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SOT106, a novel best-in-class antibody-drug conjugate targeting LRRC15, to treat sarcomas and other advanced solid cancers

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sotio

Disclosure Information

Michaela Fojtů, Ph.D.

I have the following relevant financial relationships to disclose:

Employee of: SOTIO Biotech a.s.

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TARGETING MESENCHYMAL TUMORS, RARE CANCERS OF CONNECTIVE TISSUE

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- LRRC15 is a transmembrane protein involved in cell-cell and cell-ECM interactions
- Normal tissue expression is low and limited to mesenchymal cells in restricted tissue types (tonsils, hair follicles)
- LRRC15 is expressed directly on tumor cells in mesenchymal tumors and on TGF-β–driven cancer-associated fibroblasts (CAFs) within the stroma of numerous solid tumors
- Targeting LRRC15$^+$ fibroblasts relieves CD8$^+$ T-cell immunosuppression

Article

LRRC15$^+$ myofibroblasts dictate the stromal setpoint to suppress tumour immunity

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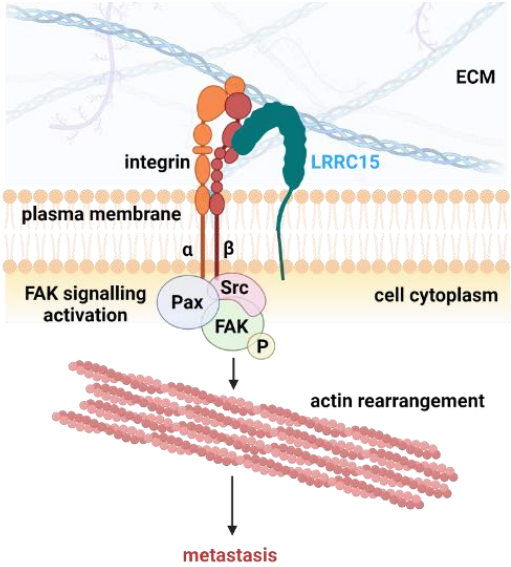

LRRC15 and its function in enhancing cancer metastasis via focal adhesion kinase signaling activation.
Adapted according to Upasana *et al.*, Cancer research vol. 82,9 (2022): 1675-1681, created with BioRender.com.

LRRC15 is expressed on mesenchymal tumors and in the tumor stroma

LRRC15 EXPRESSION ON CANCER AND STROMAL CELLS

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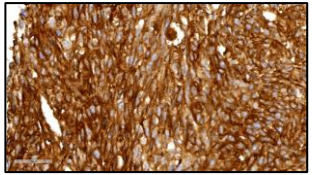
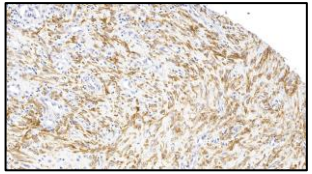
LRRC15 expression mainly on tumor cells

