

DESIGNED

TO DELIVER

**Next-Generation High DAR TOPO1i x
DDRi Dual-Payload ADCs to Improve
Efficacy, Overcome Resistance &
Enhance Safety**



October 12th, 2026

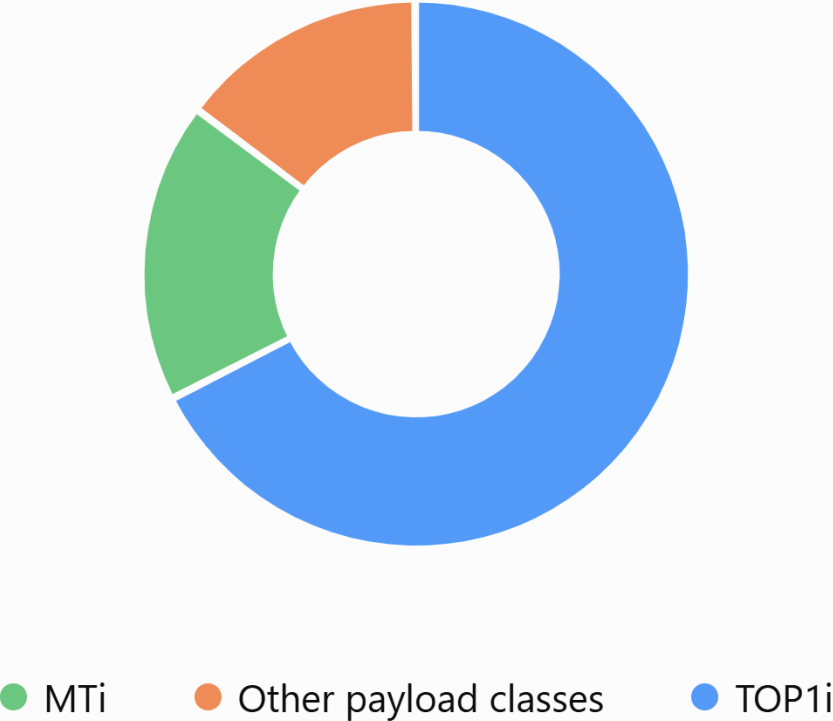
SUTRO
BIOPHARMA

Krishna Bajjuri, PhD
Executive Director, ADC Chemistry



Emerging Clinical Challenge: TOP1i Payload Cross-Resistance Limits ADC Efficacy

Clinical ADCs by Payload Class

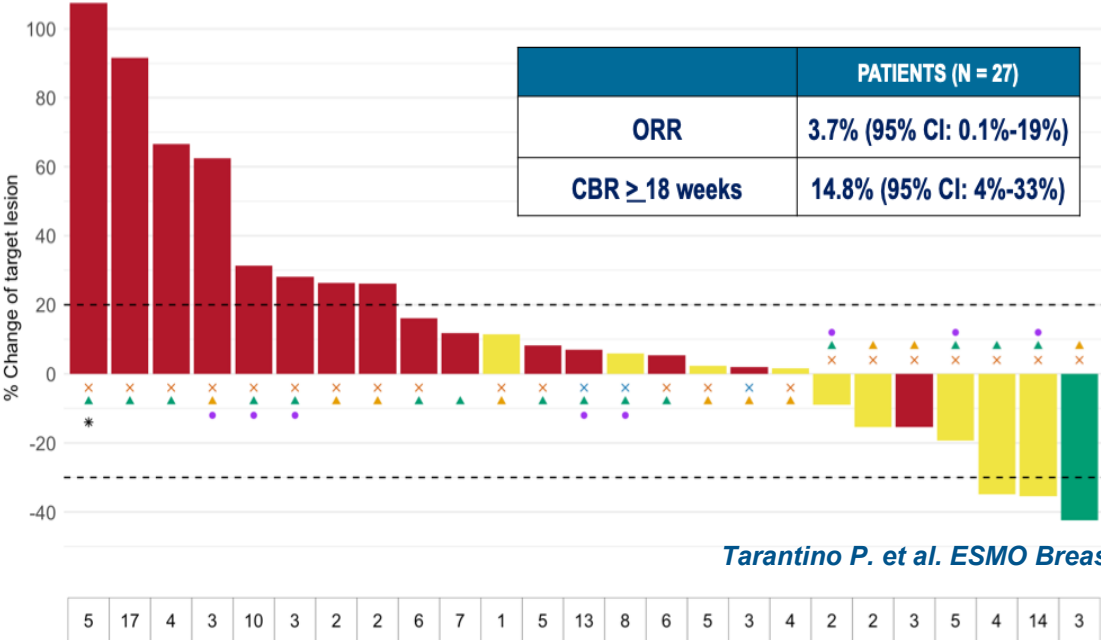


Source: *ClinicalTrials.gov landscape analysis, 2026*

TOP1i deliver good response rates, but most pts eventually progress

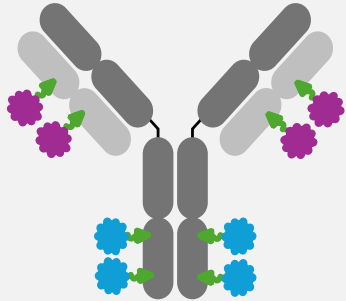
Re-treatment with same MoA ADC shows reduced ORR, PFS & OS

TOP1i ADC Cross-Resistance: SATEEN (T-DXd → SG + Trastuzumab) Showed 3.7% ORR in HER2+ mBC

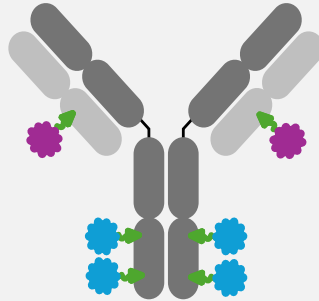


Sutro's Next-Gen Dual-Payload ADCs: Diverse MoA Payloads & Controlled DAR Ratios to Overcome Resistance & Improve Tolerability

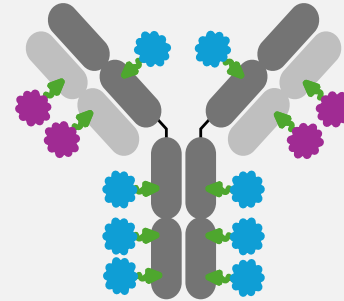
**Controlled
DAR Ratios**



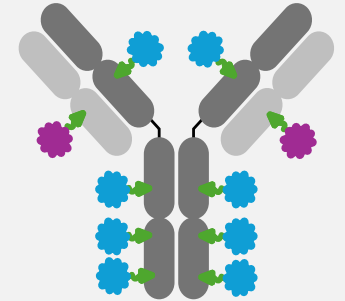
DAR 4+4



DAR 4+2



DAR 8+4



DAR 8+2

TOPO1i x DDRi

TOPO1i x MTi

STRO-227 (aPTK7 dpADC)

TOPO1i x Immune Agonist

ASP2998 (aTROP2 iADC)

ASP388B (aTAA1 iADC)

TOPO1i x Novel MoA

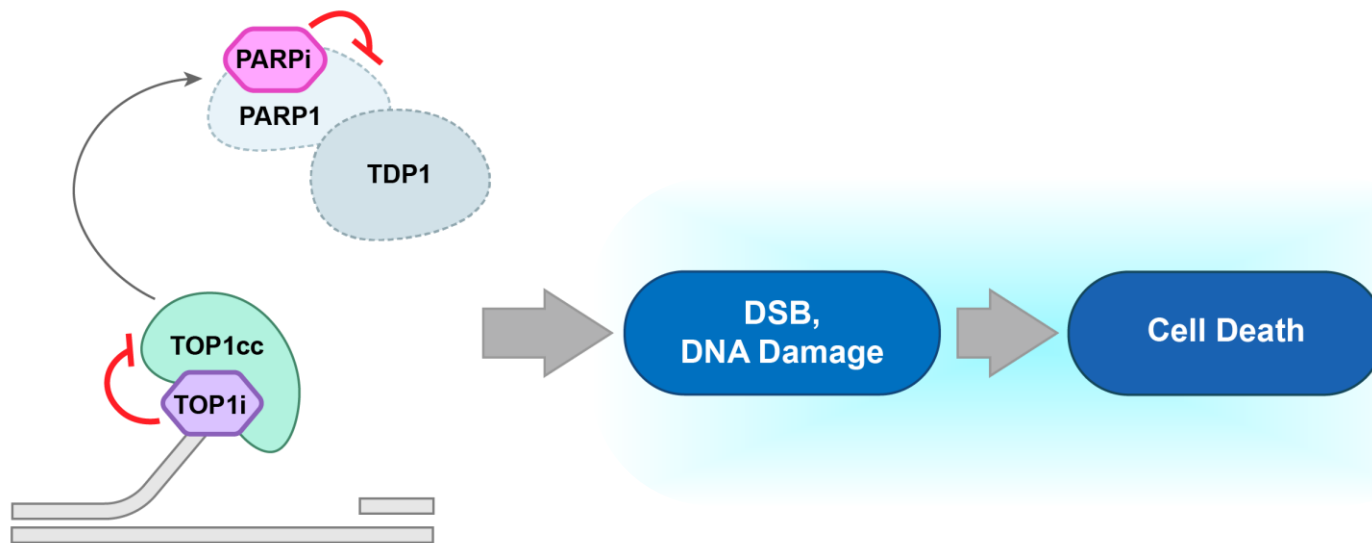
- Matching payloads to tumor biology
- Potential to delay resistance and enable more durable responses & prolonged PFS

TOPOi + DDRi Combinations Are Challenging in the Clinic Due to DLT

High DAR TOPO1i x DDRi dpADCs to Drive Synthetic Lethality, Overcome Resistance

TOPO1i x PARPi

Mechanistic Rationale for Combining TOPO1i with PARPi for Synergetic Activity



Earlier evidence of PARPi enhancing
TOPO1 induced cytotoxicity
Mattern MR, et al. Cancer Research (1987)

Preclinical and emerging clinical evidence supports potential utility in HRD & HRP tumors, including PARP resistant patients

