TARGETING LEUCINE-RICH REPEAT-CONTAINING PROTEIN 15 (LRRC15): SOT106 ANTIBODY-DRUG CONJUGATE FOR SOFT TISSUE SARCOMA AND OSTEOSARCOMA TREATMENT

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INTRODUCTION

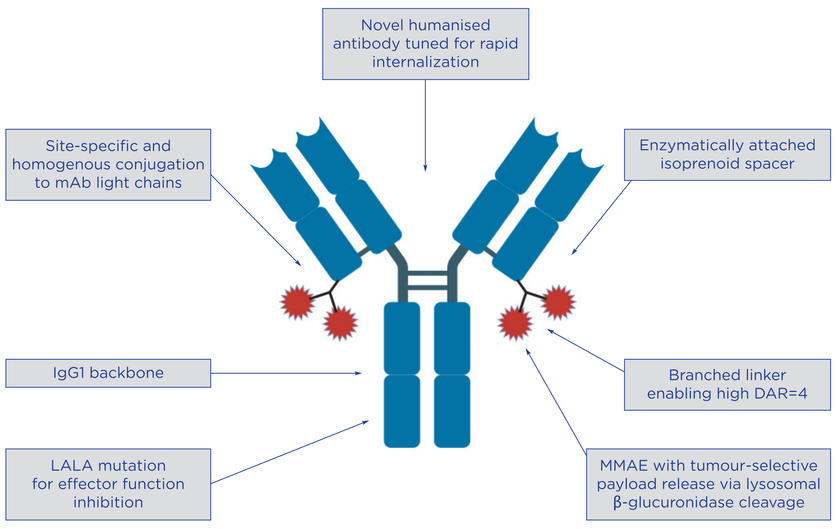
Background: Soft tissue sarcomas (STS) and osteosarcoma (OS) are difficult to treat and associated with poor prognoses. Current therapies are limited to chemotherapy and surgery, with few effective targeted treatments. The leucine-rich repeat-containing protein 15 (LRRC15), a protein overexpressed in many sarcomas, has emerged as a promising therapeutic target.

Methods: SOT106, a novel LRRC15-targeted antibody-drug conjugate (ADC) conjugated with monomethyl auristatin E (MMAE) via a beta-glucuronidase cleavable linker, was developed for targeted cytotoxic payload release. *In vitro* assays evaluated binding, internalization, and cytotoxicity. In vivo efficacy was assessed using multiple mouse and patient-derived xenograft (PDX) sarcoma models. Pharmacokinetics and toxicity profiles were examined in cynomolgus monkeys. A novel antibody that detects LRRC15 in FFPE samples was also developed for patient selection in upcoming clinical trials.

Results: SOT106 showed potent, antigen-specific cytotoxicity *in vitro* with nanomolar activity and a robust bystander effect. In vivo, it achieved dose-dependent tumor regression, including complete responses at 1 mg/kg. It outperformed current benchmarks in both soft tissue sarcoma and osteosarcoma PDX models, even in tumors with low-to-medium LRRC15 expression and in orthotopic models of osteosarcoma. In non-human primates, SOT106 showed favorable pharmacokinetics (half-life of 4.5–6 days), no premature payload release, and a high therapeutic index. Dose-limiting toxicities aligned with known MMAE effects.

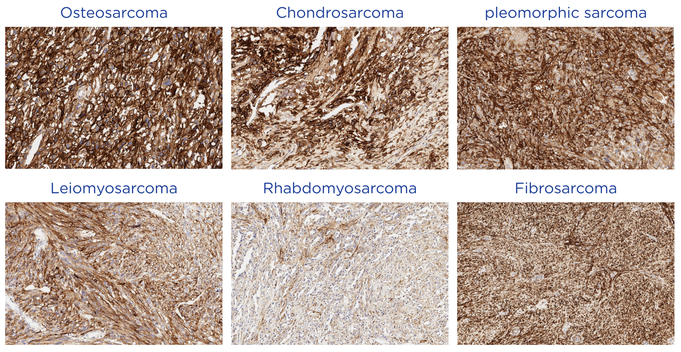
Conclusions: Our findings, showing the high prevalence of LRRC15 expression in sarcomas and the antitumor potency of SOT106 in preclinical models, strongly support its clinical development as a novel therapy for treating STS and OS, including pediatric cases. Combined with its superior performance over clinical benchmark, these results underscore the potential of SOT106 as a best-in-class targeted treatment for these challenging malignancies.

