16th ANNUAL WORLD adc SAN DIEGO 2025

SUTRO BIOPHARMA

Development of Site-Specific, High-DAR Dual-Payload ADCs

Daniel Calarese

Dual Payloads to Overcome Treatment Resistance

Challenge: Development of resistance to single payload ADCs in solid tumors

- Drivers of resistance are the payloads, not target downregulation[1]
- Increased focus on novel payloads/dual payload ADCs

Compelling clinical evidence for multi-MOAs improving pharmacology

- Chemotherapy combines different toxin classes[2]
- Drivers of success seen with CPI combos: MOA diversity and non-overlapping toxicity[3]

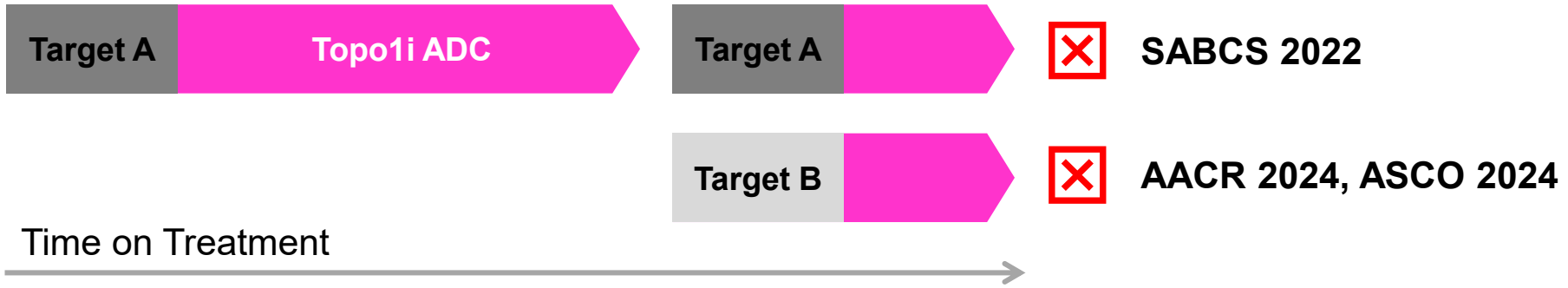
Sutro is positioned to become a leader in multi-payload ADCs

- Payload diversity (Topo1i, MMAE, DDRi, IO)
- Key design advantages enabled by our cell-free platform
- Preclinical efficacy without compromising tolerability

[1] Shitara & Yamaguchi, Nat Med, 2024 [2] Palmer & Sorger, Cell, 2017; Schmidt & Chen, AnRevCanBiol,2023; [3] Jin & Bernards, Nature, 2023; Schmidt & Uebele, JAMA, 2020

Emerging Clinical Challenge: Payload Resistance Limits ADC Efficacy

Payload Resistance to Topo1i Limits ADC Efficacy, Irrespective of the Target Antigen



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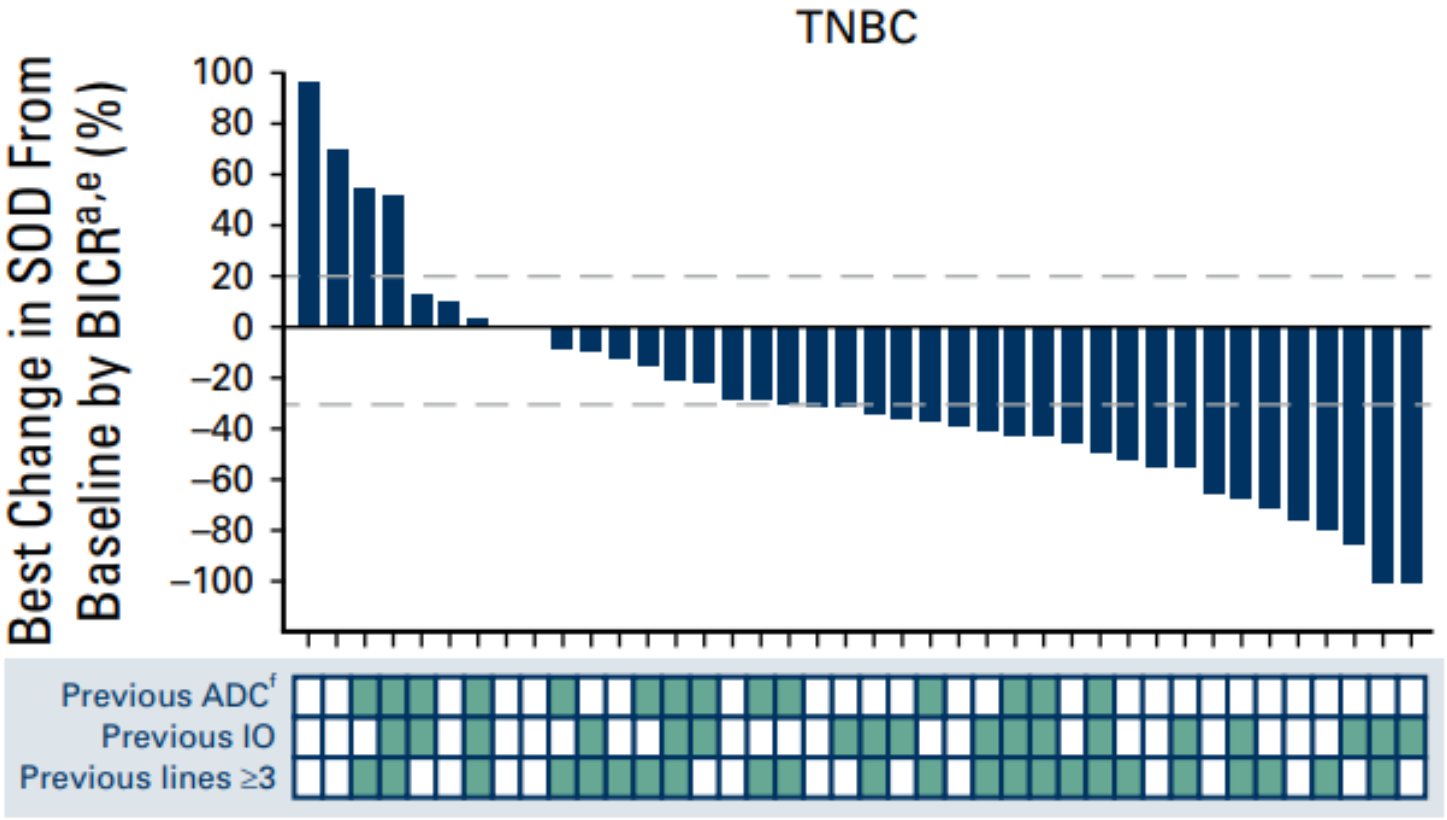

TROPION-PanTumor01
Dato-DXd in TNBC

14 patients had received prior Topo1 ADC: 11 SG, 2 T-DXd, 1 HER3-DXd

Confirmed overall response rate of **40%** (12/30) in Topo1-Naïve vs **15%** (2/14) in patients with prior Topo1 ADC

Figure reproduced from Bardia A, Krop IE, Kogawa T, et al. Datopotamab Deruxtecan in Advanced or Metastatic HR+/HER2- and Triple-Negative Breast Cancer: Results From the Phase I TROPION-PanTumor01 Study. *J Clin Oncol*. 2024;42(19):2281-2294 under the creative commons license (https://creativecommons.org/licenses/by-nc-nd/4.0/). No changes were made.

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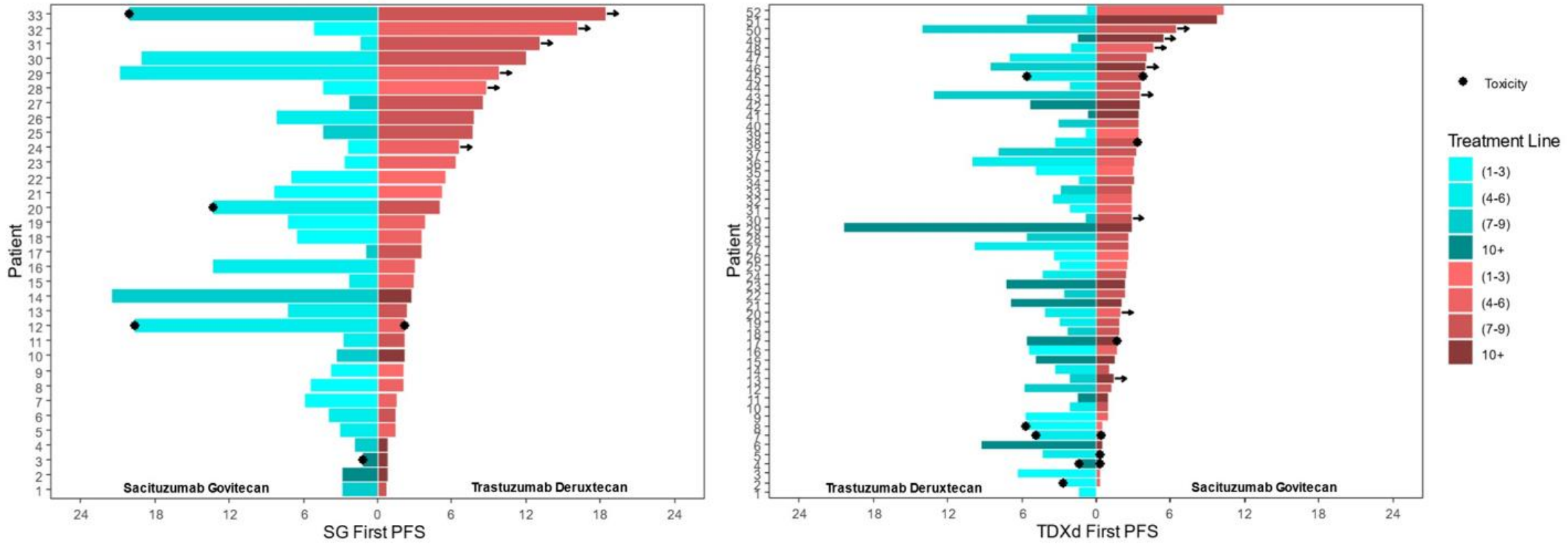


While there are patients that see significant benefit to a second Topo1i-payload ADC, there is significantly shorter PFS regardless of ADC sequence (SG, Enhertu in mBC)

Figure reproduced from Nicholas Mai et al., Real world outcomes of sequential ADC therapy in metastatic breast cancer: Patients treated with sacituzumab govitecan and trastuzumab deruxtecan.. *JCO* 42, 1085-1085(2024)

Emerging Clinical Challenge: Payload Resistance Limits ADC Efficacy

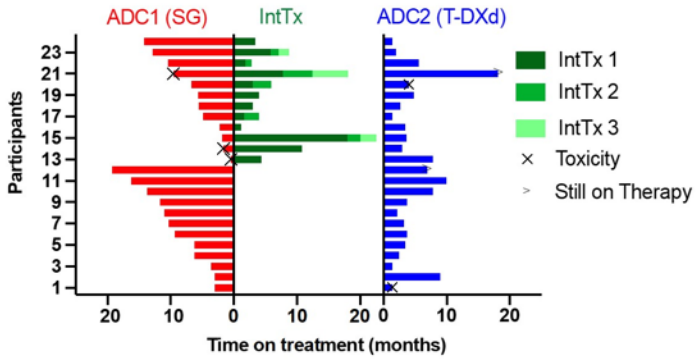
HR+/HER2-low Efficacy Data (n=56)

SG → T-DXd
(n=24, 42.9%)

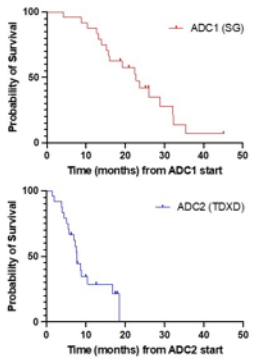
- Median lines of therapy for MBC prior to SG:
  - Median lines chemo: **2.0** (range 0-7)
  - Median total lines therapy: **3.0** (range 0-9)
- IntTx between ADCs: 50.0%

	ADC1 (SG)	ADC2 (T-DXd)
Median rwPFS from time of each ADC start, months	6.5	3.6
Median rwOS from time of each ADC start, months	20.1	7.7

rwPFS



rwOS

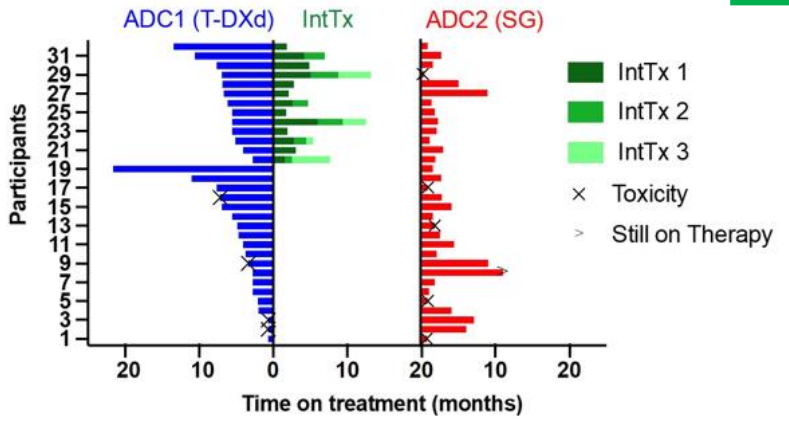


T-DXd → SG
(n=32, 57.1%)

- Median lines of therapy for MBC prior to T-DXd:
  - Median lines chemo: **2.0** (range 0-6)
  - Median total lines therapy: **4.5** (range 2-10)
- IntTx between ADCs: 40.6%

	ADC1 (T-DXd)	ADC2 (SG)
Median rwPFS from time of each ADC start, months	5.3	2.1
Median rwOS from time of each ADC start, months	15.1	5.6

rwPFS



rwOS

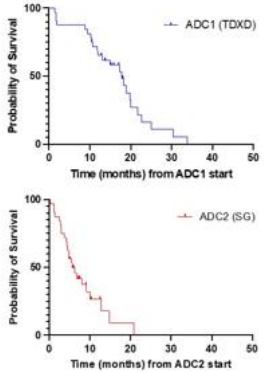


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Figure was adapted from Laura Ann Huppert et al., Multicenter retrospective cohort study of the sequential use of the antibody-drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in patients with HER2-low metastatic breast cancer (MBC): Updated data and subgroup analyses by age, sites of disease, and use of intervening therapies.. *JCO* **42**, 1083-1083(2024)

