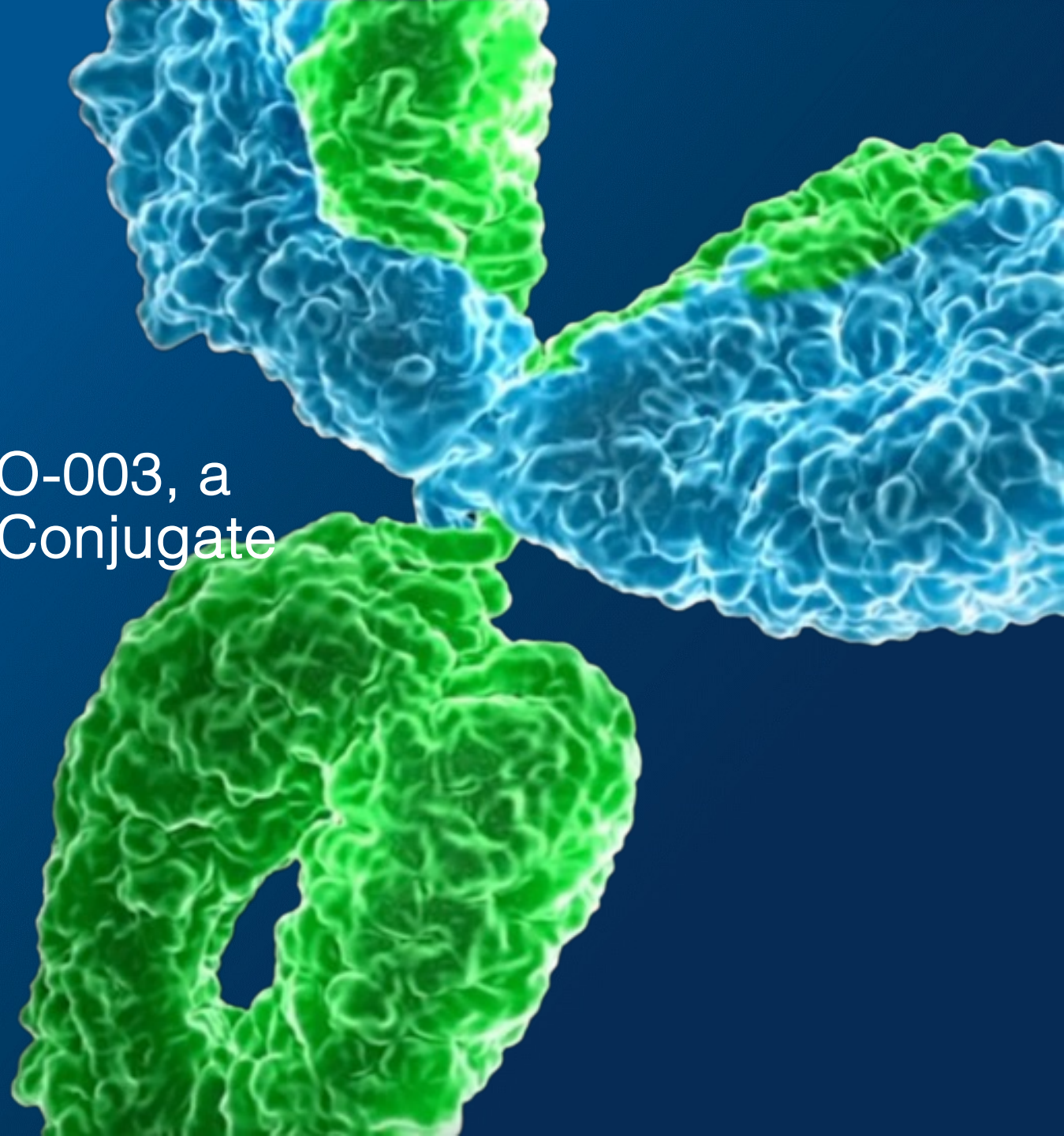
SUTRO BIOPHARMA

Preclinical Development of STRO-003, a ROR1 Targeted Antibody-Drug Conjugate

14th Annual World ADC San Diego 2023



STRO-003: A Novel ROR1 Targeted ADC is Designed for Purpose

ROR1 biology makes it an attractive ADC target

ROR1: **Role in cancer progression** and expressed in tumor and tumor-initiating cells

Low potential for on-target toxicity due to **restricted normal tissue expression and clinical safety validation**

Expansive indication space in oncology

Clinical validation of ROR1 in **hematological malignancies***

and **broad potential opportunity in solid tumors**, including large indications such as NSCLC and breast cancer

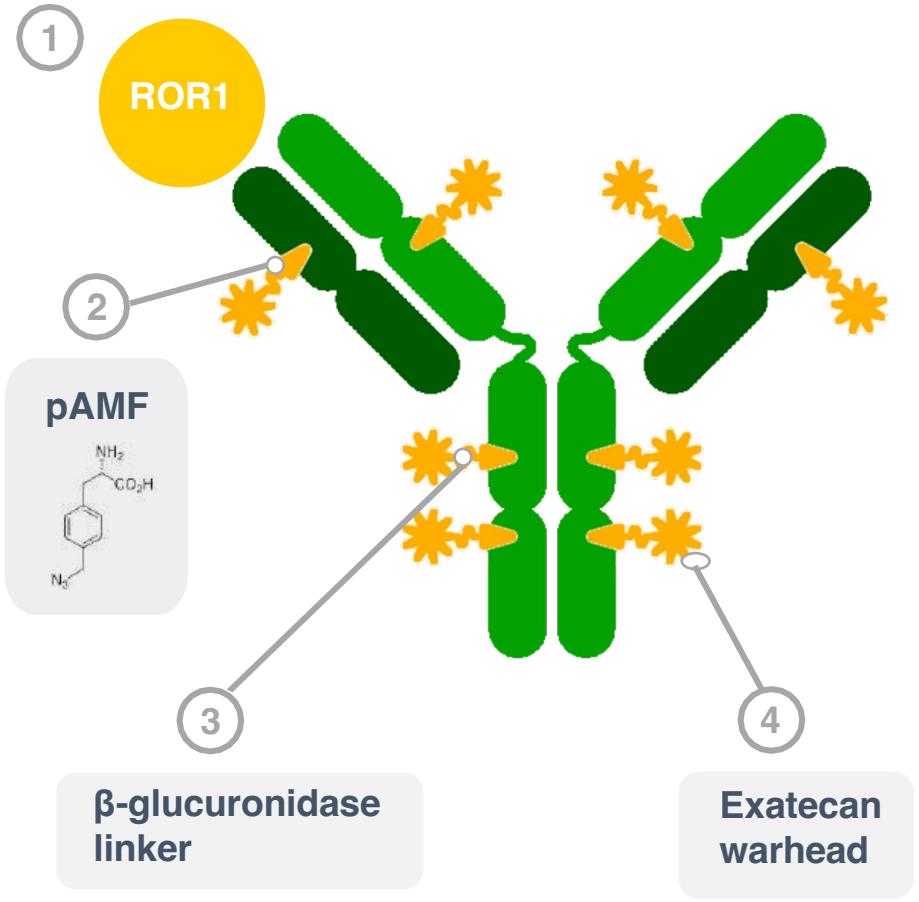
* **With a tubulin inhibitor ADC**

Potential for attractive clinical performance

Low copy number and heterogeneous expression of ROR1 antigen in solid tumors favors potent ADCs with bystander activity and great tolerability