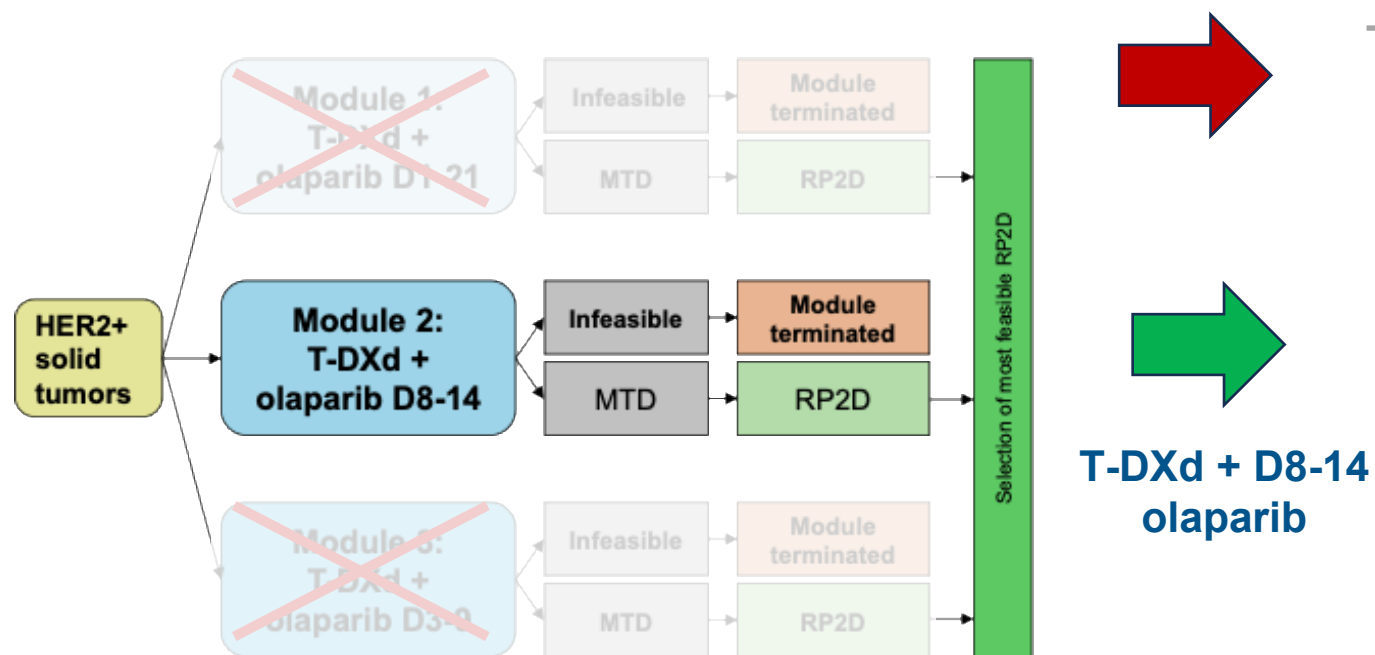
Can We Improve Efficacy & Safety by Delivering TOPO1i via ADC in Combination with PARPi?

TOP1i ADC	PARPi	Phase	Indication	Clinical Activity	Clinical Tox	Status
Trodelvy	Talazoparib	NCT04039230; Phase I/II	mTNBC	ORR 30%; PFS 6.2 mo; OS 18 mo	High hematologic/GI tox; dose reduction 58%	Not recruiting
Trodelvy	Rucaparib	NCT03992131 Phase I/II	TNBC, OC; UC, endometrial	small dataset (n= 6), preliminary responses reported	Overlapping hematologic/GI tox	Terminated
Enhertu	Olaparib	NCT04585958; Phase 1	HER2+ OC, endometrial	ORR 54%	Myelosuppression & GI	Recruiting
Enhertu	AZD5305 (PARP1i)	NCT04644068/ PETRA	Advanced solid tumors	NA	NA	Not recruiting
Dato-DXd	AZD5305	PETRA	Advanced solid tumors	NA	NA	Not recruiting

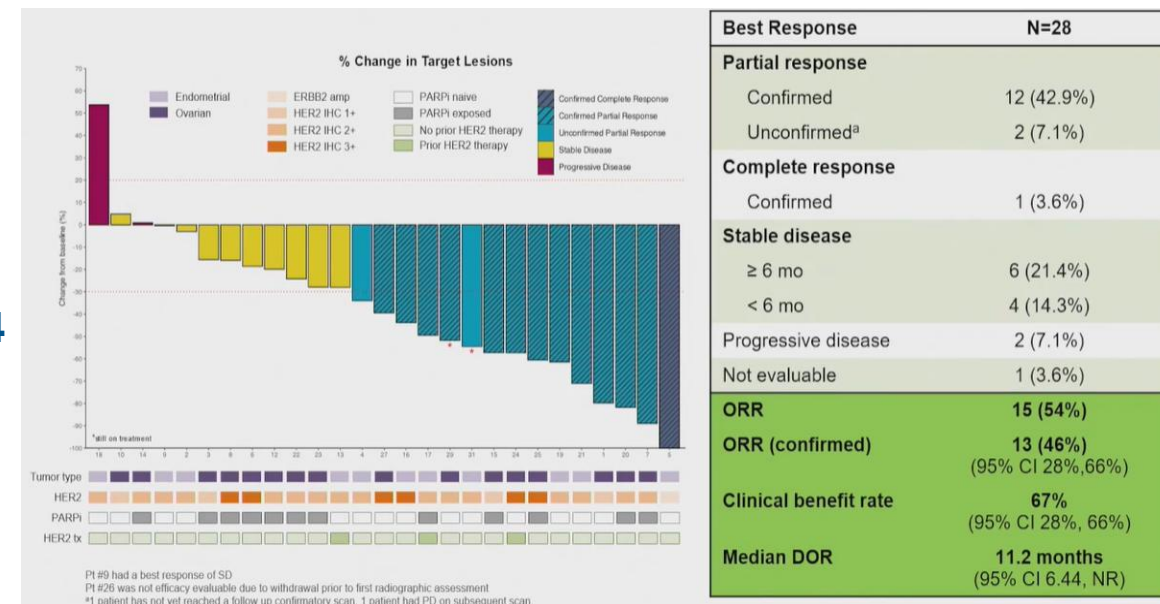
TOPOi ADCs with PARPi combinations: Overlapping toxicity is a key clinical challenge

T-DXd + Olaparib: Concurrent Dosing Limited by Overlapping Toxicity

NCT04585958 Phase 1 (Dr. Elizabeth Lee et al. AACR 2026)



T-DXd + continuous or early olaparib was unfeasible, with multiple DLTs, mostly **febrile neutropenia**



Key challenges with TOPO1i ADC + PARPi

- Clinical proof of superior PFS/OS remains limited
- Gapping schedule may reduce combo benefit?
- Different ROAs may limit optimal tumor sensitization?

Sutro's Cell-Free Platform & Diverse MoA Payloads Enables Site-Specific Single- and Dual-Payload ADCs

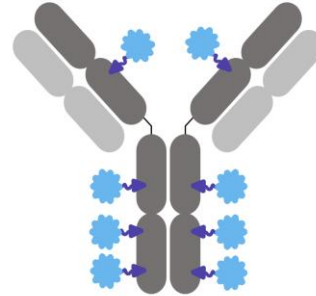
 Rapid Make/Test Cycle to Optimize ADC, dpADC & iADC Design

Antibody Discovery Platform

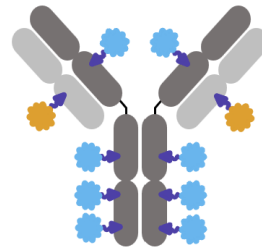
- XpressCF+® synthesis derived IgGs with non-natural amino acid(s)
- 4000L GMP run demonstrated

Site-Specific Conjugation Chemistry

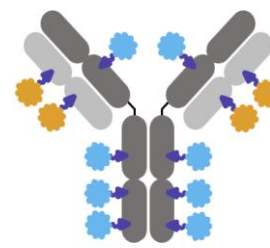
- Stable homogenous high DAR (8, 12 & 16) ADCs
- Dual non-natural amino acids enabled for dpADC & iADCs



Homogenous DAR8 ADCs
(STRO-004 & STRO-006)



DAR 8+2



DAR 8+4

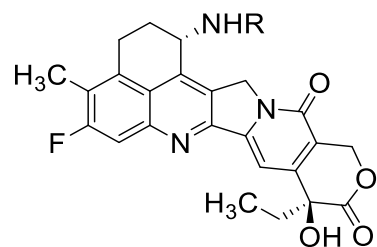
Optimal Ratios of dpADC/iADCs
to Enhance Potency, Overcome
Resistance

Diverse MoA Payloads

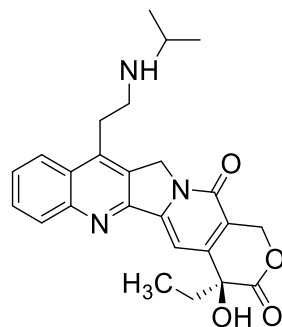
Proprietary Tumor Selective Linkers

Diverse MoA Payloads for ADC, dpADC & iADC Development to Target Multiple Tumor Indications

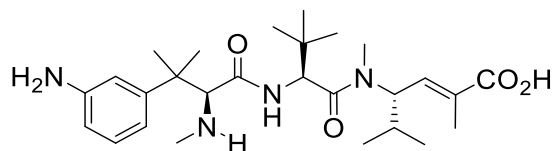
Cytotoxin Payloads



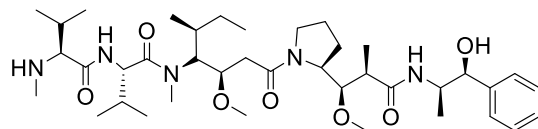
R = H (Exatecan)
R = Gly (Gly-Exatecan)



Belotecan



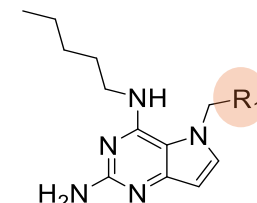
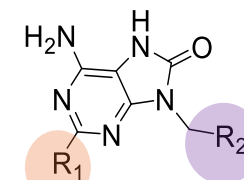
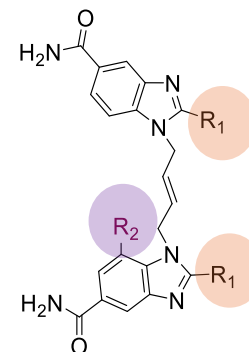
Hemiasterlin analog



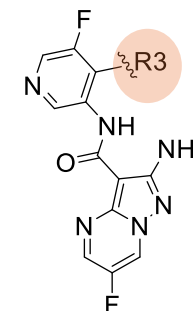
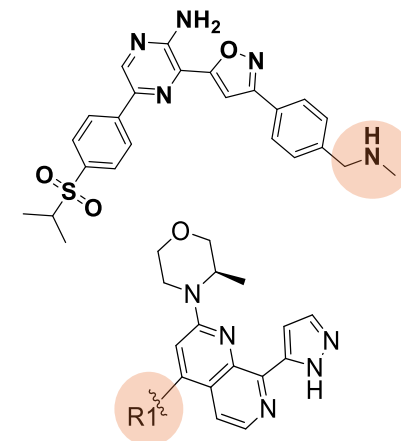
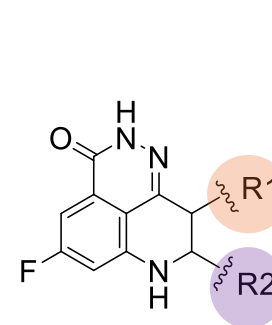
MMAE

