease, along with the Pike estimator of the hazard ratio (HR) based on the log-rank test
	Trastuzumab-capecitabine	269	27.3 m (23.7; NR)							
ORR	Lapatinib-capecitabine	271	27 %	- 5%	NA	p= 0.2731	NA	NA	NA	Fisher's exact tests were used for the difference in ORR
	Trastuzumab-capecitabine	269	32%							
HQoL	Lapatinib-capecitabine	271	NA	NA	NA	NA	NA	NA	NA	
	Trastuzumab-capecitabine	269	NA							

Table 29. Results of the SOPHIA study

Table A3a Results of study SOPHIA										
Trial name:	CP-MGAH22-04 (SOPHIA)									
NCT number:	NCT02492711									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
PFS median (BIRC, DCO Oct. 2018)	margetuximab + chemotherapy	266	5.8 month (5.52;6.97)	0.9 month	NA	NA	HR=0.76	0.59;0.98	P=0.03	In ITT population, Kaplan-Meier methods were used to estimate median PFS and 95% CIs for each treatment group. The stratified log rank test was used to compare time-to-event end points between groups. A stratified Cox proportional hazards model, with treatment as the only covariate, was used to estimate PFS HRs and 95% CIs.
	trastuzumab + chemotherapy	270	4.9 month (4.17;5.59)							
PFS median (Inv. Ass., DCO Oct. 2018)	margetuximab + chemotherapy	266	5.6 month (5.06;6.67)	1.4 month	NA	NA	HR=0.70	0.56;0.87	P=0.001	In ITT population, Kaplan-Meier methods were used to estimate median PFS and 95% CIs for each treatment group. The stratified log rank test was used to compare time-to-event end points between groups. A stratified Cox proportional hazards model, with treatment as the only covariate, was used to estimate PFS HRs and 95% CIs.
	trastuzumab + chemotherapy	270	4.2 month (3.98;5.39)							
PFS median (Inv. Ass., DCO Sep. 2019)	margetuximab + chemotherapy	266	5.7 month (5.22;6.97)	1.3 month	NA	NA	HR=0.71	0.58;0.86	P<0.001	In ITT population, Kaplan-Meier methods were used to estimate median PFS and 95% CIs for each treatment group. The stratified log rank test was used to compare time-to-event end points between groups. A stratified Cox proportional hazards model, with treatment as the only covariate, was used to estimate PFS HRs and 95% CIs.
	trastuzumab + chemotherapy	270	4.4 month (4.14;5.45)							
OS median (DCO Sep. 2019)	margetuximab + chemotherapy	266	21.6 month (18.86;24.05)	1.8 month	NA	NA	HR=0.89	0.69;1.13	P=0.33	In ITT population, Kaplan-Meier methods were used to estimate median OS and 95% CIs for each treatment group. The stratified log rank test was used to compare time-to-event end points between groups. A stratified Cox proportional hazards model,
	trastuzumab + chemotherapy	270	19.8 month (17.54;22.28)							

										with treatment as the only covariate, was used to estimate OS HRs and 95% CIs
ORR (BIRC, DCO Oct. 2018)	margetuximab + chemotherapy	262	58 (22.1%)	16 (6.1%)	17.11;27.16	P=0.0597	NA	NA	NA	The P value for the between group comparison of the percentage of patients who had a confirmed objective response was calculated with the use of a stratified Cochran–Mantel–Haenszel test
	trastuzumab + chemotherapy	262	42 (16.0%)		11.59;21.47					
ORR (Inv. ass., DCO Sep. 2019)	margetuximab + chemotherapy	266	67 (25.2%)	30 (11.5%)	20.1;30.9	P=0.006	NA	NA	NA	The P value for the between group comparison of the percentage of patients who had a confirmed objective response was calculated with the use of a stratified Cochran–Mantel–Haenszel test
	trastuzumab + chemotherapy	270	37 (13.7%)		9.8;18.4					
AE grade 3 or higher (DCO Apr. 2019)	margetuximab + chemotherapy	264	142 (53.8%)	2 (1.2%)	NA	NA	NA	NA	NA	
	trastuzumab + chemotherapy	266	140 (52.6%)							
Discontinuation due to AE (DCO Apr. 2019)	margetuximab + chemotherapy	266	8 (3.0%)	1 (0.4%)	NA	NA	NA	NA	NA	
	trastuzumab + chemotherapy	270	7 (2.6%)							
QoL(34)	margetuximab + chemotherapy	NA	-1.99: NFBSI-16 total scores -0.93: EQ-5D-5L	0.14: NFBSI-16 total scores 3.0: EQ-5D-5L	(-3.395; -0.594): NFBSI-16 total scores (-4.493; 2.637): EQ-5D-5L	NA	HR=0.88: NFBSI-16 total scores NA: EQ-5D-5L	0.672; 1.164: NFBSI-16 total scores NA: EQ-5D-5L	p=0.382: NFBSI-16 total scores NA: EQ-5D-5L	Changes from baseline in NFBSI-16 total score and in EQ-5D- 5L utility score were assessed using mixed model repeated measures analysis (MMRM) with treatment group, stratification factors, time, and treatment group by time interaction as covariates. A Cox proportional hazard model was used to assess time to symptom progression, defined as a ≥ 5-point decrease from baseline in NFBSI-16, using the same covariates as in MMRM analyses.
	trastuzumab + chemotherapy	NA	-2.13: NFBSI-16 total scores -3.93: EQ-5D-5L		(-3.794; -0.469): NFBSI-16 total scores (-8.253; 0.387):					

					EQ-5D-5L					

Table 30. Results of the NALA study

Table A3a. Results of the NALA study										
Trial name:	**PUMA-NER-1301 (NALA)**									
NCT number:	NCT01808573									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
PFS median (BIRC)	Neratinib + capecitabine	307	5.6	0.1 month	4.9; 6.9	NA	HR= 0.76	0.63; 0.93	P=0.0059	Primary efficacy end points were assessed in the ITT population. The Kaplan-Meier method was used to represent time-to-event end points and stratified Cox proportional hazards model to estimate HRs and 95% CIs.
	Lapatinib + capecitabine	314	5.5		4.3; 5.6					
OS median	Neratinib + capecitabine	307	21.0 month	2.3 month	NA	NA	HR= 0.88	0.72;1.07	P=0.2086	Primary efficacy end points were assessed in the ITT population. The Kaplan-Meier method was used to represent time-to-event end points and stratified Cox proportional hazards model to estimate HRs and 95% CIs.
	Lapatinib + capecitabine	314	18.7 month							
ORR	Neratinib + capecitabine	256	32.8%	6.1%	27.1%; 38.9%	P=0.1201	NA	NA	NA	The P value for the between group comparison of the percentage of patients who had a confirmed objective response was calculated with the use of a stratified Cochran–Mantel–Haenszel test
	Lapatinib + capecitabine	270	26.7%		21.5%; 32.4%					
AE grade 3 or higher	Neratinib + capecitabine	303	184 (60.7%)	4 (0.3%)	NA	NA	NA	NA	NA	
	Lapatinib + capecitabine	311	188 (60.4%)							
Discontinuation due to AE	Neratinib + capecitabine	303	42 (13.9%)	14 (4.1%)	NA	NA	NA	NA	NA	
	Lapatinib + capecitabine	311	56 (18.0%)							
QoL	Neratinib + capecitabine	279	81.8 points	0.4 points	NA	P=0.00008	HR=0.94	0.63; 1.40	NS	QLQ-C30 summary score of ≥10 points was clinically meaningful. Kaplan-Meier and log-rank tests were used for

	Lapatinib + capecitabine	286	81.3 points							time-to-deterioration (TTD) of ≥10 points and mixed models estimated the change over time.

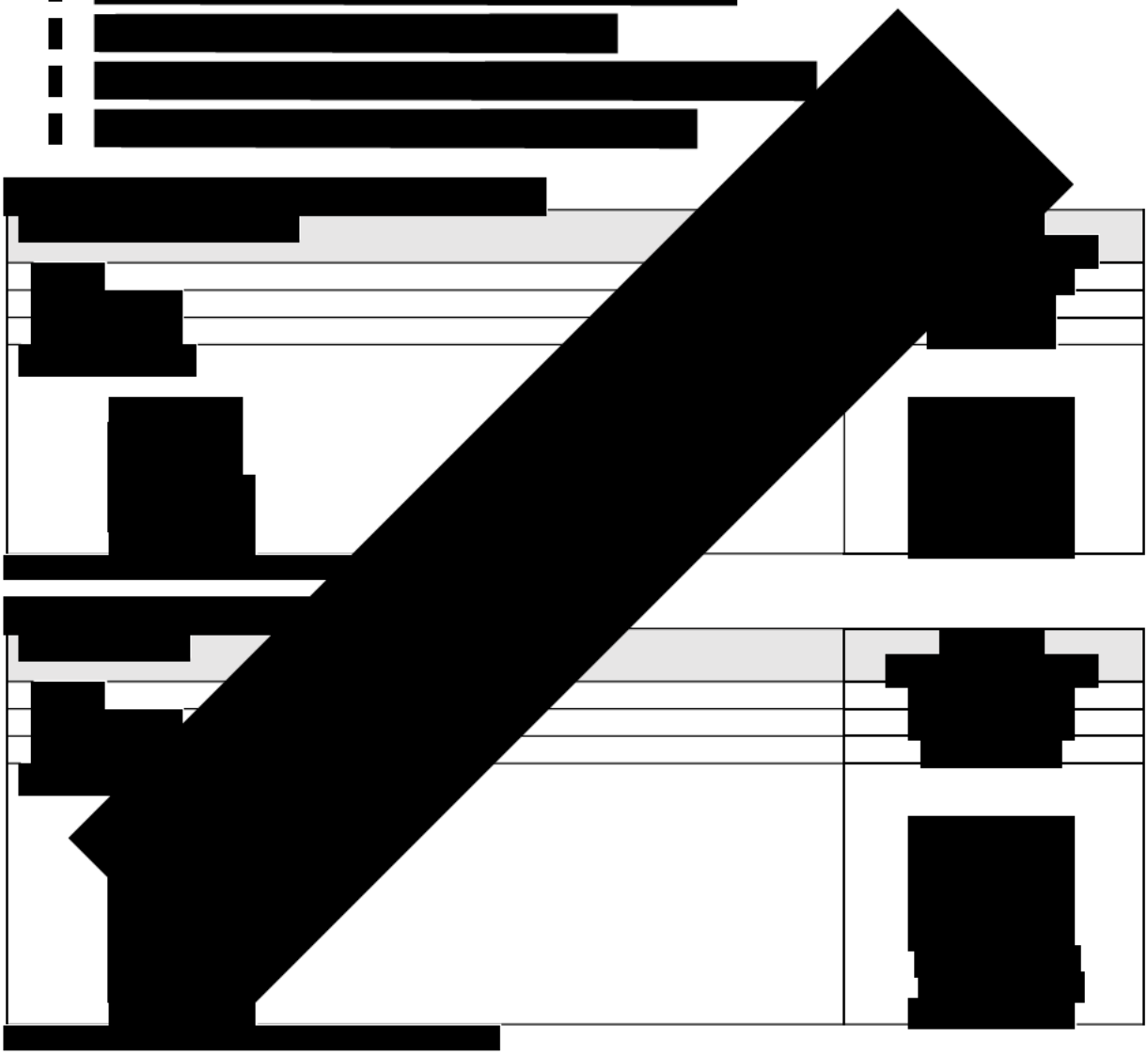
9.1.4. Results per PICO (Clinical question 1)

Table 31. Summary of relevant results related to clinical question 1

Table A4 Results referring to clinical question 1								
Results per outcome:								
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Median overall survival (naïve)	DESTINY-Breast01 (16), NALA, (7)	+5.9	2.4; 9.4	< 0.001	0.52	0.39; 0.69	< 0.001	*Estimates of difference in medians were obtained by bootstrapping from the distribution of medians from the respective studies and subtracting these. The 95% CI were obtained as the 2.5% and 97.5% quantiles in the bootstrap sample of differences.* *Confidence intervals and p-values for relative differences were based on unadjusted indirect comparisons using patient-level data estimated based on published KM-curves.*
Median overall survival (adjusted analysis)	DESTINY-Breast01 (16), NALA, (7)	+5.9	N/A	<0.001	0.29	0.14; 0.60	<0.001	*Details of the methodology to perform the MAICs are presented in text in section 5.1.3 and additional details in appendix*
AE (grade>3 AE)	DESTINY-Breast01 (16), HER2Climb (9)	0.36%	-9.68%, 10.40%	0.9438N	0. 472	0.8071, 1.2207	0.9438	Risk ratios and absolute difference was estimated based on the events reported from the studies

Table A4 Results referring to clinical question 1								
AE (grade>3 AE)	DESTINY-Breast01 (16), NALA (9)	3.078%	-6.04% , 12.19%	0.254	0.9402	0.7820 - 1.1304	0.5117	Risk ratios and absolute difference was estimated based on the events reported from the studies. The NALA study do not report comparable data on the proportion with grade 3/4 event. We have conservatively assumed that all with Grade 4/5 also had a Grade 3 event. P-value one-sided hypothesis for absolute difference.
HRQoL	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Median progression-free survival (naïve)	DESTINY-Breast01 (16), NALA, (7)	+13.9	8.4; 19.4	< 0.001	0.23	0.17; 0.30	< 0.001	*Estimates of difference in medians were obtained by bootstrapping from the distribution of medians from the respective studies and subtracting these. The 95% CI were obtained as the 2.5% and 97.5% quantiles in the bootstrap sample of differences.* *Confidence intervals and p-values for relative differences were based on unadjusted indirect comparisons using patient-level data estimated based on published KM-curves.*
Median progression-free survival (MAIC)	DESTINY-Breast01 (16), NALA, (7)	+16.7	N/A	< 0.001	0.16	0.08; 0.29	< 0.001	Details of the methodology to perform the MAICs are presented in text in section 5.1.3 and additional details in appendix
Overall response rate	DESTINY-Breast01 (16), NALA, (7)	34.7%	25.5 – 44.0	< 0.001	2.30	1.93 - 2.64	< 0.001	Odds ratio was calculated and converted to risk ratios using the formula in appendix 17 in the DMC method guide. An assumed rate of 25% was used for assumed control group rate based on the DMC protocol.

[redacted]



Trastuzumab deruxtecan (Enhertu) as treatment of HER2-positive metastatic breast cancer after two previous lines of HER2-targeted treatment

- **Cost-analysis for DMC**
- **Submitted 07.05. 2021. Updated 14.06.2021**

INCLUDE CONFIDENTIAL DATA

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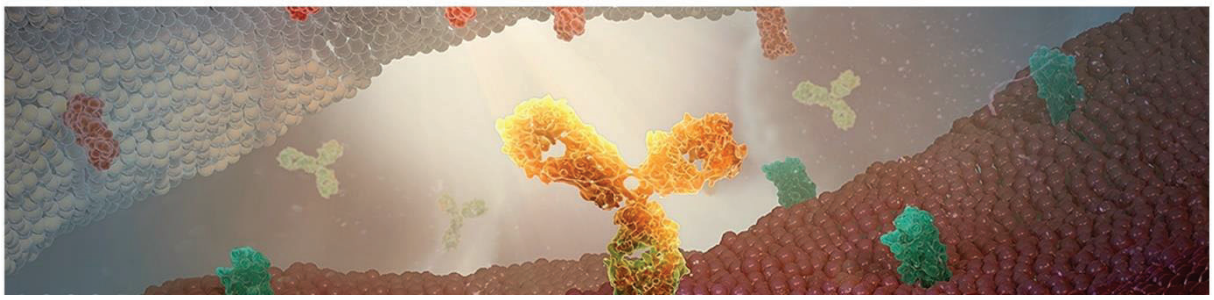


Executive summary

Background

Breast cancer is the most common cancer in women in Denmark as well as worldwide (1, 2). Approximately 14 percent of breast tumors have a gene amplification of the HER2, which untreated leads to an increased aggressiveness of the tumor, high risk of recurrence and increased mortality (3). In Denmark, ~680 HER2 positive breast cancer diagnoses were reported in 2019(4) and ~25% of these patients are expected to develop metastatic disease (5).