STRO-003's optimized linker design and payload selection—along with precise positioning of 8 linker-payloads per antibody—provides **potent efficacy** in low antigen expressing solid human tumors (PDX) and is very well tolerated in preclinical studies

Our Innovative Design: STRO-003 is a Novel Optimized ROR1 ADC, Featuring TOPO-1 Inhibitors Linked with β-Glucuronidase Cleavable Linkers, DAR 8



STRO-003 is a single homogeneous antibody drug conjugate (ADC) with a drug-antibody ratio (DAR) of 8, targeting ROR1 tumor antigen

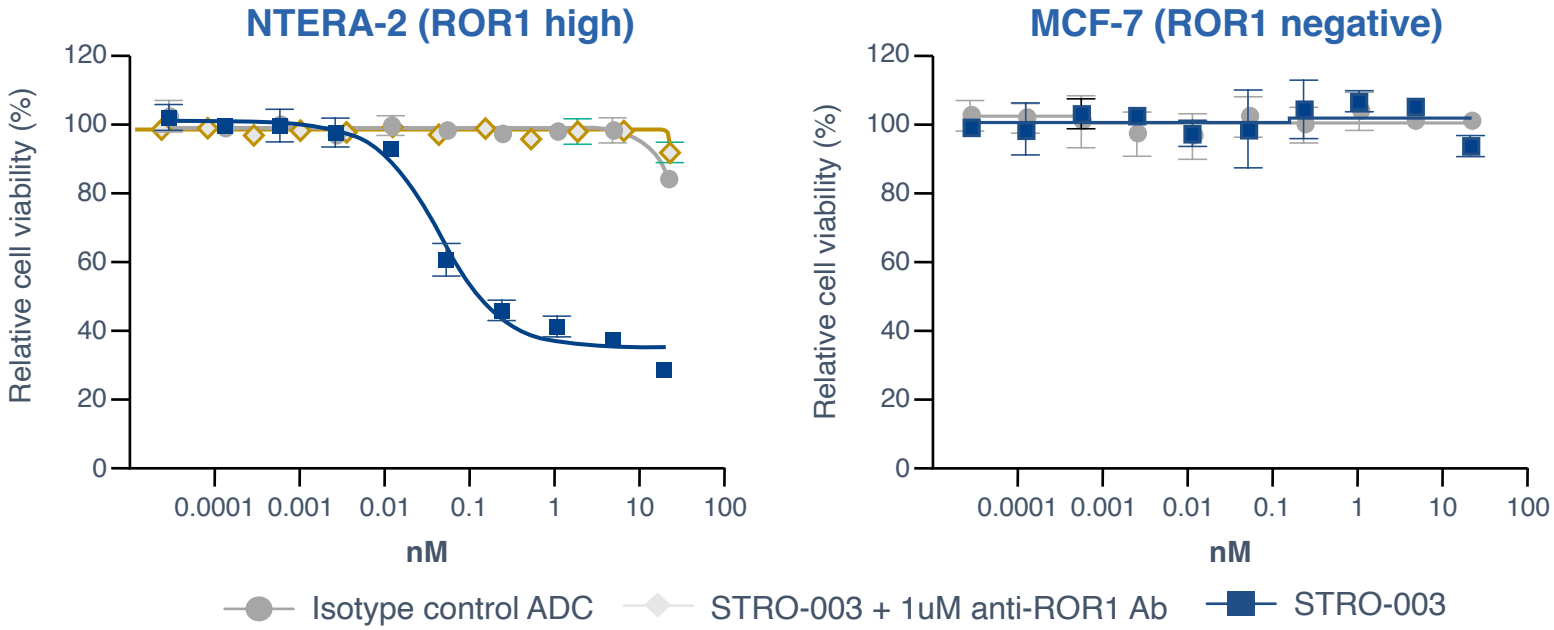
1. **Targeted ROR1 epitope** is overexpressed in diverse cancers including **hematological and solid tumor indications**
2. **Precisely positioned non-natural amino acids**, p-azidomethyl-L-phenylalanine (pAMF), **to enable DAR8** and optimal conjugation sites for enhanced performance and stability
3. **Stable β-glucuronidase cleavable linkers** demonstrate tumor specificity and encouraging preclinical tolerability. Preclinical data has shown marked **improvement over CatB linkers regarding neutropenia and lung tolerability issues** seen with tubulin and TOPO-1 inhibitors in the clinic
4. **Exatecan warhead inhibits TOPO-1 causing DNA disruption**. It elicits potent tumor cell killing, bystander activity and immunogenic cell death

STRO-003 Binds With High Affinity To Human, Cynomolgus, and Rodent ROR1 and Shows Potent ROR1-Dependent Tumor Killing

In vitro Cell Binding

CHO-hROR1		HEK293-mROR1		HEK293-rROR1	
Bmax	Kd (nM)	Bmax	Kd (nM)	Bmax	Kd (nM)
22446	0.32	16117	3.7	20818	2.4

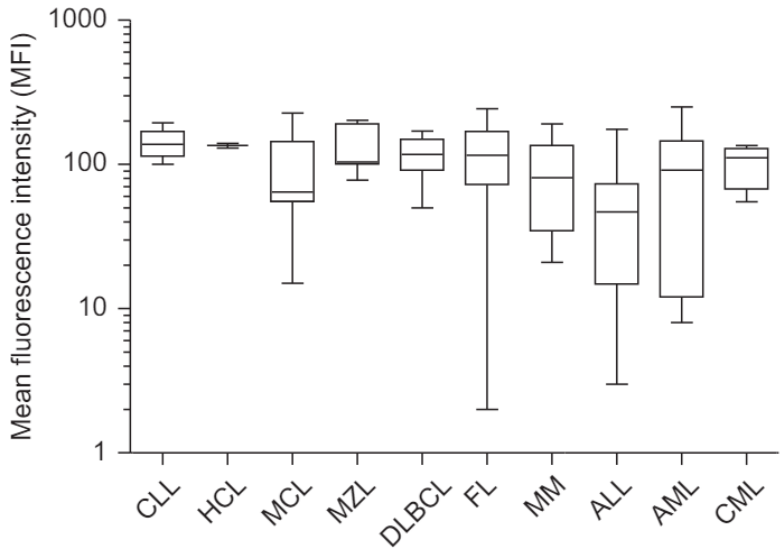
In vitro Cell Killing



- STRO-003 binds with high affinity to human, cynomolgus, and rodent ROR1 with a Kd in the low nM range
- STRO-003 demonstrates potent tumor cell killing of ROR1 positive cells *in vitro*
- STRO-003 cell killing is ROR1-dependent and can be blocked with a competing anti-ROR1 antibody

