Discovery of ZL-6201, a Novel LRRC15-targeting Antibody Drug Conjugate (ADC) for the Treatment of Sarcomas and Epithelial Solid Tumors

Abstract #2399

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Background and Introduction

Leucine-rich repeat-containing protein 15 (LRRC15) is a transmembrane protein involved in cell-cell and cell-extracellular matrix interactions. It is overexpressed in tumors of mesenchymal origin which include sarcomas, glioblastoma and melanoma, where its expression has been implicated in promoting metastasis. Additionally, LRRC15 is upregulated in cancer-associated fibroblasts (CAFs) that are found in the tumor microenvironment (TME) of multiple epithelial tumors. Its predominant expression in tumors and CAFs, coupled with minimal or absent expression in normal cells, makes LRRC15 a selective and potentially effective therapeutic target for antibody-drug conjugate (ADC) development.

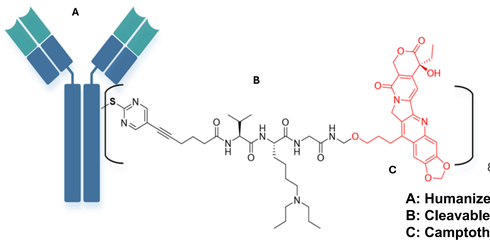
ZL-6201 is an innovative ADC targeting LRRC15, built on the tumor microenvironment-activable linker-payload (TMALIN®) platform. It comprises a humanized anti-LRRC15 antibody, a hydrophilic protease-cleavable linker, and a novel camptothecin-derived topoisomerase I inhibitor payload C24. Site-specific conjugation yields an average drug-to-antibody ratio (DAR) of 8. ZL-6201 binds human and cynomolgus monkey LRRC15 with high affinity and specificity.

In vitro, cell-surface binding and target-dependent internalization selectively occurred in tumor cells expressing LRRC15. This resulted in C24 payload release, the induction of DNA damage response, cell cycle arrest, and ultimately cytotoxicity to tumor cells. The internalization of ZL-6201 in LRRC15-expressing human tumor cells and CAFs, followed by payload release and diffusion, mediated cytotoxicity against LRRC15-negative tumor cells in co-culture via the bystander effect.

In vivo studies demonstrated efficacy of ZL-6201 in human patient-derived xenograft (PDX) sarcoma models expressing endogenous LRRC15. Additionally, CAF-mediated payload release and the resultant efficacy were evaluated in two model systems: (1) cell-derived xenograft (CDX) models with low or no endogenous LRRC15 expression in tumor cells but high LRRC15 expression in mouse-derived CAFs using a mouse-reactive ZL-6201 surrogate, and (2) syngeneic tumor models with human LRRC15 knock-in mice using ZL-6201. Both ZL-6201 and the surrogate were well tolerated and demonstrated dose-dependent anti-tumor activity. Finally, ZL-6201 showed acceptable toxicokinetic and safety profiles in non-human primates (NHP).

Collectively, these data support advancing ZL-6201 into clinical development as a therapeutic candidate for sarcomas and epithelial solid tumors characterized by LRRC15 expression within the tumor microenvironment.

Chemical Structure of ZL-6201



A: Humanized anti-LRRC15 IgG_1 mAb
B: Cleavable tripeptide-based linker
C: Camptothecin derivative payload, C24

LRRC15 is Expressed in a Variety of Solid Tumors with High Unmet Need

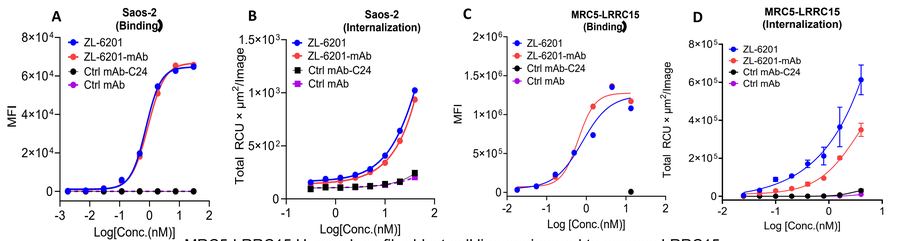
Sarcoma – Tumor Cells

Tumor type	% LRRC15⁺ tumor cells
Osteosarcoma	87% (40/46)
Chondrosarcoma	71% (12/17)
Liposarcoma	55% (16/29)
Sarcomatoid carcinoma	52% (21/40)
UPS	49% (36/73)
Leiomyosarcoma	44% (16/36)
Synovial sarcoma	28% (11/39)
Rhabdomyosarcoma	19% (7/36)

