For public - redacted

NICE National Institute for Health and Care Excellence

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies

Lead team presentation

1st appraisal committee A meeting
Chair: Brian Shine
Lead team: Andrew Champion, Steve Edwards, Pam Rees
ERG: LRIG-TAG
Technical team: Rebecca Thomas, Caroline Bregman, Ewa Rupniewska, Janet Robertson
Company: Daiichi-Sankyo
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Key clinical issues

- Issue 1 : The evidence available for trastuzumab deruxtecan is from a single-arm phase II trial
- Issue 2: The evidence available for trastuzumab deruxtecan is still immature
- Issue 3: Is the population included in the DESTINY-Breast01 trial broadly representative of patients treated in UK clinical practice?
- Issue 4: Can the comparative effectiveness of trastuzumab deruxtecan be robustly assessed against the comparators in the scope given the differences in trial populations and lack of evidence?

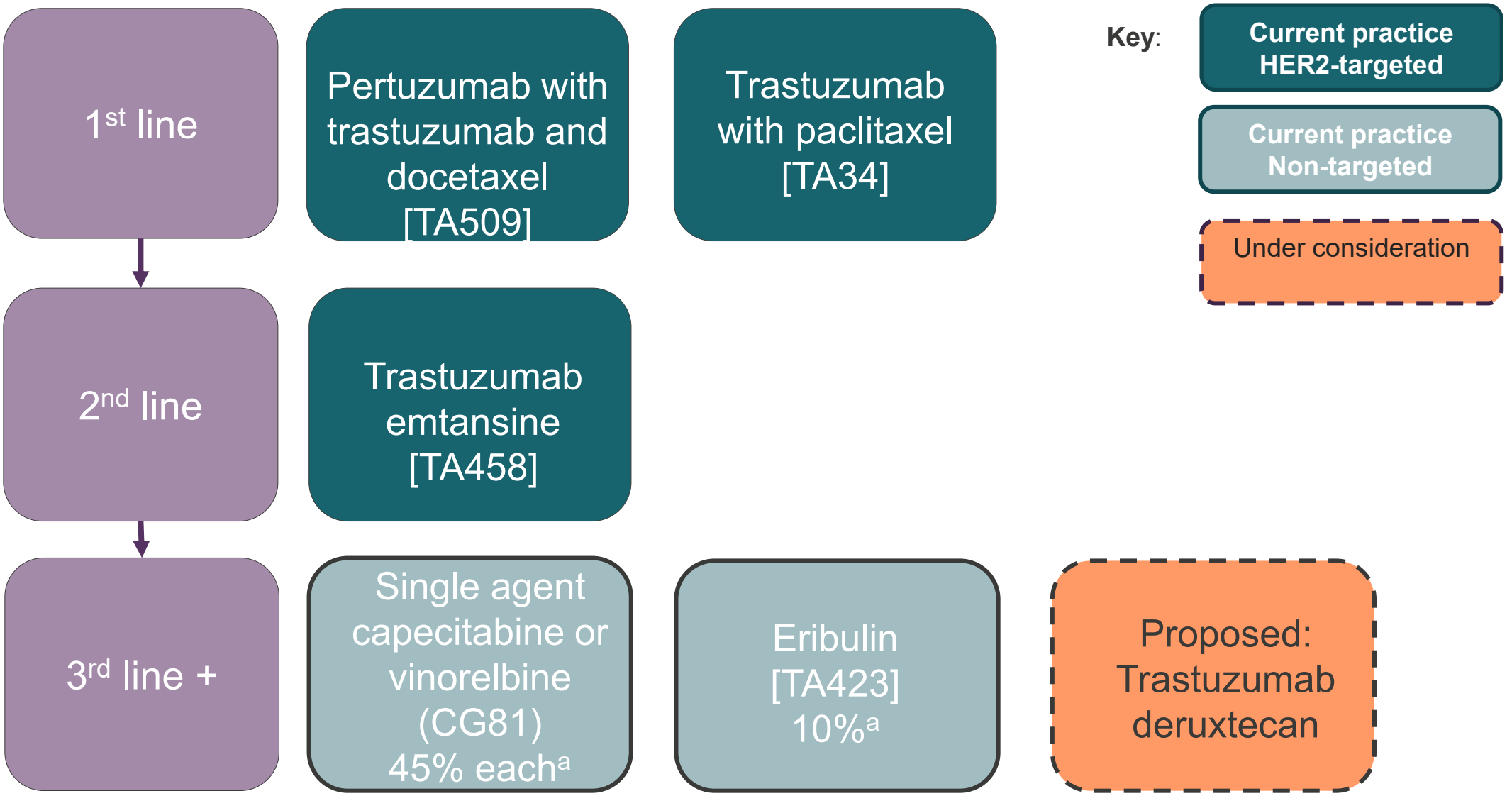
Trastuzumab deruxtecan (T-DXd)

Conditional Marketing authorisation	Indicated for adults with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 therapies
Dosage and administration	Intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Recommended dosage is 5.4mg/kg
Mechanism of action	Trastuzumab deruxtecan is a HER2-directed antibody drug conjugate. Following binding to HER2 on tumour cells, trastuzumab deruxtecan undergoes internalisation, and linker cleavage. Upon release, the membrane-permeable deruxtecan causes DNA damage and apoptotic cell death.
Average list price per course of treatment	£1,455 per 100mg vial • Cost per cycle: £4,912.81 • Cost per course: £117,857.55 Patient Access Scheme (PAS) approved by NHS England

Disease background

- **Unresectable** breast cancer and **metastatic breast cancer** are the **most advanced** forms of breast cancer.
- There were approximately **2,300 people** with metastatic breast cancer in the UK in 2016 (National Cancer Registration and Analysis Service).
- Human epidermal growth factor receptor 2 (**HER2**) is a receptor for a growth factor which occurs naturally in the body and is **overexpressed** in approximately **13-20%** of metastatic breast cancer tumours.
- Patients with HER2+ metastatic breast cancer who have progressed on two or more prior HER2 targeted therapies have a **high symptom burden**, and built up **treatment resistance** to multiple previous lines of therapy.
- No HER2-targeted therapies in people with HER2+ unresectable or metastatic breast cancer whose disease has progressed on or after two anti-HER2 therapies – **high unmet need**

Treatment pathway- HER2 metastatic breast cancer



[a] Expected use in NHS practice in 3rd line setting; eribulin more likely to be used 4th line (ERG clinical advice).
Note: Trastuzumab + chemotherapy is prescribed by some oncologists in the third line setting but not standard care across the NHS (source: clinical advice to the ERG)

Patient and carer perspectives (Breast Cancer Now)

- Being diagnosed with metastatic breast cancer is extremely difficult to come to terms with both for patients and their family and friends.
- Currently no HER2-targeted treatment recommended for use after 2 or more prior treatment lines – urgent need for new and clinically-effective treatments
- “It is scary. I am permanently scared about my future and what my family will have to deal with without me”.
- “Every time I meet my clinician we horizon-scan... It’s always a pretty depressing conversation. There isn’t anything else out there beyond Kadcyla (trastuzumab emtansine) apart from broad spectrum chemotherapies. I’m always looking for something which is effective and has similar or more tolerable side effects…”
- One of the main disadvantages of this treatment are the side effects associated with it. People’s experiences with side effects will vary, as will people’s willingness to risk the side effects associated with treatment.

