



Preclinical Safety and Activity of STRO-004, a Tissue Factor ADC

Alice Yam, PhD

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STRO-004: ADC Targeting Tissue Factor with Broad, Pan-Tumor Potential (IND 2H 2025)



Tissue Factor is an attractive pan-tumor target

Tumor expression:

Broadly expressed across **multiple solid tumor indications** with high unmet need, such as HNSCC and lung

Normal tissue expression:

Low expression in **eye, skin**
Factor X **coagulation pathway**



Expansive indication space in oncology

Clinical validation in metastatic cervical cancer with an approved tubulin inhibitor ADC

Broad potential opportunity in many other solid tumors of significant unmet need



Potential for improved clinical performance

Site specific conjugation and different positioning of **novel exatecan beta-glu linker-payload**

Reduce neutropenia risk

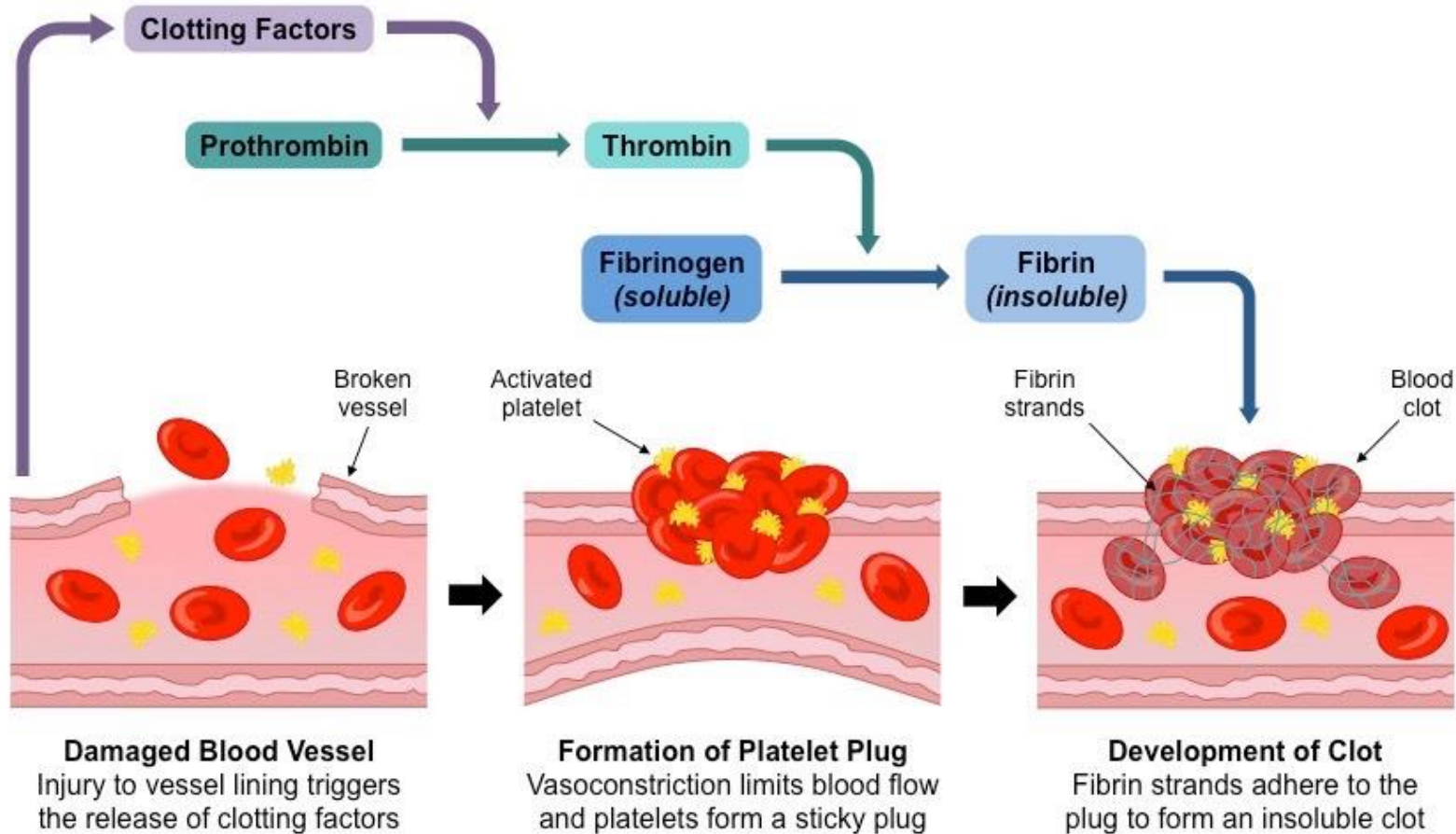
Avoid bleeding risk

Avoid ocular toxicities

Improved potency to reach low copy number patients

Tissue Factor activates Factor X which initiates the coagulation cascade

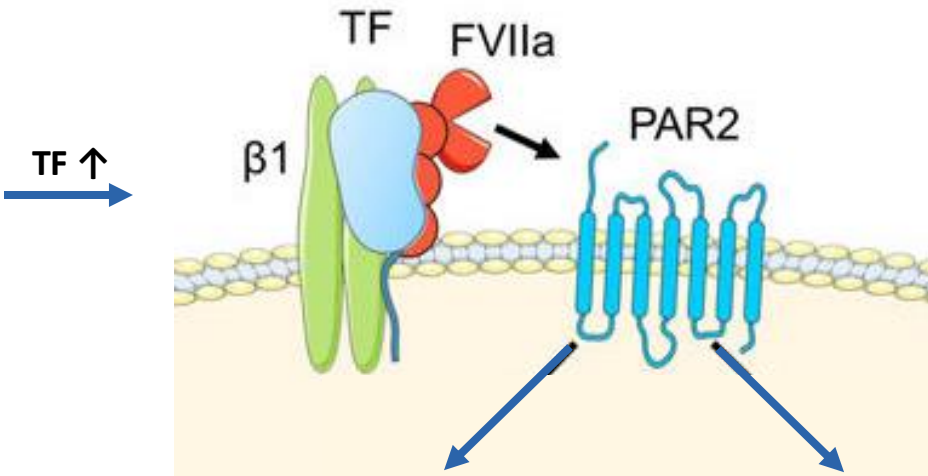
TF-mediated activation



- Tissue Factor is expressed in the subendothelium
- When endothelium is damaged, tissue factor combines with circulating factor VII to activate factor X
- Activated factor X initiates the coagulation cascade

