Abstract # 4436 Sutro's Site-Specific DAR16 Dual-Payload ADCs Combining TOPO1i and DNA Damage Response Inhibitors to Enhance Efficacy, Overcome Resistance, and Improve Safety

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Introduction

- ADCs have transformed cancer therapy, but single payload ADCs show limited efficacy in low-antigen, heterogeneous tumors and frequently develop resistance
- Resistance to TOPO1i ADCs is driven by payload-specific mechanisms, including enhanced DNA repair and drug efflux, and is poorly overcome by sequential dosing of TOPO1i ADCs
- TOPO1i-induced replication stress is rapidly resolved by PARP- and ATR-dependent DNA damage response pathways, supporting combined TOPO1 and DDR inhibition
- The clinical use of TOPO1i, DDRi combinations is limited by systemic toxicity which leads to sub-therapeutic dosing of one or both agents, highlighting the need for tumor targeted delivery approaches
- Site-specific, high DAR dual-payload ADCs co-delivering TOPO1i and DDRi offer a promising strategy to improve efficacy, overcome resistance, and enhance the therapeutic window

Harnessing the Sutro's Cell-Free Platform and Diverse MoA Payloads to Enable Next-Generation Site-Specific Dual-Payload ADCs

Optimal Ratios of dpADCs to Enhance Potency, Overcome Resistance

Dual-Payload ADCs

- XpressCF+® synthesis derived IgGs with two distinct non-natural amino acid(s)
- Robust process, 4000L GMP run demonstrated
- Efficient delivery of orthogonal payloads with precise stoichiometries
- Increased efficacy in target low patient population
- Overcome payload resistance mechanism from conventional ADCs
- Enhanced efficacy and therapeutic index
- We expect dual-payload ADCs to delay resistance and lead to more durable responses and longer PFS

Synergy Between TOPO1i and PARPi; Clinical Challenges and Path Forward with Dual-Payload ADCs

DNA Damage → Cell Death

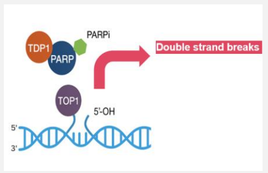


Figure: Mechanistic Rationale for Combining TOPO1i with PARPi for Synergetic Activity

Clinical Challenge

- Overlapping toxicity results in sub-therapeutic dosing of PARPi and/or TOPO1i
- Concurrent dosing of Trodelvy and Talazoparib is clinically intolerable due to a narrow therapeutic window

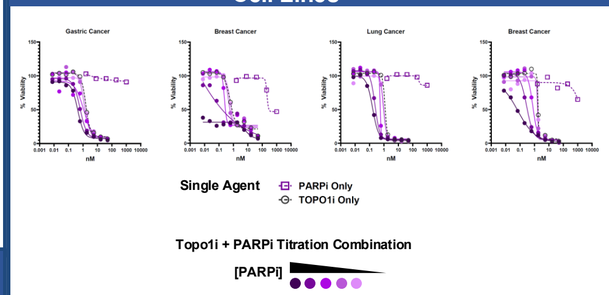
Solution

- Simultaneous delivery of dual payloads via dpADC to maximize tumor cell efficacy
- Leverage best-in-class dpADC technology to achieve enhanced synthetic lethality with improved safety

Sutro's Proprietary Pan-PARPi Displayed Excellent Binding, Trapping and Not Substrate of the Drug Efflux Transporters for Next Generation dpADCs

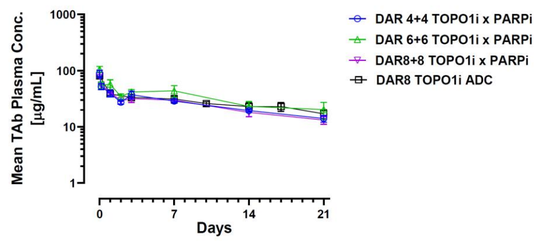
Assay	Sutro's Pan-PARPi
CAPAN-1 *in vitro* cell killing EC_{50} (nM)	198
PARP1 inhibition/trapping EC_{50} (nM)	0.98/4.1
PARP2 inhibition/trapping EC_{50} (nM)	0.26/7.4
PARP3 inhibition EC_{50} (nM)	31
PARP4 inhibition EC_{50} (nM)	11
PARP5a/TNKS1 inhibition EC_{50} (nM)	70
PARP5b/TNKS2 inhibition EC_{50} (nM)	5.7
PARP16 inhibition EC_{50} (nM)	0.45
Caco-2 Efflux Ratio, $P_{app(BA)}/P_{app(AB)}$	3.0
Caco-2 + P-gp inhibitor Efflux Ratio	2.0
Caco-2 + BCRP inhibitor Efflux Ratio	3.0
hERG inhibition, 10 µM (% inhibition)	-7.8

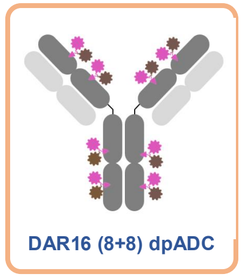
Proprietary Pan-PARPi Potentiates the Activity of TOPO1i Across Diverse Cancer Cell Lines



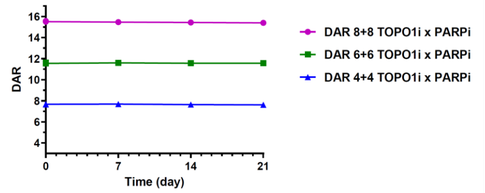
aHER2 TOPO1i x DDRi DAR16 Dual-Payload ADCs Exhibited Excellent Mouse PK and *In-Vivo* DAR Stability

