Prioritying tumor types for treatment with a novel immunotherapy: LYC-55716 a small-molecule RORγ agonist

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BACKGROUND & STRATEGY

- RORγ (retinoic acid receptor–related orphan receptor γ) acts as a master control switch for the development and function of Th17 and Tc17 cells
- RORγ agonists, by enhancing Th17 and Tc17 cells, can mediate potent anti-tumor immune responses by decreasing immune suppression and increasing immune activation in preclinical studies (Figure 1)
- The first-in-class, oral, small-molecule LYC-55716 is an investigational agent that selectively activates RORγ
- Phase 1 clinical testing of LYC-55716 identified a pharmacodynamically active dose and demonstrated that this agent was well tolerated in cancer patients
- In preparation for Phase 2a expansion (NCT02929862), preclinical and bioinformatics assessments were performed to prioritize tumor types to include in the Phase 1/2a clinical trial

TARGET EXPRESSION

- Analysis of preclinical data indicated that the anti-tumor efficacy of an RORγ agonist was impacted by recruitment or enhancement of RORγ+ cells, but not baseline RORγ- levels (Figures 3 and 4)
- Correlation with post-treatment RORγ (RORC2) expression

TARGET BIOLOGY

- Certain sterols can function as RORγ ligands that partially activate RORγ, but sterol levels are likely low in exhausted T cells and can be influenced by cancer cells in the tumor microenvironment
- TCGA analysis of sterol efflux gene expression (a surrogate for endogenous ligand levels) revealed differential expression across tumor types (Figure 6)
- Tumor types with low sterol efflux will likely respond better to RORγ agonist

IMMUNE PROFILE

- Analysis of TCGA RNA sequencing data indicated high expression of T cell markers such as CD3e across cancer types, including those that have been reported to respond to treatment with checkpoint inhibitors (Figure 8)
- Review of the literature indicated a high mutational burden in the checkpoint inhibitor–approved tumor types
- Consideration of tumors with immune infiltrates, high mutational burden, and reports of prior immunotherapy responses highlighted 10 tumor types

CONCLUSION: TUMOR SELECTION

- Five tumor types were selected based on RORγ expression, RORγ biology, and immune profile criteria
- Bladder cancer (urothelial carcinoma) was also selected based on RORγ target expression and immune profile criteria
- Literature review also indicated that IL-17 is implicated in the efficacy of Bacillus Calmette-Guérin immunotherapy
- A total of 6 tumor types were prioritized for inclusion in the Phase 2a expansion (Table 1)

Table 1. Tumors Selected for Inclusion in Phase 2a Expansion

<table>
<thead>
<tr>
<th>Indication</th>
<th>Non–small-cell lung cancer</th>
<th>Esophageal / gastric cancer</th>
<th>Head and neck squamous cell cancer</th>
<th>Ovarian cancer</th>
<th>Renal cell carcinoma</th>
<th>Uterine carcinoma</th>
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REFERENCES


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