Poster nr. 91P

Targeting Leucine-Rich Repeat-Containing Protein 15 (LRRC15): SOT106 Antibody-Drug Conjugate for Soft Tissue Sarcoma and Osteosarcoma Therapy

Fojtů Michaela[1*], Jabůrek Filip[1], Valentová Iva[1], Ranger Ann[2], Jensen-Smith Amy[2], Adkins Irena[1,3], Palová Jelínková Lenka[1,3], Moebius Ulrich[1], Steegmaier Martin[1], Špíšek Radek[1,3]

[1]SOTIO Biotech a.s., Českomoravská 2532/19b, Prague 9, 190 00, Czech Republic; ; [2]SOTIO Biotech Inc., 180 Canal St, Suite 300, Boston, MA 02114, USA [3]Department of Immunology, 2nd Faculty of Medicine and University Hospital Motol, Charles University, V Úvalu 84, Prague 5, 150 06, Czech Republic

INTRODUCTION

Background: Soft tissue sarcomas (STS) and osteosarcoma (OS) represent significant challenges in cancer therapy, often associated with poor prognosis. Treatment options are mainly limited to conventional chemotherapy and surgery, lacking effective targeted approaches. The leucine-rich repeat-containing protein 15 (LRRC15) has emerged as a promising target due to its overexpression in several sarcoma subtypes. SOT106 is currently being developed as an LRRC15-targeted antibody-drug conjugate (ADC) with monomethyl auristatin E (MMAE) using the ConjuAll™ platform engineered for tumor-specific payload release licensed from LigaChem Biosciences.

Methods: Immunohistochemistry (IHC) analysis was conducted on tissue microarrays (TMAs) to evaluate LRRC15 expression across bone cancer and STS samples, utilizing a proprietary diagnostic antibody. This antibody was designed to support prospective patient selection in clinical trials. Target expression was assessed in 51 pediatric and 37 adult OS samples, as well as in chondrosarcoma and multiple STS subtypes, including undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma, and rhabdomyosarcoma. *In vivo* efficacy studies in patient-derived xenograft (PDX) models were conducted in several STS models and pediatric OS models with moderate to high LRRC15 expression.

Results: Our analysis revealed the highest tumor expression of LRRC15 in OS, with 77% of adult patients and 59% of pediatric patients exhibiting ≥10% LRRC15+ cells. In chondrosarcoma, LRRC15 expression was observed in 58% of cases (n=38). Among STS, LRRC15 expression was identified in UPS (41%, n=79), leiomyosarcoma (40%, n=30), and rhabdomyosarcoma (30%, n=23). SOT106 demonstrated strong antitumor activity in a variety of STS and OS PDX models outperforming clinical benchmark across several parameters.

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.

IN VITRO PROFILE

G-292 osteosarcoma
LRRC15 + (75 000 receptors/cell)

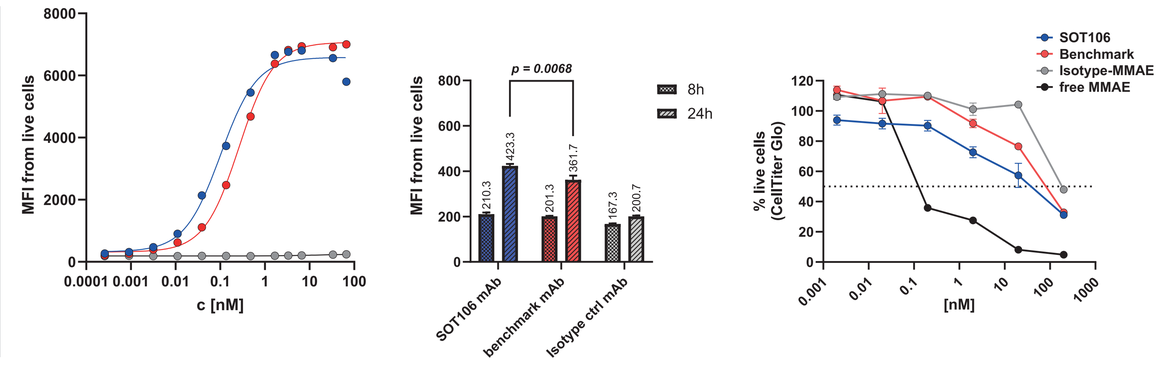
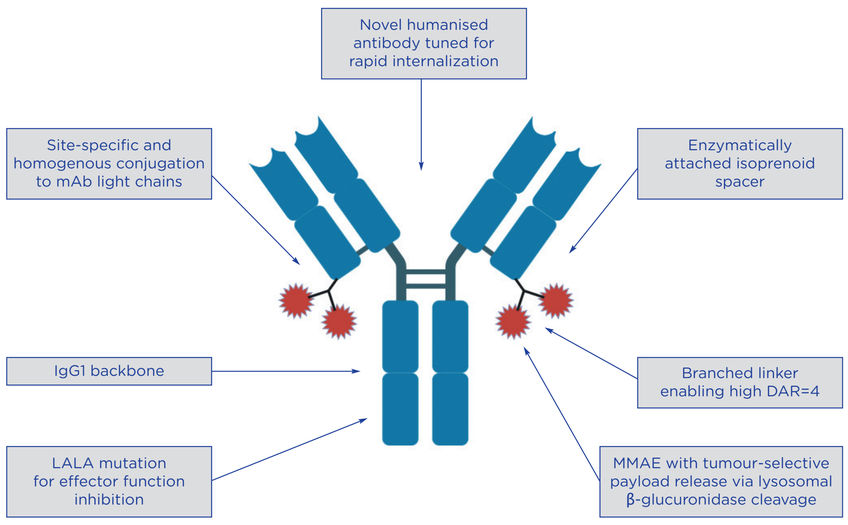