Despite advances in metastatic breast cancer (mBC) treatment and the benefit associated with HER2-targeting therapies, especially the introduction of pertuzumab plus trastuzumab and T-DM1 in first and second line respectively, survival outcomes in third-line HER2+ mBC remain poor (median PFS of 4-6 months and median OS of 17-20 months (6)). Disease progression in mBC increases patients' suffering, worsening symptoms such as fatigue, appetite loss and nausea, and further deteriorating their quality of life (7). This emphasizes a continuously great need for an innovative approach to treatment for these approximately 102 yearly patients with high unmet need.

Clinical evidence

Trastuzumab deruxtecan (T-DXd) is indicated for the treatment of adult patients as monotherapy with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens (8) based on evidence from the DESTINY-Breast01 study. DESTINY-Breast01 is a phase II, multicenter study of T-DXd in patients with HER2+, unresectable, and/or metastatic breast cancer who were previously treated with T-DM1. In an updated analysis, patients experienced a median progression-free survival of 19.4 months (95% CI: 14.1 - NE), 74% of the patients were estimated to be alive after 18 months, 61% achieved an objective response and almost all (97%) achieved disease control (9). All these endpoints greatly exceed what is previously reported for this patient population. Hence, T-DXd was granted and accelerated assessment and approval by EMA and was later deemed cost-effective by NICE (10, 11).

Given the single-armed study, a rigorous matching-adjusted indirect comparison was conducted to model the relative effectiveness of T-DXd versus trastuzumab plus capecitabine. In the covariate adjusted analysis versus the comparator preferred by DMC, T-DXd reduced the risk of death with 71% while the risk of progression or death were decreased with 84%.

Cost analysis and budget impact model

The cost analysis model is the first to evaluate the cost and budget impact of T-DXd within its metastatic breast cancer license in Denmark. The analysis uses the available trial data to inform safety and treatment effectiveness and uses the latest relevant Danish data sources for other inputs such as costs.

The analysis showed that the use of T-DXd implies an incremental cost per patient of approximately DKK 900 000 versus trastuzumab plus capecitabine. This results in a budget impact of approximately DKK 44 million per year at peak uptake.

Conclusions

T-DXd is an efficacious treatment with a reasonable cost per patient when compared to relevant available regimens for the treatment of unresectable or metastatic HER2+ breast

cancer in patients previously treated with at least two HER2+ targeted therapies in Denmark. The results in DESTINY-Breast01 is unprecedented, the 19.4 months median PFS in the study is in recent 3L trials with comparable patient populations between 5 and 8 months (6, 12, 13). Further, the CLEOPATRA study, which changed the global SoC with docetaxel, trastuzumab, pertuzumab triple combination for 1L metastatic patients, showed a median PFS of 18.7 months (14). T-DXd, if recommended in Denmark, has the potential to significantly improve outcomes for patients that today have a very poor prognosis and treatment options with limited efficacy.

Abbreviations

3L	Third line
3L+	Third line and beyond
AE	Adverse event
AIC	Aka ke information criterion
BIC	Bayesian information criterion
CI	Confidence interval
CT	Computed tomography
DB01	DESTINY-Breast01 study
DBCG	Danish Breast Cancer Group
DMC	Danish Medicine Council
DXd	The payload of T-DXd, a potent topoisomerase I inhibitor
ECOG	Eastern Cooperative Oncology Group
HER2	Human Epidermal Growth Factor receptor 2
HR	Hormone Receptor
HR	Hazard ratio
IV	intravenous
MAIC	Matched adjusted indirect comparison

mBC	Metastatic Breast Cancer
N/A	Not available
NE	Not evaluated
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
Q3W	Every three weeks
SD	Standard deviation
DKK	Danish krona
SLR	Systematic literature research
SoC	Standard of Care
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TTD	Time to treatment discontinuation
vs	Versus

Contents

Figures

Tables

1. Background

Breast cancer is the most common cancer in Danish women as well as worldwide (2). In Denmark approximately 4 900 breast cancer diagnoses were reported 2019 (15, 16). Men are also affected but a large majority of the diagnosed individuals are women (15).

Approximately 5% of breast cancers are considered metastatic at diagnosis (17-19) and up to 30% of existing Stage I-III cancers are expected to become metastatic during the course of the disease (5, 20-22).

The five-year survival rate for breast cancer in Denmark is around 90 percent (1). The course after a breast cancer diagnosis varies greatly and the outcome is strongly linked to several different factors. Prognostic and predictive factors are important for the risk of relapse, premature death and the effectiveness of a specific treatment.

One such factor is hormone receptor status where only receptor-positive tumors respond to antiestrogen therapy. Further, approximately 14% of breast tumors have a gene amplification of the HER2 (Human Epidermal Growth Factor receptor 2) (15), which untreated leads to an increased aggressiveness of the tumor, higher risk of recurrence and increased mortality (4, 17).

Based on the protocol from the DMC (16), the relevant clinical question for assessing the clinical value of T-DXd (trastuzumab deruxtecan) as 3L treatment in unresectable or metastatic HER2+ breast cancer:

- **What is the added clinical value of T-DXd compared to trastuzumab in combination with capecitabine in patients that progressed on HER2+ targeted treatment?**

2. Treatment guidelines for advanced or metastatic HER2+ breast cancer

2.1.1. Summary of current Danish guidelines and standard of care

Current Danish clinical practice is summarized in Table 1. In Denmark, there is no clear standard-of-care treatment for patients with advanced HER2+ tumors following progression on treatment with pertuzumab plus trastuzumab and vinorelbine, and T-DM1 in first- and second-line, respectively. This is partly due to that, despite the advances in breast cancer treatment and the benefit associated with HER2-targeted therapies, survival outcomes in third-line HER2+ mBC remain poor (median PFS of 4-6 months and median OS of 17-20 months (6, 12, 13)) and more than a quarter of patients gain no measurable benefit from their care.

The continuous blockade of HER2 signaling is recognized as the key element for improvement of survival outcomes in HER2+ mBC (23); therefore, clinical experts ([redacted] hereafter referred to as Danish clinical experts) approached during the preparation of this submission stated that, as the guidelines are followed in clinical practice, most patients with HER2+ mBC would after second line treatment get trastuzumab plus chemotherapy.

Table 1. DBCG: treatment overview metastatic HER2 positive breast

Treatment line	After adjuvant chemotherapy	Have not had earlier adjuvating chemotherapy
1. line	Vinorelbine + trastuzumab + pertuzumab	
2. line	T-DM-1	T-DM-1 or docetaxel + trastuzumab
3. line+	**Capecitabin + trastuzumab** (or lapatinib) Docetaxel + trastuzumab Paclitaxel + trastuzumab Gemcitabine + trastuzumab CMF + trastuzumab Eribulin + trastuzumab Epirubicin Trastuzumab + lapatinib T-DM-1	

Key: T-DM1: ado-trastuzumab emtansine.

2.1.2. Selection of comparators

Comparators for the cost-analysis was selected based on the Medicine Council's (DMC) protocol (16):

- **trastuzumab plus capecitabine**

In the base-case, the chemotherapy combined with trastuzumab is assumed to be capecitabine in line with DMC protocol (16) but scenario analyses are performed where docetaxel is used instead.

3. Trastuzumab deruxtecan - Intervention

3.1. Indication

The following indication was conditionally approved by EMA on 18 January 2021:

T-DXd is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens (8).

This indication is in line with the DMC protocol for T-DXd (16).

3.2. Dosing and administration

The recommended dose of T-DXd is 5.4 mg/kg administered as an intravenous (IV) infusion once every 3 weeks until disease progression or unacceptable toxicity (8).

T-DXd for injection 100 mg is provided in glass vials where each vial reconstitutes a concentration of 20 mg/mL. The initial dose of T-DXd will be infused for approximately 90 minutes; if there is no infusion-related reaction, it will be administered for approximately 30 minutes thereafter (8).

This dosing and administration is in line with the DMC protocol (16).

4. Comparative evidence

4.1. Existing evidence on current standard of care

4.1.1. Systematic literature review

No head-to-head data of T-DXd versus currently used treatments are currently available, as the DESTINY-Breast01 study did not include a comparator arm (9). In order to indirectly assess relative effectiveness of T-DXd versus trastuzumab plus capecitabine, a systematic literature review (SLR) was conducted. Details from the SLR is provided in the clinical application.

In addition to studies including trastuzumab plus capecitabine (6) and in line with the DMC protocol, studies of lapatinib plus capecitabine (13) and trastuzumab combined with other chemotherapies than capecitabine (12) were consider relevant for assessing the relative effectiveness of T-DXd.

In the next three sections, the relevant evidence identified in the SLR is briefly summarized. It is also outlined whether the identified studies overlap sufficiently with DESTINY-Breast01 in terms of study design, inclusion criteria, patient characteristics, definition of outcome measures and reporting of data to be comparable in indirect comparisons. The studies were assessed qualitatively on an individual basis, but together with Danish clinical experts five main criteria were used in the assessment to remove between-study differences that are difficult to adjust for:

1. Included studies should have available Kaplan–Meier data to perform indirect comparisons.
2. Treatment of interest for clinical practice in Denmark.
3. The included studies should have a prospective and controlled study design, such as phase II+ trails.
4. More than 50% of the patients in the study should have received pertuzumab and T-DM1 in prior lines. Danish clinical experts stated that studies conducted before pertuzumab and T-DM1 were standard of care and are not comparable with DESTINY-Breast01 as they might include different types of patients.
5. Included studies should not exclude patients with stable brain metastases.

Studies fulfilling these criteria are listed in the tables in the next two sections.

4.1.2. Trastuzumab in combination with chemotherapy

Studies on trastuzumab in combination with chemotherapy as 3L+ identified in the literature review and whether the studies overlap sufficiently with DESTINY-Breast01 are provided in Table 2. As shown in the table, two randomized controlled trials (RCTs) were identified as relevant for Denmark and both significantly overlapped with DESTINY-Breast01 in terms of patient population and study design.

Table 2. Trastuzumab in combination with chemotherapy

Study	Summary of study design and patient population	Overlap with DESTINY-Breast01 and represent current SoC in Denmark?
Murthy et al., 2020 (6)	Phase 2 randomized (2:1), parallel, double blind, controlled interventional study HER2+ mBC previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine With or without brain metastases 18 years or older, median age 54.0 / 54.0 Population: 612 (410 / 202) Enrolment period: 23 February 2016 – 3 May 2019 Intervention: • Tucatinib or placebo • In combination with trastuzumab and capecitabine Previous lines (total / for metastatic cancer): • Tucatinib: 4 (2-14) / 3 (1-14) • Placebo: 4 (2-17) / 3 (1-13)	Yes, control arm expected to be reflective of current standard of care and the study significantly overlap with the DESTINY-Breast01 study.
Rugo et al., 2021 (12)	Phase 3, Randomized (1:1), parallel, open label, interventional study Advanced HER2+ mBC who have received at least 2 prior line of HER2 directed therapy in the metastatic setting, or in case of having received (neo)adjuvant pertuzumab, at least 1 prior line of anti-HER2 directed therapy in the metastatic setting and who have received at least one, and no more than three, lines of therapy overall in the metastatic setting 18 years or older, median age 55 / 56 Population: 536 (266 / 270) Study active, not recruiting Intervention: • Margetuximab or trastuzumab • In combination with chemotherapy (capecitabine or er bulin or gemcitabine or vinorelbine) Previous lines (total / for metastatic cancer): a. Margetuximab + chemotherapy: ≤2: 66% >2: 34% • Trastuzumab + chemotherapy: ≤2: 67% >2: 33%	Yes, control arm expected to be reflective of current standard of care and the study significantly overlap with the DESTINY-Breast01 study.

Key: HER2+: Human Epidermal Growth Factor receptor 2, mBC: metastatic breast cancer.

4.1.3. Chemotherapy in combination with lapatinib

The studies, the RCT by Saura et al., (13), were deemed to significantly overlap with DESTINY-Breast01 and was the study with a survival that is similar to the survival in Danish clinical practice according to the DMC protocol.

Table 3. Studies of chemotherapy in combination with lapatinib in 3L HER2+ mBC

Study	Summary of study design and patient population	Overlap with DESTINY-Breast01 and represent current SoC in Denmark?
Saura et al., 2020 (13)	Phase 3, randomized (1:1) active-controlled, open-label, parallel, interventional study Patients with HER2+ mBC previously treated with 2 HER2-directed regimens Adults 18 years and older (3 men in Lapatinib + chemotherapy - arm) Median age: 55 / 54 Population: 621 (307 / 314) Enrolment period: 29 May 2013 to 21 July 2017 Interventions: • Neratinib or lapatinib • In combination with capecitabine Prior HER2-directed regimens • Neratinib + capecitabine: 2 - 70%, ≥3 – 30% • Lapatin b + capecitabine: 2 – 68.5%, ≥3 – 31.5%	Yes, the control arm in the study is expected to be reflective of current standard of care and the patient population significantly overlap with the DESTINY-Breast01 study.

Key: HER2+: Human Epidermal Growth Factor receptor 2, mBC: metastatic breast cancer, OCT: octreotide long-acting release, PFS: Progression free survival, OS: Overall survival.

4.1.4. Summary

Three of these studies were considered appropriate for indirect comparisons with DESTINY-Breast01 as they overlapped significantly in terms of study design and setting (fulfilling criteria 1 - 5 listed in section 4.1.1):

1. Saura et al., (13): lapatinib plus capecitabine
2. Murthy et al., (6): trastuzumab plus chemotherapy
3. Rugo (12): trastuzumab plus chemotherapy

These three studies were also the studies that Danish clinical experts deemed most appropriate for an indirect comparison versus DESTINY-Breast01 and the studies EMA selected for their naïve comparison in their assessment of T-DXd (10). The study by Saura et al. (13) was also the study that was identified as the most relevant by DMC (16).

A summary of the results of the three trials that overlap with DESTINY-Breast01 in 3L HER2+ mBC is presented in Table 4.

However, naïve comparisons have limitations, even though these studies were deemed to significantly overlap with DESTINY-Breast01 (see Table 2-Table 3). These limitations are mainly due to remaining between-study differences such as differences in inclusion criteria, study setting and patient characteristics. In order to reduce the uncertainty due to potential study differences, there are methods available to perform indirect comparisons also for studies that lack potential connection in a network meta-analysis. The most commonly used method for adjusting based on covariates is matching-adjusted indirect comparisons (MAIC).

Table 4. Naïve presentation of T-DXd and the treatments used in Denmark

	T-DXd	Trastuzumab + chemotherapy	Trastuzumab + capecitabine	Lapatinib + capecitabine
	DESTINY-Breast01 (9)	Rugo et al., (12)	Murthy et al., (6)	Saura et al., (13)
Median progression-free survival, months (95% CI)	19.4 (14.1 – NE)	4.4 (4.1 – 5.5)	5.6 (4.2 – 7.1)	5.5 (4.3 – 5.6)
Median overall survival, months (95% CI)	24.61 (23.1 – NE)	19.8 (17.5 – 22.3)	17.4 (13.6 – 19.9)	18.7 (15.5 – 21.2)
Overall response rate, % (95% CI)	61.4% (54.0 – 68.5)	13.7% (9.8 – 18.4)	22.8% (16.7 – 29.8)	26.7% (21.5 – 32.4)
Duration of response, months (95% CI)	20.8 (15.0 – NE)	7.0 (5.6 – 8.2)	NR	5.6 (4.2 – 6.4)
Overall survival HR unweighted (95% CI)		0.58 (0.43 – 0.78)	0.43 (0.31 – 0.60)	0.52 (0.39 – 0.69)
Progression-free survival HR unweighted (95% CI)		0.20 (0.15 – 0.26)	0.26 (0.19 – 0.36)	0.23 (0.17 – 0.30)

Key: N/A: Not Available, HR: Hazard ratio, NE; not estimable. *Month=4.35 weeks;

4.2. Matching-adjusted indirect comparisons

Adjusted indirect comparisons were conducted to assess comparative efficacy of T-DXd versus comparators used in Denmark. Adjusted analyses on patient level data could not be conducted for the studies identified in the SLR due to the lack of patient level data of the comparators. Hence, MAICs were performed of trials identified for the relevant comparator in section 4.1.4:

1. Saura et al., (13): lapatinib plus capecitabine
2. Murthy et al., (6): trastuzumab plus chemotherapy
3. Rugo (12): trastuzumab plus chemotherapy

The MAICs was carried out systematically following the guidelines from various HTA authorities (24-29). The SLR, which was the basis for the inclusion of clinical evidence, and whether the identified studies overlap sufficiently in terms of study design, inclusion criteria, patient characteristics, definition of outcome measures and reporting of data is presented in section 4.1.

