Novel Small-Molecule RORγ Agonist Immuno-oncology Agent LYC-55716: Tumor Selection and Evaluation of Renal Cell and Bladder Cancer for Inclusion in Phase 2a Expansion

Abstract #67

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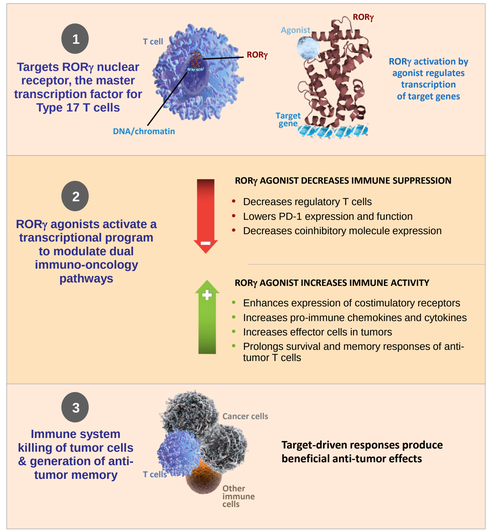
BACKGROUND

- Retinoic acid receptor-related orphan receptor γ (RORγ) is the master transcription factor responsible for type 17 effector T cell differentiation and function.
- Synthetic RORγ agonists can modulate immune cell gene expression by enhancing type 17 helper (Th17) and cytokine (Tc17) T cells, stimulating a potent antitumor response that includes increased immune activity and decreased immune suppression based on preclinical models (Figure 1).[1]
- RORγ agonists have shown promise as monotherapy and combination therapy in syngeneic tumor models.
- LYC-55716 is a first-in-class, oral, small-molecule 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.
- Preclinical and bioinformatics analyses were conducted to support the inclusion of patients with renal cell carcinoma (RCC) and bladder cancer (BC) in a Phase 2A expansion trial (NCT02929862).

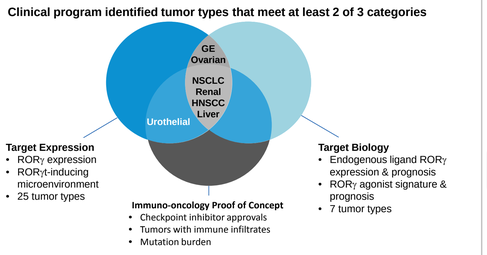
Figure 1. RORγ agonist as a novel immuno-oncology approach



METHODS

- Bioinformatic analyses were conducted using data on patients with RCC and BC from The Cancer Genome Atlas (TCGA). The resulting dataset was evaluated for (Figure 2):
  - Expression of RORγ and RORγ-inducing cytokines;
  - Signature genes associated with RORγ biology, biomarkers for endogenous RORγ ligands, and correlations with patient survival rates; and
  - Tumor microenvironment immune profiles.

Figure 2. Factors considered in tumor selection



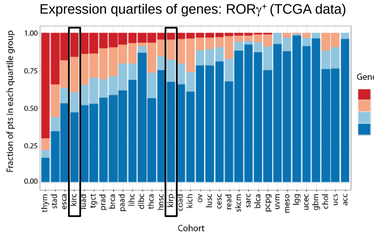
GE, gastroesophageal; HNSCC, head & neck squamous cell carcinoma; NSCLC, non–small-cell lung cancer.

- RORγ expression and the in vitro effects of a RORγ agonist on peripheral blood mononuclear cells (PBMCs) were assessed from patients with genitourinary (GU) cancer.

TARGET EXPRESSION

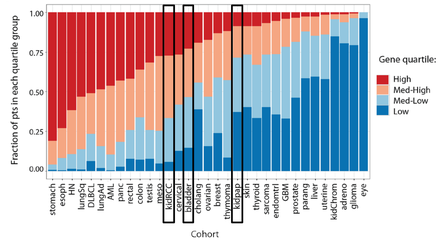
- RNA sequencing analysis identified RORγt expression in a significant fraction of RCC and BC samples (Figure 3).
  - >40% RCC patients and 20% of renal papillary patients have high RORγt expression, implying they are infiltrated by Type 17 T cells.
  - A low percentage of BC patients express high RORγt.

Figure 3. RORγt expression across tumor types



- RORγ-inducing cytokines (IL-1β, IL-6 and IL-23) that support type 17 differentiation were highly expressed in both RCC and BC.
  - >50% of RCC and BC patients have expression of genes that would support the formation of RORγ+ T cells (Type 17 cells) (Figure 4).

