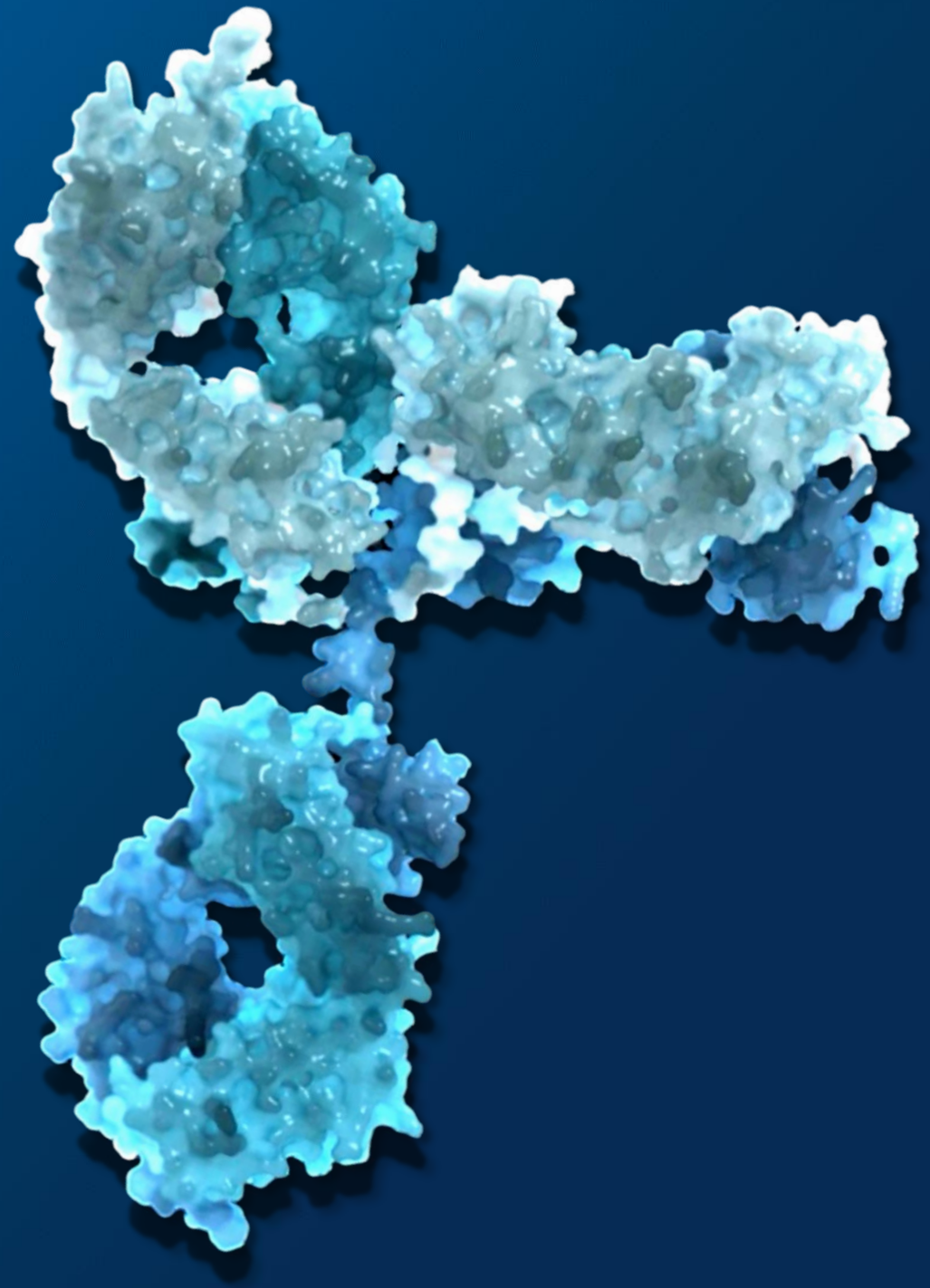
SUTRO BIOPHARMA

Enhancing ADCs Both Within and Outside the Tumor with Sutro's Platform Technologies Leads to a Higher Therapeutic Index

Hans-Peter Gerber, Ph.D.
CSO

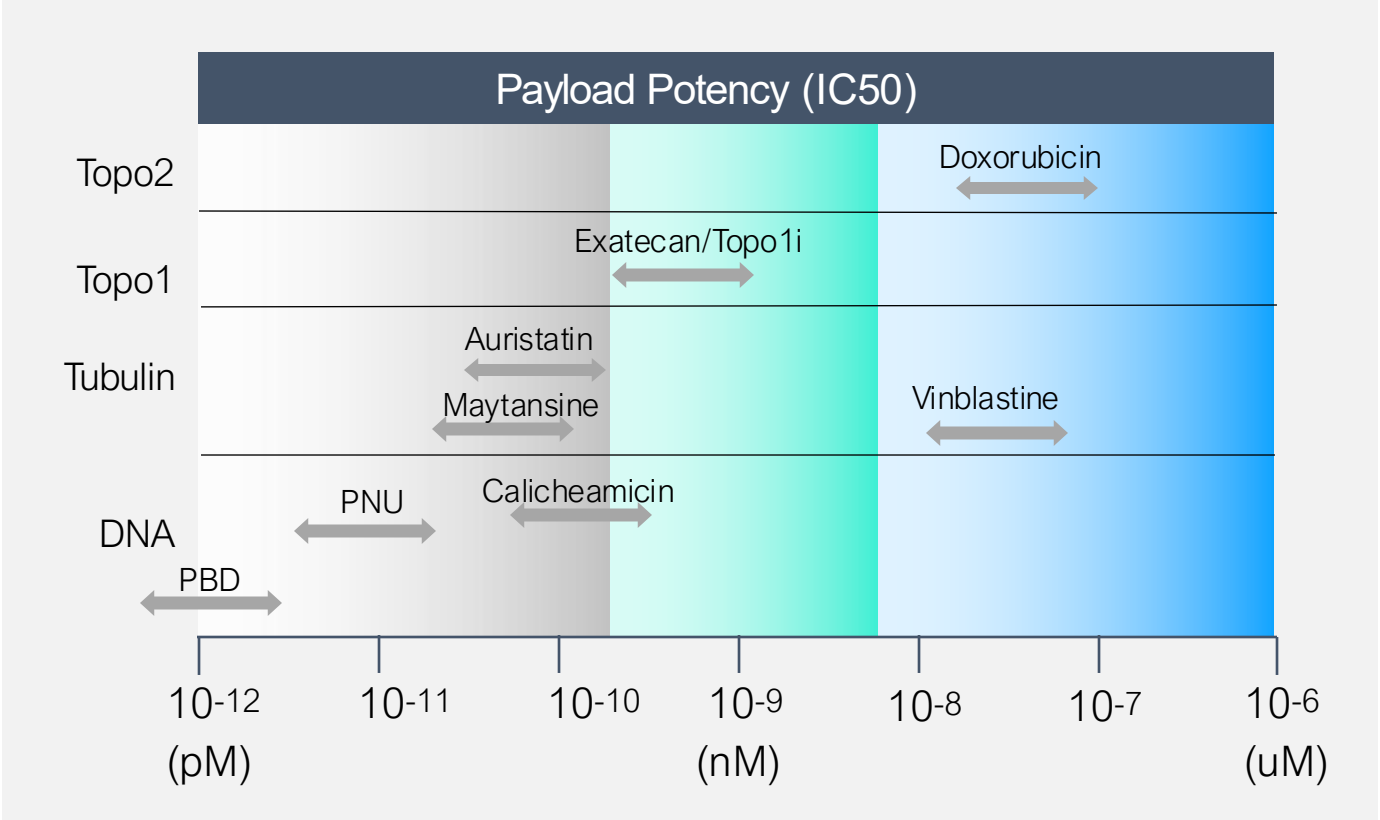
PEGS, May 16, 2025



ADC Development Up to 2020: Focus on Optimizing ADC Potency

ADC Technology Focus Areas

- Higher potency payloads
  - PBDs, PNUs, etc.
- Novel conjugation chemistry
- Improved ADC activity
  - *In vitro* potency
  - *In vivo* xenograft

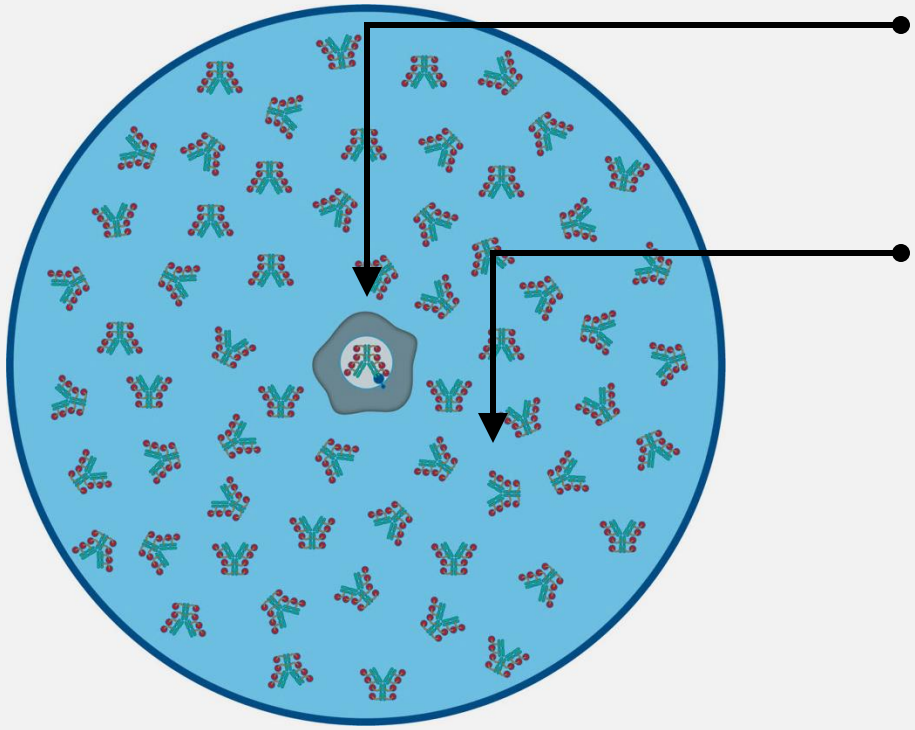


However…

Clinical ADC breakthrough in 2019 with lower potency Camptothecin/Exatecan/Topo1i ADCs

PBD – pyrrolobenzodiazepines; PNU – a highly potent secondary metabolite of nemorubicin belonging to the anthracycline class of natural products; Topo1i – topoisomerase 1 inhibition

Lower Potency Topo1 Payload Enables Higher Dosing and Exposure, Which Drives ADC Efficacy