Novel undisclosed MoA payload class to address unmet need in ADC development

Immune Agonists (STING, TLR7 & TLR7/8)

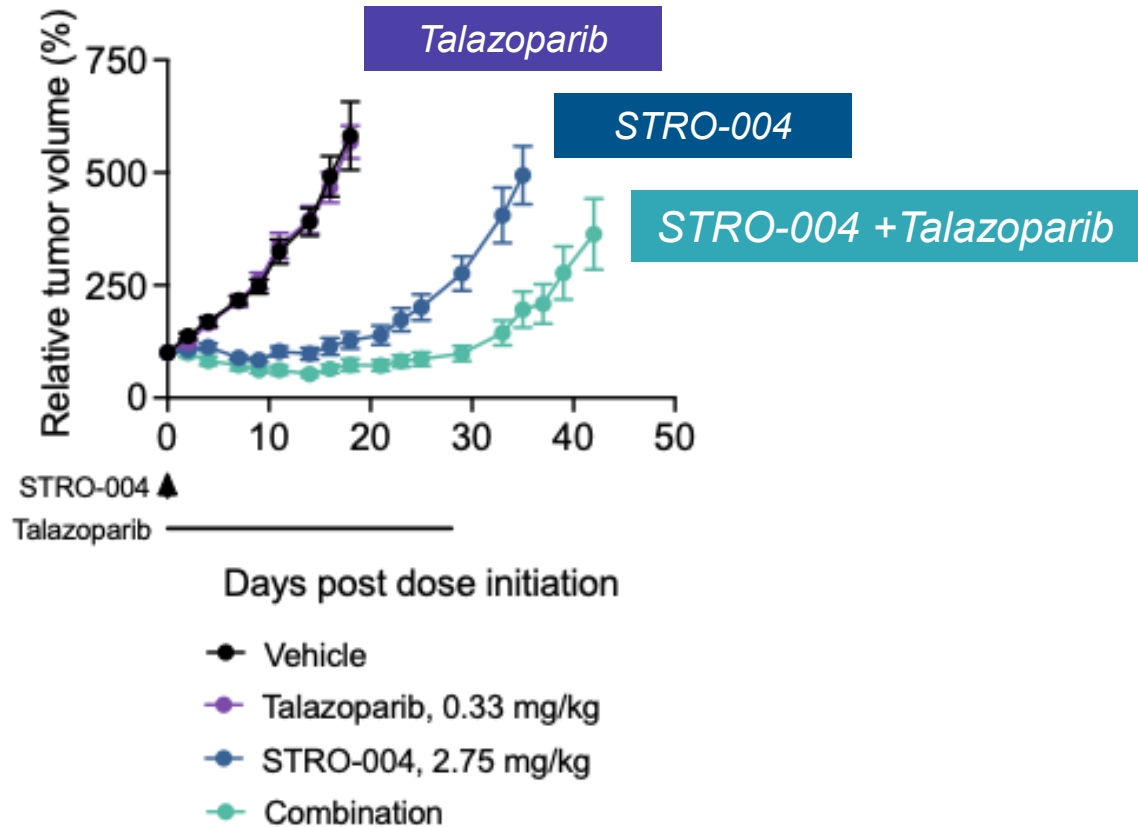


DNA Damage Response Inhibitors (PARPi & ATRi)



aTF DAR8 TOPO1i ADC (STRO-004) + Talazoparib Demonstrates Improved Efficacy vs STRO-004 in mCRPC Model

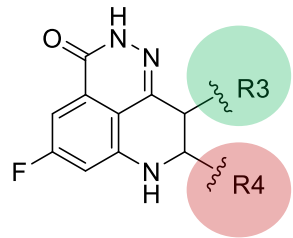
mCRPC (wtBRCA)
Frequent Dosing of Tala + Single Dose STRO-004



TOPO1i ADC and PARPi combo effect well established in preclinical studies

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

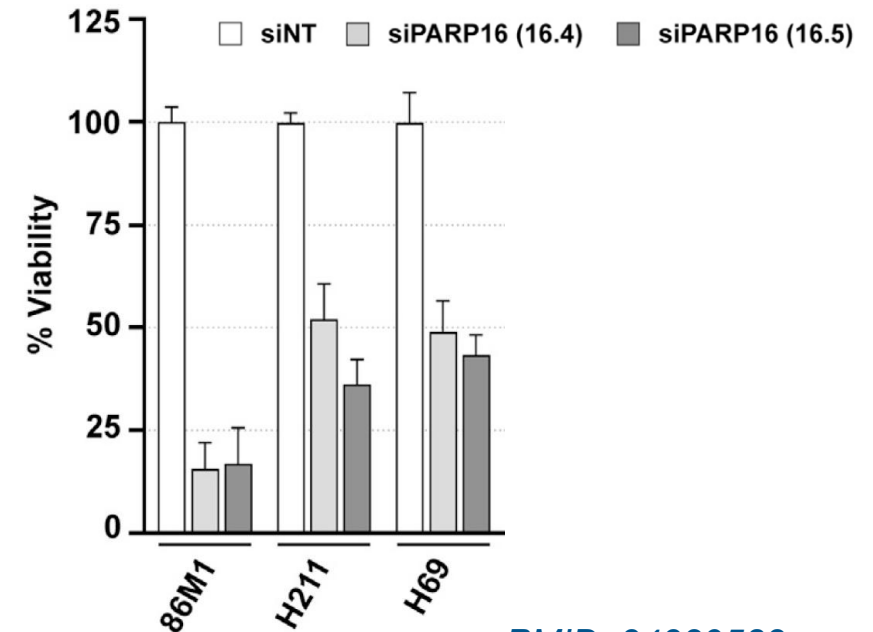
PARPi Characterization



Sutro Pan-PARPi

Assay	Sutro's Pan-PARPi
CAPAN-1 <i>in vitro</i> 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

Silencing PARP16 Significantly Reduces Cell Survival in SCLC

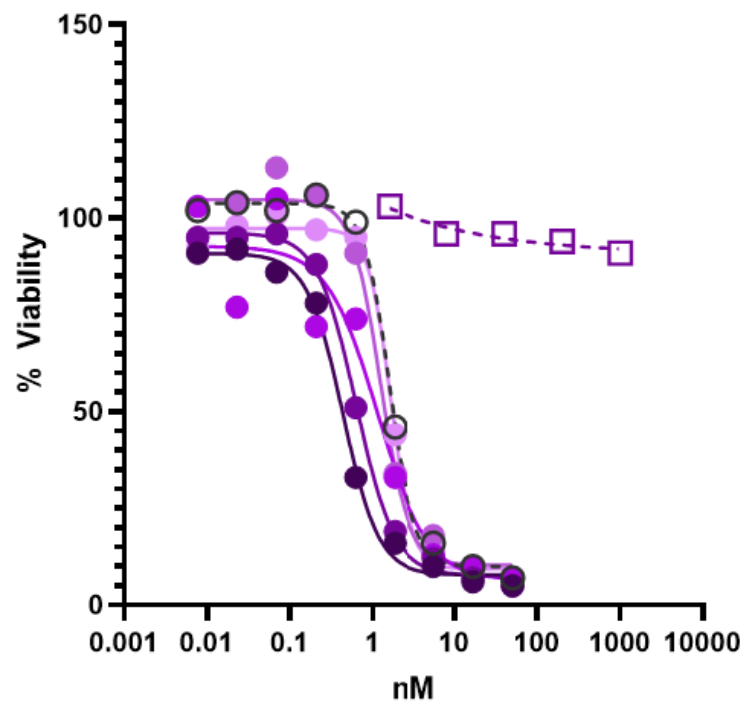


PMID: 34329582

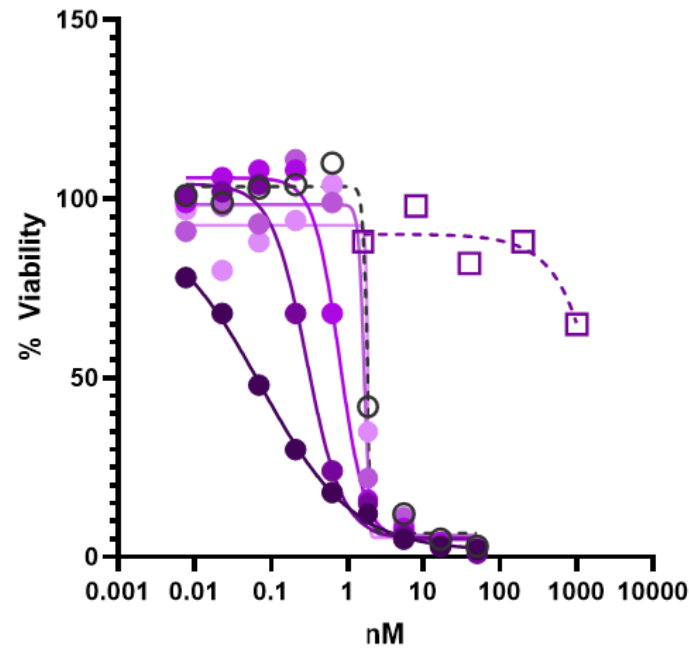
Sutro's Pan-PARPi Potentiates TOPO1i Activity Across Diverse Cancer Cell Lines

Cell Viability Assay

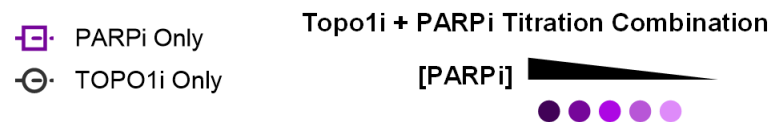
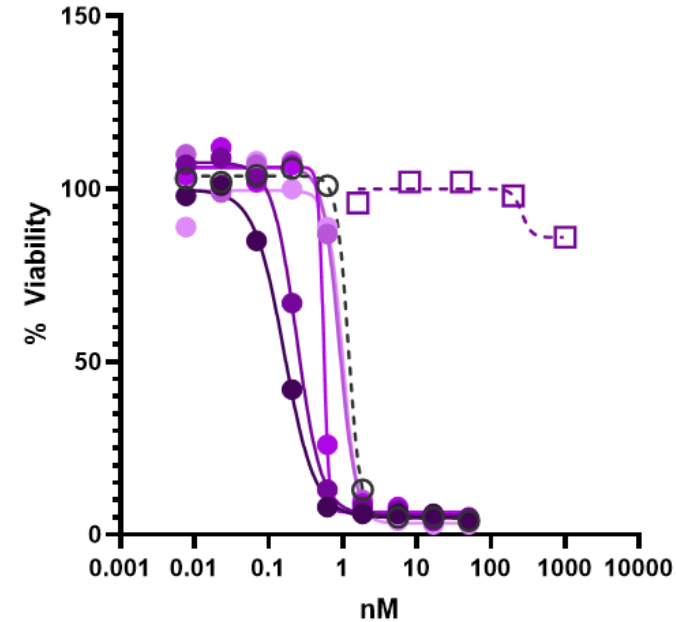
Gastric Cancer Cell Line (wtBRCA)