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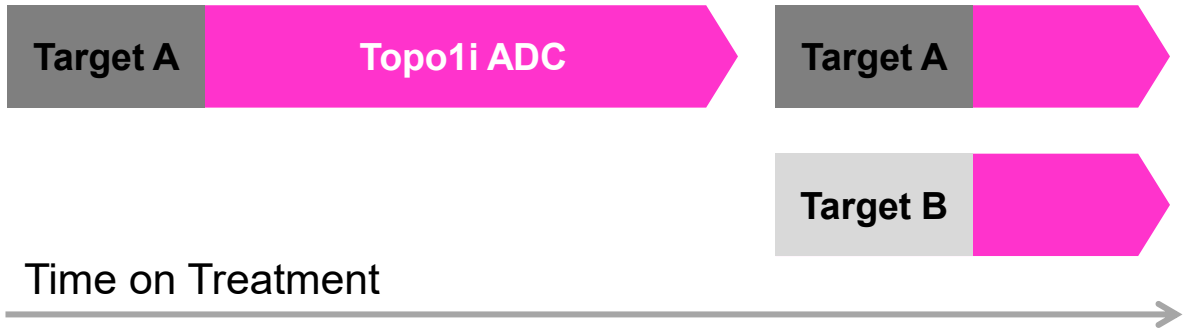
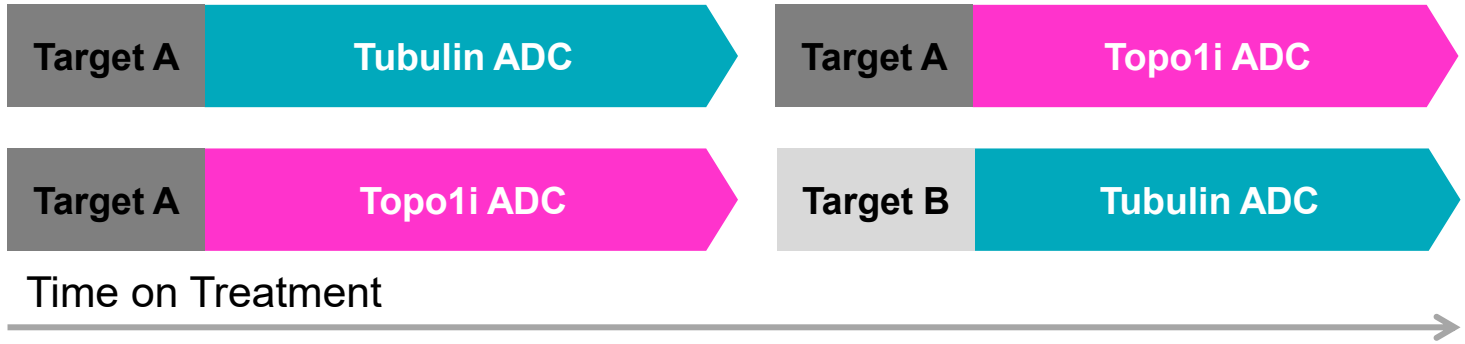


SABCS 2022

AACR 2024, ASCO 2024

Switching Payload Class Maintains ADC Efficacy, Irrespective of the Target Antigen



Lancet 2024

ASCO 2024, ASCO 2025

SABCS – San Antonio Breast Cancer Symposium; ASCO – American Society of Clinical Oncology

Switching Payloads: MTI ADC Sequenced After Topo1i ADC

EV-202

TNBC cohort subgroup analysis

PFS by prior SG treatment

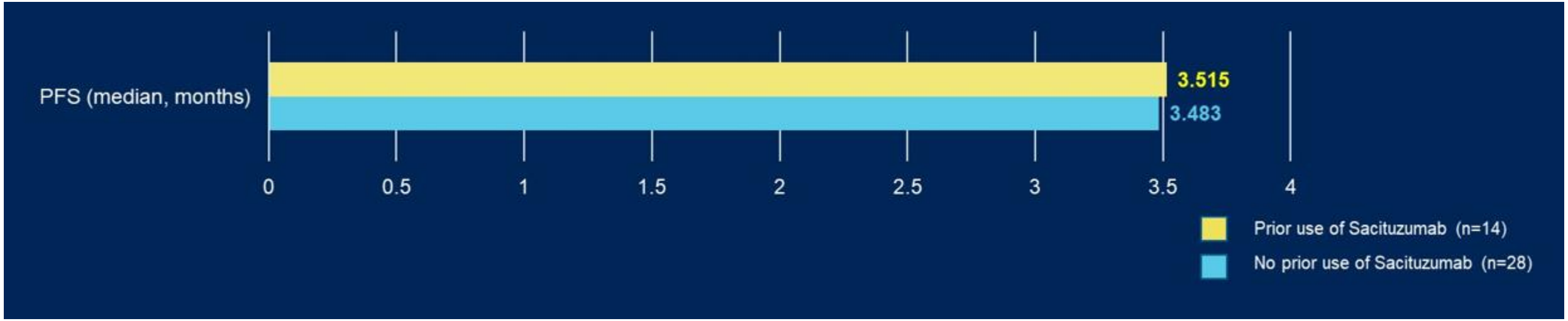
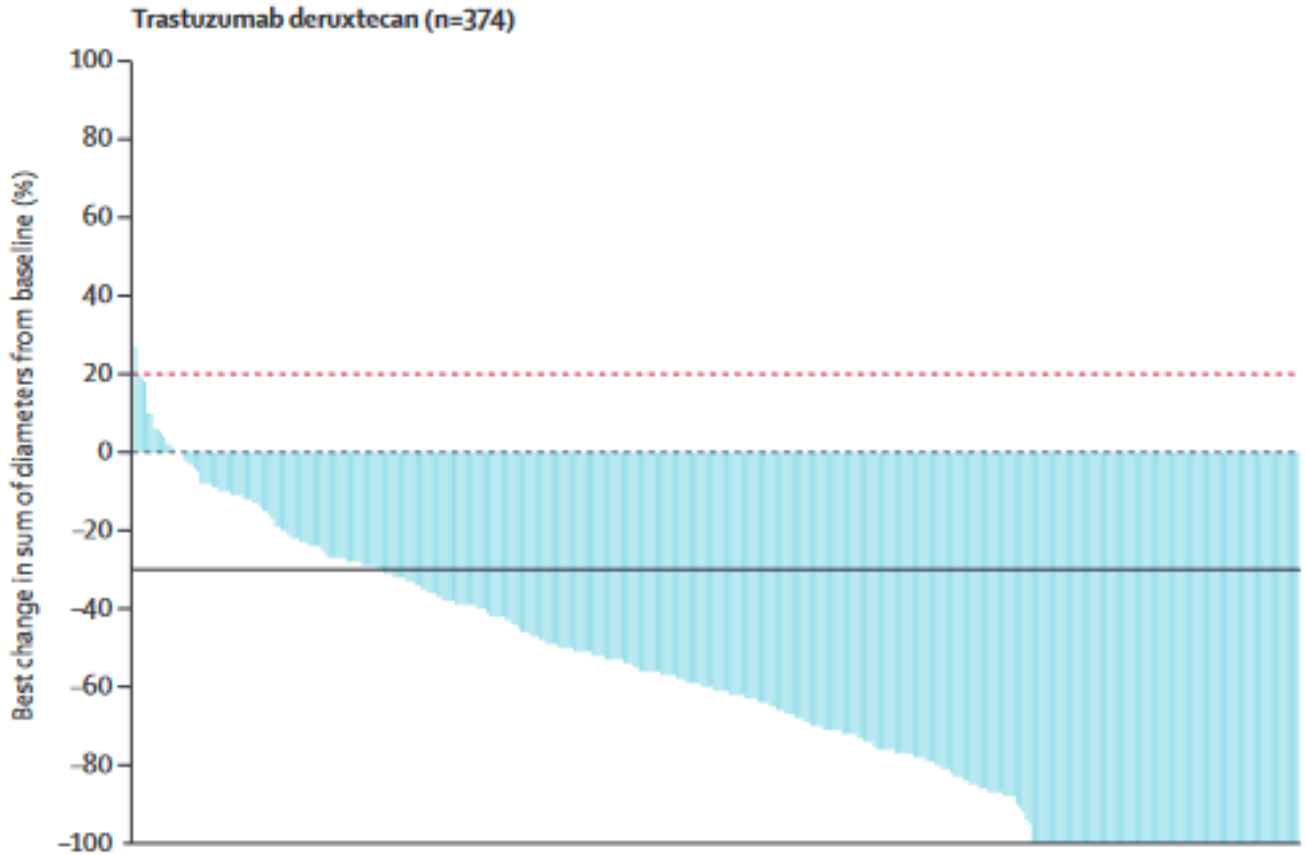


Figure reproduced from Antonio Giordano et al., Enfortumab vedotin (EV) in triple-negative breast cancer (TNBC) and HR+/HER2- breast cancer (BC) cohorts of EV-202.. *JCO* **42**, 1005-1005(2024)

Switching Payloads: Topo1i ADC Sequenced After MTI ADC



DESTINY-Breast02

Virtually all patients (>99%) had been treated with prior Kadcyla

70% confirmed overall response rate with 17.8 months progression-free survival (compared to 29% response rate and 6.9 month PFS with treatment of physician's choice)

Figure reproduced from André, Fabrice et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. The Lancet, Volume 401, Issue 10390, 1773 – 1785 under the creative commons license (https://creativecommons.org/licenses/by-nc-nd/4.0/). No changes were made.

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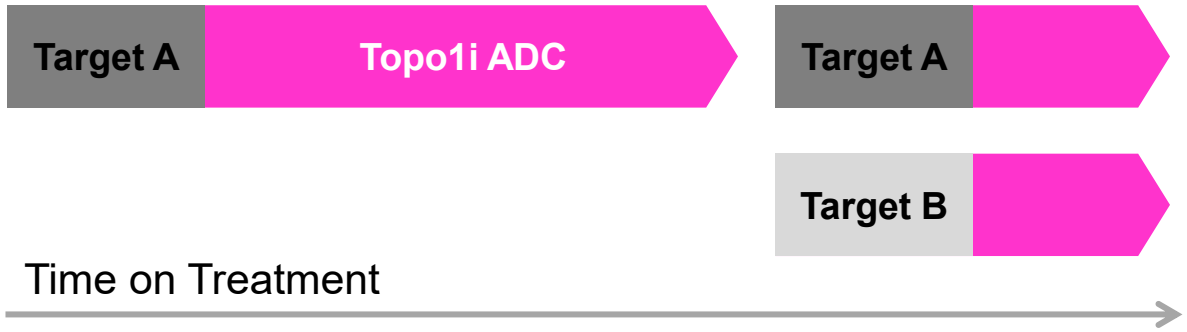

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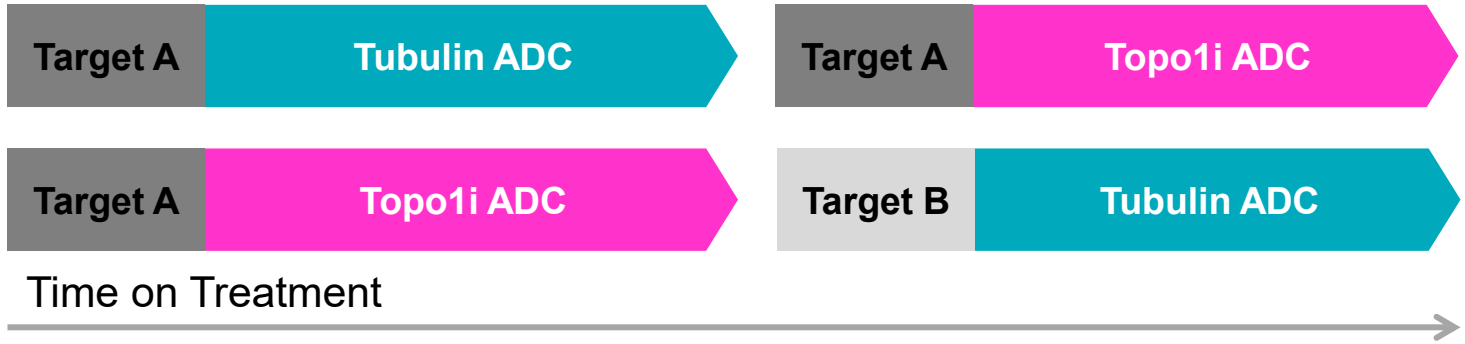

