Development of Site-Specific Dual Payload ADCs Featuring Novel Linker Payloads to Overcome Resistance Mechanisms

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Presentation Outline

❑ Increasing ADC Potency and Safety

– Exploration of novel tumor-selective β-glu cleavable linker payloads to enhance efficacy and therapeutic index of high DAR site-specific ADCs

❑ Site-Specific TOPO1i x DDRi Dual-Payload ADCs

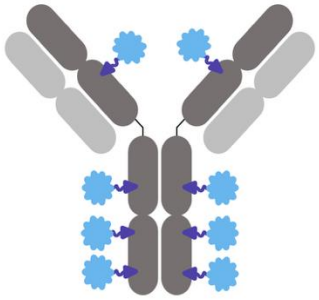
– Development of novel PARPi and ATRi LPs for combining with TOPO1i to increase potency and overcome tumor resistance

Harnessing the Cell-Free Platform and Diverse MoA Payloads to Enable Next-Generation Single and Dual-Payload ADCs

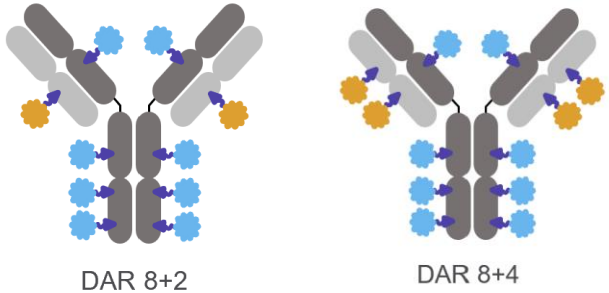
Rapid Make/Test Cycle to Optimize ADC, dpADC & iADC Design

Antibody Discovery Platform
- XpressCF+® synthesis derived IgGs with non-natural amino acid(s)
- Robust process, 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)



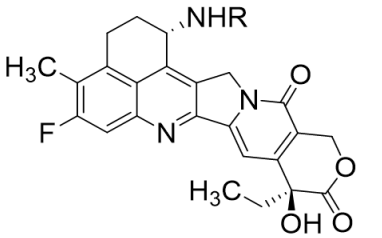
Optimal Ratios of dpADC/iADCs to Enhance Potency, Overcome Resistance

Diverse MoA Class Payloads
- Microtubule inhibitors
- Topo1 inhibitors
- DNA repair inhibitors
- Immune stimulants
- Novel MoA payload class

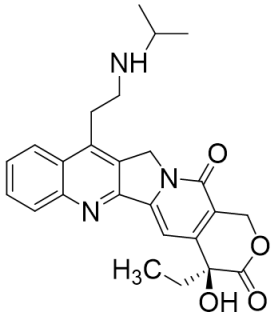
Proprietary Tumor Selective Linkers
- Hydrophilic β-glucuronidase & protease cleavable linkers
- Branched homo & hetero linker payloads
- Non-cleavable linkers

Diverse Novel Payload Platforms for ADC, Dual-Payload ADC and iADC Development to Target Multiple Tumor Indications

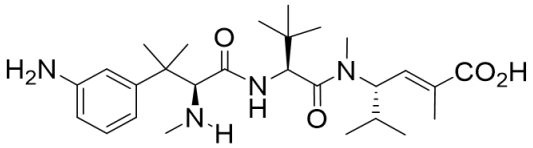
Cytotoxin Payloads



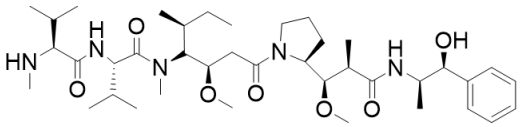
R = H (Exatecan)
R = Gly (Gly-Exatecan)



Belotean



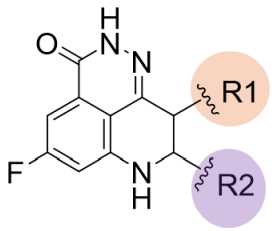
Hemiasterlin analog

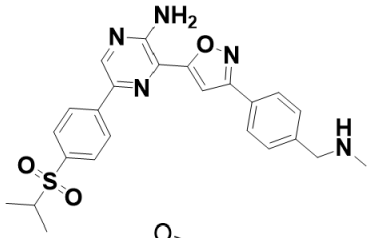


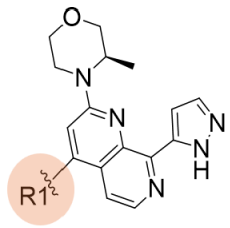
MMAE

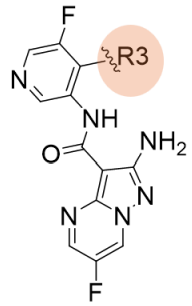
& Novel MoA payload class to address unmet need in ADC development

DNA Damage Response Inhibitors (PARPi & ATRi)

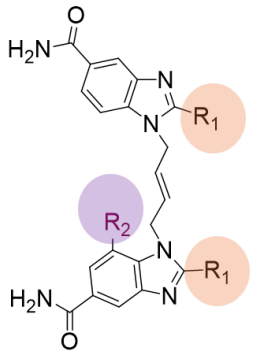


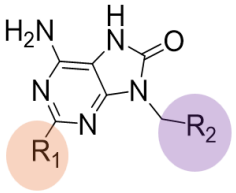


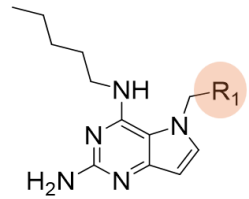




Immune Agonists (STING, TLR7 & TLR7/8)

