CO89

Safety and Efficacy of Antibody Drug Conjugate (ADCs) in Pretreated Breast Cancer (BC): Systematic Literature Review (SLR)

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Background and Objective

- Globally among women, breast cancer is the most diagnosed tumor and largely accounts for cancer-related mortality.(1)
- Despite advances in systemic therapies, patients with early-stage and metastatic breast cancer (mBC) continue to experience poor clinical outcomes such as 5-year survival rates ranging from 47.4% to 89.6% depending on disease stage and molecular subtype.(1)
- ADCs have emerged as a transformative class of therapeutics offering targeted cytotoxic delivery with a manageable safety profile.(2)
- This SLR examines the efficacy and safety of ADCs in non-triple negative breast cancer patients who previously received surgical or systemic treatments, irrespective of the line of therapy.

Methods

- For this SLR, searches were conducted across MEDLINE, Embase, Cochrane databases, from January 2015 to September 2024. Along with this, last four years of ASCO and ESMO conference proceedings, ClinicalTrials.gov, and bibliographies of relevant SLRs were also hand searched.
- All the retrieved citations were screened using prespecified PICOTS criteria (Table 1). Citations were independently screened by two reviewers at both title/abstract and full-text stages, with conflicts resolved by a third reviewer. Data extraction was performed by one reviewer and quality checked by a second reviewer.
- From 24,957 citations, 920 citations were included in this SLR. Of these, 30 unique trials from 114 publications (84 secondary) reporting data on pretreated breast cancer were identified (Figure 1).
- Included trials evaluated ADCs across varied patient populations (HER2+, HR+/-; HER2-, HR+; HER2-, HR+/-; HER2-/+, HR+ and HER2+ with unknown HR status)

Table 1: Eligibility Criteria

Parameter	Inclusion Criteria	Exclusion Criteria
Population(s)	Adult patients (≥18 years of age) with any type of solid tumors	Any other disease; pediatric patients
Interventions	ADCs: SG, MIRV, T-DXd, T-DM1, TV, EV, DV, Dato-DXd, and SHR-A1921	Any other ADCs or interventions
Comparators	No restriction	Not applicable
Outcomes	Efficacy; Safety	Any other outcome
Study design	RCTs (phase II, III, II/III, IV); non-RCTs; single-arm trials	Any other study design
Time	Jan 2015-Sept 2024	Prior to 2015
Language	English	Any other language
Country	Global	Not applicable

Abbreviations: ADC: Antibody Drug Conjugate; Dato-DXd: Datopotamab deruxtecan; DV: Disitamab vedotin; EV: Enfortumab vedotin; MIRV: Mirvetuximab soravtansine; RCTs: Randomized Controlled Trials; SG: Sacituzumab govitecan; SHR-A1921: SHR-A1921 (investigational ADC); T-DM1: Trastuzumab emtansine; T-DXd: Trastuzumab deruxtecan; TV: Tisotumab vedotin.

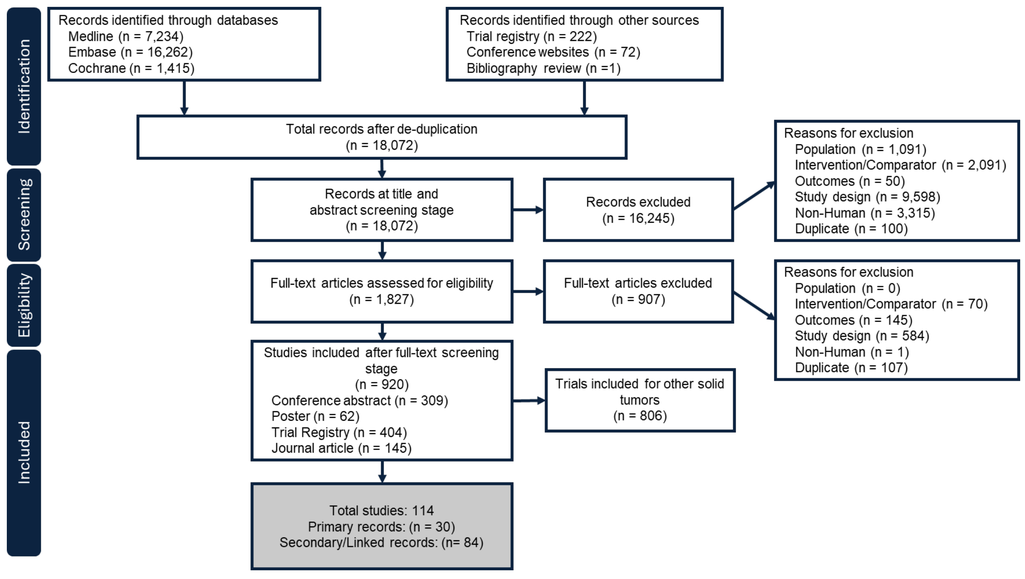

Figure 1: PRISMA Flowchart

Results

Study Characteristics

- Of the 30 unique clinical trials identified in the SLR, 27 investigated ADCs in patients with locally advanced and/or metastatic (LA/m) breast cancer, while the remaining 3 focused on early-stage disease. In the LA/m setting, 17 evaluated T-DM1, five assessed SG, three focused on T-DXd, and one each investigated Dato-DXd and EV.
- Seventeen were RCTs, three were non-RCTs, and ten were single-arm studies. The trials included sample sizes ranging from 6 to 928 participants. Median ages varied between 46 and 69 years.

