Exploring Synergistic ADC-ICI Combinations in Breast Cancer: Clinical Insights from a Scoping Review

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Presented at ISPOR Europe 2025: November 9-12, 2025; Glasgow, Scotland

INTRODUCTION

- Breast cancer continues to be a leading cause of cancer-related mortality among women worldwide.
- Despite therapeutic progress, **monotherapy approaches** often face challenges such as **limited durability of response**, **tumor immune evasion**, and **acquired resistance** in metastatic settings.
- The integration of **antibody–drug conjugates (ADCs) and immune checkpoint inhibitors (ICIs**) represents a novel therapeutic strategy aimed at overcoming resistance and improving survival .
- ADCs induce **immunogenic cell death**, releasing tumor antigens that enhance immune response, while ICIs restore T-cell activity.
- Combination therapy offers **potential synergy** by targeting both tumor cells and the tumor immune microenvironment.

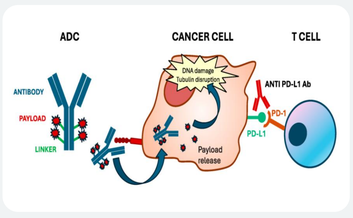


Fig. 1: Mechanism of action of ADC and ICI. Source: Nucera et al., 2024.

- **Target & Attack**: ADCs precisely deliver cytotoxic payloads to tumor cells.
- **Unblock Immunity**: ICIs restore T-cell activation for immune-driven tumor kill.
- **Synergize for Impact**: ADC-triggered antigen release may boost ICI response—offering a dual-pathway advantage in breast cancer.

Dual Forces, One Goal — Target. Destroy. Immune Reactivate

OBJECTIVE

- To synthesize and evaluate clinical evidence on efficacy, safety, and translational potential of ADC–ICI combinations across breast cancer subtypes—HER2$^+$, HER2-low, HR$^+$, and TNBC.

METHODS

Data Sources:

PubMed, Google Scholar, and ClinicalTrials.gov (Phase 1 and 2 only) from Mar 2015–Mar 2025

Search Terms:

"ADCs," "ICIs," "ADC–ICI combination," "synergistic potential," and "breast cancer."
Scoping review conducted per Joanna Briggs Institute (JBI) guidance and reported using the PRISMA-ScR framework.

Inclusion Criteria:

- English-language studies evaluating ADC–ICI combinations in breast cancer (HER2$^+$, HER2-low, HR$^+$, TNBC subtypes).
- Reported efficacy and/or safety outcomes.
- Human clinical studies (interventional or observational).

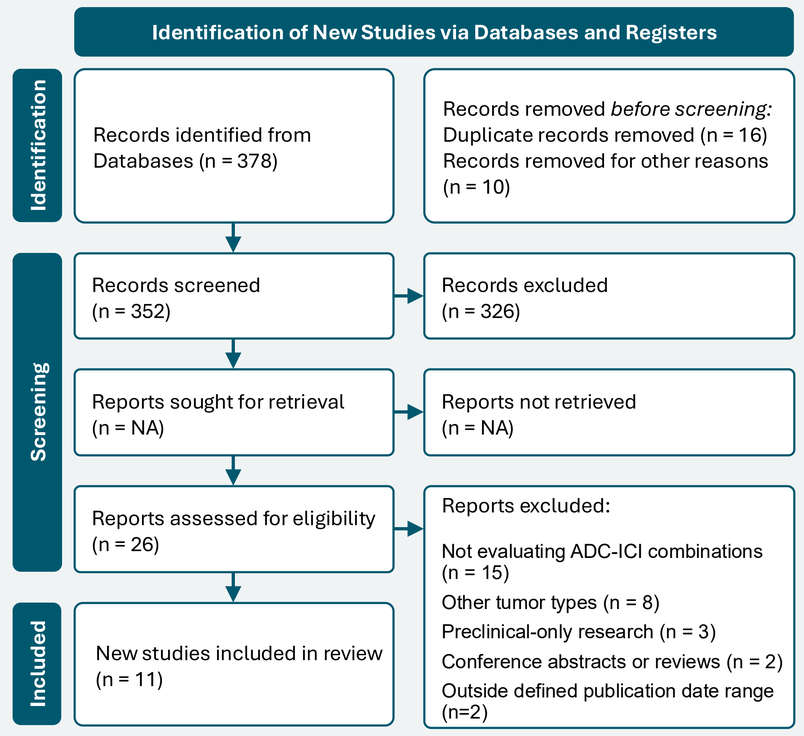
Exclusion Criteria:

- Studies unrelated to breast cancer or not involving ADC–ICI combinations.
- Monotherapy, preclinical, or review-only publications.

Outcomes:

- Objective Response Rate (ORR), Progression-Free Survival (PFS), Overall Survival (OS), and Adverse Events (AEs).

RESULTS



- **11 clinical studies** involving **498 patients** with breast cancer evaluated various **ADC–ICI combination regimens** across **HER2$^+$**, **HER2-low**, and **TNBC** subtypes.
- Consistent evidence supports the **synergistic activity** of ADC–ICI therapy across disease settings.

RESULTS

Overall Efficacy

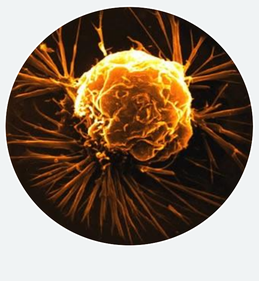
- Pooled ORR: 56% (95% CI: 46 –70%)
- Median OS: Ranged from 11.6 to 18.5 months
- Median follow-up: 10.5–14.2 months, supporting consistency in response assessment

Safety

- Grade ≥3 AEs: 28–40%
- Common AEs: Fatigue, GI issues, neutropenia, diarrhea.
- ILD and hepatic events need monitoring.
- Overall manageable safety profile.