Decision problem

	Final scope issued by NICE	Evidence used in the model
Population	People with HER2-positive, unresectable or metastatic breast cancer who have received 2 or more prior anti-HER2 therapies	As per scope
Intervention	Trastuzumab deruxtecan	As per scope
Comparators	• capecitabine • vinorelbine • eribulin (for people who have had 2 or more chemotherapy regimens)	As per scope
Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rate • duration of response • adverse effects of treatment • health-related quality of life	From DESTINY-Breast01 clinical trial: • progression-free survival • overall survival • objective response rate according to ICR (primary endpoint) (to inform progression-free, on treatment utility values) • adverse effects of treatment Alternative sources: • health-related quality of life

Clinical trial evidence – DESTINY-Breast01

Study design	Phase II, multicentre, open-label, single-group study
Location	72 sites in eight countries in Europe (Belgium, France, Italy, Spain, UK), North America (US) and Asia (Japan, South Korea).
Population (N = 184)	Adults with HER2+ unresectable or metastatic breast cancer who had received previous treatment with trastuzumab emtansine
Intervention	Trastuzumab deruxtecan evaluated at a dose of 5.4 mg/kg
Outcomes	Primary outcome: Objective response rate (ICR assessed) Secondary outcomes: Progression free survival (ICR assessed) Overall survival (ICR assessed) Adverse events

ICR: Independent Central Review

- The company's initial submission was based on data cut from August 2019
  - (median follow-up 11.1 months [range, 0.7 to 19.9]) .
- The company later submitted an addendum based on a data cut **from June 2020**
  - (median follow-up 20.5 months [redacted]).
- **The evidence presented in these slides are based on the June 2020 data cut.**

DESTINY-Breast01 trial- Baseline characteristics

Characteristic	Trastuzumab deruxtecan 5.4mg/kg (N=184)
Age, median (range), years	55.0 (28.0-96.0)
Female, n (%)	184 (100)
ECOG 0 or 1, n (%)	183 (99.5)
Patients with metastatic disease, n (%)	172 (93.5)
Median no. of previous regimens (range) (excluding hormone therapy)	**6 (2-24)**
≥3 prior therapies (excluding hormone therapy)	**167 (90.8)**
Previous systemic cancer therapy, n (%) Trastuzumab Trastuzumab emtansine Pertuzumab Other anti-HER2 therapy Hormone therapy Other systemic therapy	 184 (100) 184 (100) 121 (65.8) 100 (54.3) 90 (48.9) 183 (99.5)
Complete/partial response to prior trastuzumab emtansine therapy, n (%)	40 (21.7)

Source: Table 7, Document B, company submission

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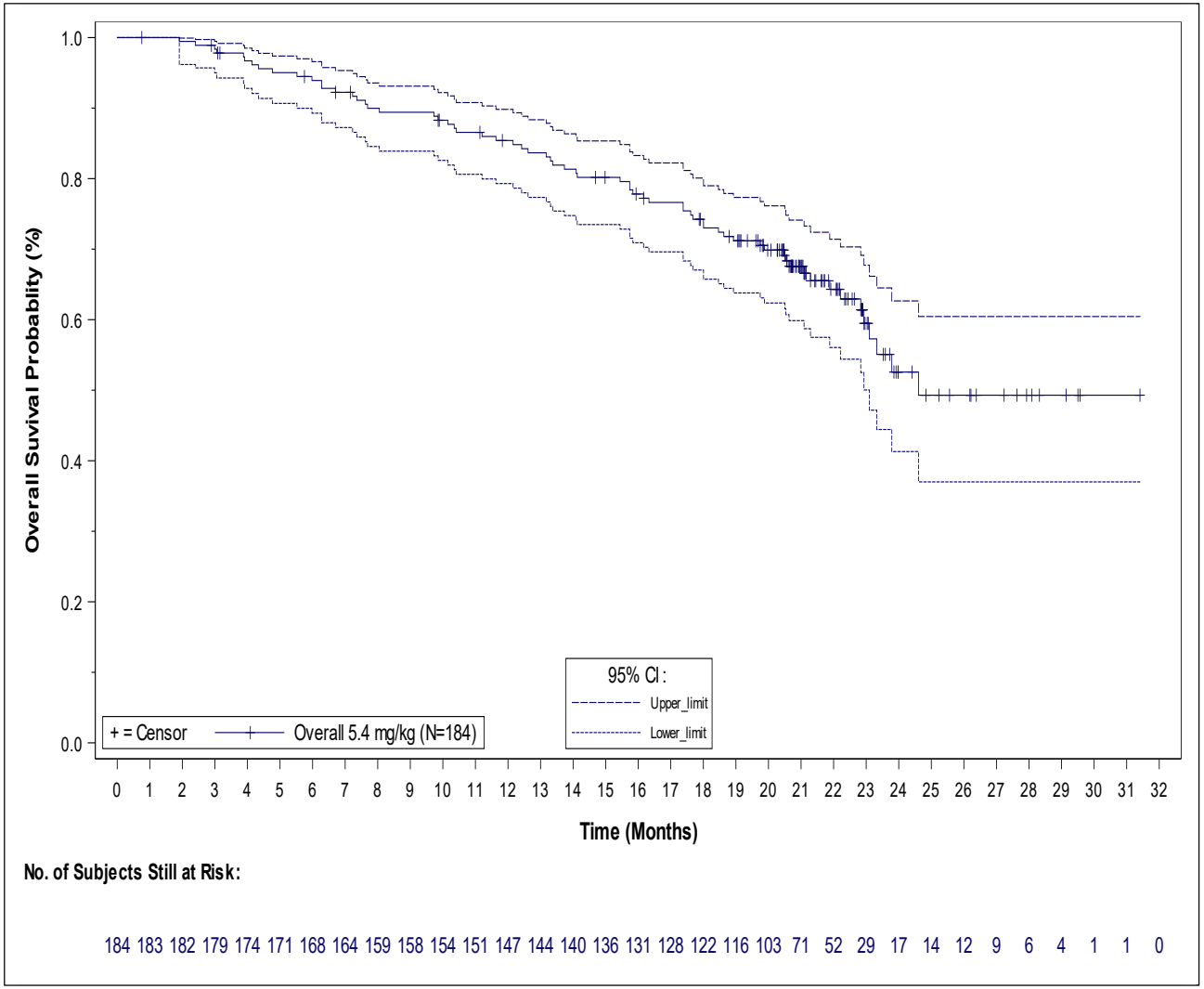
Clinical trial evidence – DESTINY-Breast01

Primary endpoint	Trastuzumab deruxtecan (N=184)
Overall response rate (ORR), n (% [95% CI])	113 (61.4 [redacted]
Complete response, n (%)	12 (6.5)
Partial response, n (%)	101 (54.9)
Stable disease, n (%)	66 (35.9)
Progressive disease, n (%)	[redacted]
Not evaluable, n (%)	[redacted]

Evidence based on the June 2020 data cut. CI: Confidence Interval

- ORR is the primary endpoint in DESTINY-Breast01 trial
- Independent central review-assessed by 2 independent radiologists, with adjudication as needed by a 3rd independent radiologist
- ORR: proportion of subjects who achieved a best overall response of complete response (no detectable evidence of tumour) or partial response (decrease in tumour size) based on RECIST 1.1.

