Optimal Post-ADC Treatment Strategies in HER2-Low Advanced Breast Cancer with ADC Resistance: A Multicenter, Retrospective Real-World Study

1. Abstract

Item	Description
Study Title	Optimal Post-ADC Treatment Strategies in HER2-Low Advanced Breast Cancer with ADC Resistance: A Multicenter, Retrospective Real-World Study
Objective	To evaluate the efficacy and safety of post-ADC treatment in patients with HER2-low advanced breast cancer who have developed resistance to prior ADC therapy
Study Design	Multicenter, retrospective cohort study
Study Population	HER2-low advanced breast cancer patients with ADC resistance who received post-ADC treatment
Sample Size	220 patients
Primary Outcomes	PFS, OS, ORR, CBR, safety (grade 3/4 AE and SAE incidence)
Secondary Outcomes	Comparison of different post-ADC regimens; impact of visceral metastasis; impact of prior ADC treatment benefit
Statistical Methods	Log-rank test, Kaplan-Meier method, Chi-square/Fisher's exact test, Cox proportional hazards regression

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2. Background

Breast cancer is a highly heterogeneous disease. The concept of HER2-low expression (IHC 1+ or IHC 2+/ISH-negative) has redefined the traditional HER2-positive/HER2-negative dichotomy. Approximately 55% of breast cancer patients are classified as HER2-low, representing a distinct therapeutic subtype with unique molecular and clinical characteristics.

The advent of antibody-drug conjugates (ADCs) has revolutionized the treatment landscape of breast cancer. DESTINY-Breast04 and DESTINY-Breast06 trials demonstrated that Trastuzumab Deruxtecan (T-DXd) significantly improves progression-free survival (PFS) compared to physician's choice chemotherapy in HER2-low advanced breast cancer. Sacituzumab Govitecan (SG) and Sacituzumab Tirumotecan (sac-TMT, SKB264) have also shown significant efficacy in HER2-low populations.

However, approximately 50% of HER2-low breast cancer patients experience disease progression during or after ADC therapy. Currently, there is no standard treatment strategy for post-ADC disease progression. Real-world studies have shown limited efficacy of sequential ADC use

(median PFS of 2.7 months) and variable outcomes with different post-ADC approaches. To date, no prospective studies or large-sample real-world studies in Chinese populations have explored optimal post-ADC treatment strategies.

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3. Study Objectives

Primary Objective:

- To evaluate the efficacy and safety of post-ADC treatment in HER2-low advanced breast cancer patients with ADC resistance

Secondary Objectives:

- To compare patient characteristics, treatment patterns, efficacy, and safety across different post-ADC regimens
- To evaluate the efficacy and safety of post-ADC treatments in patients with visceral metastasis
- To compare the impact of prior ADC treatment benefit on post-ADC outcomes
- To identify preferred patient populations for different post-ADC strategies

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4. Study Design

This is a multicenter, retrospective cohort study. The study will enroll HER2-low advanced breast cancer patients who received ADC therapy and subsequently experienced disease progression between January 2018 and December 2025 from three centers:

- Jiangsu Province Hospital (The First Affiliated Hospital of Nanjing Medical University)
- Nanjing Drum Tower Hospital
- Nanjing General Hospital of Nanjing Military Command

Study Period: March 2026 to August 2027

Efficacy Assessment: RECIST 1.1 criteria

Safety Assessment: CTCAE 4.0 (grade 1-5)

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5. Study Population

5.1 Inclusion Criteria

#	Criterion
1	Age ⩾18years
2	Histologically confirmed HER2-low recurrent/metastatic breast cancer. HER2-low defined as: IHC 2+ with FISH negative for HER2 amplification, or IHC 1+
3	No prior ADC therapy before the first ADC in advanced setting (ADC1). ADC type not restricted
4	Received at least one line of post-ADC treatment after progression on ADC1, with at least one documented efficacy assessment
5	KPS score ≥ 70
6	At least one measurable lesion per RECIST 1.1

5.2 Exclusion Criteria

#	Criterion
1	HER2-positive breast cancer at any stage
2	Presence of second primary malignancy
3	Incomplete clinical pathology or follow-up data

5.3 Sample Size Calculation

Based on real-world data, the expected median PFS for post-ADC treatment is 6.0 months. Setting RR = 0.8, $\alpha = 0.05$, $\beta = 0.10$, the calculated sample size is 200patients. Considering multicenter data variability and subgroup analyses, the target sample size is **220 patients**.

