Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy (ID3935)

Technology appraisal committee A [7 November 2023]

For **Public** – contains redacted ■ information (PART 1 only)

Chair: Radha Todd

External assessment group: ScHARR

Technical team: Catherine Spanswick, Claire Hawksworth, Janet Robertson

Company: Daiichi Sankyo

Treatment pathway for HER2-negative mBC

Trastuzumab deruxtecan (T-DXd) after chemotherapy

	HR+	HR-
1L	• Anthracyclines or docetaxel (CG81) • Gemcitabine + paclitaxel (TA116)	• Atezolizumab + nab-paclitaxel (TA639)* • Pembrolizumab + chemotherapy (paclitaxel or nab-paclitaxel; TA801)*
2L	• Vinorelbine or capecitabine (CG81) • **Trastuzumab deruxtecan?**	• Sacituzumab govitecan (TA819)**
3L	• Vinorelbine or capecitabine (CG81)*** • Eribulin (TA423) • **Trastuzumab deruxtecan?**	• Sacituzumab govitecan (TA819)**

Draft guidance conclusions:

- Treatment options for HER2-negative mBC after chemotherapy are relevant
- Positioning of T-Dxd at 2L and 3L is appropriate
- T-Dxd is not recommended: most likely cost-effectiveness estimates above the range NICE considers an acceptable use of NHS resources

NICE

*PD-LI+ disease only; **after ≥2 systemic therapies, 1 for advanced disease; ***whichever was not used at 2nd line; TA639, TA801 and TA819 in triple negative disease; 1L/2L/3L, first/second line/third line; CG, clinical guideline; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; TA, technology appraisal; T-DXd, trastuzumab deruxtecan

Draft guidance: consultation comments (1/2)

Patient organisation comments received from METUPUK and Breast Cancer Now:

- Severity modifier not flexible enough to capture impact of this devastating disease
  - If 1.2XQALYs is applied to ICER threshold, gives £36,000/QALY gained, but treatments meeting end of life criteria under old NICE methods were eligible for a maximum ICER of £50,000/QALY gained
- NICE methods do not take into personal circumstances of patients – people who work and are carers for young children, grandchildren and elderly parents
- Unmet need – trastuzumab deruxtecan is the only drug shown to increase median OS and PFS in a phase 3 clinical trial for patients with HER2-low metastatic breast cancer

~270 web comments from patients, carers and other commentators, across 6 main themes:

• **Impact of condition** in women, many of whom work and care for young children or for parents	• **Lack of treatment options** in secondary low HER-2 BC, a new BC subtype	• **T-Dxd is recommended** by NICE in HER-2 positive BC; is US/EU approved in low HER-2 BC
• **Clinical evidence** clearly shows treatment is effective (OS nearly 2 years and improved PFS)	• **Extra line of therapy** in TNBC, T-Dxd is an alternative to sacituzumab govitecan	• **Committee decision** is based on cost alone, patient voice is given too little value

Abbreviations: BC, breast cancer; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire; HER2, human epidermal growth factor receptor 2; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TNBC, triple-negative breast cancer; TPC, treatment of physician choice

Draft guidance: consultation comments (2/2)

Company (Daiichi Sankyo) provided an updated base case with a new PAS and new model with requested scenario analyses:

- Base case reflects post hoc analysis of DESTINY-Breast04 – "DB-04 NHS" cohort
  - Patients in both arms assigned to gemcitabine and 2L eribulin pre-randomisation have been reallocated (committee preference)
  - This new cohort used for efficacy data and utility values
  - New cohort population does not change any of company's preferred distributions
- For progression-free utilities, updated base case uses linear mixed model (EAG preference)
- Corrected treatment administration costs applied (noted by CDF Lead)ǂ

Company maintains that 1.2xQALY severity modifier underestimates severity of the condition