Wound-healing processes are hijacked by cancer

**Hypoxia
Inflammation
Signaling** (TGFb, EGF, HGF)



Signaling
MAPK, PI3K

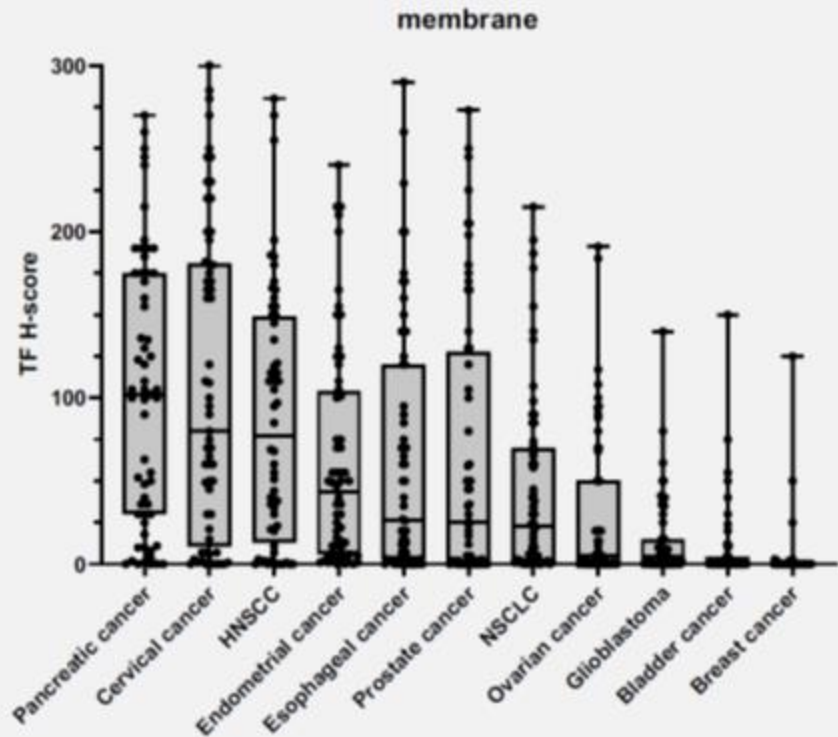
**Proliferation
Survival**

Cytokines
VEGF, IL8, CXCL1

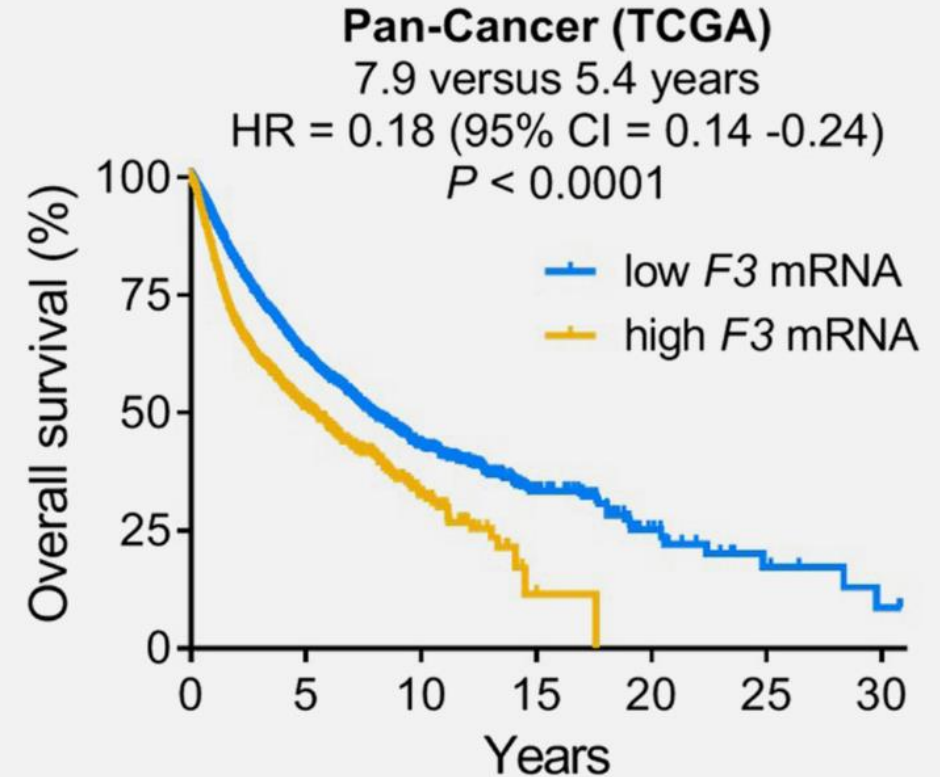
**Angiogenesis
Inflammation
Metastasis**

Tissue Factor is Highly Expressed Across Multiple Solid Tumor Indications

TF is Broadly Expressed Across Solid Tumor Indications

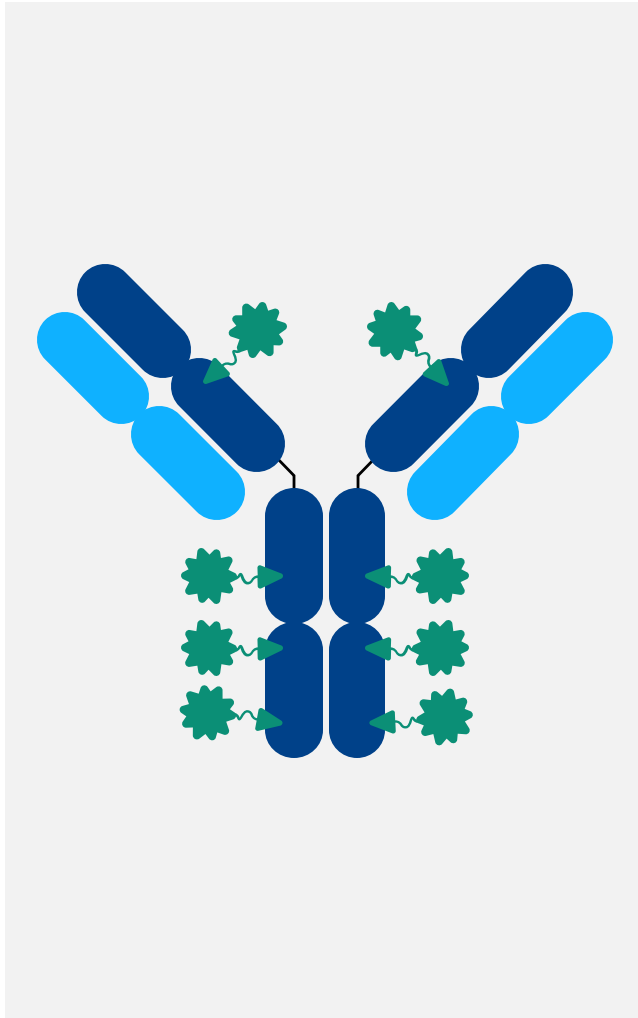


High TF Expression is a Negative Prognostic Marker

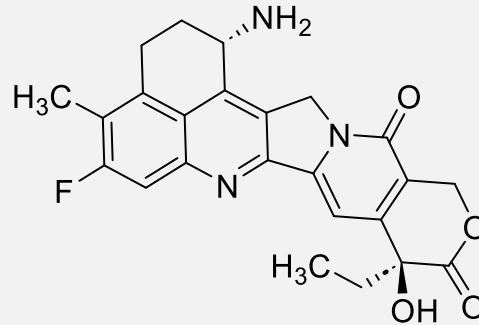


De Bono (2022) Cancer Reports
Unruh and Horbinski (2020) J Hematology & Oncology
TF – Tissue Factor; TCGA – The Cancer Gene Atlas; HR –hazard ratio; mRNA – messenger RNA

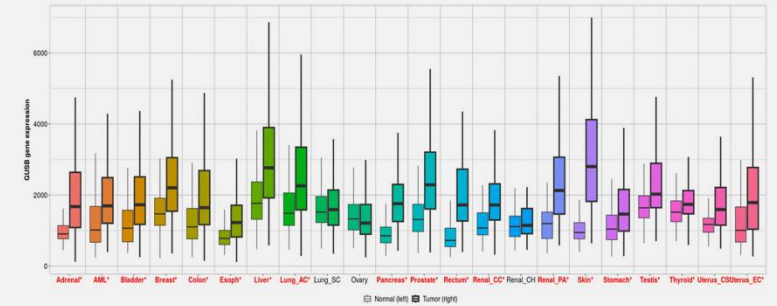
STRO-004: DAR8 Exatecan Payload ADC Designed for Enhanced Stability, Potency and Tumor Selectivity