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6. Treatment Regimens (Post-ADC)

Post-ADC treatments include, but are not limited to:

Category	Examples
ADC (ADC2)	T-DXd, Sacituzumab Govitecan, Sacituzumab Tirumotecan
Chemotherapy	Capecitabine, eribulin, gemcitabine, vinorelbine, etc.
Endocrine Therapy	Fulvestrant, aromatase inhibitors (± CDK4/6 inhibitors)
Immunotherapy	Immune checkpoint inhibitors (± chemotherapy)

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7. Outcome Measures

7.1 Primary Outcome Measures

Outcome	Definition
Progression-Free Survival (PFS)	Time from initiation of post-ADC treatment to disease progression or deat from any cause
Overall Survival (OS)	Time from initiation of post-ADC treatment to death from any cause
Objective Response Rate (ORR)	Proportion of patients achieving CR or PR per RECIST 1.1
Clinical Benefit Rate (CBR)	Proportion of patients achieving CR, PR, or SD (≥ 24 weeks) per RECIST 1.1
Safety (Grade 3/4 AE and SAE)	Incidence of grade 3/4 adverse events and serious adverse events per CTCAE 4.0

7.2 Secondary Outcome Measures

Outcome	Description
Comparative efficacy of different post-ADC regimens	ADC2 vs. chemotherapy vs. endocrine therapy vs. immunotherapy
Visceral metastasis subgroup	Impact of visceral metastasis on post-ADC outcomes
Prior ADC benefit subgroup	Impact of ADC1 treatment benefit on post-ADC outcomes

7.3 Exploratory Outcome Measures

Exploration of preferred patient populations for different post-ADC strategies, including analysis of:

- Age
- Comorbidities
- Tumor size
- Clinical stage
- HER2 expression level
- HR expression level
- PD-L1 expression
- BRCA mutation status
- Treatment line

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8. Data Collection

Timeline:

- March 2026 - August 2026: Retrospective data collection from three centers
- September 2026 - February 2027: Statistical analysis
- March 2027 - August 2027: Manuscript writing and submission

Data to be collected:

- Demographic and clinical characteristics
- Treatment history (prior ADC and post-ADC regimens)
- Efficacy outcomes (PFS, OS, ORR, CBR)
- Safety outcomes (adverse events)

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9. Statistical Analysis

Software: SAS 9.4

Analysis Sets:

- **Full Analysis Set (FAS):** All enrolled patients meeting inclusion/exclusion criteria with complete medical records
- **Efficacy Evaluable Set:** FAS patients with at least one post-baseline tumor assessment

Primary Analyses:

- PFS and OS: Kaplan-Meier method with log-rank test; median survival with 95% CI
- ORR and CBR: Proportions with 95% exact CI
- Subgroup comparisons: Chi-square/Fisher's exact test for categorical variables; log-rank test for time-to-event outcomes

- Multivariable analysis: Cox proportional hazards regression

Significance Level: $\alpha = 0.05$ (two-sided), 95% CI

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10. Data Monitoring and Quality Control

- All adverse events will be recorded and followed until resolution or stabilization
- Serious adverse events will be reported to the IRB and relevant authorities per regulations
- Data access is restricted to authorized study personnel only
- All electronic data will be stored on encrypted hospital servers
- Data will be retained for 10 years after study completion, then securely destroyed

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11. Ethics and Confidentiality

This study will be conducted in accordance with the Declaration of Helsinki and relevant local regulations. The study protocol will be submitted to and approved by the Institutional Review Board (IRB) or Ethics Committee prior to study initiation.

Privacy Protection Measures:

- **De-identification:** All participants will be assigned a unique study ID. Direct identifiers (name, ID number, contact information) will be stored separately from study data and managed by authorized personnel only
- **Access control:** Role-based access with minimum necessary permissions; all data operations are logged
- **Data encryption:** All electronic data stored on encrypted hospital intranet servers; encrypted transmission for data transfer
- **Data destruction:** After the 10-year retention period, all identifiable information mapping tables will be destroyed; electronic data will be irrecoverably deleted; paper documents will be shredded

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12. Dissemination of Results

Results will be disseminated through:

- 1-2 conference abstracts/presentations
- 1-2 peer-reviewed SCI-indexed publications

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13. Study Timeline

Period	Activity
March 2026 - August 2026	Case screening and data collection
September 2026 - February 2027	Data analysis and statistical analysis
March 2027 - August 2027	Manuscript writing and submission

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14. References

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