**QL415, a tumor targeted IL-15 fusion protein stimulating both lymphoid and myeloid immune cells**

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**Background**

Cytokines are potent stimulators of the immune system and have long been investigated and used as therapeutics to treat cancer. However, free cytokines have a short half-life and the lack of tumor targeting often results in systemic toxicity. IL-15 is a stimulatory cytokine and its receptor shares the beta and gamma common chains with IL-2. In contrast to IL-2, IL-15 is more selective for NK and effector memory T cells, with less proliferative effect on Th2, making it a more preferred therapeutic candidate. QL415 is a PD-L1 x IL-15 fusion protein that was designed to enhance accumulation in tumors and prolong circulation in blood, thereby widening the therapeutic window.

**Design Parameters**

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<tr>
<th>PD-L1 Binding</th>
<th>Inhibits tumor targeting and accumulation</th>
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<td>Minimal toxicity associated with peripheral activation of immune effector cells</td>
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**Target Validation**

QL415 binds to NK92 cells expressing PD-L1, and to CHO-K1 cells expressing IL-2 receptor. By flow cytometry, QL415 specifically binds to PD-L1 and IL-2 receptor by demonstrated using a sandwich ELISA.

**In Vitro Activity**

QL415 blocked the binding of PD-1 on cells analyzed by flow cytometry. PD-1 blocking released the inhibitory signal and reactivated TCR signaling in an NFAT reporter assay.

QL415 induced the proliferation of IL-15 expressing NK92 and M07e cells. Phosphorylation of STAT5 downstream of IL-2 receptor was observed in M07e cells by flow cytometry.

QL415 was incubated with PBMC in the presence of A411 cancer cells expressing PD-L1. QL415 induced the proliferation of primary immune cells, selective for CD8+ T and NK cells. Each data point represents one of 4 donors.

QL415 induced the expression of NK-functional markers CD107α, granzyme B and perforin in a dose-dependent manner.

**In Vivo Efficacy**

QL415 induced the proliferation of mouse CD8+ and NK1.1+ cells in C57BL/6 mice following a single IV dose.

QL415 inhibited the growth of MC38-hPD-L1 tumors in C57BL/6 mice and instilled protective memory. Tumor-free mice were rechallenged with MC38-hPD-L1 and B16F10 cancer cells, but only B16F10 tumors grew.

QL415 was safe in cynomolgus monkeys up to 1.5 mg/kg after 5 repeated weekly s.c. dosing, well above the expected efficacious therapeutic dose. Expansion of CD8 T and NK cells was observed after the first dose, supporting the results shown in vitro as well as in vivo mouse model studies.

**Disclosures**

† I Tang, L Schimmel, M Jin, Shenda Gu, Wei Wei Prior, A Capaci, HV Tran, A Chan, A McClain, and S Chen are current or former employees of QLSF Biotherapeutics, Inc. receiving salary compensation and stock options.

C Cao, X Wu, T Xu, D Goring, X Chen, and X Su are current or former employees of QILU Pharmaceutical Co., Ltd. receiving salary compensation.

**NHP Toxicology**

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<tr>
<th>Dose (mg/kg)</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>0.001</td>
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<td>10.00</td>
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**Phase 1 Clinical Study**

- Objectives: safety, tolerability, and early efficacy as monotherapy or combination.
- Format: 3+3 IV infusion, DLT period = 28 days.
- Indications: locally advanced, recurrent or metastatic solid tumors

**Summary**

- QL415 is a potent PD-L1 targeted IL-15 cytokine fusion protein that is selective for effector T cells and NK cells.
- QL415 had robust activity in vivo and anti-tumor efficacy in vivo.
- QL415 was well-tolerated in cynomolgus monkeys.
- QL415 is currently being evaluated in a phase 1 dose escalation study.