SOT106 KEY MOLECULAR FEATURES



- **improved molecule stability:** ConjuAll™ platform utilizes novel linker chemistry combined with site-specific enzymatic conjugation, which helps to achieve precise and homogeneous conjugation of the payload to the antibody
- **minimized systemic toxicity:** superior linker stability enabling minimal deconjugation of payload from antibody in blood circulation
- **tumor specific drug release:** payload cleavage triggered by β-glucuronidase, leveraging the enzyme widespread overex-pression in multiple cancer types

LRRC15 EXPRESSION ACROSS MULTIPLE SARCOMA SUBTYPES



Tumor type	% of patients with ≥10% of LRRC15⁺ cells*	# of samples tested
Osteosarcoma	83	87
Chondrosarcoma	57	21
UPS	49	79
Leiomyosarcoma	61	26
Rhabdomyosarcoma	50	24
Fibrosarcoma	28	14
Liposarcoma	0	24
Other STS subtypes	25	20

*LRRC15 expression determined by IHC staining using a proprietary LRRC15 antibody

IN VITRO PROFILE

Binding

Internalization

Cytotoxicity

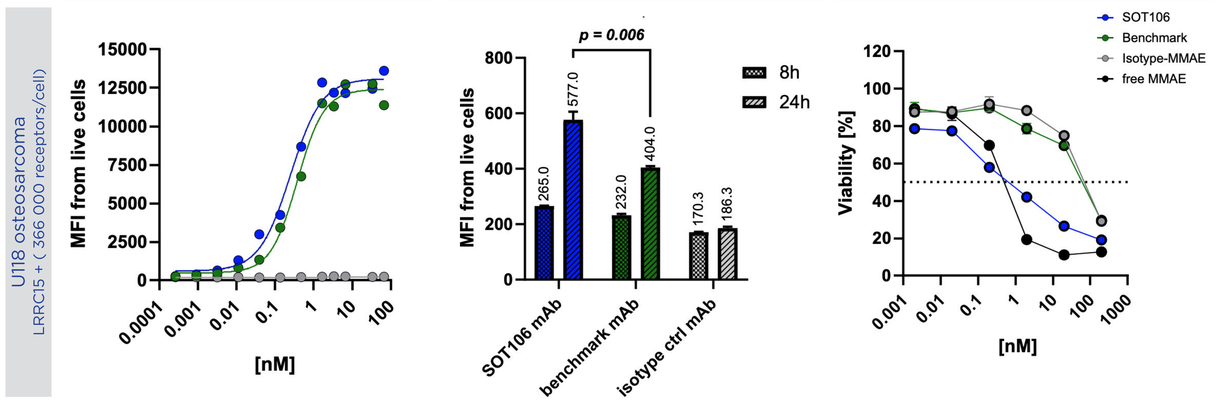


Table 1. *In vitro* characterization of SOT106 binding, internalization, and cytotoxicity in the U118 osteosarcoma cell line.

	SOT106	benchmark	isotype control	MMAE
Binding [nM]	0.25	0.37	NA	NA
Cytotoxicity [nM]	0.65	80.0	>150	0.48

Figure 1: *In vitro* characterization of SOT106 in the U118 osteosarcoma cells. Binding affinity of SOT106 compared to the benchmark and the isotype control ADCs. Internalization kinetics of SOT106 evaluated at 8 and 24 hours post-incubation showing significantly enhanced internalization relative to the benchmark. Cytotoxic activity of SOT106 after 120-hour incubation period, demonstrating improved potency compared to the benchmark ADC. Data represent the mean ± SEM from at least three independent experiments.

Bystander killing *in vitro*

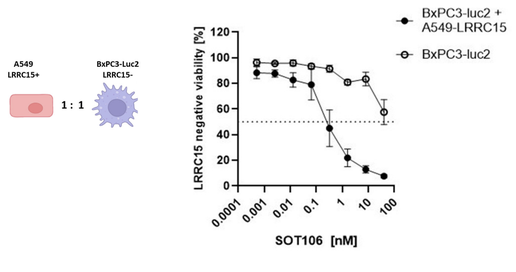


Figure 2: Bystander cytotoxicity of SOT106 in tumor cells. LRRC15-negative BxPC3-luc2 cells (luciferase-expressing) co-cultured with LRRC15-positive A549 cells (1:1 ratio) in presence of SOT106. Viability of LRRC15-negative BxPC3-luc2 cells measured by luminescence after 5 days, with loss of luciferase signal indicating SOT106-mediated bystander cytotoxicity. Data represent the mean ± SEM from at least three independent experiments.