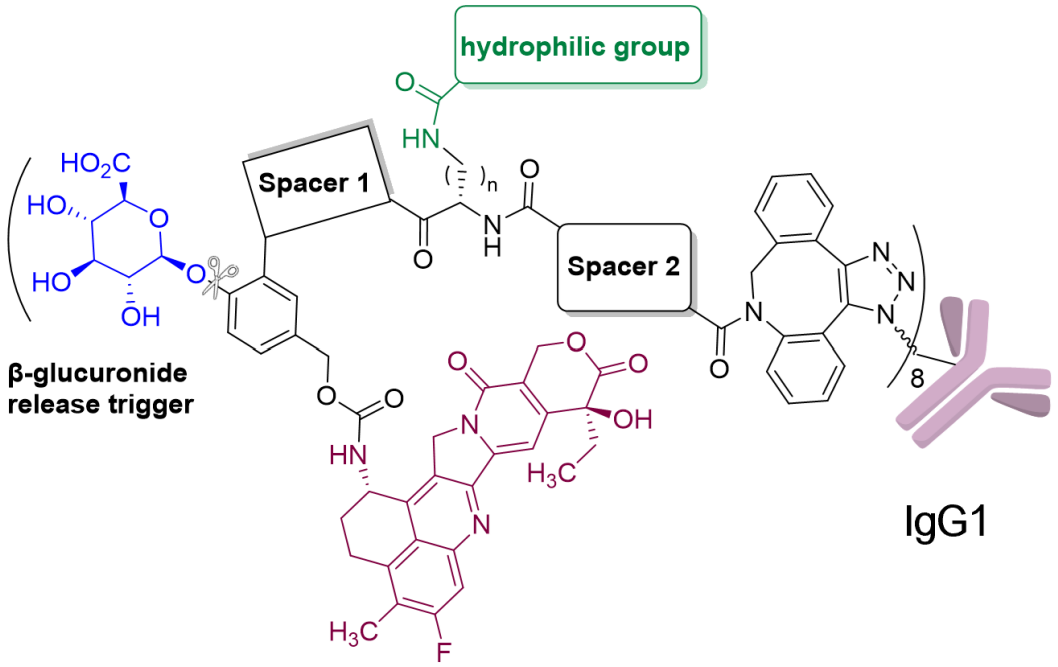




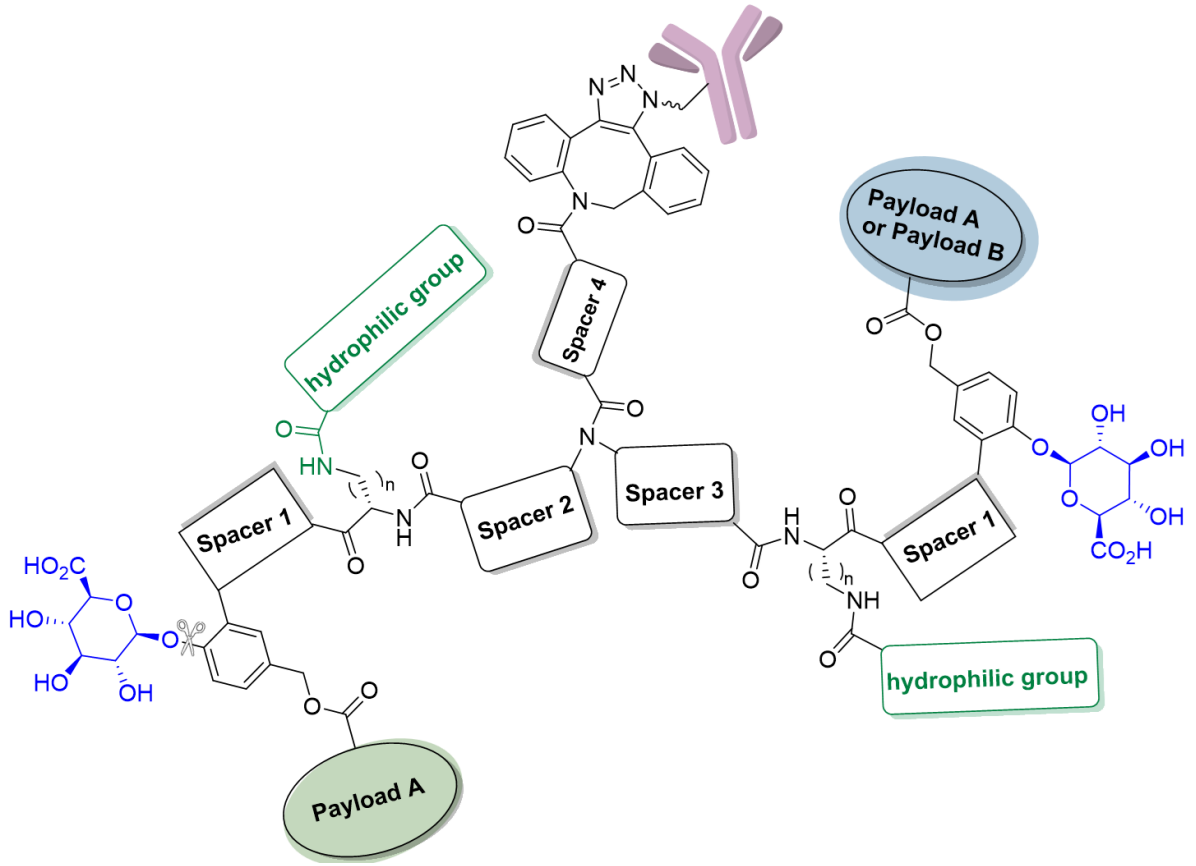


Hydrophilic β-glucuronidase Cleavable LPs for High DAR Single & Dual Payload ADCs With Improved Efficacy and Safety

Homogeneous β-glu cleavable Exatecan DAR8 &12 ADCs

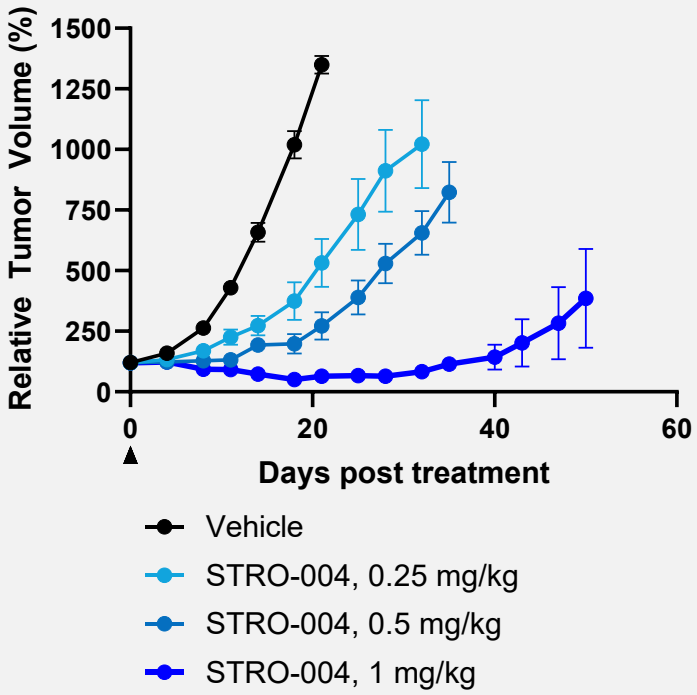


Branched β-glu cleavable single & dual payload DAR16 ADCs

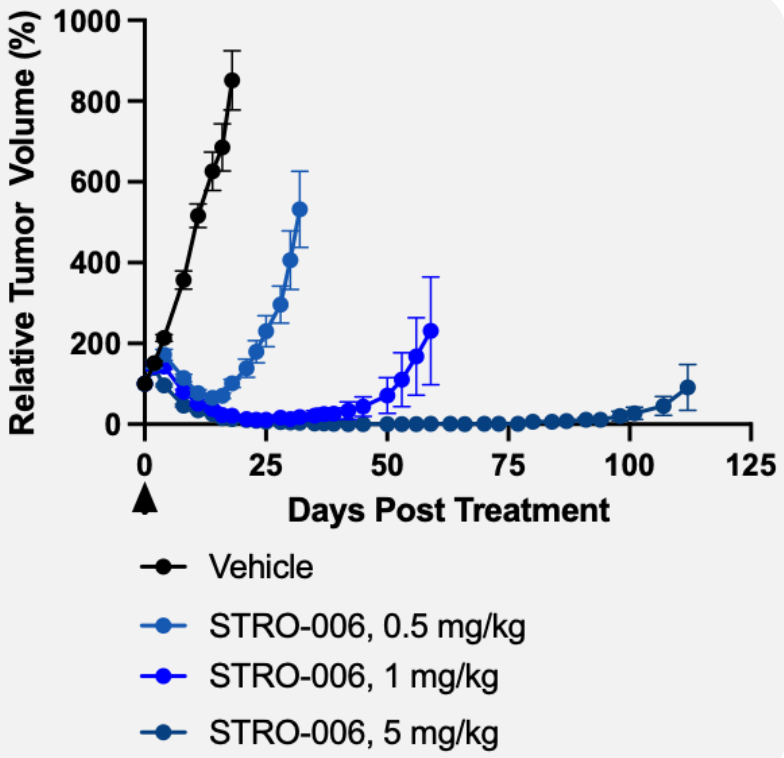


Sutro's Site-Specific DAR8 ADCs Utilizing the Hydrophilic β-glu Cleavable Exatecan LP Displayed Potent Efficacy and Improved Safety