Details of the MAICs are provided in Appendix A. Briefly, the patients from the DESTINY-Breast01 were assigned weights, so that the weighted average patient characteristics equal to what is reported from the comparator studies presented in section 4.1.

Based on covariates reported in the literature and feedback from clinical experts approached during the preparation of this submission, the following patient characteristics were considered for most important and used for the matching (when available for the comparator study):

- Hormone receptor status (positive/negative)
- Presence of visceral disease at baseline (yes/no)
- Number of lines of prior therapy (</≥3 or mean)
- Brain metastases (yes/no)
- ECOG status
- Age (continuous, where available mean was used; however, if not reported the median taken as a proxy)
- Prior pertuzumab exposure (yes/no)

A summary of the reported patient characteristics from the comparator studies is presented in Table 5. As shown, for most covariates the comparator studies and DESTINY-Breast01 reported similar data. Two important differences were that the number of prior lines were higher in DESTINY-Breast01 than in the other studies and that the proportion of the patients with brain metastases were higher in Murthy et al., (6). Prior use of pertuzumab and visceral metastases were the only predictive factors that were missing from more than one of the studies. According to feedback from Danish clinical experts, this is expected to have a small impact on the matching as these are considered to be the least important for predicting progression-free and overall survival.

Table 5. Summary of the reported patient characteristics relevant for the matching

	T-DXd	Trastuzumab + chemotherapy		Lapatinib + capecitabine
	DESTINY-Breast01	Rugo et al., (12)	Murthy et al., (6)	Saura et al., (13)
Mean age	56.0	56.0	54.0	54.0
Mean prior lines in mBC	6.6	-	3.0	-
Prior lines ≥3	90.8	33.0	-	31.5
ECOG PS = 0 (%)	55.4	60.0	47.5	52.2
HR+ (%)	52.7	63.0	61.9	59.2
Brain metastases (%)	13.0	NR	44.4	15.9
Visceral disease (%)	91.8	NR	NR	86.0
Prior pertuzumab (%)	65.8	NR	99.4	NR

Key: NR: Not reported, *HR+*: hormone receptor positive, mBC: metastatic breast cancer.

4.2.1. Lapatinib plus capecitabine

One relevant MAIC was conducted for the relative effect estimates of T-DXd compared with lapatinib plus capecitabine (Table 6 and Table 7). All baseline characteristics except for prior pertuzumab usage were available from the study. The MAIC results provide effect estimates in the same direction, providing evidence that T-DXd has improved PFS and OS outcomes compared with lapatinib plus capecitabine.

Overall survival

Table 6: Hazard ratios for OS - T-DXd vs Lapatinib plus capecitabine

Method	Hazard ratio (95% CI)
Saura et al., 2020 (13) (n=314)	
Unadjusted (n=184)	0.52 (0.39, 0.69)
Weighted standard CI (ESS=24.6)	0.29 (0.14, 0.60)
Weighted bootstrapped CI	0.28 (0.11, 0.60)

Key: CI: Confidence interval, OS: Overall survival

Sources: Saura et al., 2020 (13)

Progression-free survival

Table 7: Hazard ratios for PFS - T-DXd vs Lapatinib plus capecitabine

Method	Hazard ratio (95% CI)
Saura et al., 2020 (13) (n=314)	
Unadjusted (n=184)	0.23 (0.17, 0.30)
Weighted standard CI (ESS=24.6)	0.16 (0.08, 0.29)
Weighted bootstrapped CI	0.16 (0.08, 0.29)

Key: ESS: Effective sample size, CI: Confidence interval, PFS: Progression free survival

Sources: Saura et al., 2020 (13)

For the comparison versus lapatinib plus capecitabine, three additional MAICs were conducted for PFS and two for OS. These MAICs were performed using the studies that reported data in 3L+ mBC but did not sufficiently overlap with DESTINY-Breast01. The main reason why the studies did not overlap were because of retrospective or unclear study designs. The results of these MAICs are reported in full in Appendix A.

4.2.2. Trastuzumab plus capecitabine

One MAIC was conducted for the relative effect estimates of T-DXd compared with trastuzumab plus capecitabine. In the MAICs the studies were matched on mean age, ECOG, number of prior lines of treatment and percent HR positive. Presence of visceral disease at baseline, percent prior pertuzumab and percent brain metastases was not available from the study.

Table 8 and Table 9 presents the HR from the MAIC for T-DXd compared with trastuzumab plus capecitabine. Both MAIC results provide effect estimates in the same direction, providing evidence that T-DXd has improved OS and PFS outcomes compared with trastuzumab plus capecitabine.

Overall survival

Table 8: Hazard ratios for OS - T-DXd vs trastuzumab plus capecitabine

Method	Hazard ratio (95% CI)
Rugo et al., 2021 (12)	
Unadjusted	0.58 (0.43, 0.78)
Weighted standard CI	0.27 (0.14, 0.50)
Weighted bootstrapped CI	0.27 (0.15, 0.44)

Key: CI: Confidence interval, OS: Overall survival

Sources: Murthy et al., 2020 & Rugo et al. 2021 (6, 12)

Progression-free survival

Table 9: Hazard ratios for PFS - T-DXd vs Trastuzumab plus capecitabine

Method	Hazard ratio (95% CI)
Rugo et al., 2021 (12)	
Unadjusted	0.20 (0.15, 0.26)
Weighted standard CI	0.12 (0.06, 0.21)
Weighted bootstrapped CI	0.12 (0.06, 0.20)

Key: CI: Confidence interval, PFS: Progression free survival

Sources: Murthy et al., 2020 & Rugo et al. 2021 (6, 12)

4.2.3. *Trastuzumab plus chemotherapy*

One MAIC were conducted for the relative effect estimates of T-DXd compared with trastuzumab plus chemotherapy. In the MAICs the studies were matched on mean age, ECOG, number of prior lines of treatment and percent HR positive, percent prior pertuzumab and percent brain metastases. Presence of visceral disease at baseline was not available from the study.

Table 10 and Table 11 presents the HR from the MAIC for T-DXd compared with trastuzumab plus chemotherapy. Both MAIC results provide effect estimates in the same direction, providing evidence that T-DXd has improved OS and PFS outcomes compared with trastuzumab plus capecitabine.

Overall survival

Table 10: Hazard ratios for OS - T-DXd vs trastuzumab plus chemotherapy

Method	Hazard ratio (95% CI)
Murthy et al., 2020 (6)	
Unadjusted	0.43 (0.31, 0.60)
Weighted standard CI	0.51 (0.20, 1.32)
Weighted bootstrapped CI	0.49 (0.36, 0.70)

Key: CI: Confidence interval, OS: Overall survival

Sources: Murthy et al., 2020 & Rugo et al. 2021 (6, 12)

Progression-free survival

Table 11: Hazard ratios for PFS - T-DXd vs Trastuzumab plus chemotherapy

Method	Hazard ratio (95% CI)
Murthy et al., 2020 (6)	
Unadjusted	0.26 (0.19, 0.36)
Weighted standard CI	0.09 (0.03, 0.22)
Weighted bootstrapped CI	0.12 (0.04, 0.31)

Key: CI: Confidence interval, PFS: Progression free survival

Sources: Murthy et al., 2020 & Rugo et al. 2021 (6, 12)

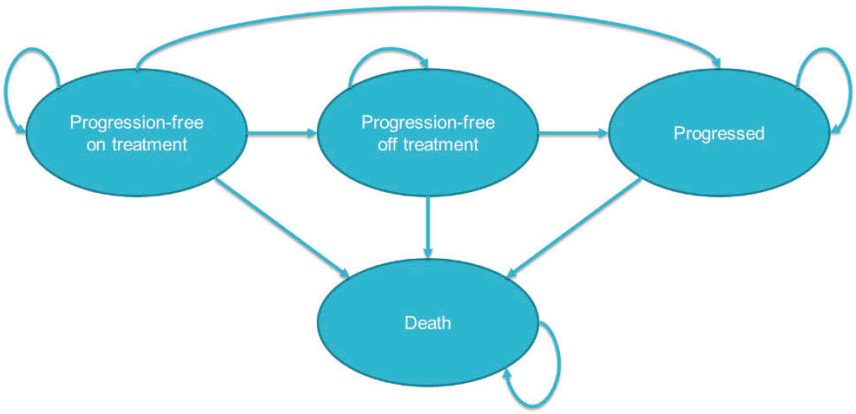
5. Cost analysis model of T-DXd

The global cost-effectiveness model was adapted to the Danish setting and DMC guidelines (30-32). The results presented in this report is based on the adapted version. The adapted cost analysis model was developed to estimate the incremental costs per patient as well as the budget impact of T-DXd compared to capecitabine in combination with trastuzumab for patients with metastatic HER2+ breast cancer, who have progressed on two HER2-specific treatments.

5.1. Health economic model

The cost-analysis model used in this submission contains four health states. Figure 1 presents the flow of patients in the model. All patients enter the model in the 'progression-free on treatment' state, receiving T-DXd or comparator treatment. Patients may remain on-treatment while progression free, discontinue treatment while remaining progression-free, their disease may progress, or they may die. Patients whose disease has progressed can remain alive with progressed disease or die.

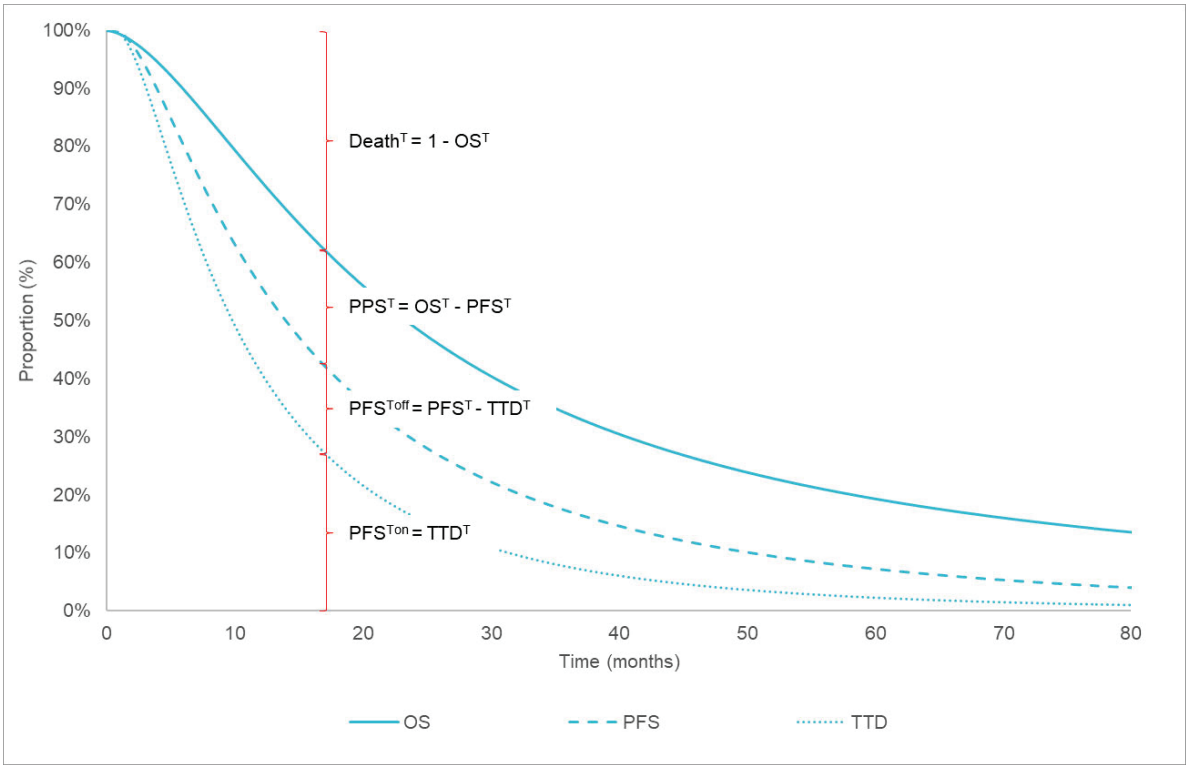
Figure 1: Model structure



Health state membership is determined using a partitioned survival analysis approach, which is the most common type of economic modelling of oncology treatments and widely accepted. Other model types such as Markov models were considered to add complexity without improving the accuracy of the predictions. To inform the partitioned survival analysis model, parametric curves are fitted to OS, PFS and TTD data from DESTINY-Breast01. Parametric survival models are used to extrapolate outcomes beyond the observed data for a lifetime horizon. The 'standard' selection of parametric models were fitted, in line with guidance for various HTA authorities (31, 33, 34). These comprise exponential, Weibull, log-normal, log-logistic, Gompertz, and generalized gamma models.

Figure 2 graphically demonstrates how parametric survival curves are used to calculate health state occupancy. The proportion of patients in the death health state at time T is calculated as one minus OS^T, where OS^T is the probability a patient is alive at time T. The proportion of patients in the progressed disease state is equal to OS^T minus PFS^T, where PFS^T is the probability of being alive and progression-free at time T. TTD is used to separate the pre-progression health state into on and off treatment periods, allowing costs and health outcomes to be modelled more accurately. The proportion of patients alive, progression-free and off treatment is equal to PFS^T minus TTD^T, and the proportion of patients who are progression-free and on treatment is equal to TTD^T.

Figure 2: Partitioned survival analysis - health state membership at time *T*



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

5.2. Model settings

5.2.1. General model setting

The model had a restricted societal perspective and simulated treatment costs and effects over a lifelong time horizon (30 years in base-case) in line with the DMC guidelines (30). The user can select a time horizon with five-year increments from 5 year to 30 years in the model for sensitivity analyses. The time horizon is sufficiently long to capture all relevant costs as no patients are alive after 30 years, regardless of treatment.

A 1-week cycle length is used to adequately capture transitions and reflect changes in health, while also allowing drug cycles to be appropriately costed. A 1-week cycle length ensures that the model can consider the different dosing schedules across the comparator arms, while also reflecting the T-DXd 3-weekly dosing cycle. Due to the short cycle length, a half cycle correction is not applied in the base case as this would introduce an unnecessary complexity without adding any meaningful accuracy.

In the base case, a discount rate of 3.5% per annum is used for costs in line with DMCs guidelines (30).

5.2.2. Target population

The cost-analysis model evaluates the use of T-DXd as third line treatment in patients with HER2+ metastatic breast cancer who are resistant or refractory to T-DM1. Hence, the patient population considered in the cost-analysis model is therefore fully aligned with the approved indication and the DMC protocol.

5.2.3. *Population characteristics*

Baseline patient characteristics were taken from the DESTINY-Breast01 study (Table 12) as these inputs were deemed representative of the Danish clinical practice by clinical experts (35). The inputs were used in the model to assign age-stratified general mortality and to calculate treatment doses.

Table 12: Baseline patient characteristics (DESTINY-Breast01)

Characteristic	Mean
Age (years)	56.0
Weight (kg)	62.47 (SD 14.04)
Height (cm)	160.00
Sex (% Female)	100%

Key: SD: standard deviation.

5.2.4. *Modelling of the clinical benefit*

5.2.4.1. Trastuzumab deruxtecan

Where data are non-existent or not sufficiently mature, extrapolated survival curves were used to inform health state occupancy over a lifetime horizon in the model. Time-to-event data used to model the T-DXd arm were taken from DESTINY-Breast01 (Figure 3). For PFS, OS and TTD, standard parametric models (exponential, Weibull, Log-normal, Log-logistic, Gompertz and Generalized gamma) were fitted to the data from DESTINY-Breast01 in line with best practice.