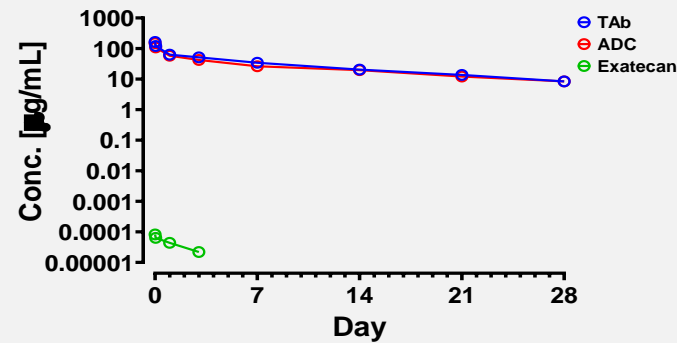
Potent exatecan topo1 inhibitor



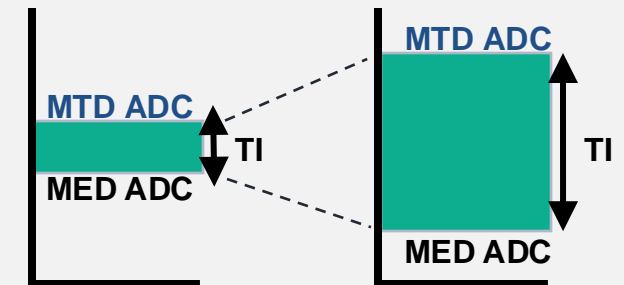
β -glucuronidase upregulated in tumor



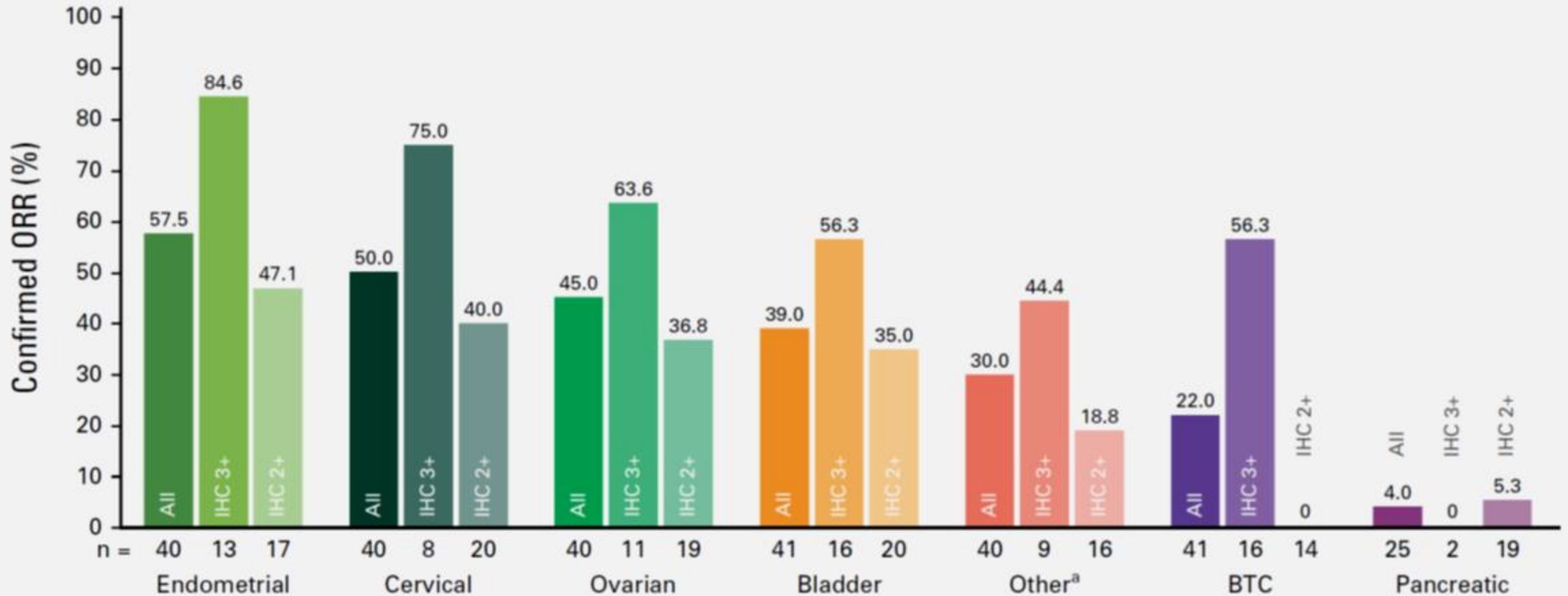
Hydrophilic design for optimal PK



Enhanced therapeutic window



Delivering More Payload Corresponds to Greater Clinical Response (Enhertu Example)



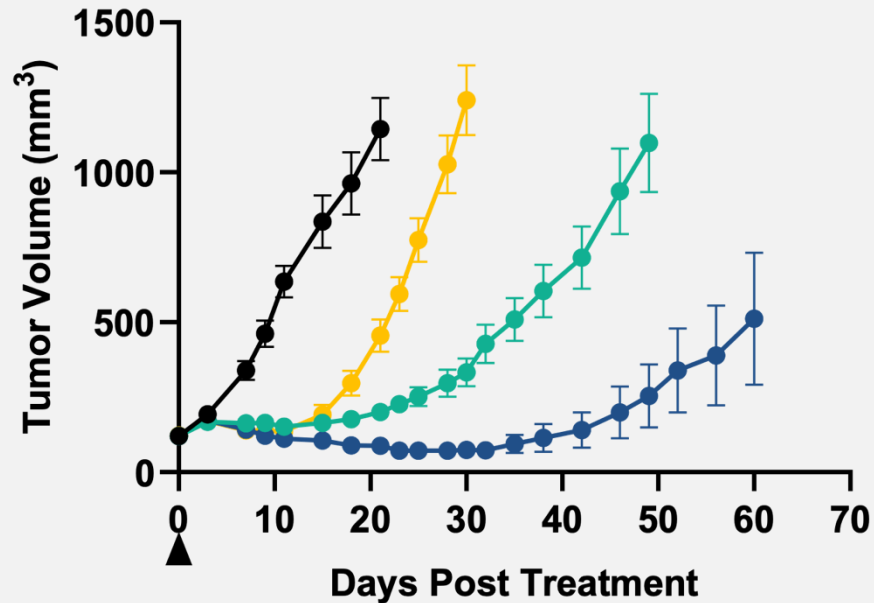
Meric-Bernstam, et al (2023) J Clin Oncology. DESTINY-PanTumor02 trial

a – Responses in the other tumors cohort include responses in extramammary Paget disease, oropharyngeal neoplasm, head and neck cancer, and salivary gland cancer.

ORR – objective response rate; BTC - biliary tract cancer; IHC – immunohistochemistry

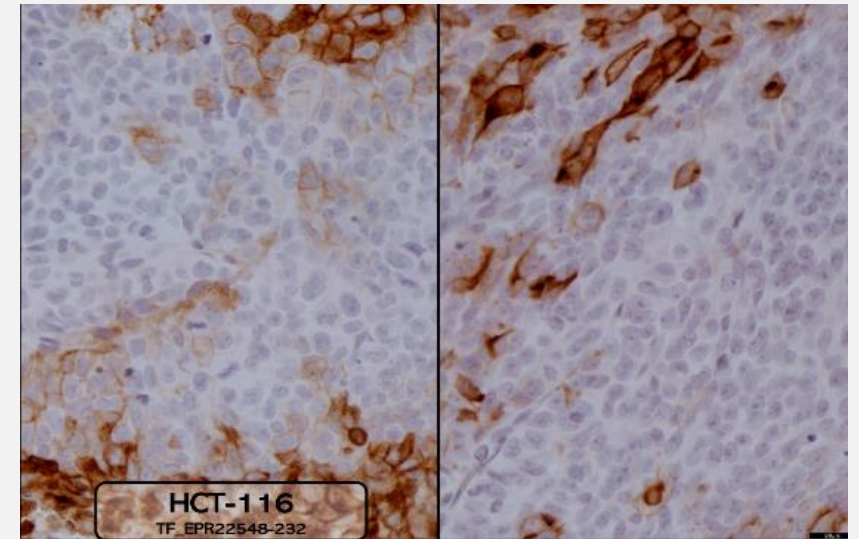
Selected DAR8 ADC Delivers More Payload to Low-TF Expressing Tumors Corresponding to Greater Anti-Tumor Response

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



- Vehicle control
- aTF DAR8-exatecan (STRO-004), 7.5 mg/kg
- aTF DAR4-MMAE, 15 mg/kg
- aTF DAR4-exatecan, 15 mg/kg (approved)

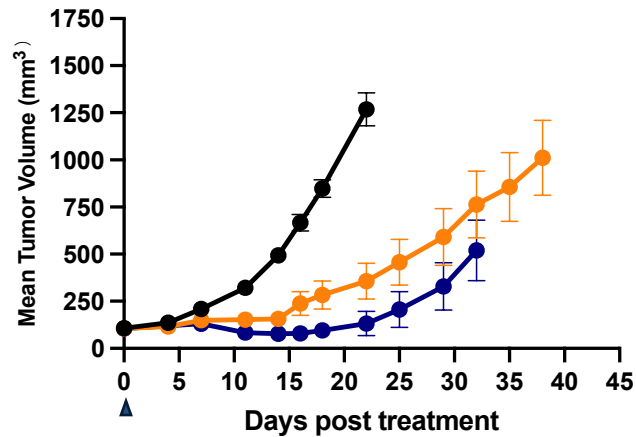
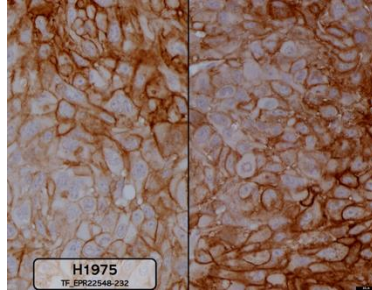
HCT-116
(colorectal model, TF – low)



DAR8 ADC has greater superiority to a DAR4 ADC in low target expressing tumors

Lung (TF+++)

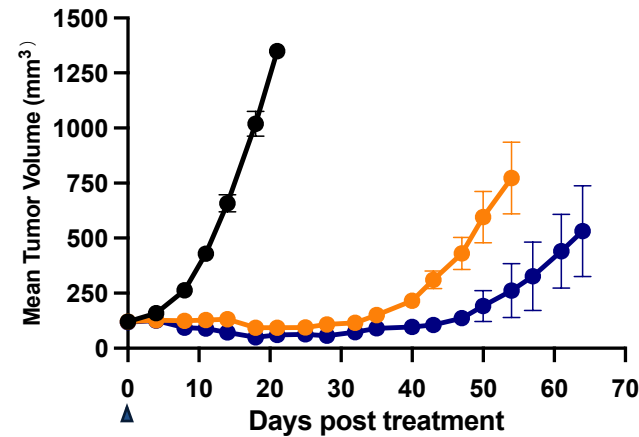
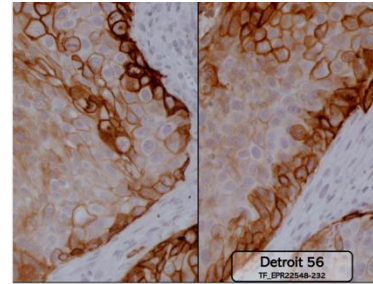
H1975 (NSCLC)



- Vehicle (PBS)
- 1 mg/kg, aTF DAR4
- 0.5 mg/kg, aTF DAR8 (STRO-004)

Head and Neck (TF++)

