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Matching-Adjusted Indirect Comparison of T-DXd vs. Eribulin, Capecitabine, and Vinorelbine for Treating HER2+ Unresectable or Metastatic Breast Cancer After Two or More Anti-HER2 Therapies

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Background

- Approximately 13–20% of breast cancers (BCs) are human epidermal growth factor receptor two-positive (HER2+) (1), a subtype characterised by HER2 overexpression on the surface of tumour cells. HER2+ BC is associated with more aggressive disease with worse outcomes (2)
- First- and second- line HER2 targeted therapies have provided survival gains in patients with HER2+ unresectable or metastatic (u/m) BC but, until recently, no targeted therapies were available at third- and later- lines for HER2+ u/mBC. National Institute for Health and Care Excellence (NICE) pathways previously recommended non-targeted therapies (eribulin, capecitabine, and vinorelbine) which offer limited overall survival (OS) (3-11) and progression-free survival (PFS) (3-12)
- Trastuzumab deruxtecan (T-DXd) is a HER2-targeted antibody drug conjugate indicated for adults with HER2+ u/mBC who have received ≥2 prior anti-HER2 therapies (13)
- DESTINY-Breast01 is a Phase 2, single arm trial evaluating T-DXd in this patient population (14,15). At the June 2020 data-cut (the latest available at the time of analysis; N=184; median follow-up 20.5 months), T-DXd was associated with an objective response rate (ORR) of 61.4%, median duration of response of 20.8 months, and median PFS of 19.4 months (15). Median OS data were immature but encouraging (24.6 months)
- In April 2021, T-DXd was approved by NICE for use within the Cancer Drugs Fund (CDF) for patients with HER2+ u/mBC who have received ≥2 prior anti-HER2 therapies (16)

Objectives

- To evaluate the clinical efficacy of T-DXd vs. UK-recommended non-targeted therapies eribulin, capecitabine, and vinorelbine in the absence of comparative randomised controlled trial data

Methods

- Comparative efficacy was assessed using unanchored matching-adjusted indirect comparisons (MAICs). This method was selected as individual patient data (IPD) were available for DESTINY-Breast01, while only aggregate data were available for the comparator studies
- The DESTINY-Breast01 June 2020 data-cut (the latest available at the time of analysis) was the principal source of data for T-DXd. A systematic literature review identified relevant studies for the comparators (eribulin (3-6), capecitabine (7-11), vinorelbine (12); Table 1). The study populations included patients with u/mBC and mixed, unknown or HER2+ status who had received ≥2 prior chemotherapy regimens
- Prognostic factors and treatment effect modifiers, used as covariates in the matching process, were identified based on published evidence and discussions with a UK clinical expert (Table 2)
- Baseline characteristics for factors where matching was possible are presented in Table 3
- In the comparator studies, OS and PFS over time were extracted from published Kaplan-Meier curves to reconstruct pseudo IPD
- Clinical experts did not consider OS data from the only identified vinorelbine study (12) to be clinically plausible compared with the reported PFS or expected OS in a UK patient population; the OS gain observed may have been driven by post-progression trastuzumab emtansine (T-DM1) use (given T-DM1 was not available at the start of the study). The results of a MAIC between T-DXd and vinorelbine for OS would therefore not offer a realistic comparison and are not presented
- MAICs were performed separately for each comparison, by study. IPD for T-DXd was weighted using a logistic regression model to match the mean baseline characteristics of patients in the comparator trial
- Hazard ratios (HRs) were calculated for survival outcomes and odds ratios (ORs) for response outcomes. The standard errors were calculated using a bootstrap or sandwich estimator

Table 1: Overview of studies used in the MAICs

	T-DXd	Eribulin				Capecitabine			Vinorelbine
	DESTINY-Breast01 (unadjusted) (14,15)	Cortes 2011 (EMBRACE) (3)	Barni 2019 (4)	Cortes 2010 (5)	Gamucci 2014 (6)	Study EGF100151 (7-9)	Fumoleau 2004 (10)	Blum 2001 (11)	Sim 2019 (12)
Study summary									
Study design	Phase 2, single arm, open-label, multicentre	Phase 3, randomised, open-label, multicentre, active controlled	Multicentre, retrospective cohort	Phase 2, single arm, open-label, multicentre	Multicentre, observational	Phase 3, randomised, open-label, multicentre, active controlled	Phase 2, single arm, multicentre	Phase 2, single arm, multicentre	Phase 2, randomised, open-label, multicentre, active controlled
HER2 status	HER2+	Mixed	Mixed, with HER2+ subgroup data for OS and PFS	Mixed	Mixed	HER2+	Mixed	Mixed	HER2+
Previous therapy	T-DM1	Chemotherapies	N/R	Anthracycline, a taxane and capecitabine	≥2 previous lines of chemotherapy	Anthracycline, taxane, and trastuzumab regimens	Anthracycline and taxane	Failed taxane therapy	Trastuzumab and lapatinib