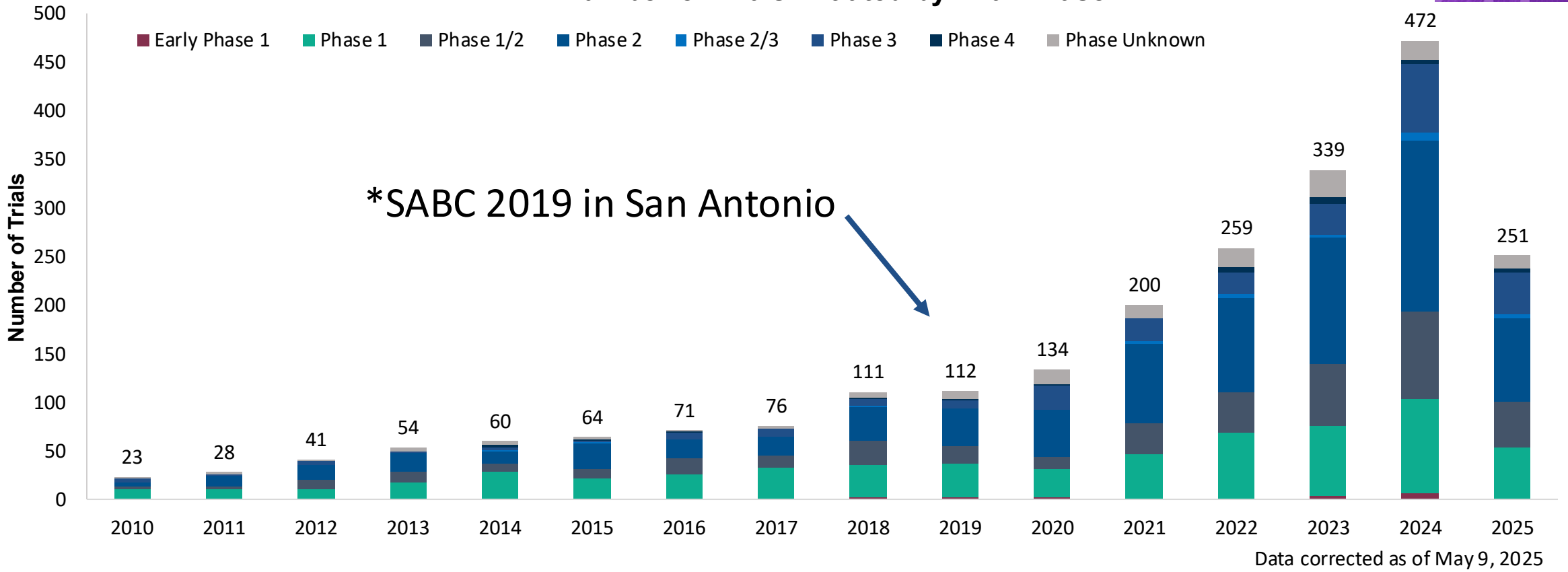
Only 1% of ADCs reach tumors, targeting the tumor effectively when it gets there

99% reside outside tumors, limiting ADC exposure as premature payload release causes platform toxicity

Topo1i ADCs outside the tumor are less toxic to healthy cells:

Reduced "Platform" Toxicity → Higher Dose → Higher Exposure → Drives Efficacy

Clinical Trial Inflection Point: Exatecan ADCs Triggered the ADC Turnaround



*First report of clinical response rates of a Her2-Exatecan/Topo1 DAR 8 ADC in Her2+ mBC

Topo1/Exatecan ADCs All Look Promising Preclinically…
How Can we Identify the "Winners" Early ?

Top 10 Adjectives Describing ADC Efficacy

Adjective	Freq	Payloads
Effective	90	MMAE, DM1, PBDs, Exatecan
Potent	85	MMAE, MMAF, PBDs, SN-38
Promising	73	MMAE, DM1, SN-38, Tubulysins
Robust	68	DM1, PBDs, Exatecan, Tubulysins
Durable	60	Exatecan, SN-38, DM4
Significant	58	MMAE, PBDs, Amanitin
Superior	52	PBDs, Exatecan, Tubulysins
Sustained	49	Exatecan, SN-38
Efficient	46	MMAF, DM1, SN-38
Encouraging	44	DM4, Tubulysins, Amanitin

Top 10 Adjectives Describing ADC Safety

Adjective	Freq	Payloads
Tolerable	85	MMAE, MMAF, DM1, PBDs
Manageable	78	MMAE, MMAF, DM1, Exatecan
Acceptable	62	DM1, DM4, SN-38
Favorable	58	SN-38, Exatecan, MMAF
Predictable	53	DM1, DM4, MMAF
Reversible	49	DM1, DM4, SN-38, Exatecan
Dose-limiting	44	PBDs, Amanitin, Tubulysins
Severe	30	PBDs, Amanitin
Serious	27	PBDs, Amanitin
Challenging	25	Amanitin, PBDs

Only about 10% of all BioTx entering clinical development may ultimately get approved….

Key Preclinical Data to Identify "Winner" ADCs

- PK
  - Long half-life, low clearance
- Safety
  - High exposure & HNSTD (highest non severely toxic dose)
- Activity
  - In models predictive for clinical responses
  - At clinically relevant dose levels
  - In models reflecting emerging resistance to ADCs

STRO-004 (TF-Topo1-DAR8): Well-Tolerated at 50 mg/kg (Non-GLP in NHP)

Objective:

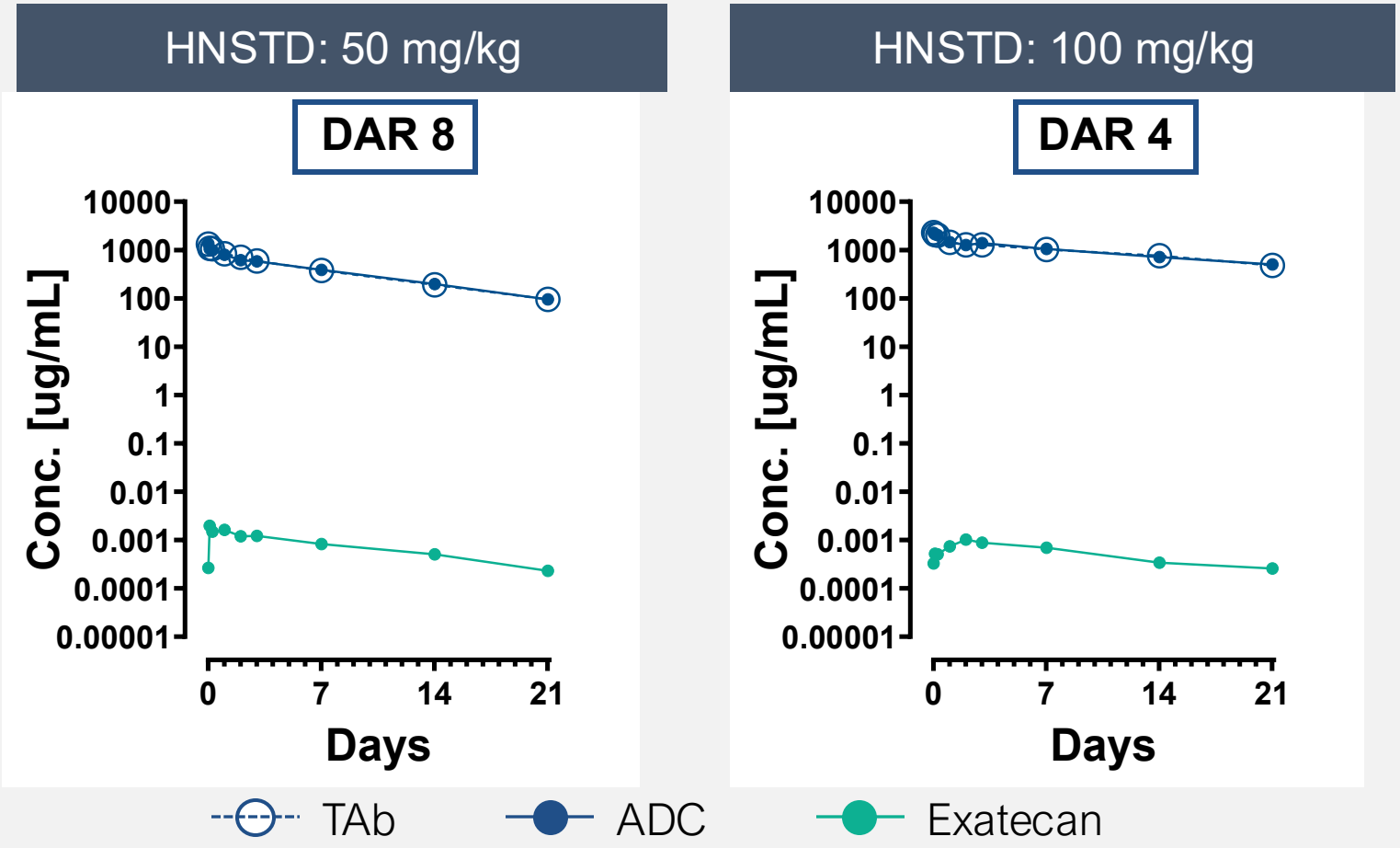
Compare nonclinical safety of DAR8 and DAR4 TF exatecan-ADC

Study:

Dosed twice, three weeks apart, payload-matched doses

Findings:

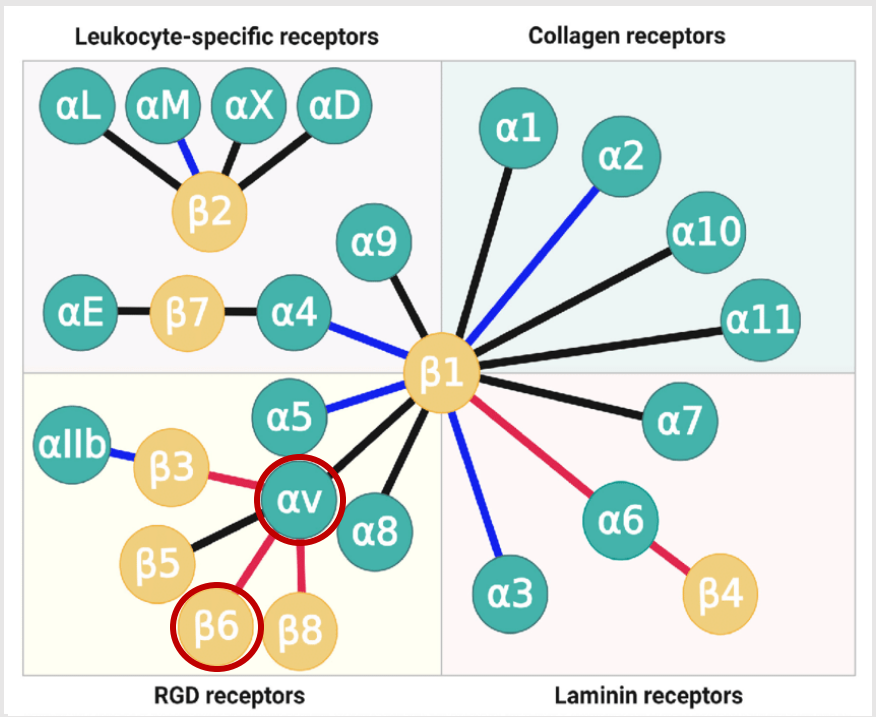
- DAR8 and DAR4 ADCs were well-tolerated up to 50 and 100 mg/kg, respectively
- DAR8 50 mg/kg $t_{½}$ of 6.9 days
- No evidence of eye toxicity
- Mild skin toxicity observed in both DAR8 and DAR4