Non-Sarcoma – Fibroblasts

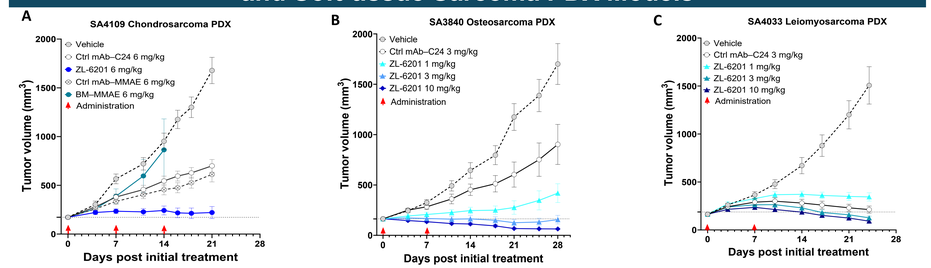
Tumor type	%LRRC15⁺ fibroblasts
Breast	97% (36/37)
TNBC	96% (100/104)
Lung	92% (33/36)
HNSCC	89% (33/37)
Colon	86% (24/28)
Stomach	73% (27/37)
PDAC	71% (24/34)
Malignant melanoma	51% (39/77)
HCC	41% (9/22)
Ovary	44% (16/36)

ZL-6201 Bound and Was Efficiently Internalized in LRRC15⁺ Cells *in vitro*



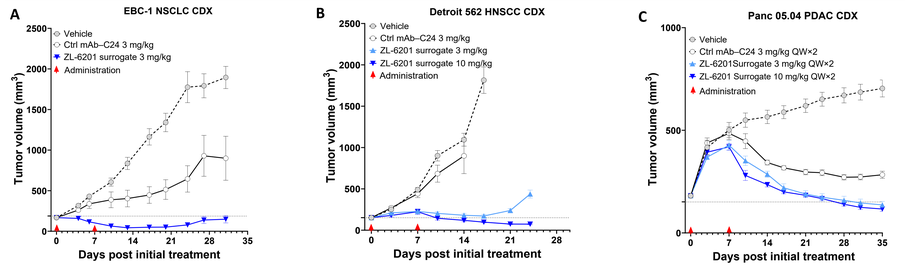
MRC5-LRRC15:Human lung fibroblast cell line engineered to express LRRC15.

ZL-6201 Drove Dose-dependent Tumor Growth Inhibition in LRRC15⁺ Bone and Soft-tissue Sarcoma PDX Models

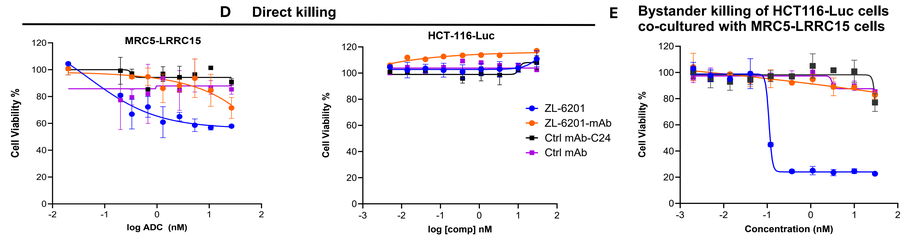


LRRC15 is highly expressed on the tumor cell surface of the following sarcomas: SA4109 chondrosarcoma PDX (**A**); SA3840 osteosarcoma PDX derived from a 12-year-old female patient (**B**); SA4033 leiomyosarcoma PDX (**C**).

ZL-6201 Surrogate Efficacy in Non-sarcoma CDX Models is Mediated by LRRC15⁺ Mouse CAFs and a Strong Bystander Effect

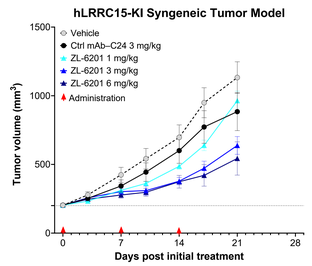


1) In non-sarcoma solid tumor CDX models NSCLC EBC-1 (**A**), HNSCC Detroit 562 (**B**), and pancreatic cancer Panc 05.04 (**C**), while tumor cells exhibit minimal LRRC15 surface expression, it is highly expressed on the surface of stromal cells from CAFs. To investigate the anti-tumor effect, a rodent cross-reactive surrogate ADC was employed.



