Multicenter retrospective cohort study of the sequential use of antibody drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in patients with HER2 low metastatic breast cancer (MBC): a subgroup analysis of next generation sequencing (NGS) results

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Background

- T-DXd and SG are both approved antibody drug conjugates (ADCs) for patients (pts) with HER2 low metastatic breast cancer (MBC).
- In a cohort of patients (pts) with HER2 low MBC treated with both ADCs (in either sequence) at 5 institutions, we previously reported real world efficacy and subgroup analyses by age, sites of disease, and use of intervening therapies.
- Biomarkers that predict response and/or resistance to sequential use of these therapies are needed.

Study Design

- Pts in the original cohort who underwent next-generation sequencing (NGS) were identified and included from 4 of the 5 institutions.
- Results from the subset of pts who underwent liquid and/or tissue NGS testing at any of the following time points were included: prior to ADC1, prior to ADC2, or after receipt of both ADCs.
- Genomic information captured included specific genomic mutations, microsatellite instability status (MSI), and tumor mutation burden (TMB).
- Commercial testing per routine clinical practice was performed by Guardant Health, Foundation Medicine, Tempus, Caris, and/or UCSF CLIA-approved testing.
- Cox proportional hazard analysis was performed to evaluate the relationship between patient and treatment characteristics and genomic expression with real-world overall survival (rwOS) from start of ADC1.

Descriptive Summary of NGS Testing Completed

- The study cohort included 74 pts from 4 sites, of these 66/74 (89%) had available NGS data from at least one time point [n=47 (71%) HR+/HER2 low and n=19 (29%) HR-/HER2 low].
- The median number of tissue NGS was 1 for both the HR+ (range: 0-4) and HR - (range: 0-3) cohorts.
- The median number of liquid NGS was 1 (range 0-3) and 0 (range 0-4) for the HR+ and HR- cohorts, respectively.
- The median total number of NGS (any combination of liquid/tissue) was 2 (range 1-5) and 1 (range 1-5) for the HR+ and HR- cohorts, respectively.

Demographic Data and Treatment History

	HR+/HER2-low MBC (n=47)	HR-/HER2-low MBC (n=19)
Demographic Data		
Median age at time of ADC1, yrs (range)	63.0 (33.0-83.7)	52.0 (38.0-62.0)
Sex, n (%)		
Female	46 (97.9%)	19 (100.0%)
Male	1 (2.1%)	0 (0%)
Ethnicity, n (%)		
Non-Hispanic	38 (80.9%)	15 (78.9%)
Hispanic	8 (17.0%)	4 (21.1%)
Unknown	1 (2.1%)	0 (0%)
Race, n (%)		
White	37 (78.7%)	13 (68.4%)
Black	2 (4.3%)	4 (21.1%)
Asian	3 (6.4%)	2 (10.5%)
Other/unknown	5 (10.6%)	0 (0.0%)
Histology, n (%)		
Ductal	36 (76.6%)	16 (84.2%)
Lobular	9 (19.1%)	1 (5.3%)
Other/unknown	2 (4.3%)	2 (10.5%)
De novo metastatic disease, n (%)	9 (19.1%)	5 (26.3%)
Sites of metastatic disease prior to ADC1		
Bone	36 (76.6%)	13 (68.4%)
Liver	29 (61.7%)	8 (42.1%)
Lung	15 (31.9%)	10 (52.6%)
CNS	8 (17.0%)	6 (31.6%)
Visceral disease prior to ADC1	40 (85.1%)	13 (68.4%)
Treatment History		
Median time from MBC diagnosis to ADC1, months (range)	44.0 (18.5-75.9)	11.9 (7.3-15.7)
Median lines of therapy prior to ADC1 by type of therapy:		
Median lines endocrine therapy, number (range)	2 (1-5)	0 (0-4)
Median lines chemotherapy, number (range)	2 (1-5)	1 (1-3)
Median total lines of therapy, number (range)	4 (3-6)	2 (1-3)