NHP – Non-human primate; TF – Tissue factor; TAb – Total antibody; HNSTD – Highest non-severely toxic dose

Integrin β6 is an Attractive ADC Target with Complex Biology

Integrin Family



Steiger, et al (2021) EJNMMI Research

ITGB6 Biology

- Integrin β6 (ITGB6) is overexpressed in numerous solid tumors and has been shown to be a negative prognostic indicator in many cancers
- ITGB6 targeted therapies are seeing strong clinical activity in NSCLC
- It functions in tissue remodeling and repair, processes that can be exploited by tumors to promote invasiveness and survival
- ITGB6 is a heterodimer (αv/β6) that belongs to an integrin family of adhesion proteins; cross-specificity in targeting can introduce significant safety risks

STRO-006 Targeting ITGB6 is Well-Tolerated in NHPs up to 25 mg/kg: Long Half-Life and Low Levels of Unconjugated Exatecan

Objective:

Evaluate toxicity profile of STRO-006 in a dose-range finding study in NHPs to inform IND-enabling GLP study

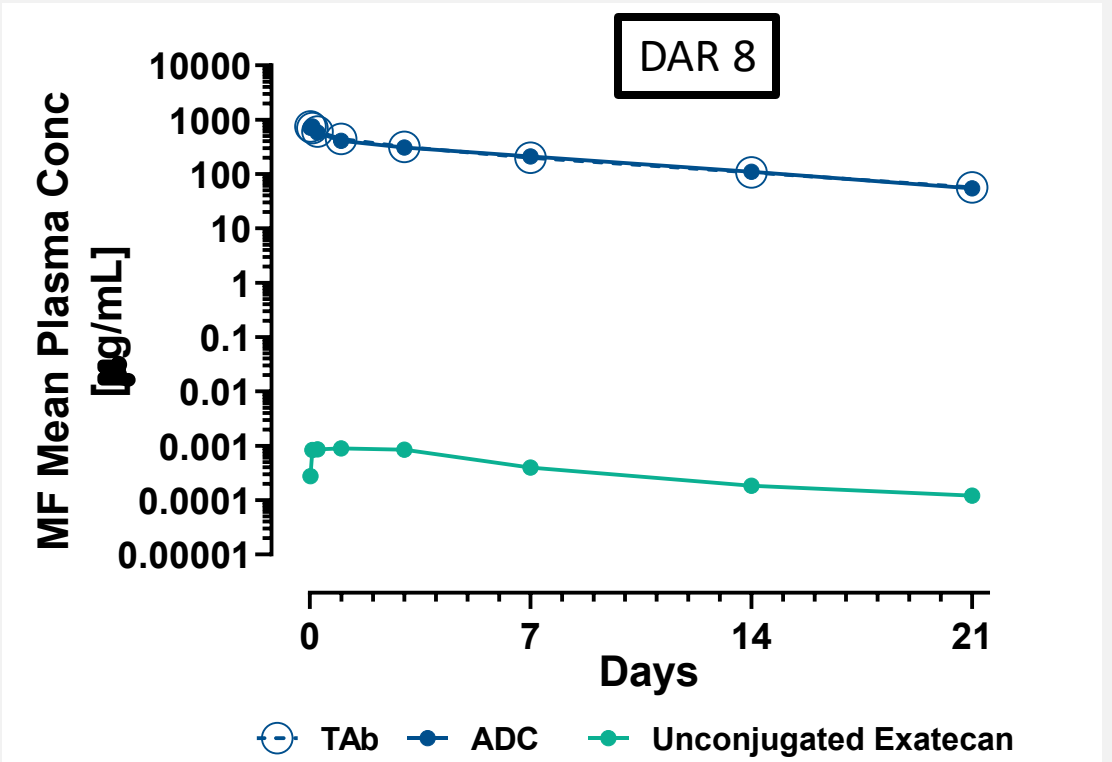
Study:

Six-week duration study (1M/1F), two IV doses of 10, 25, or 50 mg/kg administered once every 3-weeks → necropsy D43

Findings:

- STRO-006 was well-tolerated up to 25 mg/kg with no body weight loss
- No signs of neutropenia or lymphopenia
- Stable ADC, long $t_{½}$ of 7-8 days, no ADA
- Ratio conjugated/unconjugated exposure (AUC) of Exatecan = 10120

HNSTD: 25 mg/kg



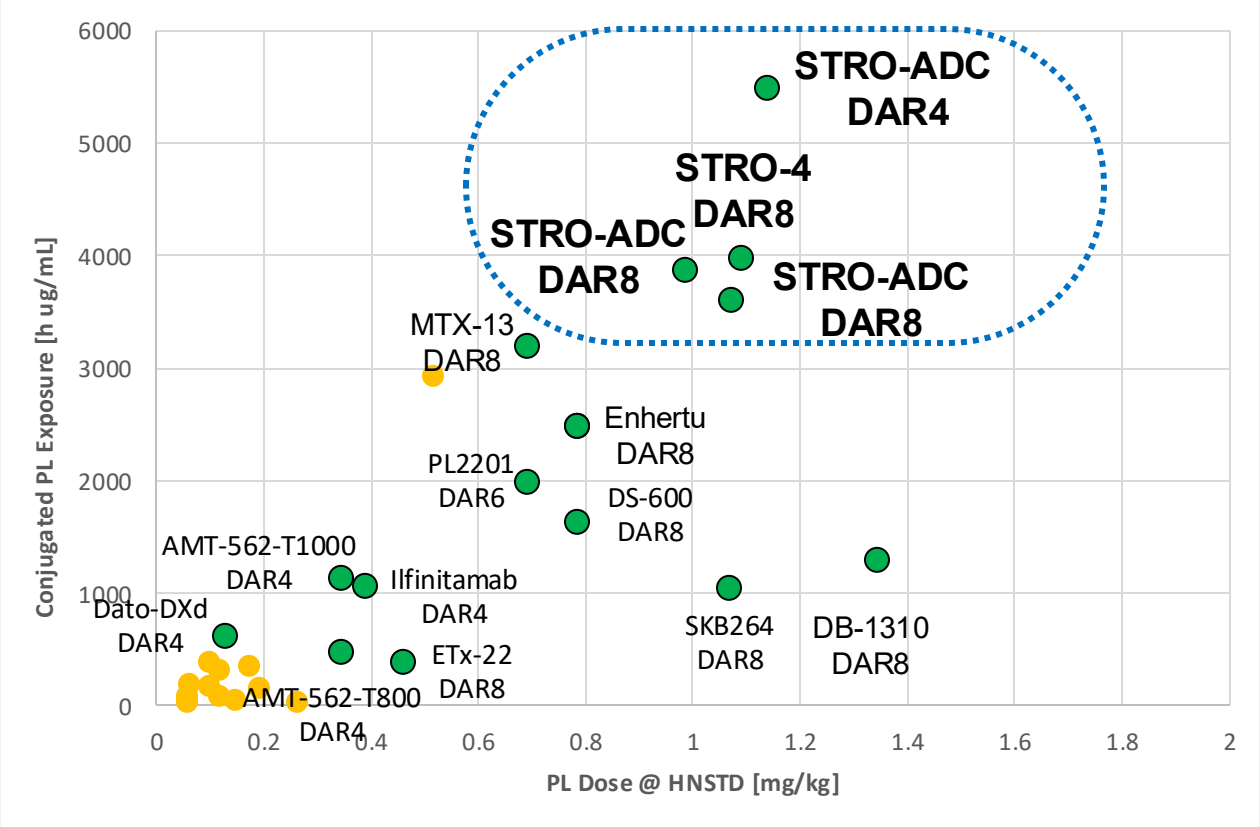
Analyte	CL (mL/d/kg)	V_{ss} (mL/kg)	$t_{½}$ (d)
TAb	5.66	55.4	7.7
ADC	5.77	55.0	7.2

NHP – Non-human primate; TF – Tissue factor; TAb – Total antibody; HNSTD – Highest non-severely toxic dose

SUTRO BIOPHARMA

High ADC Exposure in NHP Correlates with Better Safety: Sutro's Cell-Free Manufacturing Approach Enables Industry-Leading ADC Exposure

Comparison of Exposure Levels in NHPs at Highest Non-Severely Toxic Dose (HNSTD) Levels in DAR Equivalents



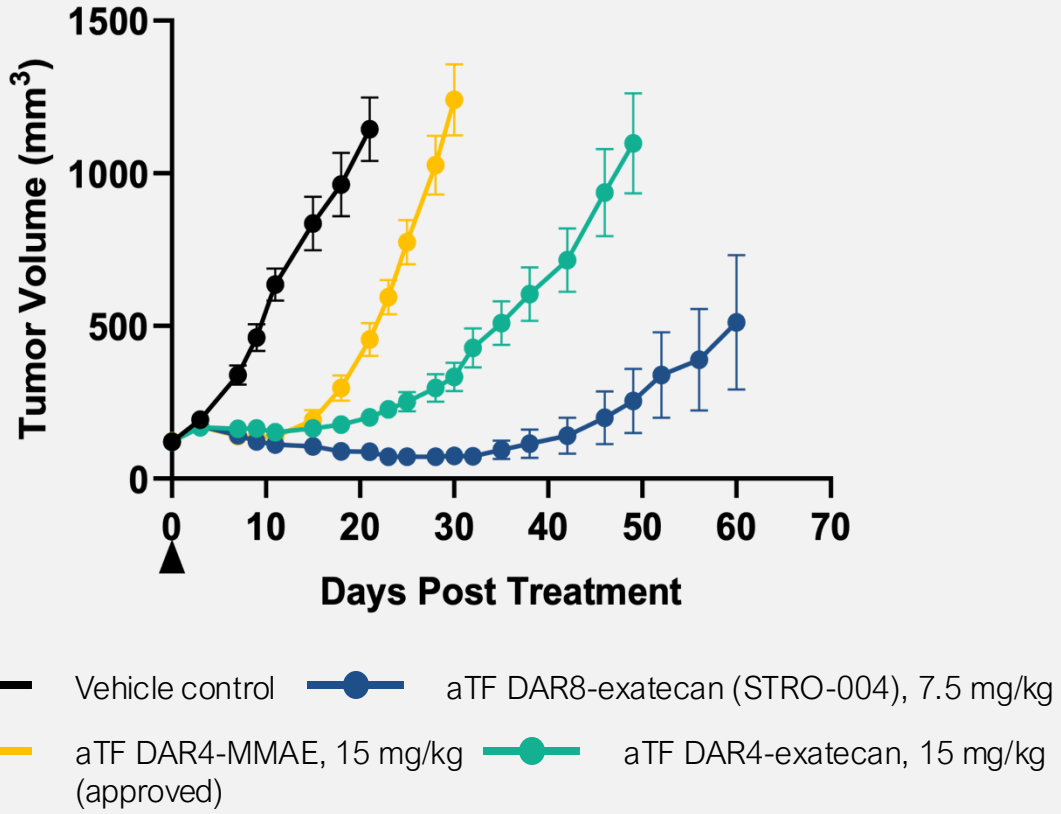
Why does it matter?