PK profile of high DAR ADCs in C57BL/6 mice



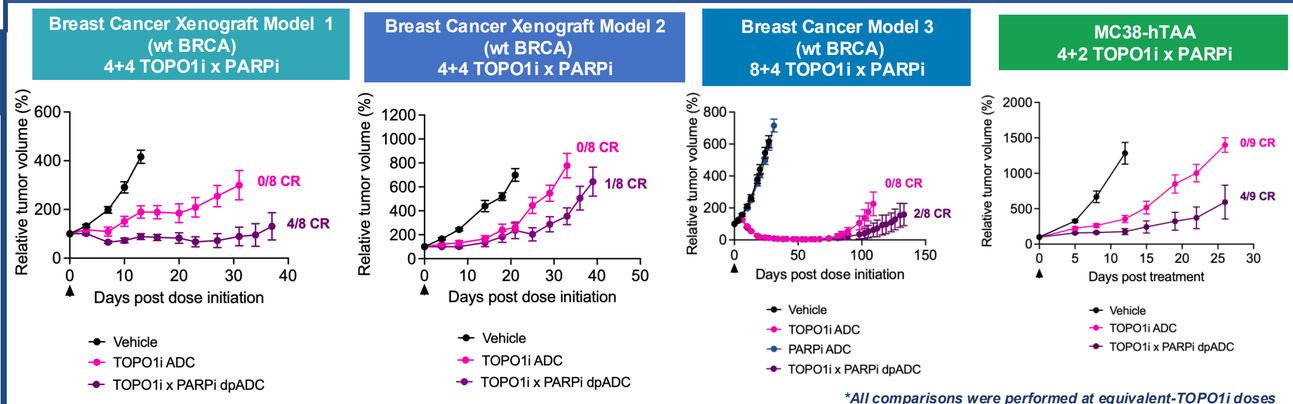


In-Vivo DAR Stability



ID	DAR	$t_{1/2}$ (d)	CL (mL/d/kg)	Cmax (ug/mL)	$AUC_{0\text{-}tlast}$ (d·ug·mL^{-1})	V_{ss} (mL/kg)
αTAA 8+8 TOPO1i x PARPi dpADC	16 (8+8)	13.2	3.92	80.4	512	73.8
αTAA 6+6 TOPO1i x PARPi dpADC	12 (6+6)	14.9	2.65	106	692	57.8
αTAA 4+4 TOPO1i x PARPi dpADC	8 (4+4)	12.9	3.79	88.8	529	71.4

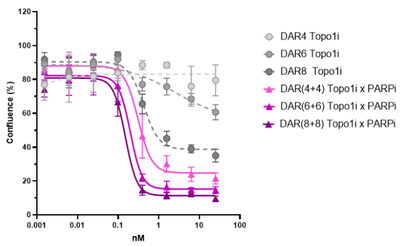
Site-Specific aTAA TOPO1i x PARPi dpADCs Outperform TOPO1i Single-Payload ADCs Across Varied DAR Formats



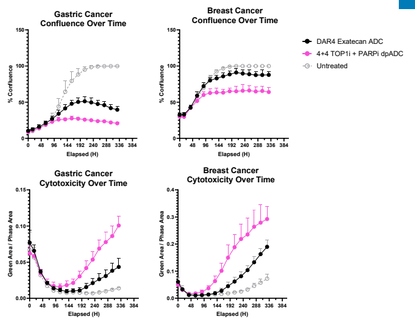
**All comparisons were performed at equivalent-TOPO1i doses*

aHER2 TOPO1i x PARPi Dual-Payload ADC Outperforms Single-Payload ADCs in Cell Killing Assay and Induces Higher Level of DNA Damage

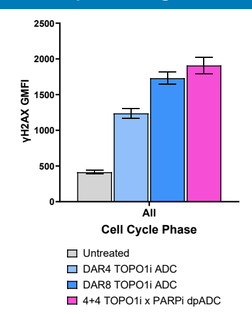
Breast Cancer Cell Line (wt BRCA) *Cell viability assay*



Increased Cytotoxicity



Increased DNA Damage *γH2AX Signal*



Conclusions

- First-in-class site-specific TOPO1i × DDRi dpADCs enabling simultaneous delivery of TOPO1 and DDR inhibitors with controlled stoichiometries to enhance synthetic lethality while overcoming resistance and safety limitations
- Proprietary pan-PARPi and exatecan payloads are not substrates of drug efflux pumps, potentially reducing resistance mechanisms
- Proprietary tumor-selective hydrophilic β-glucuronidase cleavable linker technology, combined with site-specific conjugation, enables the generation of stable high-DAR dpADCs with strong preclinical properties
- TOPO1i × PARPi dpADCs demonstrate enhanced cytotoxic activity, sustained DNA damage and greater antitumor efficacy compared with single-payload ADCs
- High DAR (16) dpADCs exhibit favorable mouse pharmacokinetics and excellent DAR stability
- Preclinical activity suggests potential utility in HRD and HRP solid tumors, including patient populations resistant to PARPi or TOPO1i therapies
- This dpADC strategy may overcome clinical limitations associated with sub-therapeutic dosing of TOPO1i and DDR inhibitors, improving tumor delivery, enhancing synthetic lethality, and potentially increasing the therapeutic index