QL401, a tumor targeted CD47 and PD-L1 blocker without blood toxicity

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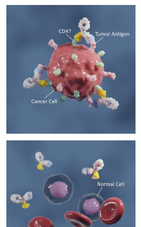
Background

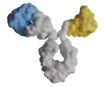
Upregulation of CD47, a "Don't Eat Me" signal, is observed in nearly all solid and hematological malignancies. Engagement of CD47 on tumor cells with SIRPα on macrophages inhibits phagocytosis of tumor cells. Anti-CD47 antibody blocks the CD47 – SIRPα engagement and reactivates phagocytosis of tumor cells by macrophages. The ubiquitous expression of CD47 on normal cells, including red blood cells, presents a therapeutic challenge. Systemic targeting of CD47, by either anti-CD47 monoclonal antibodies or SIRPα-Fc fusion proteins, yielded only moderate clinical benefit due to severe adverse side effects, mainly anemia. QL401 is PD-L1 x CD47 bispecific antibody with reduced binding to red blood cells while retaining potent phagocytic activation of macrophages in vitro and delayed tumor growth in vivo.

Design Parameters

PD-L1 Binding
- Promotes tumor targeting and accumulation
- Reduces binding to normal cells not expressing PD-L1
- Blocks the PD-1 / PD-L1 checkpoint pathway

CD47 Binding
- Blocks SIRPα binding to CD47 the "Don't Eat Me" signal, allowing phagocytosis
- Monovalent arm reduces binding to normal cells expressing only CD47

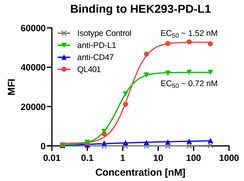


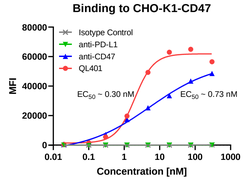


Human IgG4 Fc
- No ADCC or CDC, no depletion of effector cells
- Human IgG4 provides an ADCP "Eat Me" signal

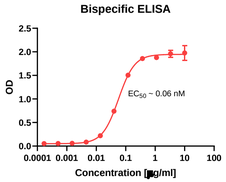
Functional Validation

Each arm of QL401 bound to PD-L1 or CD47 on cells with affinity comparable to that of the parental antibodies.



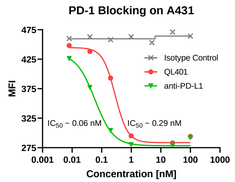


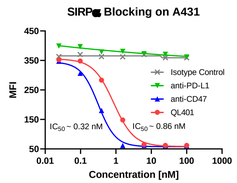
QL401 simultaneously binds to PD-L1 and CD47 as shown by a sandwich ELISA. PD-L1 was coated onto plates and QL401 was subsequently captured. His-tagged CD47 was used for detection.



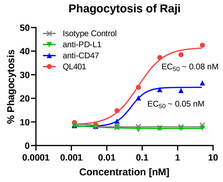
In Vitro Activity

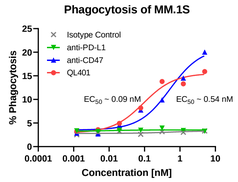
QL401 blocked the binding of PD-1 and SIRPα on A431 cells by flow cytometry.





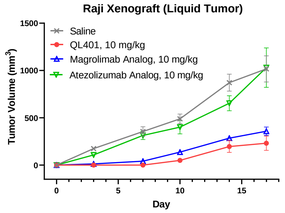
QL401 induced the phagocytosis of Raji and MM.1S cells in vitro with improved potency compared to that of the parental CD47 monoclonal antibody. Macrophages were derived from PBMC by culturing with M-CSF and IL-10. Target cells were labeled with CSFE and incubated with macrophages for 2 hours at 37 °C with the indicated antibodies on an ultra-low binding plate. Macrophages were stained with anti-CD36 antibodies and analyzed on a flow cytometer looking for a double positive cell population.

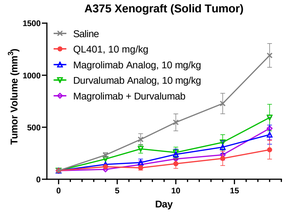




In Vivo Efficacy

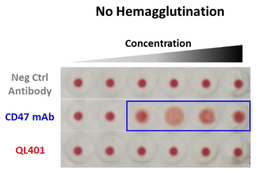
The anti-tumor efficacy of QL401 in vivo was comparable to that of clinical anti-CD47 and anti-PD-L1 antibodies or their combination. Raji and A375 were implanted followed by human PBMC and treatment of the indicated antibodies.



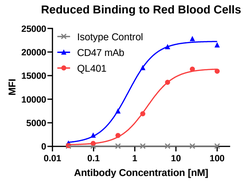


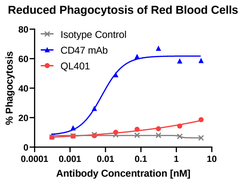
Blood Safety

QL401 did not induce hemagglutination in contrast to CD47 monoclonal. Fresh whole blood was diluted with PBS and aliquoted onto a U-bottom 96-well plate. Antibodies were added and incubated for 2 hours at room temperature.



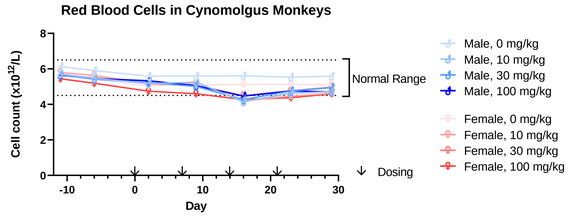
QL401 has reduced binding to red blood cells when compared to the parental CD47 monoclonal and induced significantly less phagocytosis of red blood cells than the CD47 monoclonal antibody.





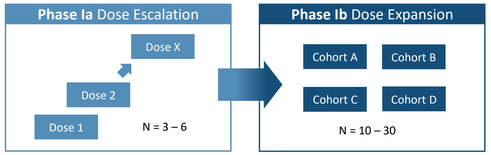
NHP Toxicology

QL401 was safe in cynomolgus monkeys up to 100 mg/kg, with red blood cell count remained mostly within the normal range.



Phase 1 Clinical Study

- Ongoing, first patient dosed in March of 2022.
- Objectives: safety, tolerability, and early efficacy
- Format: i3 + 3, QW IV infusion, DLT period = 21 days
- Indications: locally advanced, recurrent or metastatic solid tumors, or hematological tumors (r/r AML, MDS, PTCL)



Summary

- QL401 blocks CD47, the "Don't Eat Me" signal and provides an "Eat Me" signal at the same time
- QL401 activates both innate (phagocytosis) and adaptive (PD-L1 blockade) immune responses
- QL401 has reduced binding to red blood cells, is safe in cynomolgus monkeys up to 100 mg/kg without severe anemia or the need of a priming dose
- A Phase 1 clinical trial is ongoing

Disclosures

I Tang, L Schwimmer, S Gu, WW Prior, HV Tran, A Chan, A McClain, and S Chen are current or former employees of QLSF Biotherapeutics, Inc. receiving salaried compensation and stock options.
C Cao, C Sun, M Si, and G Wang are current employees of QILU Pharmaceutical Co., Ltd. receiving salaried compensation.