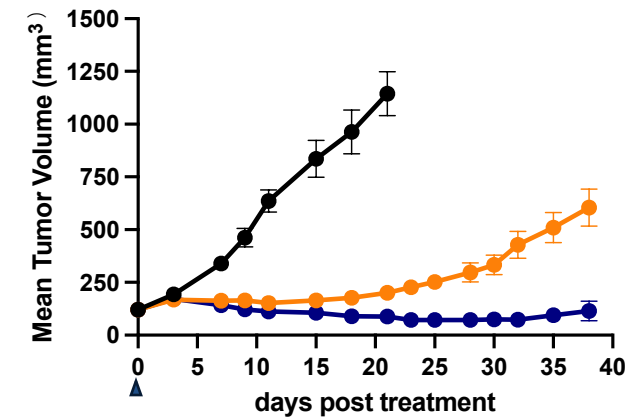
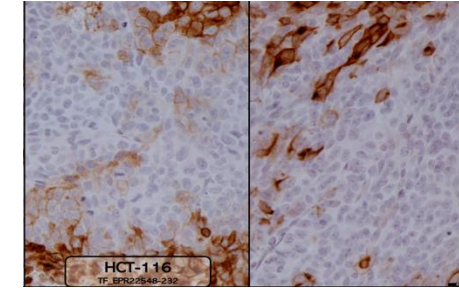
Detroit562 (HNSCC)



- Vehicle (PBS)
- 2 mg/kg, aTF DAR4
- 1 mg/kg, aTF DAR8 (STRO-004)

Colorectal (TF+)

HCT-116 (CRC)

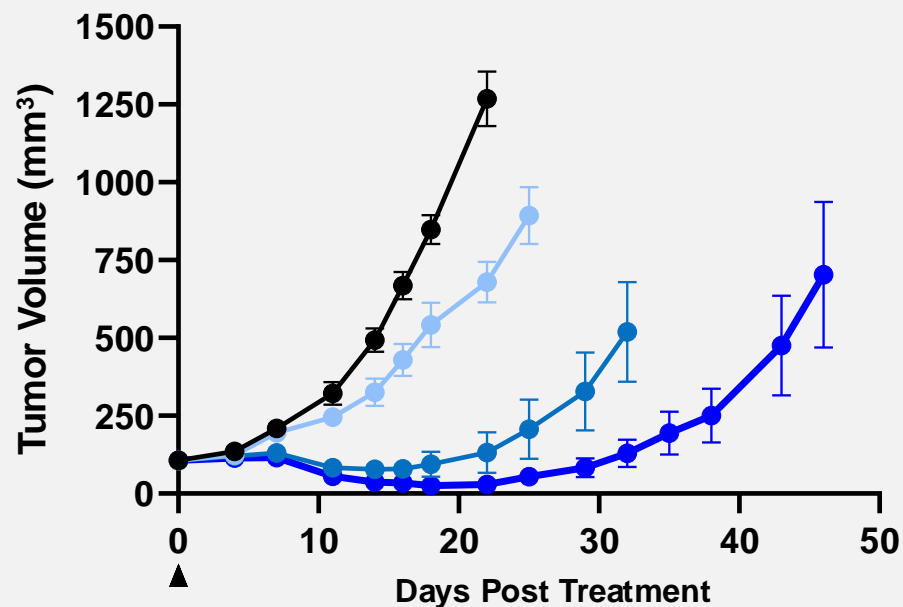


- Vehicle (PBS)
- 15 mg/kg, aTF DAR4
- 7.5 mg/kg, aTF DAR8 (STRO-004)

STRO-004 DAR8 Exatecan Achieves Sustained Tumor Regressions in Xenograft Models of NSCLC and HNSCC at Low Doses

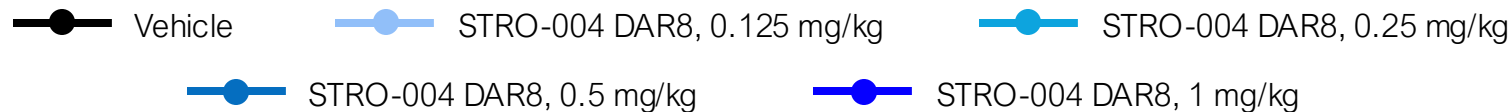
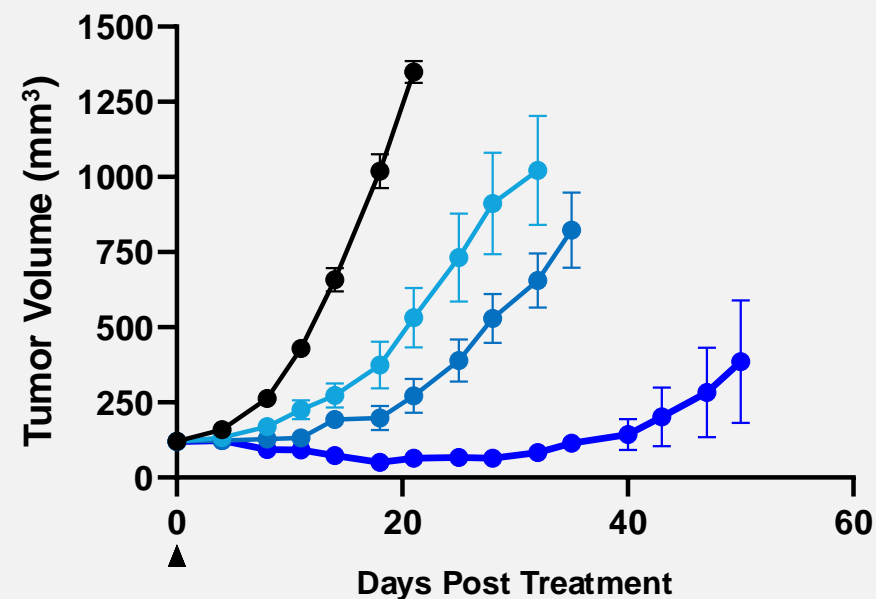
Lung (TF+++)

H1975 Growth Curves



Head and Neck (TF++)

Detroit562 Growth Curves

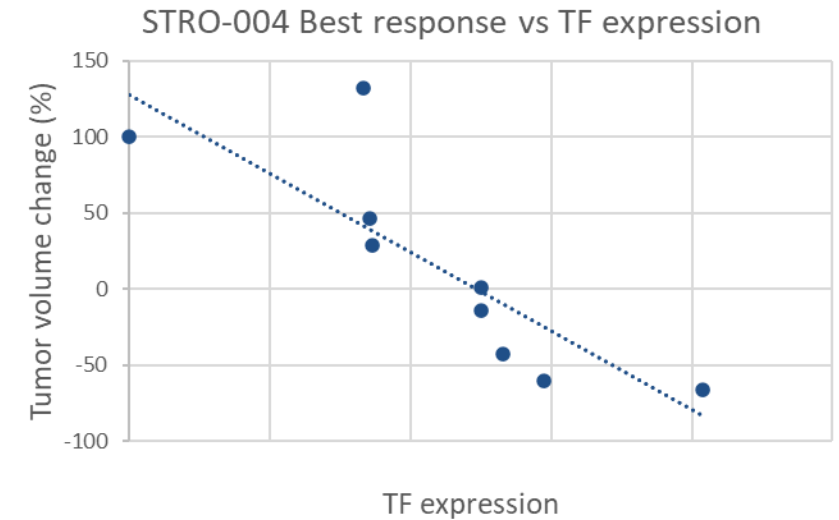
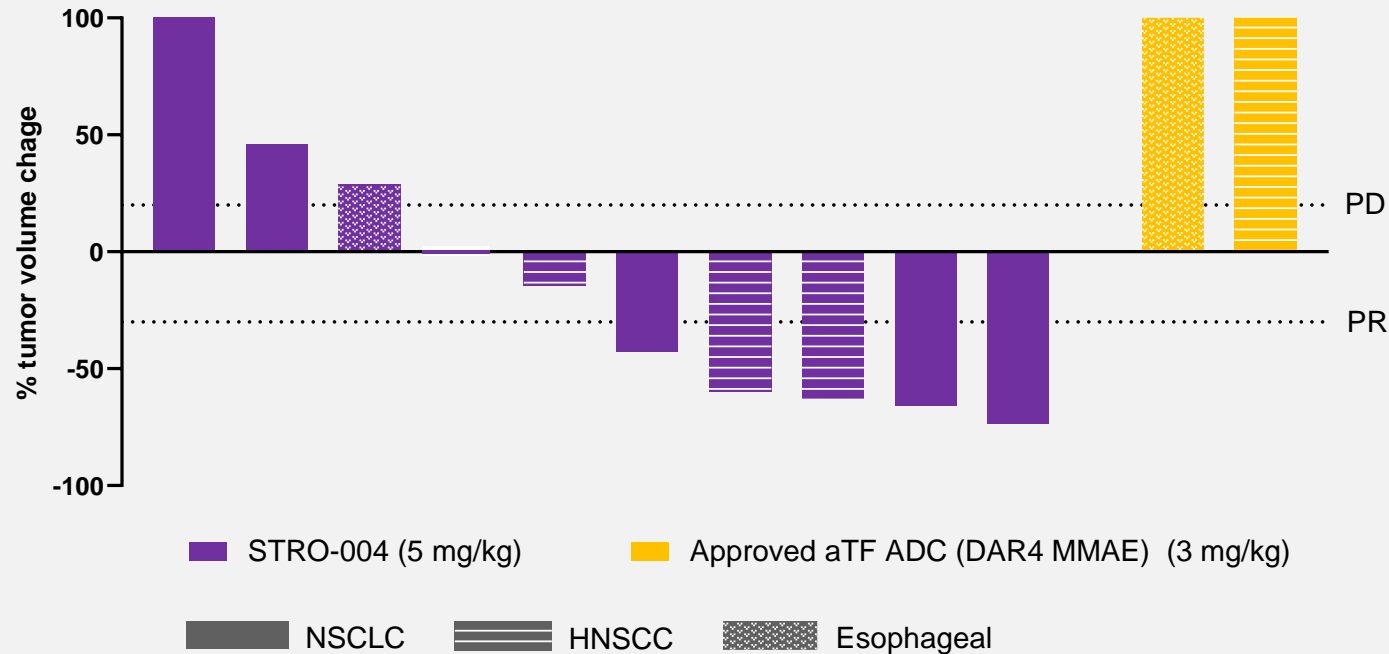