☑ Lancet 2024

☑ ASCO 2024, ASCO 2025

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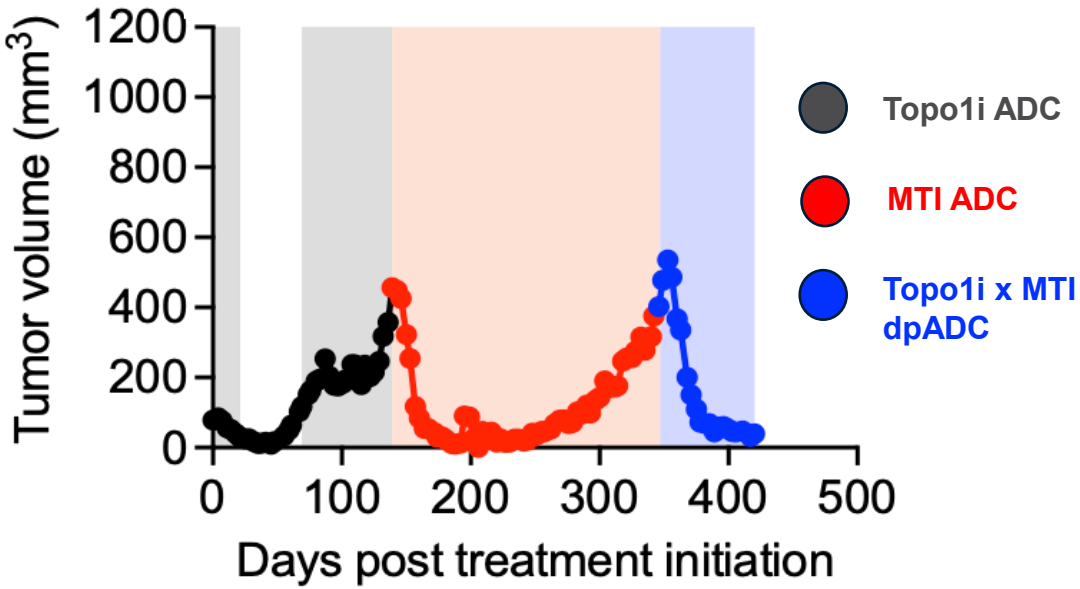
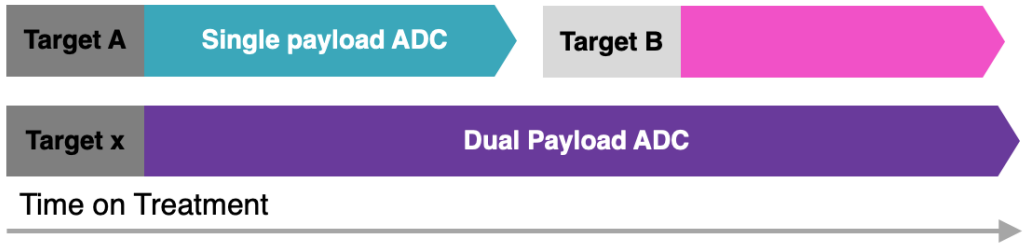
Dual-Payload ADCs Have Potential to Overcome Resistance and Expand Clinical Opportunities

Tumors Resistant to both Topo1i and MTIs respond to dpADC

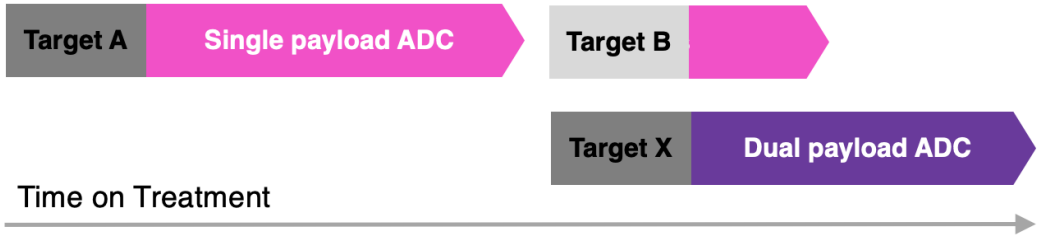


Clinical Development Opportunity: Relapse to Front-Line

Early Line: Instead of two sequential spADCs



Late Lines: dpADC after relapse from spADC



Sutro's ADC Platform is Fundamentally Different: Manufacturing of Proteins in Cell-Free Extracts

DNA Vector Engineering → Genome Sequencing → Strain Engineering

Prokaryotic Cells

1977: Somatostatin
1978: Insulin
1979: HGH

1976

Genentech: Boyer (UCSF)
Purpose: Manufacture Protein Therapeutics

DNA - deoxyribonucleic acid; HGH – human growth hormone; UCSF – University of California, San Francisco

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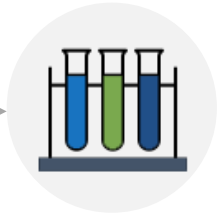

Enzymes
Proteases
Cytokines

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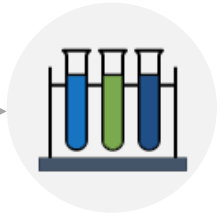

Enzymes
Proteases
Cytokines

Sutro Cell Free
2010: 100L CF demonstration
2011: mAbs
2013: nnAA incorporation and ADCs
2014: bsAb and ADC
2016: CF GMP manufacturing
2024: 4,000L GMP run

Advantages to Improve Therapeutic Index of ADCs
- Site Specific Conjugation
- Immune Stimulatory (iADC)
- High DAR (>8)
- Dual-Payload ADCs

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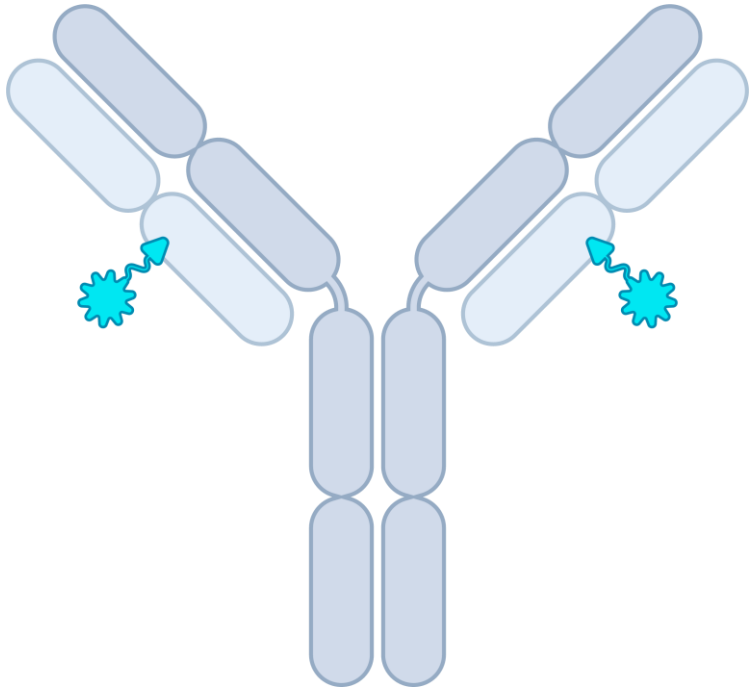
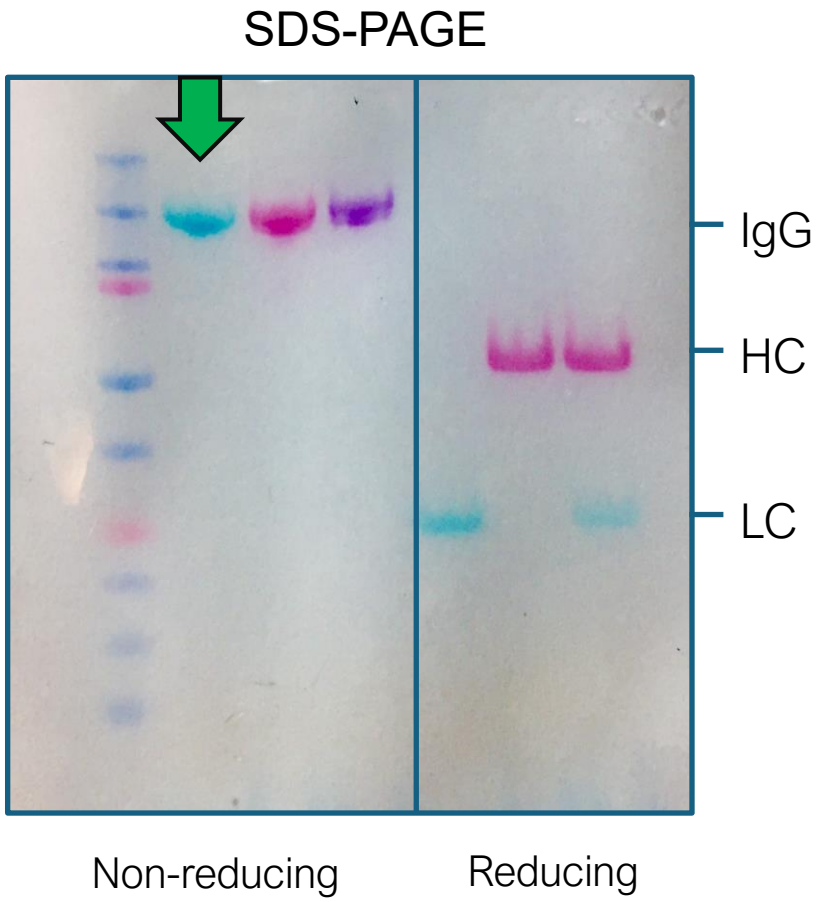
2025

Sutro Milestones
Manufacture Cheaper, Faster, Better

nnAA – non-natural amino acids; CF – cell-free; bsAb – bispecific antibody; GMP – good manufacturing practice

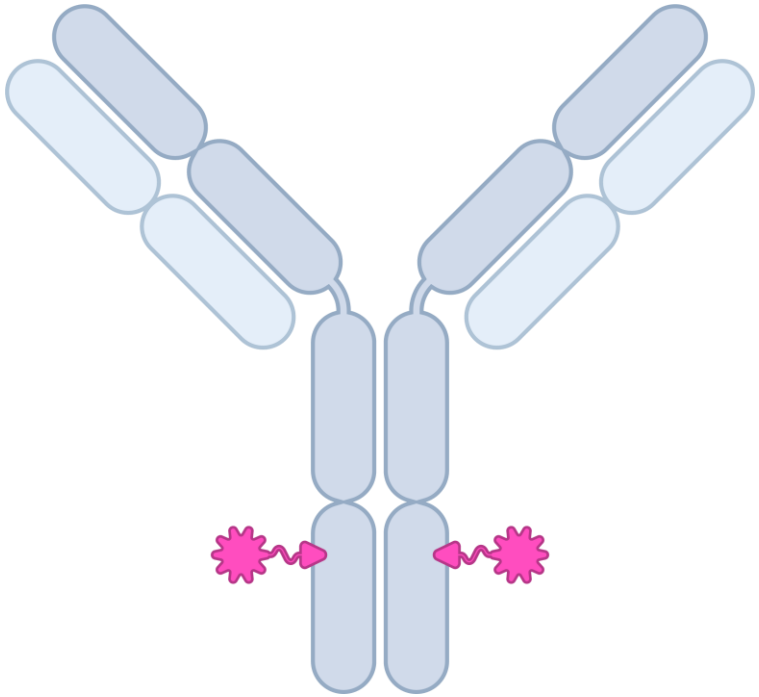
Sutro Cell-Free Platform Allows Precise Tuning of Linker-Payloads

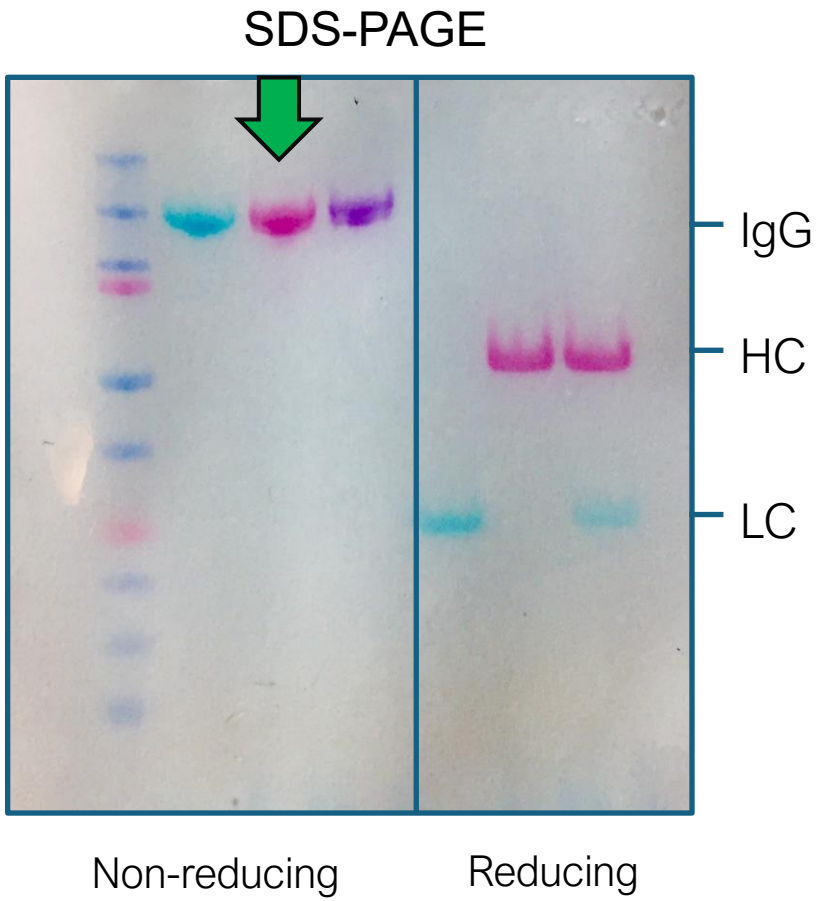




Wen M, Yu A, Park Y, Calarese D, Gerber HP, Yin G. Homogeneous antibody-drug conjugates with dual payloads: potential, methods and considerations. *MAbs*. 2025;17(1):2498162. doi:10.1080/19420862.2025.2498162

Sutro Cell-Free Platform Allows Precise Tuning of Linker-Payloads





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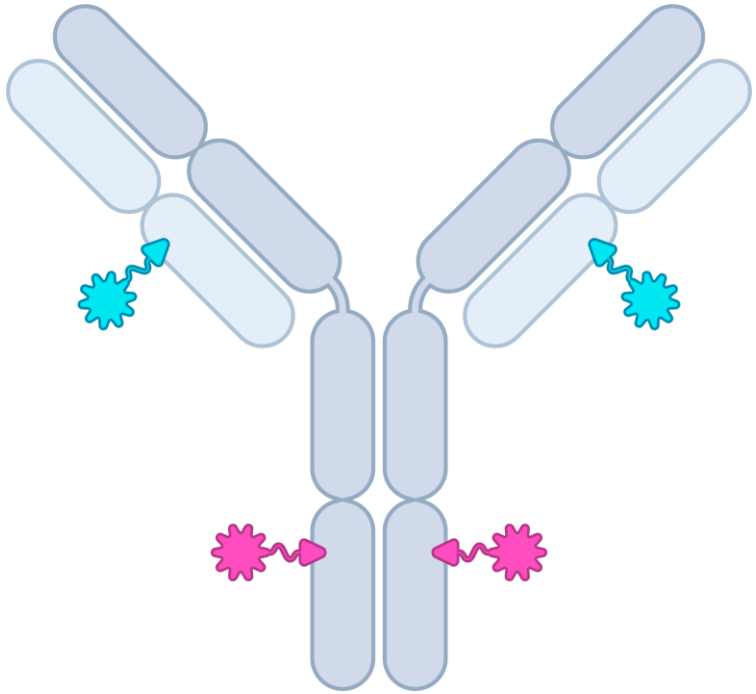

