Overcoming ADC Resistance in Breast Cancer: Payload Diversification as a Strategy for Sequential Therapy

Dileep Reddy Rampa[1], Nanae Ogata[1], Nithya Sridhar[3], Fujii Takeo[4], Chalothorn Wannaphut[5], Jennifer Maynard[6], Kyoji Tsuchikama[7], George W. Sledge Jr.[8], Naoto T. Ueno[1,2], Jangsoon Lee[1,2]

[1]Preclinical Core, Cancer Biology Program, [2]Translational Clinical Research, University of Hawai'i Cancer Center, Honolulu, HI. USA, [3]Baylor College of Medicine, Houston, TX. USA, [4]Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD. USA, [5]Department of Internal Medicine, John A. Burns School of Medicine, University of Hawai'i at Manoa, Honolulu, HI. USA, [6]Department of Chemical Engineering, University of Texas, Austin, Texas, USA, [7]Institute of Molecular Medicine, The University of Texas Health Science Center at Houston, Houston, TX. USA, [8]Caris Life Sciences, Phoenix, AZ, USA

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Introduction

- Using ADCs based on HER2 or TROP2 sequentially has not yet demonstrated a significant extension of progression-free survival when switching to a second regimen compared to the first.
- Currently, there is limited data connecting payload type to resistance or the order of treatment decisions. Although payloads based on Topoisomerase 1 (Topo1) inhibitors are commonly used, optimal sequencing strategies after progression on initial ADC therapy are still unclear.
- We developed preclinical models resistant to T-DXd and Sacituzumab Govitecan (SG) to study resistance mechanisms [1].

HYPOTHESIS & OBJECTIVES

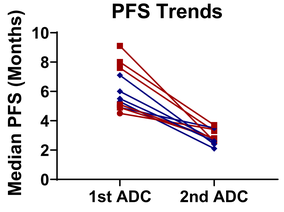
Hypothesis: Switching to ADCs with a different payload class overcomes resistance to Topo1-inhibitor-based ADCs.

Objectives

- To define mechanisms of resistance to Topo1-inhibitor-based ADCs in HER2+ and TNBC preclinical models.
- To determine whether switching to ADCs with different payload classes restores antitumor activity and informs rational sequencing strategies.

Clinical limitation

Clinical Cohorts Indicate Limited Second-line Benefit when Both Sequential ADCs Use Topo1 Inhibitor Payloads

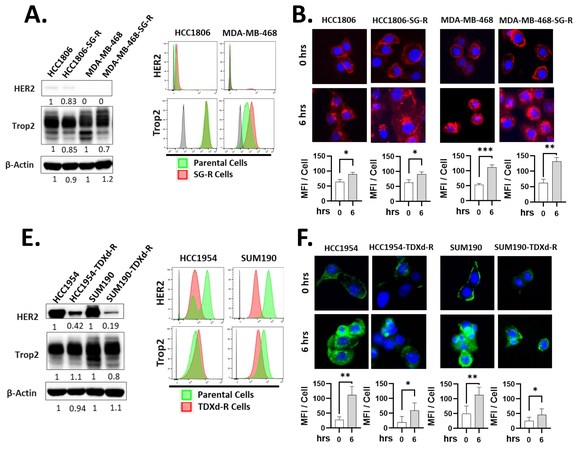


Sequential treatments			
1st, [median PFS]		2nd, [median PFS]	
SG	[5.1]	T-DXd	[2.9]
T-DXd	[5.5]	SG	[2.6]

Figure 1. Back-to-back treatment of Topo1-inhibitor ADCs showed shorter median PFS in breast cancer. Retrospective data analysis of clinical trials with Topo1 inhibitor-conjugated ADCs [2-5].

RESULTS

Topo1-inhibitor ADC Resistance is Payload-driven, Not Due To Antigen Loss or Internalization Defects



C.

Fold change in IC_{50}		
Payload	HCC1806-SG-R	MM-468-SG-R
SN38	49	17
DXd	191	17
MMAE	4	1
MMAF	2	1

ADC	HCC1806-SG-R	MM-468-SG-R
SG	4425	14
S-MMAF	1	1
Dato-DXd	2	3

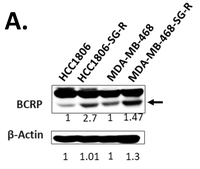
G.