- For ADCs, exposure drives efficacy
- Based on PK data, our exatecan ADCs are positioned to be differentiated on safety and efficacy versus on-market ADCs

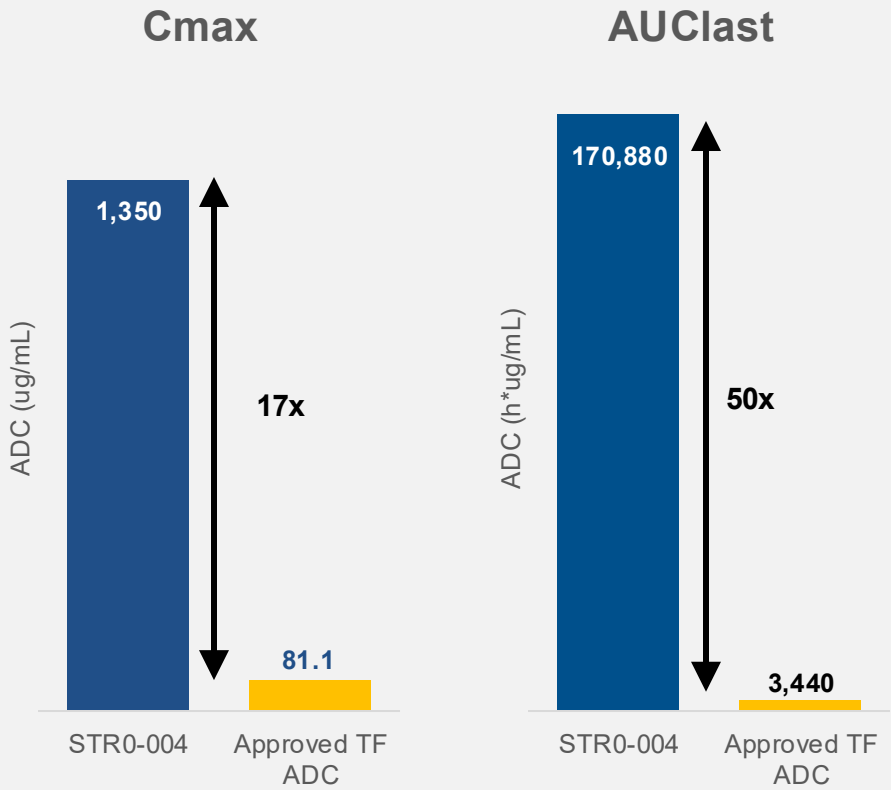
Exatecan/Topo1i ADCs Tubulin inhibitor ADCs

STRO-004 is Safe, but is it Active?
Superior Anti-Tumor Activity Compared to First Generation TF ADCs

STRO-004 (DAR8 TF ADC) Improves Anti-Tumor Activity at a Lower Dose



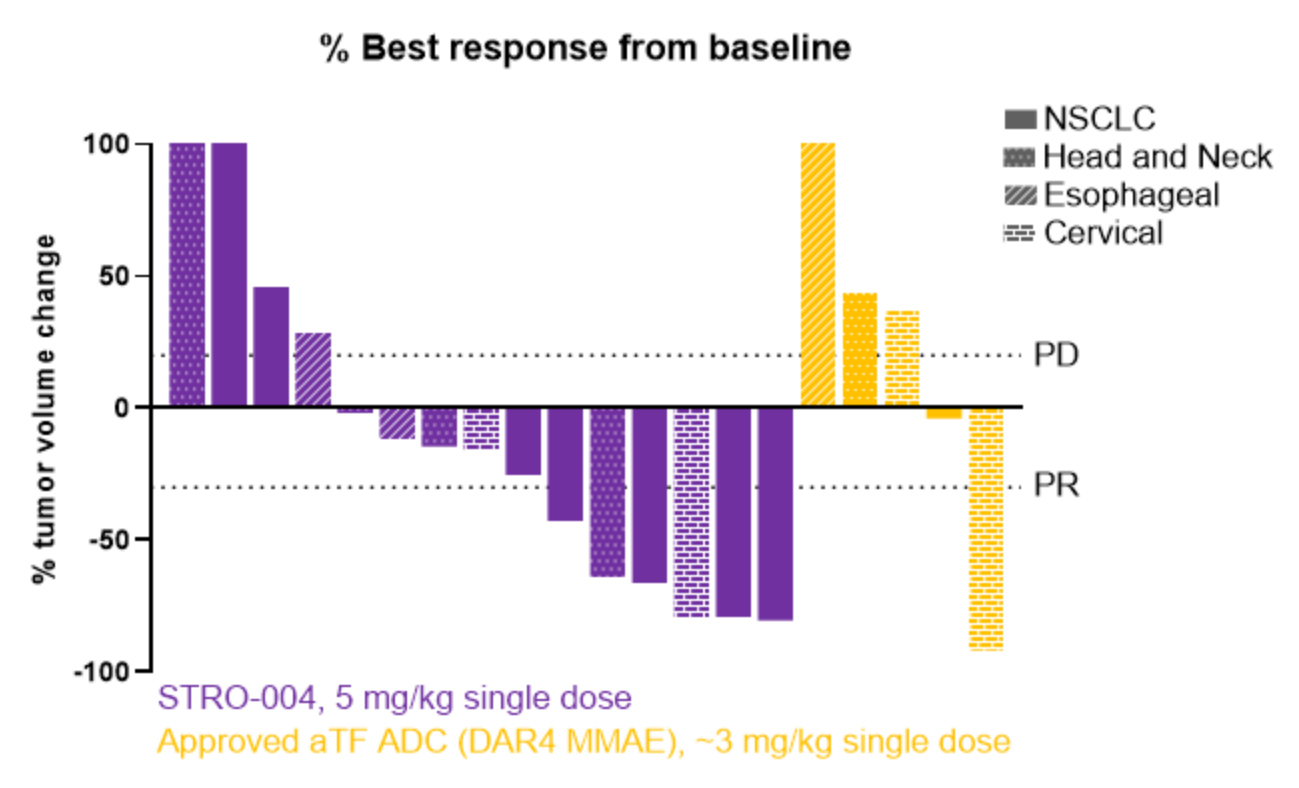
Increased Tolerability Leads to Enhanced Drug Exposure



*Breij & Parren, Can Res, 2014 # Sutro. 2024 interim data
Cmax – maximum concentration; AUClast - drug exposure over the specified time period; h – hour

Superior Anti-Tumor Activity of STRO-004 in PDX (Patient Derived Xenograft) Models at Clinically Relevant Dose Levels Compared to Tisotumab-Vedotin

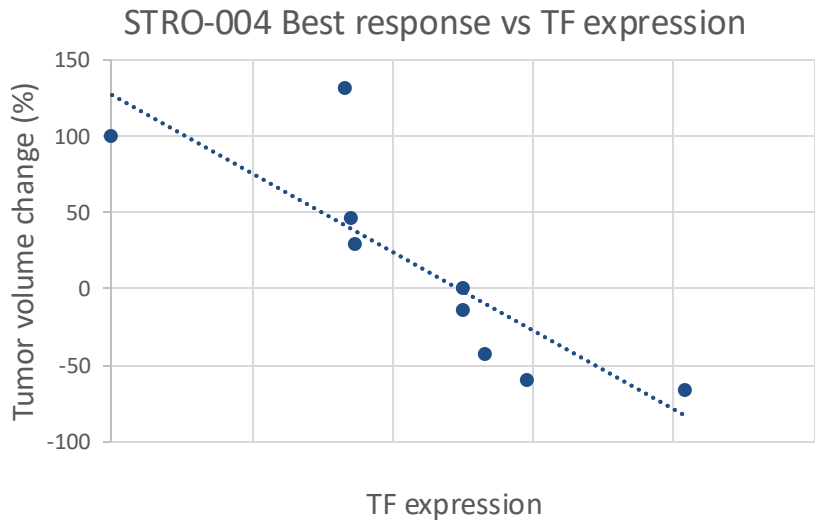
> 50% of Tumors Respond to STRO-004 at Low Dose



Clinically Relevant ADC Dose

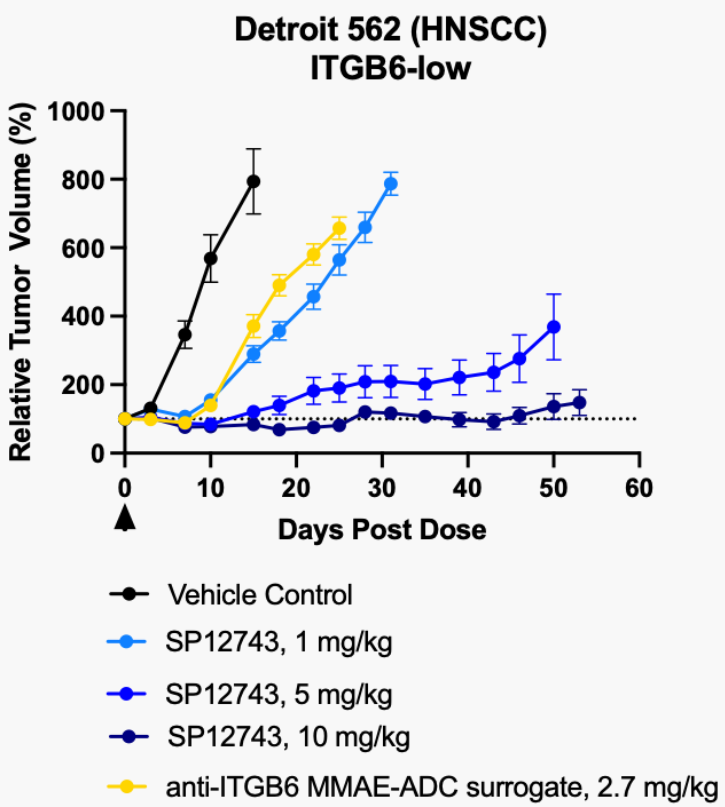
"ADCs administered at a similar weight-based [milligrams per kilogram (mg/kg)] dosing in mice that is tolerated in the clinic"