Abbreviations: HER2, human epidermal growth factor receptor two; MAICs, matching-adjusted indirect comparisons; N/R, not reported; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Table 2: Proposed prognostic factors and treatment effect modifiers

Factor	Matching possible	Reason for exclusion
Number of lines of prior therapy	✔	–
Hormone receptor status (positive/negative)	✔	–
Presence of visceral disease (yes/no)	✔	–
Age	✔	–
ECOG-PS (0/1+)	✔	–
Prior hormone therapy (yes/no)	✔	–
HER2 status	~	100% of patients in DESTINY-Breast01 were HER2+; HER2+ subgroup data were compared as far as possible for comparator studies
Prior treatment with pertuzumab (yes/no)	✖	Not reported by comparator studies
Brain metastases (yes/no)	✖	Reported by Barni 2019 (4), however the definition differed from DESTINY-Breast01, therefore matching was not appropriate
Number of metastatic sites	✖	Not reported by DESTINY-Breast01
Comorbidities	✖	Not reported by comparator studies
Prior treatment with trastuzumab (yes/no)	✖	100% of patients in DESTINY-Breast01 had received prior trastuzumab treatment

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; HER2, human epidermal growth factor receptor two.

Table 3: Baseline characteristics†

	T-DXd	Eribulin				Capecitabine			Vinorelbine‡
	DESTINY-Breast01 (unadjusted) (14-15) N=184	Cortes 2011 (EMBRACE) (3) N=508	Barni 2019 (4) N=95	Cortes 2010 (5) N=269	Gamucci 2014 (6) N=133	Study EGF100151 (7-9) N=201	Fumoleau 2004 (10) N=126	Blum 2001 (11) N=74	Sim 2019 (12) N=74
Mean [median] age (years)	56.0 [55.0]	[55]	[59.5]	[56]	[62]	[51]	[54]	52.5	[52]
ECOG-PS = 0 (%)	55.4	42.7¶	40.9¶	37.2	–	58.2	43.7¶	–	25.7
Prior hormone therapy = yes (%)	48.9	85.0	–	–	69.2	–	–	70.2	–
Prior lines ≥3 (%)§	91.8	–	–	–	–	81.6	–	–	100
Prior chemotherapy lines ≥3 (%)	–	87.0	64.6	89.6	50.4	–	45.2	66.2	–
Visceral disease = yes (%)	91.8	–	59.4	–	80.5	78.6	–	79.7	50.0

† Only baseline characteristics where matching was possible are reported; ‡ When all published confounding factors were included in the vinorelbine comparison, the effective sample size (ESS) was very small, potentially yielding unstable estimates of the relative treatment effect. Given the relationship between age and survival, with potentially both young and older patients fairing worse than those of median age, age was removed to explore the impact of this variable. The ESS for the comparison increased, thus results without including age as a matching factor are presented here; ¶ Missing data counted as no/negative in calculation of %; § The mean number of prior lines of therapy were not reported by comparator studies.
Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; T-DXd, trastuzumab deruxtecan.