Figure 3: T-DXd – Kaplan–Meier data

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

Progression-free survival

5.2.4.2. Curve selection

Curve selection for extrapolations of OS, PFS and TTD curves were carried out systematically in line with guidelines from various HTA authorities (29, 31, 34, 36):

- Statistical methods; Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used together with graphic evaluations to study which of the parametric functions that accurately fitted the trial data from DESTINY-Breast01.
- Clinical validity and biologically plausibility were assessed using feedback from Danish HER2+ mBC experts.

Clinical validity is difficult to assess as T-DXd has not been studied in this population before and Danish clinical experts have limited experience of new treatments with no available long-term data (such as T-DXd). Thus, the last point was, therefore, mainly used to disregard extreme cases.

Further, only proportional hazard models were considered for extrapolation of PFS and OS for the comparator treatment as the proportional hazard assumption hold (see below and in appendix A for details).

Figure 4 show all parametric curves for PFS based the DESTINY-breast01 study; Table 13 presents the AIC and BIC values.

Key: KM: Kaplan-Meier, PFS: progression-free survival, T-DXd: [fam-]trastuzumab deruxtecan.

As shown by the color coding in Table 13, the Generalized gamma and Log-normal curve has the best statistical fits to the observed data for PFS.

Table 13: T-DXd – progression-free survival – AIC/BIC

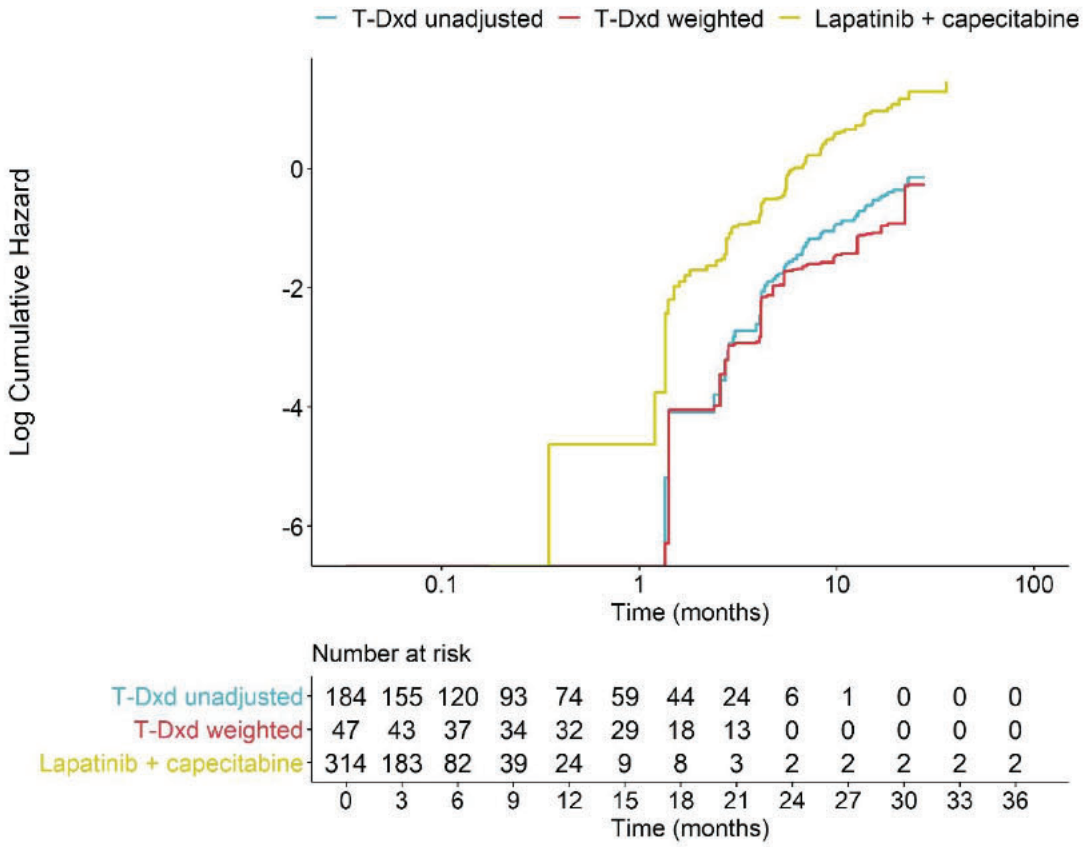
Model	AIC	BIC
Exponential	613.20	616.41
Weibull	611.37	617.80
Log-normal	600.50	606.93
Log-logistic	605.89	612.32

Gompertz	615.13	621.56
Generalized Gamma	597.79	607.43

Key: AIC: Aka ke information criterion, BIC: Bayesian information criterion, T-DXd: [fam-]trastuzumab deruxtecan. Color coding based on rule of thumb in Burnham & Anderson (37): Dark green = Best statistical fit, Light green (<2 AIC/BIC) = substantial support, Yellow (3-10) = considerably less support and Red (<10) = essentially no support in the data.

Figure 5 present the hazards for PFS over time. As shown in the figure, the hazards appear to be parallel in the DESTINY-Breast01 study and in the control arm of the NALA study.

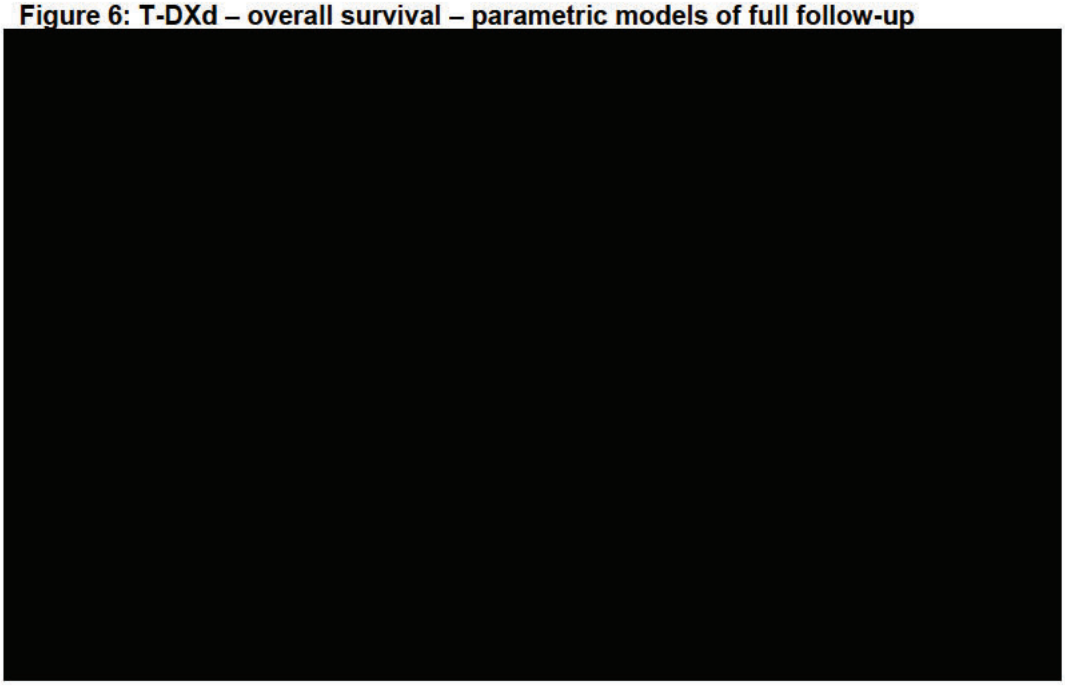
Figure 5: Log Cumulative hazard plot – Progression-free survival



Overall survival

Figure 6 show all parametric curves for OS.

Figure 6: T-DXd – overall survival – parametric models of full follow-up



Key: KM: Kaplan-Meier, OS: overall survival, T-DXd: [fam-]trastuzumab deruxtecan.

While the visual fit is similar for most of the parametric models, the Weibull curve has the best statistical fit to the observed data as shown by the dark green highlight in Table 14. Thus, this parametric model was used in the base-case.

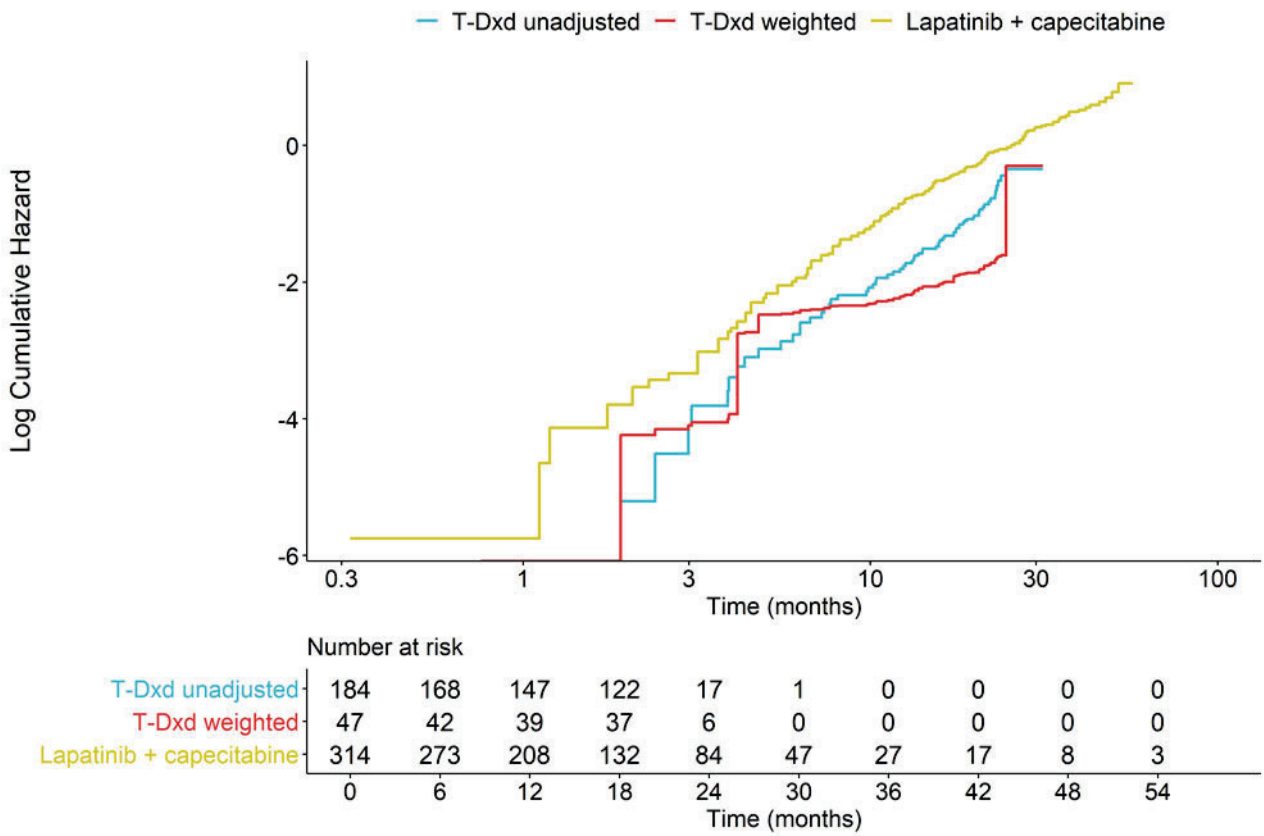
Table 14: T-DXd – overall survival – AIC/BIC

Model	AIC	BIC
Exponential	643.45	646.67
Weibull	628.44	634.87
Log-normal	630.83	637.26
Log-logistic	629.50	635.93
Gompertz	630.18	636.61
Generalized Gamma	630.17	639.81

Key: AIC: Aka ke information criterion, BIC: Bayesian information criterion, T-DXd: [fam-]trastuzumab deruxtecan. Color coding based on rule of thumb in Burnham & Anderson (37): Dark green = Best statistical fit, Light green (<2 AIC/BIC) = substantial support, Yellow (3-10) = considerably less support and Red (<10) = essentially no support in the data.

Figure 7 present the hazards for OS over time. As shown in the figure, the hazards appear to be parallel in the DESTINY-Breast01 study and in the control arm of the NALA study.

Figure 7: Log Cumulative hazard plot – overall survival



5.2.4.3. Relative effectiveness versus comparators

When modelling PFS and OS, the HRs reported from the MAICs, comparing the trastuzumab + capecitabine and T-DXd are inversed and applied to a baseline T-DXd curve for each comparator assuming proportional hazards over time. The DMC protocol stated that the survival from Saura et al., was most relevant for the Danish 3L population (16). Thus, HRs from the MAIC for PFS and OS versus Saura et al., was used in the base-case. The MAIC results used in the model as base-case are summarized in Table 15. The impact of using unadjusted indirect comparisons were tested in scenario analyses (see section 6.3).

Table 15. Summary of the relative effectiveness estimates from the MAICs used in the model

	Lapatinib + capecitabine	Trastuzumab + chemotherapy (available as scenario in the model)	Trastuzumab + capecitabine (available as scenario in the model)
	Saura et al., 2020 (13)	Rugo et al., 2021 (12)	Murthy et al., 2020 (6)
Subjects in the study	314	270	202
OS HR covariate adjusted (95% CI)	0.29 (0.14, 0.60)	0.27 (0.14, 0.50)	0.51 (0.20, 1.32)
PFS HR covariate adjusted (95% CI)	0.16 (0.08, 0.29)	0.12 (0.06, 0.21)	0.09 (0.03, 0.22)

Key: DB01: DESTINY-Breast01 study, T-DXd: Trastuzumab deruxtecan, OS: Overall survival, HR: Hazard ratio, PFS: Progression free survival. Note: All the HR are inverted in the model to function correctly.

Progression free survival

For PFS, the Log-normal, log-logistic and generalized gamma models had support in the data from DESTINY-Breast01 (Table 13), showed good visual fit and were all considered clinically plausible. All the other models should be disregarded as they had no support in the data and had poor visual fit. Both the Log-normal and the Generalized gamma distributions had the best statistical fit but the Log-normal model was chosen as the base-case as it provided more conservative estimates. The long-term extrapolation of using Log-normal for all the treatment arms are presented in Figure 8. A less optimistic model, such as an exponential model, was tested in a scenario analysis (see section 6.3).

Figure 8 Log-normal extrapolation of PFS for all treatment arms

Key: T-DXd: Trastuzumab deruxtecan, PFS: Progression free survival.

Overall survival

For OS, all the parametric curves had similar visual fit to the data except for the exponential model, which showed to be a poor fitting distribution (Figure 4). The Weibull curve had the best statistical fit and was used for the base-case. Alternative extrapolations were tested in scenario analyses (see section 6.3).

Figure 9 Weibull extrapolations versus comparators

Key: T-DXd: Trastuzumab deruxtecan, PFS: Progression free survival.

5.2.4.1. Discussion on the modelling of survival benefits

The model outcome using both adjusted and unadjusted indirect comparisons are provided in the tables below. As shown the unadjusted results are in line with the Danish real-word data. The data was not mature enough to estimate mean using the Danish data but the data indicate the PFS might be slightly underestimated for the comparator. However, we have kept this assumption as there is considerable uncertainty and that shorter PFS for the comparators means more conservative estimates of the drug costs in current clinical practice (higher incremental cost of T-DXd).

Table 16. Estimated mean survival in the model*

	Life years	Progression-free survival (years)	Treatment duration (years)
T-DXd	2.640	2.175	1.367
Trastuzumab + capecitabine (adjusted)	1.266	0.460	0.460
Trastuzumab + capecitabine (unadjusted)	1.790	0.608	0.608

*1 year = 52 weeks assumed

Table 17. Estimated median survival in the model

	Life years	Progression-free survival (years)	Treatment duration (years)
T-DXd	2.357	1.533	0.872
Trastuzumab + capecitabine (adjusted)	1.112	0.345	0.345
Trastuzumab + capecitabine (unadjusted)	1.591	0.460	0.460

DBCG (unadjusted)	[redacted]	[redacted]	[redacted]

*1 year = 52 weeks assumed

It is generally difficult to validate the long-term survival for new innovations since there is limited long-term data available. Hence, we have relied mostly on the best statistical fit to the observed data for the intervention arm.