DESTINY-Breast01: Overall survival

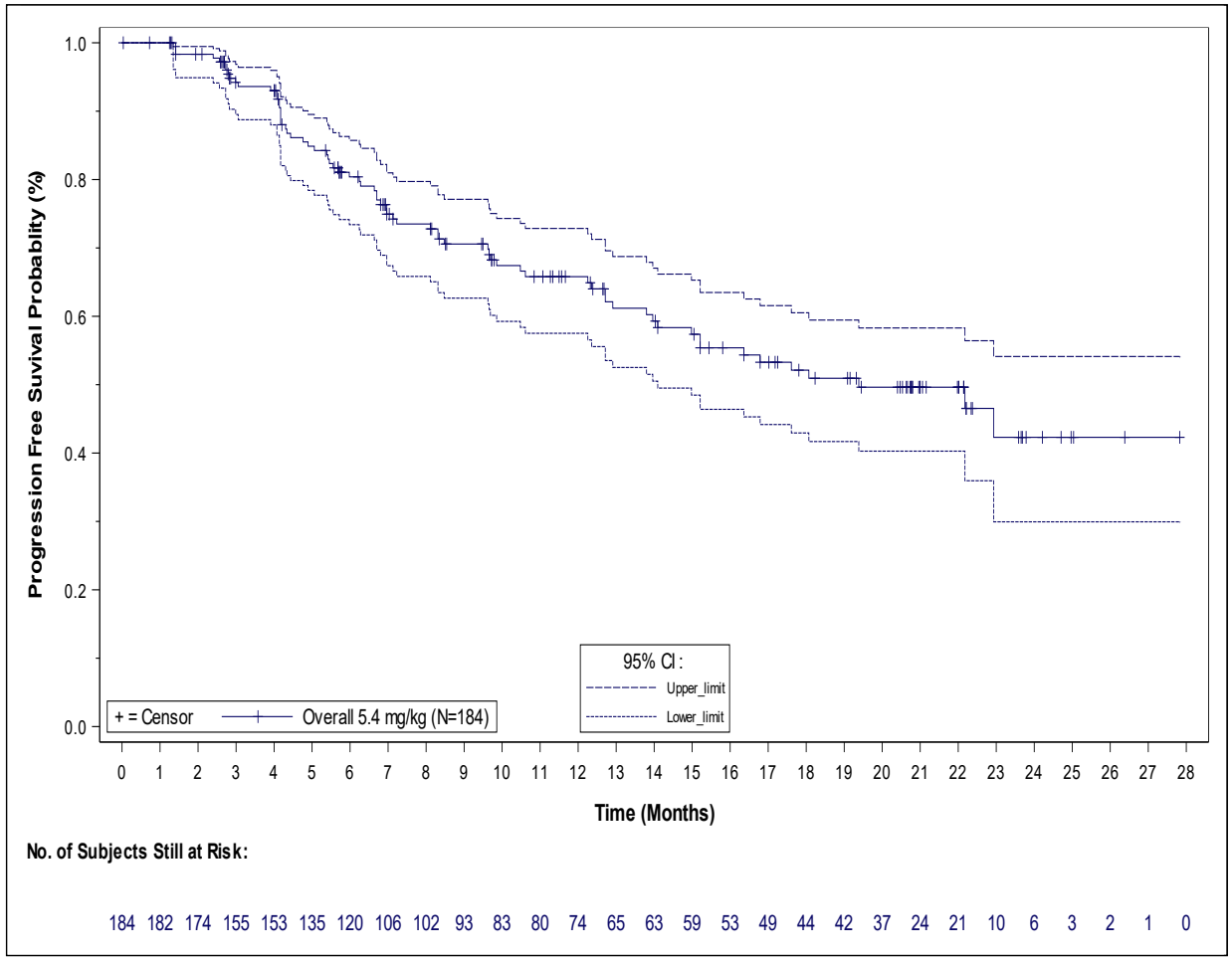


Endpoint	Trastuzumab deruxtecan (N=184)
Preliminary median OS, months (95% CI)	**24.6 (23.1, NE)**
Events	[redacted]
Censored, n (%)	119 (64.7)

- Median follow-up 20.5 months [range, 0.7 to 31.4]
- Data for 119 patients were censored
- **Median OS data are preliminary, estimated at 35% maturity.**
- High number of censoring from **20 months onwards**
- Dashed lines indicate 95% CI

Source: Figure 3 from company addendum, **June 2020 data cut**

DESTINY-Breast01: Progression-free survival



Endpoints	Trastuzumab deruxtecan (N=184)
Median PFS, months (95% CI)	**19.4 (14.1, NE)**
Events, n (%)	[redacted]
PD, n (%)	[redacted]
Death, n (%)	[redacted]
Censored, n (%)	114 (62.0)

- Median follow-up 20.5 months [range, 0.7 to 31.4]
- Data for **114** patients were censored
- Disease progression was assessed with the use of the modified RECIST version 1.1.
- The dashed lines indicate the 95% CI

Source: Figure 2 from company addendum, **June 2020 data cut**

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Clinical evidence - safety

Type of treatment-emergent adverse event (TEAE), n (%)	DESTINY-Breast01 (N=184)
TEAEs	183 (99.5)
Drug-related TEAEs	[redacted]
TEAEs Grade ≥3	113 (61.4)
Drug-related TEAEs Grade ≥3	[redacted]
Most common TEAEs Grade ≥3	
Decreased neutrophil account	[redacted]
Neutropenia	[redacted]
Anaemia	[redacted]
Nausea	[redacted]
Interstitial lung disease (ILD)*	28 (15.2)
Grade 3	[redacted]
Grade 5	5 (2.7)

Evidence based on the June 2020 data cut. *adjudicated by independent committee

- Clinical experts considered the safety profile to be acceptable
- Patients considered side effects to be the main disadvantage of the treatment (Breast Cancer Now)
- Company noted that education and close monitoring for signs and symptoms of ILD recommended for early detection

Issue 1: DESTINY-Breast01 is a single arm trial
Issue 2: The evidence is still immature

Background

- DESTINY-Breast01 is **a single-arm trial** – no direct comparative evidence and data **immature**

Company response to TE - June 2020 data cut off

- median follow-up 20.5 months
- median PFS 19.4 (95% CI, 14.1, NE) months
- **median OS 24.6** (95% CI, 23.1, NE) months **(35% maturity**; [redacted])
- ORR 61.4% (95% CI, [redacted])

ERG

- Available OS immature
- **No alternative dataset** for long-term results or direct comparative evidence for trastuzumab deruxtecan
- In absence of mature survival data and comparative evidence, the cost effectiveness **results are not robust**

