An in vivo platform enables evaluable drug responses in patients with soft tissue sarcoma

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Significance & Hypothesis/Techniques:

Despite advances in oncology drug development, a critical translational gap persists between preclinical models and human clinical outcomes, particularly in rare and heterogeneous diseases such as sarcoma. Conventional early-phase oncology trials are limited in their ability to generate mechanistic pharmacodynamic data in patients, constraining early insights needed to inform rational combination strategies and go/no-go decisions.

To address this gap, the CIVO platform was developed to enable multiplexed assessment of investigational agents and combinations at microdose levels within the intact human tumor microenvironment. Using this approach in sarcoma patients across multiple studies, we demonstrate the utility of CIVO as an early clinical platform capable of generating insights into drug and combination effects directly in patient tumors.

Innovation:

These studies represent the first application of CIVO for combination testing of antibody-based therapeutics, as well as the first evaluation of first-in-human investigational agents. Spatial profiling enabled characterization of drug response signatures across patients, providing a novel framework for assessing mechanism of action and therapeutic activity.

Approach:

Across three Phase 0 studies, patients with soft tissue sarcoma (STS) were administered CIVO microinjections 2–96 hours prior to surgical resection using a standardized 8-needle array delivering drugs and drug combinations. Injection sets included vehicle controls and replicate conditions. Drug deposition was spatially tracked using co-administered fluorescent microspheres (CIVO GLO), detectable during tissue processing and FFPE IHC slide imaging.

In total, 18 patients (6 per study) contributed 144 injection sites, evaluated across multiple tumor depths. Biomarker analyses, tailored to drug mechanisms of action, included protein and transcript quantification using fIHC, fISH, and GeoMx Digital Spatial Profiling. Previously established analytical methods were applied to quantify localized pharmacodynamic responses (2,3).

Results:

Across the 18 patients in these three studies, all but one resulted in evaluable drug responses in the patient, with 89.6% of injected needles recovered in viable tumor tissue. Data generated from these studies has been used to demonstrate drug pharmacodynamics in STS for two potential clinical drug combinations and two First in Human investigational drugs. Combinations of pembrolizumab and ILT2/3 monoclonal antibodies demonstrated less interferon pathway activation than pembrolizumab alone, which was replicated in later trial results. PBA-0405, a First in Human ROR1 afucosylated antibody, demonstrated increases in interferon and cell death at injection sites compared to vehicle sites. A second study of a First in Human afucosylated antibody, PBA-0111, has been completed, with data pending publication.

Discussion & Impact:

These results demonstrate that pharmacodynamic responses to CIVO-delivered drugs can be assessed directly within STS tumors, validating the platform's ability to generate spatially resolved, in-human mechanistic data. This positions CIVO as a critical translational bridge between preclinical research and clinical development, enabling earlier and more informed decision-making in the drug development pathway.

In addition, the high rate of evaluable injections at the patient level supports the feasibility and reliability of this approach. Together, these findings highlight the potential for CIVO to evolve beyond a translational research tool into a patient-centric platform, with future applications in personalized medicine to help guide therapeutic selection.

References:

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(2) Gundle, K. R. Early, precise, and safe clinical evaluation of the pharmacodynamic effects of novel agents in the intact human tumor microenvironment. *Front Pharmacol* **15**, (2024).

(3) Derry, J. Trackable Intratumor Microdosing and Spatial Profiling Provide Early Insights into Activity of Investigational Agents in the Intact Tumor Microenvironment. *Clinical Cancer Research* **6**, (2023).

Figures:

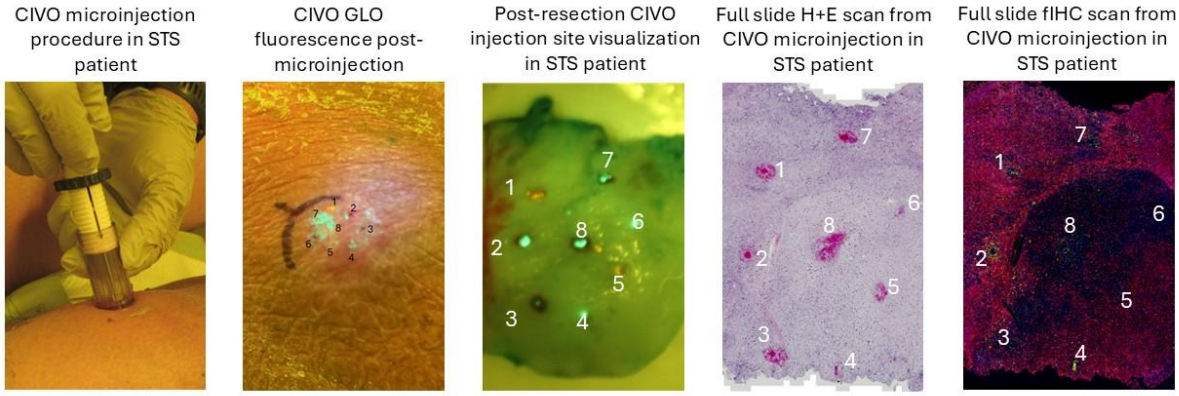

Figure 1: CIVO Microinjection Workflow in Soft Tissue Sarcoma Patients. Examples of CIVO microinjection of eight separate drug conditions co-formulated with fluorescent tracking microspheres, with injection sites then visualized using an ultraviolet flashlight, one day prior to surgery. After surgical resection, tissue is grossed perpendicular to injection columns, producing multiple gross sections containing all injected drugs, and injection sites are again visualized with the ultraviolet flashlight. Tissues are then fixed, processed, stained, and scanned, producing full slide images that maintain all injection sites in a single slide as well as preserving the tracking microspheres, which are visible using fluorescent microscopy. Multi-omic analysis of underlying microenvironment, tumor characteristics, and drug-induced changes are quantified at each injection site, enabling comparison of up to seven drug effects in an intact clinical tumor across multiple gros sections from a single patient sample.

Patient	Diagnosis	Needles	Needles Identified	% Needles	Depth	Location	Sub-Location	Evaluable?
MRA1	Synovial sarcoma	8	8	100%	17	Leg	Left lower leg	Y
MRA2	Myxofibrosarcoma	8	8	100%	12.5	Arm	Left forearm	Y
MRA3	Myxofibrosarcoma	8	8	100%	17	Leg	left anterior leg	Y
MRA4	UPS	8	6	75%	30.5	Leg	Left anterior thigh	Y
MRA7	Leiomyosarcoma	8	8	100%	20	Leg	Left lower leg	Y
MRA8	UPS	8	8	100%	20	Leg	Right Inguinal	Y
PBL1	Angiosarcoma	8	8	100%	14	Head	L scalp superior ear pinna	Y
PBL3	Myxofibrosarcoma	8	7	88%	10	Leg	Left medial calf	Y
PBL4	Pleomorphic Dermal Sarcoma	8	8	100%	9.5	Head	Right scalp	Y
PBL5	UPS	8	7	88%	14	Arm	L elbow	Y
PBL6	Myxofibrosarcoma	8	0	0%	17	Leg	Right gluteus	N
PBL8	Myxoid liposarcoma	8	7	88%	26	Leg	Left posterior thigh	Y
PRM1	UPS	8	8	100%	26	Leg	R mid thigh	Y
PRM2	Spindle cell sarcoma	8	7	88%	14	Arm	Right arm	Y
PRM3	Myxofibrosarcoma	8	8	100%	17	Leg	Right thigh	Y
PRM4	Myxofibrosarcoma	8	7	88%	17	Arm	L forearm	Y
PRM5	Spindle cell sarcoma	8	8	100%	20	Leg	Left thigh	Y
PRM6	Spindle cell/Pleomorphic sarcoma	8	8	100%	17	Thorax	Right periscapular/flank	Y
	Total:	**144**	**129**	**89.6%**				

Figure 2: Table of Patient Characteristics and Injection Evaluability. Locations, diagnoses, CIVO device settings, and evaluability assessment for all Phase 0 soft tissue sarcoma patients. Across a broad range of subtypes and tumor locations, evaluability was high, with 17/18 (94.4%) tumors evaluable via immunohistochemistry and 129/114 (89.6%) of all injection sites recovered and analyzed. Injection site evaluability defined as distinct injection sites in viable tumor tissue, patient evaluability defined as >60% of injection sites evaluable.