Preclinical Development of LYL119, a ROR1-Targeted CAR T-Cell Product Candidate Incorporating Four Novel T-Cell Reprogramming Technologies to Overcome Barriers to Effective T Cell Therapy for Solid Tumors

Abstract 278
Viola C. Lam, Aileen Li, Meri Galindo Casas, Jennifer Barragan, Jessica Briones, Grant Vrats, Jia Lu, Purvina Sundar, Rowena Martinez, Candace Sim, Shobha Potluri, Omar Ali, Alexander S. Cheung, and Rachel C. Lynn
Lyell Immunopharma, Inc., South San Francisco, CA and Seattle, WA

Background
- T-cell exhaustion and lack of durable activation (defined as the ability of cells to proliferate, persist, and secrete cytokines) are key barriers to effective T-cell therapy in solid tumors.
- Lyell has developed multiple genetic and epigenetic T-cell reprogramming strategies to overcome these barriers.

Results
High NR4A3 genomic editing results in significantly reduced NR4A3 protein expression
- Within 3 days of T-cell therapy, NR4A3 KO ROR1 CAR T cells manufactured with or without Stim R and TIGIT technology had significantly reduced NR4A3 protein expression compared to non-edited T cells.

LYL119 demonstrates superior in vitro activity compared to ROR1 CAR T cells lacking one or more reprogramming technologies
- LYL119 exhibits an improved phenotype following antigen restimulation compared to non-edited ROR1 CAR T cells lacking one or more reprogramming technologies.
  - Further reduction of T-cell exhaustion
  - Increased cytokine production and significant down-regulation of multiple exhaustion-associated gene signatures

LYL119 exhibits an improved phenotype following antigen restimulation and expresses increased cytotoxicity, cytokine production, and durable antitumor activity
- LYL119 demonstrates superior cytotoxicity and sustained cytokine production following antigen restimulation compared to non-edited ROR1 CAR T cells.

Conclusions
- LYL119, which combines a NR4A3-overexpression, NR4A3 KO, Epi R protocol, and Stim R technology, exhibited:
  - Potent cytotoxicity and enhanced cytokine secretion upon antigen restimulation with multiple differences from non-edited ROR1-expressing solid tumor cell lines.
  - An enhanced memory-like and effector phenotype with reduced T-cell exhaustion after antigen restimulation.
  - Improved antitumor activity, superior ROR1 + CAR T-cell expansion, and improved survival in vivo compared to non-edited ROR1 CAR T cells.

Methods
- NSCLC patient-derived LYL119 products demonstrate robust cytotoxicity in vitro and in vivo.
- NSCLC patient-derived LYL119 demonstrates superior cytotoxicity compared to patient ROR1 Cem CAR T cells lacking 1 or 2 reprogramming technologies (Figure 7).

Abbreviations
- CAR: Chimeric antigen receptor
- CAR T: Chimeric antigen receptor T-cell
- CAR T cell: Chimeric antigen receptor T-cell
- CAR T product: Chimeric antigen receptor T-cell product
- CAR T therapy: Chimeric antigen receptor T-cell therapy
- CAR T cell therapy: Chimeric antigen receptor T-cell therapy
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References
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