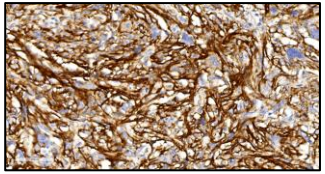
Osteosarcoma



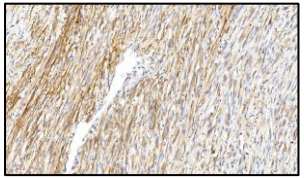
Chondrosarcoma



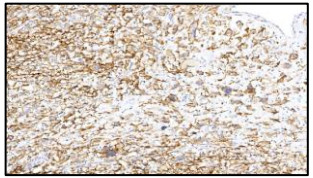
Undifferentiated pleomorphic sarcoma



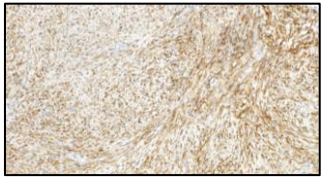
Leiomyosarcoma



Rhabdomyosarcoma

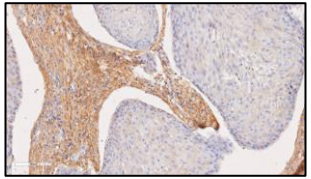


Fibrosarcoma

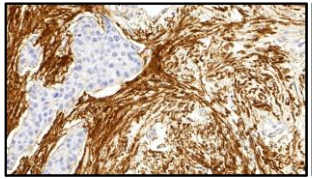


LRRC15 expression mainly on stromal cells

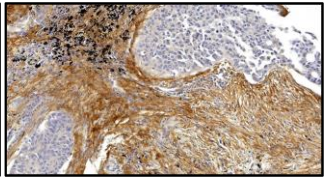
HNSCC



Breast cancer



Lung squamous cancer



HNSCC = head and neck squamous cell carcinoma, UPS = undifferentiated pleomorphic sarcoma, STS = soft tissue sarcomas

Tumor type	% of patients with ≥10% of LRRC15⁺ cells*	# of samples tested
Osteosarcoma (adult)	77	51
Osteosarcoma (children)	59	37
Chondrosarcoma	58	38
UPS	41	79
Leiomyosarcoma	40	30
Rhabdomyosarcoma	30	23
Fibrosarcoma	8	25
Synovial sarcoma	10	41
Liposarcoma	0	24
Other STS subtypes	35	11
HNSCC**	95	87
Breast cancer primary/LN metastasis**	90/64	50/50
Lung squamous cancer**	55	123

*IHC score defined as presence of ≥10% LRRC15⁺ cells in tumor tissue
** stromal score

SOT106 KEY MOLECULAR FEATURES UTILIZING LIGACHEM BIOSCIENCES´S CLINICALLY-VALIDATED CONJUALL™ ADC PLATFORM

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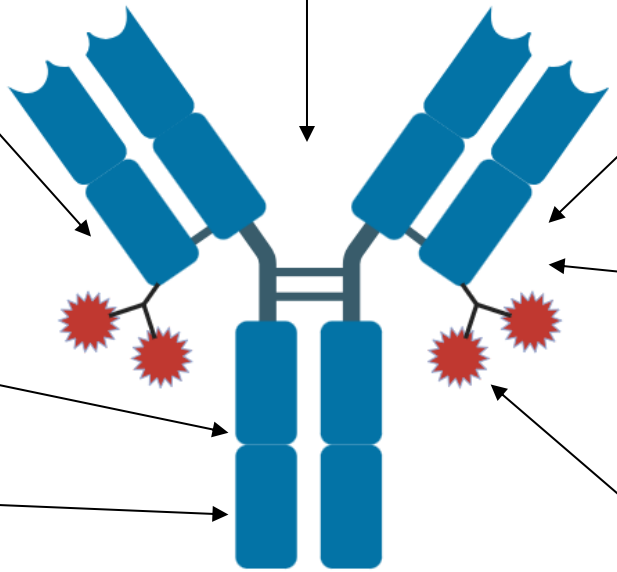
LigaChemBio
ConjuALL™

Novel humanised antibody enabling rapid internalization

Site-specific and homogenous conjugation to mAb light chains

Enzymatically attached isoprenoid spacer



Branched linker enabling DAR=4

IgG1 backbone

LALA mutation for effector function inhibition

MMAE with tumor-selective payload release via lysosomal β-glucuronidase cleavage

EFFICIENT BINDING, INTERNALIZATION, AND KILLING OF LRRC15-POSITIVE GLIOBLASTOMA CELLS

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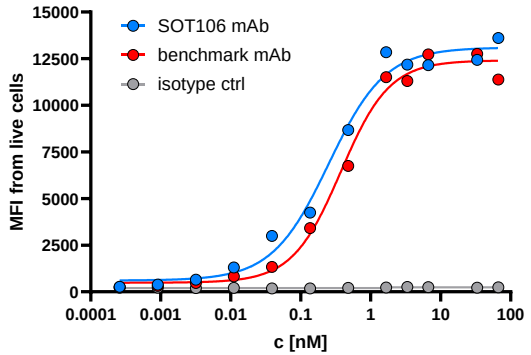
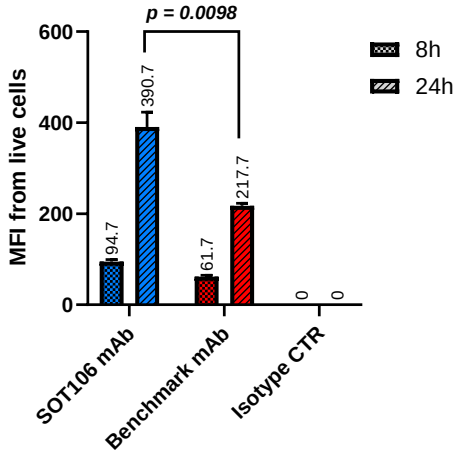
U118 MG, IHC LRRC15^{HIGH}