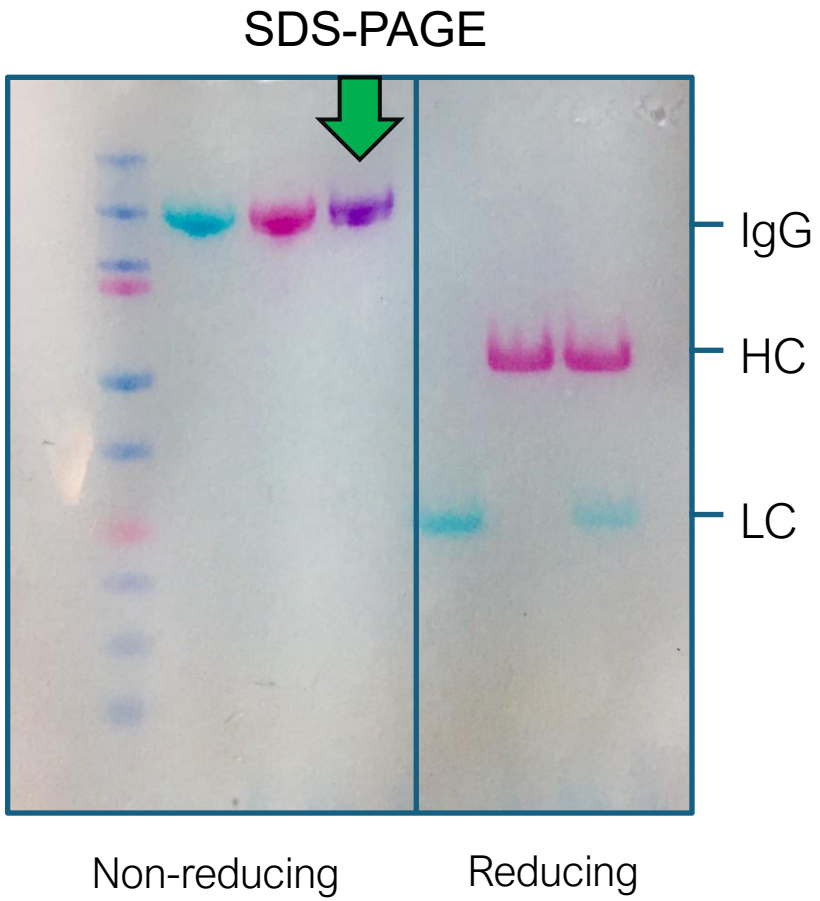

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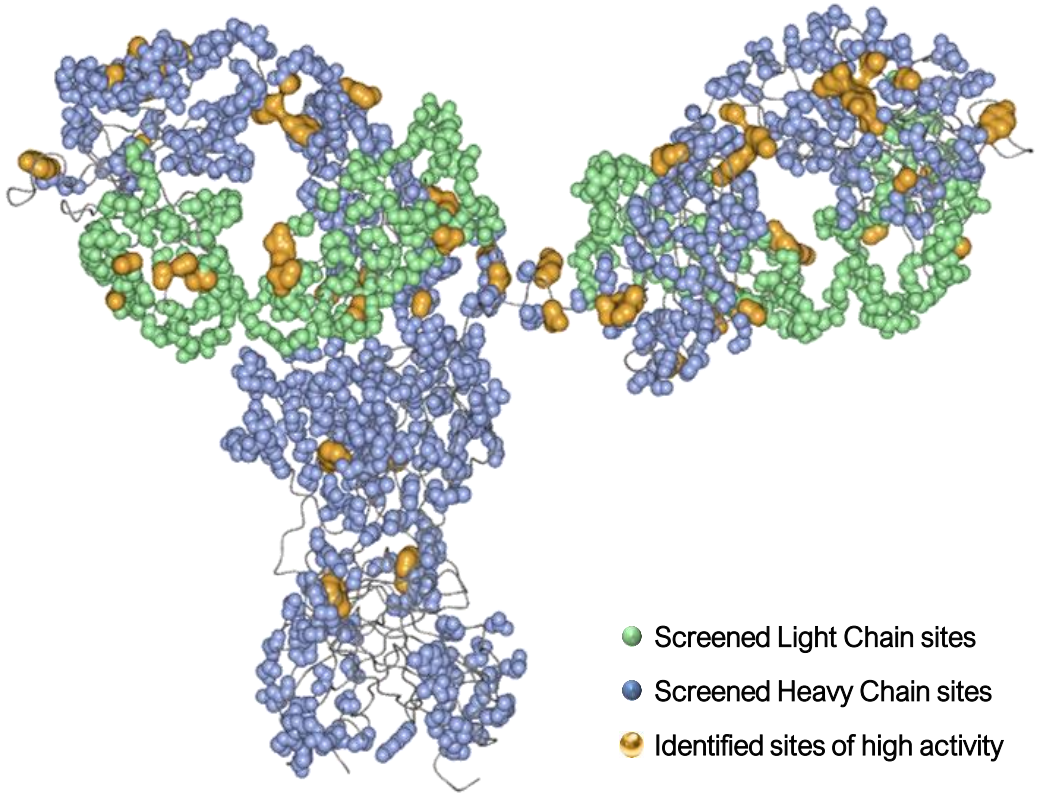
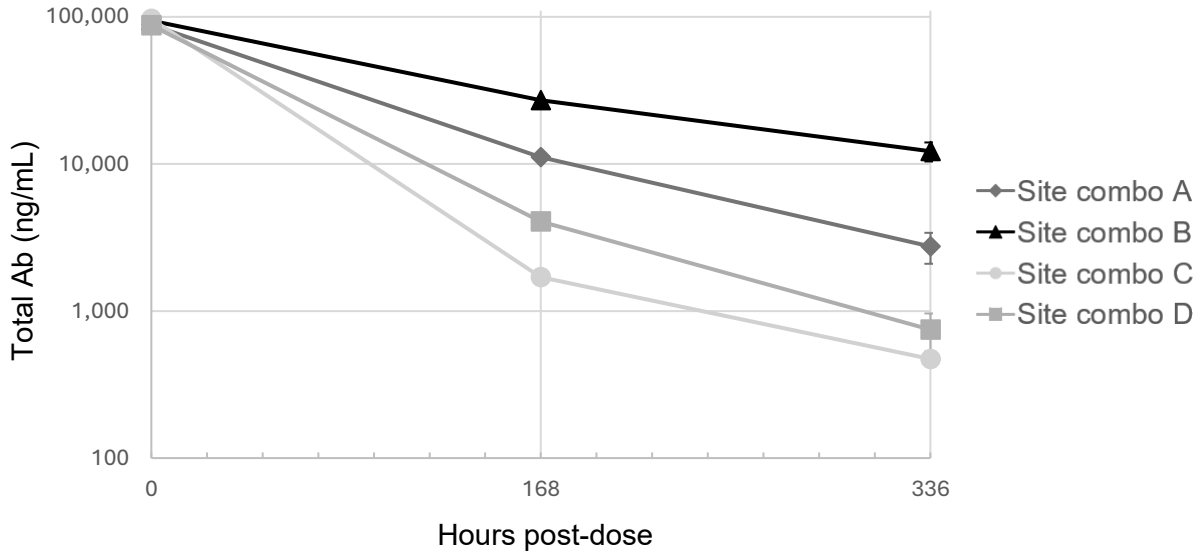
Sutro Cell-Free Manufacturing Platform Enables Site-Selective ADCs with Superior Exposure and Design Flexibility

Surface Sites Screened on an IgG



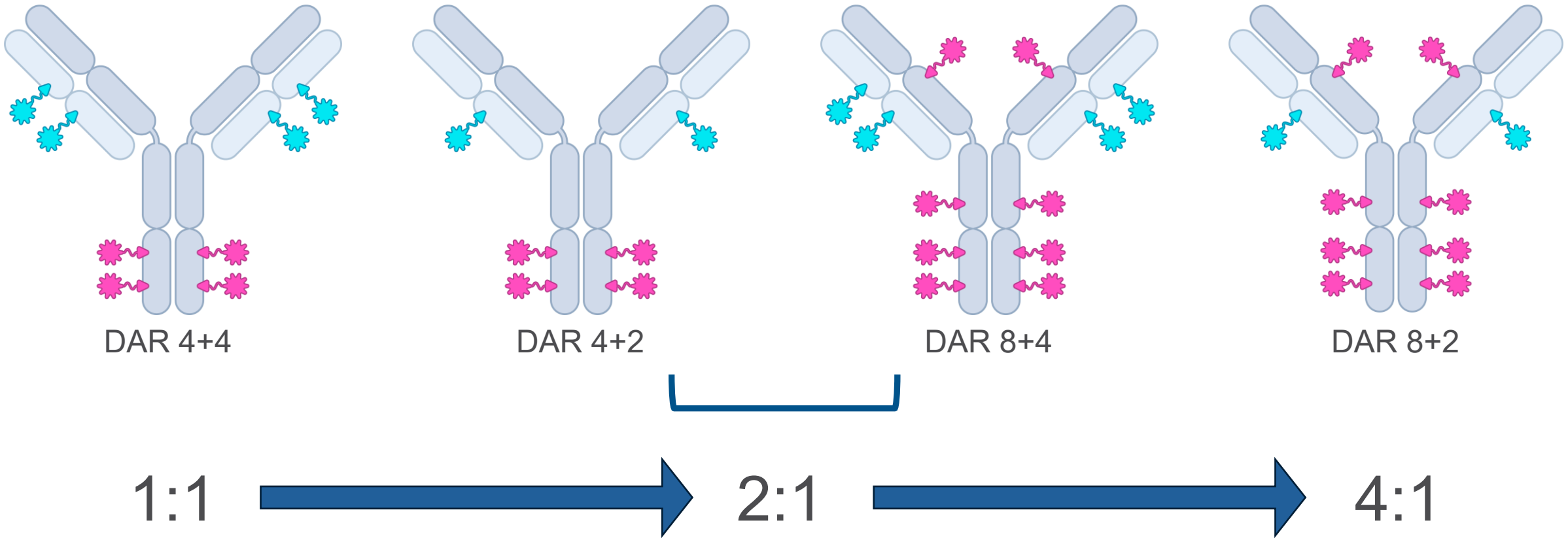
DAR16 ADCs



Choosing **the right combination** of sites can result in optimized pharmacokinetics

- Better PK
- Less ADC Clearance
- Less Systemic Toxicity

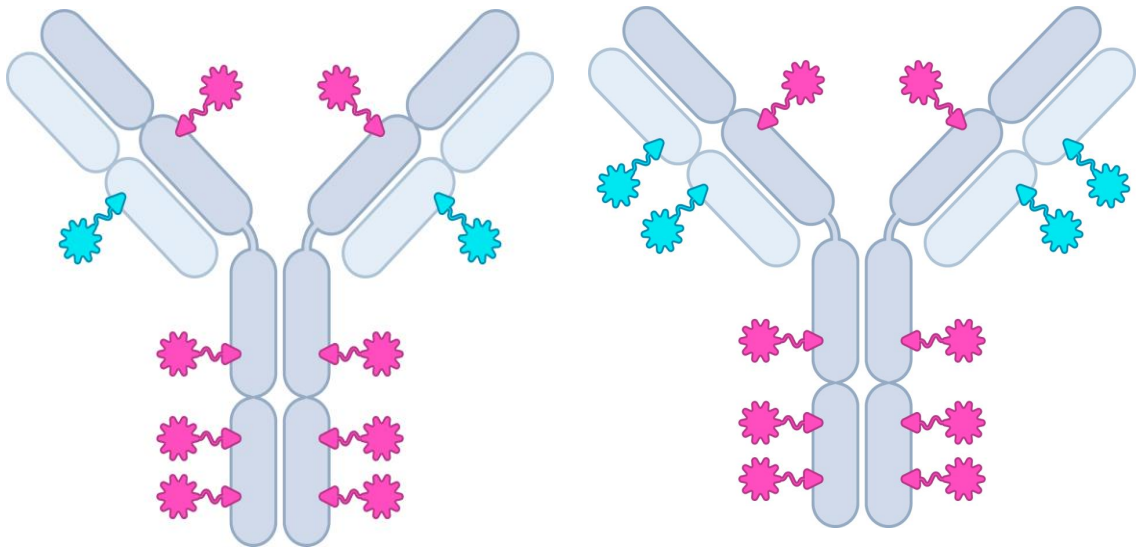
Cell-Free Platform Enables Site-Specific Tuning of Payload Ratios



Sutro Dual-Payload ADC Arsenal

Topo1 x Tubulin	Topo1 x STING	Topo1 x DDRi
Combination of clinically validated payloads to improve efficacy	Engaging immune activation to make tumors hotter	Leveraging DDRi synergy to enhance Topo1i activity
	12:30pm Today "Developing Next-Generation Immunostimulatory Dual Payload ADCs to Enhanced Therapeutic Index and Tackle Patient Resistance" – Gang Yin	**11:00am Wednesday** "Developing Site-Specific Dual Payload ADCs Featuring Novel Linker Payloads to Overcome Resistance Mechanisms" – Krishna Bajjuri

Anatomy of Topo1i + MTI Dual-Payload Her2-ADC: Designed to Deliver Superior Efficacy and Safety