Clinical expert

- TH3RESA, SOPHIA, NALA, HER2CLIMB are RCTs for other agents (trastuzumab emtansine, margetuximab, neratininb, tucatinib) - provide treatments efficacy benchmark in this setting
- Control arms were combination of chemotherapies and anti-HER2 therapies, efficacy expected to be as high (and likely higher) than chemotherapies alone
- **Efficacy for control arms** in these trials:
  - median PFS 3.3 to 5.6 months
  - median OS 15.8 to 19.8 months
  - ORR 9% to 26.7%
- DESTINY-Breast01: **only 21.7% achieved response to prior trastuzumab emtansine** - highly unlikely that high activity of trastuzumab deruxtecan result of patient selection

Issue 3: Generalisability of DESTINY-Breast01 to UK clinical practice

Background

- Trastuzumab deruxtecan to be used after 2 prior lines of anti-HER2 therapies
- DESTINY-Breast01; **most patients received ≥3 prior therapies** (median of 6 prior, range 2 to 24)
- Over half of patients received anti-HER2 therapies that are not currently recommended by NICE
- At technical engagement, company highlighted that **overall response rate** is **higher in the subgroup of people who only had 2 prior lines** compared with those with greater than two previous therapies; 76% (95% CI 50-93%; n=17 patients) versus 59% (95% CI 51-67%; n = 167 patients)

ERG

- Most patients in the NHS unlikely to receive six lines of treatment
- Generalisability unclear

Clinical expert

- **Trial population reflects the UK practice** in terms of characteristics and pre-treatment
- Patients received more prior anti HER2-targeted than currently in the NHS
- **Trastuzumab deruxtecan efficacy might even be higher in the NHS than in trial** if patients have received fewer lines of HER2-targeted therapy

Matching-adjusted indirect comparison - MAIC

- In absence of direct comparative evidence, an indirect treatment comparison was conducted to assess the comparative efficacy of trastuzumab deruxtecan versus comparators
- Studies are compared using an **unanchored MAIC**, to adjust for between-trial differences in baseline characteristics
- The patient population of the intervention study is re-weighted to match the population of the comparator study in terms of **prognostic factors and effect modifiers**.
- NICE DSU Technical Support Document 18: For an unanchored indirect comparison, population adjustment methods should adjust for **all** effect modifiers and prognostic variables

Matching factors adjusted for	Matching factors not adjusted for
• Number of lines of prior therapy • Hormone receptor status • Visceral disease • Age • ECOG-PS • Brain metastases • Prior endocrine therapy	• Comorbidities (not reported in comparator studies) • Number of metastatic sites (not collected in DESTINY-Breast01 trial) • **HER2 status** (not possible to adjust - 100% of patients in DESTINY-Breast01 were HER2+) • **Prior anti-HER2 therapy** (not possible to adjust - 100% of patients in DESTINY-Breast01 had received prior anti-HER2 therapy)

Matching-adjusted indirect comparison – MAIC results

Comparator	Study	Hazard ratio (95% CI) trastuzumab deruxtecan vs. comparator	
		OS	PFS
Eribulin	**Cortes 2011**	[redacted]	[redacted]
	Barni 2019	[redacted]	[redacted]
	Cortes 2010	[redacted]	[redacted]
	Gamucci 2014	[redacted]	[redacted]
Capecitabine	Fumoleau 2004	[redacted]	[redacted]
	Blum 2001	[redacted]	[redacted]
	EGF100151 Study*	[redacted]	[redacted]
Vinorelbine	**Sim 2019 (KCSG BR11-16)**	[redacted]	[redacted]

Source: Table 3 from addendum, June 2020 data cut, *added with company's response to TE

MAIC results show trastuzumab deruxtecan associated with **improved OS and PFS but limitations**:

- Studies conducted in broad patient populations (HER2+, mixed or unknown HER2 status)
- Few published data for comparators used solely in HER2+ disease: only **Sim 2019 (vinorelbine)** and **EGF100151 Study (capecitabine)**
- **MAICs** results **inform PFS** in the cost-effectiveness model
- **Proportional hazards assumption may be violated** for
  - OS in the capecitabine MAIC (issue 4) and PFS in the vinorelbine MAIC (issue 5)
  - Company fitted accelerated failure time parametric models to weighted data
- MAICs for ORR inform estimates of utilities for cost-effectiveness model
- Following clinical expert feedback, an alternative approach was taken to modelling OS (issue 6)

Issue 4 : Can the comparative effectiveness of trastuzumab deruxtecan be robustly assessed against comparators? (1)

Background

- **Eribulin** trials were not wholly conducted in HER2-positive patients who had received ≥2 anti-HER2 therapy

Response to TE

- Eribulin not a HER2-targeted therapy
- Additional data are therefore unlikely to become available in the HER2-positive subgroup
- MAIC vs eribulin has not been updated after TE

ERG

- HER2+ status and prior anti-HER2 therapy the most important variables to adjust for
- Company couldn't adjust for these factors in initial MAIC
- ERG considered MAIC vs eribulin not suitable for decision-making

Issue 4 : Can the comparative effectiveness of trastuzumab deruxtecan be robustly assessed against comparators? (2)

Background

- Initial company submission: **Capecitabine** trials were not wholly conducted in HER2-positive patients who had received ≥2 anti-HER2 therapy

New MAIC (post TE) for trastuzumab deruxtecan versus capecitabine:

- Company **identified EGF100151,** RCT of **capecitabine** vs lapatinib+capecitabine in a HER2-positive population who received ≥2 prior therapies (at least **one** anti HER2)
- Company updated MAIC with this trial and also fitted accelerated failure time parametric models, which showed **significant improvement in OS and PFS** with trastuzumab deruxtecan versus capecitabine

ERG

- Study **EGF100151 is more relevant to this appraisal**
- Still some **uncertainty in the new MAIC vs capecitabine:**
  - Conducted in population who had received at **least one prior anti-HER2 therapy**
  - ideally, results from patients who had received **at least 2 anti-HER2 therapies** should have been included in analysis
  - Only patients who did not cross over were included (i.e. excluded 36 patients who did crossover - **selection bias)**
  - Number of patients included in the analysis is unclear

Issue 4: Can the comparative effectiveness of trastuzumab deruxtecan be robustly assessed against comparators? (3)

Background

- Company conducted the MAIC of trastuzumab deruxtecan versus **vinorelbine** using the KCSG BR11-16 trial, conducted in a **population that matched the population of the scope**
- To use the HR derived from the MAIC, the proportional hazard (PH) assumption is required
- The PH assumption was violated for PFS
- For PFS, company conducted analyses using **accelerated failure time** parametric models; trastuzumab deruxtecan was shown to be associated with **statistically significantly longer PFS**
- Company noted that the **OS results** from KCSG trial are **inconsistent** with results from other studies – this may be due to subsequent treatment following progression

ERG

- Considers that the KCSG trial is **informative**
- Considers that using a **HR to summarise the relative OS** for trastuzumab deruxtecan versus vinorelbine is **acceptable**
- However, ERG notes that **concerns remain** about some covariates no being adjusted for (age, comorbidities, brain metastases, number of metastatic sites, prior hormone therapy, prior anti-HER2 therapies)

Key clinical issues

- Issue 1 : The evidence available for trastuzumab deruxtecan is from a single-arm trial
- Issue 2: The evidence available for trastuzumab deruxtecan is still immature
- Issue 3: Is the population included in the DESTINY-Breast01 trial broadly representative of patients treated in UK clinical practice?
- Issue 4: Can the comparative effectiveness of trastuzumab deruxtecan be robustly assessed against the comparators in the scope given the differences in trial populations and lack of evidence?

