LYC-55716, a First-in-Class RORγ Agonist: Rationale and Preclinical Data to Support Clinical Combinations with Established Immunotherapies

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BACKGROUND & STRATEGY
- Retinoic acid receptor-related orphan receptor γ (RORγ) is the master transcription factor regulating type 17 effector T cell differentiation and function.
- Synthetic RORγ agonists can modulate gene expression in immune cells by enhancing type 17 helper (Th17) and cytolytic (Tc17) T cells, stimulating a potent antitumor response that includes increased immune activity and decreased immune suppression in preclinical models (Figure 1).

COMBINATION WITH IMMUNOTHERAPY
- RORγ agonists modulated expression of genes that promote immune responses (Figure 2).

COMBINATION WITH CHEMOTHERAPY
- Combination with anti-CTLA-4: Rationale:
  - Anti-CTLA-4 induces inducible T cell costimulator (ICOS) expression.
  - Successful treatment with the anti-CTLA-4 antibody ipilimumab is associated with increased ICOS+CD4+ T cells in bladder cancer and melanoma.2,3
  - ICOS signaling induces and sustains RORγ expression.4
  - Figure 3. Anti-CTLA-4 treatment (A) decreased MC38 tumor volume and (B) increased ICOS and ICOSγ expression in splenic CD4+ T cells.

CONCLUSIONS
- Preclinical studies suggest that in some tumor models, a combination of LYC-55716 and ipilimumab relieves PD-1/PD-L1 inhibition and stimulates antitumor responses.
- These clinical and preclinical results support the combination of LYC-55716 with other immuno-oncology agents to further enhance antitumor activity.

REFERENCES