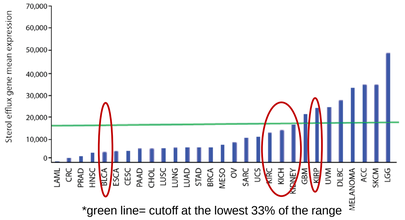
Figure 4. Expression of genes that support RORγt expression



TARGET BIOLOGY

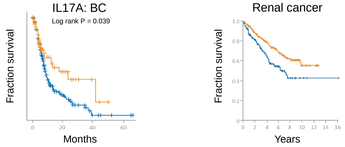
- Certain sterols can function as RORγ ligands and partially activate RORγ,[2] but sterol levels are likely low in exhausted T cells and can be influenced by cancer cells in the tumor microenvironment.
  - TCGA analysis of sterol efflux gene expression (a surrogate for endogenous ligand levels) revealed differential expression across tumor types (Figure 5).
  - Low expression of sterol efflux genes in BC tumors suggested low levels of endogenous RORγ ligands in the tumor microenvironment.
  - Medium levels of sterol efflux genes were found in kidney renal clear cell (KIRC), kidney chromophobe (KICH), and kidney renal papillary cell (KIRP) carcinomas.

Figure 5. Expression of sterol efflux genes across tumor types



- Analysis revealed a positive correlation between patient survival and expression of RORγt (or the RORγ signature gene IL17A).
  - IL17A expression is associated with statistically significant improvements in survival in BC (Figure 6).
  - High expression of RORγ (both isoforms) is also associated with better survival in patients with KIRC, KICH, and KIRP.

Figure 6. Correlation between RORγ and IL17A expression and patient survival

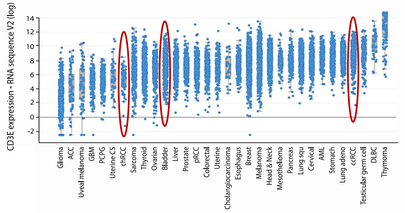


- A literature review also indicated that IL-17 is implicated in the efficacy of Bacillus Calmette-Guérin immunotherapy for bladder cancer.[3]

IMMUNE PROFILE

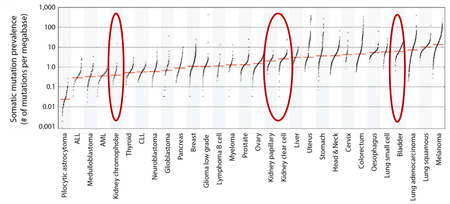
- Studies have shown a positive correlation between immunotherapy efficacy and infiltration of T cells (eg, CD3e, CD4, CD8a) in the tumor microenvironment.[4,5]
  - Analysis of TCGA RNA sequencing data indicated a high expression of T cell markers such as CD3e in RCC and BC (Figure 7).

Figure 7. Tumor-infiltrating lymphocytes across tumor types



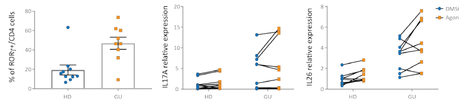
- The immune system may recognize tumors with a high mutational burden; patients with such tumors have shown improved response to immunotherapy and longer progression-free survival.[6,7]
  - Analysis of RCC and BC tumors indicated a high mutation burden (Figure 8), which are associated with immunotherapy efficacy.

Figure 8. Mutational burden across tumor types



- PBMCs from patients with GU cancer (RCC, n=5; urothelial, n=4) showed increased expression of RORγt mRNA by qPCR compared with healthy donors (HD) (Figure 9A).
- Consistent with higher basal levels of RORγ protein, PBMC from 6/9 GU patients express high levels of RORγ target genes (IL-17A, IL-26) prior to treatment with RORγ agonist compound. In most patients, the addition of RORγ agonist further enhances target gene expression (Figure 9B).
- These data suggest that immune cells from GU patients are responsive to RORγ agonist treatment.

Figure 9. PBMC expression of (A) RORγt and (B) target genes IL17A and IL26



CONCLUSIONS

- RCC and BC express RORγ and RORγ-supportive genes, and this expression is correlated with improved patient survival.
- RORγ biology suggests RCC and BC are likely to respond to RORγ agonist therapy.
- These translational and bioinformatics studies of RORγ expression, biology, and tumor immune profiles support the inclusion of RCC and BC (Urothelial carcinoma) patients in an ongoing Phase 2a expansion trial of LYC-55716 (Table 1).

Table 1. Tumors selected for Phase 2a Expansion

Tumor Types
Non–small-cell lung cancer
Gastroesophageal cancer
Head and neck squamous cell carcinoma
Ovarian cancer
Renal cell carcinoma
Urothelial carcinoma

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