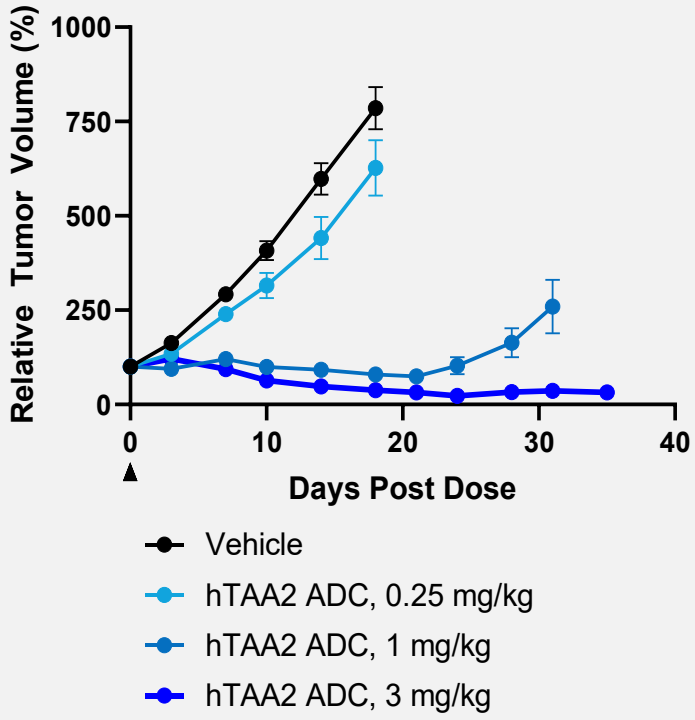
Head and Neck



Lung



Gastric

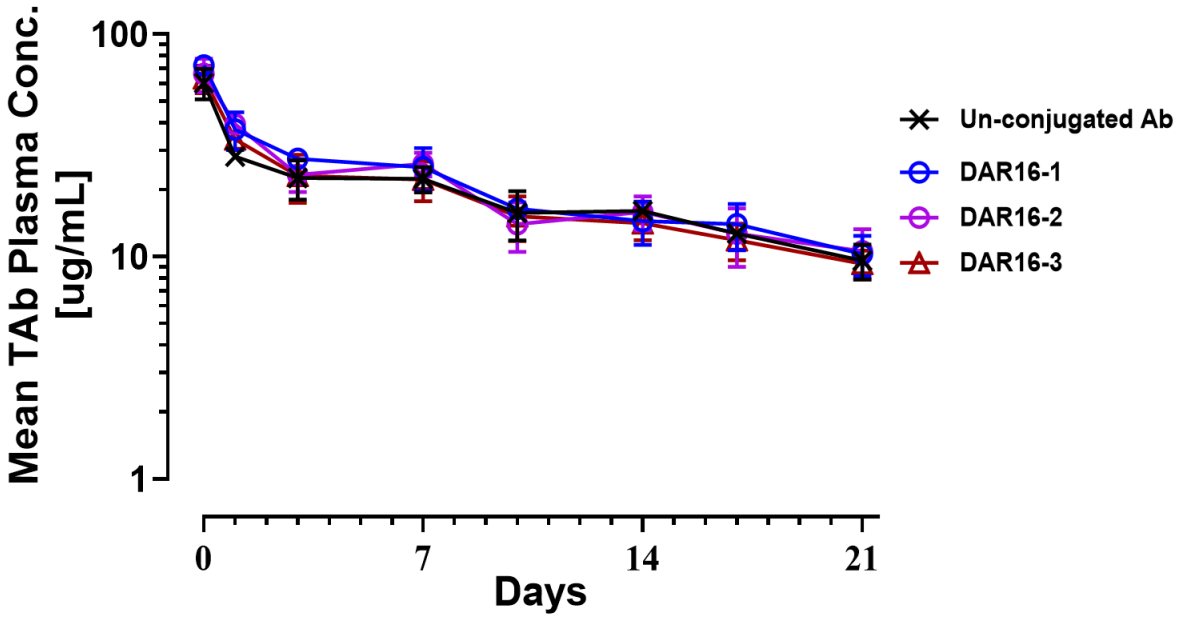


STRO-004 is well tolerated in NHP HNSTD in NHPs (q3w x 2) 50mg/kg

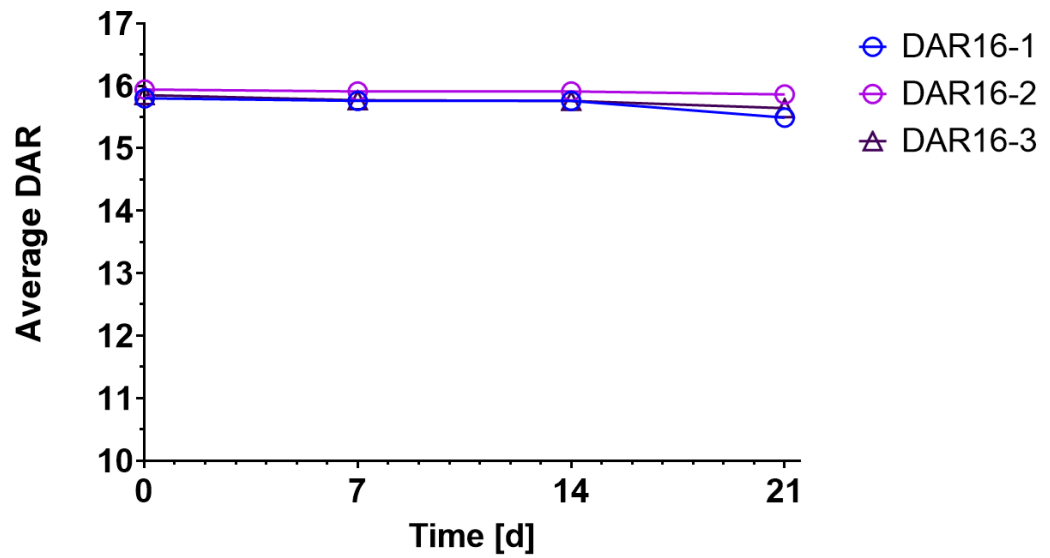
STRO-006 is well tolerated at 25mg/kg in NHPs

Site-Specific DAR16 ADCs Exhibited Excellent Mouse PK & *In-Vivo* DAR Stability for Targeting Low Antigen Tumors

Single IV PK profile of high DAR ADCs in C57BL/6 mice



In-Vivo DAR Stability



ID	DAR	$CL_{\_obs}$ ($mL \cdot d^{-1}/kg$)	$T_{1/2}$ (d)
Unconjugated Ab	0	5.07	14.6
DAR16-2	16	4.67	14.6

Site-Specific TOPO1i x DDRi Dual-Payload ADCs to Overcome Resistance Mechanisms

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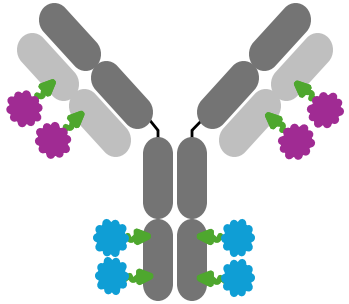
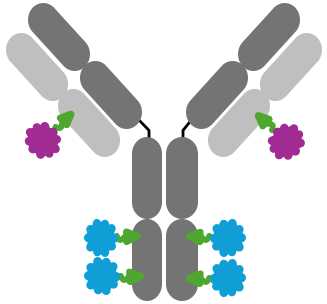
Next-Gen Dual-Payload ADCs With Controlled DAR Ratios to Overcome Tumor Resistance & Improved Tolerability