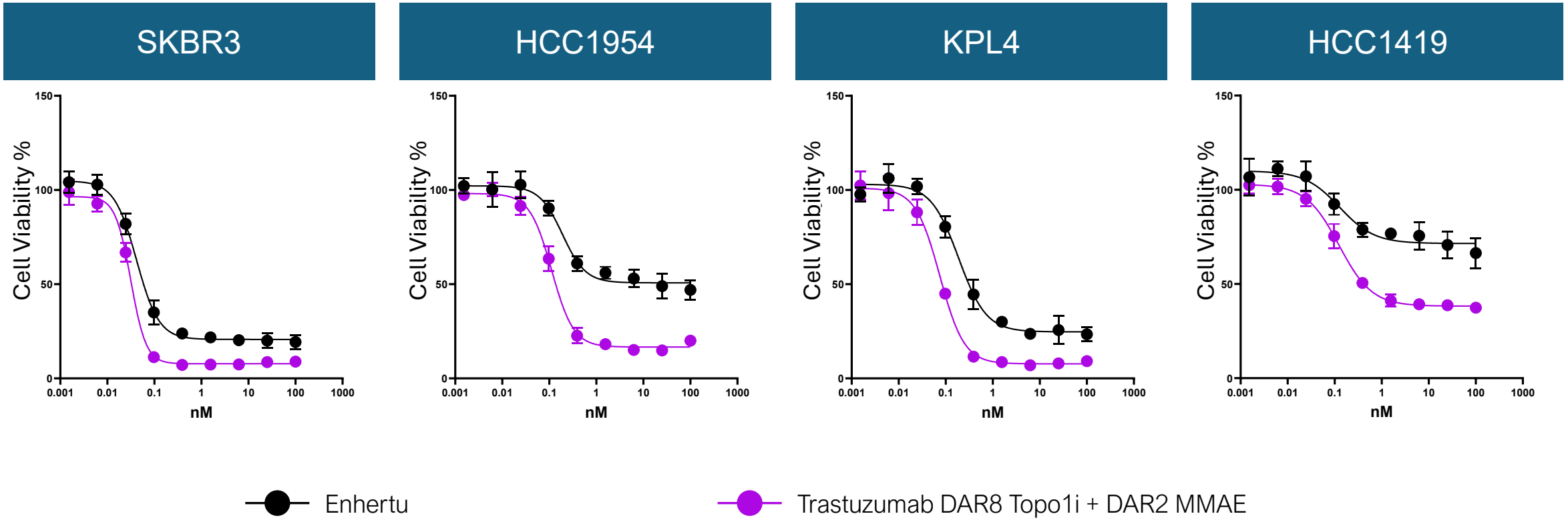


DAR8: TOPO1i

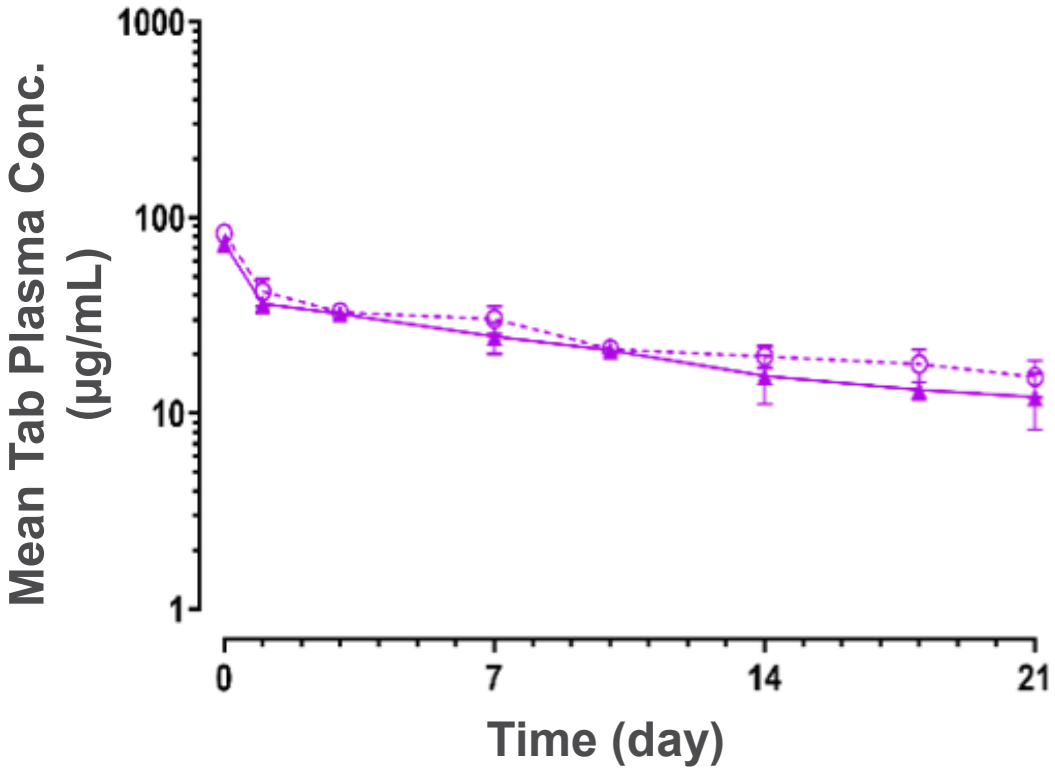
DAR2: MTI

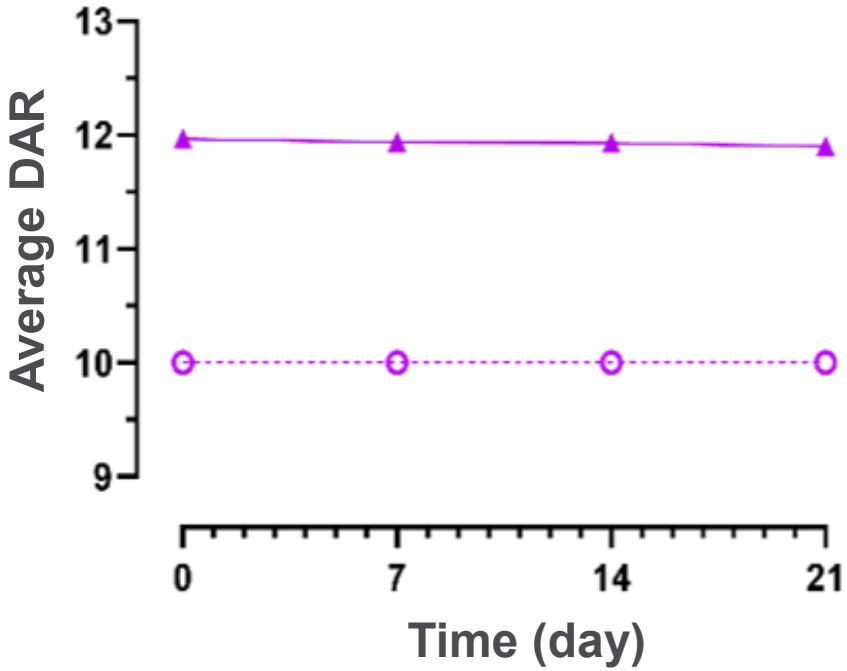
1. **Optimally positioned non-natural amino acids**, p-azidomethyl-L-phenylalanine (pAMF), combined with ultra stable click chemistry
2. **β-glucuronidase cleavable linkers** with tumor selective cleavage, strong stability while in circulation, and added hydrophilicity led to **best-in-class PK**
3. **Exatecan payload causing DNA disruption** and potent tumor cell killing, with high bystander activity, and immunogenic cell death (ICD)
4. **MMAE payload causing Tubulin disruption** and potent tumor cell killing, with high bystander activity, and immunogenic cell death (ICD)
5. **Lack of FcγR interactions** limits uptake by alveolar macrophages, reducing risk of interstitial lung disease (ILD)

Improved *In Vitro* Activity of Dual-Payload ADC



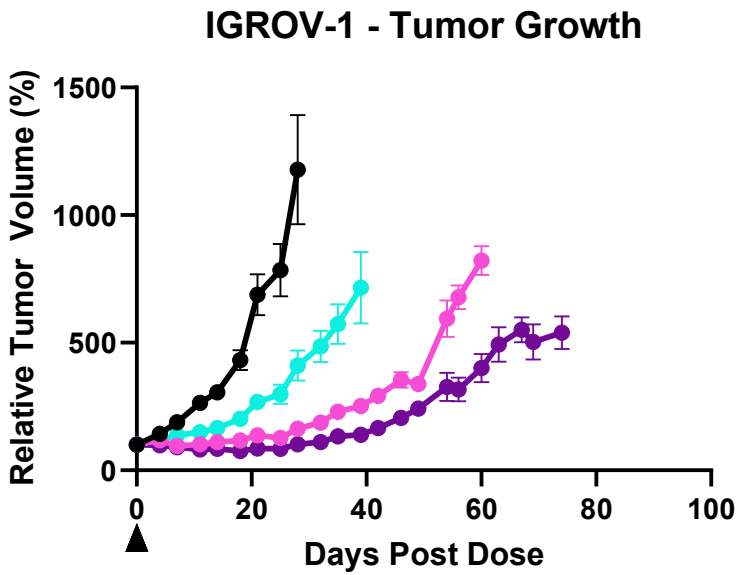
Dual-Payload ADCs have Desirable *In Vivo* PK and Stability

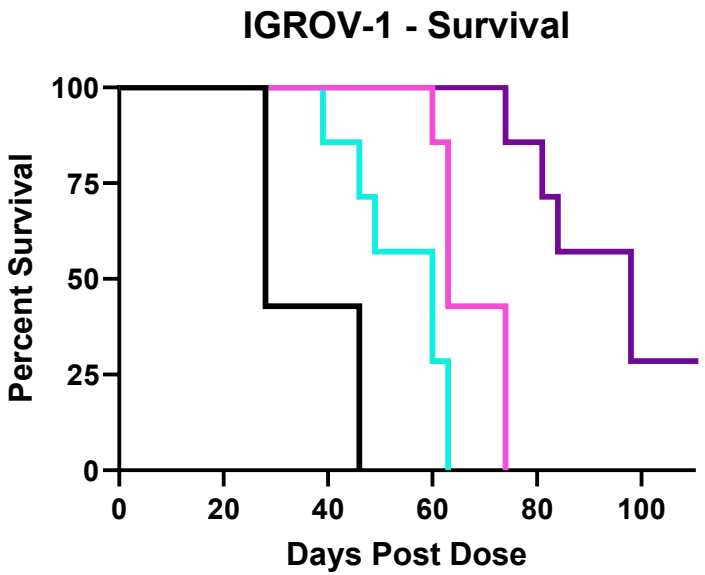


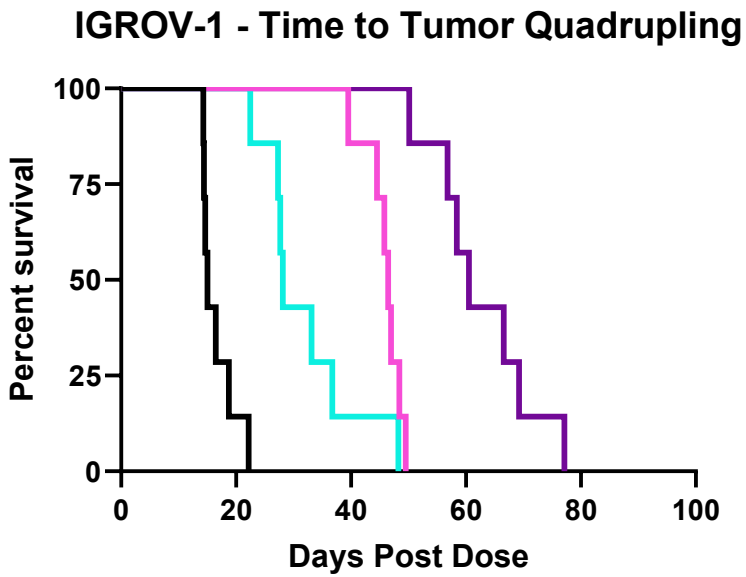


	DAR		Cl_{obs} ($mL \cdot d^{-1}/kg$)	V_{ss} (mL/kg)	$t_{1/2}$ (days)
	Topo1i	MMAE			
○	8	2	3.3	75.8	16.3
▲	8	4	4.2	81.4	14

Dual-Payload ADCs Show Improved *In Vivo* Efficacy in an Ovarian Cancer Xenograft Model

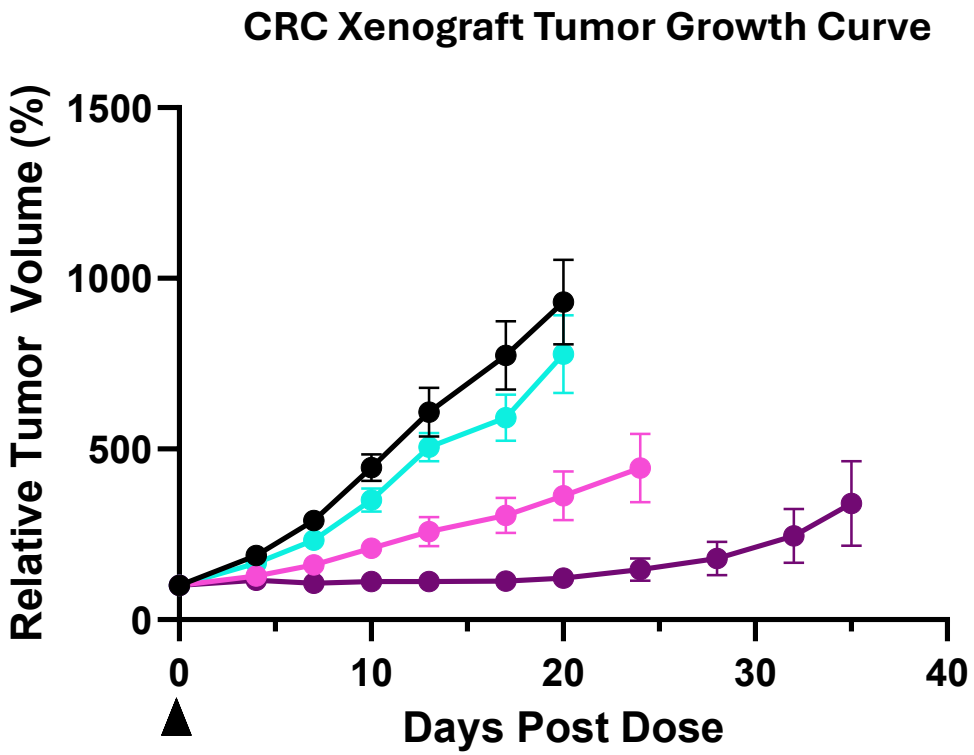






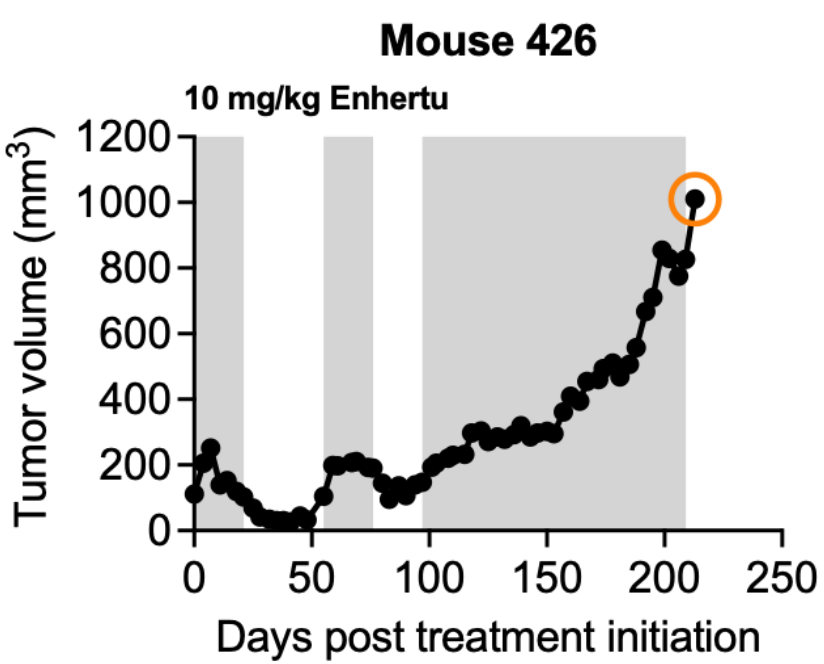
Vehicle control
Trastuzumab DAR4 MTI ADC (5 mg/kg)
Trastuzumab DAR8 Topo1i ADC (5 mg/kg)
Trastuzumab DAR(8+4) Topo1i + MTI dpADC (5 mg/kg)