Table 1. *In vitro* characterization of SOT106 binding, internalization, and cytotoxicity in the G-292 osteosarcoma cell line.

	SOT106	benchmark	isotype control	MMAE
Binding [nM]	0.10	0.26	NA	NA
Cytotoxicity [nM]	40.44	71.56	>150	0.14

Figure 1: In vitro characterization of SOT106 in the G-292 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 its 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.

SOT106 KEY MOLECULAR FEATURES

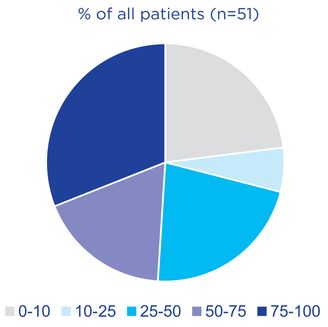


- **improved molecule stability:** ConjuAll™ platform utilizes novel linker chemistry combined with site-specific enzymatic conjugation, which helps to achieve precise and homogeneous conjugation of the payload to the antibody
- **minimized systemic toxicity:** superior linker stability enabling minimal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

LRRC15 EXPRESSION ACROSS MULTIPLE SARCOMA SUBTYPES

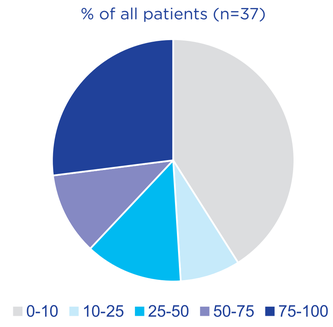
Bone sarcomas

Osteosarcoma adults



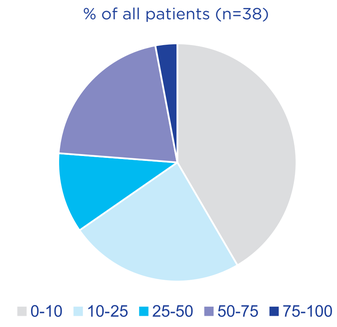
% of LRRC15+ cells	number of patients	% of all patients
0 – 10	12	23
10 – 25	3	6
25 – 50	11	22
50 – 75	9	18
75 - 100	16	31
total	51	100

Pediatric osteosarcoma



% of LRRC15+ cells	number of patients	% of all patients
0 – 10	15	41
10 – 25	3	8
25 – 50	5	13
50 – 75	4	11
75 - 100	10	27
total	37	100

Chondrosarcoma

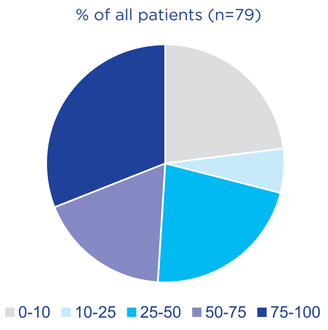


% of LRRC15+ cells	number of patients	% of all patients
0 – 10	16	42
10 – 25	9	24
25 – 50	4	10
50 – 75	8	21
75 - 100	1	3
total	38	100

*target expression in bone sarcomas determined by IHC staining using proprietary diagnostic antibody