Binding



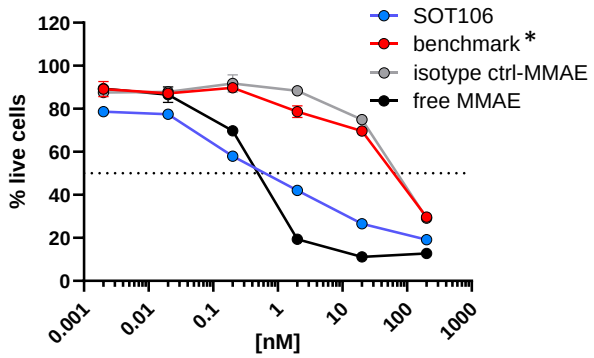
IC_{50} = 0.37 – 0.25 nM

Internalization



The isotype control signal was subtracted from all conditions to reduce unspecific background

Cytotoxic assay (120h)



IC_{50} = 0.65 nM

* benchmark = ABBV-085, LRRC15 targeting ADC with DAR2 mc-vcMMAE, in previous Phase I clinical trial ORR in sarcoma 20%

SOT106 clinical lead candidate outperforms clinical benchmark

ANTI-TUMOR EFFICACY IN A PDX SARCOMA MODEL
HIGH-GRADE LEIOMYOSARCOMA – LRRC15^{HIGH}

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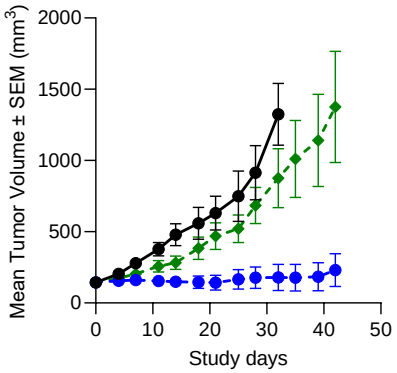
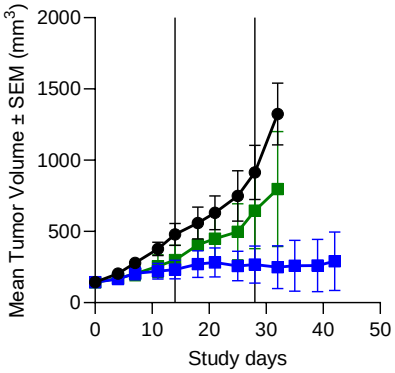
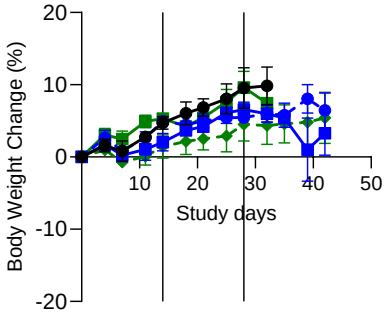
single dose