For the trastuzumab + capecitabine arm, we have validated the data from the NALA study with data from Danish clinical practice(38). In the survival in the comparator arm before adjustment followed the overall survival in Danish clinical practice very closely. The long-term survival curve from the DBCG is smooth and has no drastic changes in the hazard, which imply that the extrapolated curve would provide valid long term estimates for the comparator arm, at least when unadjusted data is used.

Figure 10 Validating OS*

*The real-world data from DBCG had few patients at risk after 47 months (<5%).

Figure 11 Validating the PFS*

*The real-world data had few patients at risk after 23.5 months (<5%)

We currently do not have adjusted data from the Danish registry. Hence, the long-term outcomes of the adjusted comparator arm can currently not be validated.

Finally, long-term and stable treatment effects have been observed in trials of HER2-targeted treatments in mBC; there is no evidence to suggest that the same would not be true for T-DXd,

- In the CLEOPATRA study comparing pertuzumab + trastuzumab + chemotherapy against trastuzumab + chemotherapy, a stable (or potentially improving) hazard ratio was observed throughout the 8-9 years follow-up (14).
- In late line studies of T-DM1, the proportional hazards (PH) assumption was verified and the shapes of the curves do not suggest a violation of the PH assumption, indicating no change in treatment effect over the 6-year follow-up (39, 40).
- Long-lasting treatment effects have also been observed with HER2-acting agents in an adjuvant setting, where the HERA trial showed consistent treatment effect of trastuzumab throughout the 11-year follow-up when adjusting for crossover (5).

Hence, we have assumed a stable proportional hazard over time for both PFS and OS in the model.

5.2.5. Adverse events

In the T-DXd arm of the model, grade 3+ treatment-emergent AEs are included if either ≥5% of patients experienced the AE or if the event was identified as special interest. Special interest AEs include:

- AEs mentioned as important to consider by clinicians in a clinical advisory board to validate the modelling approach for T-DXd
- AEs listed as of special interest in the DESTINY-Breast01 clinical study report

The number of events is used to calculate the proportion of patients with a specific event (Table 18), which were used to estimate costs associated with the management of AEs for patients on T-DXd.

For the comparator treatments, Grade 3+ AEs were taken from the literature sources used to inform efficacy data in the model. For trastuzumab plus capecitabine, AEs (Table 18) were taken from Murthy et al. (6) as this study most closely reflect the clinical practice in Denmark of the studies identified in the SLR. AEs from Saura et al., which was deemed as the most relevant comparator study for the efficacy by DMC are available in the model, but the AE profile from Murthy et al., is assumed to be most reflective of Danish clinical practice. The full AE profile is not available for the comparators, which means that the incremental cost for T-DXd is likely overestimated in relation to the comparators. AE events of special interest were included for the comparators if they were available and fulfilled the criteria listed above.

Table 18: Adverse event profiles for all treatments – Grade 3/4 events

Adverse event	DESTINY-Breast01	Trastuzumab plus capecitabine, Murthy 2020(6)
Neutrophil count decreased	20.65%	0.00%
Anemia	15.22%	0.00%
Neutropenia	20.11%	0.00%
Nausea	8.70%	3.05%
Fatigue*	8.15%	4.06%
White blood cell count decreased*	5.98%	0.00%
Dyspnea**	1.63%	0.00%
Febrile neutropenia**	1.63%	0.00%
Electrocardiogram QT prolonged**	1.63%	0.00%
Interstitial lung disease**	1.09%	0.00%
Ejection fraction decreased**	0.54%	0.00%
Pneumonitis**	0.54%	0.00%
Vomiting**	0.00%	3.55%
Diarrhea	N/A	8.63%
Palmar-Plantar Erythrodysesthesia	N/A	9.14%

Key: SoC: standard of care, T-DXd: [fam-]trastuzumab deruxtecan, N/A: Not available. * Fatigue and/or asthenia.** Included as a AE of special interest

5.3. Resource use and costs

The model uses 2021 prices in Danish kroner (DKK) (41). The model includes the following costs:

- Drug acquisition costs (section 6.4.1)
- Drug administration costs (section 6.4.2)
- Disease management costs (section 6.4.3)
- Adverse event costs (section 6.4.4)
- Subsequent treatment and terminal care costs (section 6.4.5)
- Time and transportation costs (section 5.3.6)

5.3.1. Drug acquisition

5.3.1.1. Drug cost - trastuzumab deruxtecan

The *apotekets indkøbspris* (AIP) of T-DXd in the cost-analysis model is DKK 12 234.16 per 100 mg vial and the recommended dose is 5.4 mg/kg every 3 weeks. The actual dose the patients received in DESTINY-breast01 trial was used as the basis for the drug cost calculation as this is the dose that is the basis for the clinical effect used throughout this submission. The mean relative dose intensity of T-DXd in DESTINY-breast01 was [redacted] when dose-interruptions and dose-adjustments was taken into consideration. Based on feedback from clinical experts, no wastage was assumed as the base-case in this submission. This was assumed as clinics try to minimize the wastage by coordinating specific treatment days for these patients or rounding the doses to a specific number of vials. However, this assumption is tested in scenario analyses in Section 6.3. A scenario with 50% wastage was tested in section 6.3

The resultant cost per dose is [redacted] every 3 weeks without wastage, based on the patient weights and the relative dose intensity in DESTINY-Breast01. The resulting cost per day is [redacted]

The treatment duration was based on the actual treatment duration in DESTINY-Breast01. Figure 12 show the parametric curves for the time to treatment discontinuation in the DESTINY-Breast01 population. As shown in by the color coding in Table 19, the log-normal curve has the best statistical fit to the observed data and was deemed clinically plausible. Hence, this curve was used for the base-case.

Figure 12. Time to treatment discontinuation in DESTINY-Breast01

Key: KM: Kaplan-Meier, T-DXd: [fam-]trastuzumab deruxtecan, TTD: time to treatment discontinuation.

Table 19. Statistical fit to time to treatment discontinuation in DESTINY-Breast01

Model	AIC	BIC
Exponential	1098.31	1101.52
Weibull	1088.40	1094.83
Log-normal	1078.73	1085.16
Log-logistic	1081.10	1087.53
Gompertz	1096.53	1102.96
Generalized Gamma	1080.66	1090.31

Key: AIC: Aka ke information criterion, BIC: Bayesian information criterion, T-DXd: [fam-]trastuzumab deruxtecan. Color coding based on rule of thumb in Burnham & Anderson (37): Dark green =Best statistical fit, Light green (<3 AIC/BIC) = substantial support, Yellow (4-10) = considerably less support and Red (<10) = essentially no support in the data.

5.3.1.2. Drug cost - comparators

Drug acquisition costs for the comparators in the model were sourced from medicinpriser.dk drug cost data base (42). All drug prices are in AIP. The dosing information was sourced from the SmPC label for each treatment in the model. The average weight in DESTINY-Breast01 was used to calculated weight-based dosing. The dose-intensity in DESTINY-Breast01 was used as a proxy for the comparators when no data for this parameter was identified in the literature. According to Danish clinical experts and the DMC protocol (16), capecitabine is the most commonly used chemotherapy for these patients and was therefore used in the base-case while docetaxel was tested in a scenario analysis.

Table 20 presents the resulting costs per dose.

Table 20: Drug costs per dose

Treatment	Frequency	Dose per admin	Cost per dose (excl. RDI, DKK)	Cost per dose (Including RDI, DKK)	Relative dose intensity (RDI)	Reference
T-DXd	q3w	337 mg	41 270	[redacted]	[redacted]	DESTINY-Breast01 (35)
Trastuzumab (week 1)	Initial dose	500 mg	12 536	[redacted]		Assumed to be same as T-DXd
Trastuzumab (week 4+)	q3w	375 mg	9 402	[redacted]		
Docetaxel	q3w	133 mg	473	431	0.91	Lyman et al.(43)
Capecitabine	Twice daily for 2 weeks, 1 week off	1666 mg	6.94	[redacted]	[redacted]	Assumed to be same as T-DXd

Key: IV: intravenous, q3w: every three weeks, SoC: standard of care, T-DXd: [fam-]trastuzumab deruxtecan.

Note: RDI is calculated as: Relative dose intensity (%)= Dose intensity / Assigned dose level (mg/kg) where: Dose intensity (mg/kg/3weeks) = Total amount of doses taken (mg/kg) / (Treatment duration / 21). No wastage was assumed for capecitabine because it would be difficult to estimate given different sizes of packages for capecitabine and would also have limited impact due to the low price.

As TTD Kaplan–Meier curves are scarcely reported in the literature, it was not possible to generate naïve or weighted HRs comparing TTD for patients on T-DXd and patients on capecitabine plus trastuzumab, lapatinib plus capecitabine, or lapatinib plus trastuzumab. Hence, PFS were used as a proxies in the base-case and are given the short PFS expected to be accurate predictions of the treatment lengths.

5.3.2. *Drug administration*

The drug administration costs are taken from the DRG system 2021 (44) (Table 21). Administration costs are applied to all patients on treatment with IV treatments. Oral and subcutaneous treatments are assumed to have no administration costs.

A DRG code (1-day rate for simple procedures) was used for the infusions rather than a micro-costing approach. A micro-costing approach using the administration times from the SmPCs and the time cost for a nurse was tested but as the DRG cost provide more conservative estimates (a higher cost per administration) we used that in the model. There is also not clear how many patients one nurse can treat at the same time, which would make the micro-cost approach uncertain.

Table 21: Drug administration costs

Method	Cost (DKK)	Source
Oral	0	Assumption
IV infusion 60 min	1 735	09MA98 MDC09 1-dagsgruppe, pat. mindst 7 år

Key: IV, intravenous.

5.3.3. *Disease management*

The disease management costs are split into progression-free and progressed disease health state costs per week in the model. However, in the base-case the frequency of visits were considered to be the same regardless of progression status. Table 22 summarizes the routine follow-up resource use and costs associated with pre- and post- progression obtained from Danish DRG system 2021 (44). The types and frequencies of medical resource use were informed by previous technology assessments and were validated by Danish clinical experts.

Table 22: Unit cost of Routine Follow-up

Resource	Frequency per week in pre- and post-progression	Cost (DKK)	Source
Specialist physician/ Oncologist	0.10	1 482	DRG 2021 (23MA04) "Kontrolundersøgelse"
Blood tests	0.35	49	"Medicinrådets værdisætning af enhedsomkostnigner v. 1.4. 2020" Blood test
ECHO/MUGA-scanning, cardiological examination	0.08	2 820	DRG 2021 (05PR04) "Kardiologisk undersøgelse, kompliceret "
CT-scanning	0.10	2 007	DRG 2021 (30PR06) "CT-scanning, kompliceret"

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

5.3.4. *Adverse event costs*

Table 23 shows the costs associated with the management of AEs sourced from the price list of the Danish DRG system 2021 (44).

In the T-DXd arm of the model, AE probabilities were sourced from the DESTINY-Breast01 patient level data. For the comparator arms, the frequencies of AEs were obtained from published literature as outlined in section 5.2.5. The product of the probability of experiencing an AE and the cost per event is summed across all AEs to calculate an average AE cost per patient.

In line with previous DMC assessments (45), the cost for AEs such as *neutropenia* and *neutrophil count decreased* were set to zero under the assumption that these are only treated in the occurrence of fever or infection. The cost for *neutrophil count decreases* and *neutropenia* is at risk of being double counted since they share DRG code and are usually treated in the occurrence of fever or infection and therefore the rate for *febrile neutropenia* is more accurate in this type of patient.

Table 24 present average per-patient AE management costs for each arm of the model.

Table 23: Adverse events – hospital cost per event

Adverse event	Cost per event (DKK)	Source (DRG 2021)
Neutrophil count decreased	0	-
Anemia	40 604	16MA05 Hæmolystiske anæmier og anæmier forårsaget af enzymatiske forstyrrelser m.m.
Neutropenia	0	-
Nausea	5 130	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.
Fatigue	3 987	23MA03 Symptomer og fund, u. kompl. bidiag.
White blood cell count decreased	35 483	16MA03 Granulo- og trombocytopeni
Dyspnea	19 691	04MA23 Symptomer fra luftveje
Febrile neutropenia	18 889	18MA04 Feber af ukendt årsag, pat. mindst 18 år, uden biopsi og/eller scopi
Electrocardiogram QT prolonged	2 820	05PR04 Kardiologisk undersøgelse, kompliceret
Interstitial lung disease	41 260	04MA17 Interstitielle lungesygdomme
Ejection fraction decreased	30 433	05MP42 Hjertesvigt, herunder kardiogent shock, proceduregrp. A
Pneumonitis	25 695	04MA14 Lungebetændelse og pleurit, pat. 18-59 år
Vomiting	5 130	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.
Diarrhea	5 130	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.
Palmar-plantar erythrodysesthesia syndrome	11 157	09MA03 Lettere eller moderat hudsygdom, u. kompl. bidiag.

Table 24: Total adverse event costs in all treatment arms included in the model

Action	T-DXd	Chemotherapy plus trastuzumab
Total adverse event cost (DKK)	10 499.77	1 962.55

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

5.3.5. Subsequent treatment and terminal care

A one-off terminal care cost of 64 133 DKK in line with the DMC assessment of T-DM1 was used in the base-case (46). The cost is derived from the UK study which estimates the end-of-life costs for four different types of cancer, including breast cancer. The study is based in a UK setting and includes patients starting palliative treatment to death. The estimate is the most relevant data identified as an end-of-life cost for these patients. Only the costs for health care and social care were included thereby excluding the informal care and Charity care costs included in the study. The currency exchange rate conversion was done 28.02.2021 and the Danish "nettoprisindeks excl. Energy" was used to project the 2021 value from 2015, which is when the UK study was conducted (46, 47).

No subsequent treatment was assumed in the base-case as the introduction of T-DXd is not expected to have a relevant impact on the cost for subsequent treatment given that the modelled survival after progression is shorter for T-DXd than for the trastuzumab plus capecitabine according to the model. A small additional cost for subsequent treatment could be added if DMC, in addition to the survival benefit in progression-free disease, believe that patients treated with T-DXd will also live (and be treated) longer after progression than in current clinical practice. However, clinical experts have indicated that the survival after progression will be similar regardless of treatment.

5.3.6. Time and transportation costs

Transportation costs are calculated by applying 3.44 DKK/km which is the tax-free driving allowance for 2021 according to "Skattestyrelsen". This cost per kilometer is applied to the average distance of 14 km to a nearby hospital assumed to take 45 minutes each way. (47)

Patient time costs are estimated to 179 DKK/hour according to DMC guidelines (30). A round trip to the hospital including visit will amount to 2 hour per visit. This cost is applied to hospital visit for the patient. It is assumed that in most cases specialist visits and scans will be done in the same visit as when blood tests are taken. Thus, in order to not overestimate the patient costs, the visit with the highest frequency per week were used to calculate the number of visits for the patients.

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

Table 25: Time and transportation costs

Action	Units	DKK	Source
Proportion of patient that incur costs	100 %	-	Medicinrådets værdisætning af enhedsomkostninger v. 1.4. 2020
Average distance to hospital	28 km		Medicinrådets værdisætning af enhedsomkostninger v. 1.4. 2020
Cost per km		3.44	Medicinrådets værdisætning af enhedsomkostninger v. 1.4. 2020
Average visits per week	0.33		
Total transport costs per week		32.12	Calculation
Time spent per visit	2 hours		Assumption
Patient cost per hour		179	Medicinrådets værdisætning af enhedsomkostninger v. 1.4. 2020
Patient treatment time per visit	0.5 hours	89,5	Assumption
Total patient time cost per week		119.38	Calculation
Total patient cost per week		151.50	Calculation

Key: km: kilometer.

5.4. Summary of model inputs

All economic models include approximations, and cost-analysis results are dependent on assumptions and choices with respect to methodology and inputs. In this analysis, key assumptions were necessary because of the clinical trial data that are currently available to inform treatment effectiveness in the model. Firstly, DESTINY-Breast01 is a Phase II single-arm trial; the model therefore relies on indirect comparisons MAIC-generated HRs when estimating relative effectiveness, in the absence of direct head-to-head trial data. Secondly, the data for OS and PFS are immature in DESTINY-Breast01, the model, therefore, relies on extrapolations.