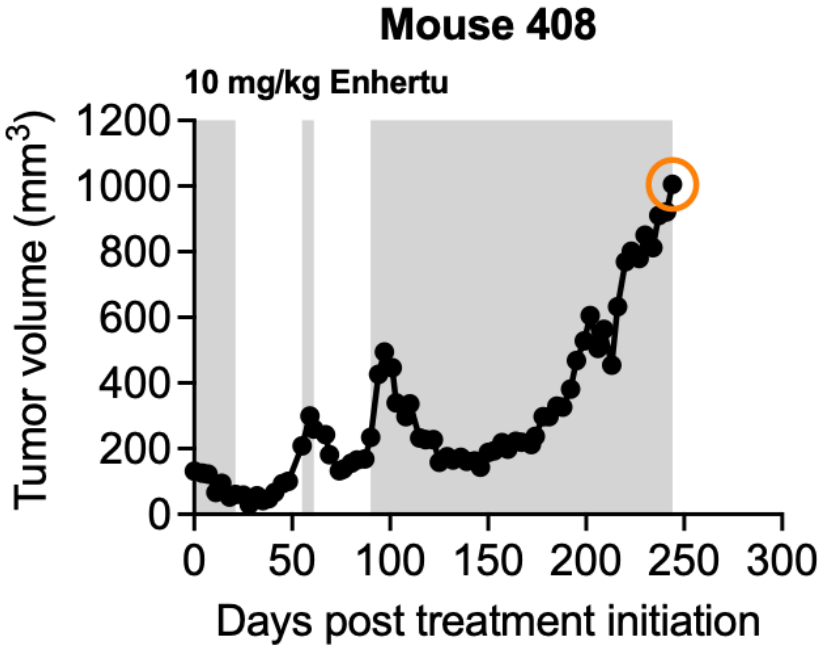
Dual-Payload ADCs Show Improved *In Vivo* Efficacy in an MTI-Resistant CRC Xenograft Model



Vehicle control
Trastuzumab DAR4 MTI (MMAE) ADC (5 mg/kg)
Trastuzumab DAR8 Topo1i ADC (5 mg/kg)
Trastuzumab DAR(8+4) Topo1i + MTI dpADC (5 mg/kg)

In Vivo Selection of Enhertu-Resistant Ovarian Cancer Cell Lines

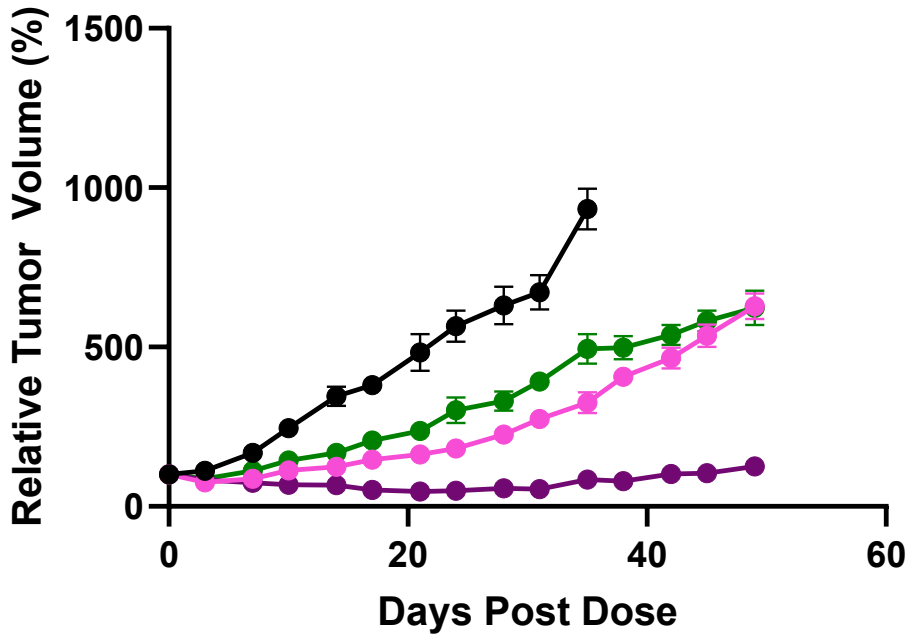




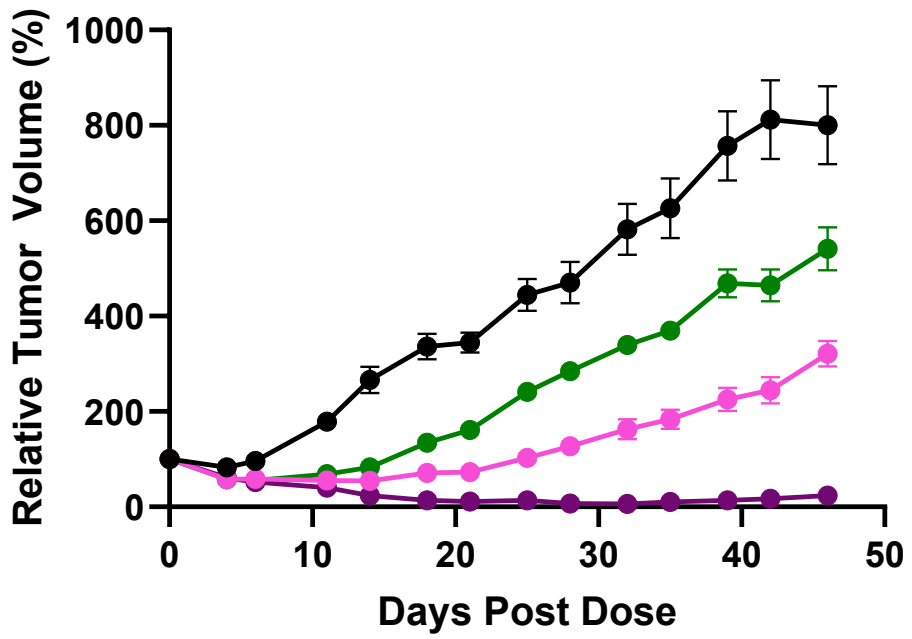
Upon reaching ~1,000 mm^3 during continuous weekly treatment with Enhertu, tumors were harvested to establish resistant cell lines

Dual-Payload ADCs Display Improved *In Vivo* Efficacy in Ovarian Cancer Models With Reduced Enhertu/Topo1 Sensitivity

OvCa-ENR1 Tumor Growth Curves



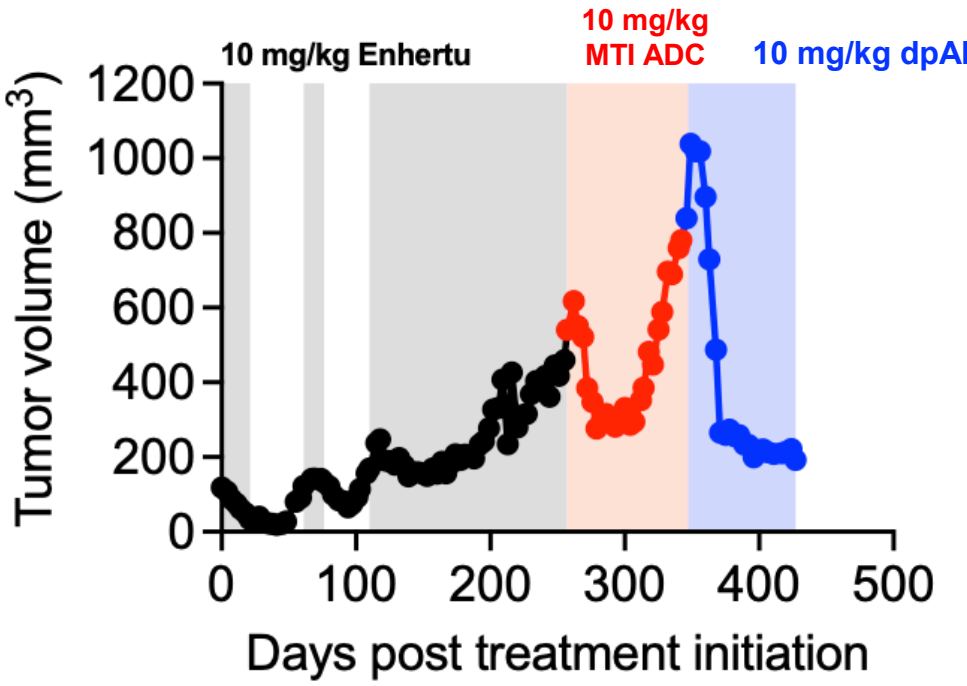
OvCa-ENR3 Tumor Growth Curves



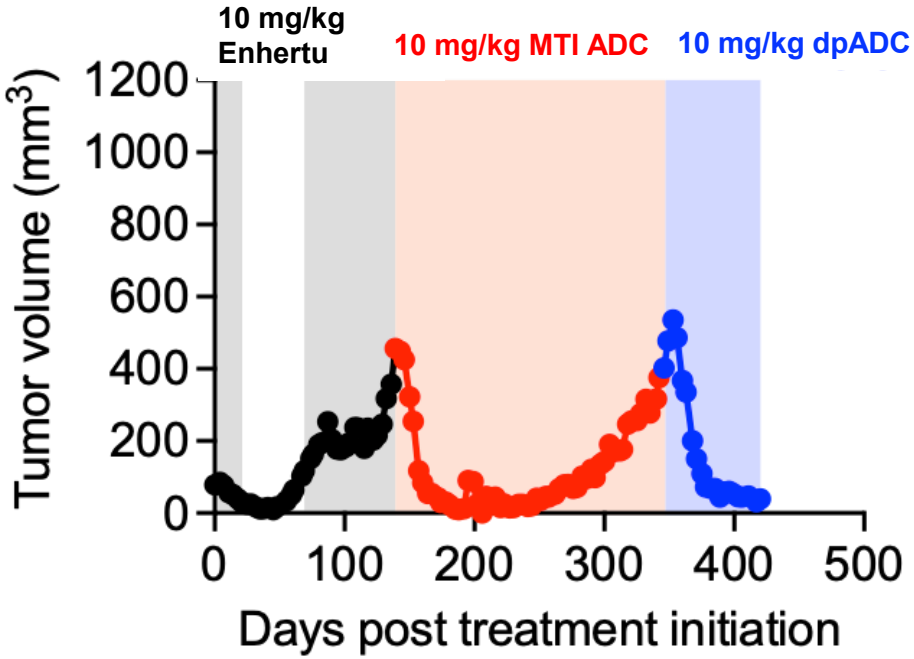
Vehicle control
Trastuzumab DAR8 Topo1i ADC (10 mg/kg)
Trastuzumab DAR(8+4) Topo1i + MTI (MMAE) dpADC (10 mg/kg)
Enhertu (10 mg/kg)

