QL315, A CD3 Bispecific Antibody Redirecting T cell Activation to Tumor Stroma Antigen LRRC15

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Introduction

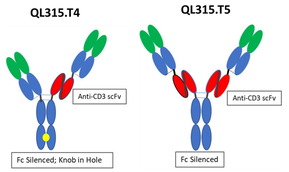
The tumor stroma is a critical component of tumor microenvironment, which involves in supporting tumor growth, yielding therapy resistance and orchestrating an immune suppressive environment. Targeting tumor stroma has becoming an attractive strategy to improve cancer therapy. Leucine-rich repeat containing 15 (LRRC15) is highly expressed on stromal fibroblasts of multiple solid tumors, as well as cancer cells of mesenchymal origin. With its low expression in normal tissues, these characteristics together make it an ideal tumor stroma target.

Targeting LRRC15 as an antibody-drug conjugate (ABBV-085) has demonstrated clinical benefit in LRRC15 positive sarcoma patients (1-2). In pre-clinical models, ABBV-085 suppressed tumor growth in which only stromal cells but not cancer cells express LRRC15 (1). Furthermore, targeting LRRC15 improved therapeutic effect of anti-PDL1 treatment (3).

To explore the potential of T cell-mediated immunotherapy to LRRC15-expressing tumor stroma, we have produced IgG-based anti-CD3 x anti-LRRC15 bispecific molecules with excellent stability. The optimized molecule, QL315, robustly and conditionally induced T cell activation and proliferation only when LRRC15 was present. Furthermore, QL315 potently induced tumor cell lysis in vitro and led to significant tumor regression in mouse xenograft models.

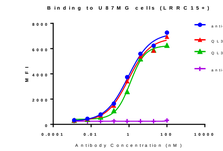
Toxicologic evaluation of QL315 in cynomolgus monkeys showed antibody-like stability and half-life, and good tolerability with no obvious toxicity. Transient changes of circulating blood cell homeostasis and cytokine increase was observed.

Design and Validation

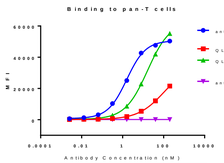


Molecule Antigen	Tested	KD (M)	kon(1/Ms)	kdis(1/s)
huCD3ε	QL315.T4	1.19E-08	9.48E+05	1.13E-02
huCD3ε	QL315.T5	1.49E-08	5.30E+05	7.89E-03
huLFL2	QL315.T4	6.43E-09	4.09E+05	2.63E-03
huLFL2	QL315.T5	6.85E-09	4.05E+05	2.78E-03

QL315 is built on a silenced human IgG1 backbone to eliminate Fc gamma receptor dependent functions. QL315.T4 comes in a 2+1 format while QL315.T5 has both anti-CD3 and anti-LRRC15 on each arm.



anti-LRRC15 mAb	QL315.T4	QL315.T5
EC50(nM)	0.8796	0.927	1.178

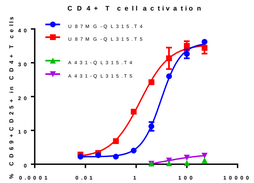


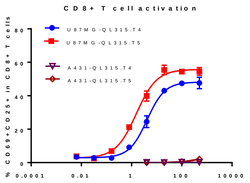
anti-CD3 mAb	QL315.T4	QL315.T5
EC50(nM)	1.582	106.6	16.44

Both QL315.T4 and QL315.T5 showed good binding affinity to LRRC15+ cancer cells and human T cells.

Functional Evaluation

a. QL315 induced human T cell activation only in the presence of LRRC15 expression on co-cultured cancer cells



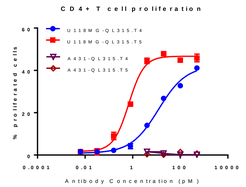


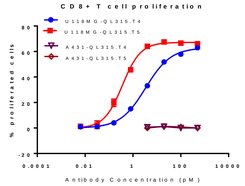
U87MG	QL315.T4	QL315.T5
EC50(pM)	9.675	1.472

U87MG	QL315.T4	QL315.T5
EC50(pM)	4.141	1.545

Human PBMCs were incubated with antibody and cancer cells for 2 days and T cell activation was determined through co-expression of CD25 and CD69 on T cells.

b. QL315 promoted human T cell proliferation with LRRC15+ tumor cells, which was diminished without LRRC15 expression on tumor cells.



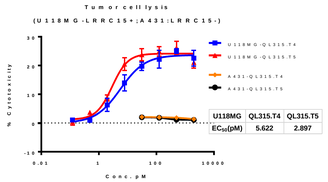


U118MG	QL315.T4	QL315.T5
EC50(pM)	12.12	0.688

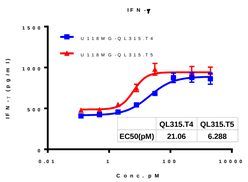
U118MG	QL315.T4	QL315.T5
EC50(pM)	3.399	0.3625

Human pan-T cells were isolate from PBMCs and incubated with antibody and cancer cells for 5 days. Proliferation was tracked through brightness of CellTrace dye labeled on T cells for measuring daughter cell generation.

c. QL315 stimulated tumor cell lysis, along with interferon (IFN)-γ release, by co-cultured T cells in a LRRC15 expression-dependent manner.