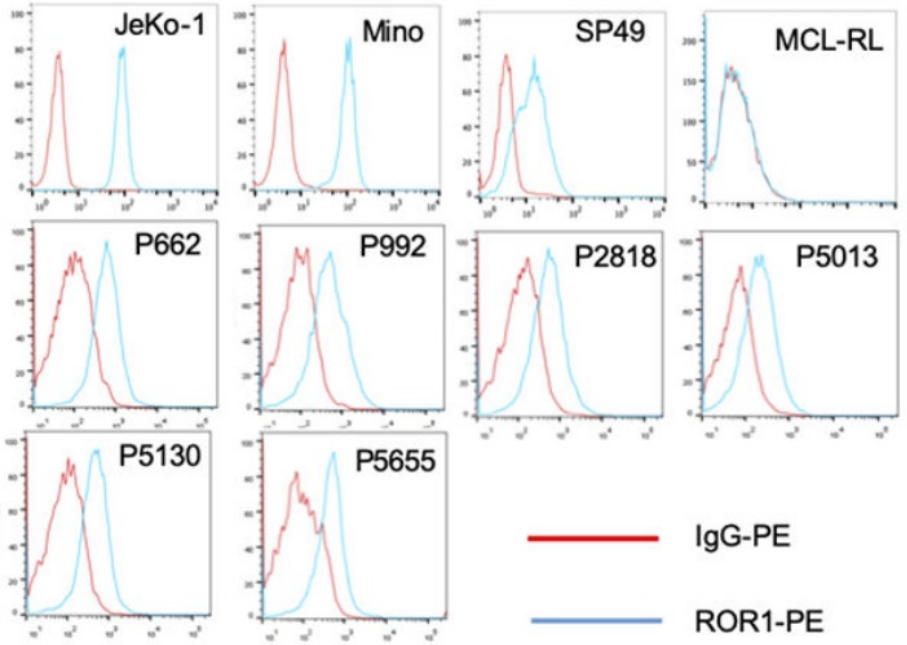
ROR1 Is Widely Expressed Across Hematological Malignancies

ROR1 shows homogenous expression across hematological malignancies



Daneshmanesh et al, *Leukemia & Lymphoma* (2013)

The MCL cell lines JeKo-1 and Mino show ROR1 expression comparable to patient samples



Zhang et al., *J Immunol* (2019)

B-CLL ROR1 cell surface expression based on antibody binding capacity (ABC) is 2,773-7,090 molecules/cell

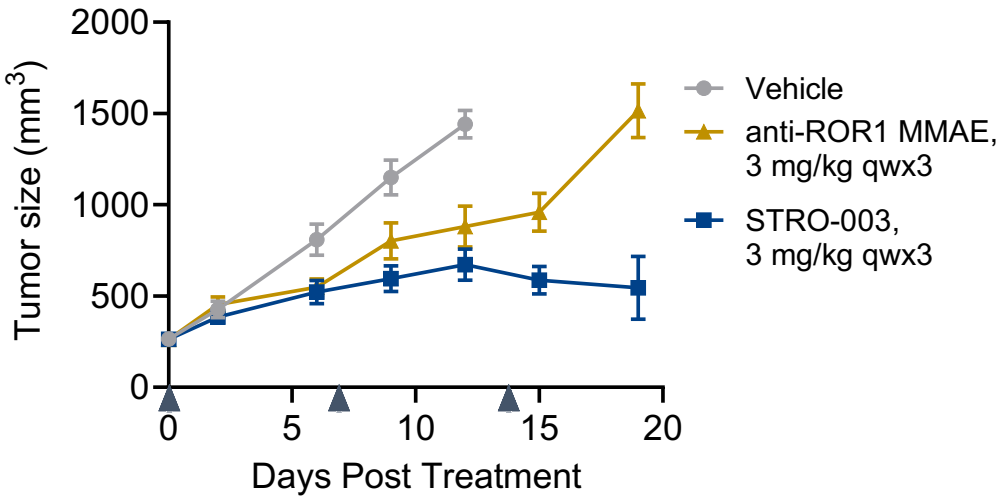
Baskar et al, Clin Cancer Res (2008)

JeKo-1 and Mino ROR1 cell surface expression based on antibody binding capacity (ABC):

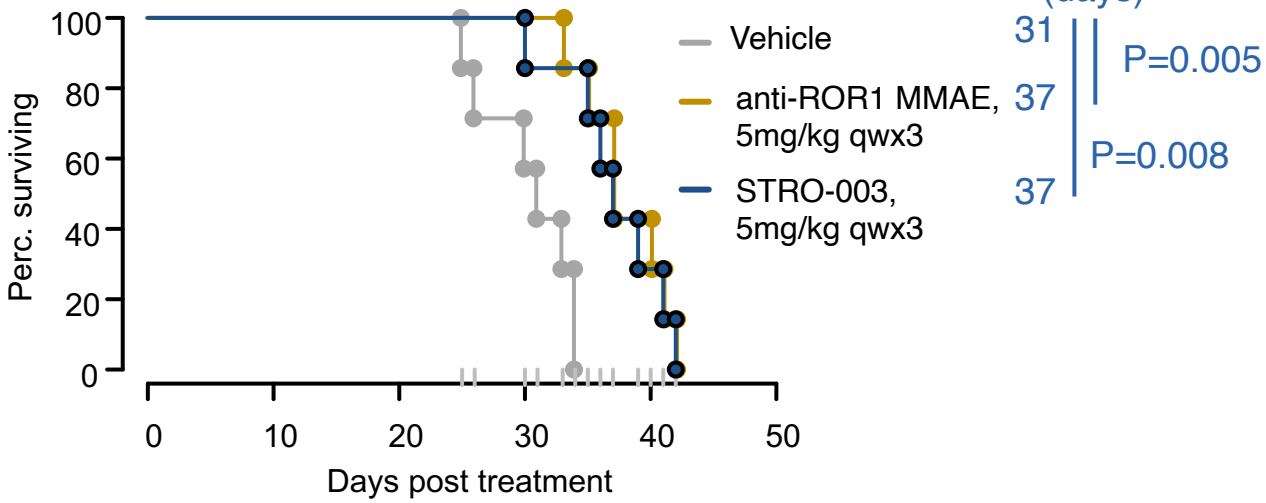
JeKo-1	19,683
Mino	17,217

STRO-003 Shows Anti-tumor Activity in Localized and Disseminated Xenograft Models Of Mantel Cell Lymphoma (MCL) with Moderate ROR1 expression

JeKo-1
Mantle cell lymphoma
(localized)



Mino
Mantle cell lymphoma
(disseminated)

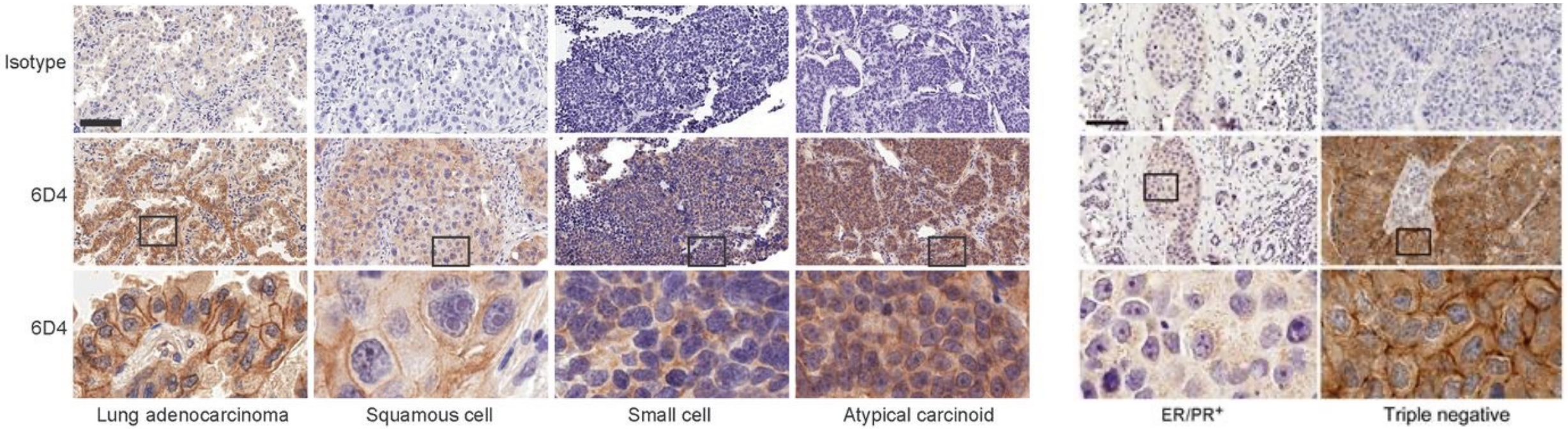


- STRO-003 demonstrates anti-tumor activity in a subcutaneous xenograft model of MCL
- STRO-003 provides a moderate but significant survival benefit in a disseminated xenograft model of MCL
- STRO-003 shows comparable activity to a ROR1 targeted DAR4 MMAE ADC