- Rubahamya & Thurber, Sci.Adv.2024

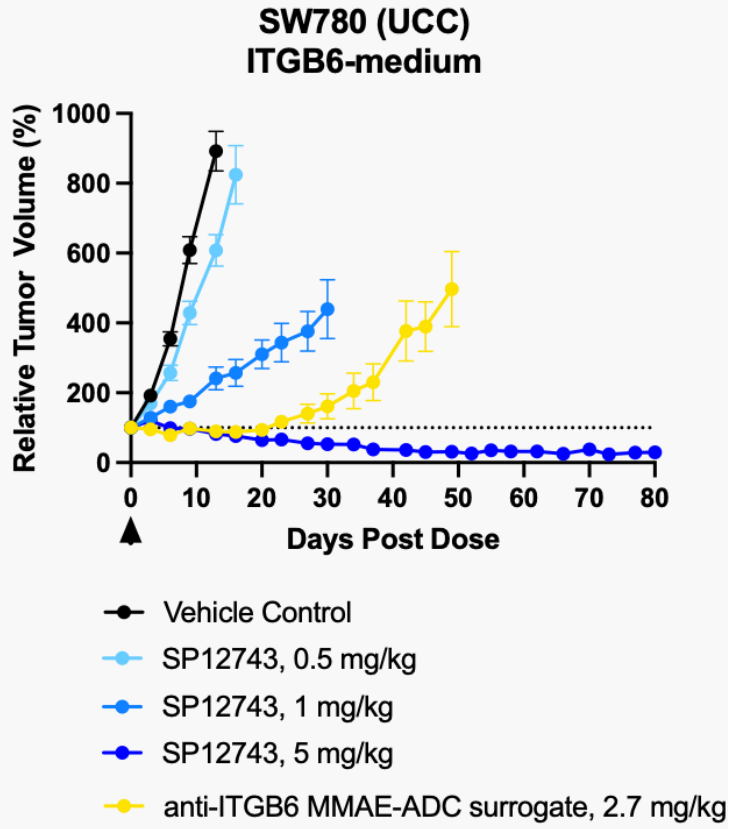


Superior Anti-Tumor Activity of STRO-006 Compared to First Generation Integrin Beta 6 (ITGB6) ADCs at Clinically Relevant Dose Levels

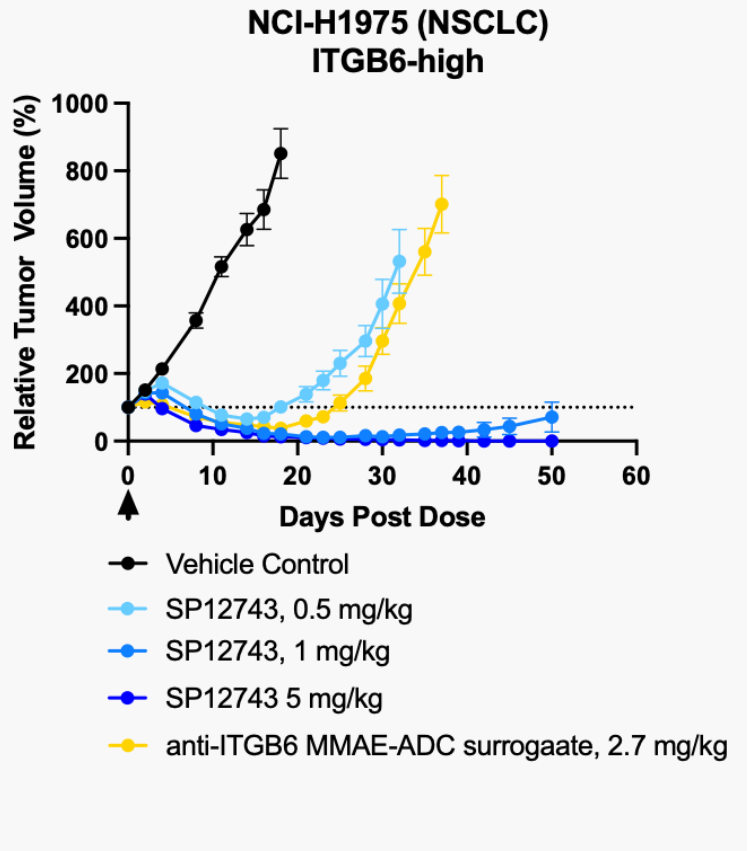
Head and Neck (ITGB6+)



Bladder (ITGB6++)

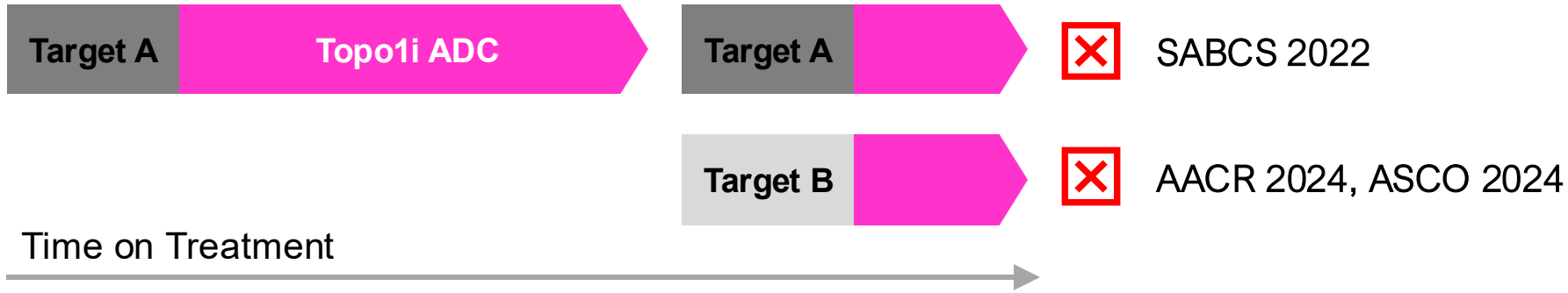


Lung (ITGB6+++)

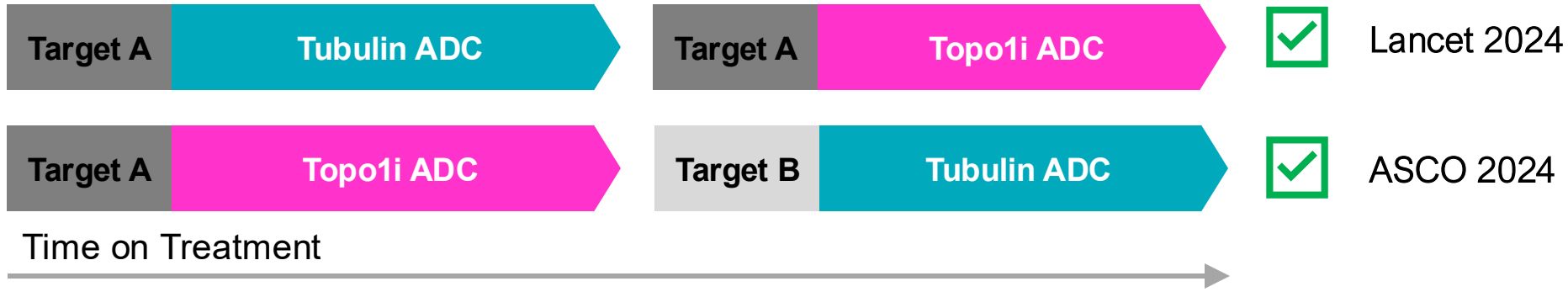


Efficacy In Models Reflective of Emerging Resistance Towards ADCs

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

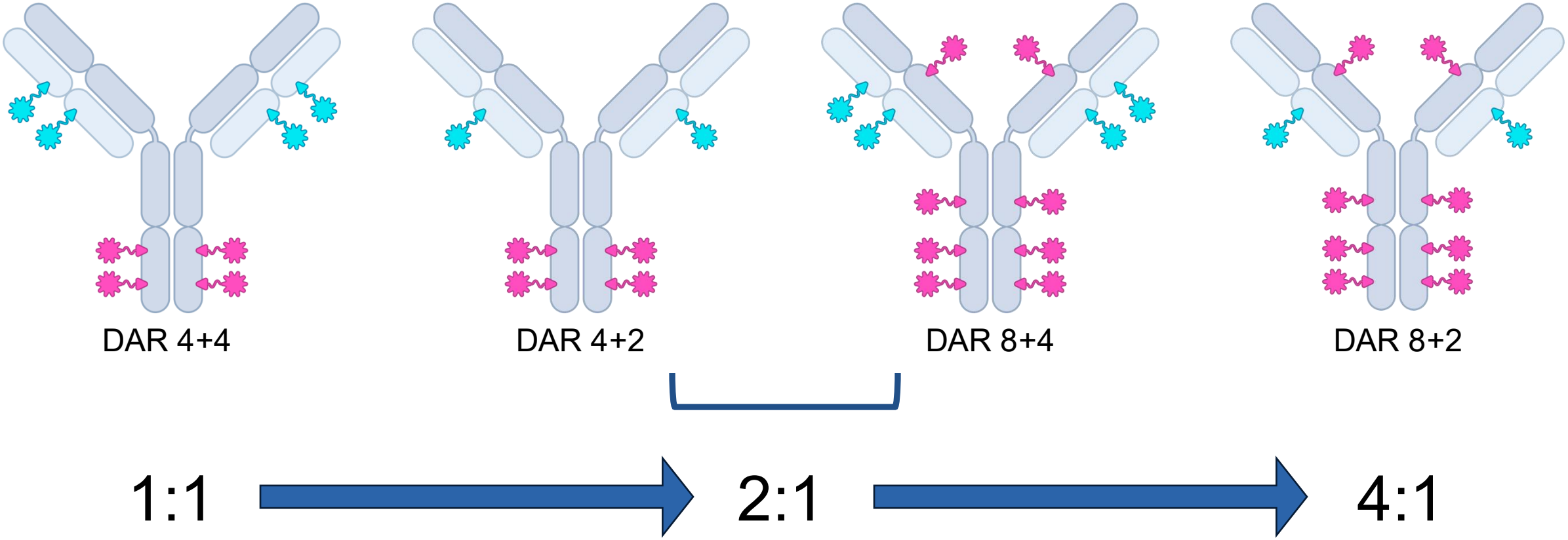


Switching Payload Class Maintains ADC Efficacy, Irrespective of the Target Antigen

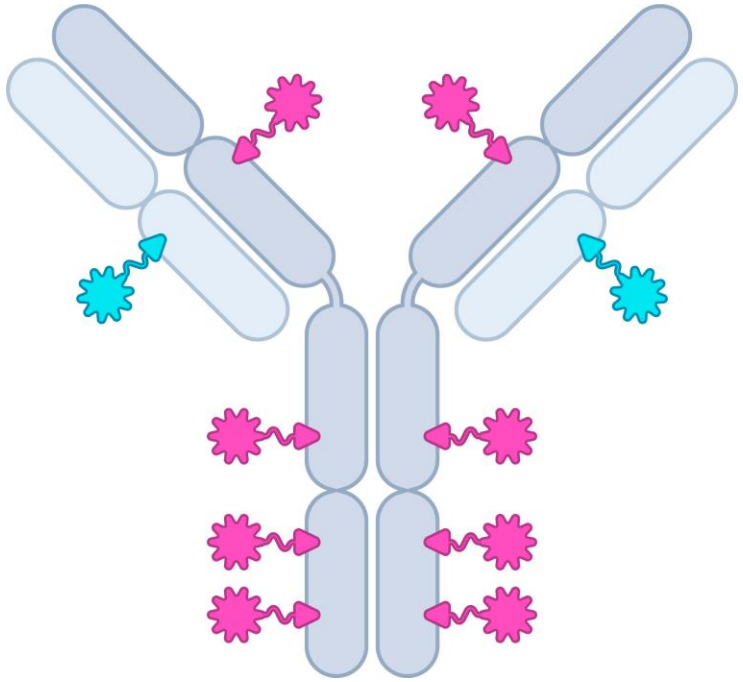


SABCS – San Antonio Breast Cancer Symposium; ASCO – American Society of Clinical Oncology