Considers there are uncaptured benefits (DESTINY trial): QALY does not capture statistically significant delay in time-to-definitive deterioration in EORTC QLQ-C30 domains of body image, sexual function, and social functioning for T-DXd vs TPC

ǂ Updated costs have been provided

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire; HER2, human epidermal growth factor receptor 2; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TPC, treatment of physician choice

Equality considerations

- Concern that absolute shortfall in severity modifier calculation discriminates against protected characteristic of age and proportional shortfall does not adequately reduce this impact
- Commentators on draft guidance note the impact of the condition in younger women, many of whom work and care for young children or for parents

Key issues remaining at ACM2

ICER impact key: Large or medium, Small, Unknown

Key issues following consultation on draft guidance: focus of ACM2 discussion

Key issues for discussion	**Resolved?** Company approach at ACM2
TPC modelling	**Yes:** DB-04 NHS cohort reflects NHS clinical practice, but has some limitations. *Updated approach impacts all key issues informing the ICERs for T-Dxd vs TPC
OS extrapolation used* → **Large ICER impact**	**Partially**: Cohort used, but company and EAG disagree on extrapolation for T-Dxd arm
PFS extrapolation used* → small ICER impact	**Partially**: Cohort used, but company and EAG disagree on extrapolation of both arms
TTD extrapolation used* → small ICER impact	**Partially**: Cohort used, but company and EAG disagree on extrapolation for T-Dxd arm
PP utilities modelling* → medium ICER impact	**Partially**: company and EAG disagree on model used, differential benefit after progression is reduced
Uncertainty in comparison vs sacituzumab govitecan	**No**: EAG disagrees with company that equivalent efficacy can be assumed. Uncertainty remains.

ICER above impacts refer to difference vs company when applying approach preferred in EAG base case

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Abbreviations: ACM2, 2nd appraisal committee meeting; ITC, indirect treatment comparison; OS, overall survival; PF(S), progression-free (survival); PP, post-progression; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice; TTD, time-to-treatment discontinuation

Key issue: TPC modelling

Cohort of DESTINY-Breast04 now used, reflecting TPC in NHS clinical practice

Background

- Committee: model TPC to reflect NHS clinical practice – exclude gemcitabine and 2L eribulin
- Company should justify its choice of survival distribution in the updated cohort

Company's consultation comments:

- "DB-04 NHS" cohort now used in revised base case
  - TPC arm distribution: [redacted] 3L eribulin, [redacted] capecitabine, [redacted] nab-paclitaxel, [redacted] paclitaxel
- Reflects post hoc analysis of DESTINY-Breast04 with reallocation of patients assigned to gemcitabine and 2L eribulin pre-randomisation (removes costs and effectiveness of gemcitabine and 2L eribulin from both treatment arms). Baseline characteristics similar to FAS population
- Implemented for OS, PFS and TTD extrapolations, and PF and PP utility calculations

Population	T-DXd, n	TPC, n
Cohort (N=365)	**247**	**118**
FAS (N=557)	373	184

EAG: Agrees → applies DB-04 NHS cohort to EAG base case

- Cohort has smaller sample size than FAS and more later-line treatment ([redacted] of T-Dxd arm and [redacted] of TPC arm had ≥2 lines prior chemotherapy in metastatic setting, vs [redacted] and [redacted] in FAS)

Is the committee satisfied that the DB-04 NHS cohort reflects NHS clinical practice?

Abbreviations: 2L, second line; FAS, full analysis set; OS, overall survival; PF(S), progression-free (survival); PP, post-progression; TPC, treatment of physician choice; TTD, time-to-treatment discontinuation

Key issue: OS extrapolation used for DB-04 NHS cohort (1/2)

Company prefers log-logistic extrapolation for OS for cohort

Background

- Company re-examined OS distributions for DB-04 NHS cohort (OS data mature)

Company's consultation comments:

- Log-logistic curve preferred in both arms – statistical fit, clinical plausibility
- 5-year OS estimate for T-DXd of [redacted] - Clinically plausible as clinical experts estimate TPC 5-year survival of 5–10%