Biopsy Type & Timing Relative to Receipt of ADC

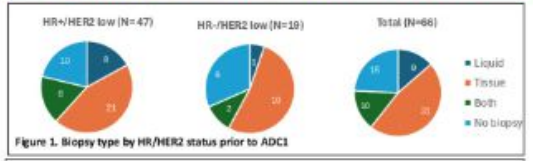


Figure 1. Biopsy type by HR/HER2 status prior to ADC1

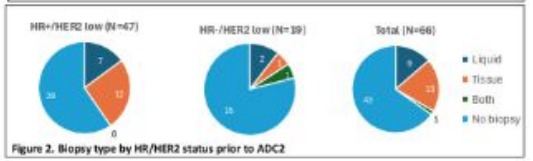


Figure 2. Biopsy type by HR/HER2 status prior to ADC2

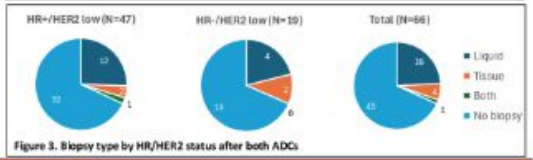
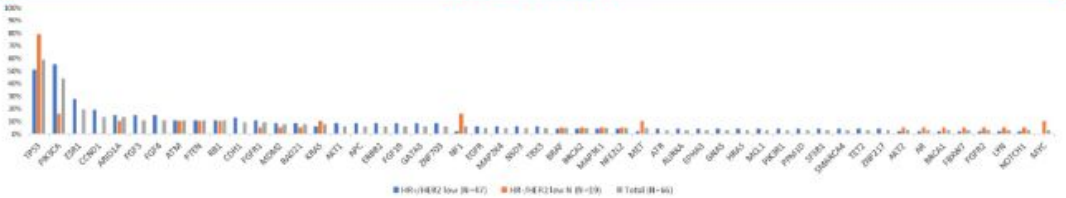


Figure 3. Biopsy type by HR/HER2 status after both ADCs

rwOS From Start of ADC1

Cox model for OS stratified by Hormone receptor status		N (%)	HR (univariable)	HR (multivariable)
Age		-	0.98 (0.95-1.00, p=0.103)	0.98 (0.95-1.01, p=0.149)
Time since MBC Diagnosis		-	0.98 (0.97-0.99, p=0.002)	0.98 (0.97-1.00, p=0.016)
Lines of prior chemotherapy		-	1.03 (0.84-1.27, p=0.746)	1.29 (1.01-1.66, p=0.045)
ADC order	SG>T-DXd	39 (59.1)	-	-
	T-DXd>SG	27 (40.9)	0.84 (0.46-1.54, p=0.581)	0.62 (0.31-1.25, p=0.179)
Visceral disease prior to ADC1	No	13 (19.7)	-	-
	Yes	53 (80.3)	0.85 (0.41-1.74, p=0.652)	0.94 (0.41-2.16, p=0.884)
CNS metastatic disease prior to ADC1	No	52 (78.8)	-	-
	Yes	14 (21.2)	1.56 (0.80-3.03, p=0.189)	2.07 (0.90-4.75, p=0.086)
De novo metastatic disease	No	52 (78.8)	-	-
	Yes	14 (21.2)	0.54 (0.25-1.17, p=0.118)	0.43 (0.18-1.02, p=0.056)
TP53 mutation	No mutation	27 (40.9)	-	-
	Mutation	39 (59.1)	1.06 (0.59-1.91, p=0.855)	0.65 (0.33-1.27, p=0.207)
PIK3CA mutation	No mutation	37 (56.1)	-	-
	Mutation	29 (43.9)	0.84 (0.46-1.52, p=0.566)	1.40 (0.70-2.81, p=0.338)

Genomic Alterations*



*** % shown represent the proportion of patients with each alteration, though some genes were not analyzed in all assays.**

- HR+/HER2-low: Most frequently detected mutations were PIK3CA in 26 (55.3%), TP53 in 24 (51.1%), and ESR1 in 13 (27.7%).
- HR-/HER2-low: Most frequently detected mutations were TP53 in 15 (78.9%), PIK3CA and NF1 in 3 (15.8%).
- Median TMB was 4.70 (range: 1-14) for HR+ patients and 3.85 (range: 0.78-17.37) in HR- patients.
- MSI testing demonstrated microsatellite stability (MSS) in all 66 patients.

Conclusions

- In this real-world cohort of pts with HER2-low MBC who were treated with sequential ADCs, most pts underwent NGS testing. The genomic landscape of mutations was consistent with the incidence in the reported literature, although reported percentages may not fully reflect the true prevalence of genomic alterations, as some genes were included even if they were not analyzed across all assays utilized.
- The presence of TP53 or PIK3CA mutations did not impact rwOS from start of ADC1.
- Given the heterogeneity in the type of NGS testing and the timing related to ADC administration, correlations with outcomes are limited.
- This study highlights the need for prospective evaluation of NGS information to clarify mechanisms of response and resistance to ADCs.

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References

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