ROR1 Is Expressed In Solid Tumors, Including NSCLC And Triple Negative Breast Cancer (TNBC)

Lung cancer

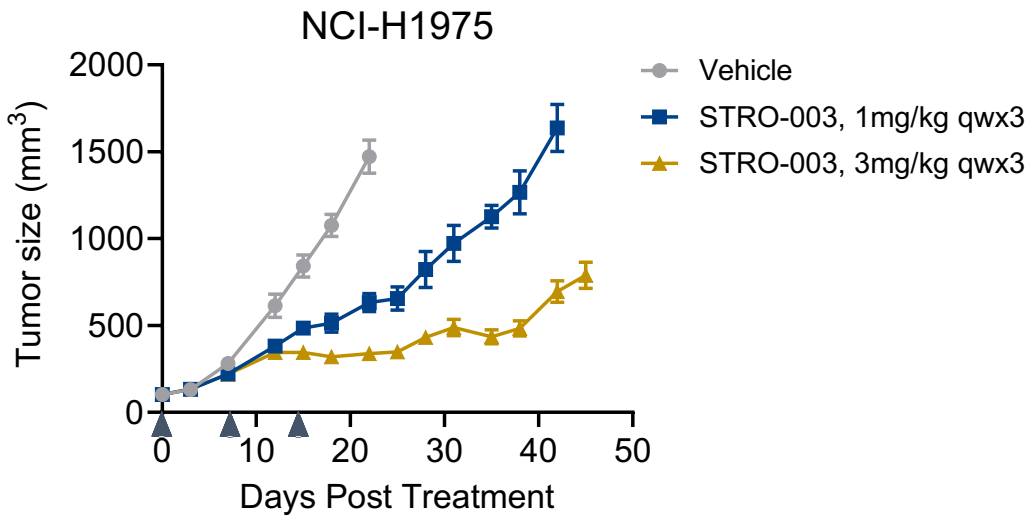
Breast cancer



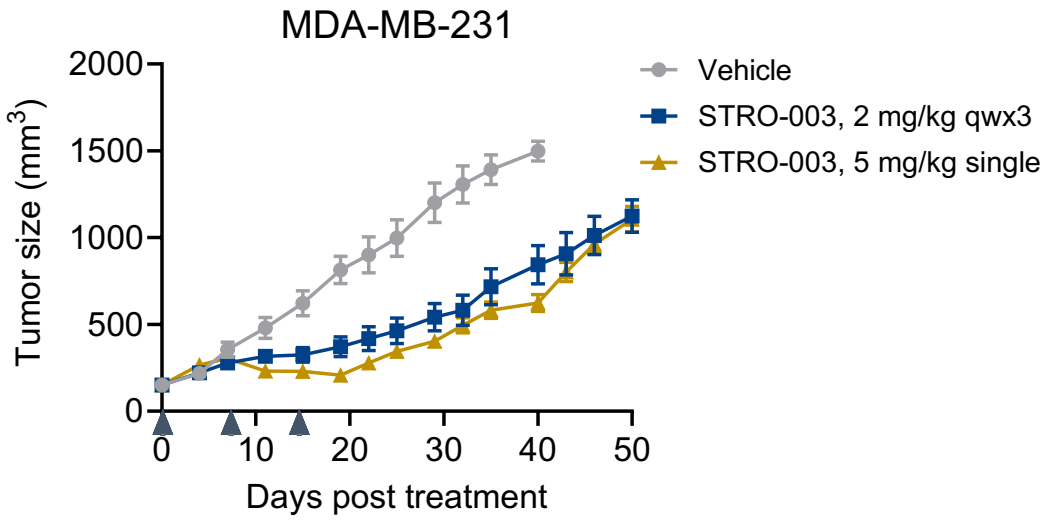
Bhalakrishnan et al., *Clin Cancer Res* (2017)

STRO-003 Shows Anti-tumor Activity in Mouse Xenograft Models of Lung and Breast Cancer with Moderate ROR1 Expression

NSCLC CDX

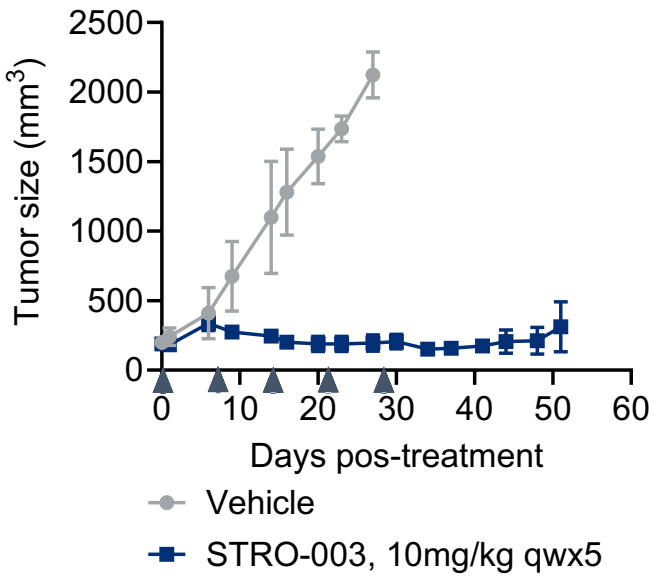


TNBC CDX

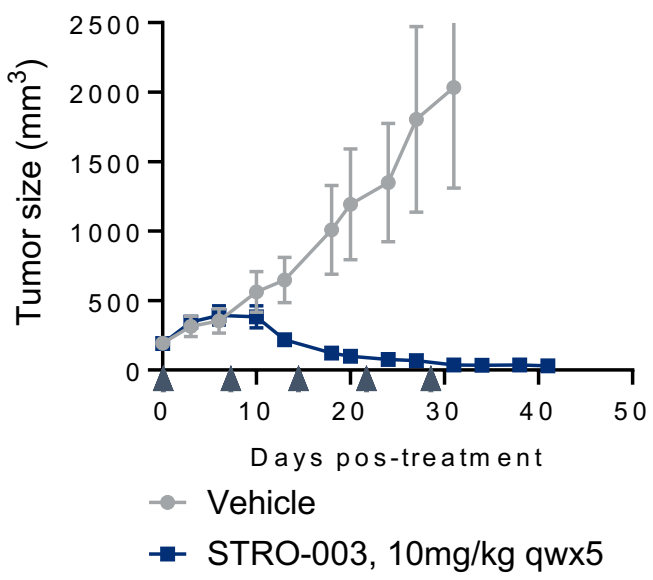


STRO-003 Demonstrates Complete Regression of Human NSCLC PDX Expressing Low and Heterogeneous ROR1 Antigen Levels