OS	1-year	2-year	3-year	5-year	10-year
DB-04 NHS cohort: Log-logistic distribution					
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flatiron NHS cohort (N=507): observed Kaplan–Meier data					
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Aligns with RWE from Flatiron study – relevant to inform long-term extrapolations since HER2-low is a new disease classification lacking evidence on long-term outcomes with standard care
  - "Flatiron NHS cohort": [redacted] patients with HER2-low mBC who had 1 ([redacted]) or 2 ([redacted]) lines of prior chemotherapy in metastatic setting. Broadly comparable with DB-04 NHS cohort
- Weibull and gamma curves give highly pessimistic long-term estimates, particularly at 5 years where greatest clinical experience lies

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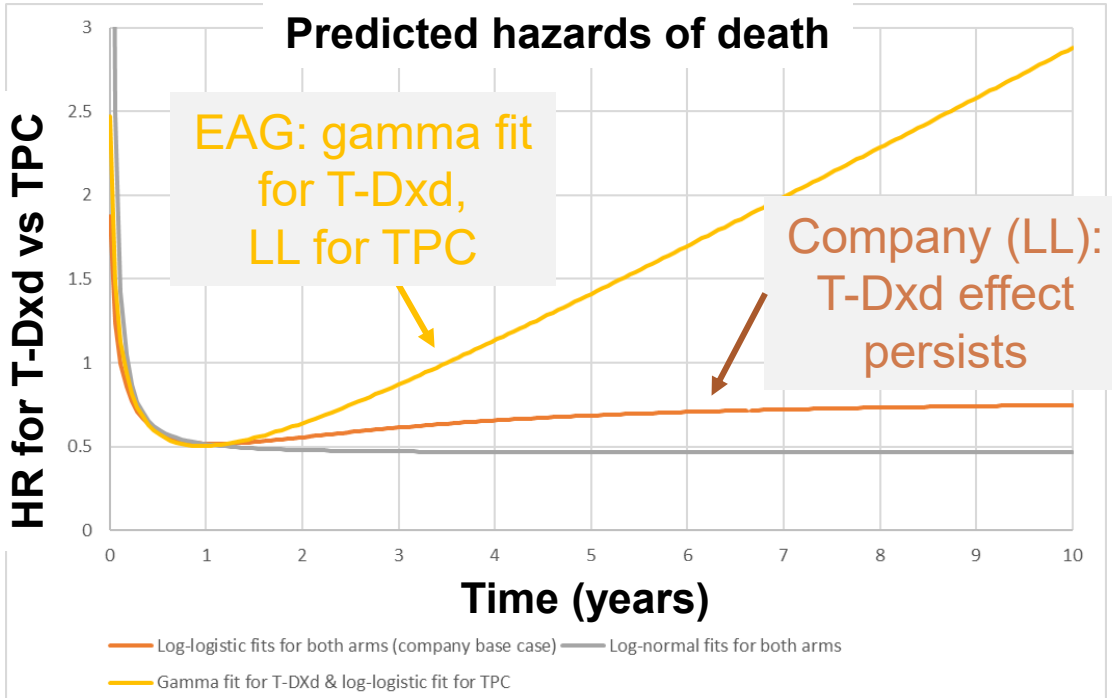
Abbreviations: CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; OS, overall survival; RWE, real world evidence; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice

Key issue: OS extrapolation used for DB-04 NHS cohort (2/2)

EAG prefers modified gamma fit for T-Dxd arm, agrees Log-logistic for TPC arm

EAG critique:

- Agrees Log-logistic suitable for TPC arm
- Uncertain treatment effect size for T-Dxd after 5 years. Implausible it persists (HR<1) for 10+ years (most discontinue by [redacted] mo.):



- For T-DXd, gamma fit gives [redacted] 5-year OS, between Weibull ([redacted]) and LL ([redacted])
- Gamma for T-Dxd: HR>1 seen after 3.5 years, but implausible T-Dxd has higher hazard of death than TPC at any time, so capped applied (HR≤1)
- EAG preferred approach → **large ICER impact**
- Scenario: LN for TPC → medium ICER impact

Overall survival

[redacted]

Abbreviations: LL, Log-logistic; max., maximum; OS, overall survival; HR, hazard ratio; mo., months; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice

Which OS extrapolation for T-Dxd does the committee prefer for the DB-04 NHS cohort?