NSCLC – non-small cell lung cancer

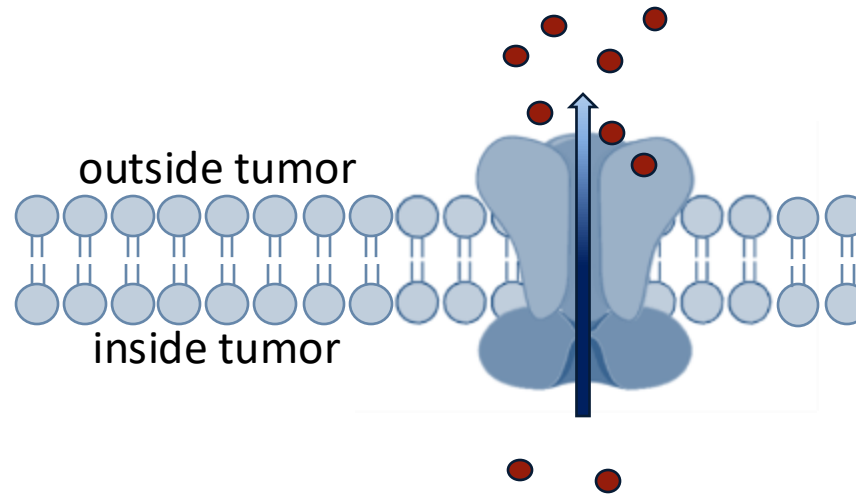
STRO-004 Shows Promising Anti-tumor Activity In TF Positive PDX Models of HNSCC, NSCLC, and Esophageal Cancer

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

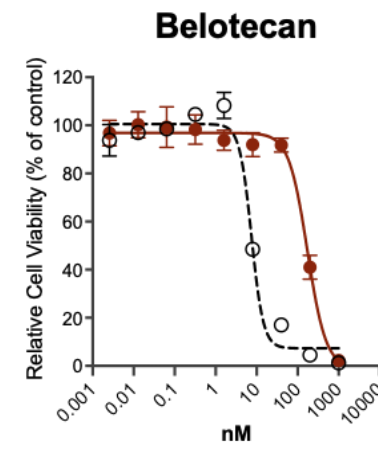
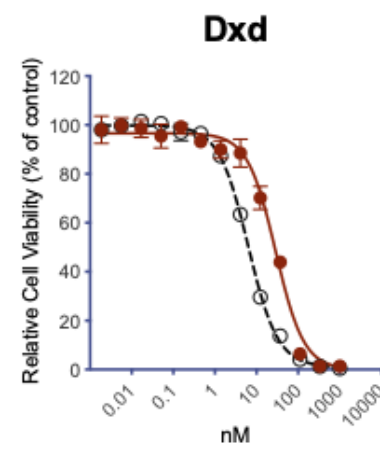
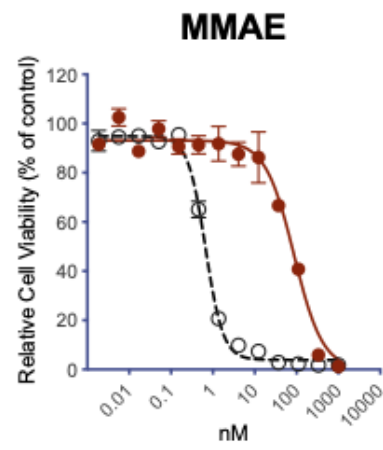
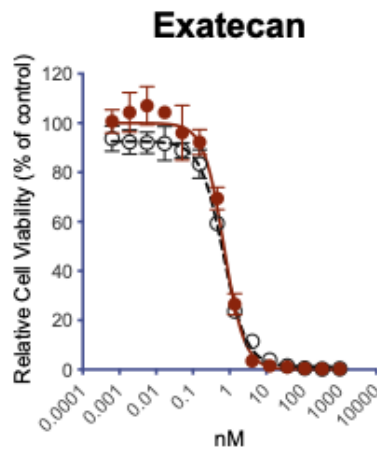
% Best response from baseline



Exatecan is Less Susceptible to Resistance Mechanisms Associated with Drug Efflux



P-gp drug efflux



—○— MES-SA (P-gp -)
—●— MES-SA/MX2 (P-gp +++)

P-gp – P-glycoprotein

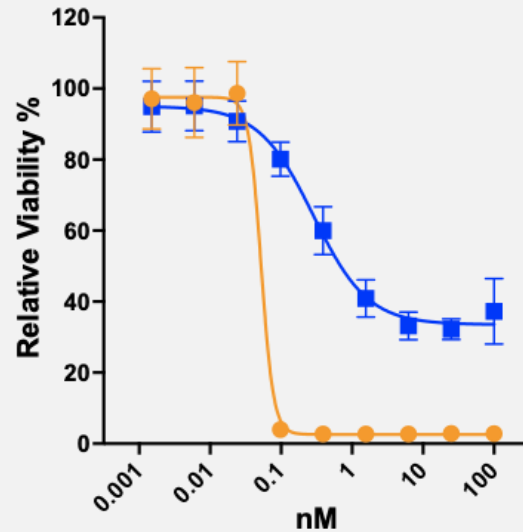
STRO-004 Demonstrates Reduced On-target Toxicity Due to Site Specific Linker-Payload Design

STRO-004 Lower Toxicities vs. Approved aTF ADC



Eye Inflammation

Human Corneal Epithelial Cells

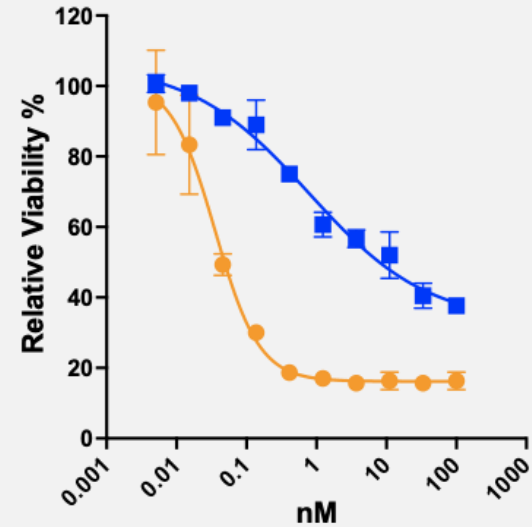


■ STRO-004 (DAR8-exatecan)



Skin Toxicities

Human Keratinocyte



■ Approved aTF ADC (DAR4-MMAE)

STRO-004 Well-Tolerated in NHP up to 50 mg/kg

Objective:

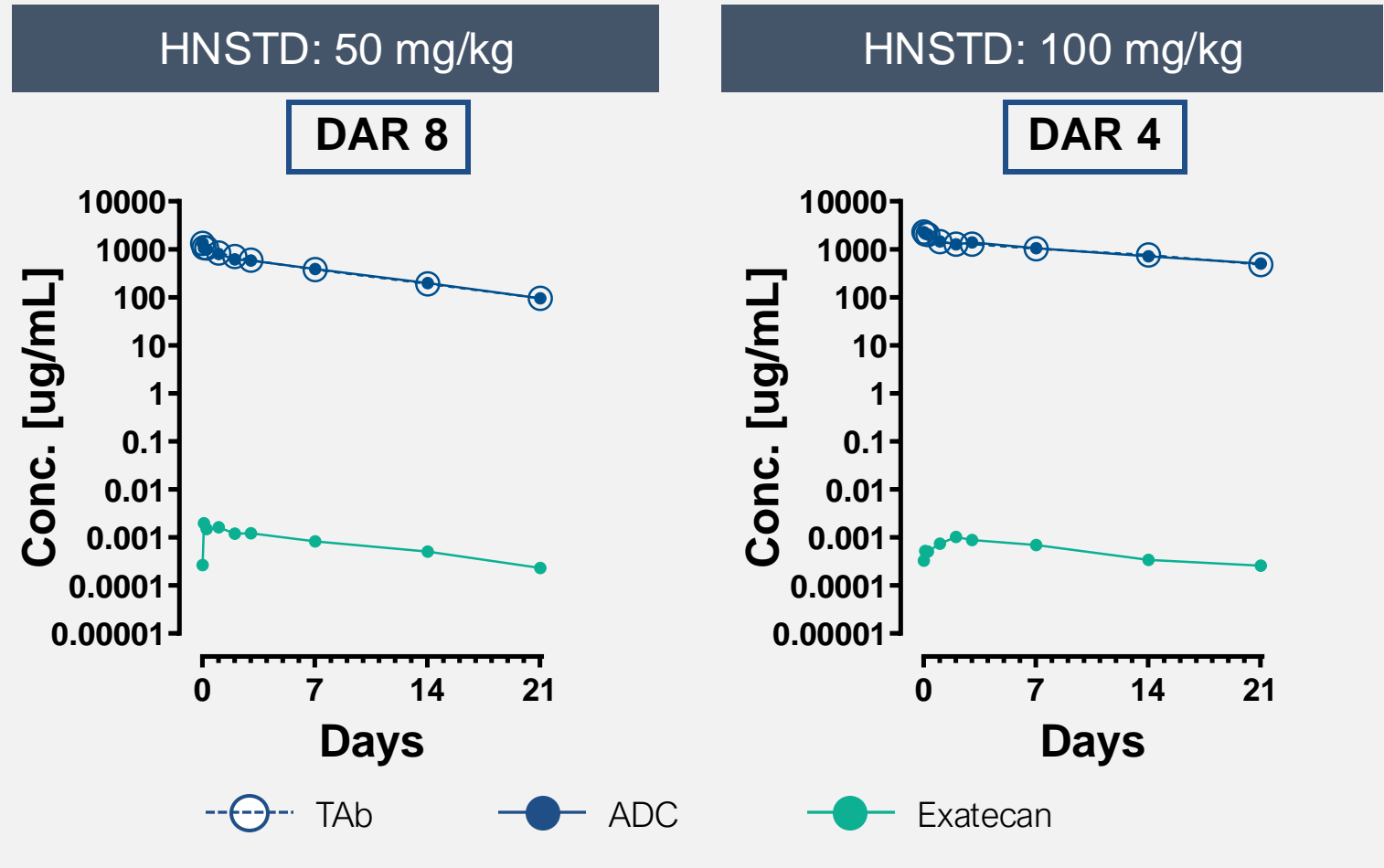
Compare nonclinical safety of DAR4 and DAR8 TF exatecan-ADC

Study:

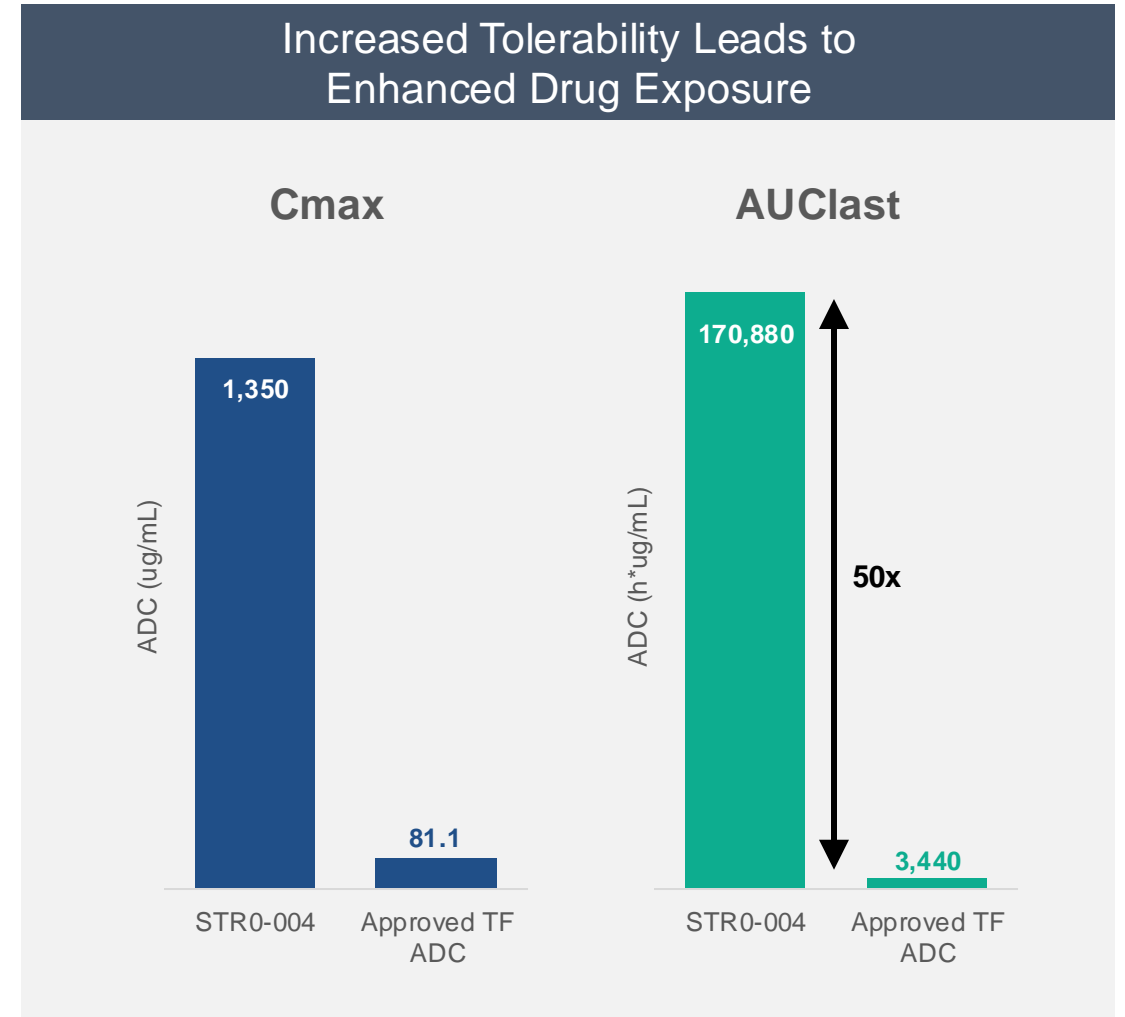
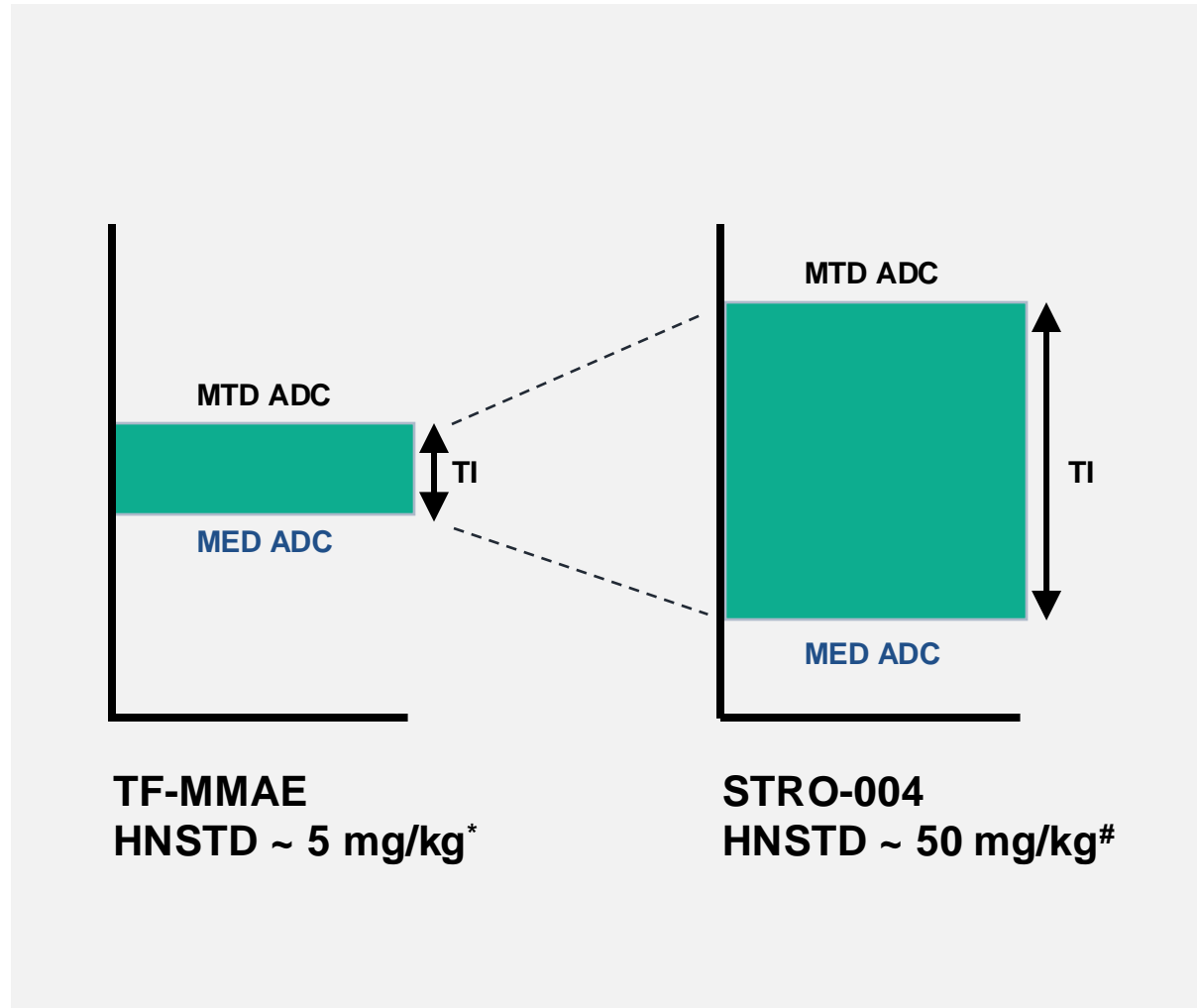
Dosed twice, three weeks apart, payload-matched doses

