# Transcriptomic biomarkers of therapeutic response and resistance to antibody-drug conjugates in metastatic breast cancer: a comprehensive multi-center study

Samer Alkassis[1], Marla Lipsyc-Sharf[1], Catherine Traverso[2], Adam Joseph Dugan[2], Binyam Yilma[2], Yuan Yuan[3], Funda Meric-Bernstam[4], Hope S. Rugo[5], Joyce O'Shaughnessy[6], Mothaffar F. Rimawi[7], Rachel Schiff[7], David Elashoff[1], John A Glaspy[1], Martina Mcdermott[1], Amy Lauren Cummings[1], Jessica Symons[2], Stamatina Fragkogianni[2], Jacob Mercer[2], Calvin Chao[2], Aditya Bardia[1]

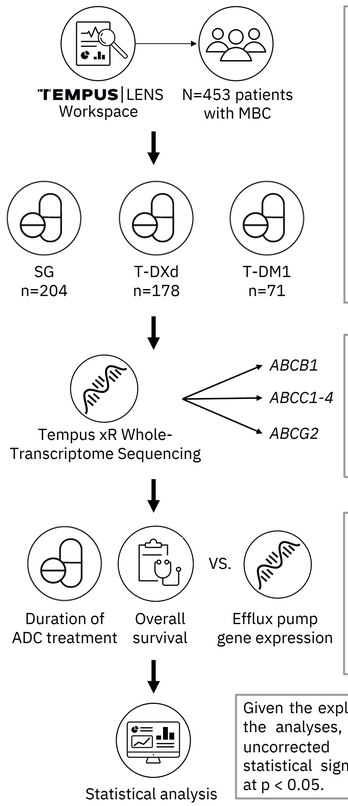
[1]UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA; [2]Tempus AI, Inc., Chicago, IL; [3]Cedars-Sinai Medical Center, Los Angeles, CA; [4]University of Texas, MD Anderson Cancer Center, Houston, TX; [5]University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; [6]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; [7]Baylor College of Medicine, Houston, TX

**Abstract #1041**

## INTRODUCTION

Antibody-drug conjugates (ADCs) have markedly improved outcomes for patients with metastatic breast cancer (MBC). However, most patients with MBC treated with ADCs ultimately have disease progression via either primary or acquired ADC resistance. Therefore, identifying biomarkers predictive of ADC efficacy is critical. Here, we characterized the transcriptomic profile of drug efflux genes in MBC prior to ADC treatment to explore biomarkers of response and resistance to three of the ADCs FDA-approved for treatment of MBC as of January 1, 2025: sacituzumab govitecan (SG), trastuzumab deruxtecan (T-DXd), and trastuzumab emtansine (T-DM1).

## METHODS




Retrospective analysis of pre-treatment biopsies collected from patients with MBC (36% TNBC, 26% HR+/HER2-, 20.5% HER2+, 19% NOS) 1 year prior to or up to 15 days post-treatment ADCs.

Six drug efflux genes were identified as genes of interest from transcriptomic data.

Relationships between duration of treatment (DoT), overall survival (OS), and efflux gene expression were evaluated.

Given the exploratory nature of the analyses, all p-values are uncorrected and nominal statistical significance was set at $p < 0.05$.

## SUMMARY

- Multi-modal analysis identified drug efflux pump gene expression as a potential biomarker of resistance, primarily to T-DXd.
- These findings should be further validated, and combinatorial clinical trial strategies may be explored.

## RESULTS

### Overview of the Cohort

| Characteristic | All (N=453) | T-DM1 (n=71) | T-DXd (n=178) | SG (n=204) | P-value[1] |
|---|---|---|---|---|---|
| Age at Primary Diagnosis, Median (Q1, Q3) | 52 (44, 63) | 55 (46, 64) | 54 (45, 64) | 52 (43, 62) | 0.104 |
| Race, n (%) | | | | | 0.518 |
| Asian | 9 (2.0%) | 1 (1.4%) | 5 (2.8%) | 3 (1.5%) | |
| Black or African American | 64 (14%) | 7 (9.9%) | 23 (13%) | 34 (17%) | |
| Other Race | 23 (5.1%) | 2 (2.8%) | 13 (7.3%) | 8 (3.9%) | |
| Unknown | 109 (24%) | 22 (31%) | 40 (22%) | 47 (23%) | |
| White | 248 (55%) | 39 (55%) | 97 (54%) | 112 (55%) | |
| Ethnicity, n (%) | | | | | 0.97 |
| Not Hispanic or Latino | 228 (88%) | 32 (89%) | 89 (88%) | 107 (87%) | |
| Hispanic or Latino | 32 (12%) | 4 (11%) | 12 (12%) | 16 (13%) | |
| Breast Cancer Subtype, n (%) | | | | | <0.001 |
| TNBC | 161 (36%) | 4 (5.6%) | 30 (17%) | 127 (62%) | |
| HR+, HER2- | 122 (27%) | 4 (5.6%) | 78 (44%) | 40 (20%) | |
| NOS | 83 (18%) | 15 (21%) | 33 (19%) | 35 (17%) | |
| HR+, HER2+ | 50 (11%) | 32 (45%) | 17 (9.6%) | 1 (0.5%) | |
| HR-, HER2+ | 37 (8.2%) | 16 (23%) | 20 (11%) | 1 (0.5%) | |
| Days of ADC Treatment, Median (Q1, Q3) | 130 (76, 225) | 148 (63, 306) | 144 (103, 221) | 116 (62, 198) | 0.102 |
| Line of Therapy, n (%) | | | | | 0.001 |
| 1 | 106 (23%) | 25 (35%) | 30 (17%) | 51 (25%) | |
| 2 | 148 (33%) | 24 (34%) | 51 (29%) | 73 (36%) | |
| 3 | 86 (19%) | 12 (17%) | 35 (20%) | 39 (19%) | |
| 4+ | 113 (25%) | 10 (14%) | 62 (35%) | 41 (20%) | |

[1]Reported p-values are from comparisons between treatment types.