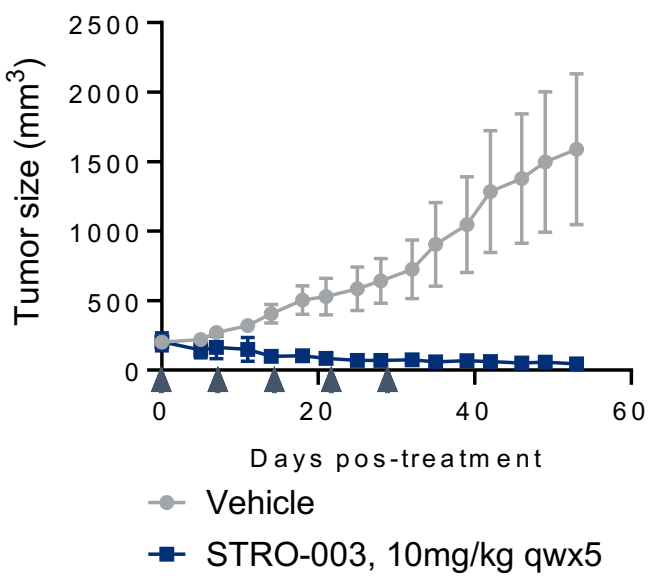
ROR1 moderate

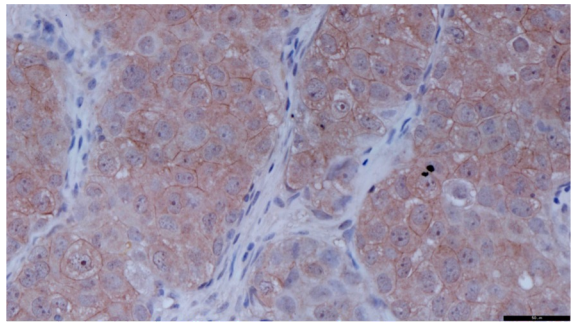


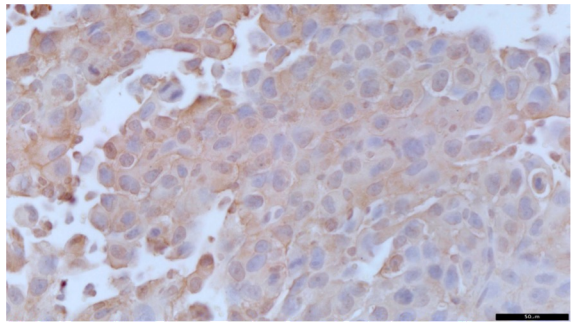
ROR1 moderate

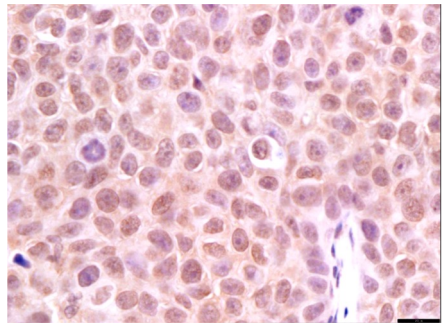


ROR1 low

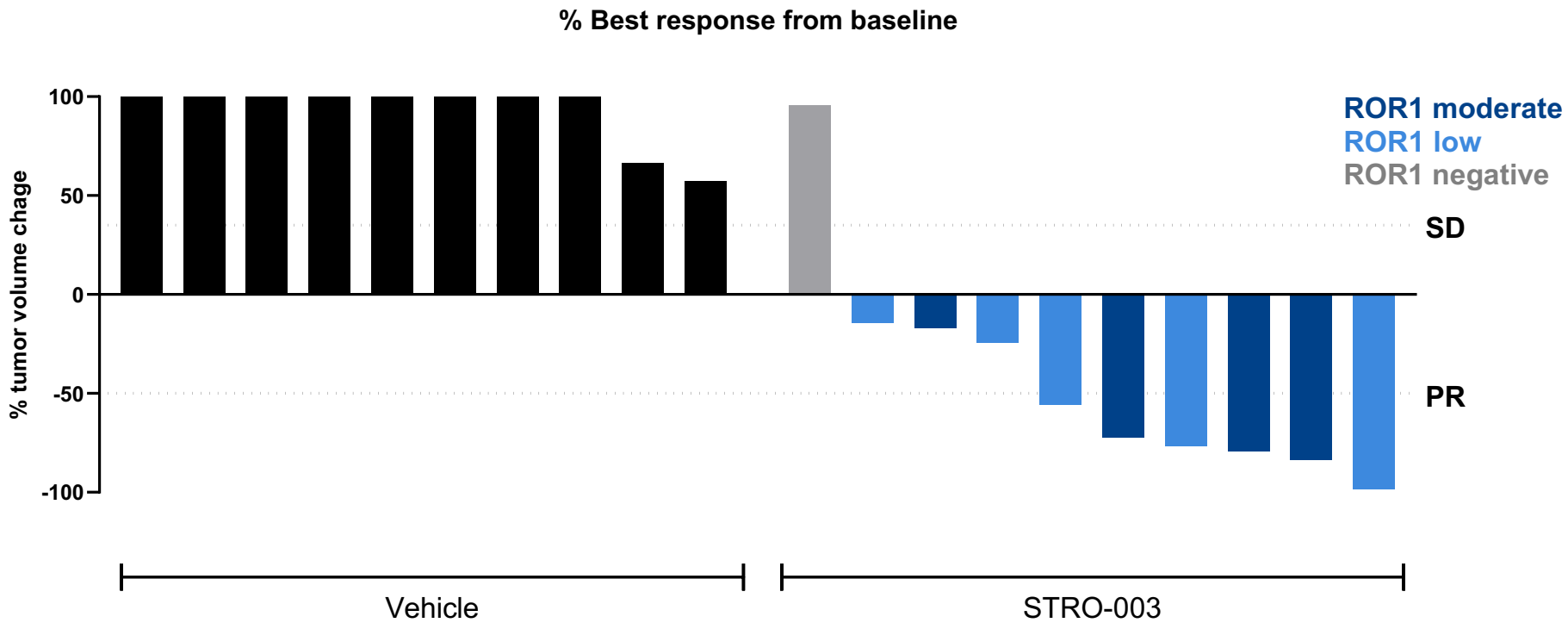






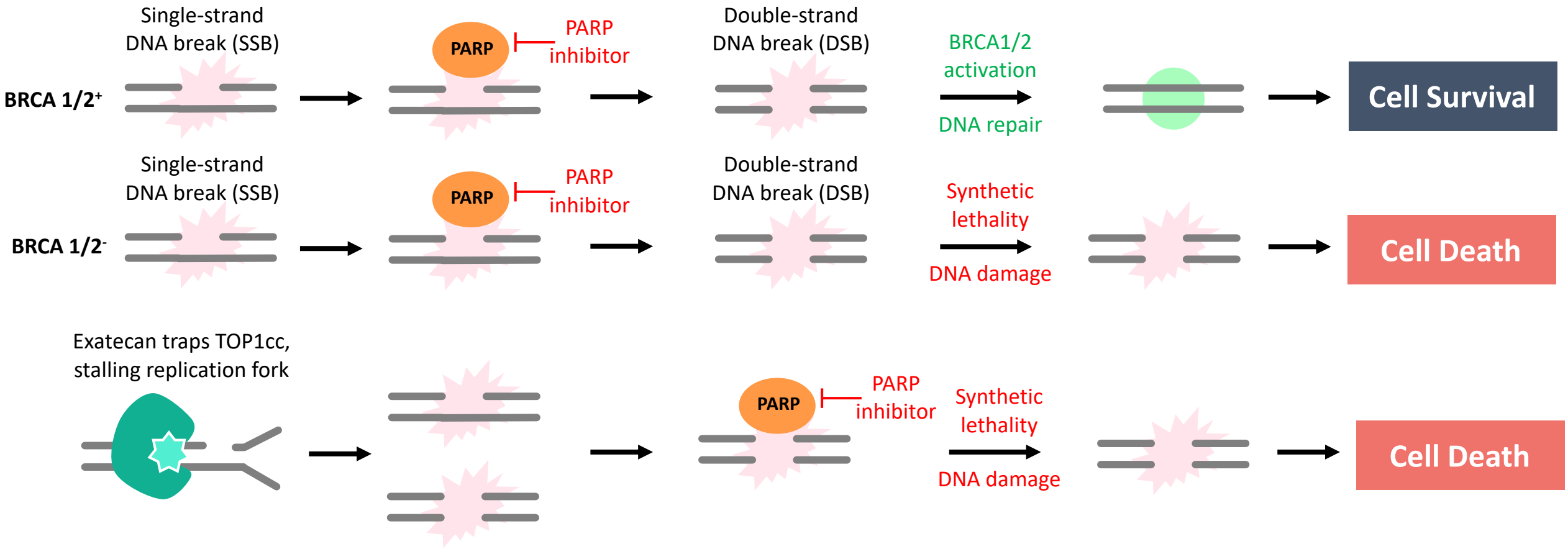


STRO-003 Demonstrates Complete Regression of Human NSCLC PDX Expressing Low and Heterogeneous ROR1 Antigen Levels



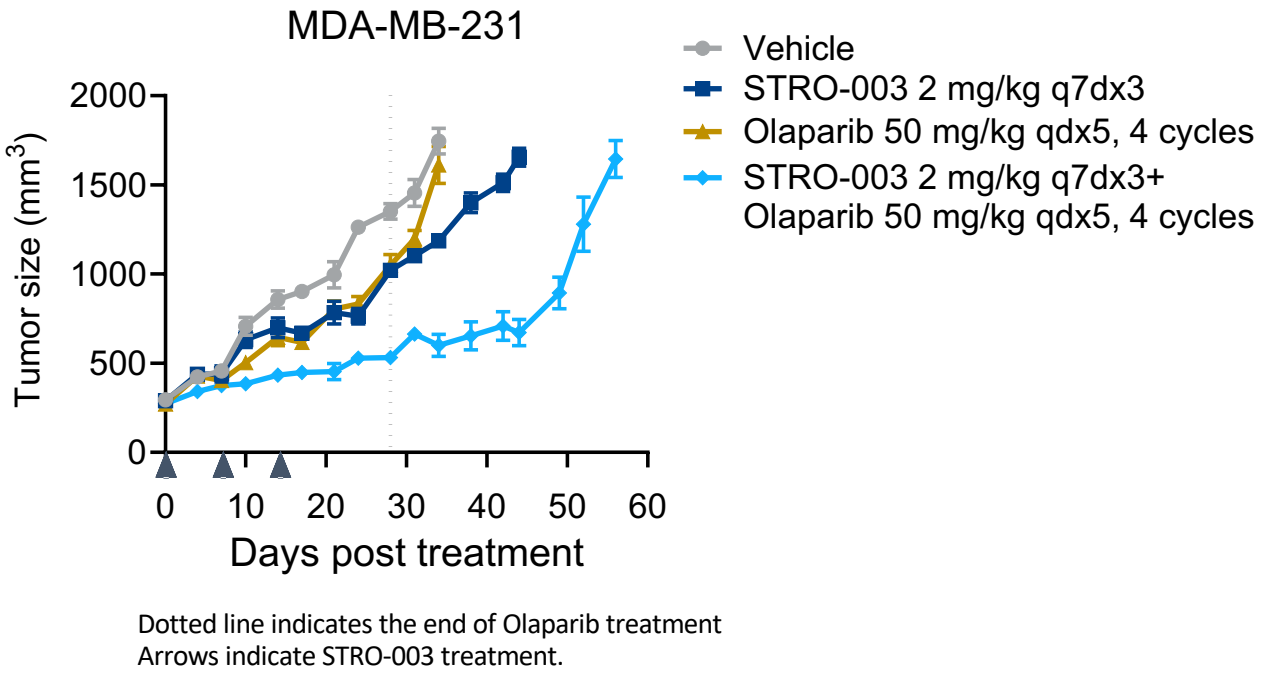
- STRO-003 showed maximum tumor regression of >50% (PR/CR) in 68% of ROR1 positive PDX models expressing low and heterogeneous antigen levels

Exatecan MoA Provides a Strong Rationale for Combination with DNA Damage Repair Inhibitors Due to the Potential for Synthetic Lethality