Author / Study (NCT)	Phase	ADC + ICI Combination	Breast Cancer Subtype	Sample Size (n)	Age Range / Median (Years)	Median Follow-up (months)	Key Efficacy	Safety
Hamilton et al., 2021 (Cohort 1B, 2B, 2C)	Ib	T-DM1 + Atezolizumab	HER2$^+$ (mBC, eBC)	6 / 14 / 20	48–57	12	ORR 35% (mBC), pCR 70% (eBC)	Any grade 100%; G3–G4: 50–80%; SAE: 20–57%
Modi et al., 2024 (DESTINY-Breast07, NCT04538742)	II	T-DXd + Nivolumab / Durvalumab	HER2$^+$ / HER2-low	86	54	11.6	ORR 65.6–82%; PFS 11.6 mo	ILD 12–14%; manageable with corticosteroids
Bardia et al., 2024 (ASCENT 05, NCT05633654)	II	Sacituzumab Govitecan + Atezolizumab	TNBC	61	52	12.5	ORR 76.7%; pCR increase post-neoadjuvant	Neutropenia, diarrhea, fatigue (G3: 32%)
Gianni et al., 2024 (BEGONIA, NCT03742102)	II	Datopotamab Deruxtecan + Durvalumab	TNBC / HER2-low	58	50	10.5	ORR 79%; HER2-low ORR 100% (n = 6)	Stomatitis, fatigue (G3: 28%)
Schmid et al., 2020 (KEYNOTE-522, NCT03036488)	II	Ladiratuzumab Vedotin + Pembrolizumab	TNBC (neoadjuvant)	1174	49	15	pCR 64.8%; EFS improved	Peripheral neuropathy, fatigue
Verma et al., 2023 (KATE2, NCT02924883)	II	T-DM1 + Atezolizumab	HER2$^+$	202	54	13	PFS trend favoring PD-L1$^+$ subgroup	Elevated LFTs, thrombocytopenia
Xu et al., 2024 (RC48-ADC, NCT05726175)	II	Disitamab Vedotin + Penpulimab	HER2-low	70	51	9	pCR 42% vs 28% (control)	Manageable hematologic AEs
TROPION-Breast03, 2024 (NCT05629585)	II	Datopotamab Deruxtecan + Durvalumab	TNBC / HER2-low	50	50	12	ORR 79%; DOR 6.5 mo	Stomatitis, fatigue
MORPHEUS-panBC / KEYNOTE-721, 2024	II	Ladiratuzumab Vedotin + Atezolizumab	TNBC	61	48	10	ORR 54–61%; DOR 6.5 mo	Peripheral neuropathy, fatigue
Modi et al., 2024 (DESTINY-Breast06, NCT04494425)	II	T-DXd + Pembrolizumab	HER2-low / HR$^+$	90	53	11	ORR 74%; DCR 89%; PFS ongoing	ILD 10%; fatigue, nausea
Emens et al., 2021 (IMpassion-050, NCT03726879)	II	Atezolizumab + Trastuzumab Emtansine (T-DM1)	HER2$^+$ (adjuvant)	454	52	14	No added benefit vs T-DM1 alone	Grade ≥3 AEs 46%; hepatic toxicity

Abbreviation: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAIR, Catalyst Access and Information Repository; CI, confidence interval; CSR, clinical study report; DCR, disease control rate; DOR, duration of response; eBC, early breast cancer; EFS, event-free survival; G3–G4, grade 3–4; HER2, human epidermal growth factor receptor 2; HR$^+$, hormone receptor positive; ILD, interstitial lung disease; LFT, liver function test; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SAE, serious adverse event; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.



Subgroup Outcomes

- **HER2$^+$ metastatic breast cancer:** T-DXd + Nivolumab achieved an ORR of 65.6% with median PFS up to 11.6 months.
- **TNBC:** Sacituzumab Govitecan + Atezolizumab and Datopotamab Deruxtecan + Durvalumab showed ORRs of 76.7% and 79.0%, respectively.

Clinical Implications

- ADC–ICI combinations enhance immune activation and promote durable response in previously resistant settings.
- Biomarker-driven selection (HER2, PD-L1, Trop-2) is essential for treatment optimization.
- Continuous evaluation of toxicity management strategies (ILD, hepatic AEs) is critical.

STRENGTHS AND LIMITATIONS

Strengths:
- Inclusion of recent global studies (2015–2025) across breast cancer subtypes.
- Combined analysis of efficacy and safety for balanced interpretation.
- Median follow-up consistency (10.5–14.2 months) strengthens data reliability.

Limitations:
- Variability in trial designs and endpoints.
- Limited mature OS data for ongoing trials (BEGONIA, ASCENT 05).
- Small HER2-low sample sizes restrict broader conclusions.

CONCLUSION AND RECOMMENDATIONS

- **ADC–ICI combinations** demonstrate **promising antitumor activity** with **manageable safety** across breast cancer subtypes.
- Highest efficacy observed in **HER2$^+$** and **TNBC** subgroups.
- **Future directions:**
  - Optimize ADC–ICI sequencing and partner selection.
  - Refine biomarker-driven patient selection (HER2, PD-L1, Trop-2).
  - Expand evidence to HER2-low and HR$^+$ subtypes.
  - Capture long-term and real-world outcomes.

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