As endpoints are modelled independently, partitioned survival analysis models can produce logically inconsistent scenarios, for example it is possible for the extrapolated PFS curves to fall above the extrapolated OS curve. However, the model accounts for this by capping the PFS curve to be the minimum of the PFS extrapolation and the OS extrapolation.

Other key base-case settings and assumptions used in the model are presented in Table 26.

Table 26. Key settings and assumptions used in the model

Parameter	Base case Value / Assumption	Section for justification
Model settings		
Intervention	T-DXd	5.2.2
Comparators	Trastuzumab plus capecitabine	2.1.2
Discount rate	3.5%	5.2.1
Time horizon	30	5.2.1
Year length	52 weekly cycles, and thus, each month is 4.33 weeks long	
Population / Indication	Patients in third line treatment of HER2-Positive Metastatic Breast cancer who are resistant or refractory to T-DM1	5.2.2
Start age	56	5.2.3
Perspective	Restricted societal	5.2.1
Cycle length	1 week	5.2.1
% Female	100%	5.2.3
Clinical inputs		
Weight	62.47 kg	5.2.3
OS curve fit	We bull	5.2.4.2
PFS curve fit	Log-normal	5.2.4.2
Treatment duration	Log-normal	5.3.1
Main source for clinical efficacy of the comparator	Saura et al., (2020) (13)	4.2.1
Main source for AE of the comparator	Murthy et al., 2020 (6)	5.3.4
Cost inputs		
Wastage	Not included	5.3.1.1
Dose intensity	93%	5.3.1.1

Key: PFS: Progression-free survival, PD: Progressed disease, RWE: Real-world evidence.

6. Cost per patient results

6.1. Base-case results

The cost-analysis results for the base-case are presented as pairwise comparisons in Table 27. T-DXd is predicted to imply an incremental cost of approximately 900 000 DKK. As expected, the major cost-driver is the drug cost (~90% of total incremental cost).

Table 27: Deterministic results – named comparators – incremental analysis (discounted)

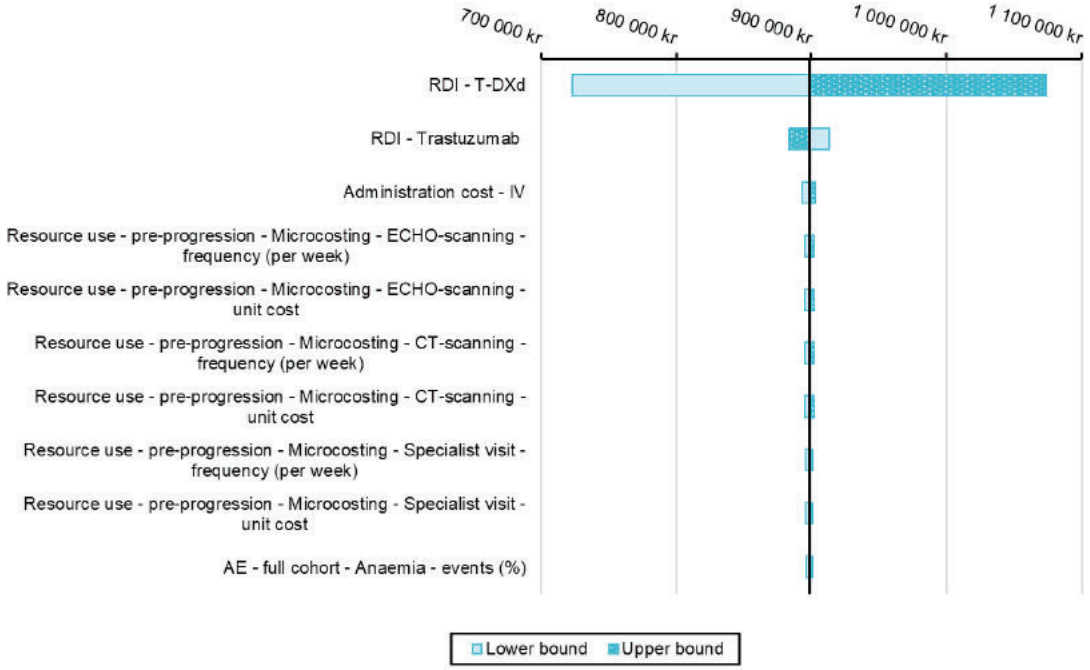
Cost category	T-DXd	Trastuzumab + capecitabine	Incremental cost per patient
Drug costs	894 795	76 997	817 798
Administration costs	40 366	14 377	25 989
Resource use costs	76 566	37 859	38 707
AE costs	10 500	1 963	8 537
EOL costs	59 690	62 510	-2 820
Patient costs	20 078	9 940	10 137
Total	1 101 994	203 646	898 348

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

6.2. Deterministic sensitivity analysis

In the one-way sensitivity analysis, each parameter was varied in turn at its lower and upper bound, which is obtained from the 95% confidence interval. Figure 13 presents a summary of the most influential parameters with corresponding cost per patient. The results show that the relative dose intensity is the most influential parameter.

Figure 13: Tornado diagram - T-DXd versus Trastuzumab plus capecitabine



Key: HR: hazard ratio, IV: intravenous, MAIC: matching-adjusted indirect comparison, PFS: progression-free survival, T-DXd: [fam-]trastuzumab deruxtecan, RDI: Relative Dose Intensity.

6.3. Scenario analysis

Table 28 shows the scenario analyses that were deemed relevant to the decision problem. As shown in the table, the base-case results were relatively robust and using a naïve comparison versus the NALA study implied that the incremental cost of using T-DXd was reduced as the patients in DESTINY-Breast01 live much longer when we adjust for them being more heavily pre-treated. Using docetaxel as the chemotherapy had no relevant impact on the results. When more optimistic extrapolation were tested for OS (LogNormal), the incremental cost increased with less than 10%, indicating that this is not the extrapolation is not an important parameter.

Table 28: Scenario analyses (DKK)

#	Scenario name	Total costs T-DXd	Total costs Trastuzumab+ capecitabine	Incremental costs
#	**Base-case**	1 101 994	203 646	898 348
1	Discount rates - 0%	1 141 496	206 092	935 404
2	Discount rates - 6%	1 076 985	202 023	874 962
3	Time horizon - 5 years	1 059 308	203 630	855 678
4	Time horizon - 10 years	1 101 815	203 646	898 169
5	Time horizon - 20 years	1 101 994	203 646	898 348
6	Log-Normal extrapolation OS - T-DXd	1 166 831	205 533	961 298

7	Exponential extrapolation PFS - T-DXd	1 098 808	192 137	906 671
8	Unadjusted HRs for OS and PFS	1 101 994	248 550	853 443
9	Docetaxel as chemotherapy	1 101 994	205 743	896 250
10	Include 50% wastage	1 168 388	218 795	949 593

Key: OS: overall survival, PFS: progression-free survival, IV: Intravenous.

7. Budget impact analysis

7.1. Patient population in Denmark

In the protocol DMC estimate that 730 patients are diagnosed with HER2+ BC every year in Denmark (16). However, in Denmark 2019, 569 patients were reported with HER2+ breast cancer in DBCG (15). It should be noted that the DBCG database do not include all patients, which means that the true number is likely slightly higher. However, given the inclusion criteria in DBCG it is not likely that the proportion of patients with HER2+ is higher in the full BC population than in the DBCG population. Thus, we have conservatively assumed that the proportion of the patients in the DBCG database with HER2+ disease (13.9%) is the same for the cohort reported from NORDCAN. Using 13.9%,(15) which is more similar to the 12-14%(17, 48, 49) reported in registries in Sweden, Norway and Finland would mean that 680 Danish patients will get HER2+ breast cancer every year.

We agree that only few percent of these patients are metastatic at diagnosis (17), but historically, approximately 20-30% of the patients with stage I-III would be expected to develop metastatic disease during the course of the disease. The company accept the DMC assumption that approximately 25% of the patients will develop metastatic disease during the course of the disease, even though, some clinical experts have estimated that only 15%-20% would be metastatic during the course of the disease based on improved screening and more adjuvant treatment (5, 50-52).

The company agree that approximately 94%, 79% and 81% of the patients will get first, second and third line treatment, respectively. These figures are in line with what Danish clinical experts have estimated when approached by the company.

Based on the minor adjustment with a more accurate figure for proportion with HER2+, it is expected that approximately 102 patients are receiving 3L treatment for HER2+ mBC in Denmark every year (Table 29). Of these patients [redacted], are estimated to be considered appropriate for T-DXd, as not all patients will be fit enough for the treatment. The exact proportion of 3L patients that is appropriate for T-DXd is difficult to estimate, but the[redacted] is the average answer from global and Danish clinical experts approached during the preparation of this dossier. They stated that, they expect that other treatment options would be considered for some patients, for instance patients with prior lung disease, patients with brain-metastases and older fragile women.

Table 29. Estimate of eligible patients in 3L HER2+ metastatic breast cancer

	% of the subjects	N (subjects)	Reference
HER2+	13.9%	680	DBCG data 2019 (15)
Metastatic during course of the disease (HER2+)	25%	168	Expert opinion based on literature (HERA, APHINITY) + RADS Anti-HER2 (2016)
Receive 1L treatment	94%	158	Expert opinion + RADS Anti-HER2 guidelines (2016)

Receive 2L treatment	79%	126	Expert opinion + RADS Anti-HER2 (2016) + RWE
Receive 3L treatment	81%	102	Expert opinion + RADS Anti-HER2 (2016) + RWE
Appropriate for T-DXd*	[redacted]	[redacted]	Expert opinion + Survey AZ/DS 2020

Key: HER2+: human epidermal growth factor receptor 2 positive, DBCG: Danish breast cancer group, 3L: third line, RWE: Real world evidence, AZ: Astra Zeneca, DS: Daiichi-Sankyo. *Remaining patients are expected to receive a mix of other treatments such as chemotherapy without trastuzumab, HER2-targeted alone, endocrine , experimental, or no treatment.

7.2. Budget impact estimate

The base-case is based upon the patient numbers presented in Table 29 and the parameters and assumptions reported in section 5.

Uptake is based on an assumption of a quick uptake due to the fast implementation of new drug recommendations in Denmark. The analysis estimates a gradual uptake over 5 years based on the complexity of 3L breast cancer treatment and the current plethora of treatment options available for patients. Market share is eventually estimated to plateau at 90% for T-DXd at year 5, if recommended by the DMC, as not all patients will be candidates for treatment with T-DXd. This is illustrated below in Table 30.

Table 30: Uptake for the following five years if recommended

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
T-DXd	80%	80%	85%	85%	90%
Trastuzumab + capecitabine	20%	20%	15%	15%	10%

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

The patient numbers used in the budget impact model are presented in Table 31. The patient numbers correspond to the market share estimates and the patient numbers in Table 29.

Table 31: Patient numbers for the following years with the estimated market share if recommended

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
If recommended					
T-DXd	46	46	49	49	52
Trastuzumab + capecitabine	11	11	9	9	6
If NOT recommended					
Trastuzumab + capecitabine	57	57	57	57	57

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

The cost per patient over time is for T-DXd is presented in Table 32 and the corresponding cost over time for trastuzumab plus capecitabine is presented in Table 33.

Table 32. Undiscounted cost per patient over time for T-DXd

T-DXd	Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs	508 829	195 913	98 350	50 102	30 071
Administration costs	22 954	8 838	4 437	2 260	1 357
Resource use costs	29 092	21 848	14 183	8 021	4 009
EOL costs	9 678	16 430	15 159	10 796	6 411
AE costs	10 500	-	-	-	-

Total	581 053	243 029	132 130	71 179	41 848

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

Table 33. Undiscounted cost per patient over time for trastuzumab plus capecitabine

Trastuzumab+ Capecitabine	Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs	73 680	3 179	236	23	4
Administration costs	13 733	617	46	5	1
Resource use costs	25 355	10 240	2 409	354	34
EOL costs	27 648	25 909	8 745	1 629	187
AE costs	1 963	-	-	-	-
Total	142 379	39 945	11 435	2 010	226

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

In Table 34 below, the results of the budget impact analysis are presented. The analysis is conducted without discounting and patient costs are excluded in line with the guidelines. The costs presented in Table 32 and Table 33 is multiplied with the patient number in Table 31.

The results of the budget impact analysis is presented in table 30. The table presents the budget impact of recommending T-DXd over the next 5 years, with a yearly budget impact ranging from ~20 million DKK to ~44 million DKK in year 5.

Table 34: Results of budget impact over the next 5 years for recommendation of T-DXd as standard treatment (undiscounted)

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5
Total with T-DXd	28 301 118	39 913 260	47 366 880	51 239 250	54 766 990
Total with current SoC	8 168 137	10 459 719	11 115 742	11 231 057	11 244 003
Budget impact	**20 132 981**	**29 453 541**	**36 251 138**	**40 008 193**	**43 522 987**

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

7.2.1. Scenario using patient numbers from the protocol

Patient numbers is in this scenario analysis based upon the protocol (16). As noted above, we expect that the DMC calculation overestimates the number of patients with HER2+ breast cancer. Further, based on feedback from clinical experts, the company do not expect that all patients in 3L is appropriate from T-DXd treatment. However, for completeness the DMC scenario is illustrated below in Table 35 while all other assumptions remained the same.

Table 35: Patient numbers for the following years with the estimated market share if T-DXd is recommended

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
If recommended					
T-DXd	88	88	94	94	99
Trastuzumab + capecitabine	22	22	17	17	11
If NOT recommended					
Trastuzumab + capecitabine	110	110	110	110	110

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

In Table 36 below the results of the budget impact analysis is presented. The analysis is conducted without discounting and patient costs are excluded.

Table 36: Results of budget impact over the next 5 years for recommendation of T-DXd as standard treatment with patient number estimates from protocol (undiscounted)

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5
Total with T-DXd	54 265 004	76 530 307	90 821 994	98 246 938	105 011 080
Total with current SoC	15 661 713	20 055 628	21 313 497	21 534 604	21 559 427
Budget impact	**38 603 292**	**56 474 679**	**69 508 497**	**76 712 334**	**83 451 653**

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

7.2.1. Scenario using docetaxel as chemotherapy in 20% of the patients

In this scenario, in line with the DMC protocol we assumed that 20% of the patients were treated with docetaxel instead of capecitabine. All other assumptions were the same as in the base-case analysis. As shown, this had a minimal impact on the results.

Table 37: Results of budget impact over the next 5 years for recommendation of T-DXd as standard treatment with docetaxel as chemotherapy (undiscounted)

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5
Total with T-DXd	28 305 714	39 918 064	47 370 550	51 242 870	54 769 457
Total with current SoC	8 191 118	10 483 739	11 139 839	11 255 161	11 268 108
Budget impact	20 114 596	29 434 325	36 230 711	39 987 709	43 501 349

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

8. Discussion

Breast cancer is a leading cause of death in Danish women, and HER2+ mBC represents a particularly aggressive form of the disease. Although the availability of HER2-targeted therapies has improved outcomes in these patients, more efficacious and tolerable options are needed after treatment fails, especially after the second line of treatment. T-DXd has demonstrated clinically meaningful and durable survival and response in an open-label phase II trial of 184 patients with unresectable or metastatic HER2+ breast cancer who have received two or more prior anti-HER2 therapies (9). Patients experienced a median PFS of 19.4 months (95% CI: 14.1 -NE), 74% were alive after 18 months, 61% of patients achieved an objective response and almost all (97%) achieved disease control, all these endpoints greatly exceed what is previously reported for this patient population. Recent 3L trials in comparable patient populations has resulted in median PFS-values between 5 and 8 months. As a reference, the CLEOPATRA study, which changed the global SoC with docetaxel, trastuzumab, pertuzumab triple combination for 1L metastatic patients, showed a median PFS of 18.7 months (14). Hence, despite the lack of a phase-III study and head-to-head data from the DESTINY-Breast01 study, T-DXd have received accelerated approvals by both EMA and FDA.