Key cost effectiveness issues

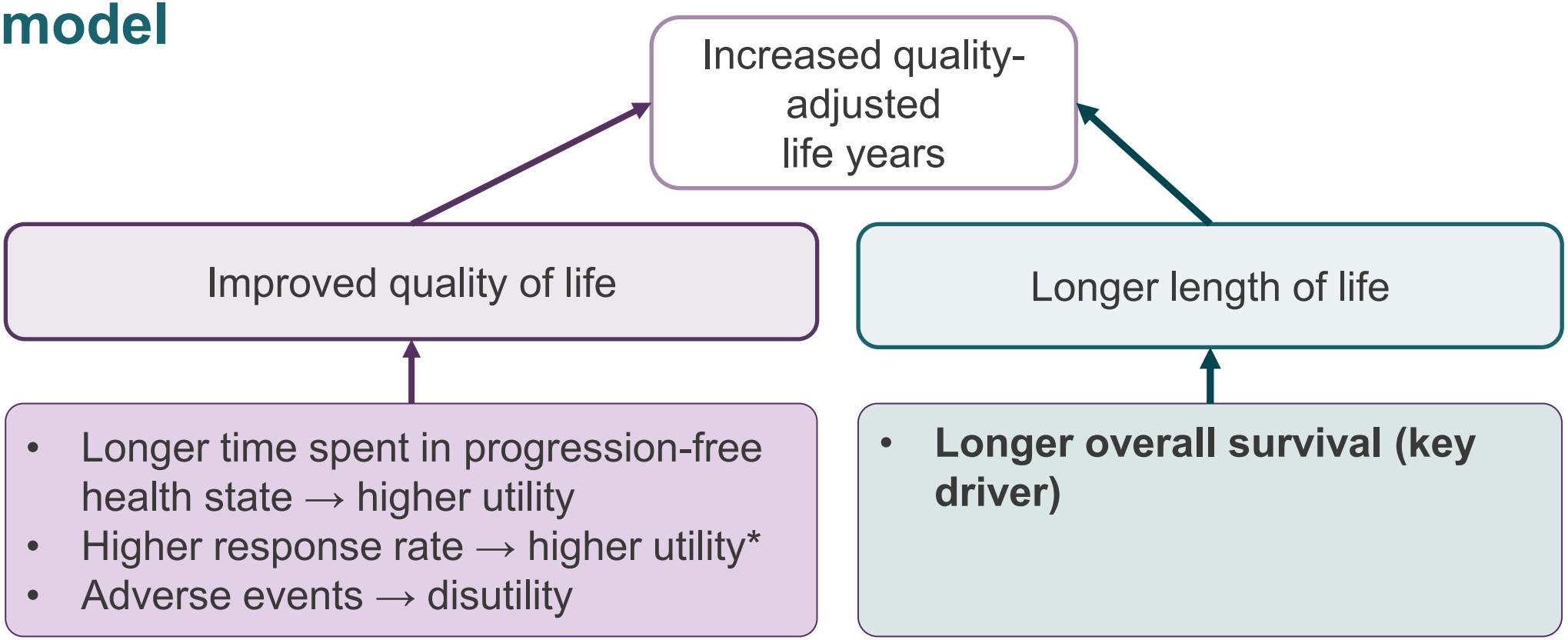
- Issue 6: To model trastuzumab deruxtecan overall survival, the company based its approach on the OS data of trastuzumab emtansine from the TH3RESA trial
  - Is it reasonable to assume that trastuzumab deruxtecan and trastuzumab emtansine survival curves would have the same shape?
  - Does this approach result in realistic estimates of long-term OS for trastuzumab deruxtecan ?
- Issue 7: OS for comparators is modelled using the comparators trial data directly which is a naïve comparison
  - Is it reasonable to assume that the survival curves shape of trastuzumab deruxtecan and comparators would be different and that a hazard ratio cannot be applied?
  - Does this approach result in realistic estimates long-term OS for comparators?
- Issue 8: Does trastuzumab deruxtecan meet NICE end of life criteria?
- Can trastuzumab deruxtecan be considered a cost-effective use of NHS resources?

Company's model

Model type	Partitioned survival model (progression-free on treatment, progression-free off treatment, progressed, death)
Population	Individuals with HER2-positive, unresectable or metastatic breast cancer who have received two or more prior anti-HER2 therapies
Intervention	Trastuzumab deruxtecan
Comparator	Eribulin, capecitabine and vinorelbine
Time horizon	40 years
Model cycle	1 week
Discount rates	3.5% for both health and cost outcomes
Utility values	Utility values from TA423 (eribulin) and adjusted for response
Costs	- Treatment costs: eMIT and BNF - Resource use: NHS reference costs, PSSRU Unit Cost - Wastage costs: 50% assumed in base case
Perspective	NHS and PSS

eMIT: Drugs and pharmaceutical electronic market information tool; BNF: British National Formulary, PSSRU: Personal Social Services Research Unit, PSS: Personal Social Services . Source: company document B

How quality-adjusted life years accrue in company's model



*Progression-free, on-treatment utility values calculated as function of overall response rate

Clinical expert: In metastatic breast cancer, clear link between objective response (can be associated with symptoms improvement), PFS (associated with delay or prevention of symptoms and/or QALY deterioration) and treatment-emergent adverse events

Company survival modelling

Estimates		Source and assumptions	Company's rationale
OS	**Trastuzumab deruxtecan (Issue 6)**	Estimated **OS of trastuzumab deruxtecan by estimating OS HR versus trastuzumab emtansine** (from the TH3RESA trial) TH3RESA: RCT of trastuzumab emtansine versus physician choice, in patients with HER2-positive advanced breast cancer with progression on ≥2 HER2-targeted regimens	DESTINY-Breast01 OS too immature to extrapolate. Assumed similarity of shape of the trastuzumab deruxtecan and trastuzumab emtansine OS curves
	Comparators (Issue 7)	**Naïve comparison of trastuzumab deruxtecan vs comparators** (OS from comparators studies used directly*) OS vinorelbine equivalent to capecitabine	MAIC results not suitable; OS curve shape would be different between trastuzumab deruxtecan and non-targeted comparators
PFS	**Trastuzumab deruxtecan**	Extrapolated from DESTINY-Breast01 trial	-
	Comparators	MAIC HRs applied to T-DXd PFS curve*	-
TTD	**Trastuzumab deruxtecan**	Extrapolated from DESTINY-Breast01 trial	-
	Comparators	Treatment to progression assumed	TTD data not available