Dual-Payload ADC Overcomes Sequential Resistance to Single-Payload ADCs

Ovarian Tumor #1

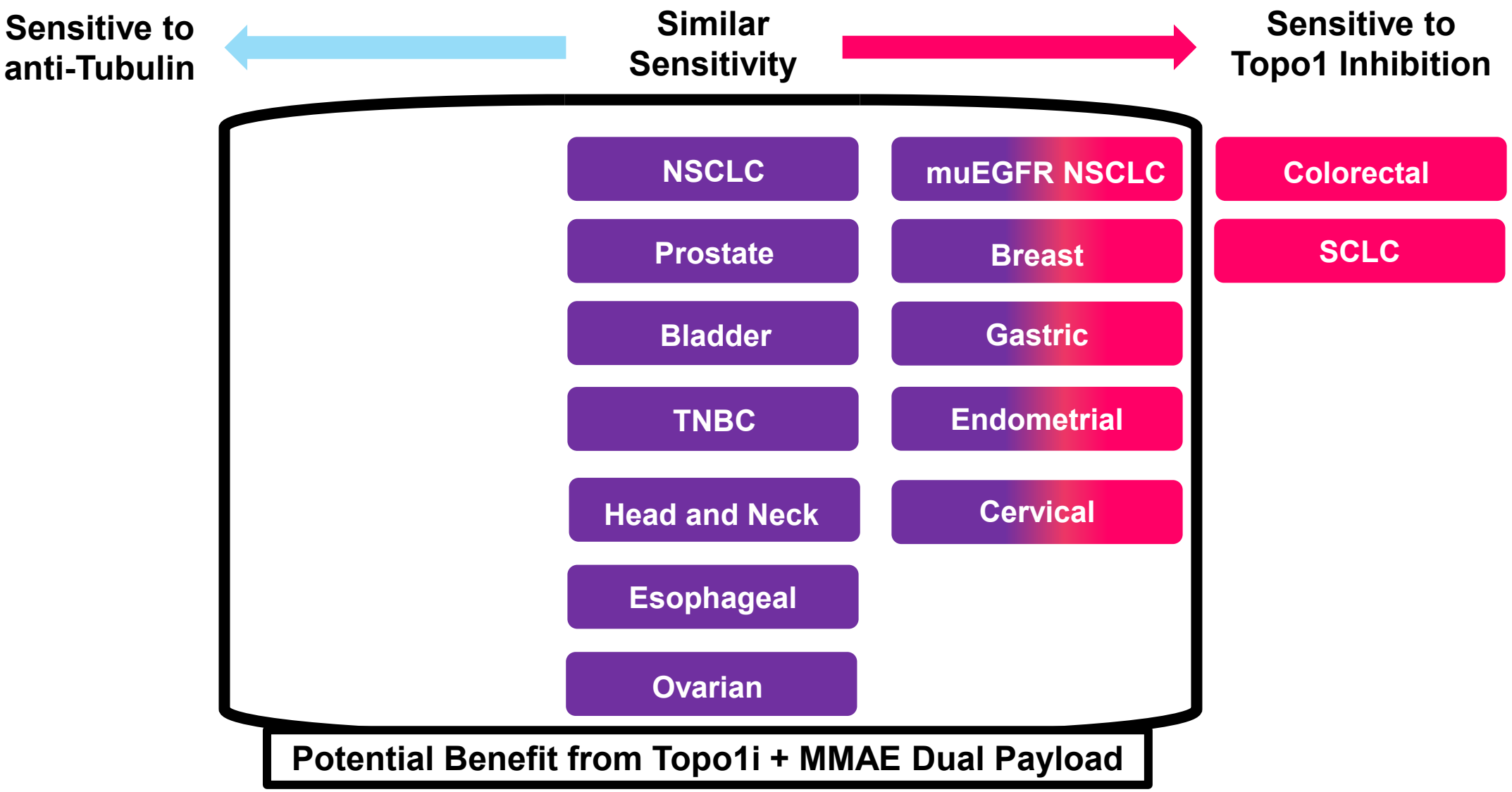


Ovarian Tumor #2

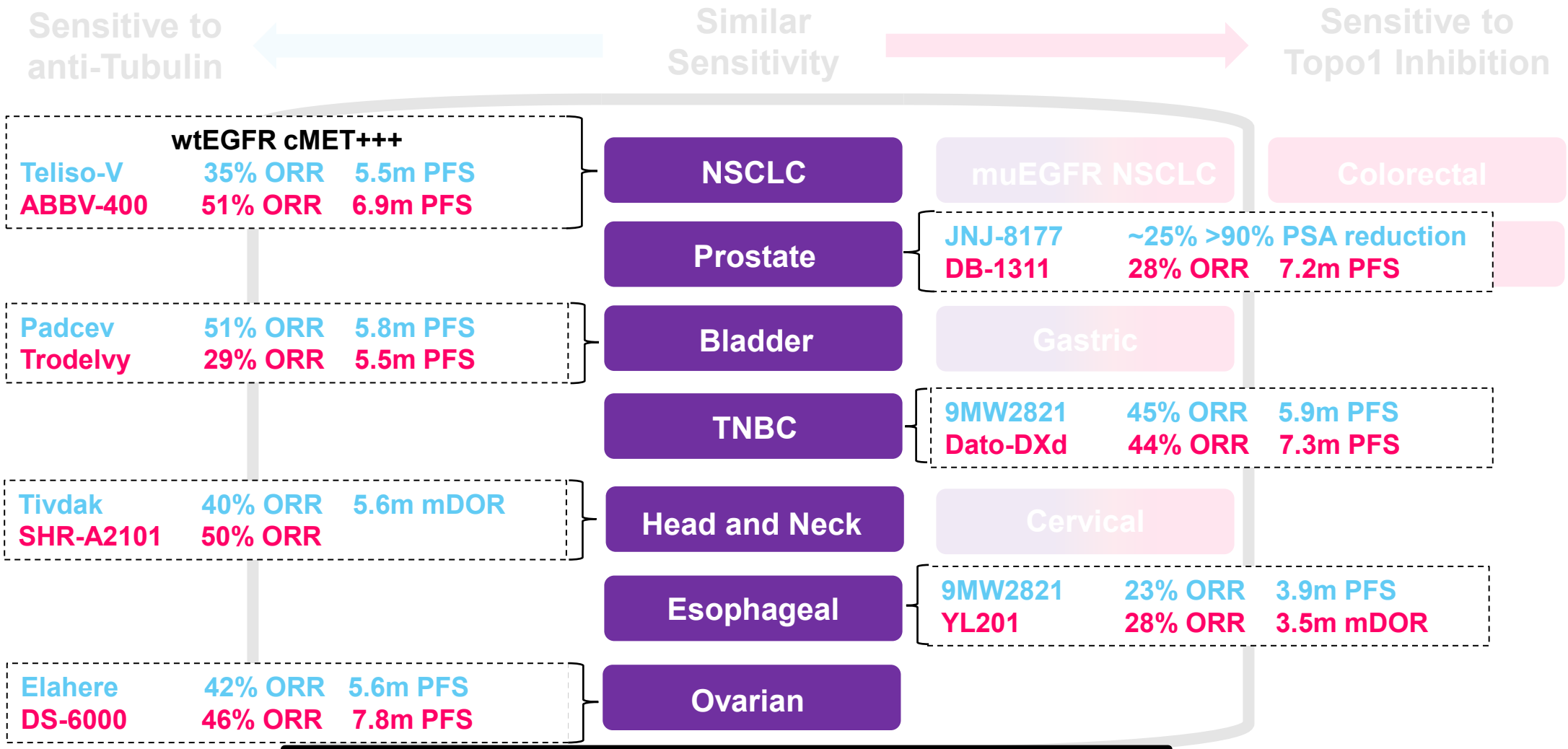


Mice with Enhertu-resistant tumors (Topo1i) were switched onto STRO-002 treatment (MTI) and subsequently onto dual-payload ADC after exhibiting STRO-002 resistance

Indications Poised to Benefit from Topo1i + MTI Dual-Payload ADCs



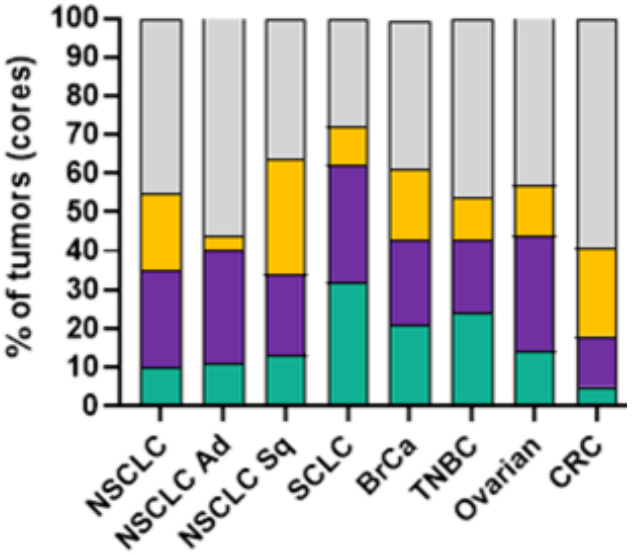
Indications Poised to Benefit From Topo1i + MTI Dual-Payload ADCs



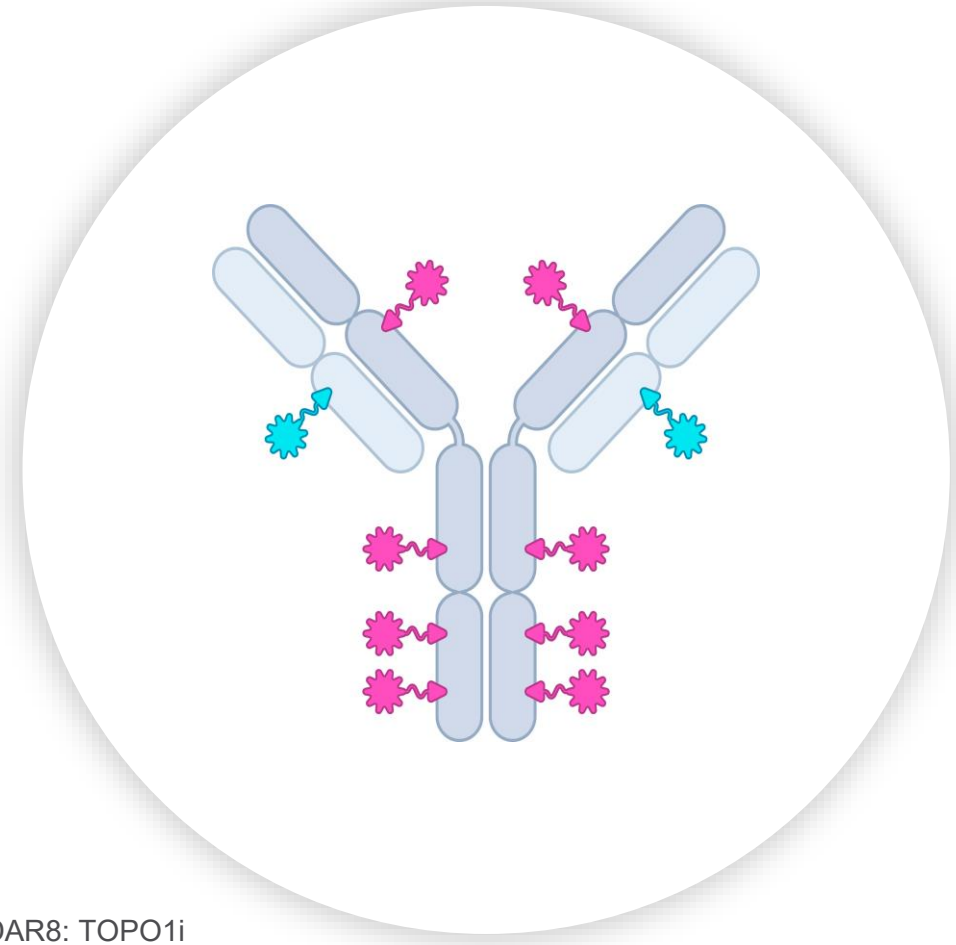
PTK7 is a Pan-Tumor Target Enriched on Tumor-Initiating Cells

- Catalytically inactive receptor tyrosine kinase involved as a co-receptor in multiple signaling pathways, particularly Wnt signaling
- Enriched on tumor-initiating cancer stem cells
- Expression correlates with poor prognosis and worse overall survival in NSCLC, TNBC, Ovarian, and ESCC