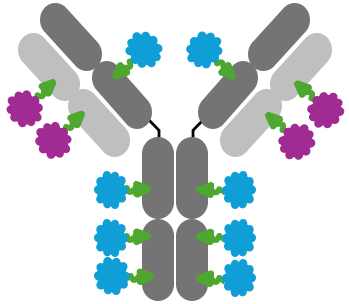
Controlled DAR Ratios



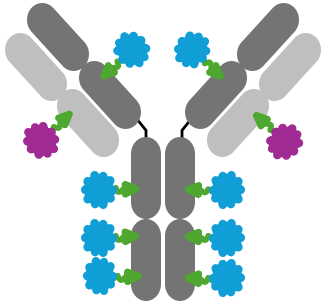
DAR 4+4



DAR 4+2



DAR 8+4



DAR 8+2

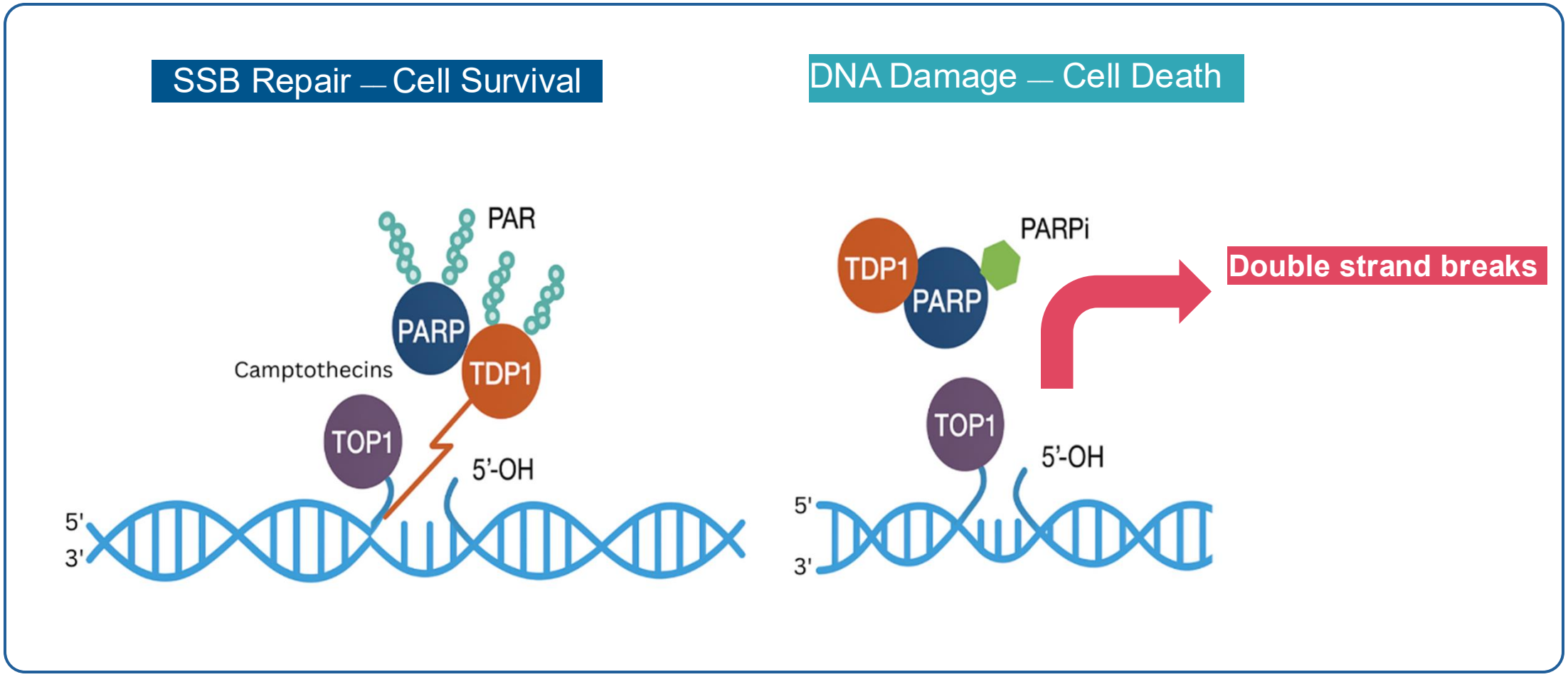
Diverse Payload Combinations

- TOPO1i x DDRi
- TOPO1i x MTi
- TOPO1i x IO

Dual-Payload ADCs

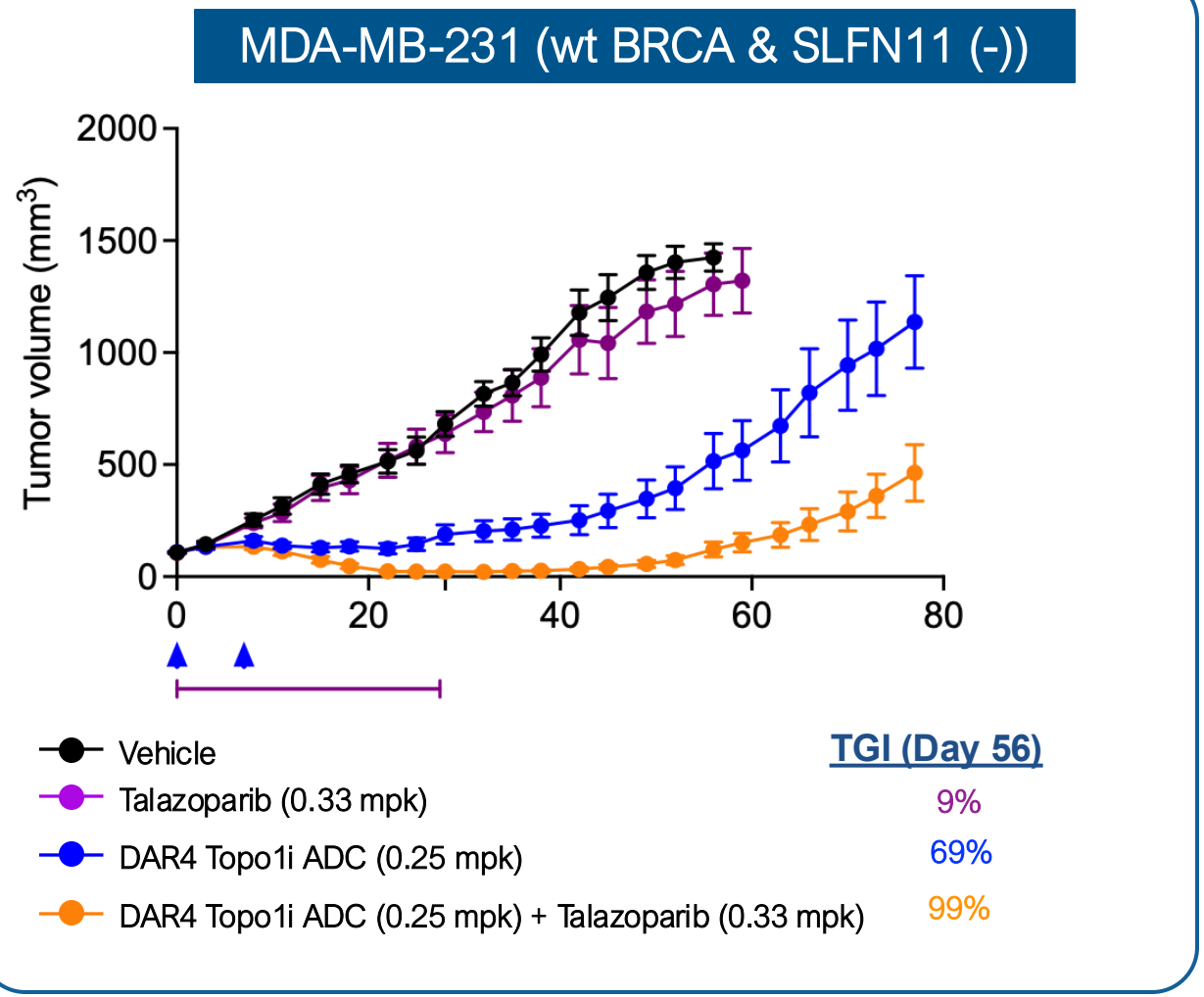
- ❑ Efficient delivery of orthogonal payloads with precise stoichiometries
- ❑ Increased efficacy in target low patient population
- ❑ Overcome payload resistance mechanism from conventional ADCs
- ❑ Enhanced efficacy and TI
- ❑ Improved DoR by addressing payload resistance

Mechanistic Rationale for Combining TOPO1i with PARPi for Synergetic Activity



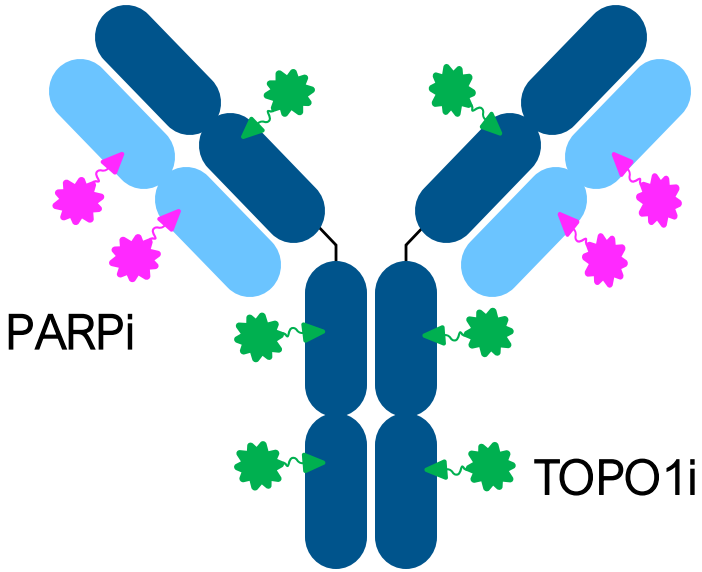
- *Mariappan L et al., Drew Y. Int J Womens Health, 2017; 9:913–924*
- *Das BB et al., Pommier Y. Nucleic Acids Res, 2014; 42(7):4435–49*

Combining PARP and TOPO1 Inhibitors: Challenges, Opportunities, and Path Forward with Dual-Payload ADCs



- Well-established preclinical synergy
- More frequent dosing of Tala combined with TOPO1i ADC (qwx2) demonstrated synergy
- Combo not realized in clinic due to myelosuppression

TOPO1i x PARPi Dual-Payload ADCs to Enhance Synthetic Lethality and Safety



Synergy between PARP and TOPO1 Inhibitors

Clinical Challenge

- ❑ Concurrent dosing of Trodelvy and TZP is clinically intolerable due to a narrow therapeutic window

Solution

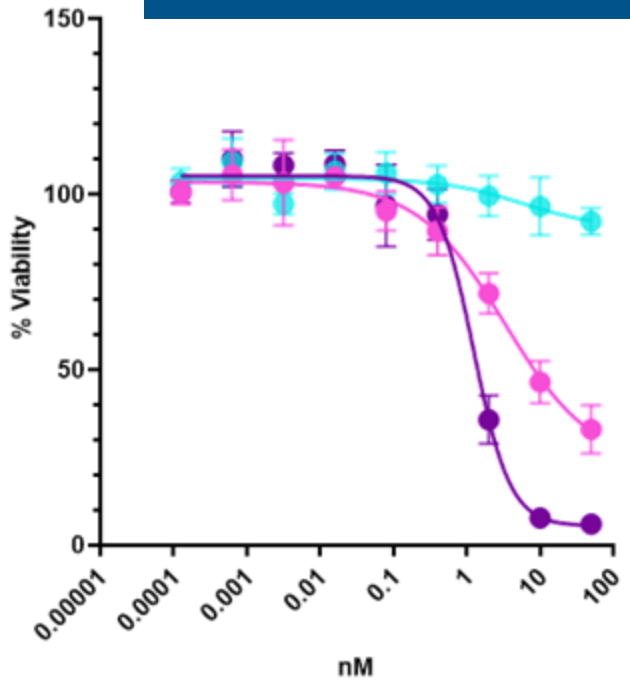
- ❑ Simultaneous delivery of dual payloads via dpADC to maximize tumor cell efficacy
- ❑ Leverage best-in-class dpADC technology to achieve enhanced synthetic lethality with improved safety

Bardia A et al. *Clin Cancer Res.* 2024;30(14):2917–24

TOPO1i x PARPi Dual-Payload ADC Demonstrates Enhanced Activity Compared to Single Payload ADC