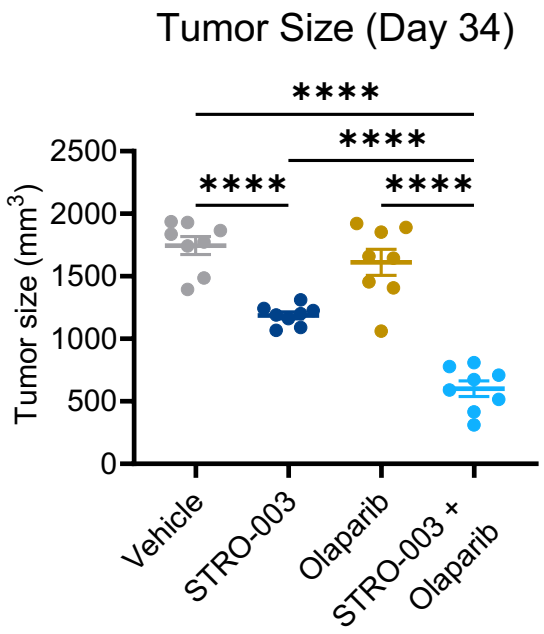


- Cancer cells are often deficient in one or more DNA repair pathways, making them more susceptible to disruption of specific pathways
- Exatecan traps TOP1cc on DNA. Subsequent collisions with replication machinery results in DNA damage
- PARP1 can initiate removal of stalled TOP1cc and plays a key role in SSB repair and NHEJ for DSB break
- Inhibition of Topo1 by exatecan and inhibition of PARP can lead to synthetic lethality in otherwise DNA repair proficient cells

STRO-003 in Combination With Olaparib Significantly Improves Efficacy in MDA-MB-231 Tumors Compared to Single Agent Treatment