IN VIVO ANTITUMOR ACTIVITY

Bone sarcoma

Pediatric osteosarcoma PDX (LRRC15$^{med, H\ score\ 161}$)

Subcutaneous model

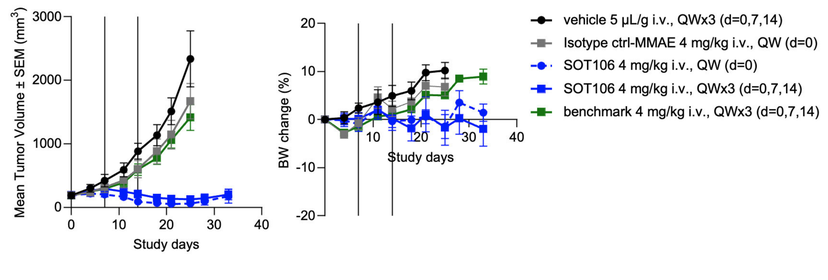
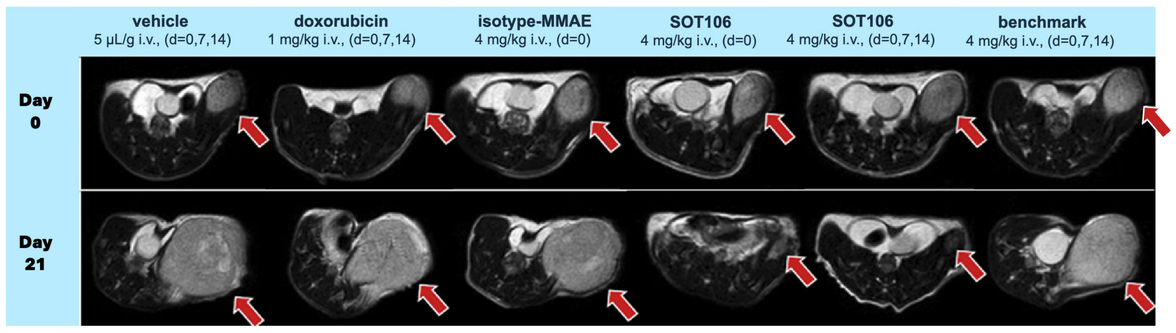


Figure 3: In vivo efficacy of SOT106 in pediatric OS PDX model. Tumor response compared to the benchmark (DAR2), including isotype control; n = 5. Data are displayed as means ± SEM.

Orthotopic model

Figure 4: In vivo efficacy of SOT106 in pediatric OS PDX model implanted in the femurs of mice and respective MRI scans. Tumor response compared to the benchmark (DAR2), including isotype control and standard of care; n = 5. Data are displayed as means ± SEM.



Pediatric osteosarcoma PDX (LRRC15$^{low, H\ score\ 81}$)

Subcutaneous model

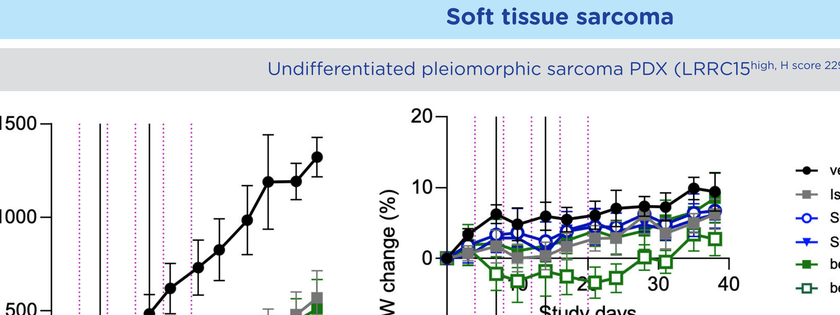


Figure 5: In vivo efficacy of SOT106 in pediatric OS PDX model. Tumor response compared to the benchmark (DAR2), including isotype control; n = 5. Data are displayed as means ± SEM.

Orthotopic model

Figure 6: In vivo efficacy of SOT106 in pediatric OS PDX model implanted in the femurs of mice and respective MRI scans. Tumor response compared to the benchmark (DAR2), including isotype control and standard of care; n = 5. Data are displayed as means ± SEM.

Soft tissue sarcoma

Undifferentiated pleiomorphic sarcoma PDX (LRRC15$^{high, H\ score\ 229}$)

Figure 5: In vivo efficacy of SOT106 in undifferentiated pleiomorphic sarcoma PDX model. Tumor response to varying concentrations of SOT106 compared to the benchmark (DAR2), including the isotype control; n = 5. Data are displayed as means ± SEM.

PHARMACOKINETICS

Table 2: SOT106 pharmacokinetic parameters in tumor-bearing mouse and cynomolgus monkey.

Species	Dose [mg/kg]		Half-life [days]	AUC_{inf} [h*µg/mL]
Mouse (tumor-bearing)	0,5	MED	6,5	492,8*
Cynomolgus monkey	10	HNSTD	4,5 – 6	20,532
Therapeutic index				**42**

*AUC_{inf} estimated from PK data coming from mice dosed at 1 mg/kg

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