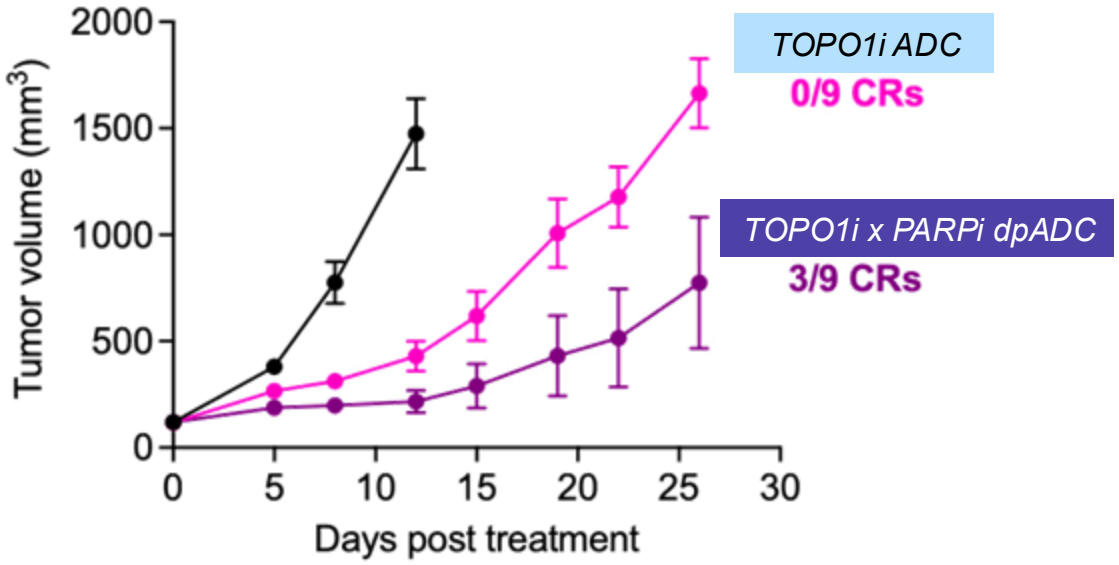
1st Gen PARPi

MC38-hTF *In vitro* potency



DAR2 PARPi ADC
DAR4 Topo1i ADC
DAR4 Topo1i + DAR2 PARPi dpADC

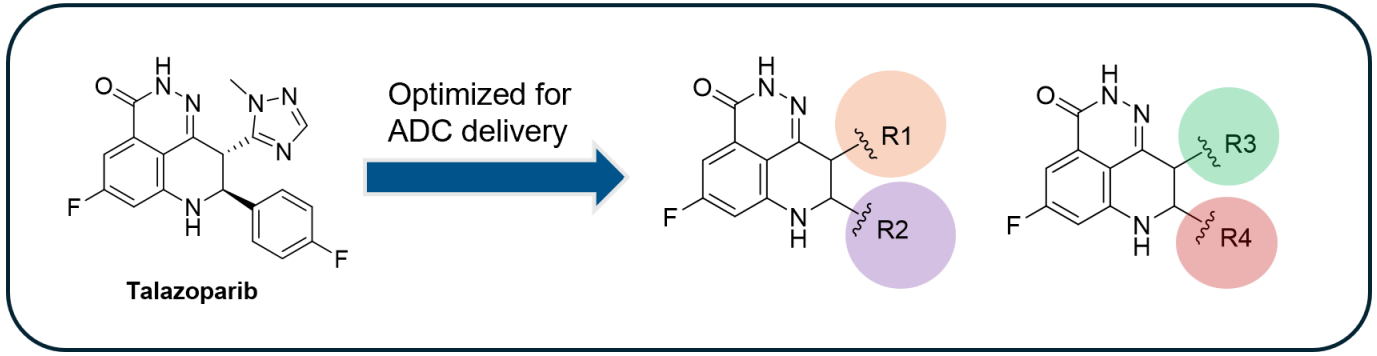
MC38-hTF *In vivo anti-tumor activity*



Vehicle (PBS)
DAR4 Topo1i ADC (5 mg/kg)
DAR4 Topo1i + DAR2 PARPi dpADC (5 mg/kg)

- TOPO1i x PARPi dpADC conjugate group had an improved TGI and CRs when compared to ADC
- dpADC & ADCs were well-tolerated

Sutro's Proprietary Pan-PARPi Displayed Excellent Binding, Trapping and Not Substrate of the P-gp/BCRP Efflux Transporters

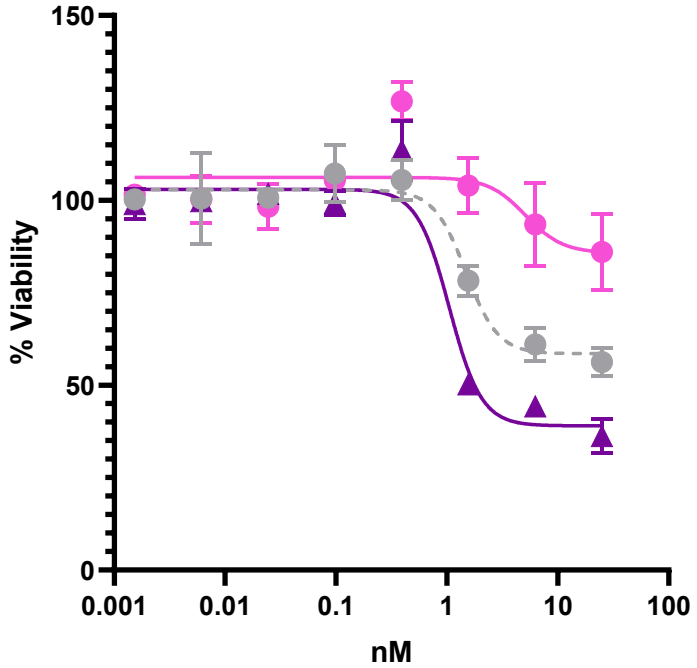


PARPi	*In-vitro* cell killing CAPAN-1 EC50 (nM)	PARP1 binding EC50 (nM)	PARP1 Trapping EC50 (nM)	PARP2 Trapping EC50 (nM)	Efflux Ratio $P_{app\ (BA)/(AB)}$	Efflux Ratio $P_{app\ (BA)/(AB)}$ + Vpm.)	Efflux Ratio $P_{app\ (BA)/(AB)}$ + Ko143)
Talazoparib	30	0.66	3.9	11	18.85	1.44	14
Sutro 2nd Gen	73	1.1	4.8	5.1	**0.75**	**0.67**	**0.5**
Sutro 2nd Gen	198	0.98	4.1	7.4	**3.0**	**2.0**	**3**

- Sutro's 2nd gen pan-PARPi payloads with less/no P-gp/BCRP substrates compared to Talazoparib
- All the new analogs demonstrated excellent lysosomal stability

2nd Gen PARPi Dual-Payload ADC Continues to Show Improved Activity Compared to TOPO1i Single-Payload ADC