Efficacy Outcomes

- In the LA/m setting, T-DM1 showed favorable efficacy with mPFS ranging from 4.1 to 16.9 months (HER2+, HR+/-) and mOS from 9.5 (HER2-, HR+/-) to 35.1 (HER2+, HR+/-) months, while ORR varied between 9.1% (HER2-, HR+/-) to 55% (HER2+, HR+/-).
- SG demonstrated mPFS of 4.3-8.4 months (HER2-/HR+), mOS of 12.0 (HER2-/+, HpR+) to 17.1 months (HER2-/HR+), and ORR of 16.5% (HER2-/HR+) to 31.5% (HER2-/+, HR+).
- In patients with HER2+, HR+/- patients, T-DXd demonstrated beneficial outcomes, with mPFS of 16.7 months to 21 months, mOS of 29.1-35.7 months, and ORR ranged from 62% to 78.6%.
- In patients with HER2-, HR+ overexpression, Dato-DXd showed a mPFS of 6.9 months and ORR of 36.4%, while EV yielded an mPFS of 5.4 months, mOS of 19.8 months, and ORR of 15.6%.
- No efficacy outcomes were reported for patients with early-stage disease.

Safety Outcomes

- Among patients with LA/m BC, T-DM1 showed a satisfactory safety profile with serious AEs ranging from 0% (HER2+, HR+/-) to 40% (HER2+ with unreported HR status), grade ≥3 AEs in 20% (HER2+ with unreported HR status) to 56% (HER2+, HR+/-) of patients, and AE-related discontinuation of 0-28% (HER2+, HR+/-).
- SG had manageable safety, with serious AEs in 28 (HER2-, HR+) to 35.2% (HER2-/+, HR+), grade ≥3 AEs in 74-82% (HER2-, HR+), and minimal treatment disruption with AEDR of 0-6% (HER2-, HR+). In patients with HER2+, HR+/- patients, T-DXd presented SAEs in 28.2% to 57.1%, grade ≥3 TRAEs in 41-53.8%, and TRAE discontinuation rates of 14-17.9%.
- Dato-DXd showed grade ≥3 TRAEs in 20.8% (HER2-, HR+) and low TRAE discontinuation of 2.5% (HER2-, HR+).
- Only three early-stage trials reported safety outcomes, two on T-DM1 and one on SG (Table 3).
- Treatment combination with other anti-cancer treatments and overexpression status influence the safety and efficacy of ADCs.

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Table 2: Efficacy and Safety Outcomes of ADCs in Advanced and/or Metastatic Breast Cancer