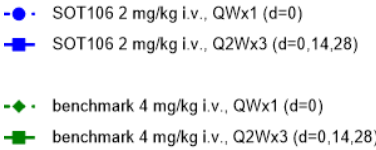


repeated dosing



body weights



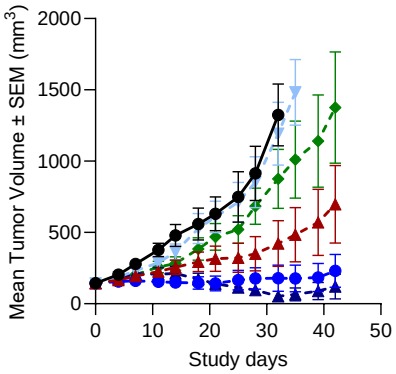


SOT106 - MMAE DAR4
benchmark - MMAE DAR2

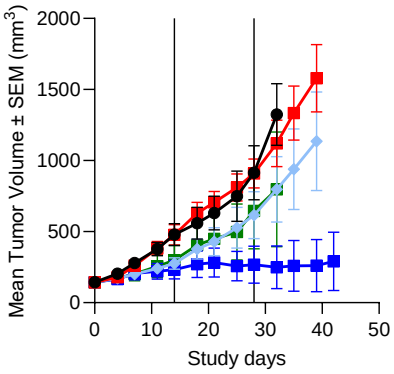
SOT106 outperforms benchmark in MMAE-equimolar comparison following single dose as well as repeated administrations

ANTI-TUMOR EFFICACY IN A PDX SARCOMA MODEL
HIGH-GRADE LEIOMYOSARCOMA – LRRC15^{HIGH}

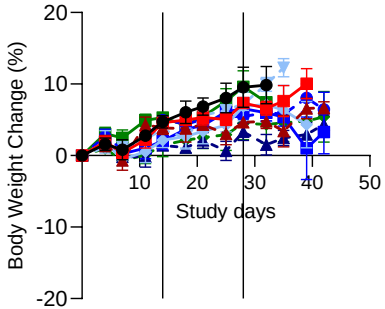
single dose

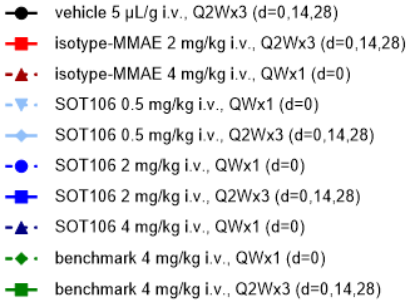


repeated dosing



body weights





SOT106 - MMAE DAR4
benchmark - MMAE DAR2

SOT106 outperforms benchmark in MMAE-equimolar comparison following single dose as well as repeated administrations

SOT106: EXCEPTIONAL EFFICACY IN OSTEOSARCOMAS – LRRC15^{LOW}

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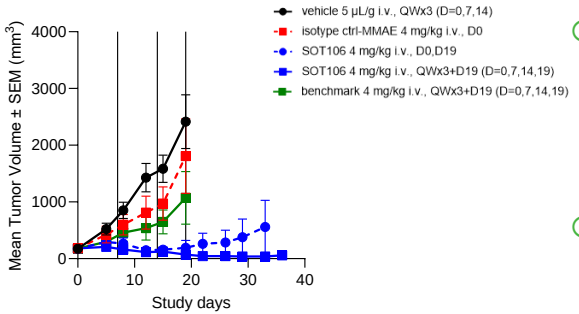
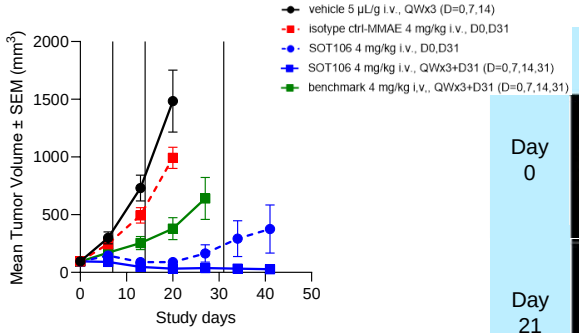
- female, 16 years old
- metastatic osteosarcoma