Breast Cancer Cell Line *in vitro potency*

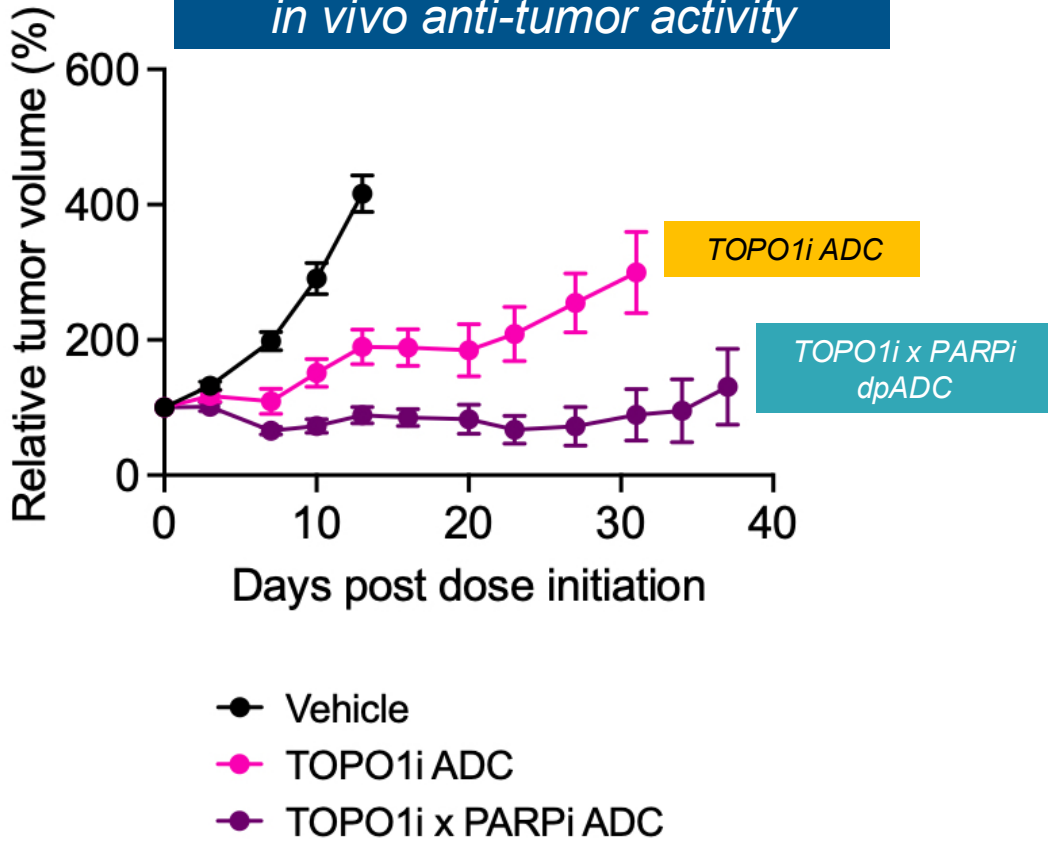


Enhertu

DAR8 Topo1i ADC

Topo1i x PARPi dpADC

Breast Cancer Xenograft Model *in vivo anti-tumor activity*

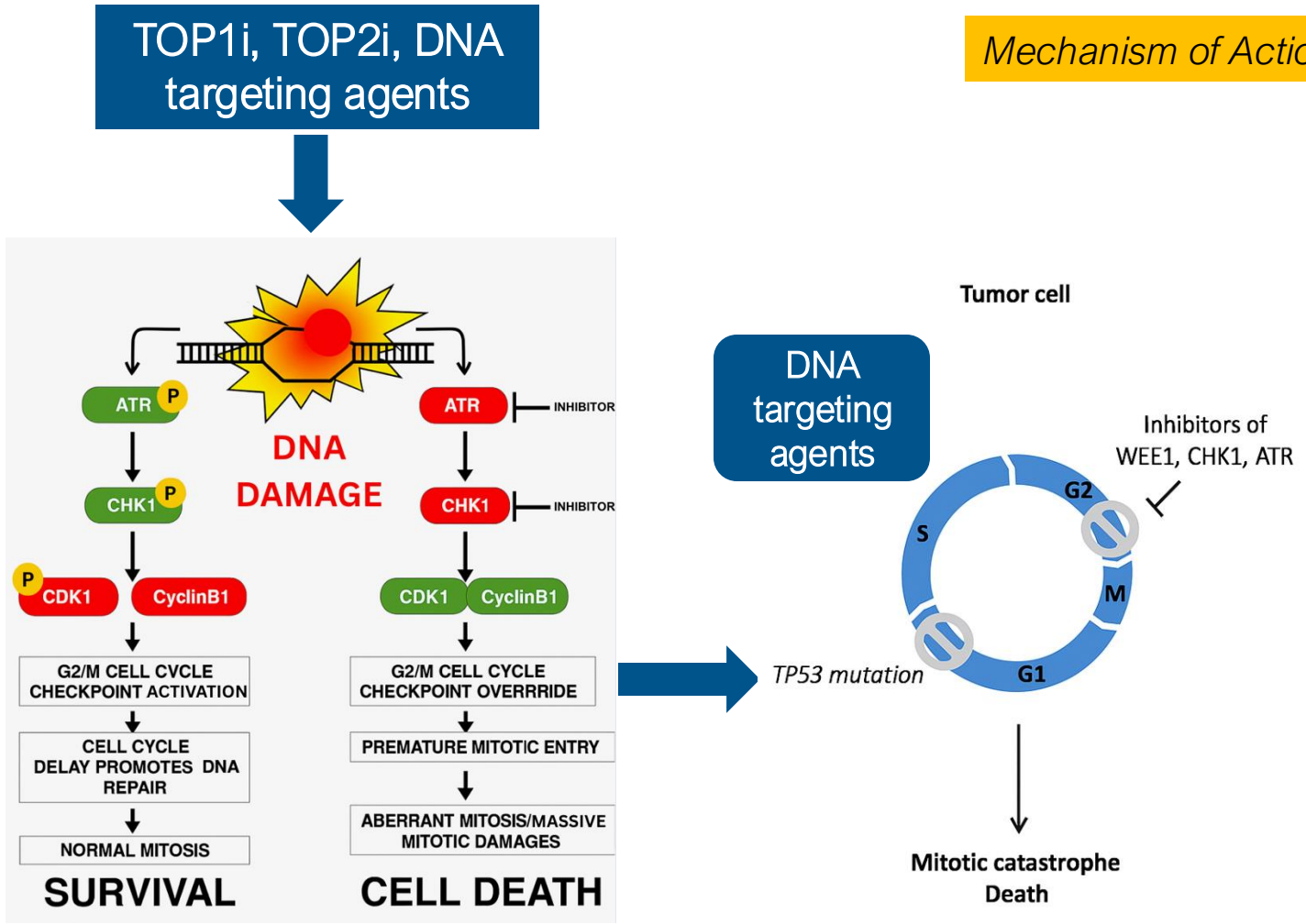


We are strategically optimizing DAR ratios in preclinical studies to advance TOPO1i x PARPi dpADC development

ATR is a Central Regulator of The DNA Damage Response

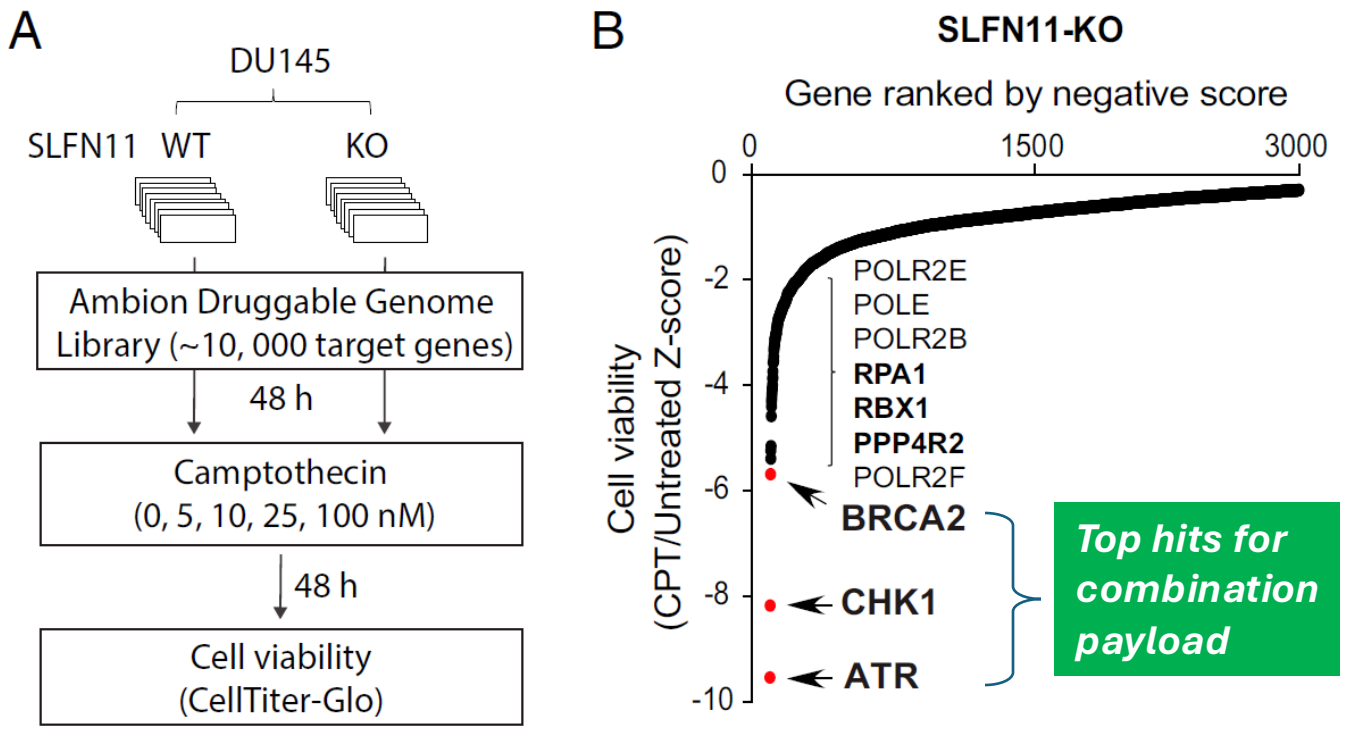
TOPO1i x ATRi dpADC

Mechanism of Action



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

Silencing ATR/CHK1 Restores TOPO1i Sensitivity in SLFN-11 Deficient Cells

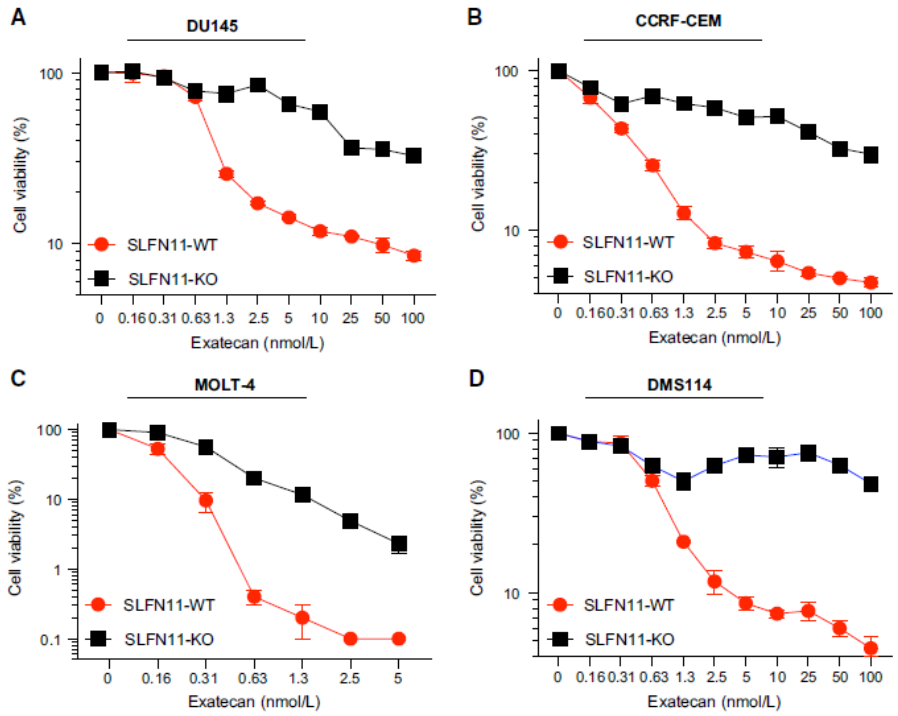


Jo U et al., Pommier Y. Proc Natl Acad Sci U S A, 2021; 118(6)

- SLFN11 inactivation in ~50% of cancer cells confers broad chemoresistance
- High SLFN11 associated with improved prognosis in pts treated with the DDA targeting agents (*Zhou K et al., Zhuang L. Front Oncol, 2025; 15:1582738)*
- TOPO1i x ATRi dpADC overcomes TOPO1i ADC resistance and improved safety

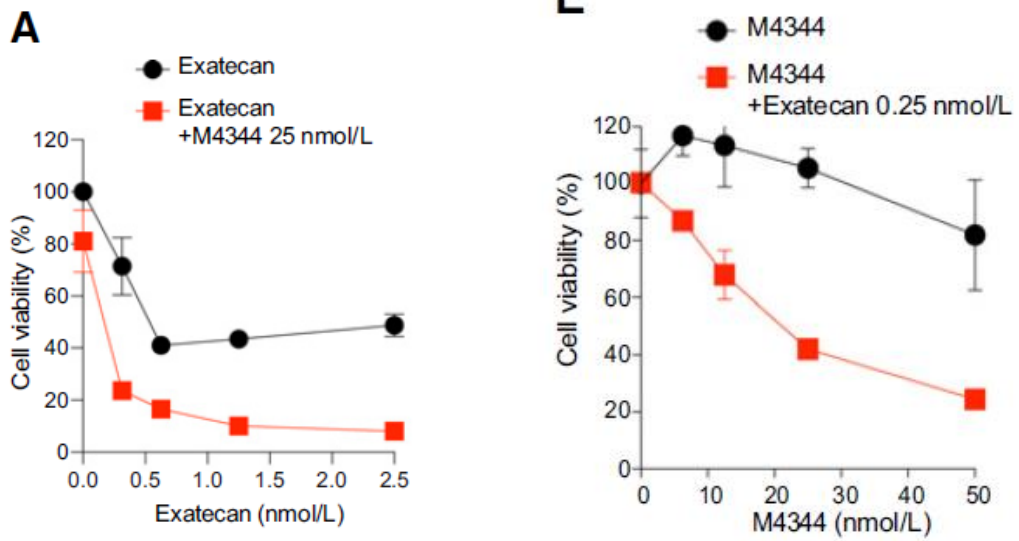
ATRi Synergies with TOPO1 Inhibitors Independent of SLFN-11 Status

