Preclinical Characterization of STRO-227: A PTK7-Targeting Dual-Payload ADC (DAR10) with Topoisomerase 1 and Tubulin Inhibitors

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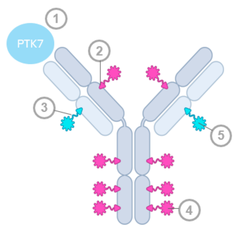
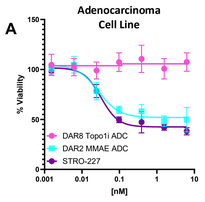
SUTRO BIOPHARMA

Introducing STRO-227



1. **PTK7** is a pan-tumor target enriched on tumor-initiating cells. Its expression is correlated with poor prognosis in multiple solid tumors
2. **Optimally positioned non-natural amino acids**, p-azidomethyl-L-phenylalanine (pAMF) or p-acetylphenylalanine (pAcF), combined with ultrastable chemistry
3. **β-glucuronidase cleavable linkers** with tumor selective cleavage, strong stability while in circulation, and added hydrophilicity led to **best-in-class PK**
4. **Eight exatecan payloads causing DNA disruption** and potent tumor cell killing, with high bystander activity, and immunogenic cell death (ICD)
5. **Two MMAE payloads causing Tubulin disruption** and potent tumor cell killing, with high bystander activity, and immunogenic cell death (ICD)

STRO-227 Exhibits Potent Cytotoxicity and Exceptional Specificity

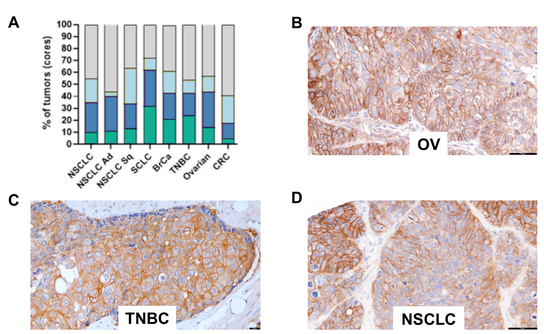


B

Gene ID	Library (Median SNR) STRO-227	Fixed Cell Confirmation (Median SNR) STRO-227	Fixed Cell Confirmation (Median SNR) Rituximab Biosimilar	Live Cell Confirmation (Median SNR) STRO-227	Live Cell Confirmation (Median SNR) Rituximab Biosimilar
PTK7	5.04	4.33	-0.01	4.05	0.08
FCGR2A	0.76	0.74	5.51	1.52	1.47
CD20	N/A	0.34	5.08	-0.14	7.12

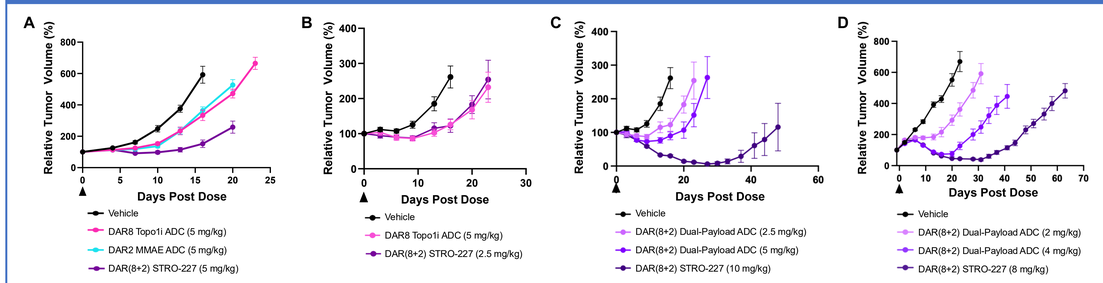
(A) Cell viability following 2D cytotoxicity assay with STRO-227. Cells were treated for 10 days, and viability was measured using CellTiter-Glo. (B) STRO-227 demonstrates high specificity for PTK7. In a Retrogenix cell-based binding assay, STRO-227 was evaluated against a panel of >6,500 human membrane and secreted proteins (including >400 heterodimers). Binding was assessed by signal-to-noise ratio, with a rituximab biosimilar included as a control