Trial Name (NCT)	Treatment (N)	OS, Median (95% CI)	PFS, Median (95% CI)	ORR, %	Any SAE, %	Any Grade ≥3 events, %	Any AEDR, %
T-DM1 in HER2+, HR+/-							
EMILIA (NCT00829166)(3, 4)	T-DM1 (495)	29.9 (26.3-34.1)	-	43.6	19	48	10
	Ca + L (496)	25.9 (22.7-28.3)	-	30.8	20	60	-
KATE2 (NCT02924883)(5)	At + T-DM1 (133)	NE	8.2 (5.8-10.7)[b]	45[b]	36; TR: 19	53	26
	Pl + T-DM1 (69)	NE	6.8 (4-11.1)[b]	43[b]	21; TR: 3	45	15
NCT03530696(6)	T-DM1 + Pal (38)	35.1 (24.9-NA)	16.9 (8.3-NA)	42.9	21.05	-	-
	T-DM1 (14)	NA (7.8-NA)	8.3 (2.7-8.8)	18.2	21.4	-	-
PERNETTA (NCT01835236)(7)	T + Pe followed by T-DM1 (44)	-	7 (4.3-11.3)	-	-	-	-
	T + Pe + Pa or V followed by T-DM1 (44)	-	5.3 (4-10.3)	-	-	-	-
TH3RESA (NCT01419197)(8, 9)	T-DM1 (404)	**22.7** (19.4-27.5)[b]	**6.2** (5.6-6.9)	31.3[b]	25	40	15
	TPC (198)	15.8 (13.5-18.7)[b]	3.3 (2.9-4.1)	8.6[b]	22	47	11
TRAXHER2 (NCT01702558)(10)	T-DM1 + Ca (81)	NE	10.2 (7.9-12.6)[c]	44.4[b]	13.4	43.9	28
	T-DM1 (80)	24.7 (24.3-NE)[c]	9.8 (7.5-13.1)[c]	36.3[b]	12.8	41	15.4
TBCRC 022 (NCT01494662)(11, 12)	Cohort 4A: T-DM1 + N (6)[d]	30.2 (21.9-NR)	5.3 (4.5-NR)	33.3	0	-	0
	Cohort 4B: T-DM1 + N (17)[d]	23.3 (17.6-NR)	4.1 (2.7-NR)	35.3	5.9	-	17.6
	Cohort 4C: T-DM1 + N (21)[d]	20.9 (14.9-NR)	4.1 (2.7-NR)	28.6	0	-	4.8
JO22997 (JapicCTI-101277)(13)	T-DM1 (73)	30.5 (25.2-NR)	5.6 (4.6-8.2)[a]; 6.9 (5.3-9.4)[b]	38.4[a] 28.8[b]	-	56	19
JO29317 (JapicCTI-132395)(14)	T-DM1 (232)	-	-	-	8.6	47	2.2
ZEPHIR (NCT01565200)(15, 16)	T-DM1 (90)	-	-	55[a]	24.1; TR: 13.2	TR: 53.3	16
ELAINA (NCT03084939)(17)	T-DM1 (151)	33.2 (27.6-43.9)[b]	7 (6-9.8)[b]	50.4[b]	20.5	54.3	11.9
	L + Ca (49)	40 (23.6-NE)[b]	6.8 (5.6-9.7)[b]	55.8[b]	20.4	57.1	4.1
EORTC 75111-10114 (NCT01597414)(18)	T-DM1 + Pe (40)	-	-	25	-	45	5.1
T-DM1 in HER2-, HR+/-							
CirCe T-DM1 (NCT01975142)(19)	T-DM1 (11)	9.5 (4-NR)	4.8 (2-NR)	9.1	-	-	-
T-DM1 in HER2+, HR status unknown							
CTRI/2018/07/014881(20)	T-DM1 biosimilar (UJVIRA) (113)	-	-	37.8[a]	12.4	-	0
	T-DM1 (55)	-	-	33.3[a]	10.9	-	0
HER2CLIMB-02 (NCT03975647)(21, 22)	T-DM1 + Tu (228)	-	9.6 (7.5-10.9)[a]; 9.5 (7.4-10.9)[b]	47.3[a]; 42[b]	30.3	-	22.1
	T-DM1 + Pl (235)	-	7.4 (5.5-8.4)[a]; 7.4 (5.6-8.1)[b]	41.1[a]; 36.1[b]	22.3	-	11.6
NCT05560308(23)	T-DM1 + Py (10)	-	7.8 (3.3-NA)	30[b]	-	20	-
NCT02658734(24)	T-DM1 (70)	NA (25-NA)	14 (8-17)	22.9	40	-	8.6
SG in HER2-, HR+							
EVER-132-002 (NCT04639986)(25)	SG (166)	-	-	21[a]	-	82	3
	TPC (165)	-	-	15[a]	-	70	4
Saci-IO HR+ (NCT04448886)(26)	SG (52)	17.1	6.2	17.3	-	-	-
	SG + Pem (52)	16.9	8.4	21.2	-	-	-
TROPiCS-02 (NCT03901339)(27-29)	SG (272)	**14.4** (13-15.7)	**5.5** (4.2-7)[a]; **4.3** (3.8-5.4)[b]	21[a]; 16.5[b]	28; TR: 14	74	6
	Chemo (ER, V, Ca, or Ge) (271)	11.2 (10.1-12.7)	4 (3.1-4.4)[a]; 3.1 (2.7-4)[b]	14[a] ; 9.2[b]	19; TR: 10	60	4
PRIMED (NCT05520723)(30)	SG + Lo + GC-SF (50)	-	-	-	-	-	0
SG in HER2-/+, HR+							
IMMU-132-01 (NCT01631552)(31, 32)	SG (54)	12.0 (9-18.2)[b]	5.5 (3.6-7.6)[b]	31.5[b]	35.2	-	5.6
T-DXd in HER2+, HR+/-							
DESTINY-Breast02 (NCT03523585)(33, 34)	T-DXd (406)	**35.7** (30.9-40.8)[b]	**17.8** (14.3-20.8)[a]; **16.7** (14.7-19.6)[b]	70[a] 74[b]	28.2; TR: 11	55.4; TR: 41	21.5; TR: 14
	Ca + T or Ca + L (202)	25 (20.4-31.5)[b]	6.9 (5.5-8.4)[a]; 5.5 (4.4-6.8)[b]	29[a] 27[b]	23.6; TR: 8	44.6; TR: 31	9.7; TR: 5
DESTINY-Breast01 (NCT03248492)(35)	T-DXd (184)	29.1 (24.6-36.1)	19.4 (14.1-25)	62[a]	-	63; TR: 53.8	19; TR: 17.9
TUXEDO-1 (NCT04752059)(36-38)	ITT: T-DXd (15)	-	21	73.3[b]	40	-	13.3
	Per Protocol: T-DXd (14)	NR (22.2-NR)	21 (13.3-NR)	78.6[b]	57.1	-	-
DATO-DXd in HER2-, HR+							
TROPION-Breast01 (NCT05104866)(39, 40)	DATO-DXd (365)	-	**6.9** (5.7-7.4)[a]; **6.9** (5.9-7.1)[b]	36.4[a]	15; TR: 5.8	32.5; TR: 20.8	3.1; TR: 2.5
	ICC (ER, V, Ca, or Ge) (367)	-	4.9 (4.2-5.5)[a]; 4.5 (4.2-5.5)[b]	22.9[a]	18.2; TR: 9.1	54.1; TR: 44.7	2.8; TR: 2.6
EV in HER2-, HR+							
KEYNOTE-F21/EV-202 (NCT04225117)(41)	EV (45)	19.8 (12.8-NE)	5.4 (3.4-5.7)	15.6	-	-	-