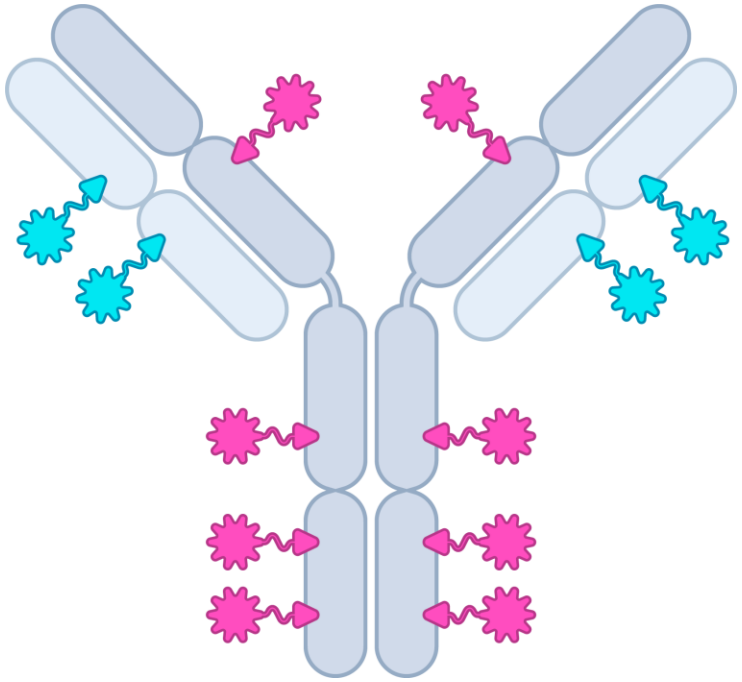
Cell-Free Platform Enables Site-Specific Tuning of Linker-Payload Ratios



Topo1 + MTI Dual-Payload Proof-of-Concept Targeting HER2

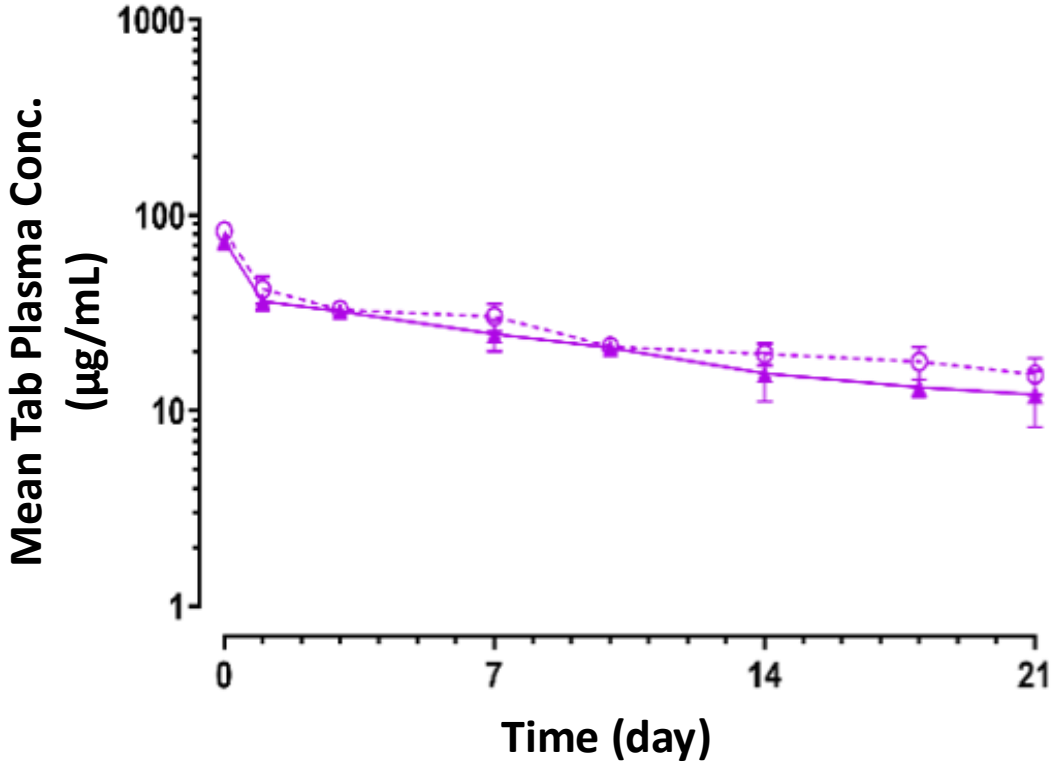


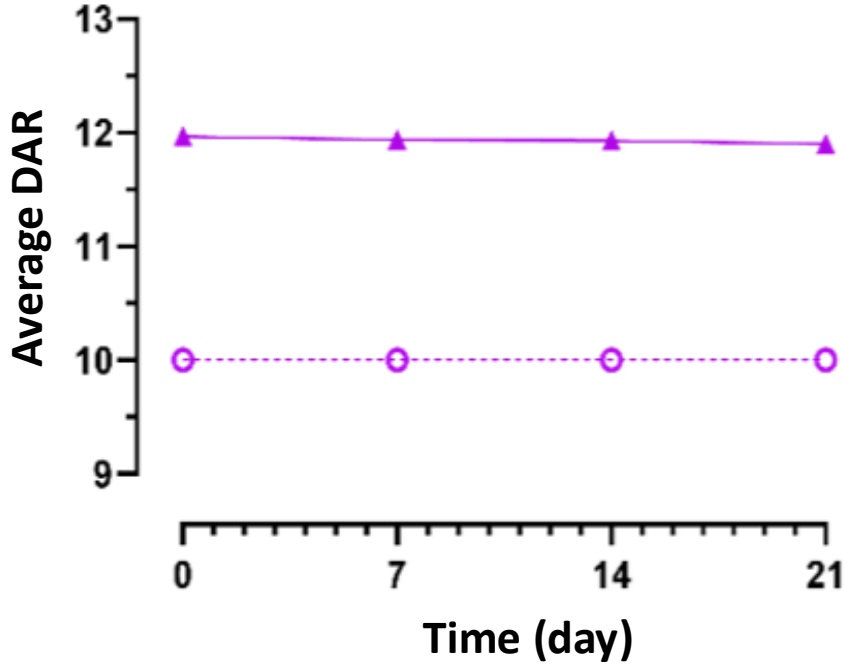
8+2



8+4

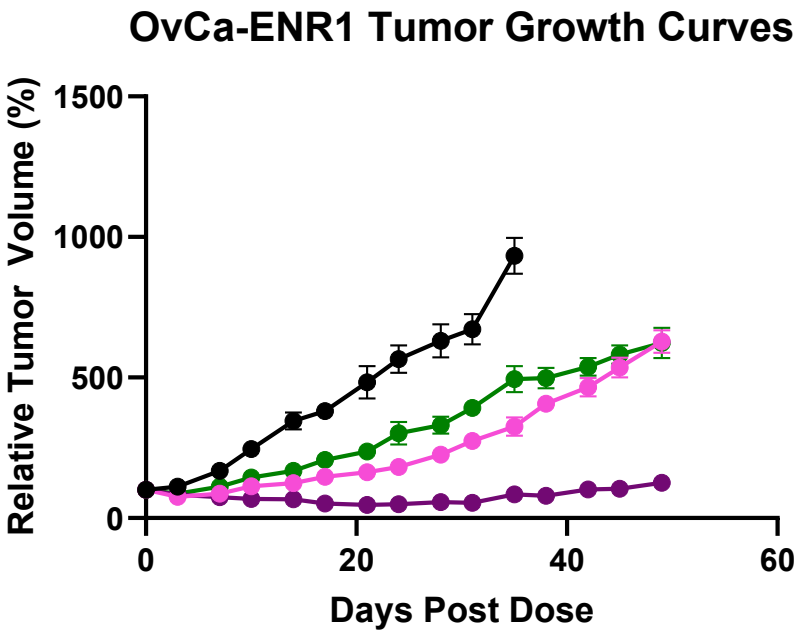
Dual-Payload ADCs have Desirable *In Vivo* PK and Stability

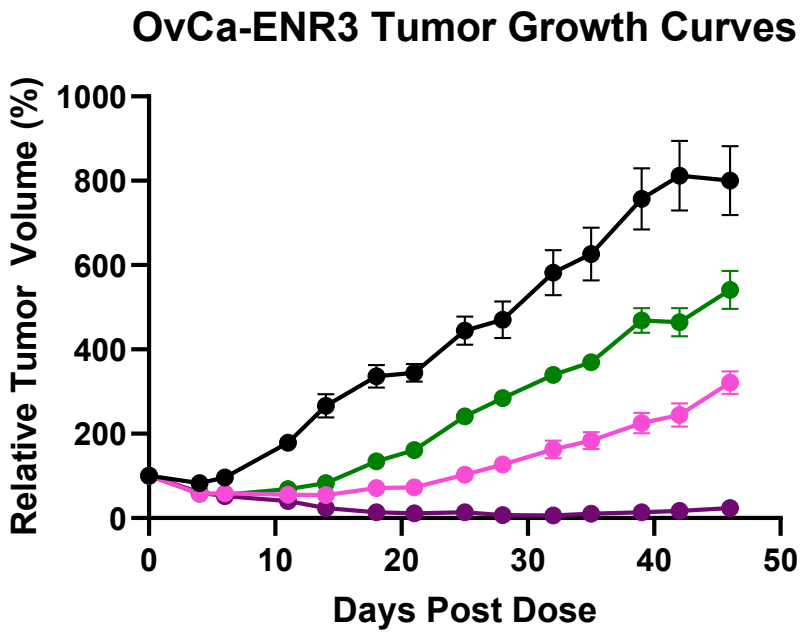




	DAR		Cl_{obs} ($mL \cdot d^{-1}/kg$)	V_{ss} (mL/kg)	$t_{1/2}$ (days)
	Topo1i	MMAE			
-(--)-	8	2	3.3	75.8	16.3
-▲-	8	4	4.2	81.4	14

