Cathepsin Protease Expression and Therapeutic Outcomes to Trastuzumab Deruxtecan (T-DXd) in Metastatic Breast Cancer

Samer Alkassis MD[1], Adam J. Dugan PhD[2], Unnati Jariwala PhD[2], Binyam Yilma MPH[2], Stamatina Fragkogianni PhD[2], Marla Lipsyc-Sharf MD[1], Alexis LeVee[1], Yuan Yuan MD PhD[3], Funda Meric-Bernstam MD[4], Hope Rugo MD[1], Joyce O'Shaughnessy MD[5], Motthafar Rimawi MD[6], Rachel Schiff PhD[6], David Elashoff PhD[1], John Glaspy MD[1], Martina McDermott PhD[1], Amy Cummings MD PhD[1], Jacob Mercer PhD[2], Aditya Bardia MD[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]MD Anderson Cancer Center, Houston, TX, [5]Texas Oncology, Sara Cannon Research Institute, Dallas, TX, [6]Baylor College of Medicine, Houston, TX

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INTRODUCTION

T-DXd is FDA approved for patients with HER2+ as well as HER2 low/ultra-low metastatic breast cancer (MBC). However, response and resistance mechanisms associated with T-DXd are not well understood. Cathepsins are a family of proteolytic enzymes that play crucial roles in cellular processes including protein degradation and turnover in endosomes/lysosomes and when secreted into the extracellular space can contribute to matrix remodeling. Proteases are also important for ADC linker cleavage and payload release. Specific extracellular and intracellular proteases, including cathepsins, may alter the efficacy of ADCs with cleavable linkers[1], such as T-DXd, as opposed to ADCs with non cleavable linkers like T-DM1 that depend on complete lysosomal degradation.

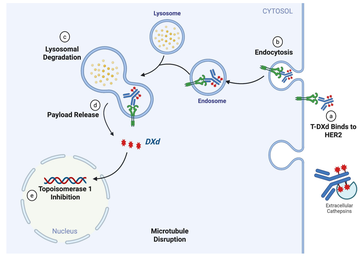
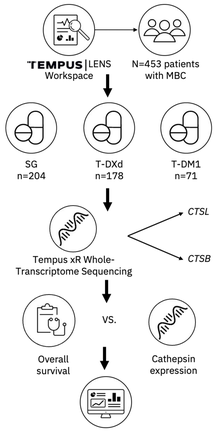


Figure 1. Cathepsin function diagram (created with BioRender.com)

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 with T-DXd and T-DM1.

Two protease genes were identified as genes of interest from transcriptomic data.

Relationship between overall survival (OS), and cathepsin expression was 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 the potential role of proteases as biomarkers of response to T-DXd in HER2 low/ultralow, but not HER2 positive/amplified breast cancer suggesting potential differential mechanism of action in HER2+ vs HER2low/ultra-low disease.
- These findings need to be validated in additional datasets but could guide biomarker-driven clinical application of ADCs.

RESULTS

Table 1. Cohort Characteristics

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%)	

Figure 2. Forest Plots for T-DXd

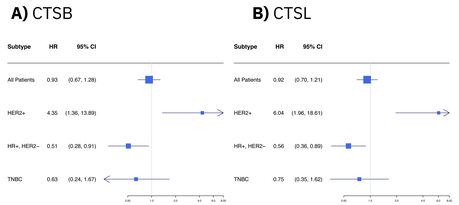
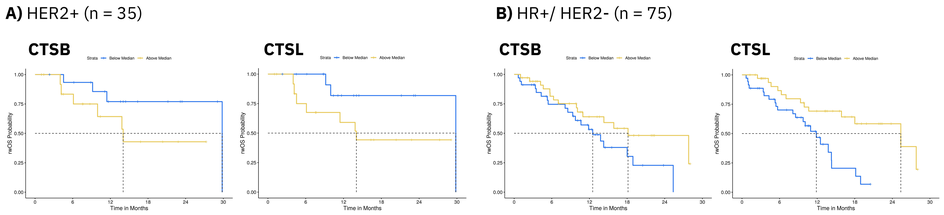


Figure 3. Associations Between Cathepsin Gene Expression and OS (T-DXd)



Figures 2 & 3. High expression of CTSB and CTSL was associated with significantly worse OS in the HER2+ subgroup (n = 35; HR 4.35; p = 0.013 and HR 6.04; p = 0.002, respectively) but associated with improved outcomes in patients with HR+/HER2− disease (n = 75; HR 0.51; p = 0.024 and HR 0.56; p = 0.013, respectively). Kaplan-Meier analyses showed separation in the survival curves when CTSB and CTSL expression were dichotomized at their respective medians. However, the corresponding log-rank tests did not reach statistical significance due to the loss of granularity with dichotomization, highlighting limitations using median as cut-off for biomarkers.

Figure 4. Forest Plots for T-DM1

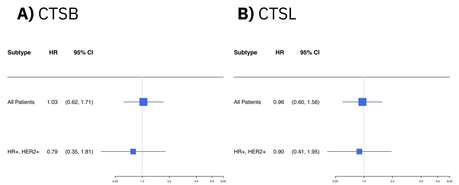
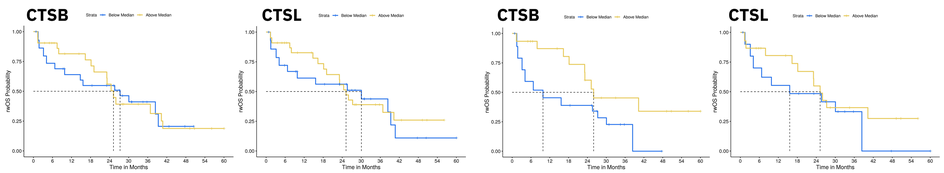


Figure 5. Associations Between Cathepsin Gene Expression and OS (T-DM1)



Figures 4 & 5. No significant associations were found between protease expression and OS (entire cohort: n = 59, HR 1.03; p = 0.9 and HR 0.96; p 0.9; HER2+cohort: n=39, HR 0.55; p = 0.10 and HR 0.69; p = 0.2 for CTSB and CTSL, respectively).

References

1) Tsao, L et al., *Nature Communications*, 16: 3167-3188 (2025)

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Correspondence: salkassis@mednet.ucla.edu