***For eribulin PFS and OS, adjustment applied to account for HER2+ status**

HR: hazard ratio, TTD: Time to treatment discontinuation

Issue 6: Company OS modelling of trastuzumab deruxtecan

Background

Company

- OS data from DESTINY-Breast01 trial **too immature** to use in the model
- OS data from **trastuzumab emtansine** arm of the **TH3RESA trial is used** as the basis for OS modelling
- **HR of trastuzumab deruxtecan** (based on DESTINY-Breast01 OS data) **versus trastuzumab emtansine** (based on TH3RESA OS data) is calculated
- Rationale based on clinical expert advice to company that trastuzumab emtansine **curve shape will be similar** to trastuzumab deruxtecan (both HER2-targeted therapies)

Clinical expert

- Clinical expert agrees OS is immature but **estimated OS rates of 82.6%** at 12 months compare very favourably with median OS of 15-19 months in other phase 3 trials in this setting, in less heavily pre-treated patients

ERG

- agrees DESTINY-Breast01 OS is still too immature to provide robust long-term OS estimates
- The corresponding ICERs are **not implausible but highly uncertain**
- ERG: modelling leads to **optimistic OS estimates** (estimated OS at 20 months is 75% versus 70% in the DESTINY-Breast01 trial
- ERG **hasn't identified any alternative approach** to generate more robust analysis

Issue 6: Scenario - Extrapolation of DESTINY-Breast01 OS

- Response to technical engagement: company ran exploratory scenario directly extrapolating June 2020 OS data from DESTINY-Breast 01 trial and compared against base case
- Kaplan Meier data to 20.5 months were used (substantial censoring beyond this)
- Company clinical advice - an average of Weibull (implausibly low) and exponential (implausibly high) curves represents the best estimate of long-term survival

Source: Company response to TE, Figure 3

ERG and company consider DESTINY-Breast01 OS is still too immature to extrapolate and provide robust long-term OS estimates

Issue 7: Company OS modelling of comparators

Background

Company

- **Naïve comparison** using **Kaplan-Meier data from comparator studies directly** and not MAIC results
- Rationale: company expert opinion that the **shape of OS** curve would be **different** between trastuzumab deruxtecan and comparators (a tail may be expected for trastuzumab deruxtecan, as observed for other antibody-drug conjugates)
- The only **alternative** would be to **use the MAIC results** however :
  - MAIC is not appropriate because the shape of OS curves would be different
  - the inability to adjust for differences in baseline characteristics results in a conservative estimate of relative trastuzumab deruxtecan efficacy (adjusting for baseline characteristics in the MAIC results in improved HR)

Clinical expert

- Although there are limitations with OS comparator modelling, results compare well with data from control arms of other recent RCT in same setting (TH3RESA, SOPHIA, NALA, HER2CLIMB)

ERG

- Approach is a **naïve comparison** - not adjusted for patient characteristics (not robust)
- But **MAIC has limitations too**
- Relative effectiveness cannot be determined with any degree of certainty

Issue 8: Does trastuzumab deruxtecan meet NICE end of life criteria?

Both criteria must be met:

1. Treatment is indicated for patients with a short life expectancy, normally less than 24 months
2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

- estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either PFS or OS
- assumptions used in the reference case economic modelling are plausible, objective and robust

Company

- All comparators studies suggest life expectancy <24m
- **EOL accepted for:**
  - Eribulin in 3rd line metastatic breast cancer TA423 (mean modelled OS of 13.53 months for treatment of physician's choice and 16.92 months for eribulin)
  - Trastuzumab emtansine in 2nd line TA458
- Upper bound comparator OS: 19 months, lower bound for trastuzumab deruxtecan: 23.1 months - OS increase >3 months
- Company modelled increase in mean survival are [redacted], [redacted] and [redacted] months compared with eribulin, capecitabine and vinorelbine, respectively

Clinical expert

- **Life expectancy is <24 months** even after trastuzumab emtansine – median OS in TH3RESA was 15.8 months

ERG

- unclear whether life expectancy of patients progressing **after T-DM1 as 2nd line** is <24 months
- OS gain **could** exceed 3 months but currently **highly uncertain** without more robust comparative OS data

Summary of company's cost effectiveness analyses

Company's base case updated after technical engagement
DESTINY-Breast01 June 2020 data cut, OS censored at 20.5 months
TH3RESA OS extrapolated with generalised gamma
Company's secondary analyses
DESTINY-Breast01 June 2020 data cut, no censoring
TH3RESA OS extrapolated with exponential and gamma functions
Company's exploratory scenario
DESTINY-Breast01 June 2020 data cut, OS censored at 20.5 months
DESTINY-Breast01 OS extrapolated directly (average of Weibull and exponential)

- In all analyses, PFS is based on MAIC results, with MAIC vs capecitabine updated (use EGF100151 study following technical engagement)

Cost effectiveness results (include PAS)

- **Company's updated base case** following technical engagement

Technologies	Total costs (£)	Total QALYs	ICER incremental (£/QALY) Deterministic	Pairwise ICERs, trastuzumab deruxtecan vs comparator (£/QALY)	
				Deterministic	Probabilistic
Capecitabine	[redacted]	[redacted]	-	£47,230	£46,314
Vinorelbine	[redacted]	[redacted]	Extendedly dominated	£44,170	£43,330
Eribulin	[redacted]	[redacted]	Dominated	£35,833	£35,364
Trastuzumab deruxtecan	[redacted]	[redacted]	**£47,230**		

- **Secondary analyses** using the full OS Kaplan-Meier data (no censoring) and the exponential and gamma functions to extrapolate TH3RESA also conducted, resulted in an incremental ICER of £51,148 and £57,844 respectively

ERG - evidence base is too uncertain, cannot provide any robust alternative analyses