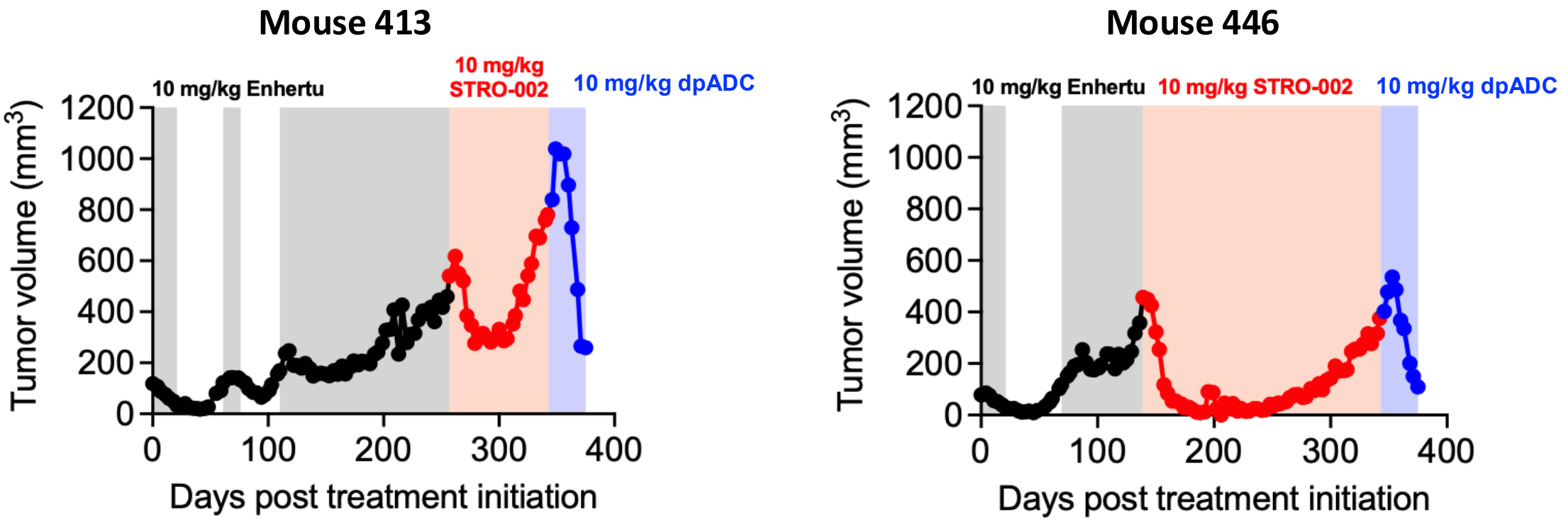
Dual-Payload ADCs have Improved *In Vivo* Efficacy in Ovarian Cancer Model with Reduced Enhertu Sensitivity





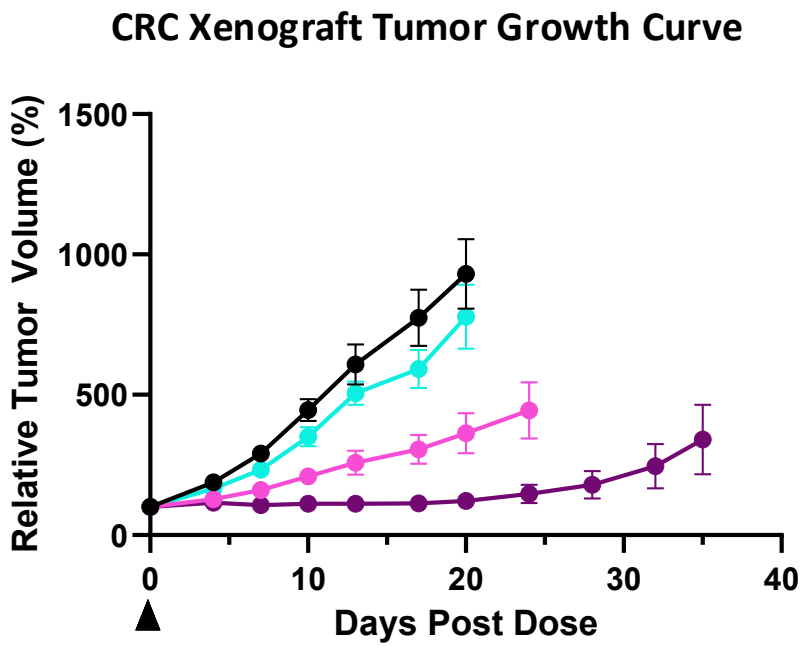
Vehicle control
Trastuzumab DAR8 Topo1i ADC (10 mg/kg)
Trastuzumab DAR8 Topo1i + DAR4 MTI (MMAE) dpADC (10 mg/kg)
Enhertu (10 mg/kg)

Dual-Payload ADC Induces Tumor Regression After Sequential ADC Resistance

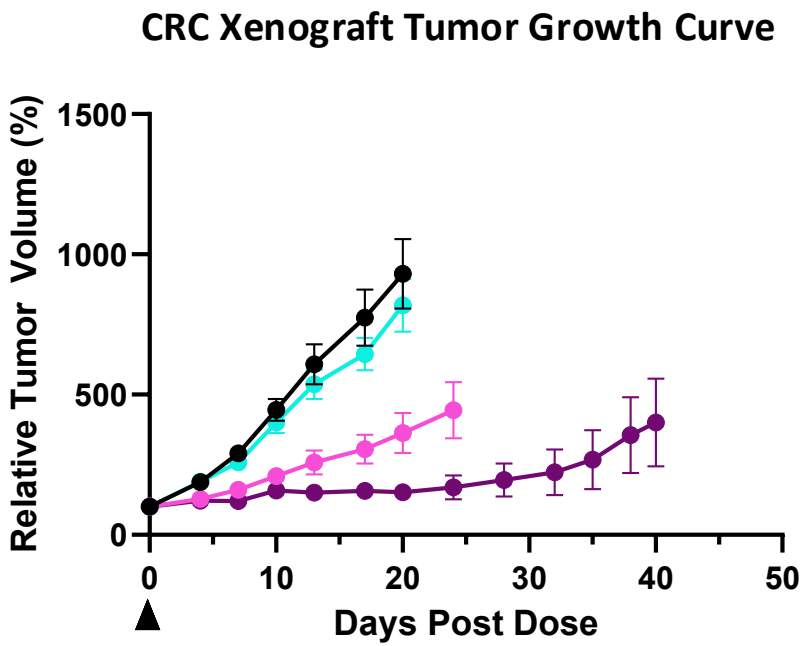


Mice with Enhertu-resistant tumors were switched onto STRO-002 treatment and subsequently onto dual-payload ADC after exhibiting STRO-002 resistance

Dual-Payload ADCs have Improved *In Vivo* Efficacy in a CRC Xenograft Model

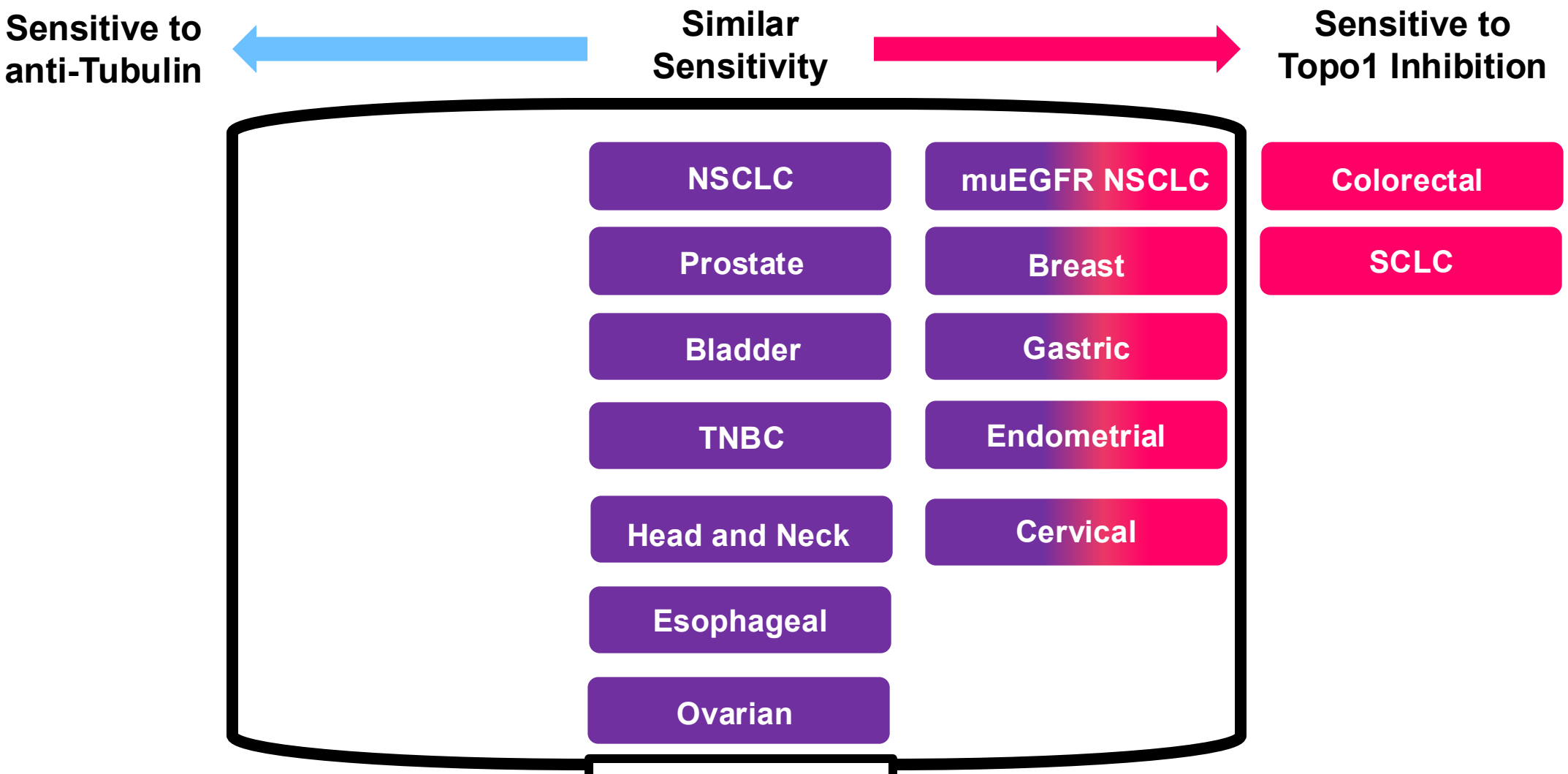


Vehicle control
Trastuzumab DAR4 MTI (MMAE) ADC (5 mg/kg)
Trastuzumab DAR8 Topo1i ADC (5 mg/kg)
Trastuzumab DAR8 Topo1i + DAR4 MTI (MMAE) dpADC (5 mg/kg)