H = 66.4

SUBCUTANEOUS MODEL

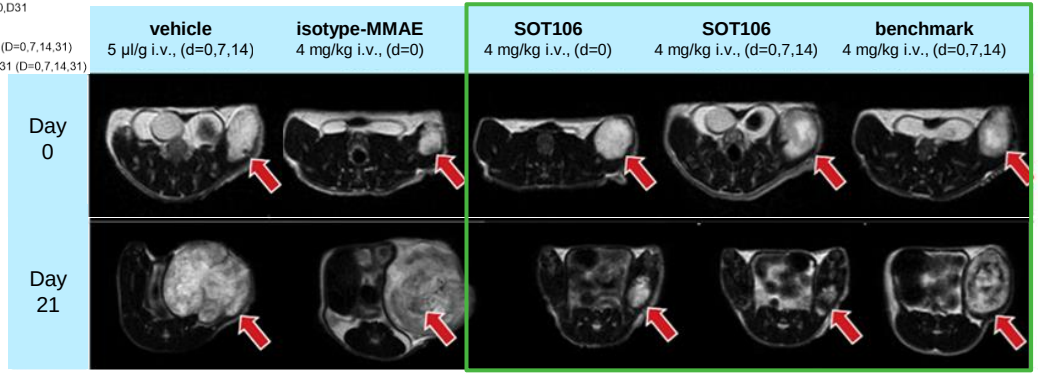


ORTHOTOPIC MODEL*



* patient tumor grafts implanted into the femurs of mice

- SOT106 demonstrates exceptional efficacy in pediatric LRRC15 low-expressing PDX models, further supporting its therapeutic potential across a broad range of expression levels
- It achieves significant tumor regression where the benchmark therapy proves to be ineffective, even after a single dose administration



ANTI-TUMOR EFFICACY IN A PANEL OF TARGET-POSITIVE PDX MODELS

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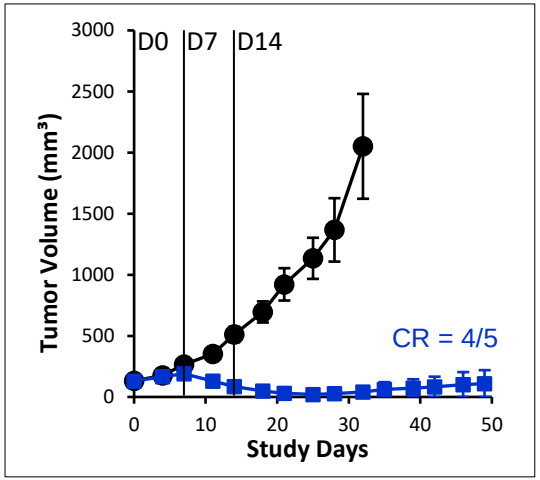
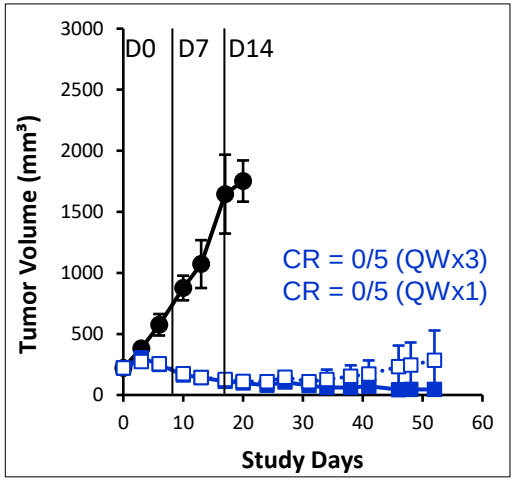
NSCLC, SCC PDX
carcinosarcoma, Crizotinib-resistant
LRRC15^{high}



NSCLC = non-small-cell lung cancer
SCC = squamous cell carcinoma
CR = complete response

HNSCC PDX
poorly differentiated, metastatic
LRRC15^{high}



HNSCC = head and neck squamous cell carcinoma
CR = complete response

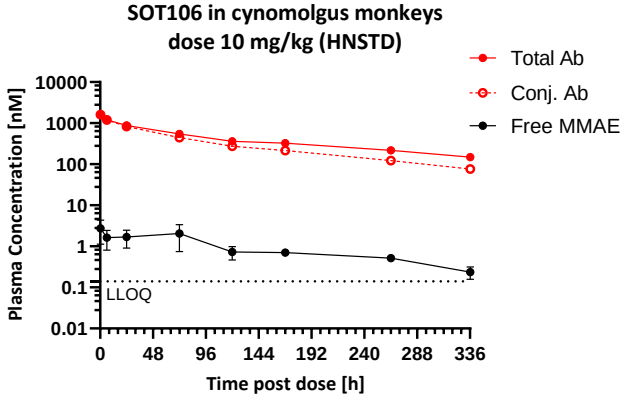
- vehicle i.v., QWx3 (d=0,7,14)
- SOT106 4 mg/kg i.v., QWx1 (d=0)
- SOT106 4 mg/kg i.v., QWx3 (d=0,7,14)

