# Single Institution Retrospective Analysis of Antibody-Drug Conjugate (ADC) Sequencing in HR+ or HR- HER2-Low Metastatic Breast Cancer

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San Antonio Breast Cancer Symposium
December 9-12, 2025

## Introduction

Antibody-drug conjugates (ADC) have made a profound impact on the treatment landscape of HR positive (+) or negative (-), HER2-low metastatic breast cancer. Sacituzumab govitecan (Trodelvy) is an ADC with a topoisomerase I (TOP1) payload bound to an anti-Trop-2 mAb that showed a significant PFS and OS benefit over chemotherapy in patients with HR+/HER2- metastatic breast who have progressed on 2-4 lines of therapy, in the TROPiCS-02 study (mPFS 5.5 months, mOS 14.4 months) [1]. Trastuzumab deruxtecan (Enhertu) is an ADC with a TOP1 payload bound to an anti-HER2 mAb that showed a significant PFS and OS benefit over chemotherapy in patients with HR+ or HR-, HER2-low metastatic breast cancer in pre-treated patients in the DESTINY-Breast04 study (mPFS 9.9 months, mOS 23.4 months) [2]. The optimal sequencing of ADC therapies remains a topic of investigation. Small retrospective studies have shown a longer median time to treatment failure (TTF) with ADC1 vs ADC2 irrespective of HR status, metastatic sites, ADC sequence, or use of intervening therapies [3, 4]. An ongoing phase II study, TRADE-Dxd, is evaluating the sequencing of Enhertu with another Trop-2 directed ADC, datopotamab deruxtecan, in patients with HER2-low metastatic breast cancer [5].

## Rationale and Approach

Our retrospective, single center study evaluated 100 patients with HR+/HER2-low and HR-/HER2-low metastatic breast cancer who were treated sequentially with Enhertu followed by Trodelvy (ET; n = 70) or Trodelvy followed by Enhertu (TE; n = 30) at the City of Hope Comprehensive Cancer Center from 01/2019-12/2023. Patients who received intervening therapies were excluded from the analysis. All patients had received at least one prior line of therapy in the metastatic setting.

## Study Objectives

The primary objective was to estimate the median combined time to progression (PFS1+ PFS2) following a treatment sequence of ET vs TE to determine if the PFS for the 2nd ADC declined significantly based on the sequence. Secondary endpoints included response rates (RR), treatment-related adverse events (AE), and overall survival (OS).

## Study Design and Methodology

- Patient demographics, treatment history, HR and HER2 status, presence of visceral metastases, and comorbidities were evaluated. PFS1 (PFS2) was defined as time to progression/discontinuation from treatment start of 1st (2nd) ADC. Total PFS (PFS1+PFS2) excluded the non-treatment time past the first progression. AE grading and investigator-assessed radiographic treatment response was per CTCAE v5.0 and RECIST 1.1 definitions, respectively. High-grade AE was defined as Grade 3 or higher. Hormone receptor (HR) and HER2 IHC status were assessed based on the most recent biopsy sample before each line of therapy. Hormone receptor positive (HR+) included patients with 10% or greater ER/PR positivity and HER2-low included patients with HER2 IHC 1+/2+ with a negative FISH.