Breast Cancer Cell Line (wt BRCA)



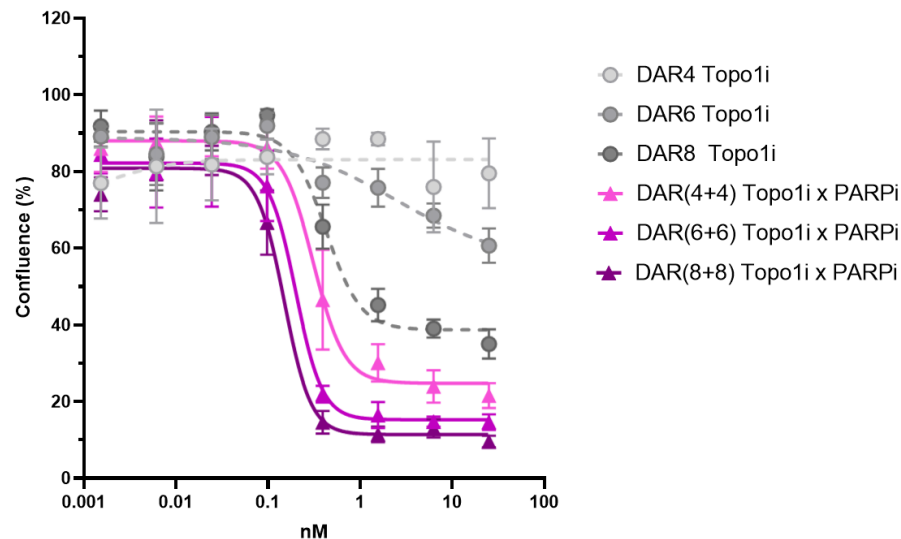
Lung Cancer Cell Line (wt BRCA)



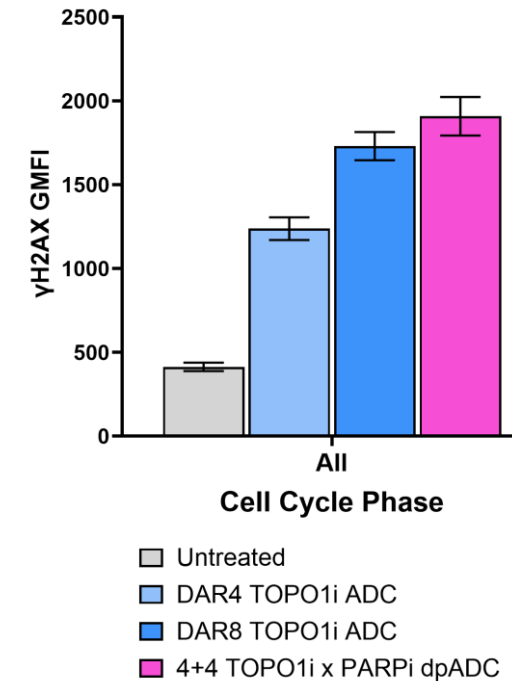
TOPO1i x PARPi dpADCs Show Superior Activity vs. Single-Payload ADCs and Induce Higher Level of DNA Damage

In Vitro Data

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



Increased DNA Damage *γH2AX Signal*

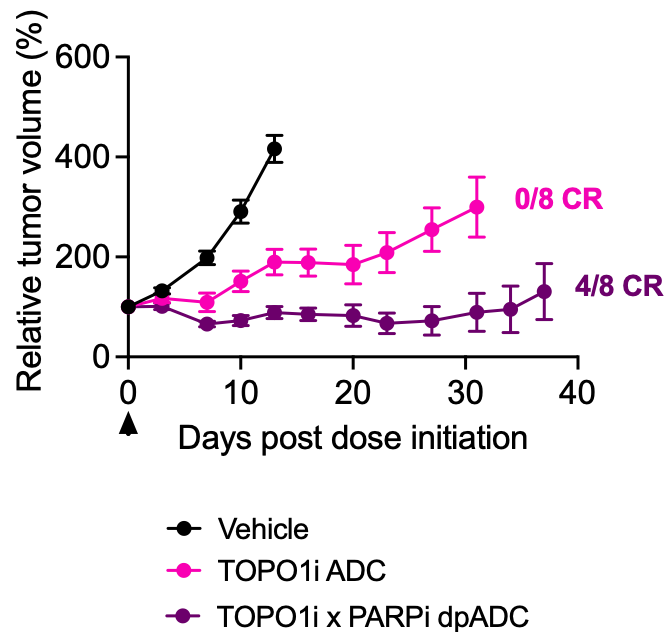


Similar trends are observed across gastric & breast cancer cell lines

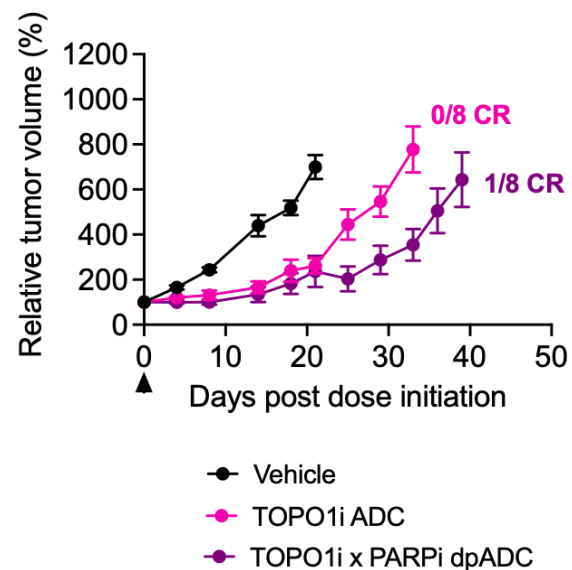
TOPO1i x PARPi dpADCs with Varied DAR Formats Demonstrated Improved Efficacy Compared to TOPO1i Single-Payload ADCs

In Vivo Across Different CDX Models

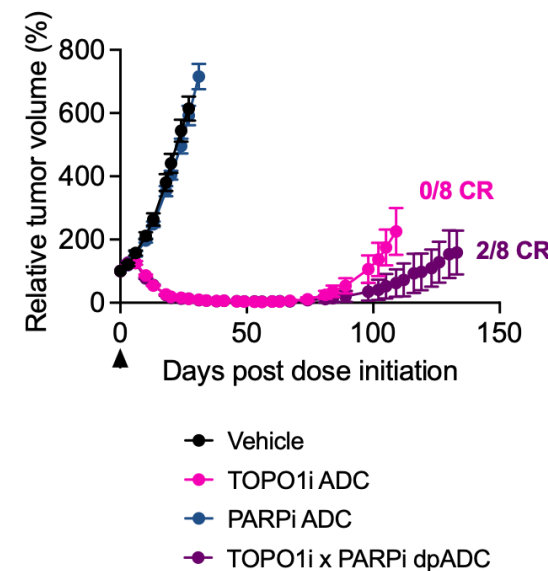
**Breast Cancer Xenograft Model 1
(wt BRCA)
4+4 TOPO1i x PARPi**



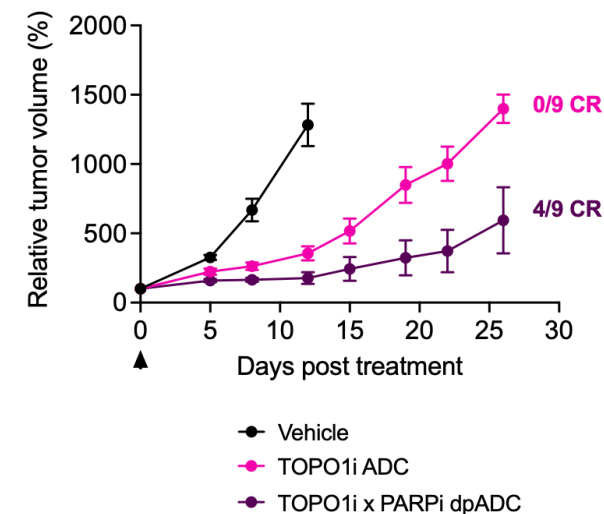
**Breast Cancer Xenograft Model 2
(wt BRCA)
4+4 TOPO1i x PARPi**