Key issue: PFS extrapolation used for DB-04 NHS cohort (1/2)

Company prefers log-logistic extrapolation for PFS in cohort

Background

- Company re-examined PFS distributions for DB-04 NHS cohort (PFS data mature)

Company's consultation comments:

- Log-logistic curve most appropriate for PFS extrapolation in both arms – statistical and visual fit and clinical plausibility
- Log-logistic curves do not intersect – more plausible than generalised gamma curves that intersect at 1 to 2 years
- PFS rate for 1 to 2 years similar in DB-04 NHS cohort observed data and using log-logistic curve

PFS	1-year	2-year	3-year	5-year
DB-04 NHS cohort: Log-logistic distribution				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]
TPC	[redacted]	[redacted]	[redacted]	[redacted]

EAG critique:

- Unaware of the reasons why the approach suggested by the EAG of using the mature KM data and only using parametric extrapolations beyond the KM data, was ignored by the company
- Agrees generalised gamma fit for both arms less plausible for cohort as it predicts higher hazard for progression for T-DXd compared to TPC by around 1 year
- Prefers log-normal distribution for TPC arm due to lower AIC/BIC scores. Scenario explored LL

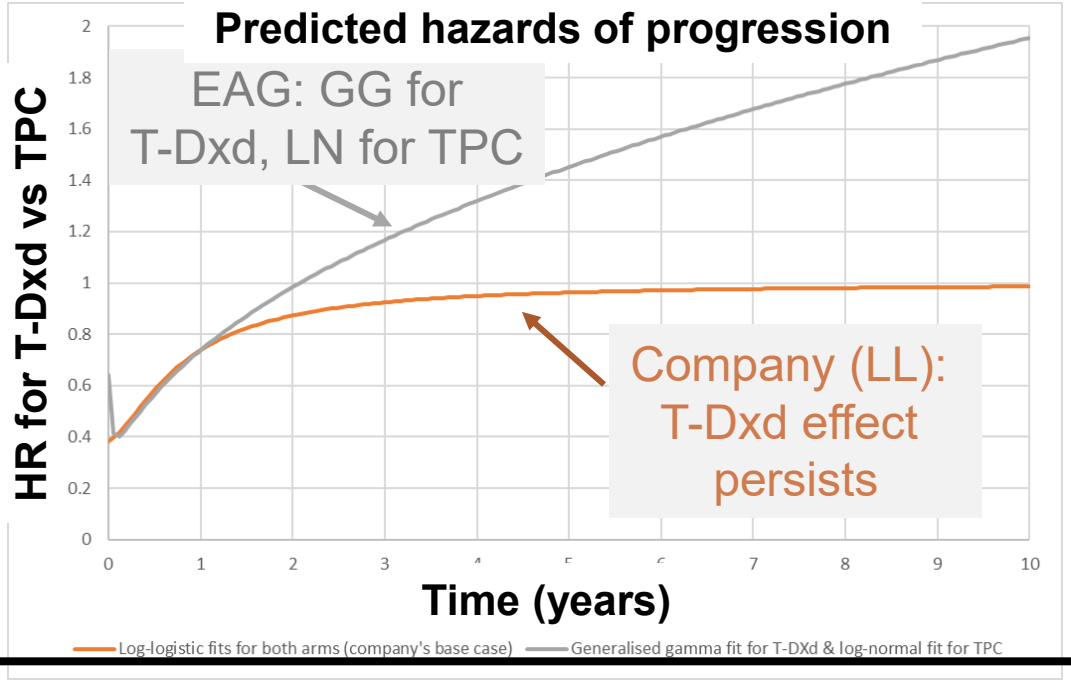
Abbreviations: AIC/BIC, Akaike/Bayesian information criterion; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; LL, Log-logistic; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice

Key issue: PFS extrapolation used for DB-04 NHS cohort (2/2)

EAG prefers modified generalised gamma for T-Dxd and Log-normal for TPC

EAG critique:

- For T-Dxd, LL and LN overestimates PFS beyond observed data. GG fit gives [redacted] 2-year PFS (vs [redacted] observed data)
- Implausible that treatment effect for T-Dxd persists (HR<1) for 10+ years:



- Generalised gamma for T-Dxd: HR>1 seen after 2 years, but implausible T-Dxd has higher hazard of progression than TPC at any time, so capped applied (HR restricted to ≤1)
- EAG preferred approach → small ICER impact
- Scenario: LL for TPC (company) → small impact

Progression-free survival

[redacted]

Abbreviations: GG, generalised gamma; LL, Log-logistic; LN, log-normal; HR, hazard ratio; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice

Which PFS extrapolations for T-Dxd and TPC does the committee prefer?

Key issue: TTD extrapolation used for DB-04 NHS cohort (1/2)

Company prefers generalised gamma to extrapolate probability of staying on treatment

Background

- Company re-examined TTD distributions for DB-04 NHS cohort (TTD data mature) and explored using Kaplan-Meier data (committee request) to directly estimate treatment stopping

Company's consultation comments:

- Generalised gamma curve most appropriate– statistical and visual fit and clinical plausibility
- All curves estimate [redacted] of patients remain on treatment by 5 years
- Scenario explored use of Kaplan-Meier data to directly estimate TTD – minimal ICER impact so maintains use of parametric curve showing good fit to cohort

TTD	1-year	2-year	5-year
Cohort: generalised gamma distribution			
T-DXd	[redacted]	[redacted]	[redacted]
TPC	[redacted]	[redacted]	[redacted]
Cohort: observed Kaplan–Meier data			
T-DXd	[redacted]	[redacted]	-
TPC	[redacted]	[redacted]	-

EAG critique:

- Log-logistic model provides better statistical fit to TPC KM than generalised gamma, but EAG accepts company's preferred generalised gamma fit for TPC arm
- Company's scenario had errors in application of KM data that EAG fixed for this the scenario

Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice; TTD, time-to-treatment discontinuation

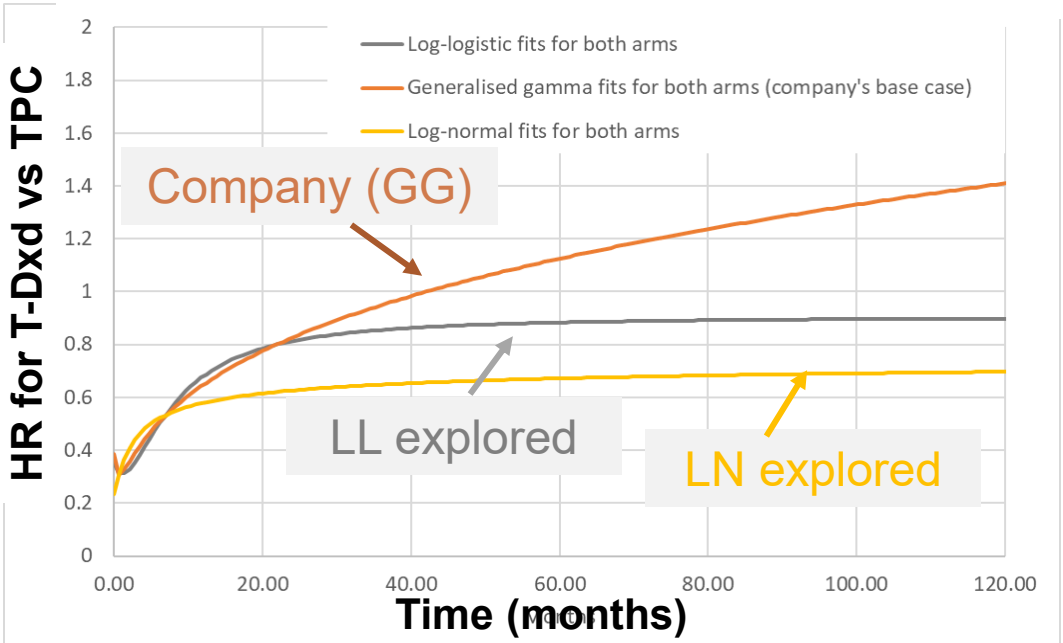
Key issue: TTD extrapolation used for DB-04 NHS cohort (2/2)