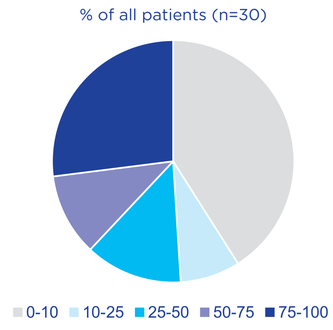
Soft tissue sarcomas

UPS



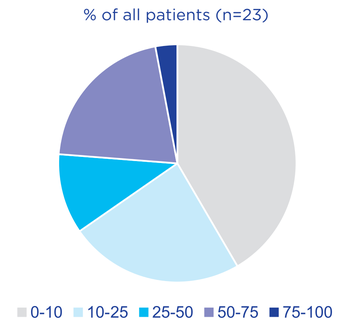
% of LRRC15+ cells	number of patients	% of all patients
0 – 10	12	23
10 – 25	3	6
25 – 50	11	22
50 – 75	9	18
75 - 100	16	31
total	51	100

Leiomyosarcoma



% of LRRC15+ cells	number of patients	% of all patients
0 – 10	15	41
10 – 25	3	8
25 – 50	5	13
50 – 75	4	11
75 - 100	10	27
total	37	100

Rhabdomyosarcoma



% of LRRC15+ cells	number of patients	% of all patients
0 – 10	16	42
10 – 25	9	24
25 – 50	4	10
50 – 75	8	21
75 - 100	1	3
total	38	100

*target expression in STS determined by IHC staining using proprietary diagnostic antibody

IN VIVO ANTITUMOR ACTIVITY

Pediatric osteosarcoma PDX (LRRC15^{med})

Subcutaneous model

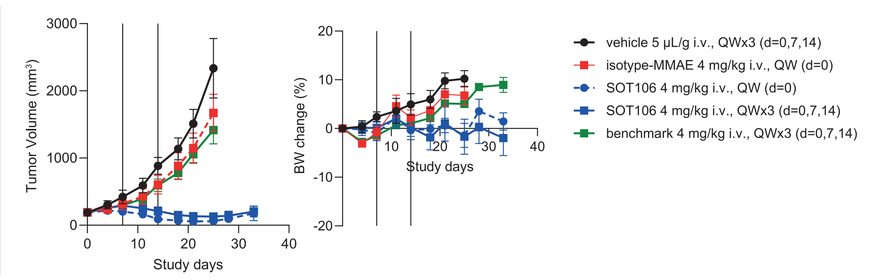


Figure 2: *In vivo* efficacy of SOT106 in pediatric OS PDX model. Tumor response compared to the benchmark, including isotype control; n = 5. Data are displayed as means ± SEM.

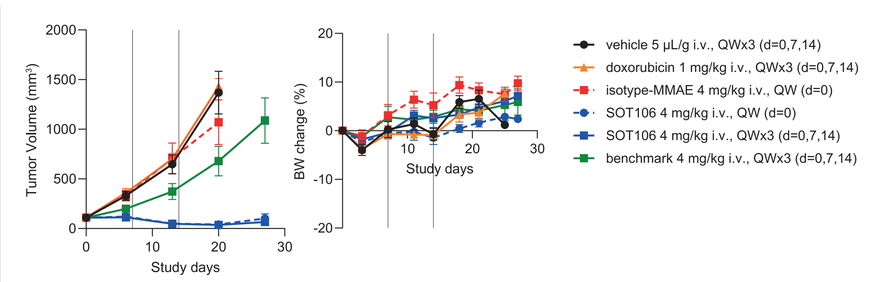
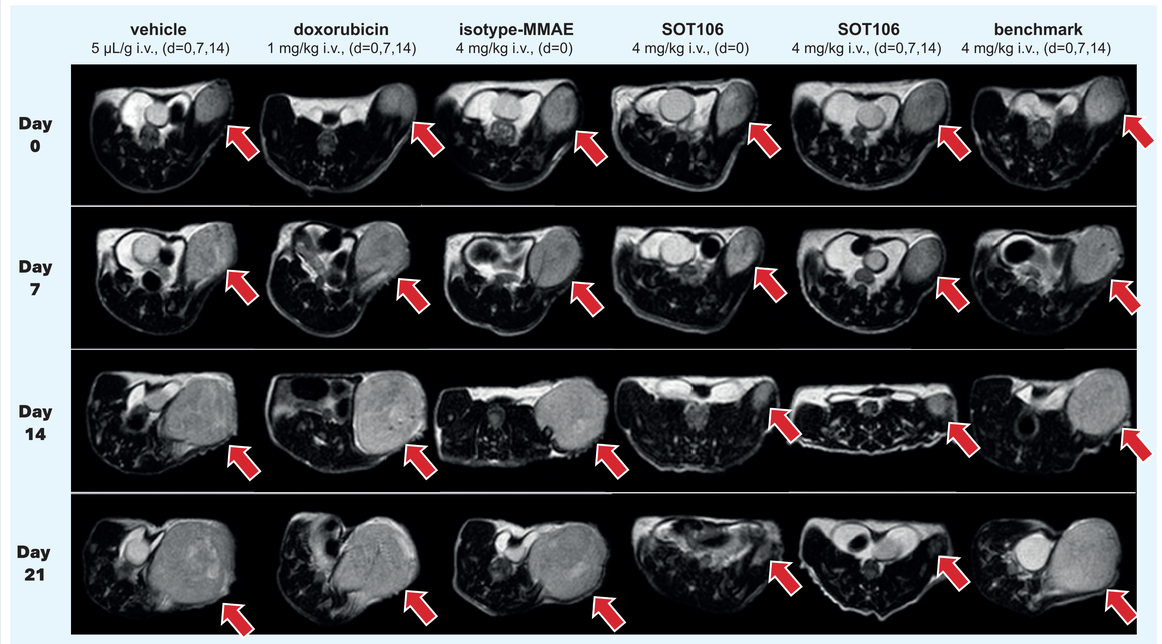