**Breast Cancer Xenograft Model 3
(wt BRCA)
8+4 TOPO1i x PARPi**



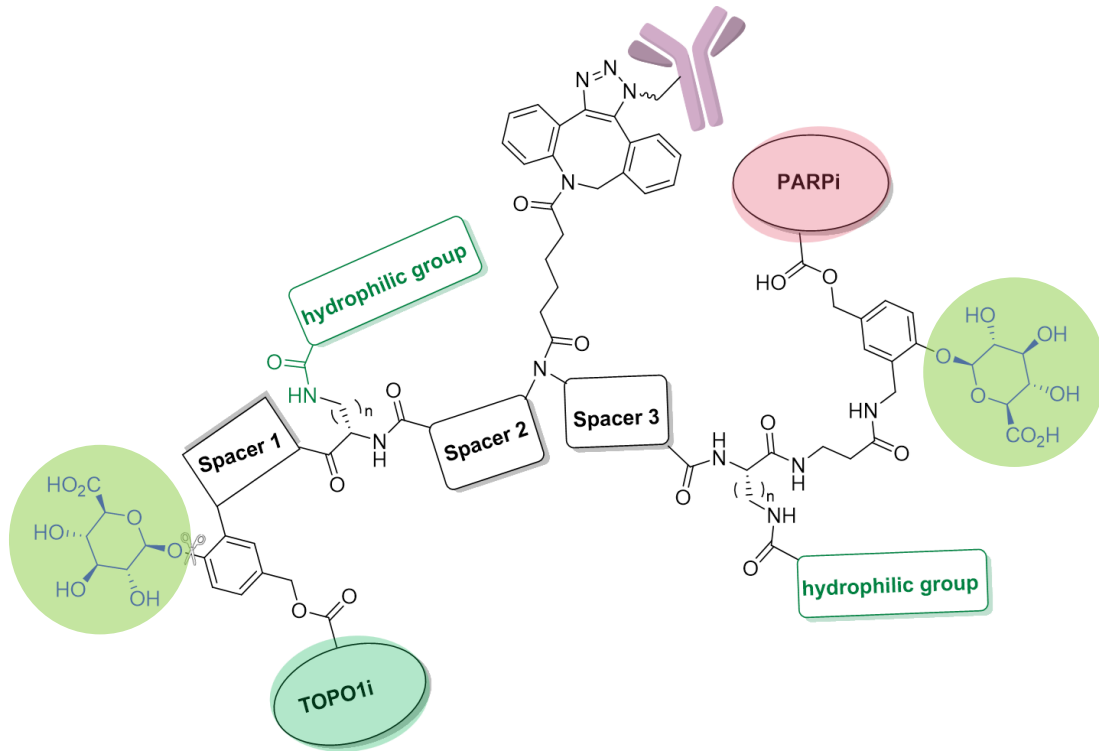
**MC38-hTAA
4+2 TOPO1i x PARPi**



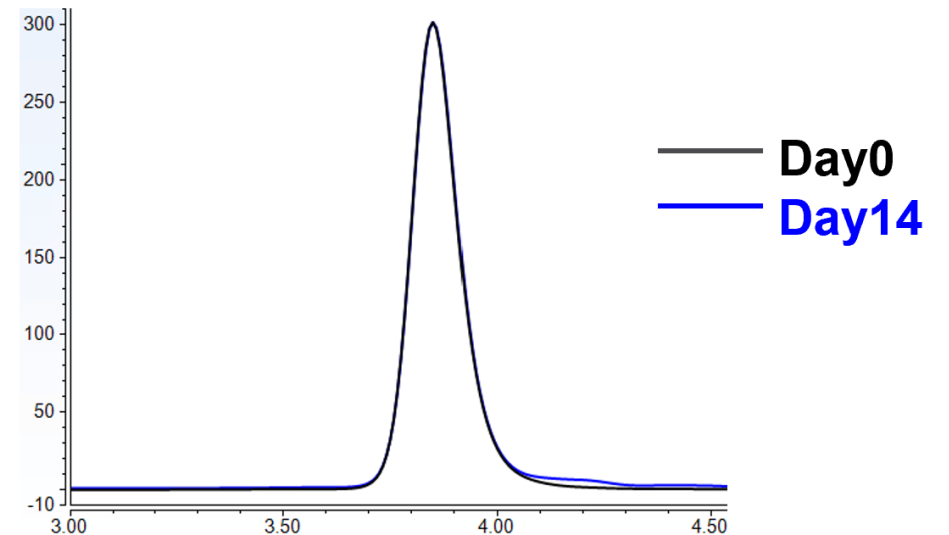
- All comparisons were performed at equivalent TOPO1i doses
- PARPi ADC alone was inactive supporting combination driven activity

Hydrophilic Tumor Selective Cleavable TOPO1i x PARPi DAR16 dpADC Demonstrates Desirable Physicochemical Properties

Branched β -glu Cleavable TOPO1i x PARPi DAR16 dpADCs



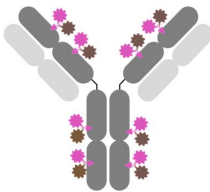
Comparison of DAR16 dpADC Monomer % by SEC After Incubation @ 40 °C



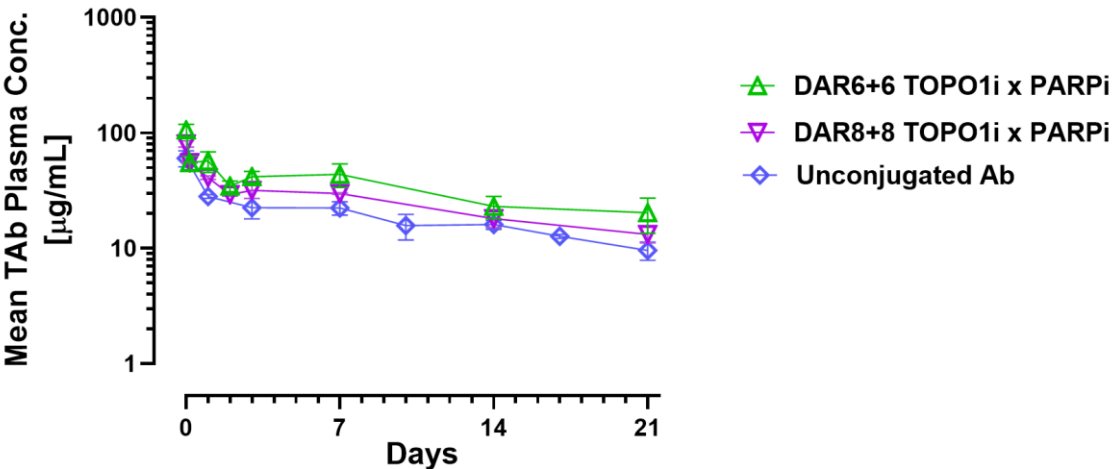
No significant changes observed in concentration, SEC, and RP-HPLC

DAR16 conjugates show FcRn binding similar to the unconjugated Ab

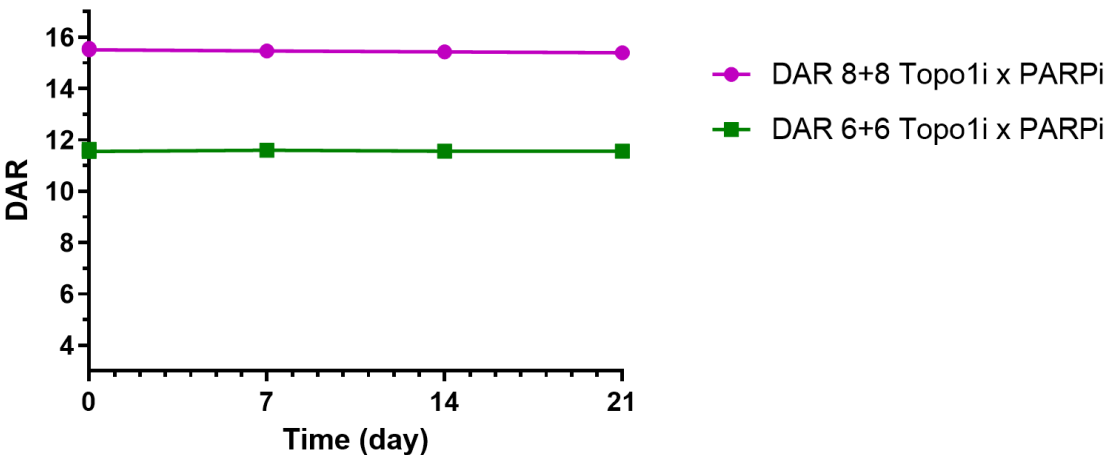
α HER2 High DAR TOPO1i x PARPi Dual-Payload ADCs Exhibited Favorable PK and *In-Vivo* DAR Stability



