LYC-55716, A Novel Small-Molecule RORγ Agonist Immuno-oncology Agent: Rationale for Tumor Selection and Clinical Evaluation of Gastric and Esophageal Carcinoma in Phase 2a Expansion

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Abstract #67

BACKGROUND & STRATEGY

- RORC is a master transcription factor required for the differentiation of Th17 cells.
- Synthetic ROR agonists have been shown to increase immune activity and enhance type 17 helper (Th17) and cytokine (Tc17) T cells, stimulating beneficial immune responses.

TARGET BIOLOGY

- Certain sterols can function as RORγ agonists and partially activate RORγ, but sterol levels are likely too low in eccrine T cells and cannot be influenced by cancer cells.
- TCGA analysis of sterol efflux genes across tumor types identified high levels of IL-17 in tumors (Figure 5).
- Tumors with low sterol efflux genes are expected to respond better to RORγ agonist therapy.
- TCGA data showed that GC and EC tumors express low levels of sterol efflux genes, suggesting that the levels of endogenous agonists in the tumor microenvironment are also low (Figure 6).

TARGET EXPRESSION

- Analysis of TCGA RNA sequencing data showed that 95% of EC and 75% of GC samples express moderate to high levels of RORC (Table 2), indicating infiltration of Type 17 T cells into the tumors (Figure 4).

TUMOR PROFILE

- A literature review indicated a significant survival advantage for EC and GC patients who have high intratumoral IL-17 expression and high levels of IL-17-producing tumor-infiltrating lymphocytes (TILs), compared to patients with low levels of IL-17 TILs (Figure 7, Table 1).
- A high mutational burden within the tumor microenvironment has also been associated with immunotherapies and improved survival (Figure 9).
- TCGA analyses indicated a high mutational burden in both EC and GC.

CONCLUSIONS

- Bioinformatics assessments indicate high expression of RORγ agonists in both EC and GC.
- Analyses of RORγ biology suggest that GC and EC tumors are likely to respond to RORγ agonist therapy.
- High expression of RORγ agonist target genes is correlated with improved survival for patients with GC and EC.
- Immunotherapy efficacy is correlated with high levels of TILs and high mutational burden, both of which occur in GC and EC.

In summary, these analyses support the inclusion of GC and EC in the Phase 2a expansion.

REFERENCES


IMMUNE PROFILE

- The infiltration of T cells into the tumor microenvironment is positively correlated with immunotherapy efficacy.
- Analysis of TCGA RNA sequencing data indicated a high expression of Th17 cells markers such as IL-17 in both EC and GC (Figure 8).