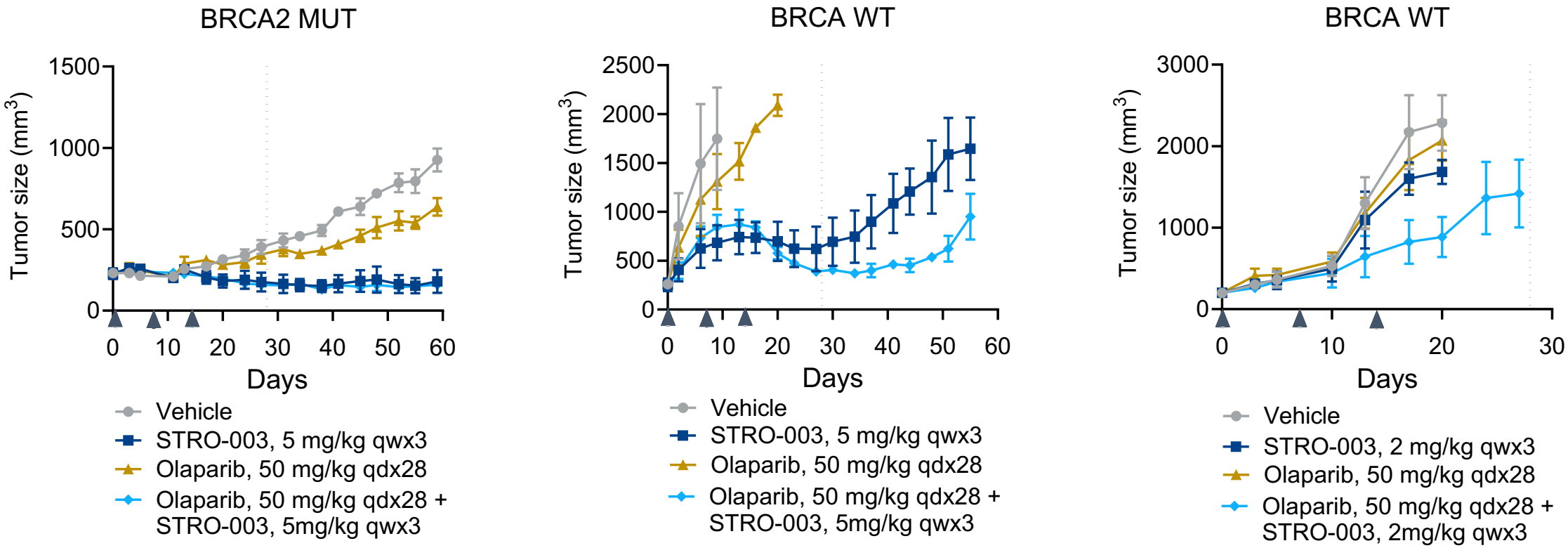


Dotted line indicates the end of Olaparib treatment
Arrows indicate STRO-003 treatment.



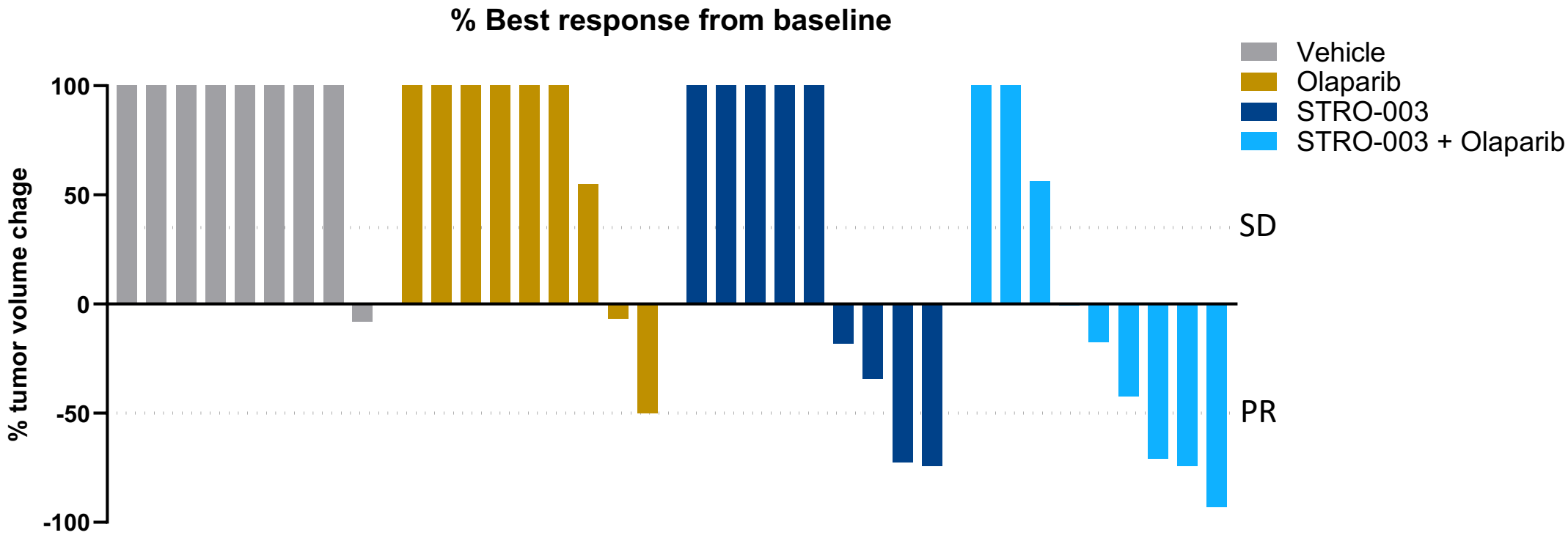
- PARP inhibitors olaparib and talazoparib are FDA-approved for the treatment of HER2- metastatic breast cancer in patients with BRCA1 or BRCA2 gene mutations
- STRO-003 plus olaparib combination treatment significantly inhibited tumor growth in large MDA-MB-231 tumors and showed significant improvement in tumor growth inhibition compared to single agent treatment
- No test article exhibited substantial toxicity.

STRO-003 Demonstrates Anti-Tumor Activity in BRCA WT Triple Negative Breast Cancer PDX Models with Moderate ROR1 expression



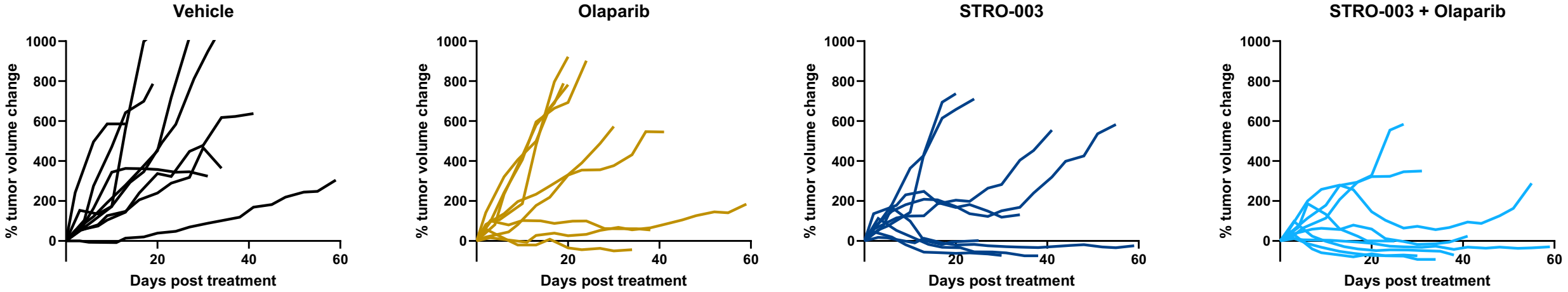
- STRO-003 shows anti-tumor activity in both BRCA WT and BRCA mut PDX models of TNBC
- STRO-003 plus olaparib combination treatment shows improved anti-tumor activity in BRCA WT PDX models of TNBC
- No test article exhibited substantial toxicity.