EAG prefers modified generalised gamma for T-Dxd arm, agrees GG for TPC arm

EAG critique:

- T-Dxd: GG fit implausible because it assumes higher hazard of discontinuation than TPC after 42 months. Hazards lower for LL and LN but with implausible HR<1 for 10+ years:

Predicted hazards of treatment discontinuation



- For T-Dxd, prefers GG fit with capped applied at 42 months (HR restricted to ≤1) with minimal impact since [redacted] still on T-DXd at that time
- EAG preferred approach → small ICER impact
- Scenario: KM data then GG fits → small impact

Time-to-treatment discontinuation

[redacted]

Abbreviations: GG, generalised gamma; KM, Kaplan–Meier; LL, Log-logistic; LN, Log-normal; HR, hazard ratio; mo., months; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice; TTD, time-to-treatment discontinuation

Which TTD extrapolation for T-Dxd does the committee prefer?

Key issue: PP utilities modelling

Company updates model to derive PP utilities, and differential benefit is reduced

Background

- Committee considered company's utility values were too high… EAG's were more plausible
- Uncertainty about differential effect in PP, so company were asked to explore no effect
- Company updated utilities for the DB-04 NHS cohort

Stakeholder comments – Breast Cancer Now

- Some utility benefit after progression on an effective treatment is reasonable, unlikely to be none

Company's consultation comments:

- Updated approach for cohort uses LMM to derive trial-based utilities
- PP values: T-DXd [redacted] TPC [redacted]
- Differential benefit PP reduced to 6 months (=EAG). If no differential benefit → small ICER impact

What do committee consider to be plausible PP utilities? Is a 6-month differential benefit reasonable?

EAG critique:

- Trial-based utilities: company previously disregarded these due to limited follow up. Biased towards earlier timepoints near progression – overestimates PP utility
- EAG's Lloyd approach (PFS – [redacted]) for cohort gives low PP utilities relative to previous appraisals: T-DXd [redacted] TPC [redacted] so explores using average of decrements predicted by LMM and Lloyd (PFS – [redacted])
- EAG preferred approach → **medium ICER impact.** Scenarios: using average decrement **reduces ICER,** assuming no differential benefit PP **increases ICER**

Abbreviations: ICER, incremental cost-effectiveness ratio; LMM, linear mixed model; PFS, progression-free survival; PP, post-progression; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice

Key issue: Uncertainty in comparison vs sacituzumab govitecan

Unresolved: EAG disagree equivalent efficacy can be assumed

Background

- At time of DESTINY-Breast04 trial, SG had not been recommended. Company presented no efficacy data for T-DXd vs SG, so comparison not included in cost-effectiveness analysis

Company's consultation comments:

- Maintains cost-minimisation analysis, which assumes equivalent efficacy, most appropriate for decision-making in small HER2-low/ hormone receptor negative subset (~10%) of full license
- Robust ITC of T-DXd vs SG infeasible. Results of unadjusted Bucher ITC… [redacted]
  [redacted] – although interpret with caution