PK Profile of High DAR ADCs in C57BL/6 Mice



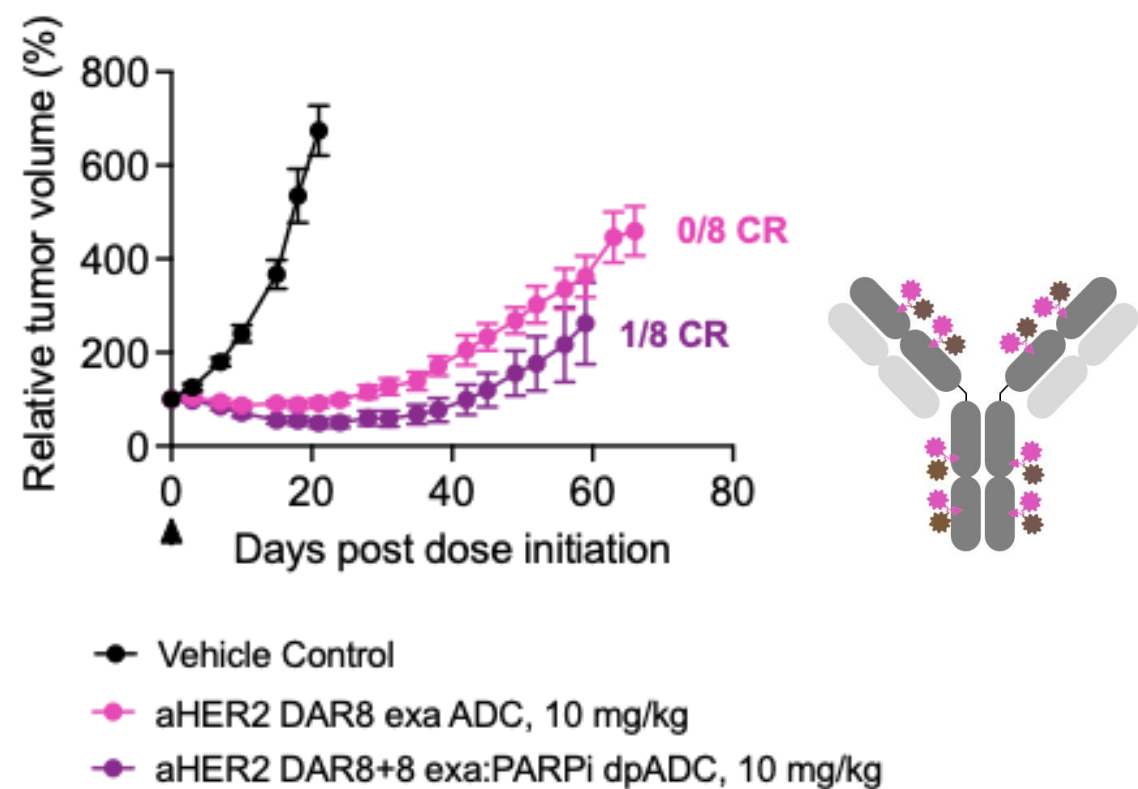
In-Vivo DAR Stability



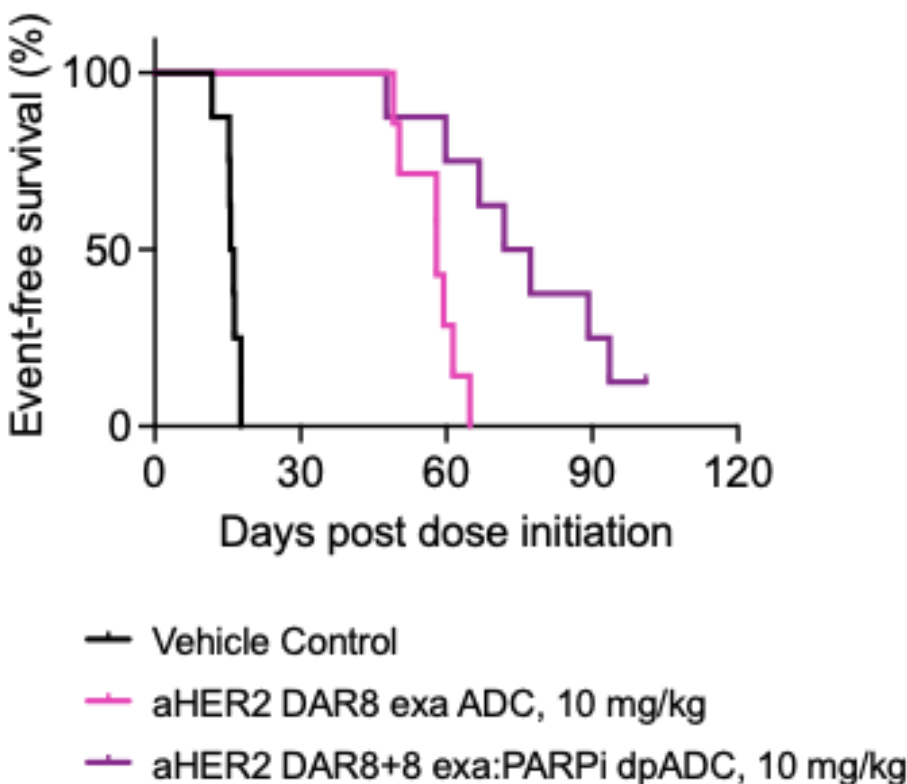
ID	DAR	t _{1/2} (d)	CL (mL/d/kg)	C _{max} (ug/mL)	AUC _{0-tlast} (d·ug·mL ⁻¹)	V _{ss} (mL/kg)
α TAA 8+8 TOPO1i x PARPi dpADC	16 (8+8)	13.2	3.92	80.4	512	73.8
α TAA 6+6 TOPO1i x PARPi dpADC	12 (6+6)	14.9	2.65	106	692	57.8
Unconjugated Ab	0	14.6	5.07	60.3	389	101

DAR16 TOPO1i x PARPi dpADC Enhances Efficacy and Delays Tumor Growth vs. TOPO1i ADC

Ovarian Cancer Xenograft Model (wt BRCA)



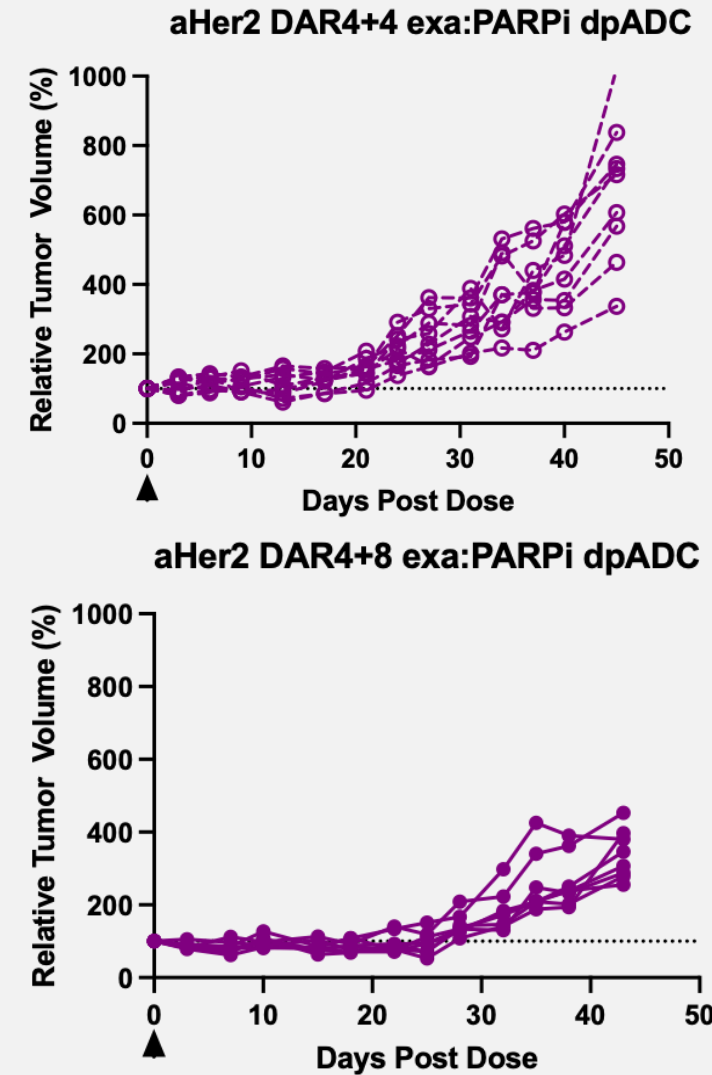
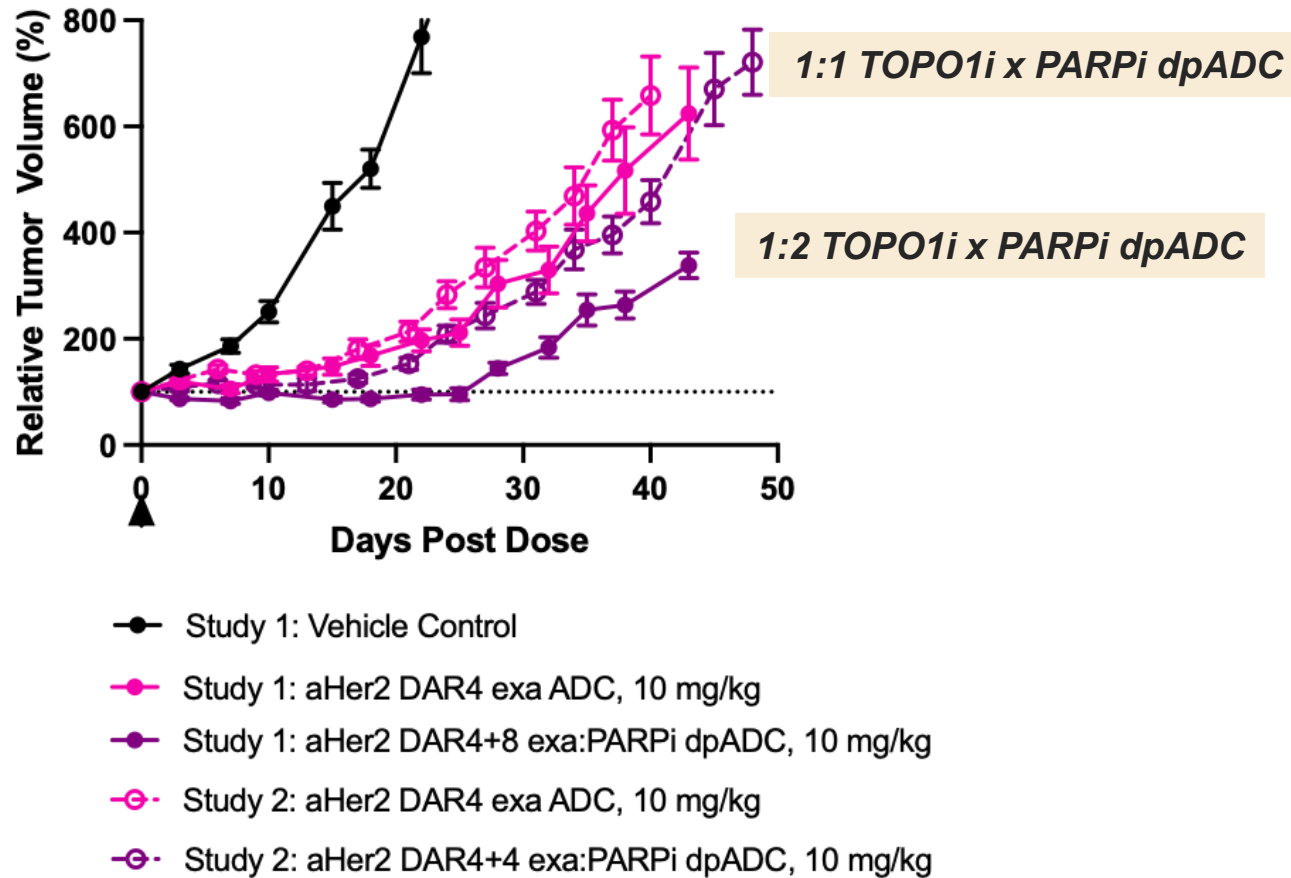
Time to Tumor Quadrupling (TVQT)



No body weight loss observed with dpADC or ADC treatment

1:2 TOPO1i x PARPi dpADC Enhances Tumor Growth Inhibition vs. Single Payload ADC

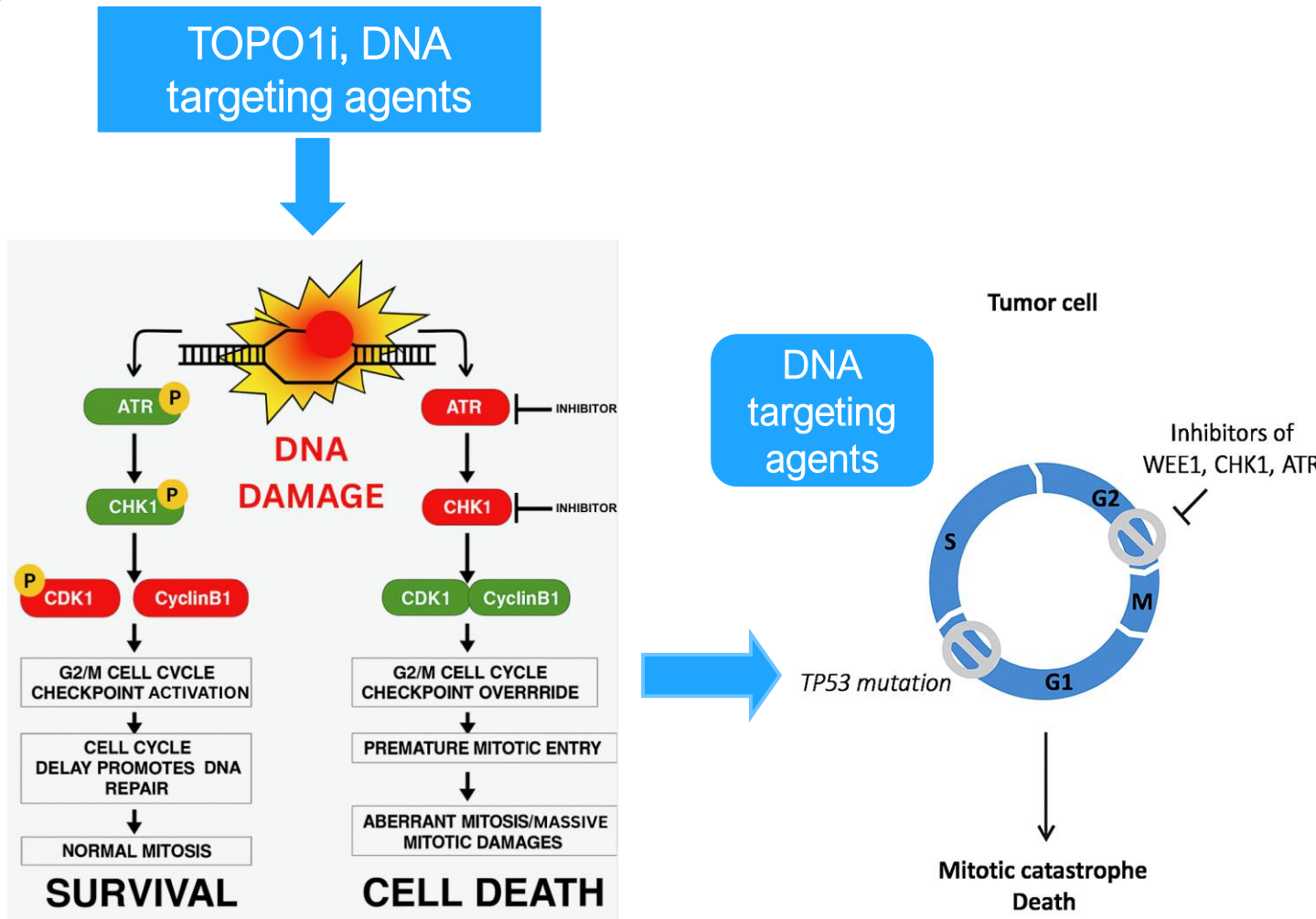
1:1 vs 1:2 TOPO1i x PARPi dpADC
Ovarian Cancer Model (wtBRCA)