Abbreviations: A: Anthracycline; At: Atezolizumab; AEDR: Discontinuation due to Aes; Ca: Capecitabine; Chemo: Chemotherapy; CI: Confidence interval; Dato-Dxd: Datopotamab deruxtecan; Er: Eribulin; EV: Enfortumab vedotin; Ge: Gemcitabine; GC-SF: Granulocyte Colony-Stimulating Factor; ICC: Investigator's choice of Chemotherapy; L: Lapatinib; Lo: Loperamide; N: Neratinib; NA: Not available; NCT: National Clinical Trial identifier; NR: Not reached; NE: Not evaluable/estimable; ORR: Overall response rate; OS: Overall survival; Pal: Palbociclib; Pe: Pertuzumab; PFS: Progression-free survival; Pem: Pembrolizumab; Pl: Placebo; Py: Pyrotinib; SG: Sacituzumab govitecan; T: Trastuzumab; Ta: Taxane; T-DM1: Trastuzumab emtansine; T-Dxd: Trastuzumab deruxtecan; TPC: Treatment of Physician's Choice; TR (treatment related; Tu: Tucatinib; V: Vinorelbine

Notes: [a]Values assessed by Independent Review Committee (IRC); [b]Values by Investigator Assessment (IA); [c]90%CI; [d]Cohort 4A included patients who had not undergone any prior CNS (central nervous system)-directed therapy. Cohorts 4B and 4C comprised patients who had experienced CNS progression following previous CNS-directed treatments, cohort 4B consisted of those without prior exposure to T-DM1, while cohort 4C included individuals who had received T-DM1 at any point in their treatment history.
Bold values indicate statistically significant results (p<0.05). Treatment-related (TR) adverse events are included if reported by the study; otherwise, only the overall AE values are presented in tables 2 and 3.

Table 3: Safety Outcomes of ADCs in Early-Stage Breast Cancer

Trial Name (NCT)	Treatment (N)	Any SAE, %	Any Grade ≥3 events, %	Any AEDR, %
T-DM1 in HER2+, HR+/-				
KAITLIN (NCT01966471)(42)	A + T-DM1 + Pe (928)	21.4	51.8	-
	A + Ta + T + Pe (918)	23.3	55.4	-
KATHERINE (NCT01772472)(43, 44)	T-DM1 (743)	12.7; TR: 0.3	25.7; TR: 0.4	18
	T (743)	8.1; TR: 0.6	15.4; TR: 0.4	2.1
SG in HER2-, HR+/-				
SASCIA (NCT04595565)(45)	SG (45)	-	-	13.6
	TPC (32)	-	-	9.4

Abbreviations: A: Anthracycline; AE: Adverse events; NCT: National Clinical Trial identifier; Pe: Pertuzumab; SG: Sacituzumab govitecan; SAE: Serious adverse events; T: Trastuzumab; Ta: Taxane; T-DM1: Trastuzumab emtansine; TR: Treatment related

Conclusion

- ADCs showed significant survival benefits in pretreated BC subtypes with favorable safety profile.
- Agents like T-DM1, SG, T-DXd, and Dato-DXd outperformed standard care in breast cancer, especially when combined with other therapies.
- Continued research may drive progress in precision medicine for better treatment of breast cancer.

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