Methods

In line with previous oncology models in HER2+ mBC, a partitioned survival model was developed to assess the cost of T-DXd within its metastatic breast cancer license. The structure of the cost-analysis model comprised four health states: progression-free on treatment, progression-free off treatment, progressed disease (PD), and death. This is a standard structure for oncology models.

The analysis uses the available trial data to inform safety and treatment effectiveness and uses the latest relevant Danish data sources for other inputs such as costs. Both naïve and

adjusted indirect comparisons were conducted to inform the efficacy for the comparator arm. In the model we also tested a range of different models for extrapolation.

Results

The analysis showed that the use of T-DXd result in a cost per patient of approximately DKK 900 000 versus trastuzumab plus capecitabine. Drug cost represented ~90% of the total incremental cost of T-DXd. The cost-analysis results were tested in a large number of sensitivity and scenario analyses, which showed that these results were robust and in most cases varied with less than +/-10%. At peak uptake, the budget impact if T-DXd is introduced is approximately 44 million.

Conclusion

T-DXd is an efficacious treatment when compared to relevant available regimens for the treatment of unresectable or metastatic HER2+ breast cancer in patients previously treated with at least two HER2+ targeted therapies in Denmark. T-DXd, if funded in Denmark, has the potential to significantly improve outcomes for patients that today has a very poor prognosis and limited effective treatment options. Introducing T-DXd as standard treatment in Denmark will result in a budget impact of approximately DKK 44 million each year assuming 52 patients per year.

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Medicinrådet

Medicinrådets protokol for vurdering vedrørende trastuzumab deruxtecan til tredjelinjebehandling af metastatisk HER2+ brystkræft

Version 1.1

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil den ansøgende virksomhed få besked.

Dokumentoplysninger	
Godkendelsesdato	6. april 2021
Dokumentnummer	111987
Versionsnummer	1.1

Indholdsfortegnelse

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 6. april 2021

1. Begreber og forkortelser

DBCG	*Danish Breast Cancer Group*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
ER	*Estrogen receptor* (østrogen receptor)
EUnetHTA:	*European Network for Health Technology Assessment*
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HER2	Human epidermal vækstfaktorreceptor 2
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention-to-treat*
MKRF:	Mindste klinisk relevante forskel
NICE:	*The National Institute for Health and Care Excellence*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
PP:	*Per protocol*
RR:	Relativ risiko
SMD:	*Standardized Mean Difference*
T-DM1	Trastuzumab emtansin
T-DXd	Trastuzumab deruxtecan

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra AstraZeneca og Daiichi Sankyo, som ønsker, at Medicinrådet vurderer trastuzumab deruxtecan (T-DXd) (Enhertu®) til patienter med metastatisk HER2+ brystkræft, som tidligere har modtaget to eller flere HER2+-rettede behandlinger. Medicinrådet modtog den foreløbige ansøgning den 16. december 2020. AstraZeneca og Daiichi Sankyo fik forhåndsgodkendelse (positive opinion) i EMA den 10. december 2020.

2.1 Metastatisk HER2+ brystkræft

Brystkræft er den hyppigste kræftform hos kvinder verden over og forekommer oftest hos kvinder over 50 år. I Danmark bliver omkring 4.900 patienter årligt diagnosticeret med brystkræft, og ca. 66.000 patienter lever med diagnosen brystkræft [1,2]. Af de 4.900 patienter, som årligt diagnosticeres med brystkræft i Danmark, vil ca. 4.400 have tidlig brystkræft, dvs. at de ikke har fjernmetastaser. Ca. 10 %, dvs. ca. 490 patienter, har ved diagnosetidspunktet derimod uhelbredelig lokalt fremskreden (inoperabel) eller metastatisk sygdom (primært dissemineret).

HER2+ brystkræft
Sygdommen kan opdeles i fire undertyper, afhængigt af om kræftcellerne er hormonfølsomme, dvs. om de udtrykker østrogen receptor (ER) og/eller human epidermal vækstfaktorreceptor 2 (HER2) [3].

Patienterne testes rutinemæssigt for HER2-status på diagnosetidspunktet ved immunhistokemi [4]. Ca. 10-15 % af patienter med brystkræft er HER2-positive (HER2+). Således bliver op til ca. 660 patienter årligt diagnosticeret med tidlig HER2+ brystkræft, mens ca. 70 patienter årligt bliver diagnosticeret med lokalt fremskreden inoperabel eller metastatisk HER2+ brystkræft [5]. Nogle af patienterne med inoperabel sygdom (ca. 30) vil blive behandlet med kurativt sigte, mens ca. 40 patienter i stedet vil modtage behandling for metastatisk sygdom (se figur 1).

Der har i de seneste år været en del udvikling ift. (neo)adjuverende behandling af HER2+ brystkræft. Fagudvalget har ikke kendskab til opgørelser eller kliniske studier, der belyser, hvor mange patienter som får metastatisk tilbagefald med den nuværende danske behandlingsstrategi. Fagudvalget skønner ud fra klinisk erfaring, at ca. 20 % af patienterne med tidlig HER2+ brystkræft (dvs. op til ca. 130 patienter) over tid vil udvikle metastaser. Dette er en smule lavere, end hvad eksempelvis RADS angav i behandlingsvejledningen vedr. HER2+-rettet behandling [6], hvilket skyldes, at den nuværende behandlingsstrategi er mere effektiv, hvormed færre patienter får tilbagefald.

Samlet set estimerer fagudvalget således, at de 40 patienter, der har metastatisk sygdom ved diagnosetidspunktet og ikke er kandidater til behandling med kurativt sigte, samt de 130 patienter med tidlig brystkræft, der får metastatisk tilbagefald, årligt er kandidater

til 1. linje metastatisk behandling, dvs. ca. 170 patienter (se yderligere beskrivelse vedr. tredjelinjebehandling i afsnit 2.3).

2.2 Trastuzumab deruxtecan (T-DXd)

T-DXd forventes at få følgende indikation af EMA: *Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti HER2 based regimens.*

T-DXd gives intravenøst, 5,4 mg/kg hver tredje uge. EMA har vurderet T-DXd i en accelereret proces.

T-DXd er en sammenkobling af deruxtecan, som er en topoisomerase-1-hæmmer (dvs. en type af kemoterapi), og trastuzumab, som er et antistof rettet mod HER2. T-DXd virker ved, at trastuzumab genkender HER2, som er overudtrykt på overfladen af brystkræftcellerne. Når T-DXd binder til HER2-proteiner, transporteres det ind i cellen, hvor kemoterapien frigives og slår cellen ihjel. Deruxtecan kan bevæge sig igennem cellemembraner og kan dermed forårsage celledød af nærliggende celler. T-DXd har et højere antal molekyler af kemoterapi koblet til hvert antistof sammenlignet med tidligere kemoterapi/antistof kombinationer.

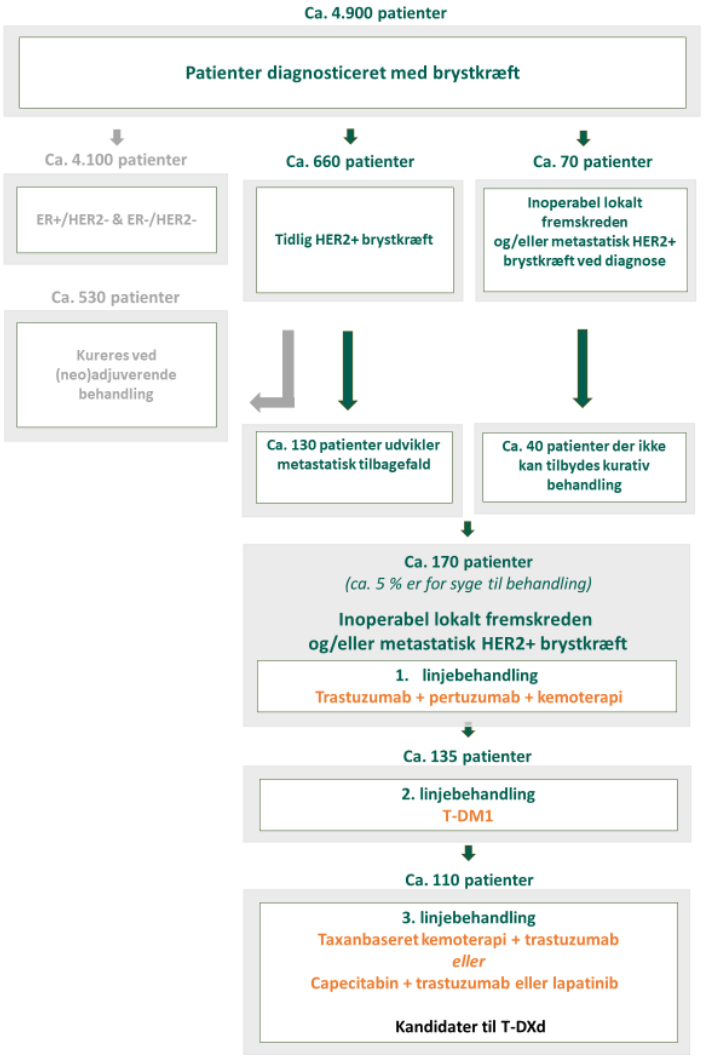
T-DXd er ikke godkendt til andre indikationer.

2.3 Nuværende behandling

2.3.1 Nuværende behandlingsrækkefølge

Patienter med HER2+ brystkræft med metastatisk sygdom modtager som udgangspunkt vinorelbine i kombination med pertuzumab og trastuzumab i første linje og T-DM1 i anden linje, se figur 1. Fagudvalget forventer, at ca. 5 % ikke får førstelinjebehandling, da de er for syge. 15 % dør eller ophører behandlingen i perioden fra første- til andenlinjebehandling, mens det er tilfældet for 20 % i perioden fra anden- til tredjelinjebehandling. Dermed er der årligt ca. 110 patienter med metastatisk HER2+ brystkræft, som kan komme i betragtning til behandling i tredje linje, se figur 1.

Figur 1. Oversigt over nuværende behandlingsrækkefølge



Hvis patienterne progredierer på andenlinjebehandling, tilbydes de en af følgende behandlinger, jf. DBCGs retningslinjer [7]:

- capecitabine i kombination med enten trastuzumab eller lapatinib
- taxanbaseret kemoterapi (typisk paclitaxel) i kombination med trastuzumab.

Valget imellem disse to behandlingskombinationer afhænger af, hvilken type kemoterapi patienten tidligere har modtaget, om patienten er progredieret på den pågældende behandling, samt hvilke bivirkninger patienten er villig til at acceptere.
F.eks. vil en patient, som tidligere er progredieret på taxanbaseret kemoterapi, modtage capecitabin.

Fagudvalget vurderer, at ca. 80 % af patienterne modtager capecitabine i kombination med trastuzumab. Som nævnt er det muligt at kombinere capecitabine med lapatinib fremfor trastuzumab. Fagudvalget vurderer, at dette sker relativt sjældent grundet mere toksicitet forbundet med lapatinib i forhold til trastuzumab. Fagudvalget vurderer, at

effekten af capecitabine i kombination med hhv. trastuzumab og lapatinib er sammenlignelig [8,9]. Derfor konkluderer fagudvalget, at capecitabine i kombination med trastuzumab er den mest relevante komparator for sammenligningen med T-DXd.

2.3.2 Patienternes almene tilstand og behandlingsmålet med den nuværende behandling

Patienter, der har progredieret på andenlinjebehandling og dermed er kandidater til tredjelinjebehandling, kan være præget af deres brystkræftsygdom. Dette er dog meget forskelligt fra patient til patient og afhænger i høj grad af metastasernes beliggenhed. Fagudvalget vurderer, at ca. 35-40 % af patienter med HER2+ brystkræft vil udvikle hjernemetastaser. Hjernemetastaser medfører ofte svære symptomer og kan være vanskelige at behandle, men også metastaser i lunger og lever, lungehinde og bughule kan medføre symptomatisk sygdom.
Patienter kan desuden være præget af bivirkninger fra tidligere behandlinger. I dansk klinisk praksis behandles patienter med performance status 0, 1 og 2 [7]. Nogle patienter er således oppegående, men hviler sig en betragtelig del af dagen, mens andre stadig kan opretholde et arbejde.

Behandlingsmålet med den nuværende tredjelinjebehandling er både symptomlindring og livsforlængelse. Behandlingen har således ikke kurativt sigte.

2.3.3 Prognose ved nuværende behandling

Fagudvalget gør opmærksom på, at det er vanskeligt at estimere patienternes overlevelse ved tredjelinjebehandling. I dette afsnit gennemgår fagudvalget derfor flere forskellige randomiserede forsøg for at give et retvisende billede af den heterogenitet i studieresultater, som gør det udfordrende at estimere prognosen for patientgruppen.

- Patienter med metastatisk HER2+ brystkræft, som modtager trastuzumab + pertuzumab + kemoterapi i første linje, har en median overlevelse på ca. 56 måneder [10].
- Den seneste udgivelse for andenlinjebehandling af metastatisk HER2+ brystkræft viser, at patienter, som modtager T-DM1, har en median overlevelse på 29,9 måneder [11].
- Der foreligger forskellige studier for tredjelinjebehandling, hvoraf ingen dog afspejler den danske patientpopulation fuldstændigt. Et studie viste en median overlevelse på ca. 17 måneder for patienter, som modtog capecitabine + trastuzumab [12]. Dette reflekterer dog ikke danske patienters prognose, da patienterne i studiet havde modtaget imellem 2-14 forskellige behandlinger for metastatisk sygdom. Det betyder, at en del patienter i studiet har dårligere prognose end danske patienter. Et andet studie viste en median overlevelse på ca. 27 måneder for patienter, som modtog capecitabine + trastuzumab [13]. Dette studie overestimerer dog prognosen, da der ikke var inkluderet patienter med hjernemetastaser, og 44 % af patienterne modtog behandling i første linje. Dermed er der selekteret for patienter med den bedste prognose. Et tredje studie viste en median overlevelse på ca. 19 måneder (gennemsnitlig overlevelse er opgjort til 22 måneder) for patienter, som modtog capecitabine + lapatinib, hvilket fagudvalget forventer har samme effekt som

capecitabine + trastuzumab [14]. Samlet set vurderer fagudvalget, at en median overlevelse på ca. 22 måneder er forventelig for danske patienter.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)), og af effektmålene.

3.1 Klinisk spørgsmål 1

Hvilken værdi har trastuzumab deruxtecan (T-DXd) sammenlignet med capecitabine i kombination med trastuzumab for patienter med metastatisk HER2+ brystkræft, som har progredieret på to HER2-rettede behandlinger?

Population
Patienter med inoperabel lokalt fremskreden og/eller metastatisk HER2+ brystkræft, som har progredieret på to HER2-rettede behandlinger.

Intervention
Trastuzumab deruxtecan (T-DXd), intravenøst, 5,4 mg/kg hver tredje uge.

Komparator

- Capecitabine (1.000 mg/m2 pr. dag oralt i 14 dage) i kombination med trastuzumab (opstartsdosering 8mg/kg, vedligeholdelsesdosering 6mg/kg) [1]

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

[1] Komparator er valgt, fordi 80 % af patienterne modtager capecitabine i kombination med trastuzumab. Fagudvalget understreger, at sammenligningen mellem T-DXd og komparator kan overføres til patienter, som modtager taxanbaseret kemoterapi i kombination med trastuzumab.

Tabel 1. Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Samlet overlevelse (OS)	Kritisk	Overlevelse	Median OS	En forskel på 5 måneder
Livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring over tid	Forskel i ændring svarende til de validerede mindste klinisk relevante forskelle for de involverede livskvalitetsspørgeskemaer (se nedenfor)
Bivirkninger	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever en eller flere grad 3-4 bivirkninger	5 %-point
			Gennemgang af bivirkningsprofil	Narrativ vurdering
Stabilisering eller forbedring af symptomer	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Median Progressionsfri overlevelse (PFS)	En forskel på 3 måneder
			Objektiv respons rate (ORR)[1]	En forskel på 20 %-point

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
**Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.
[1]Fagudvalget vurderer, at ORR er reflekteret i PFS, og vil derfor kun benytte data herfor, hvis der ikke foreligger modent PFS-data.