T-DXd vs SG	HER2-low subgroup of ASCENT, HR (95% CI)
OS	[redacted]
PFS	[redacted]

EAG critique – uncertainty in cost-minimisation analysis remiains

- Unadjusted Bucher ITC results inconclusive – disagree with company that [redacted] means [redacted]
- Maintains use of ToT in base case, but updates duration for SG based on company scenario

Is the cost-minimisation analysis suitable for use in decision making? What impact does the comparison with SG have on the recommendations for T-Dxd?

Abbreviations: CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; ToT, time-on-treatment

Summary of preferred assumptions

	Committee at ACM1	Company – updated	EAG at ACM2
TPC: remove gemcitabine and 2L eribulin; redistribute	Yes, remove for NHS cohort	Updated: DB-04 NHS cohort	Updated: DB-04 NHS cohort
OS extrapolation	Between log-logistic and Weibull (FAS)	Both arms: Log logistic	T-Dxd: modified gamma TPC: Log logistic
PFS extrapolation	Generalised gamma, capped (FAS)	Both arms: Log logistic	T-Dxd: modified GG TPC: Log normal
TTD extrapolation	Not specified; explore KM data (FAS)	Both arms: GG; explored KM data	T-Dxd: modified GG TPC: GG
PF utilities	LMM	LMM	LMM
PP utilities	[redacted] decrement, Lloyd	LMM	[redacted] decrement, Lloyd
Duration of PP utility benefit	Not specified; explore 0	6 months; explored 0	6 months
Vial sharing	75%	75%	75%
SG analysis: source of treatment-related costs	Grade ≥3 TEAEs; explore TOT	Grade ≥3 TEAEs; explored TOT	TOT, updated with company's SG value
Severity modifier	1.2xQALY	1.2xQALY	1.2xQALY

Abbreviations: FAS, full analysis set; GG, generalised gamma; LMM, linear mixed effects model; OS, overall survival; PF(S), progression-free (survival); PP, post-progression; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TOT, time on treatment; TPC, treatment of physician choice; TTD, time to treatment discontinuation

Questions for committee

Slide 7: Is the committee satisfied that the DB-04 NHS cohort reflects NHS clinical practice?

Slide 9: Which OS extrapolation for T-Dxd does the committee prefer for the DB-04 NHS cohort?

Slide 11: Which PFS extrapolations for T-Dxd and TPC does the committee prefer?

Slide 13: Which TTD extrapolation for T-Dxd does the committee prefer?

Slide 14: What do committee consider to be plausible PP utilities? Is a 6-month differential benefit reasonable?

Slide 15: Is the cost-minimisation analysis suitable for use in decision making? What impact does the comparison with SG have on the recommendations for T-Dxd?

Abbreviations: OS, overall survival; PFS, progression-free survival; PP, post-progression; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice; TTD, time to treatment discontinuation TTD, time to treatment discontinuation

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator PAS discounts

Results of cost-minimisation analysis vs SG also presented in Part 2

Impact of key issues on ICER

At ACM2, company ICERs below £30,000 using QALY weight of 1.2 (PAS only)

Key issue	Impact on ICER compared to updated company base case
OS extrapolation for T-Dxd	Large: EAG preferred approach (medium: EAG scenario)
PFS extrapolation for T-Dxd and TPC	Small: EAG preferred approach (small: EAG scenario)
TTD extrapolation for T-Dxd	Small: EAG preferred approach (small: EAG scenario)
PP utilities modelling	Medium: EAG preferred approach (small: EAG scenarios)
CMA T-DXd vs SG: time on treatment for SG from ASCENT	None: costs-only comparison not captured in ICER

Abbreviations: CMA, cost-minimisation analysis; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PP, post-progression; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TTD, time to treatment discontinuation

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Thank you