STRO-003 Combination Therapy With Olaparib Improves Anti-Tumor Activity in Triple Negative Breast Cancer PDX Models with Low and Moderate ROR1 expression



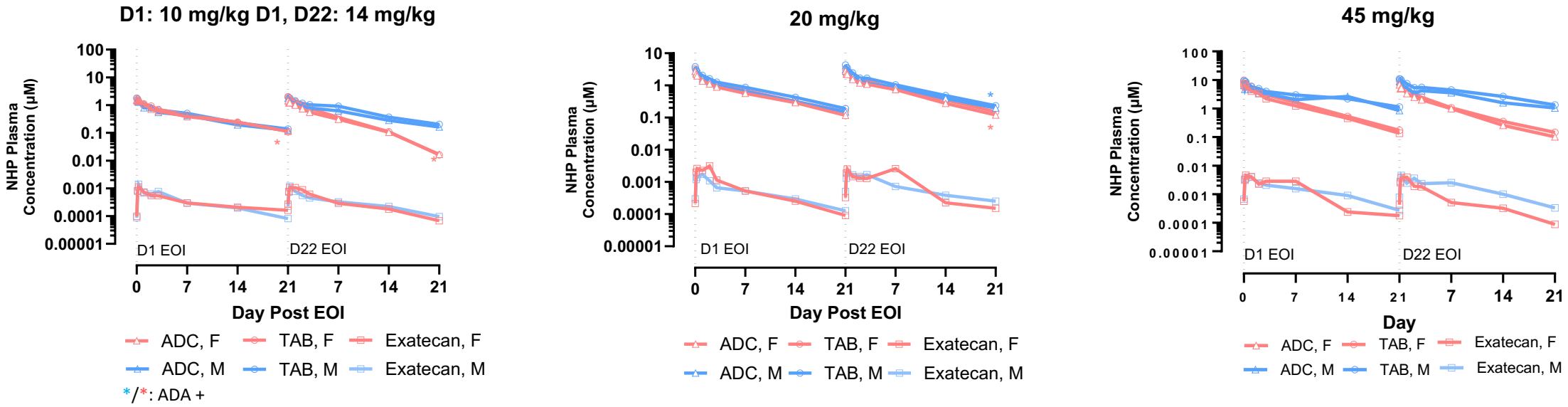
- STRO-003 induces tumor regression in PDX models of TNBC as single agent
- STRO-003 plus olaparib combination treatment shows improved anti-tumor activity in models of TNBC
- No test article exhibited substantial toxicity.

STRO-003 Combination Therapy Prolongs Anti-Tumor Response in Triple Negative Breast Cancer PDX Models with Low and Moderate ROR1 expression



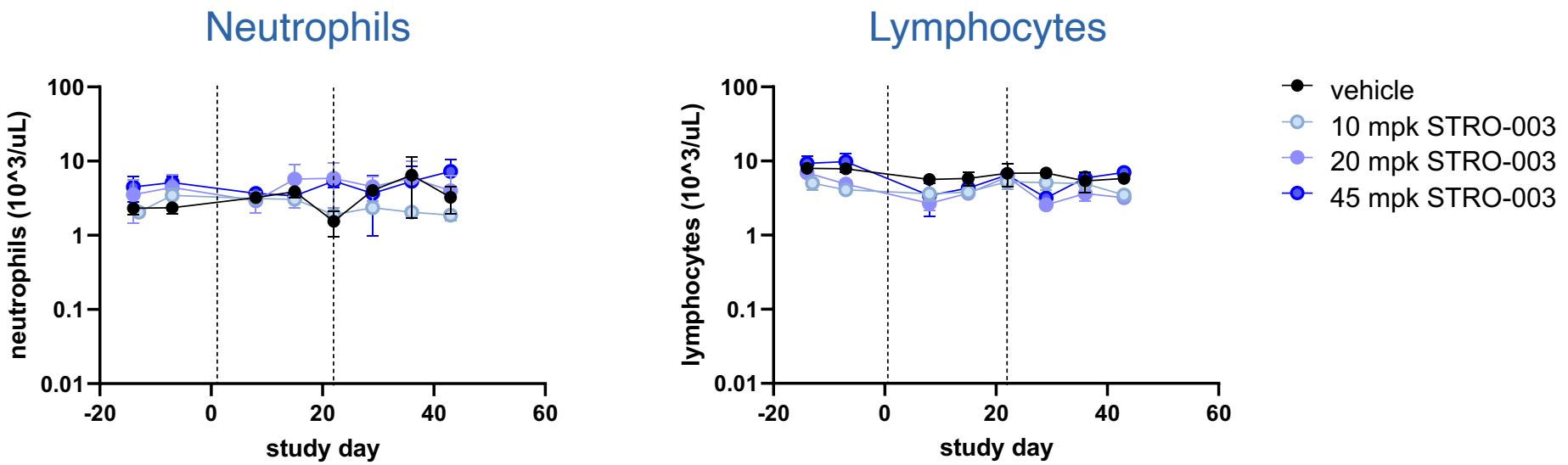
- STRO-003 induces tumor regression in a subset of PDX models of TNBC as single agent
- STRO-003 plus olaparib combination treatment shows prolonged tumor regression and/or stasis
- No test article exhibited substantial toxicity.

STRO-003 Shows Dose Proportional PK in NHP, Stable ADC and Low Levels Of Free Catabolite In Circulation



- Antibody and ADC PK exhibits low (7 – 11 mL/d/kg) clearance, and half-lives were between 4 and 10 days. Plasma concentration – time profiles follow a 2-compartment model.
- The in vivo stability of ADC is demonstrated with the superimposed plasma concentration – time profiles of both ADC and total Antibody (TAB).
- Free catabolite plasma concentrations are in the sub and low nM range, and at least 100-fold lower than TAB or ADC. Catabolite elimination profiles are generally in parallel with TAB and ADC not impacted by ADA, and similar on D1 and D22.
- ADA impacts the elimination of TAB/ADC at 14 mg/kg dose on D22 in female, but not at other ADA positive doses.

STRO-003 Demonstrated a Wide Safety Window in Multiple Cross-Reactive Species



STRO-003 is cross-reactive and well tolerated in rat at high doses

- No observed neutropenia, no elevation of liver enzymes at high doses (60 mg/kg)

STRO-003 is cross-reactive and well tolerated in a multi-dose non-GLP NHP study

- No observed neutropenia or thrombocytopenia, well tolerated up to 45 mg/kg, no changes observed in WBC

No lung toxicities observed at 45 mg/kg STRO-003 in NHPs;

- In the same preclinical NHP study, a ROR1 ADC with Cathepsin B linker exatecan ADC generated lung findings consistent with developing pneumonitis (and ILD) at 45 mg/kg
- Other CatB-linker exatecan ADCs, are associated with significant rates of clinical pneumonitis/ILD
- Improved tolerability with STRO-003 might be driven by use of new β-glucuronidase linker

STRO-003 Enables a Broad Clinical Development Strategy Through Efficient Killing of ROR1-Expressing Tumors and a Favorable Safety Profile

Expansive indication space

- ROR1 is a clinically validated target in hematological indications.
- Preclinical in vitro and in vivo data support application in hematological cancers and broad solid tumors, including NSCLC and breast cancer

STRO-003: Designed for superior clinical performance

- Optimal molecule to deliver efficient tumor killing with every antigen binding and internalization event
- High potency DNA targeting TOPO-1 inhibitor payload with compelling clinical validation
- Optimized novel linker design with improved preclinical safety compared to a CatB linker; **no lung toxicities or neutropenia observed**
- High DAR8, clinically precedented, but now with optimized conjugation positioning, to maximize payload delivery to tumor cell and improve potential efficacy in solid tumors

SUTRO BIOPHARMA

Thank you!