3.2.1 Kritiske effektmål

Samlet overlevelse (OS)
Samlet overlevelse er defineret som tiden fra randomisering til død uafhængigt af årsag. Det er afgørende for patienterne, om behandlingen forlænger deres liv, og Medicinrådet vurderer derfor, at OS er et kritisk effektmål. Fagudvalget ønsker effektmålet opgjort som median overlevelse.

Den mindste klinisk relevante forskel er valgt med udgangspunkt i ESMO's guideline *Magnitude of Clinical Benefit Scale* (MCBS). Denne indeholder skemaer, der indikerer, hvordan man kan fastsætte mindste klinisk relevante forskelle afhængigt af patienternes prognose [15]. Fagudvalget tager udgangspunkt i ESMO MCBS-skemaet, der omhandler behandlinger, som ikke forventes at være kurative, og hvor OS eller PFS er det primære endepunkt.

Fagudvalget vurderer, at en forskel ift. median OS på 5 måneder er klinisk relevant.

Livskvalitet

Livskvalitet er et patientrelevant effektmål, som udover at give indblik i sygdomsbyrden kan indikere, om bivirkningerne ved lægemidlet påvirker patienternes livskvalitet. På baggrund af dette betragter fagudvalget livskvalitet som et kritisk effektmål.
Livskvalitet kan for brystkræftpatienter måles med flere forskellige instrumenter (spørgeskemaer). Fagudvalget vurderer, at nedenstående validerede spørgeskemaer, der er nævnt i prioriteret rækkefølge, er relevante. Fagudvalget lægger i prioriteringen af rækkefølgen vægt på, at man benytter de to førstnævnte i dansk klinisk praksis.
EORTC-QLQ-C30: Dette instrument måler livskvaliteten blandt kræftpatienter [16]. Det består af fem funktionsskalaer, tre symptomskalaer og en "global" livskvalitetsskala. Der anvendes en scoringsskala fra 0-100. En høj score på de fem funktionsskalaer repræsenterer et højt/positivt funktionsniveau. En høj score for global helbredsstatus repræsenterer høj livskvalitet, mens en høj score på de tre symptomskalaer repræsenterer høj forekomst af symptomer/problemer. En lille ændring i livskvalitet er defineret som en ændring på 5-10 point i en publikation, hvor størstedelen af patienterne havde brystkræft [17]. Fagudvalget læner sig op ad denne definition og betragter en forskel på ≥ 10 point mellem T-DXd og komparator som klinisk relevant.

EORTC-QLQ-BR23: Dette er et sygdomsspecifikt instrument, der vurderer livskvaliteten blandt patienter med brystkræft [18]. Det er et tillæg til EORTC-QLQ-C30 og består af fire funktionsskalaer og fire symptomskalaer. Scoringen foregår på samme måde som ved EORTC-QLQ-C30. Da der tilsyneladende ikke er defineret en mindste klinisk relevant forskel for instrumentet, benytter fagudvalget sig af definitionen fra EORTC-QLQ-C30. Dette er konsistent med tilgangen i flere studier [19]. Dermed betragter fagudvalget en forskel på ≥ 10 point mellem T-DXd og komparator som klinisk relevant.

EQ-5D: Dette er et velvalideret generisk spørgeskema, som anvendes til at vurdere helbredsrelateret livskvalitet [20]. Spørgeskemaet består af fem dimensioner og indeholder desuden en visuel analog skala (VAS), der går fra 0 (værst tænkelige helbred) til 100 (bedst tænkelige helbred). Fagudvalget læner sig op ad definitionerne af mindste klinisk relevante forskelle baseret på britiske kræftpatienter [21]. Dermed finder fagudvalget, at en forskel på ≥ 0,08 i EQ-5D index score og ≥ 7 point i EQ-5D VAS mellem T-DXd og komparator er klinisk relevant.

3.2.2 Vigtige effektmål

Bivirkninger

Som nævnt er behandlingsmålet at forlænge patienternes liv. Fagudvalget finder, at bivirkninger (adverse reactions, AR) er et vigtigt effektmål, da det belyser, hvor godt patienterne tolererer T-DXd sammenlignet med komparator. Effektmålet er vigtigt, da det er fagudvalgets vurdering, at patienterne er relativt villige til at risikere bivirkninger for at kunne opnå en eventuel forlængelse i overlevelse. Fagudvalget ønsker data på nedenstående måleenheder.

Bivirkninger grad 3-4
Fagudvalget finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever en eller flere bivirkninger af grad 3 eller 4, er relevant for vurderingen.
Bivirkninger af grad 3-4 er defineret i henhold til National Cancer Institute CTCAE, version 4.03 [22].
Fagudvalget vurderer, at en forskel på 5 %-point i andelen af patienter, der får bivirkninger af grad 3-4, er klinisk relevant.

Gennemgang af bivirkningsprofil
Fagudvalget ønsker en gennemgang af T-DXd og komparators bivirkningsprofiler med henblik på at vurdere bivirkningernes type, håndterbarhed og reversibilitet. Ansøger bedes derfor levere bivirkningsdata fra både de kliniske studier og produktresuméet for lægemidlerne, så fagudvalget kan vurdere forskelle mellem de forskellige behandlinger. Fagudvalget udbeder sig informationer om forekomsten af interstitielle lungesygdomme, både af alle grader og en specifik opgørelse af grad 3-4. Dette skyldes, at FDA har gjort opmærksom på og udtrykt bekymring for netop denne bivirkning i deres gennemgang af T-DXd.

Bivirkninger af grad 3-4 bliver vægtet mest i den samlede vurdering af effektmålet.

Stabilisering eller forbedring af symptomer

Progressionsfri overlevelse
Fagudvalget ønsker at belyse forskellen i andel patienter, som opnår stabilisering eller forbedring af symptomer vha. PFS. PFS bliver anvendt til at vurdere, hvor lang tid der går, inden patienternes sygdom udvikler sig. PFS er defineret som tiden fra studierandomisering til første dokumentation af progression i henhold til RECIST 1.1 [23] eller dødsfald.

Tredjelinjebehandling er den sidste mulige standardbehandling for patienter med metastatisk HER2+ brystkræft. Fagudvalget vurderer derfor, at det er af stor værdi for patienterne at modtage en behandling, som stabiliserer deres sygdom og forlænger tiden til progression, og fagudvalget anser derfor effektmålet som vigtigt. Stabilisering af sygdommen betyder ofte, at patienterne undgår forværring af deres symptomer for en tid. Fagudvalget fremhæver, at det har særlig betydning for patienterne at forblive i en effektiv behandling så længe som muligt.

Den mindste klinisk relevante forskel er valgt med udgangspunkt i ESMO's guideline *Magnitude of Clinical Benefit Scale* (MCBS). Denne indeholder skemaer, der indikerer, hvordan man kan fastsætte mindste klinisk relevante forskelle afhængigt af patienternes prognose [15]. Fagudvalget tager udgangspunkt i ESMO MCBS-skemaet, der omhandler behandlinger, som ikke forventes at være kurative. Når PFS er det primære endepunkt, sættes den mindste klinisk relevante forskel til 3 måneder for at påvise en lille klinisk relevant forskel mellem T-DXd og placebo.

Objektiv respons rate (ORR)

Fagudvalget er opmærksom på, at effekten af T-DXd er undersøgt i et fase II-singlearm-studie. Det er derfor ikke givet, at der til Medicinrådets vurdering af T-DXd kan forefindes modne PFS-data, som kan benyttes til kategoriseringen. Hvis dette ikke er muligt, vil fagudvalget i stedet for PFS anvende ORR til at belyse effekten af T-DXd, omend der ikke er evidens for, at ORR kan benyttes som surrogatmål for PFS. Fagudvalget vil nedenfor gennemgå vigtige forskelle mellem effektmålene, og hvad disse betyder for den kommende vurderingsrapport.

Objektiv responsrate (ORR) anvendes til belysning af behandlingsrespons. ORR underinddeles i følgende kategorier, jf. Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [24]:

- Komplet respons (CR): Klinisk og billeddiagnostisk sygdomsfri. Alle tumorlæsioner er væk, og ingen nye er fremkommet.
- Partielt respons (PR): Mindst 30 %'s reduktion af tumorlæsionernes størrelse sammenlignet med baseline.

Objektiv respons (OR) opnås for en patient, hvis vedkommende er klassificeret som CR eller PR, og ORR defineres som CR + PR delt med det samlede patientantal.

Fagudvalget vurderer, at tumorreduktion medfører en periode med forbedring eller ingen forværring af symptomer. Som det er beskrevet under PFS, vurderer fagudvalget, at dette kan være af særlig betydning for patienterne. Fagudvalget understreger dog, at ORR ikke inkluderer den del af patienterne, som opnår stabilisering i deres sygdom, hvilket er tilfældet for PFS. Derfor vil en kategorisering baseret på ORR ikke være betegnende for patienter med stabiliseret sygdom, men kun for patienter, der opnår respons.

I det studie, som er mest betegnende for denne patientpopulations prognose, blev der opnået en responsrate på ca. 25 % [14]. MKRF for *stabilisering eller forbedring af symptomer* er fastsat til en forskel i median PFS på 3 måneder, dvs. at 50 % af patienterne skal opnå en bedring af symptomer på minimum 3 måneder, for at der er en klinisk relevant forskel. Med afsæt i responsraten ved standardbehandling og den fastsatte MKRF for PFS vurderer fagudvalget, at det tilsvarende er klinisk relevant, hvis 20 % flere patienter opnår respons. MKRF for ORR er dermed fastsat til 20 %-point. I tillæg til andelen af patienter, der opnår et respons, ønsker Medicinrådet information om varigheden af respons i henhold til RECIST 1.1 [24].

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMA) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (f.eks. NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil Medicinrådet som hovedregel ikke anvende andre data[2]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets kriteriepapir.

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor T-DXd er sammenlignet direkte med capecitabine i kombination med trastuzumab. Dette skyldes, at den primære publikation vedr. T-DXd er et fase II-enkeltarms-studie, dvs. at alle patienter i studiet modtager T-DXd. Derfor skal ansøger søge efter studier til en indirekte sammenligning.

Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for det aktuelle lægemiddel.

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Kriterier for litteratursøgning
Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, f.eks. i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur
Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement.

[2] For yderligere detaljer se Medicinrådets kriteriepapir om anvendelse af upublicerede data

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention-to-treat (ITT), per protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).

- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

Sundhedsøkonomiske analyser

En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning

og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, f.eks. behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Redegørelse for antallet af behandlingslinjer, som patienter modtager i det kliniske studie
Ansøger bedes beskrive forskelle i antallet af behandlingslinjer forud for behandling med T-DXd ift. dansk klinisk praksis og vurdere, hvad en eventuel forskel kan have af betydning for effekt af behandling med T-DXd i hhv. studiet og i dansk klinisk praksis.

Patienternes performance status
I kliniske studier indgår ofte kun patienter i PS 0 og 1. Fagudvalget understreger, at i dansk klinisk praksis behandles patienter med metastatisk HER2+ brystkræft i PS 0, 1 og 2 rutinemæssigt i tredje linje. Fagudvalget vil i vurderingsrapporten vurdere, om patienter i PS 2 også vil kunne tages i betragtning til behandling med T-DXd.

Medicinrådet ønsker informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer hvad angår type, varighed og forventet effekt.

Supplerende sundhedsøkonomiske analyser
Som supplement til den sundhedsøkonomiske analyse for sammenligningen mellem T-DXd og capecitabin + trastuzumab ønsker Medicinrådet, at ansøger estimerer de inkrementelle omkostninger pr. patient for T-DXd sammenlignet med taxanbaseret kemoterapi + trastuzumab (som nævnt i afsnit 2.3.1 er denne behandlingsmulighed også en del af nuværende dansk klinisk praksis). Endvidere ønsker Medicinrådet, at ansøger i den økonomiske model inkluderer muligheden for en af følgende modelleringer:

1. at opdele patientantallet i budgetkonsekvensanalysen procentvist mellem de nuværende to standardbehandlinger (80 % modtager capecitabin + trastuzumab og 20 % modtager taxanbaseret kemoterapi + trastuzumab)
2. at udarbejde separate budgetkonsekvensanalyser for de to nuværende standardbehandlinger.

8. Relation til behandlingsvejledning

Medicinrådet vil i forbindelse med vurderingen af T-DXd tage stilling til, hvor lægemidlet foreløbigt kan placeres i RADS' behandlingsvejledning for anti-HER2 behandling af brystkræft. Medicinrådet har i december 2020 besluttet, at denne behandlingsvejledning skal opdateres i regi af Medicinrådet.

9. Referencer

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende brystkræft

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Hanne Melgaard Nielsen *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Tamás Lörincz *Overlæge*	Region Nordjylland
Julia Kenholm *Overlæge*	Region Midtjylland
Jeanette Dupont Jensen *Overlæge*	Region Syddanmark
Vesna Glavicic *Overlæge*	Region Sjælland
Maja Vestmø Maraldo *Afdelingslæge*	Region Hovedstaden
Philip Hojrizi *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Marie Lund *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Iben Kümler *Afdelingslæge*	Danish Breast Cancer Cooperative Group (DBCG)
Susanne Geneser *Patient/patientrepræsentant*	Danske Patienter
Marianne Johansson *Patient/patientrepræsentant*	Danske Patienter
Eva Balslev *Overlæge*	Inviteret af formanden

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11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.1	6. april 2021	I afsnit 2.3.3 er beskrivelsen af to studier, der er anvendt til at estimere prognosen ved standardbehandling, præciseret ift. hhv. studiepopulation og resultater.
1.0	17. marts 2021	Godkendt af Medicinrådet.

12. Bilag

Bilag 1: Søgestrenge

Klinisk spørgsmål 1

Søgestreng til PubMed:

#	Søgestreng	Kommentar
#1	Breast Neoplasms[mh]	
#2	(breast[tiab] OR mammary[tiab]) AND (cancer[tiab] OR carcinoma[tiab])	
#3	#1 OR #2	Søgning population
#4	advanced[tiab] OR inoperable[tiab] OR "non resectable"[tiab] OR "not resectable"[tiab] OR unresectable[tiab] OR relaps*[tiab] OR metasta*[tw] OR recurren*[tw]	
#5	#3 AND #4	
#6	trastuzumab deruxtecan[nm] OR (trastuzumab[tiab] AND deruxtecan[tiab]) OR Enhertu*[tiab] OR T-DXd[tiab]	Søgning intervention
#7	Capecitabine[mh] OR capecitabine[tiab] OR Xeloda*[tiab]	Søgning komparator
#8	Trastuzumab[mh] OR trastuzumab[tiab] OR Herceptin*[tiab]	
#9	#6 OR (#7 AND #8)	
#10	#5 AND #9	Kombination, population og lægemidler
#11	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]	Eksklusion af irrelevante publikationstyper
#12	#10 NOT #11	Endelig søgning

Søgestreng til CENTRAL:

#	Søgestreng	Kommentar
#1	((breast or mammary) near/2 (cancer og carcinoma)):ti,ab,kw	Søgetermer for population
#2	(advanced or metasta* or unresectable or un-resectable or non-resectable or inoperable):ti,ab,kw	
#3	#1 AND #2	
#4	(trastuzumab next deruxtecan or Enhertu* or T-DXd):ti,ab,kw	Søgetermer for intervention
#5	(capecitabine or Xeloda*):ti,ab,kw	Søgetermer for komparator
#6	(trastuzumab or Herceptin*):ti,ab,kw	
#7	#4 OR (#5 AND #6)	
#8	#3 AND #7	Kombination, population og lægemidler
#9	("conference abstract" or review):ti,pt	Eksklusion af irrelevante publikationstyper
#10	(clinicaltrials.gov or trialsearch):so	
#11	NCT*:au	
#12	(abstract or conference or meeting or proceeding*):so	
#13	#9 or #10 or #11 or #12	
#14	#8 not #13	
#15	#14 not pubmed:an	Endelig søgning, fratrukket referencer fra Pubmed