PTK7 Prevalence by H Score



Dual-Payload Topo1i x MTI ADC Targeting PTK7



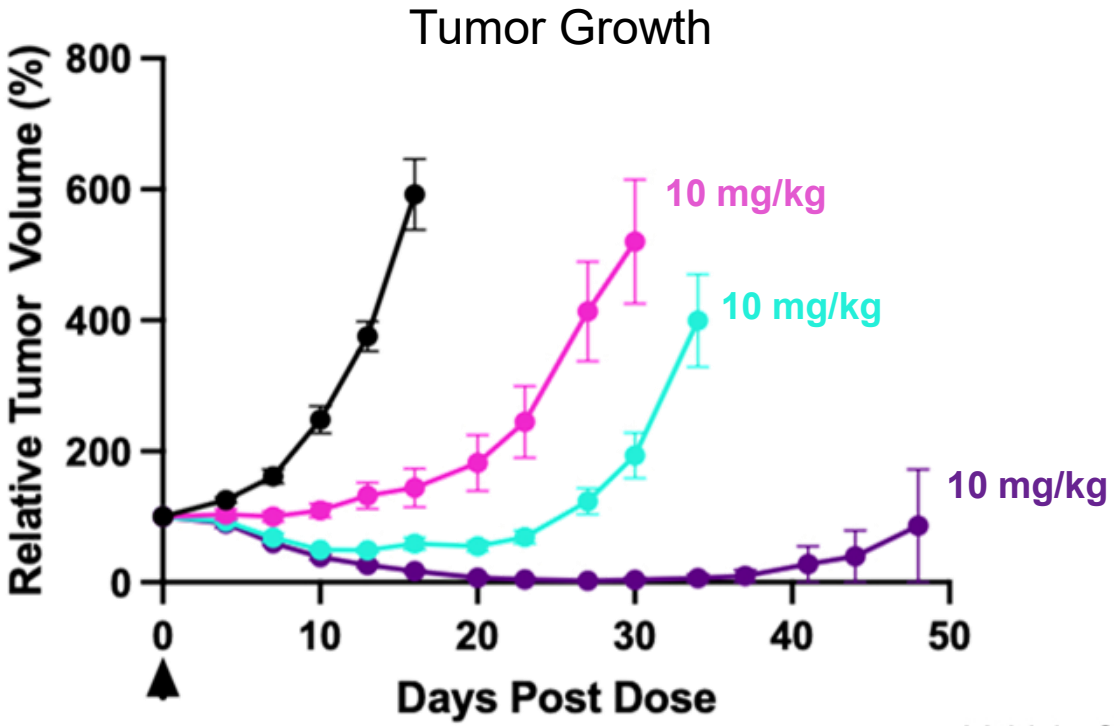
DAR8: TOPO1i

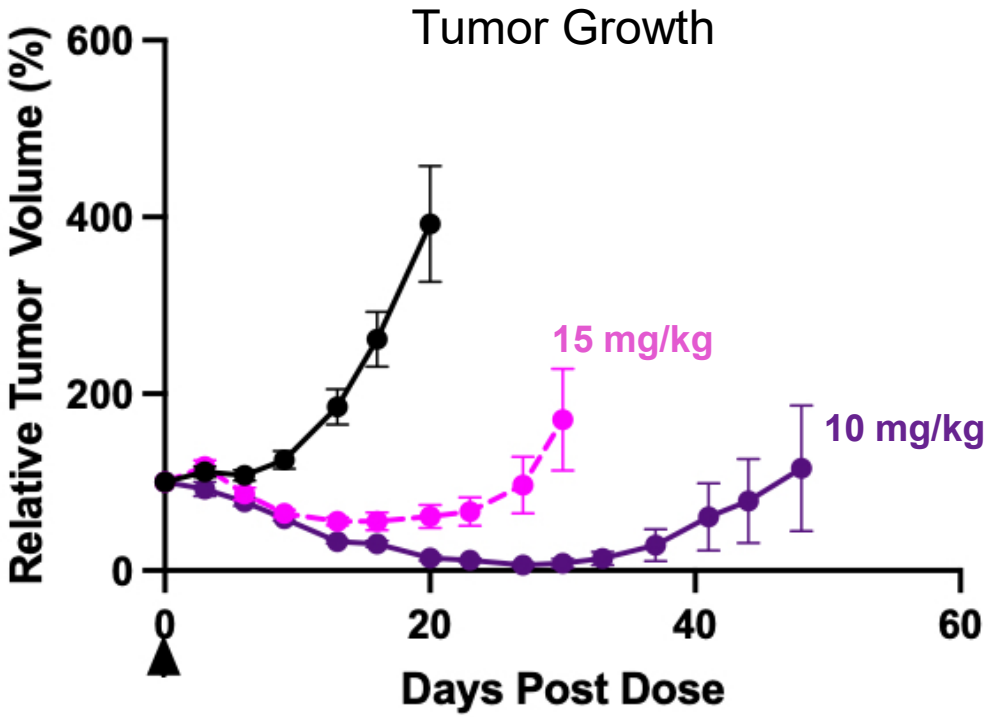
DAR2: MTI

1. **Optimally positioned non-natural amino acids**, p-azidomethyl-L-phenylalanine (pAMF), combined with ultrastable click chemistry
2. **β-glucuronidase cleavable linkers** with tumor selective cleavage, strong stability while in circulation, and added hydrophilicity led to **best-in-class PK**
3. **Eight exatecan payloads causing DNA disruption** and potent tumor cell killing, with high bystander activity, and immunogenic cell death (ICD)
4. **Two MMAE payloads causing Tubulin disruption** and potent tumor cell killing, with high bystander activity, and immunogenic cell death (ICD)
5. **Lack of FcγR interactions** limits uptake by alveolar macrophages, reducing risk of interstitial lung disease (ILD)

Better Together: Dual-Payload ADC Outperforms Single-Payload ADCs

Breast Cancer Xenograft Model

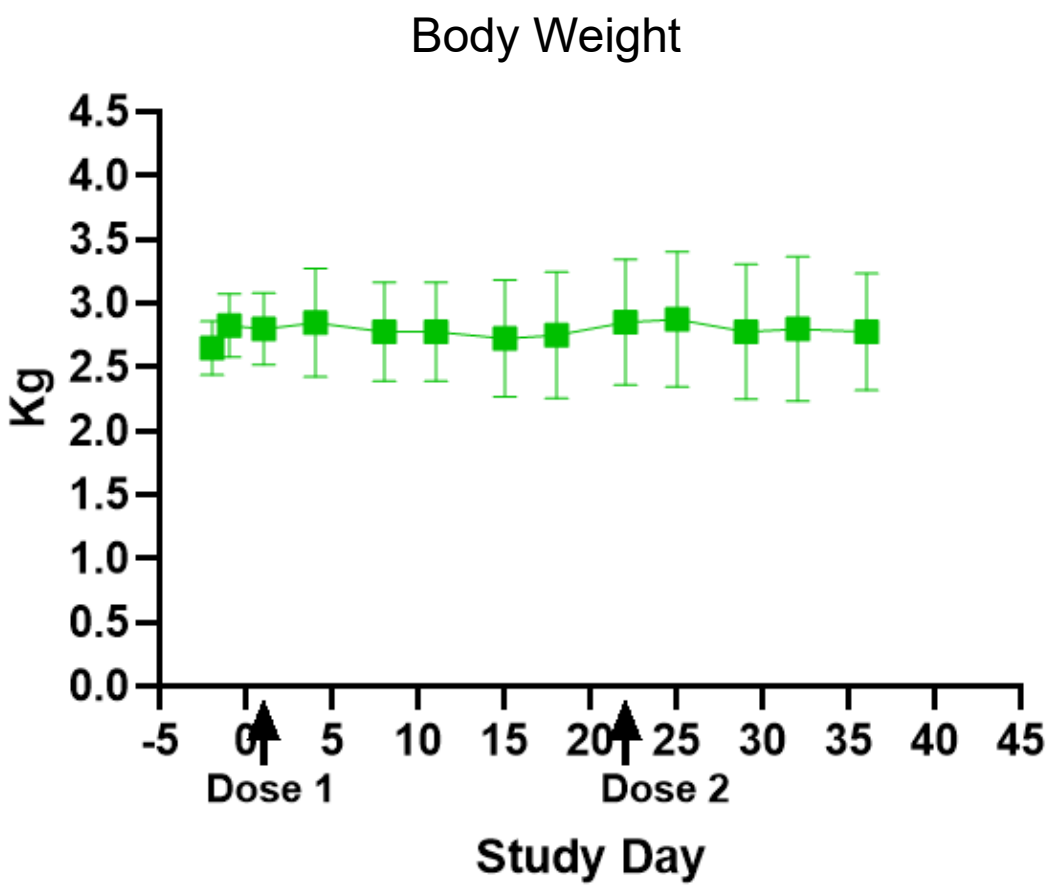




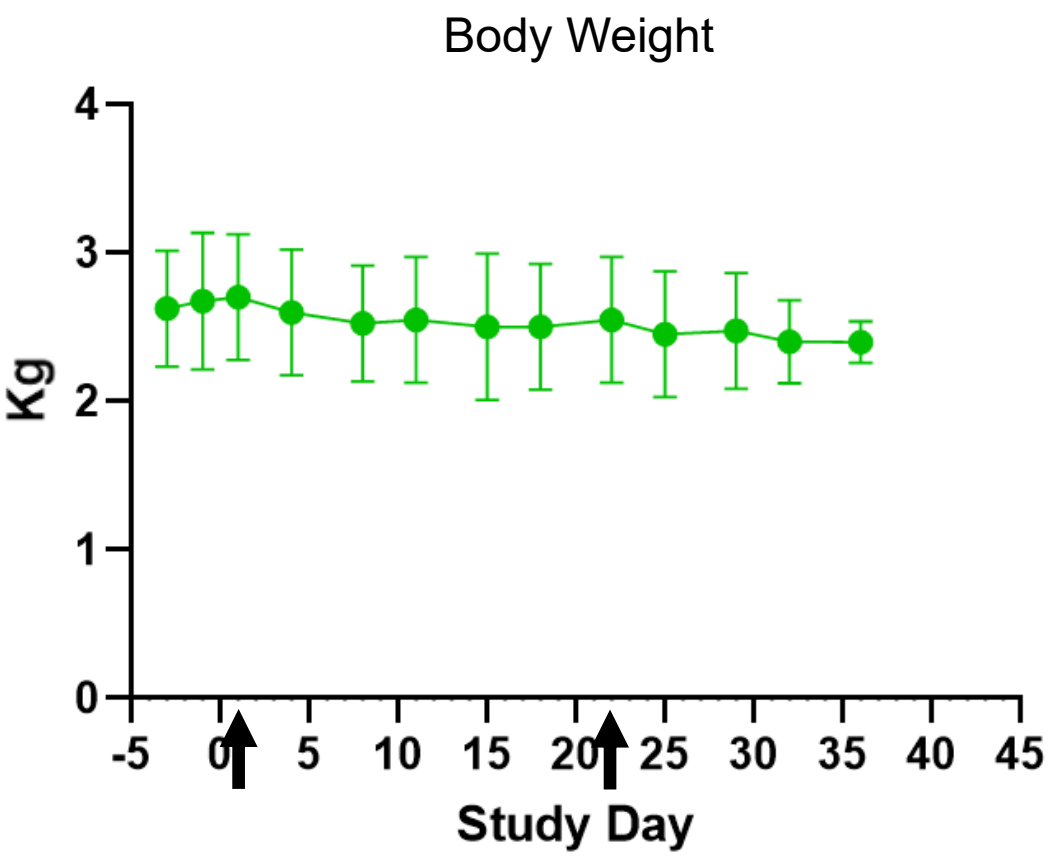
Vehicle Control
DAR8 Topo1i ADC
DAR2 MMAE ADC
DAR8+2 Dual-Payload ADC

Encouraging Safety Profile for Sutro Dual-Payload ADCs in NHP

12.5 mg/kg 8+4 HER2 dpADC (Q3Wx2)



25 mg/kg 8+2 PTK7 dpADC (Q3Wx2)



Sutro Dual-Payload ADC: Preclinical Tolerability Meets Single-Payload Benchmarks

ADC	Target	Linker	Payload	DAR	NHP HNSTD	Highest Clinical Phase
Padcev	Nectin-4	Val-cit	MMAE	4	3 mg/kg[a] (Q1Wx4)	Approved
Tivdak	TF	Val-cit	MMAE	4	3 mg/kg[a] (Q3Wx5)	Approved
SGN-B6A	ITGB6	Val-cit	MMAE	4	6 mg/kg[a] (Q3Wx2)	3
LCB84	Trop-2	β-Glu	MMAE	4	10 mg/kg[b] (Q3Wx2)	1/2
LNCB74	B7-H4	β-Glu	MMAE	4	10 mg/kg[c] (Q3Wx2)	1
Sutro dpADC	**PTK7**	**β-Glu**	**Exatecan + MMAE**	**8 + 2**	**25 mg/kg (Q3Wx2)**	**Preclinical**

[a]PMID: 38692647. [b]LCB84 doi:10.1158/1538-7445.AM2022-328. [c]LNCB74 doi:10.1158/1538-7445.AM2024-1898

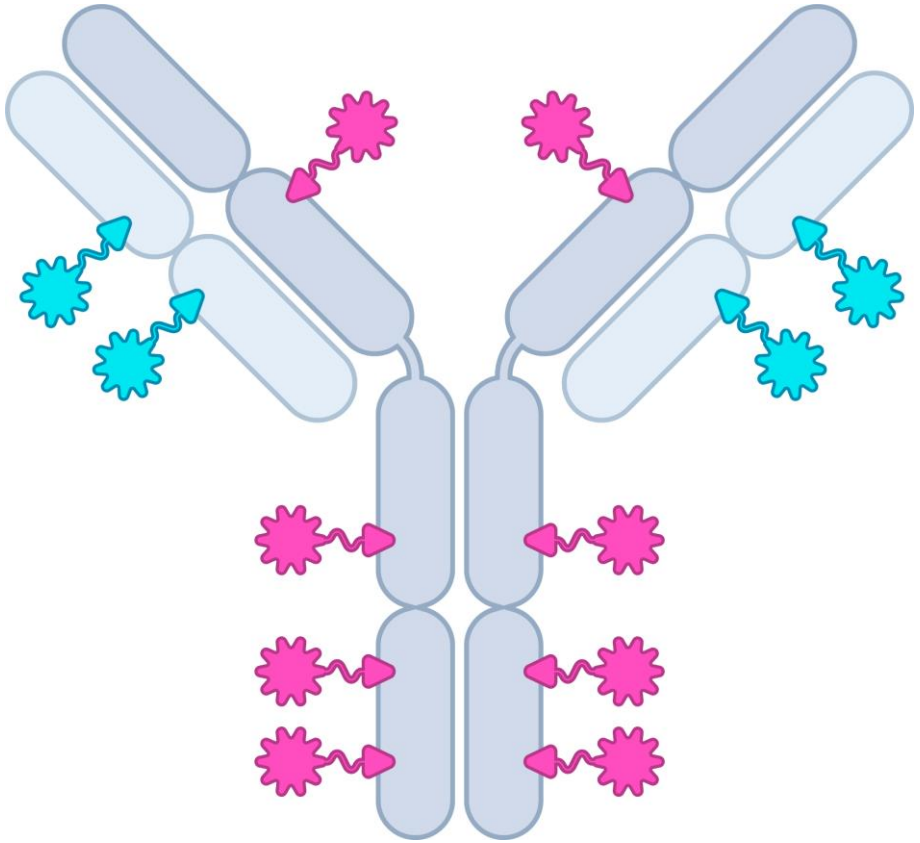
Sutro Dual-Payload ADC: Preclinical Tolerability Meets Single-Payload Benchmarks

ADC	Target	Linker	Payload	DAR	NHP HNSTD	Highest Clinical Phase
Enhertu	HER-2	GGFG	Deruxtecan	8	30 mg/kg[a] (Q3Wx3)	Approved
Datroway	Trop-2	GGFG	Deruxtecan	4	10 mg/kg[b] (Q3Wx5)	Approved
MK-1022	HER-3	GGFG	Deruxtecan	8	30 mg/kg[c] (Q3Wx5)	3
MK-2400	B7-H3	GGFG	Deruxtecan	4	30 mg/kg[d] (Q2Wx3)	3
MK-5909	CDH6	GGFG	Deruxtecan	8	30 mg/kg[e] (Q3Wx3)	2/3
Rina-S	FOLR1	Val-Cit	Exatecan	8	30 mg/kg[f] (Q3Wx2)	3
Sutro dpADC	**PTK7**	**β-Glu**	**Exatecan + MMAE**	**8 + 2**	**25 mg/kg (Q3Wx2)**	**Preclinical**

[a]PMID: 27026201 [b]PMID: 34413126 [c]PMID: 31471314

[d]PMID: 35149548 [e]PMID: 38205802 [f]DOI:10.1158/1538-7445.AM2023-CT244

Differentiation by Design: Sutro Dual-Payload ADC Platforms



Precision, Flexibility, Scalability: Optimization of conjugation sites and payload stoichiometry

Broad pipeline potential (Topo1i, MTI, IO, DDRi)

Developing next-generation ADCs to overcome resistance mechanisms and expand clinical opportunities