PTK7 Expression Across Multiple Tumor Types



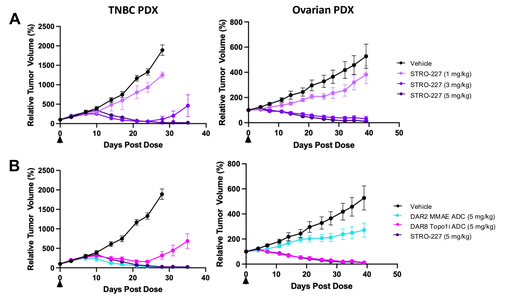
(A) Prevalence of PTK7 expression across multiple solid tumor indications, as assessed by immunohistochemistry on human tumor tissue microarrays (TMA). (B-D) Representative images of PTK7 staining (brown) with hematoxylin counterstaining (blue) of human ovarian (OV), triple-negative breast (TNBC), and non-small cell lung cancer (NSCLC) tumor tissues. Scale bar = 50 mm.

STRO-227 Delivers Robust Anti-Tumor Activity in Breast Cancer CDX Models

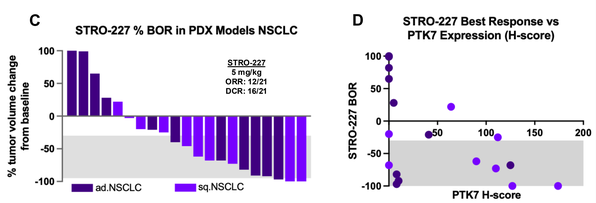


(A) STRO-227 outperforms both single-payload ADCs in a breast cancer xenograft model. The 8+2 dual-payload ADC has significant tumor growth inhibition when compared to the matched MMAE and exatecan single-payload ADCs. (B) In a dose-titration study in the previous model, the STRO-227 was observed to give similar efficacy at half the dose of the matched DAR8 exatecan ADC. (C-D) STRO-227 exhibits dose-dependent anti-tumor activity in breast cancer xenograft models. Significant tumor growth inhibition at 2-5 mg/kg and tumor regression at 4-5 mg/kg.

Broad Anti-Tumor Activity of STRO-227 Across PDX Models

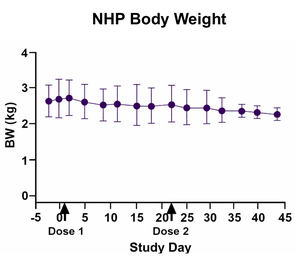


(A) STRO-227 exhibits dose-dependent anti-tumor activity in TNBC and Ovarian PDX models. Significant tumor growth inhibition and tumor regression at 3 mg/kg. (B) Comparison of STRO-227 to single-payload benchmarks in TNBC and Ovarian PDX models.



(C) STRO-227 demonstrates an overall response rate (ORR) of 57% and a disease control rate (DCR) of 76% across NSCLC PDX models spanning both adenocarcinoma and squamous histologies. Best response from each PDX model is plotted as the greatest reduction in tumor volume observed (percent tumor volume change from the start of treatment at time t ≥ 10). Models are sorted by increasing response to STRO-227. Response criteria are adapted from RECIST clinical criteria; Partial response: best response of ≤ 30%, Progressive Disease: best response of ≥ 20%. (D) Correlation of best response based on (C) to PTK7 expression (H-score) determined by IHC of vehicle-treated tumors

STRO-227 Preclinical Tolerability at 25 mg/kg (Q3W X 2) Comparable to Single-Payload ADC Benchmarks



NHP HNSTD Comparison: STRO-227 and Single-Payload MMAE ADCs

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[c] (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
STRO-227	**PTK7**	**β-Glu**	**Exatecan + MMAE**	**8 + 2**	**25 mg/kg (Q3Wx2)**	**Preclinical**