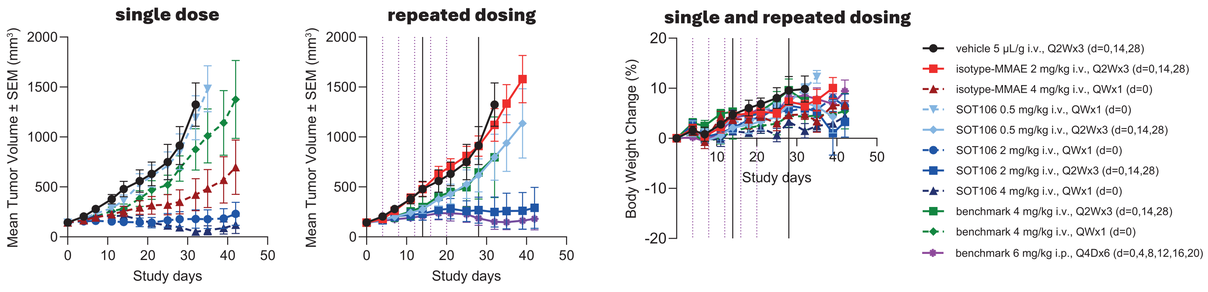
Figure 3: *In vivo* efficacy of SOT106 in pediatric OS PDX model implanted in the femur of mice and respective MRI scans. Tumor response compared to the benchmark, including isotype control and standard of care; n = 5. Data are displayed as means ± SEM.

Orthotopic model



SOFT TISSUE SARCOMA

Leiomyosarcoma PDX (LRRC15^{high})



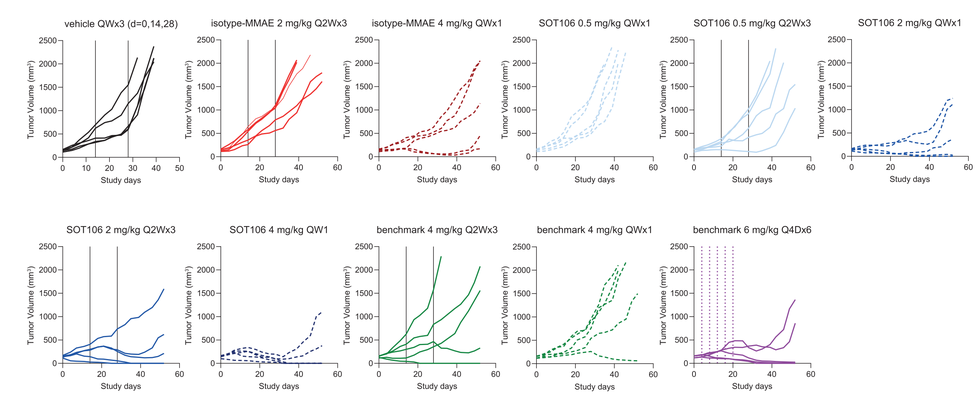


Figure 4: *In vivo* efficacy of SOT106 in leiomyosarcoma PDX model. Tumor response to varying concentrations and dosing schemes of SOT106 compared to the benchmark, including the isotype control; n = 5. Data are displayed as means ± SEM.

For more information, please contact Michaela Fojtů, Ph.D. at fojtu@sotio.com.

DISCLOSURE: Michaela Fojtů (presenting author) is a full-time employee of SOTIO Biotech a.s.