TOPO1 inhibitors sensitivity depend on SLFN-11



Jo U et al., Pommier Y. Mol Cancer Ther, 2022; 21(7):1090–1102

ATRi synergizes with TOPO1 inhibitors



Jo U et al., Pommier Y. Mol Cancer Ther, 2021; 20(8):1431–1441

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

ATRi Monotherapy and Combination Therapies in Clinic

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)

Hematologic & GI toxicities

Abel ML et al., Thomas A. Clin Cancer Res, 2023; 29(18):3603–3611
ESMO 2025

Next-Gen Dual-Payload ADCs

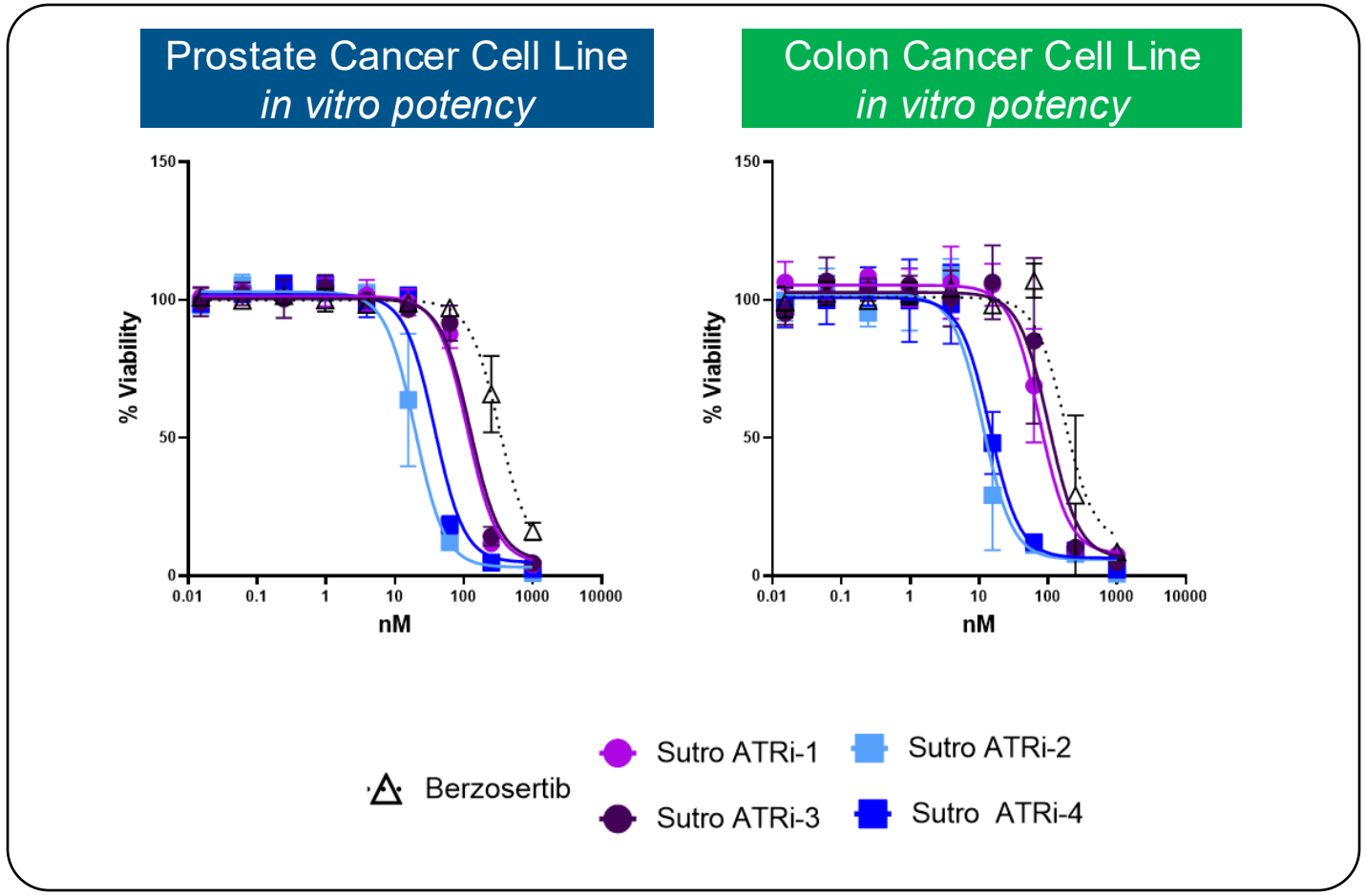
αTAA TOPO1i x ATRi Dual-Payload ADCs

- Optimized ATRi payload suitable for dpADC
- Simultaneous delivery of TOPO1i & ATRi
- Controlled DAR ratios
- Improved Safety
- Overcome resistance

Sutro's Proprietary ATRi Analogs Identified Through Structure-Based Drug Design are Not Substrate of Drug Efflux Pumps

ATRi Class 1	ATRi Class 2	ATRi Class 3
Sutro ATR1 Inhibitor	**Sutro ATR2 Inhibitor**	**Sutro ATR3 Inhibitor**
cLogD pH7.4/4.5 = 1.48/-0.13	**cLogD pH7.4/4.5 = 1.54/-0.94**	**cLogD pH7.4/4.5 = 0.30/-0.92**
DU145 EC_{50} = 609.7 nM	**DU145 EC_{50} = 19.56 nM**	**DU145 EC_{50} = 124.34 nM**
HCT116 EC_{50} = 174 nM	HCT116 EC_{50} = 11 nM	HCT116 EC_{50} = 104 nM
Caco-2 permeability:	**Caco-2 permeability:**	**Caco-2 permeability:**
(Papp) [10^{-6}cm/s] = 0.4	**(Papp) [10^{-6}cm/s] = 2.0**	**(Papp) [10^{-6}cm/s] = 0.4**
Efflux ratio = 3.57	**Efflux ratio = 2.54**	**Moderate substrate**
Good Lysosomal stability	**Good Lysosomal stability**	**Good Lysosomal stability**

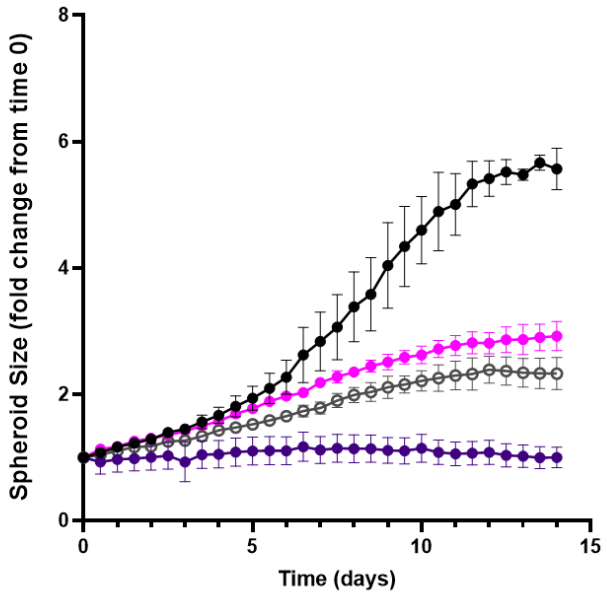
Sutro's Proprietary ATRi Analogs Outperform Over Berzosertib In Cytotoxicity Assays



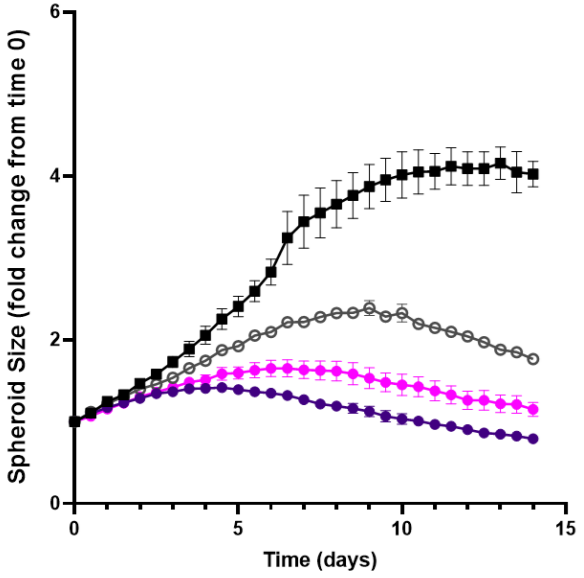
Identified distinct classes of potent ATRi payloads that are not substrates of drug efflux pumps

TOPO1i x ATRi Dual-Payload ADC Outperforms Single-Payload ADCs in Spheroid Cell Killing Assay