Payload	HCC1954-TDXd-R	SUM190-TDXd-R
SN38	25	3
DXd	11	7
MMAE	1	1
MMAF	1	4

ADC	HCC1954-TDXd-R	SUM190-TDXd-R
T-DXd	4867	5036
T-MMAF	37	231
SG	21	3
S-MMAF	0.5	1

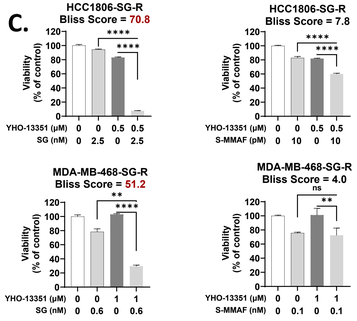
Figure 2. Payload-derived resistance in Topo1-inhibitor ADC. A and **E**: HER2/Trop2 by Western blot and surface FACS show reduced target antigen in resistant lines. **B** and **F**: Endocytosis imaging/quantification shows internalization preserved under reduced target antigen. **C** and **G**: Payload response: SG-R and T-DXd-R are resistant to Topo1 payloads (DXd, SN-38) but remain sensitive to tubulin payloads (MMAE/MMAF) and corresponding ADCs. Numbers indicate fold changes compared to parent cells.

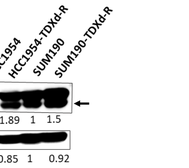
Blocking BCRP/ABCG2 Transporter Restores Topo1-inhibitor ADC Efficacy, but Tubulin-inhibitor ADC are Unaffected



B.

Bliss synergy score with YHO-13351		
Payload	HCC1806-SG-R	MM-468-SG-R
SN38	18.2	19.8
DXd	27.3	24.1
MMAE	-3.0	-1.6
MMAF	-3.4	-3.7





F.

Bliss synergy score with YHO-13351		
Payload	HCC1954-TDXd-R	SUM190-TDXd-R
SN38	12.7	0.9
DXd	17.8	-4.1
MMAE	-0.3	-2.7
MMAF	-3.9	-2.8

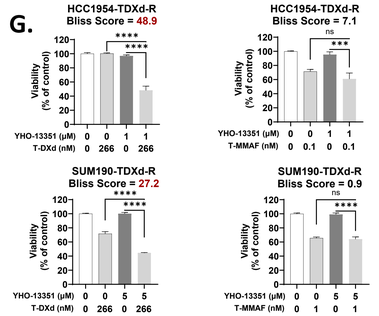


Figure 3. Microtubule-payload ADCs reverse efflux-driven resistance to Trop2-targeting Topo1-i ADCs. A and **E**: BCRP/ABCG2 is upregulated in SG-R, not T-DXd-R cells. **B** and **F**: SRB assay. BCRP inhibition restores sensitivity to Topo1-i payloads, but not to tubulin payloads. **C** and **G**: BCRP inhibition rescues Topo1-i-ADC activity, but not MMAF-ADC activity. SRB assay. YHO-13351, BCRP inhibitor.

Switching the Payload to a Microtubule Inhibitor restores the Effectiveness of ADC In SG- and T-DXd-resistant Breast Cancer Xenograft

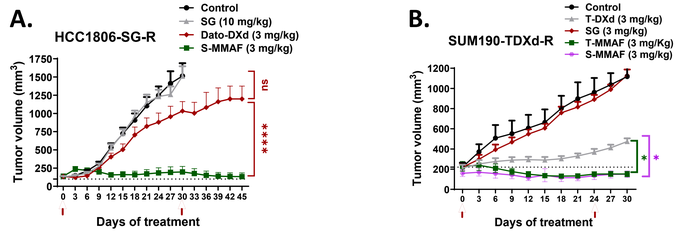


Figure 4. MMAF-conjugated ADCs effectively inhibit the tumor growth of Topo1-inhibitor ADC-resistant xenograft models. A. SG-resistant TNBC model, HCC1806-SG-R. **B**. T-DXd-resistant HER2+ model, SUM190-TDXd-R. S-MMAF: sacituzumab-MMAF conjugate, T-MMAF: trastuzumab-MMAF conjugate.

CONCLUSION

Resistance to Topo 1 inhibitor–based ADCs arises primarily from payload-related mechanisms rather than antigen loss. Switching to ADCs with alternative payloads can restore therapeutic efficacy, supporting a payload-guided sequencing strategy.

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Jangsoon Lee: jlee@cc.Hawaii.edu
Naoto T. Ueno: nueno@cc.hawaii.edu

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