Currently evaluating aTAA programs to target broad tumor indications

ATR Inhibition: A Complementary Strategy to Potentiate TOPO1i Activity

TOPO1i x ATRi



Di Rorà AGL et al., Simonetti G. *Cell Biol Toxicol*, 2024; 40(1):73 & Hauge S et al., Syljuåsen RG. *Int J Radiat Biol*, 2023; 99(6):941–950

- Emerging clinical data suggest DDR pathway upregulation in non-responders
(ICARUS-LUNG01 study of Dato-DXd)
- SLFN11 inactivation in ~50% of cancers is associated with broad chemoresistance
- ATRi restores TOPO1i sensitivity in SLFN11-deficient cells
(Jo U et al., Pommier Y. Proc Natl Acad Sci U S A, 2021; 118(6))

ATRI in Cancer Therapy: Clinical Challenges and the Path Forward with Dual-Payload ADCs

ATRI Monotherapy and Combination Therapies in Clinic

Next-Gen dpADCs

~~Elimusertib ATRi Monotherapy~~

Disease Control

- Prostate: 22.2%
- CRC: 52.2%
- Gynecologic: 72.7%
- Breast: 57.9%

Partial Response

- ATM loss: 44.1%

*DLT is grade 3–4
hematologic toxicities*

Yap TA et al., de Bono JS. *Cancer Discov*, 2025; 15(10):2019–2035

~~Elimusertib ATRi + Irinotecan~~

- 1 PR observed in pancreatic cancer
- Several SDs in CRC, gastric & other solid tumors

*Myelosuppression &
GI tox limit dose
intensity*

Krishnamurthy A et al., Villaruz LC. *Cancer Chemother Pharmacol*, 2025; 95(1):27

TOPO1i ADC + ATRi

- Trodelvy combo with Berzo (PR observed in NEPC, SCLC and several SDs)
- Enhertu combo with AZD6738 (*DASH trial, active, not recruiting*)

*Hematologic & GI
toxicities*

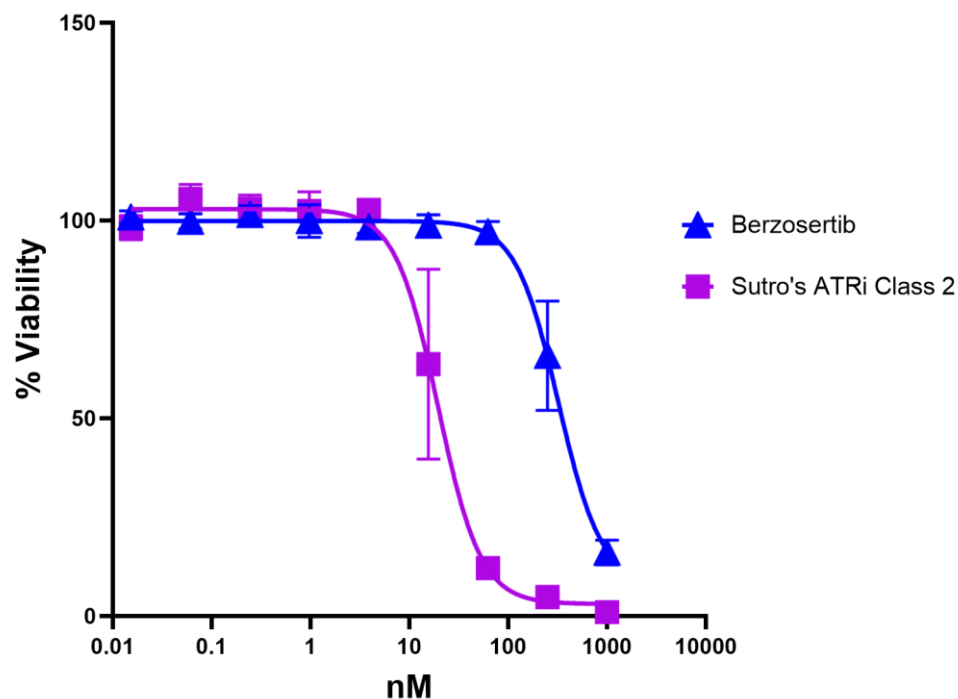
Abel ML et al., Thomas A. *Clin Cancer Res*, 2023; 29(18):3603–361 & ESMO 2025

αTAA TOPO1i x ATRi Dual-Payload ADCs

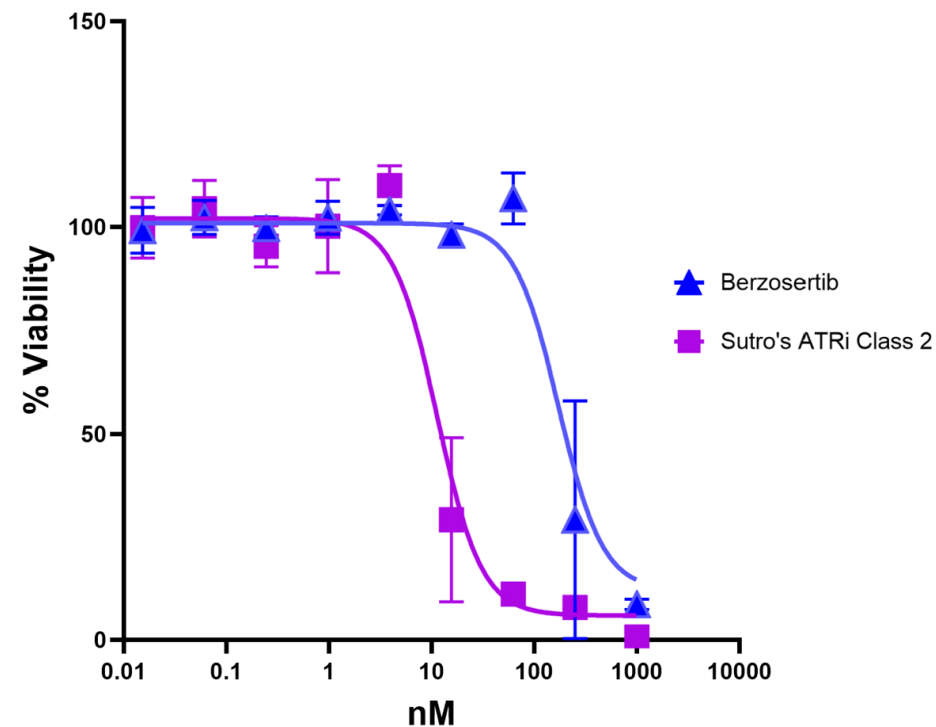
- Optimized ATRi suitable for dpADC
- Simultaneous delivery of TOPO1i & ATRi
- Controlled DAR ratios
- Potential to improve TI
- Overcome resistance

Sutro's Proprietary ATRi Analogs Demonstrate Greater Cellular Potency Than Berzosertib

Prostate Cancer Cell Line
in vitro potency



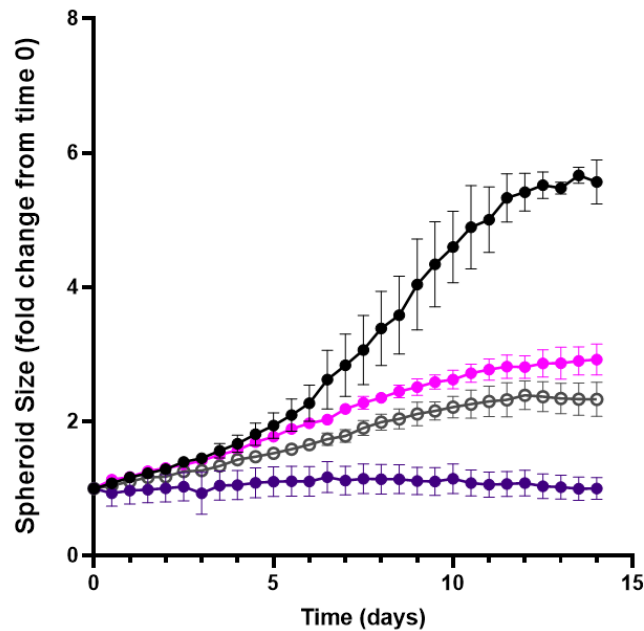
Colon Cancer Cell Line
in vitro potency



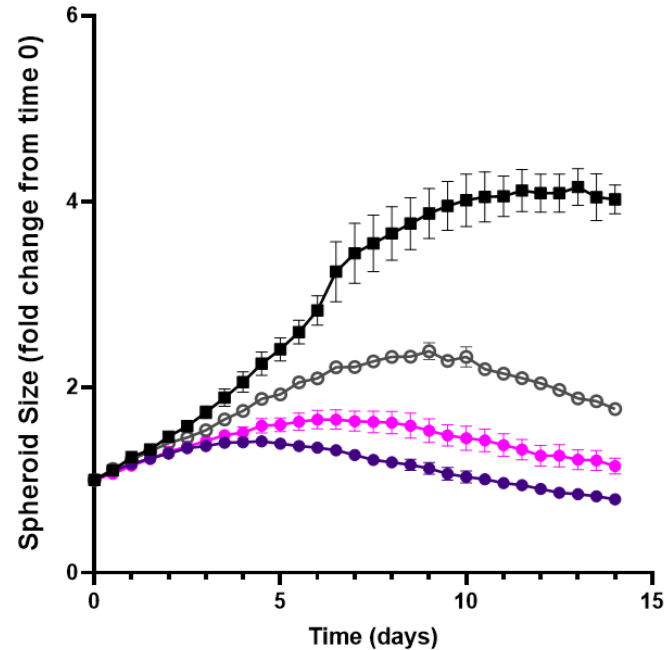
Identified distinct classes of potent ATRi that are not substrates of drug efflux pumps