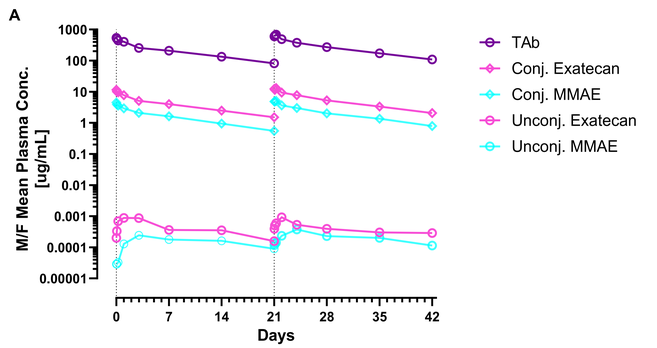
[a]PMID: 36692647; [b]LCB84 doi:10.1158/1538-7445.AM2022-328; [c]LNCB74 doi:10.1158/1538-7445.AM2024-1898

NHP HNSTD Comparison: STRO-227 and Single-Payload Topo1i ADCs

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
HER3-DXd	HER-3	GGFG	Deruxtecan	8	30 mg/kg[c] (Q3Wx5)	3
I-DXd	B7-H3	GGFG	Deruxtecan	4	30 mg/kg[d] (Q2Wx3)	3
R-DXd	CDH6	GGFG	Deruxtecan	8	30 mg/kg[e] (Q3Wx3)	2/3
Rina-S	FOLR1	Val-Cit	Exatecan	8	30 mg/kg[f] (Q3Wx2)	3
STRO-227	**PTK7**	**β-Glu**	**Exatecan + MMAE**	**8 + 2**	**25 mg/kg (Q3Wx2)**	**Preclinical**

[a]PMID: 27206201·[b]PMID: 34413126·[c]PMID: 31471314·[d]PMID: 35140548·[e]PMID: 38205802·[f]DOI:10.1158/1538-7445.AM2023-CT244

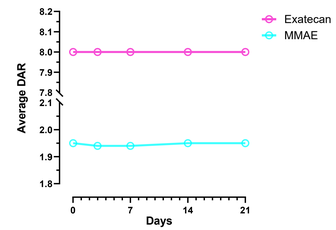
STRO-227 Demonstrates Favorable PK and DAR Stability



B

Analyte	CL (mL/d/kg)	V_{ss} (mL/kg)	$t_{1/2}$ (d)	
	C_1	C_1	C_1	C_2
TAb	4.89	70.5	10.3	10.8
ADC(Exatecan)	5.42	74.7	10.0	10.5
ADC(MMAE)	5.62	71.4	9.0	10.5

C



A) Pharmacokinetics of total antibody, conjugated payload, and free (unconjugated) payload following repeat intravenous dosing of STRO-227 (25 mg/kg, Q3W ×2) in nonhuman primates. Plasma concentrations of free payload were ~4 orders of magnitude lower than conjugated payload. (B) Summary of clearance and terminal half-life, indicating low clearance and a long terminal half-life. (C) Drug-to-antibody ratio (DAR) stability of heavy and light chains, demonstrating no measurable change in DAR throughout the study.

Conclusions

- **STRO-227, a PTK7-targeting dual-payload ADC, demonstrates robust, dose-dependent anti-tumor activity across CDX and PDX models, including TNBC, ovarian, and NSCLC (both adeno and squamous)**
- **Dual delivery of Topo1i and tubulin inhibitor payloads enables enhanced efficacy relative to single-payload ADCs, supporting a differentiated mechanism of action**
- **STRO-227 exhibits favorable pharmacokinetics, stable DAR, and limited systemic payload exposure, consistent with a highly-engineered and optimized ADC**
- **Preclinical tolerability in non-human primates is comparable to single-payload ADC benchmarks, supporting the feasibility of a dual-payload approach**
- **Together, these data support STRO-227 as a potential best-in-class PTK7-targeting ADC with broad applicability across solid tumors, with an anticipated IND in late 2026**