Complete responses and potent antitumor efficacy observed across a range of LRRC15-positive indications, including therapy-resistant model

SOT106 TOXICOLOGY AND PK PROFILE

- Cynomolgus monkey is the only relevant species for SOT106 toxicological assessment based on cross-reactivity
- Dose levels tested: 5, 10 and 15 mg/kg i.v. Q2W with 2-week observation periods → **10 mg/kg considered as preliminary HNSTD**
- **Estimated therapeutic index of ~40** (based on allometric scaling)
- Linear PK in cyno monkeys in the dose range of 5 – 15 mg/kg
- Good *in vivo* stability in plasma over the course of 14 days
- Half-life of ~ 4.5 - 6 days supporting Q3W dosing in patients

Species	Dose [mg/kg]		Half-life [days]	AUC_{inf} [h*µg/mL]
Mouse (tumor-bearing)	1	Effective	6	2,630
	2	Effective	6	5,260
Cynomolgus monkey	10	HNSTD	4.5 - 6	25,381



Concentration of deconjugated MMAE in plasma samples did not exceed 3 ng/mL

Favorable safety and PK profile, good stability in vivo, high therapeutic index

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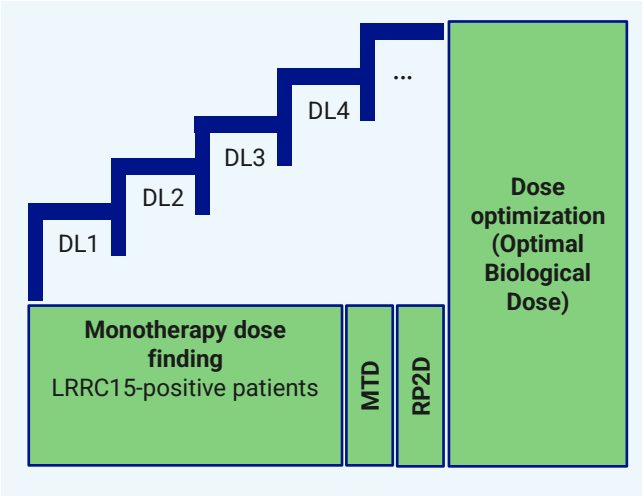
CLINICAL DEVELOPMENT STRATEGY FOR SOT106

DEVELOPMENT TOWARDS PHASE I

- Clinical candidate selected
- IND enabling CMC and GLP tox activities initiated, with IND filing planned for Q4 2026
- Parallel development of companion diagnostic with leading CDx partner
- Clinical plan includes dose escalation and expansion in LRRC15-positive tumors
- **Solid responses in sarcoma patients expected given prior clinical POC with benchmark and substantially improved molecule profile of SOT106**

PHASE I PRELIMINARY STUDY OUTLINE



- Diagnostic assay used to prospectively select LRRC15^{+} patients

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SUMMARY

- Clinically validated sarcoma target: LRRC15 is expressed at high frequency on many mesenchymal tumors and on CAFs within the stroma of numerous solid tumors. Highly restricted normal tissue expression
- Proprietary humanized mAb candidates available – substantially improved properties vs benchmark
- Utilizing **LigaChem Biosciences'** proprietary and highly validated ADC platform
  - **ConjuAll™** site-specific enzymatic conjugation by prenyl transferase
  - Cancer-selective toxin release by proprietary **beta-glucuronide linker**
  - Clinically validated tubulin inhibitor (**MMAE, DAR=4**) displaying profound bystander effect
- SOT106 displays robust and substantially improved *in vivo* activity in multiple CDX/PDX models compared to benchmark
- In NHP, a high dose of 10 mg/kg is considered as preliminary HNSTD; findings are consistent with known MMAE-mediated toxicity profile, TI ~ 40
- Proprietary, CDx assay to be used for prospective patient selection in PhI/II