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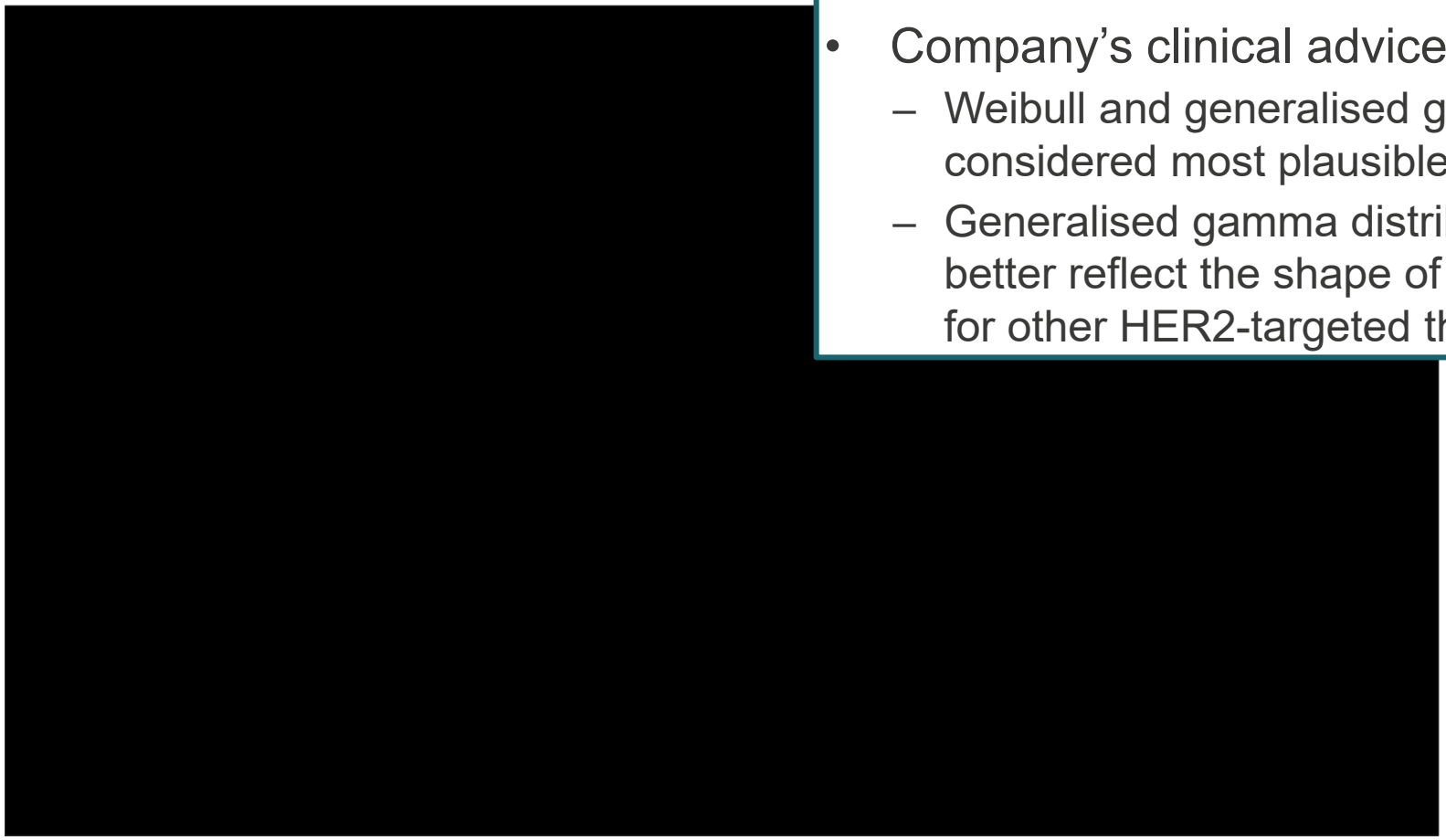
Source: Company's response to TE, Appendix E, table 19 and table 20

OS extrapolation: OS HR for trastuzumab deruxtecan applied to trastuzumab emtansine (TH3RESA)*

- Log-logistic had lowest AIC/BIC scores
- Company's clinical advice:
  - Weibull and generalised gamma distributions considered most plausible
  - Generalised gamma distribution considered to better reflect the shape of the OS curve observed for other HER2-targeted therapies



*OS HR for trastuzumab deruxtecan versus trastuzumab emtansine generated using a Cox proportional hazards model. Applied HR is from August 2019 data cut ([redacted], 95%CI, [redacted]); June 2020 HR (with trastuzumab deruxtecan OS censored at 20.5 months): [redacted], 95%CI, [redacted])
Source: Company submission figure 26 and table 70, and company addendum table 76.

Scenario analyses

- Estimates of 2 most influential parameters are varied:
  - OS HR of trastuzumab deruxtecan versus TH3RESA (censoring at 20.5 months) [redacted]
  - Distribution to extrapolate TH3RESA OS

ICERs for T-DXd vs capecitabine (deterministic, include PAS)			
OS distribution to extrapolate TH3RESA	OS HR (base case)	OS HR (lower value)	OS HR (upper value)
Company base case (generalised gamma)	£47,230	£38,607	£60,915
Log-normal	£34,453	£29,374	£43,156
Log-logistic	£35,536	£29,994	£45,163
Exponential	£42,213	£34,997	£53,730
Weibull	£53,485	£43,786	£68,653
Gompertz	£62,305	£52,088	£78,142

Direct extrapolation of DESTINY-Breast01 OS

Source: Company response to TE, Figure 2

Cost effectiveness results – exploratory scenario

- **Company's exploratory scenario (Issue 6)** – Trastuzumab deruxtecan OS trial results directly extrapolated (average of Weibull and exponential curves)

Technologies	Total costs (£)	Total QALYs	Pairwise ICER (£/QALY) Deterministic, include PAS
Capecitabine	[redacted]	[redacted]	£49,028
Vinorelbine	[redacted]	[redacted]	£45,816
Eribulin	[redacted]	[redacted]	£36,842
Trastuzumab deruxtecan	[redacted]	[redacted]	-

Source: Company's response to TE, table 4

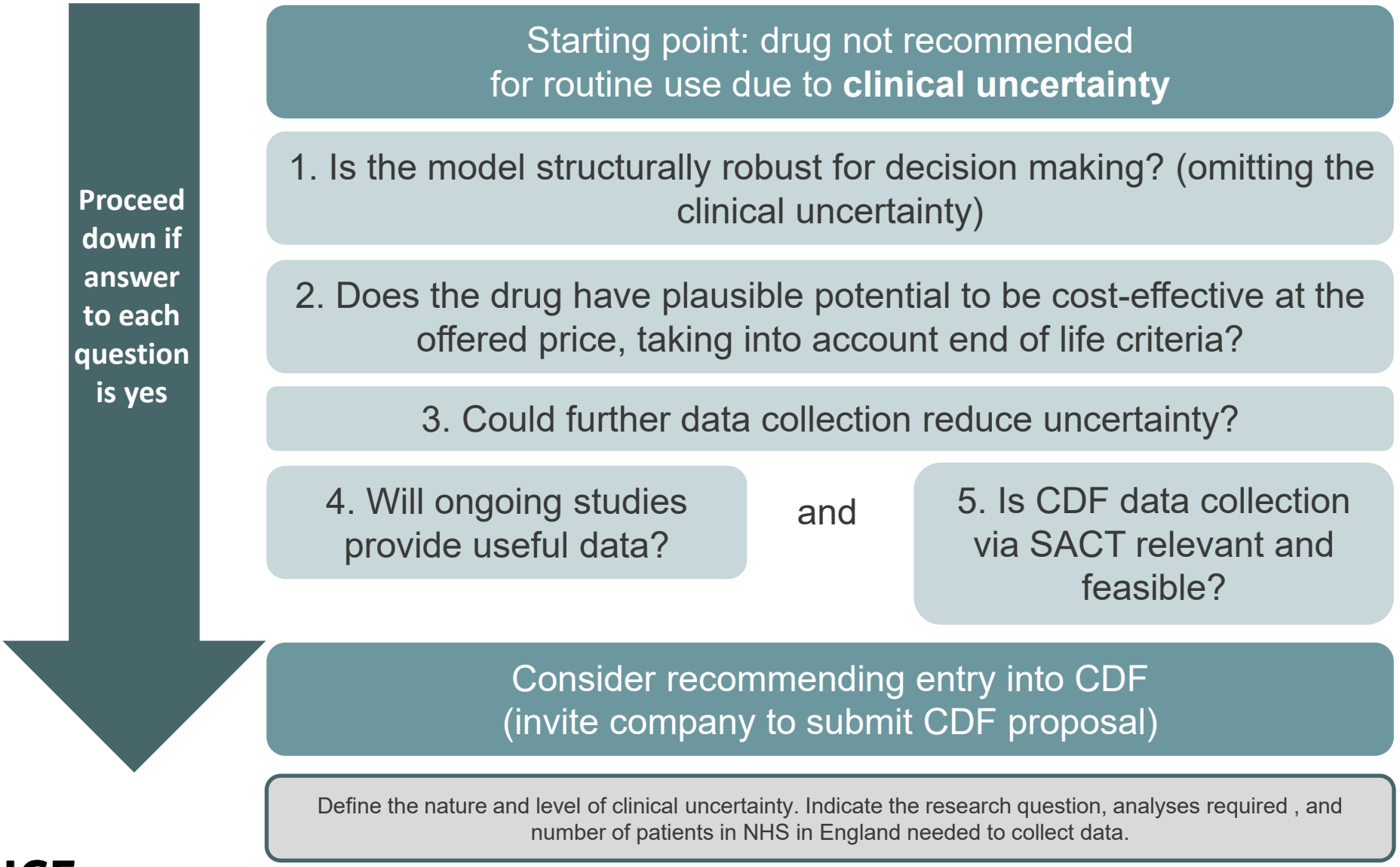
- Illustrative examples – Direct extrapolation of DESTINY-Breast01 OS