**Table 1.** This diverse cohort had a median age of 52 and a range of races (55% White, 14% Black, 7.1% Other, 24% Unknown). Median DoT across all patients was 130 days.

### Correlations Between Efflux Pump Gene Expression and ADC DoT

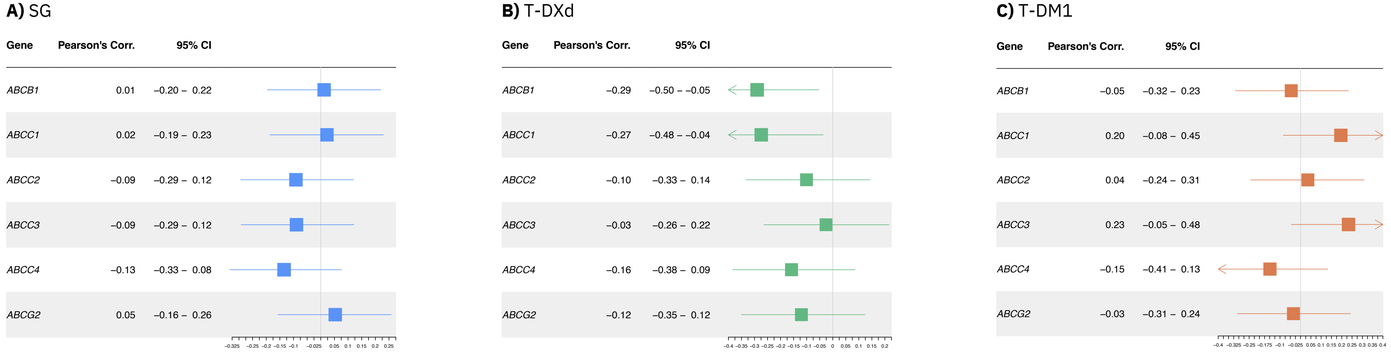



**Figure 1.** Higher expression of drug efflux pump genes was correlated with shorter DoT for T-DXd (*ABCB1*: Pearson's *r*=-0.290, p=0.017; *ABCC1*: Pearson's *r*=-0.274, p=0.025). No significant associations between efflux pump expression and DoT were found in the SG nor T-DM1 cohorts.

### Associations Between Efflux Pump Gene Expression and OS Following ADC Treatment

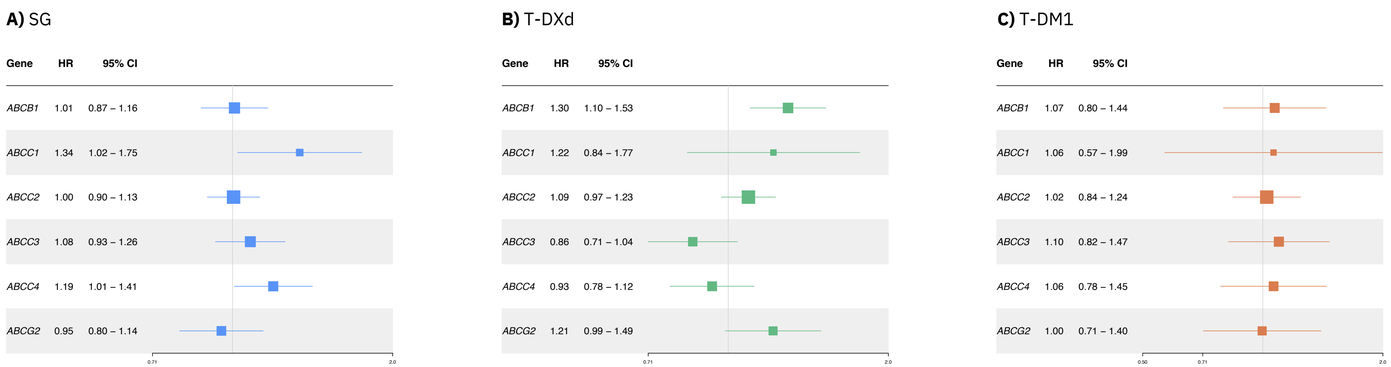



**Figure 2.** Higher expression of *ABCB1* was associated with worse OS for T-DXd (HR: 1.30, 95% CI: 1.10 - 1.53, p = 0.002). In the SG cohort, higher pre-treatment *ABCC1* and *ABCC4* gene expression was associated with worse OS (HR: 1.34, 95% CI: 1.02-1.75, p=0.034; HR:1.19, 95%CI: 1.00-1.41, p=0.042). In the T-DM1 cohort, no significant association was observed between efflux pump gene expression and OS. In evaluating rwOS, the index date was considered the ADC treatment start date, observations were censored at 5 years after treatment start, and gene expression measures were included as continuous predictors in the models. To account for immortal time bias, the risk-set adjustment method was used and the study entry date was taken to be the first date of Tempus sequencing. The proportional hazards assumption was tested for all models and results were only reported if the model met that assumption.

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Correspondence: abardia@mednet.ucla.edu