U118MG	QL315.T4	QL315.T5
EC_{50}(pM)	5.622	2.897

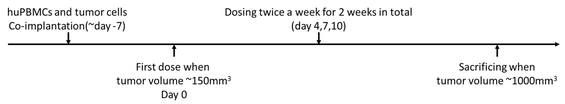


QL315.T4	QL315.T5
EC50(pM)	21.06	6.288

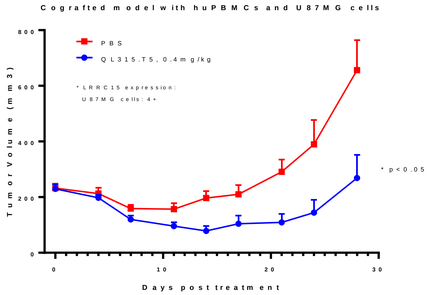
* Human pan-T cells were isolated an incubated with antibody and cancer cells for 3 days. Tumor cell lysis was measured by Cytotox-Glo from Promega and ELISA was performed for IFN-γ detection. Tumor cell lysis, as well as IFN-γ production, was nicely induced by QL315.T4 and QL315.T5 with U118MG cells that are LRRC15+. A431 didn't show detectable level of LRRC15 expression and failed in inducing tumor cell lysis with QL315 molecules.

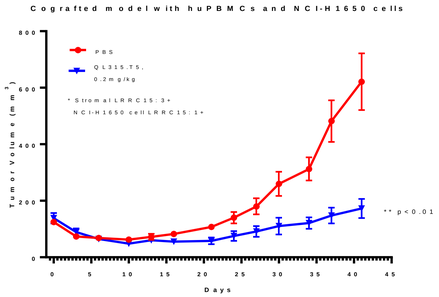
In Vivo Efficacy Study

Study Design:



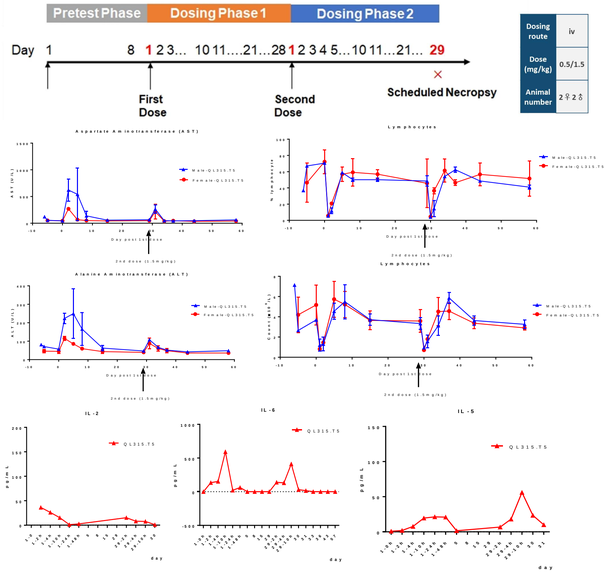
QL315.T5 significantly suppressed tumor growth





* LRRC15 is dominantly expressed in cancer cells in U87MG model compared to stromal cells, while LRRC15 expression level in stromal tissue is higher than cancer cells in NCI-H1650 model. Tumor volumes are indicated as mean ± SEM; n = 5. Significance was calculated via two-way ANOVA.

Safety study in cynomolgus monkeys



QL315.T5 in monkeys showed good tolerability with no change in body weight, food intake, or persistent change in organ function. Transient change on circulating blood cell homeostasis and cytokine were observed.

* Results of cytokine production combined data from both males and females.

Summary

- QL315 showed good affinity to both CD3 and LRRC15 as a bispecific antibody in vitro.
- With its drug-like properties, QL315 demonstrate promising capability in T cell activation, proliferation and promoting tumor cell death in vitro.
- QL315 successfully inhibited tumor growth in mouse xenograft models, even LRRC15 is more expressed in stroma compared to cancer cells.
- Toxicity study in monkeys revealed ideal tolerability of QL315, further strengthening the therapeutic potential of QL315 in treating patients through targeting LRRC15.

Reference

1. Purcell JW, Tanlimco SG, Hickson J, Fox M, Sho M, et al. LRRC15 Is a Novel Mesenchymal Protein and Stromal Target for Antibody–Drug Conjugates. Cancer research. 2018;78:4059-4072.
2. Demetri GD, Luke JJ, Hollebecque A, Powderly JD, Spira AI, et al. First-in-human phase 1 study of ABBV-085, an antibody-drug conjugate (ADC) targeting LRRC15, in sarcomas and other advanced solid tumors. American Society of Clinical Oncology; 2019
3. Dominguez CX, Müller S, Keerthivasan S, Koeppen H, Hung J, et al. Single-Cell RNA Sequencing Reveals Stromal Evolution into LRRC15(+) Myofibroblasts as a Determinant of Patient Response to Cancer Immunotherapy.Cancer Discov. 2020;10:232-253.