Findings:

- DAR4 and DAR8 ADCs were well-tolerated up to 100 and 50 mg/kg, respectively
- No evidence of eye toxicity
- Mild skin toxicity, observed in both DAR4 and DAR8



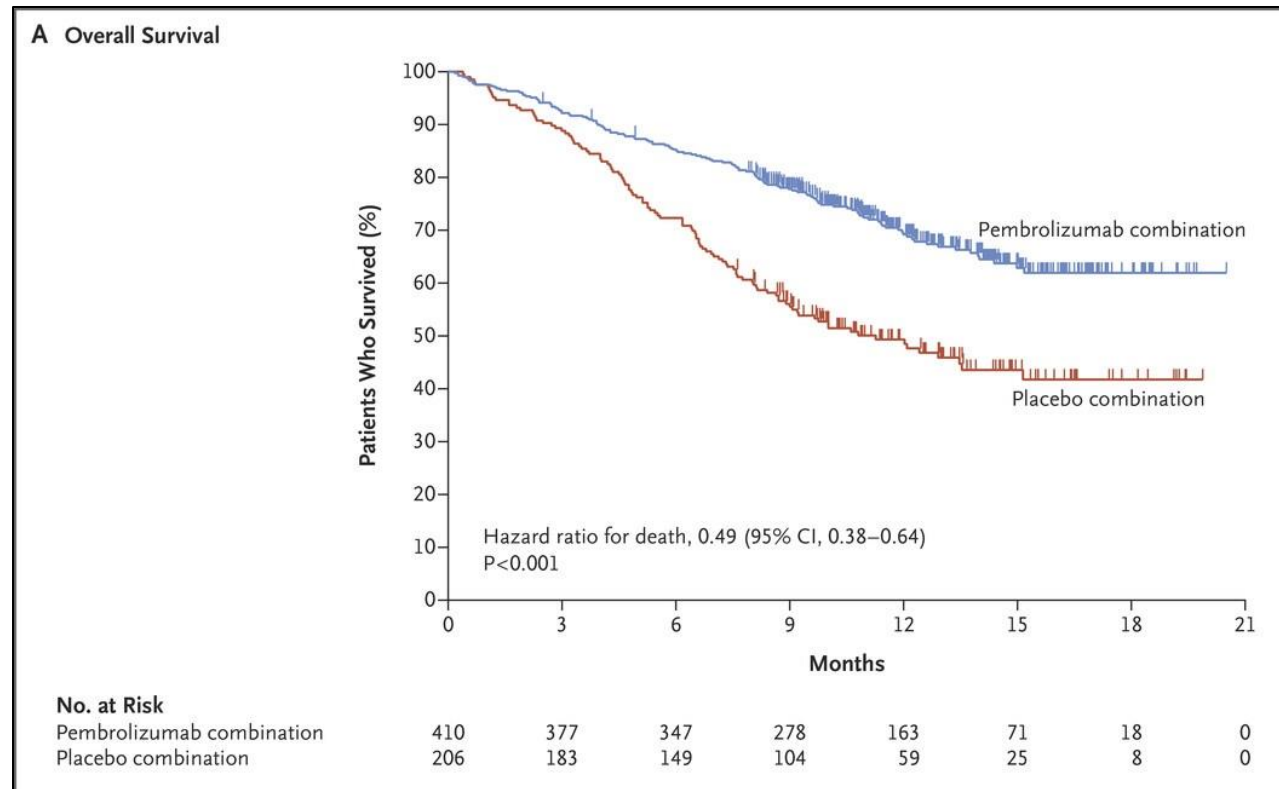
STRO-004 Widens the Therapeutic Window Compared to First Generation TF ADCs



*Breij & Parren, Can Res, 2014 # Sutro. 2024 interim data

Cmax – maximum concentration; AUClast - drug exposure over the specified time period; h – hour

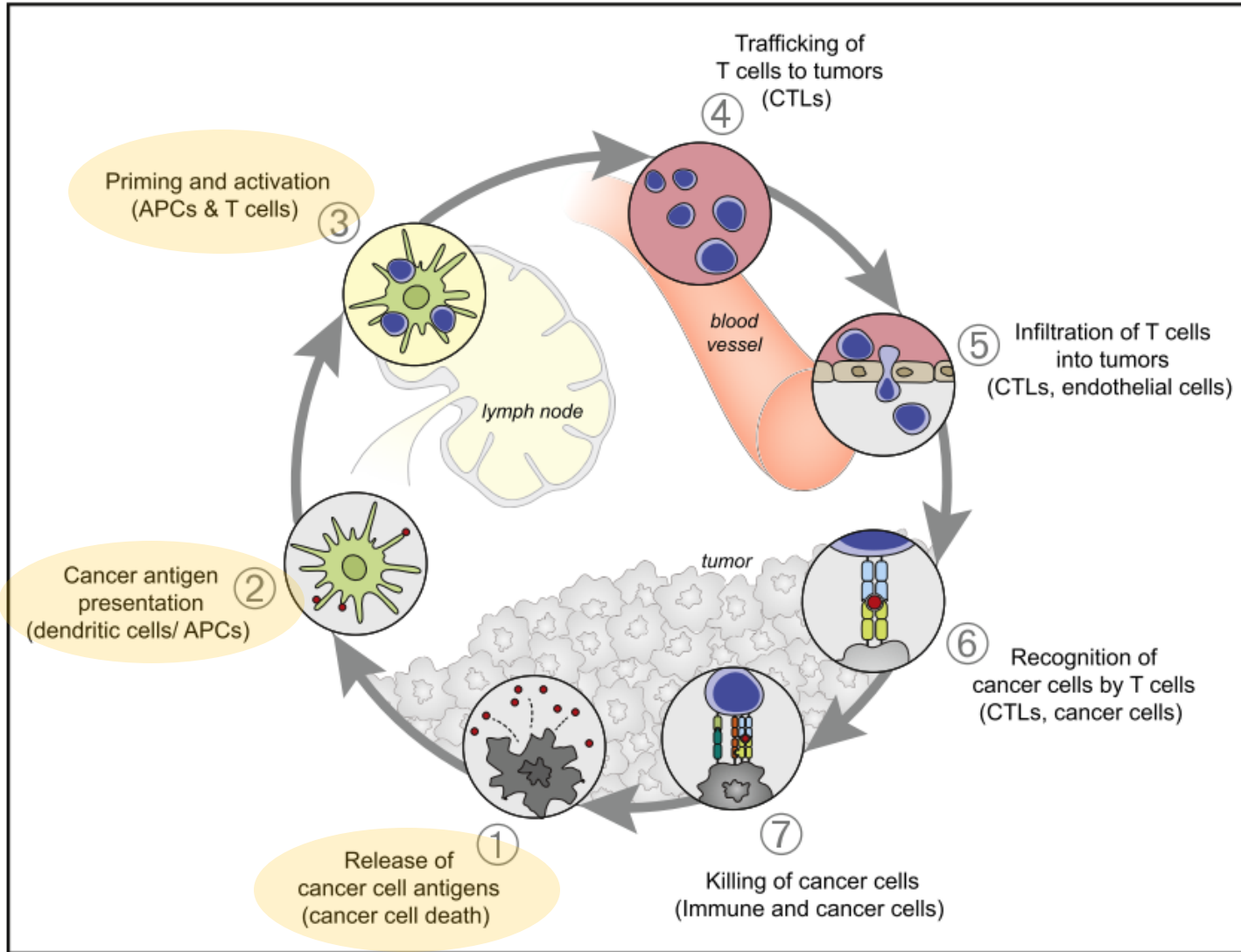
Checkpoint Blockade + Chemotherapy Results in Enhanced Overall Survival (Pembrolizumab example)