Table 4: Results of the MAICs

Comparator	Study	ESS	Method	HR for T-DXd vs. comparator (95% CI)		OR for T-DXd vs. comparator (95% CI)		
				OS	PFS	ORR	DCR	CBR
Eribulin	Cortes 2011 (3)	87.5	Naïve unadjusted	0.29 (0.22, 0.39)	0.18 (0.14, 0.24)	11.5 (7.68, 17.1)	27.4 (11.0, 68.0)	10.9 (7.29, 16.2)
			Weighted	0.34 (0.25, 0.44)	0.22 (0.16, 0.29)	9.62 (5.74, 16.1)	23.1 (7.08, 75.1)	11.7 (6.8, 20.2)
	Barni 2019 (4)	42.2	Naïve unadjusted	0.23 (0.16, 0.33)	0.12 (0.08, 0.18)	6.64 (4.62, 9.55)	34.6 (13.9, 85.8)	N/R
			Weighted	0.17 (0.11, 0.31)	0.08 (0.05, 0.14)	8.00 (4.17, 15.3)	68.3 (25.4, 183.9)	N/R
	Cortes 2010 (5)	140.5	Naïve unadjusted	0.15 (0.11, 0.21)	0.12 (0.09, 0.16)	15.5 (9.49, 26.3)	28.4 (12.5, 81.9)	15.4 (9.68, 24.6)
			Weighted	0.18 (0.13, 0.24)	0.13 (0.10, 0.17)	14.7 (8.61, 25.1)	25.9 (8.77, 76.3)	13.1 (7.96, 21.6)
	Gamucci 2014 (6)	17.1	Naïve unadjusted	0.39 (0.25, 0.61)	0.21 (0.15, 0.29)	5.97 (3.57, 9.99)	20.2 (7.72, 52.9)	5.12 (3.13, 8.35)
			Weighted	0.21 (0.10, 0.39)	0.13 (0.07, 0.22)	4.83 (1.24, 18.8)	30.6 (8.25, 113.7)	13.0 (5.45, 30.9)
Capecitabine	EGF100151 (7-9)	105.5	Naïve unadjusted	0.34 (0.25, 0.46)	0.16 (0.12, 0.22)	9.83 (5.98, 16.2)	46.9 (18.5, 119.1)	15.1 (9.17, 24.8)
			Weighted	0.37 (0.27, 0.47)	0.15 (0.11, 0.20)	12.1 (6.96, 21.2)	45.4 (15.3, 134.6)	18.1 (10.3, 32.0)
	Fumoleau 2004 (10)	40.9	Naïve unadjusted	0.42 (0.31, 0.59)	0.30 (0.22, 0.40)	4.14 (2.53, 6.78)	21.3 (8.12, 55.9)	N/R
			Weighted	0.36 (0.20, 0.54)	0.25 (0.14, 0.38)	8.95 (4.73, 16.9)	40.0 (13.9, 115.7)	N/R
	Blum 2001 (11)	53.8	Naïve unadjusted	0.27 (0.18, 0.40)	0.17 (0.12, 0.24)	4.61 (2.55, 8.45)	27.3 (10.0, 74.7)	N/R
			Weighted	0.21 (0.13, 0.31)	0.16 (0.11, 0.22)	5.57 (2.49, 12.4)	29.1 (8.10, 104.6)	N/R
Vinorelbine	Sim 2019 (12)	24.1	Naïve unadjusted	N/R	0.16 (0.12, 0.23)	7.47 (3.80, 14.7)	N/R	10.7 (5.59, 20.7)
			Weighted	N/R	0.17 (0.11, 0.25)	3.57 (1.30, 9.79)	N/R	5.24 (1.67, 16.4)

Statistically significant results in favour of T-DXd are shaded green.

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DCR, disease control rate; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; N/R, not reported; OS, overall survival; OR, odds ratio; ORR, objective response rate; PFS, progression-free survival; T-DXd; trastuzumab deruxtecan.

Results

- The MAICs demonstrated that weighted patients receiving T-DXd had significantly longer PFS vs. all comparators (Table 4)
  - The reduction in the risk of disease progression or death with T-DXd was approximately 78–92% vs. eribulin, 75–85% vs. capecitabine, and 83% vs. vinorelbine
- Weighted patients receiving T-DXd also had significantly longer OS compared with eribulin and capecitabine (Table 4); comparison with vinorelbine OS was not considered appropriate
  - Patients receiving T-DXd had a 66–83% reduction in the risk of death vs. those receiving eribulin and a 63–79% reduction vs. those receiving capecitabine
- All patients receiving T-DXd had significant improvements in response vs. all comparators (Table 4)
  - The odds of weighted patients receiving T-DXd experiencing a best overall response of complete response (CR) or partial response (PR; the ORR) were approximately 4.8–14.7 times higher than patients receiving eribulin, 5.6–12.1 times higher than capecitabine, and approximately 3.6 times higher than patients receiving vinorelbine
  - The odds of weighted patients with T-DXd experiencing a best overall response of CR, PR or stable disease (SD; the disease control rate) were approximately 23.1–68.3 and 29.1–45.4 times higher than patients receiving eribulin and capecitabine, respectively
  - The odds of weighted patients with T-DXd experiencing a best overall response of CR or PR or ≥6 months SD (the clinical benefit rate) were approximately 11.7–13.1 times higher compared with eribulin, 18.1 times higher vs. capecitabine and 5.2 times higher vs. vinorelbine

Conclusion

- This MAIC study supports the clinical efficacy of T-DXd over non-targeted therapies erubilin, capecitabine, and vinorelbine for patients with HER2+ u/mBC who have received ≥2 prior anti-HER2 therapies
- The MAICs demonstrated T-DXd may extend PFS and OS vs. current UK recommended therapies. In April 2021, T-DXd was granted reimbursement through the CDF for this population

Limitations of the study

Unanchored MAIC analysis assumes that all prognostic factors and effect modifiers are known and adjusted for in the model. Potential matching covariates are limited to those reported in the comparator trials and those collected in DESTINY-Breast01. Acknowledging these limitations, the MAIC comparisons presented are the most robust possible given the available data; they were conducted following NICE guidance (17), and where reported, with all confounding factors adjusted for in the comparisons.

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Disclosures

KD and GV are employees of Daiichi Sankyo. AP received consultancy fees for the statistical analyses presented in this poster. Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialise T-DXd in March 2019, except in Japan where Daiichi Sankyo maintains exclusive rights. Daiichi Sankyo is responsible for the manufacturing and supply of T-DXd.

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