ICER T-DXd vs.	Gompertz	Weibull	Exponential	Log-logistic	Log-normal	Gen. gamma
Capecitabine	£68,379	£59,254	£43,151	£42,269	£38,892	£31,528
Vinorelbine	£63,816	£55,286	£40,437	£39,640	£36,560	£29,875
Eribulin	£47,515	£42,583	£33,474	£32,982	£30,965	£26,391

Key cost effectiveness issues

- Issue 6: To model trastuzumab deruxtecan overall survival, the company based its approach on the OS data of trastuzumab emtansine from the TH3RESA trial
  - Is it reasonable to assume that trastuzumab deruxtecan and trastuzumab emtansine survival curves would have the same shape?
  - Does this approach result in realistic estimates of long-term OS for trastuzumab deruxtecan ?
- Issue 7: OS for comparators is modelled using the comparators trial data directly which is a naïve comparison
  - Is it reasonable to assume that the survival curves shape of trastuzumab deruxtecan and comparators would be different and that a hazard ratio cannot be applied?
  - Does this approach result in realistic estimates long-term OS for comparators?
- Issue 8: Does trastuzumab deruxtecan meet NICE end of life criteria?
- Can trastuzumab deruxtecan be considered a cost-effective use of NHS resources?

Committee decision making: CDF recommendation criteria



NICE

Ongoing study – DESTINY-Breast02 trial

- DESTINY-Breast02 trial - **Ongoing randomised controlled trial** of trastuzumab deruxtecan vs trastuzumab+capecitabine or lapatinib+capecitabine (NCT03523585)
- Estimated dates (source: Clinicaltrial.gov)
  - primary completion: February 2022
  - study completion: September 2024
- What data will be available in February 2022? (mature PFS, mature OS?)

- Estimated completion date for DESTINY-Breast01 trial: March 2021

Innovation and Equality

- **Innovation**: Clinical expert consider trastuzumab deruxtecan to be a step-change in the improvement of clinical outcomes and the management of patients with HER2-positive metastatic breast cancer who have received 2 or more prior anti-HER2 therapies

- **Equality issues**: None raised

Back-up slides

DESTINY-Breast01: Waterfall plot of change from baseline in tumour size

Source: Figure 1 company addendum, Data-cut: June 8, 2020

[redacted]

The upper horizontal line indicates a 20% increase in tumour size in the patients who had disease progression, and the lower line indicates a 30% decrease in tumour size (partial response).

Clinical trial evidence – DS8201-A-J101

Study design	Phase I, open-label, dose-escalation and dose-expansion study
Population	Adults with HER2+, unresectable BC or mBC who had received previous treatment with trastuzumab emtansine
Intervention	T-DXd evaluated at a dose of 5.4 mg/kg or 6.4 mg/kg
Comparator	No comparator
Outcomes	Progression free survival Overall survival Adverse events Objective response rate Duration of response

Clinical trial evidence – DS8201-A-J101

	T-DXd 5.4 mg/kg (N=49) or 6.4mg/kg (N=66) (overall N=115)
Evaluable for confirmed response	111 (97%)
Confirmed objective response	66 (59.5%; 95% CI: 49.7, 68.7)
Confirmed disease control (median follow-up of 9.9 months)	104 (93.7%)
Median PFS, months (95% CI)	22.1 months (95% CI: NE*)
Median OS	(95% CI: NE*). Not reached
Median time to response (TTR)	1.6 months (95% CI: 1.4, 2.8)
Median duration of response (DoR)	20.7 months (95% CI: NE*)
Tumour shrinkage	102 (93%) of 110 patients
By first 6-week post baseline tumour assessment	91 (89%)

*NE: Not evaluable

Clinical evidence - safety

Type of TEAE, n (%)*	DESTINY-Breast01 T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)	DS8201-A-J101 T-DXd 5.4mg/kg (N=49)
TEAEs	183 (99.5)	49 (100%)
Drug-related TEAEs	[redacted]	48 (98%)
TEAEs Grade ≥3	113 (61.4)	19 (39%)
Drug-related TEAEs Grade ≥3	[redacted]	
Serious TEAEs	[redacted]	8 (16%)
Drug-related serious TEAEs	[redacted]	4 (8%)
TEAEs leading to T-DXd discontinuation	34 (18.5)	2 (4%)
Drug-related TEAEs leading to T-DXd discontinuation	[redacted]	2 (4%)
TEAEs leading to dose reduction	[redacted]	4 (8%)
Drug-related TEAEs leading to dose reduction	[redacted]	3 (6%)
TEAEs leading to dose interruption	[redacted]	14 (29%)
Drug-related TEAEs leading to dose interruption	[redacted]	9 (18%)
TEAEs leading to death	10 (5.4)	NR
Drug-related TEAEs leading to death	[redacted]	NR

* TEAE relationship to study drug was determined by the treating investigator

NICE

Matching-adjusted indirect comparison - MAIC

Comparator	Study	Odds ratio (95% CI) T-DXd vs. comparator
		ORR
Eribulin	Cortes 2011	[redacted]
	Barni 2019	[redacted]
	Cortes 2010	[redacted]
	Gamucci 2014	[redacted]
Capecitabine	Fumoleau 2004	[redacted]
	Blum 2001	[redacted]
	EGF100151 Study (added at technical engagement	[redacted]
Vinorelbine	Sim 2019 (KCSG BR11-16)	[redacted]

OS extrapolation of TH3RESA trial

Source: Company model