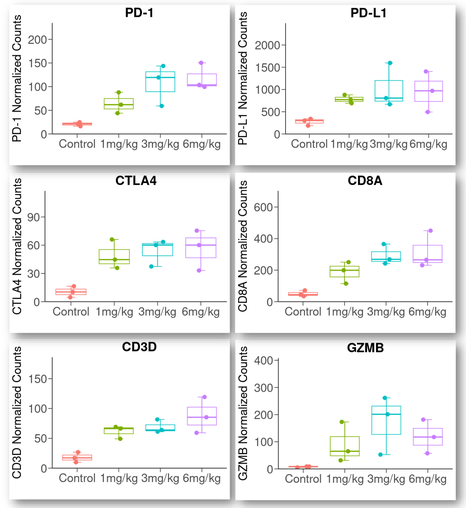
2) ZL-6201 demonstrated low cytotoxicity to MRC5-LRRC15 fibroblast cells and no effect on LRRC15-negative HCT116-Luc cells in monoculture (**D**). In a co-culture of HCT116-Luc and MRC5-LRRC15 cells (**E**), ZL-6201 induced potent killing of the HCT116-Luc cells, indicating a strong bystander effect mediated by LRRC15⁺ fibroblast cells.

ZL-6201 Exhibited Dose-dependent Efficacy and Activated Immune Response in hLRRC15-KI Syngeneic Tumor Model

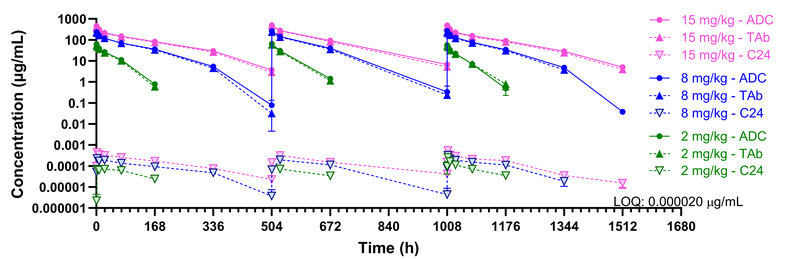


1) ZL-6201 exhibited dose-dependent tumor growth inhibition in hLRRC15-KI syngeneic tumor model.

2) RNA-seq analysis of tumors from ZL-6201-treated mice demonstrated the induction of a pro-inflammatory tumor microenvironment, evidenced by the concurrent upregulation of immune checkpoint molecules (PD-1, PD-L1, CTLA-4) and enhanced activity of T cell and NK cell signaling pathways.



ZL-6201 Preclinical Toxicology and Toxicokinetic Profile



1) ZL-6201 is stable in serum across tested species *in vitro* and *in vivo*.

2) ZL-6201 exhibited dose-dependent increases in exposure without significant serum accumulation in cynomolgus monkeys.

3) ZL-6201 demonstrated a manageable toxicity profile in in NHP studies at doses up to 25 mg/kg (Q3W*3), consistent with the established TMALIN® platform.

Key findings including: Reversible, dose-dependent decreases in neutrophils, lymphocytes, and erythrocytes.

Conclusions

1) **Broad Target Prevalence**: LRRC15 is highly expressed across multiple solid tumor types, representing a significant opportunity in areas of high unmet medical need.

2) **Potent and Specific Target Engagement**: ZL-6201 demonstrated strong binding and rapid internalization specifically in LRRC15⁺ tumor and fibroblast cells.

3) **Robust Anti-tumor Efficacy**: ZL-6201 and the surrogate drove deep tumor regression in both sarcoma PDX and non-sarcoma CDX models. Efficacy in non-sarcoma CDX models was specifically mediated by LRRC15⁺ fibroblast cells and a potent bystander effect.

4) **Clear Clinical Path**: With FDA IND clearance secured and Phase 1 dose escalation ongoing, ZL-6201 is positioned as a first- and best-in-class candidate among LRRC15-targeted ADCs.

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