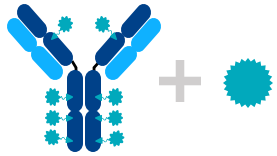
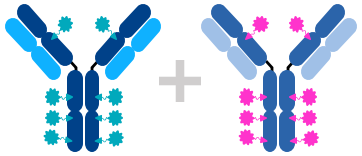
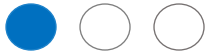


Vehicle control
Trastuzumab DAR4 MTI (Hemi) ADC (5 mg/kg)
Trastuzumab DAR8 Topo1i ADC (5 mg/kg)
Trastuzumab DAR8 Topo1i + DAR4 MTI (Hemi) dpADC (5 mg/kg)

Indications Poised to Benefit from Topo1i + anti-Tubulin Dual Payload ADCs



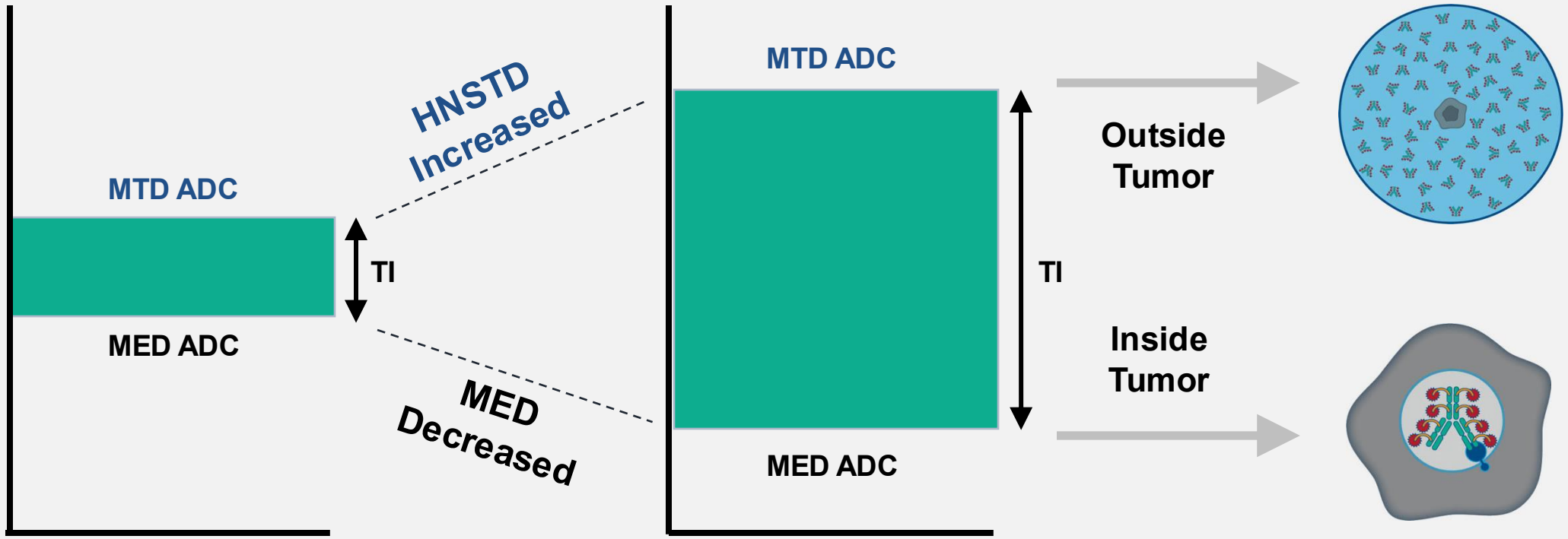
Dual Payload ADCs: Innovative Method for Delivering Targeted Combination Therapy

	ADC + Chemo	ADC + ADC	Dual Payload ADC	Potential benefits of a dual payload ADCs for targeted combination therapy
				
Safety (Compared to small molecule combinations)	 Greater SAEs reported for ADC + chemo vs ADC[1,2]			**Improved tolerability** Through reduced systemic payload exposure
Efficacy (Control over delivery of drugs to same cell)		 Binding competition impacts efficiency of delivery (for same target)[3]		**Greater control over delivery** Both payloads delivered to the same cell at the same time
Regulatory Simplicity				**Reduced clinical complexity** Single agent regulatory data package, standard monotherapy dose escalation design
Combination Study Simplicity			 Combo with modalities such as ICIs that have shown improved outcomes with ADCs[4]	**Reduced cost** Potential for combination benefit in one product

Sources: 1. PMID: 27052654; 2. PMID: 23020162; 3. PMID: 34112795; 4. PMID: 36041086; ICI – Immune checkpoint inhibitor; TGI – Tumor growth inhibition; SAE – Severe adverse event

Sutro's Platform Enables Therapeutic Index (TI) Improvements of ADCs

Maximum Tolerated Dose (MTD) vs. Minimum Effective Dose (MED)



Adapted from Gerber et al, mAbs, 2023
HNSTD – highest non-severely toxic dose

Sutro is Recognized as Emerging Leader in Dual Paylaod ADCs: Dual Payload ADC Companies with Preclinical Data Released (1)

Company	Targets	Payloads	DAR	Single Payload Clinical	Target IND
SUTRO BIOPHARMA	Her2/ND	Topo 1 x MTIs	8:2 ●●●●●●●●:●● 8:4 ●●●●●●●●:●●●●	MTI: Ph3	2027
	Her2/TF/ND	Topo 1 x PARPi	8:2 ●●●●●●●●:●● 8:8 ●●●●●●●●:●●●●●●●●	Topo1: 2025 IND	TBD
	ND	Topo 1 x IO	ND	IO: IND ND	iADC Astellas
GeneQuantum Healthcare 启德医药	Trop2	Topo 1 x TKI	ND	Topo1: Ph3	-
	Her3	Topo 1 x IO	ND	IO, TKI: No	-
Hummingbird Bioscience	Her2	Topo 1 x ATR	1:1 ratio ●:●	No	-
araris	NaPi2b	Topo 1 x Topo 1	ND	No	-
Immunwork	Her2	DXd x MTI	4:4 ●●●●:●●●●	No for MMAF	-
上海科技大学 ShanghaiTech University	Her2	DXd x TLR7	ND	No	-
OHIO STATE	B7H3	MTI x TLR7	3-4: 7-14 ●●●○:●●●●●●●○○○○○○○	No	-

Lack of Preclinical Reports from Pharma on Dual Payload ADCs

Source, Hanson Wade: Nov 2024 ADC; Digest: Dual Payload ADCs; ND = Nondisclosed; MTI = Microtubule inhibitor; TKI = Tyrosine Kinase inhibitor; ATR = Ataxia Telangiectasia and Rad3-related; TLR7 = Toll-like receptor 7

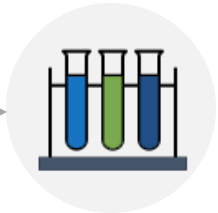
1. These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

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



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
- High DAR (>8)
- Dual-Payload ADCs
- Immune Stimulatory (iADC)

1976

Genentech: Boyer (UCSF)
Purpose: Manufacture Protein Therapeutics

2003

Sutro: Swartz (Stanford)
Purpose: Manufacture in Prokaryotic Cell Extract

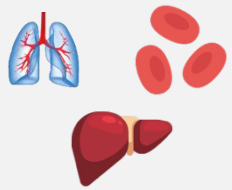
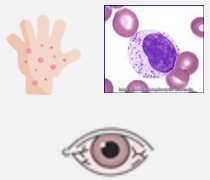
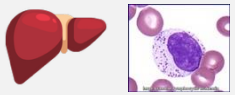
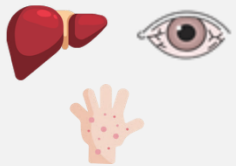
2024

Sutro Achievements

- Fully outsourced ADC CDMO Mfct
- Manufacture Cheaper, Faster, Better

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

Key Sutro Technologies to Reduce Platform Toxicities Outside the Tumor

	ADC	mAB	mAb	Linker	Conjugation Chemistry	Payload
MOA inducing Tox	Untargeted Pinocytosis	Impaired FcRn recycling	FcγR uptake	Cleavage outside tumor	De-conjugation	Catabolism "Detox"
Toxicity Types						
Sutro Technology Improvments	Linker design & mAB eng.	Site specific conjugation	Lack of FcγR engagement	Linker design & chemistry, site selection	Click chemistry	Payload & chemical engineering

PK – pharmacokinetics

Differentiated Pipeline of ADCs, Each Designed for Improved Therapeutic Index and to Address Significant Unmet Need

STRO-004 (TF)

Opportunity for pan-tumor application with validated target

- Designed for broad therapeutic benefit
- Chance to be best-in-class, and potentially first-in-class Topo1i DAR8
- **HNSTD non GLP safety in NHP: 50 mg/kg, CRs @ 1mg/kg**

STRO-006 (ITGB6)

Sutro successfully identified specific and selective antibody where others have struggled

- All-comers potential across multiple tumor types with high unmet need
- Chance to be best-in-class
- **HNSTD non GLP safety in NHP: 25 mg/kg, CRs @ 1 mg/kg**

Dual Payload Programs

Potential to overcome resistance by combining payloads

- Multiple dual payload approaches enabled by our novel proprietary platform
- Potential for deeper and more durable responses
- **Opportunity to pursue validated targets with a differentiated product profile**

TF – Tissue factor; HNSTD – Highest non-severely toxic dose; CR – Complete response

Differentiation by Design: STRO-004 and STRO-006 in NSCLC

Improved Therapeutic Index

Better Safety

ILD is a key adverse event to avoid in lung cancer patients:
Reduced ILD risk due to lack of FcγR engagement

Better Efficacy

Site-specific β-Glu linker avoids bone marrow toxicity that many other ADCs experience:
Higher dosing leads to higher exposure which will drive tumor responses

Better Targets

Trop-2 has real on-target tox liabilities, limiting Trop-2 targeting ADCs:
TF and ITGβ6 may offer better tumor selectivity. PDX studies to identify the best NSCLC subsets are ongoing

Pipeline of Next-Generation ADCs: Three New INDs Expected Over 3 Years

PROGRAM	MODALITY/TARGET	INDICATION	DISCOVERY	PRECLINICAL	PHASE 1/1B	PHASE 2	PHASE 3/ REGISTRATIONAL	WORLDWIDE OR GEOGRAPHIC PARTNER
SUTRO-LED PROGRAMS								
STRO-004	Tissue Factor ADC	Solid Tumors						
STRO-006	Integrin αvβ6	Solid Tumors						
STRO-00X	Dual Payload ADC	Solid Tumors						
STRO-00Y	Dual Payload ADC	Solid Tumors						
PARTNER PROGRAMS								
VAX-24	24-Valent Conjugate Vaccine	Invasive Pneumococcal Disease						VAXCYTE protect humankind
VAX-31	31-Valent Conjugate Vaccine	Invasive Pneumococcal Disease						
STRO-003	ROR1 ADC	Solid Tumors & Hematological Cancers						IPSEN
Undisclosed Programs	Immunostimulatory ADCs (iADCs)	Cancers						astellas

SUTRO BIOPHARMA

Questions