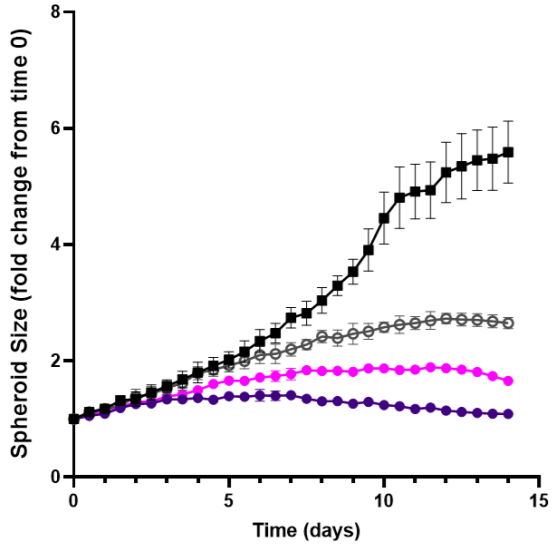
Ovarian Cancer Cell Spheroids
in vitro potency at 25 nM



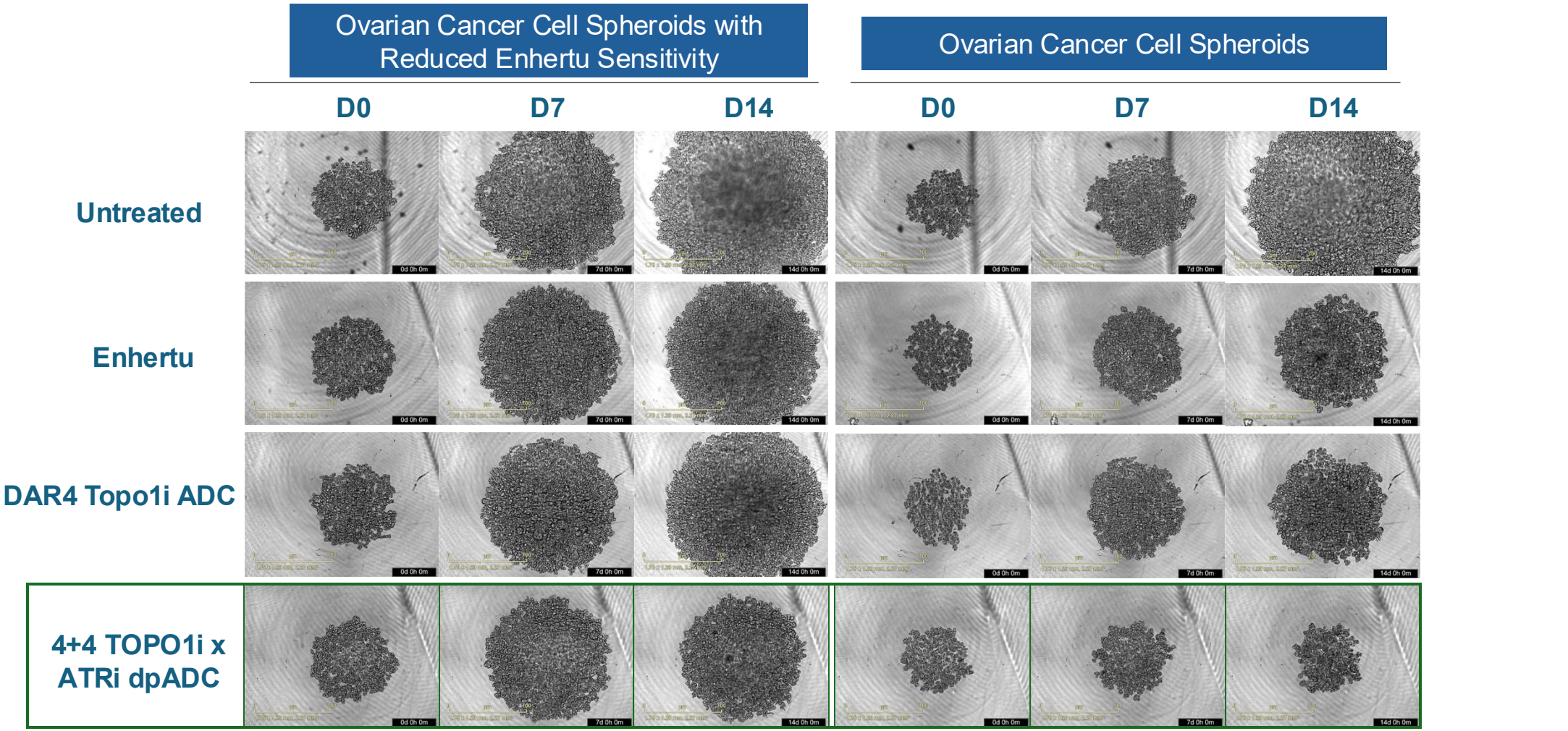
Ovarian Cancer Cell Spheroids with Reduced Enhertu Sensitivity
in vitro potency at 100 nM



Ovarian Cancer Cell Spheroids with Reduced Enhertu Sensitivity
in vitro potency at 100 nM



TOPO1i x ATRi Dual-Payload ADC Shows Superior Spheroid Growth Inhibition

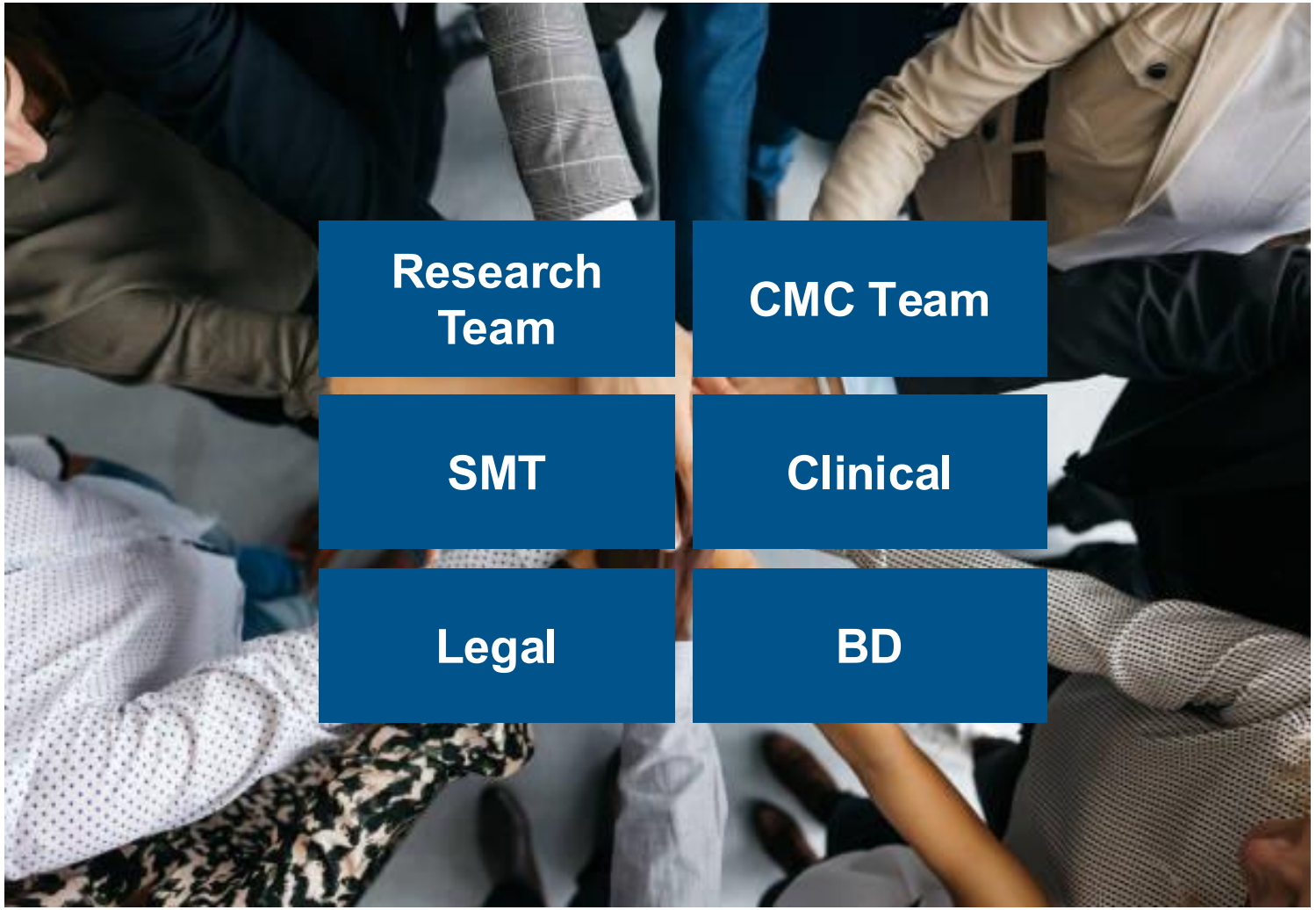


We are currently optimizing ATRi, DAR ratios in preclinical studies to select the lead TOPO1i x ATRi dpADCs

Other Presentations You May Find Interesting

- Nov 5th at 2:00PM; **Discovery Biology**; Laying Out Discovery & Development of STRO-006: A Differentiated Topo1-ADC Targeting Integrin Beta-6 **(Alice Yam)**
- Nov 5th at 3:00PM**; Discovery Chemistry**; Summary Panel Discussion: What is Showing the Most Promise & What Still Needs to be Proven in ADC Chemistry Innovation? **(Hans-Peter Gerber)**

Acknowledgments



For those interested in speaking with our BD & SMT team

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