## Results

Table 1. Baseline patient characteristics

| | All Patients (n=100) | Enhertu then Trodelvy (n=70) | Trodelvy then Enhertu (n=30) |
|---|---|---|---|
| Median Age at start of tx (y) (IQR) | 56.3 (48.1 - 64.2) | 56.3 (48.0 - 63.8) | 57.2 (48.1 - 65.3) |
| Sex | | | |
| F | 99 (99.0%) | 69 (98.6%) | 30 (100.0%) |
| M | 1 (1.0%) | 1 (1.4%) | 0 (0.0%) |
| History of lung disease | 4 (4.0%) | 2 (2.9%) | 2 (6.7%) |
| History of heart disease | 7 (7.0%) | 5 (7.1%) | 2 (6.7%) |
| UGT1A1 deficient | | | |
| Y | 41 (41.0%) | 32 (45.7%) | 9 (30.0%) |
| N | 42 (42.0%) | 29 (41.4%) | 13 (43.3%) |
| N/A | 17 (17.0%) | 9 (12.9%) | 8 (26.7%) |
| ER status | | | |
| ER+ | 54 (54.0%) | 46 (65.7%) | 8 (26.7%) |
| ER- | 46 (46.0%) | 24 (34.3%) | 22 (73.3%) |
| PR status | | | |
| PR+ | 28 (28.0%) | 24 (34.3%) | 4 (13.3%) |
| PR- | 72 (72.0%) | 46 (65.7%) | 26 (86.7%) |
| Breast cancer histology | | | |
| IBC | 1 (1.0%) | 1 (1.4%) | 0 (0.0%) |
| IDC | 85 (85.0%) | 56 (80.0%) | 29 (96.7%) |
| ILC | 13 (13.0%) | 12 (17.1%) | 1 (3.3%) |
| N/A | 1 (1.0%) | 1 (1.4%) | 0 (0.0%) |

Figure A: PFS1+PFS2

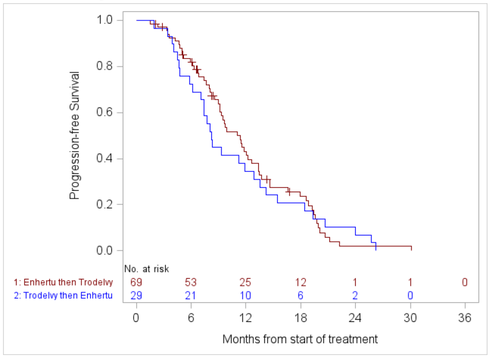
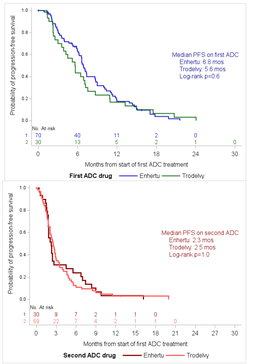
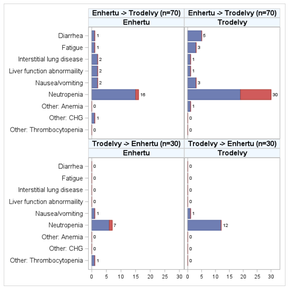



Figure B: PFS by sequence




- **PFS1 + PFS2 was comparable between the sequences** [Figure A]
  - ET: 11.1 months vs TE: 8.2 months; p=0.7
- **PFS and RR were reduced with each ADC when used 2nd in the sequence.** [Figure B]
  - PFS: Enhertu (ET: 6.8m vs TE: 2.3m; p < 0.0001), Trodelvy (TE: 5.6m vs ET: 2.5m; p = 0.0006)
  - RR: Enhertu (ET 65.7% vs TE 33.3%; p = 0.003), Trodelvy (TE 63.3% vs ET 25.7%; p = 0.0004)
- **Median OS was comparable** (ET: 22.9 months vs TE: 17.5 months; p = 0.7).
- **Cumulative high-grade AE rates were comparable** [Figure C]
  - More patients had 1+ hg-AE with ET (62.9%) vs TE (39.0%); but this was not statistically significant (p=0.23)
- A majority of ER+ patients received ET (65.7%) vs TE (26.7%), while HER2 IHC status was similar between groups with most patients being HER2 IHC 1+. [Table 1]

Figure C: AE by sequence (hg-AE in red)




## Summary

Patients with HR+ or HR-, HER2-low metastatic breast cancer who received sequential therapy (ET or TE) with the TOP1 payload ADC therapies trastuzumab deruxtecan (Enhertu) and Sacituzumab govitecan (Trodelvy) had comparable Total PFS (PFS1 + PFS2), OS, and rates of cumulative high-grade AE. There were significant reductions in PFS and RR with each ADC when used second in the treatment sequence. One limitation of our study is we did not include patients who received chemotherapy in between ADC sequencing.

## Conclusions

The optimal sequencing of ADC therapies in HR+ or HR-, HER2-low metastatic breast cancer remains a topic of investigation. Prospective studies are ongoing to determine the most effective and well tolerated sequence of ADC therapies in this patient population.

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**Study Sponsors:** N/A

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