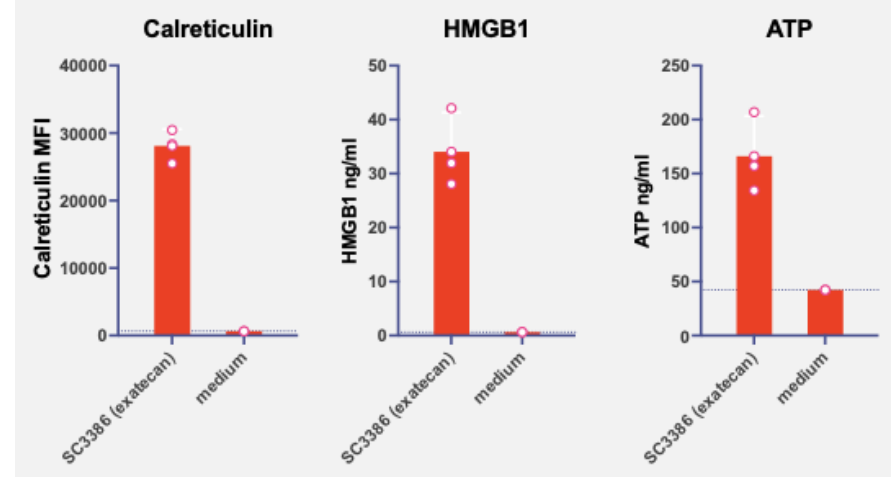
Gandhi, et al. (2018) NEJM
KEYNOTE-189: 1L metastatic nsqNSCLC without AGA; pemetrexed and Pt +/- pembrolizumab

Mechanistic Rationale for ADC and Checkpoint Blockade Combination

Exatecan is a Strong Inducer of Immunogenic Cell Death



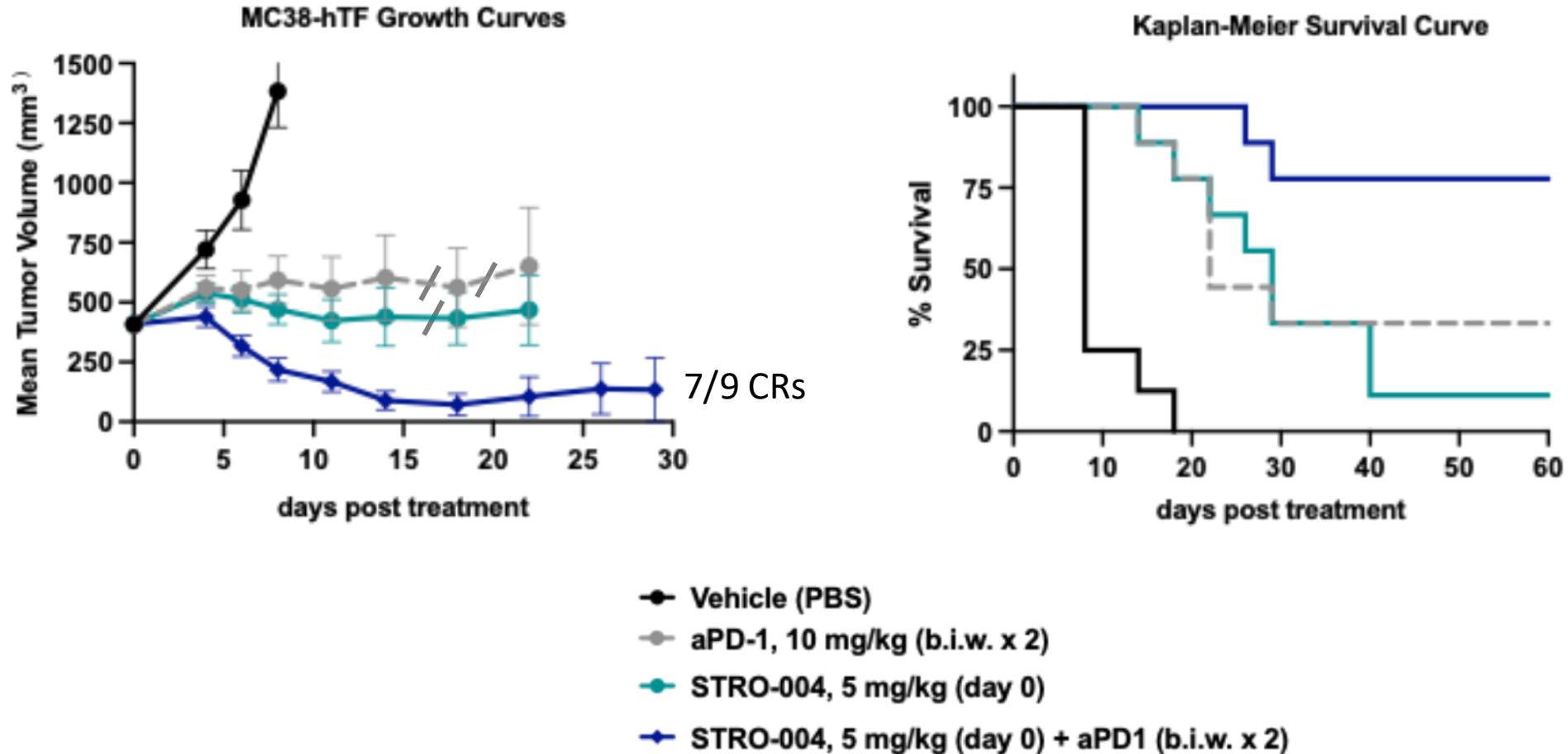
Immunogenic Cell Death (ICD)



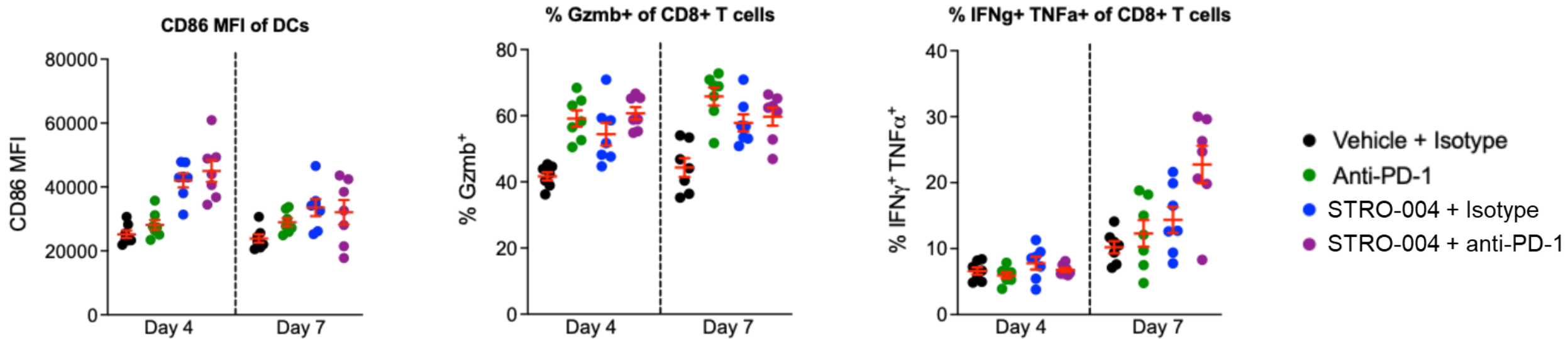
Daniel Chen and Ira Mellman, (2013) Immunity

Combination treatment of STRO-004 + aPD1 results in enhanced efficacy in a TF-expressing syngeneic model

Combination treatment of STRO-004 + aPD1 successfully debulks and clears large, rapidly growing MC38.hTF tumors



Combination Treatment of Checkpoint Blockade and STRO-004 Drives Prolonged Immune Cell Activation



- Early activation of dendritic cells
- Enhanced infiltration of Gzmb+ CD8+ T cells
- Persistent markers of T-cell activation with combination treatment of aPD1 and STRO-004

STRO-004 is a Next Generation ADC with Enhanced Therapeutic Potential

TF presents an opportunity for pan-tumor targeting

- Clinical validation of TF in cervical cancer, and signs of early activity in HNSCC, pancreatic cancer, and multiple other solid tumors with significant unmet need

STRO-004 is optimally designed for broad therapeutic benefit

- Clinically validated payload with potent activity, bystander and reduced susceptibility to resistance
- Optimized linker design with enhanced tumor selectivity and hydrophilicity
- Maximized drug performance with high DAR8 and optimized conjugation positioning
- Significant safety window, driving drug exposure and efficacy
- Strong combination potential with existing therapies

IND filing and First-in-Human studies planned for 2H 2025

SUTRO
BIOPHARMA

THANK YOU