TOPO1i x ATRi Dual-Payload ADC Shows Moderate Potency vs. Single-Payload ADCs in Spheroid Cell Killing Assay

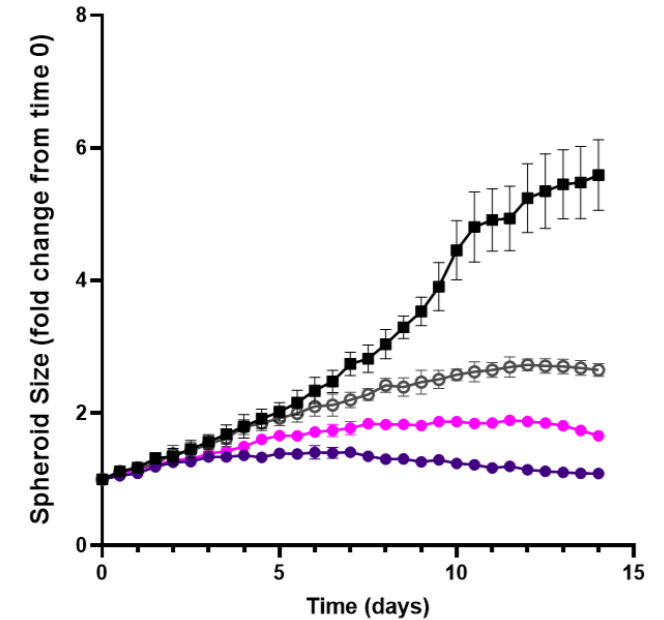
Ovarian Cancer Cell Spheroids
In vitro potency @ 25 nM



Ovarian Cancer Cell Spheroids with
Reduced Enhertu Sensitivity
In vitro potency @ 100 nM



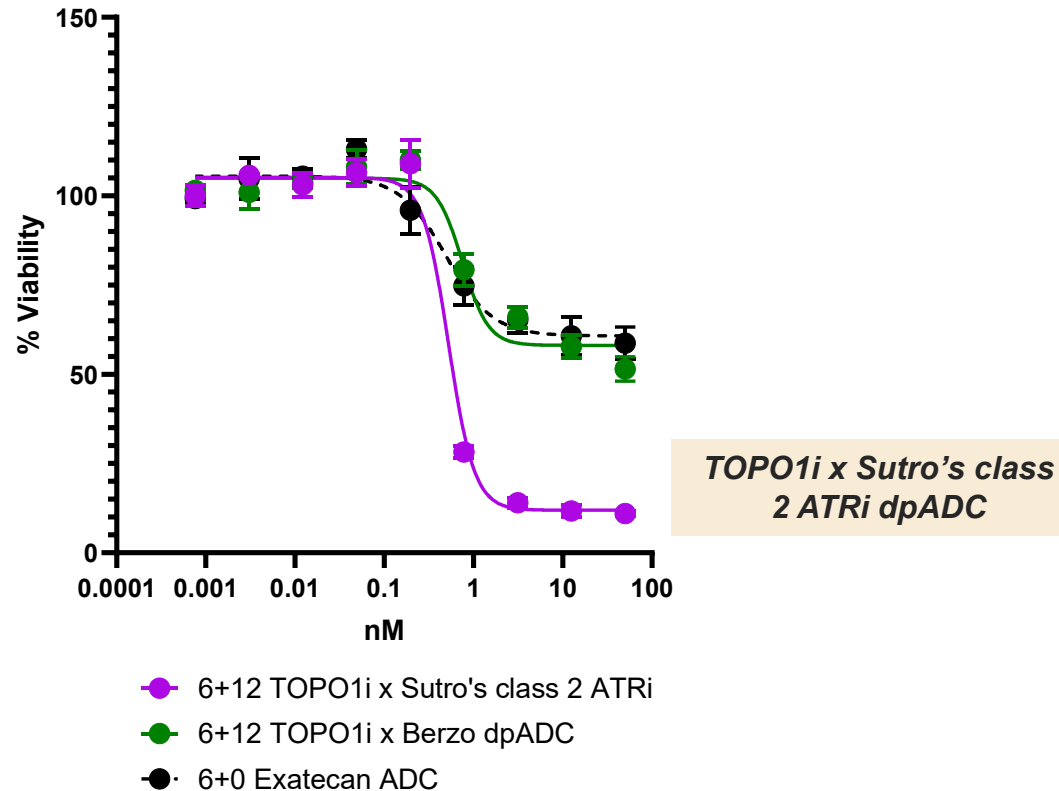
Ovarian Cancer Cell Spheroids with
Reduced Enhertu Sensitivity
In vitro potency @ 100 nM



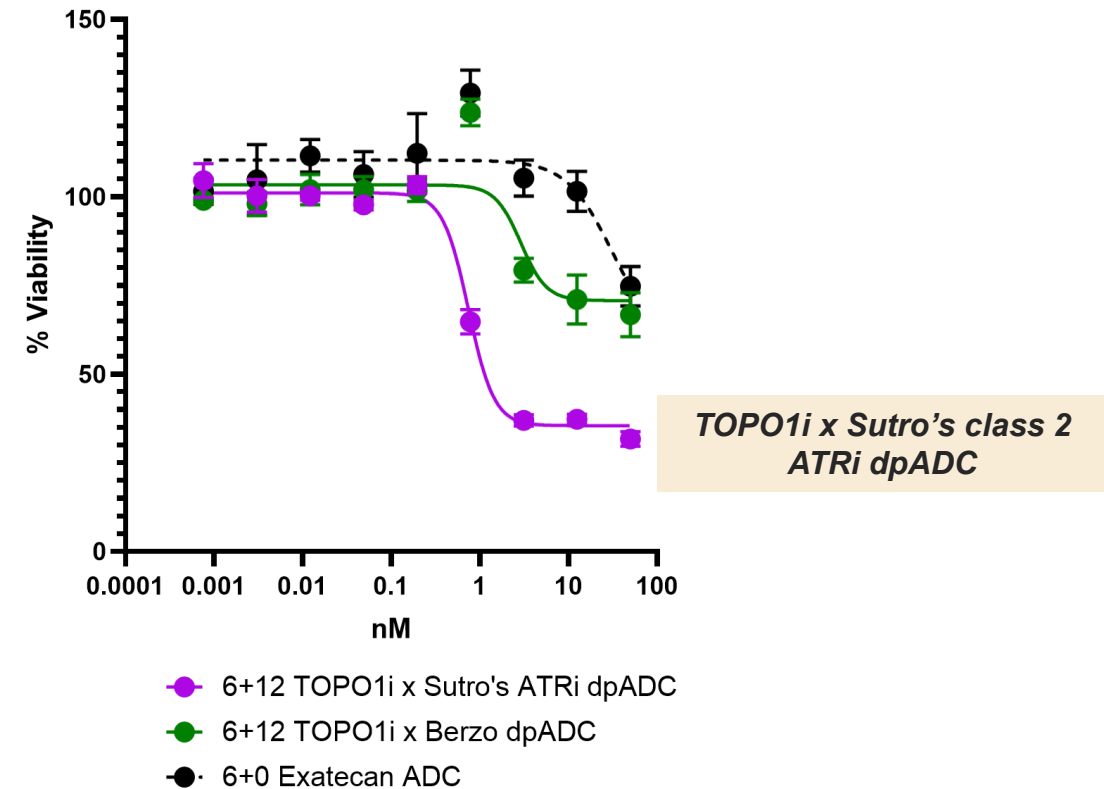
● Untreated ● TOPO1i ADC
● Enhertu ● TOPO1i x ATRi dpADC

1:2 TOPO1i x ATRi dpADC Displayed Enhanced Activity vs. Single Payload ADC

Breast Cancer Cell Line 1
6+12 TOPO1i x ATRi dpADC



Breast Cancer Cell Line 2
6+12 TOPO1i x ATRi dpADC



- 1:2 TOPO1i x ATRi dpADC outperforms 1:1 dpADC
- Evaluating aTAA programs to target replication stress across broad tumor indications

Take-Home Messages

Next-Gen High DAR 1:2 TOPO1i x DDRi dpADCs for Broad Tumor Indications

- ATRi, PARPi with reduced efflux address key resistance mechanisms
- Site-specific conjugation + tumor selective hydrophilic β -glu linkers enable controlled 1:2 high DAR dpADCs
- Simultaneous delivery TOPO1i + DDRi enhances DNA damage & anti tumor efficacy
- High DAR dpADCs demonstrate excellent PK, DAR stability & improved efficacy across diverse CDX models
- Potential to overcome systemic combination dosing limitations & widen therapeutic index and delay resistance

Sutro's Single & dpADC Portfolio Presentations at WADC26

STRO-004 (aTF DAR8 TOPO1i ADC)
Daniel Calarese, PhD on behalf of
Hans-Peter Gerber, CSO

Unveiling the Early Clinical Safety & PK
Profile of STRO-004 to Understand How
Enhanced Design & Preclinical
Characterization Links to Differentiated
ADC Clinical Performance

Oct 13th @ 9:30 AM

STRO-006 (aITGB6 DAR8
TOPO1i ADC)
Alice Yam, PhD

Driving Clinical Success With STRO-
006: Breaking Down Insights From PDX
Response & Translational Biomarkers

Oct 13th @ 12:00 PM; Preclinical

STRO-227 (aPTK7 8+2 dpADC)
Daniel Calarese, PhD

Breaking Down Preclinical
Characterization of STRO-227 Dual
Payload ADC to Evaluate Efficacy &
Safety in ADC Resistance Models

Oct 14th @ 2:30 PM; Preclinical

Acknowledgments



BD: Lucas Donigian, SVP, BD
ldonigian@sutro.bio

Research: Hans-Peter Gerber, CSO
hgerber@sutro.bio

IR: Emily White, Executive Director
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