Abstract #TPS2617

A Phase 2a Open-Label, Multicenter Trial of the Safety and Efficacy of LYC-55716, a First-in-Class Oral, Small-Molecule RORγ Agonist to Treat Select Solid Tumors

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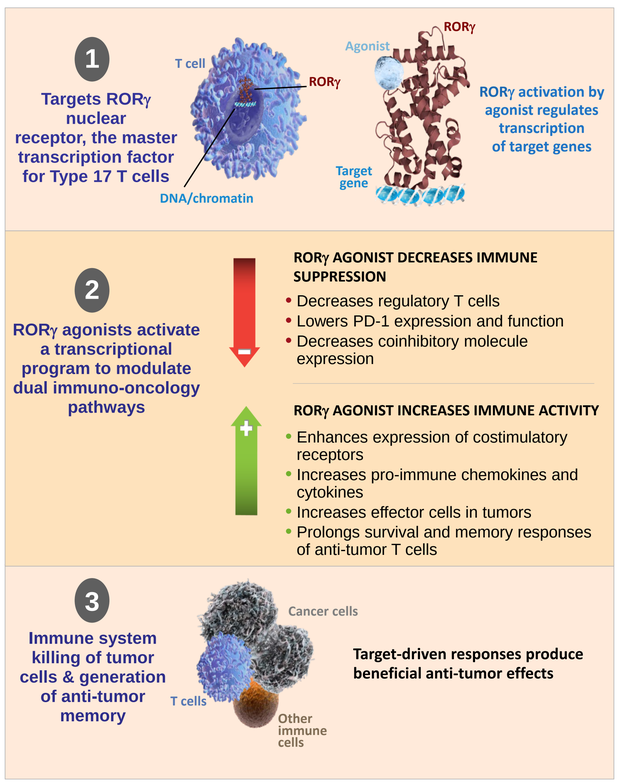
BACKGROUND

- Retinoic acid receptor–related orphan receptor γ (RORγ) is the master transcription factor responsible for Type 17 effector T cell differentiation and function (both CD4+ Th17 helper T cells and CD8+ Tc17 cytolytic T cells).
- Synthetic RORγ agonists can modulate immune cell gene expression in Type 17 T cells stimulating a potent antitumor response that includes increased immune activity and decreased immune suppression based on preclinical models (Figure 1).[1]

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



- LYC-55716 is a first-in-class oral, small-molecule RORγ agonist that is an investigational agent under development as a novel immuno-oncology agent for solid tumors.
- In the Phase 1 portion of an ongoing Phase 1/2a trial, LYC-55716 was well tolerated, with no dose-limiting toxicities (DLTs) in 32 patients.[2]
  - A confirmed partial response (PR) was observed in a patient refractory to anti-PD-1 and chemotherapy and an unconfirmed PR was seen in a patient with sarcomatoid breast cancer; 11 patients had disease stabilization, including 6 for >4 months.
- The Phase 2a dose-expansion portion of the trial (NCT02929862) is currently underway in patients with advanced non–small cell lung, gastroesophageal, head and neck, ovarian, renal cell, and urothelial cancers.

Objectives

- The overall objectives of the Phase 1/2a study are to assess the safety, tolerability, and efficacy of LYC-55716 in adults with locally advanced or metastatic cancer.
- The objectives of the Phase 2a portion of the study include determining the objective response rate and duration of response.

METHODS

Key Eligibility Criteria

- The Phase 2a portion of the study is enrolling men and non-pregnant women ≥18 y old with locally advanced or metastatic solid tumors and:
  - ≥1 measurable lesion according to response evaluation criteria in solid tumors (RECIST) v1.1.
  - Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 or Karnofsky Performance Status (KPS) score ≥70.
  - Life expectancy of ≥12 weeks.
  - Adequate organ function, as determined by the laboratory values listed in Table 1.

Table 1. Laboratory value requirements for study eligibility

Laboratory Value	Level Required for Study Eligibility
Absolute neutrophil count[a]	≥1500/mm^3 (≥1.5 x 10^9/L)
Platelets[a]	≥100,000/mm^3 (≥100 x 10^9/L)
Lymphocytes[a]	≥0.5 x 10^9/L
Hemoglobin[a]	≥9.0 g/dL
Serum creatinine or creatinine clearance[b]	≤1.5 x ULN, >50 mL/min
Total serum bilirubin	≤1.5 x ULN (<3.0 mg/dL if patient has Gilbert's syndrome)
Liver transaminases (ALT/AST)	≤2.5 x ULN (≤5.0 x ULN if liver metastases present)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

[a]Without ongoing growth factor or transfusion support. [b]Calculated using Cockroft and Gault's formula.

Figure 2. Select eligibility criteria by tumor type

Non–Small Cell Lung Cancer:
- Stage IIIB-IV NSCLC (EGFR, ALK, ROS1 mutations excluded)
- Post SOC chemotherapy and CPI; no more than 3 prior regimens

Gastric/Esophageal/G-E junction Adenocarcinoma:
- Advanced/metastatic disease with progression after 1st or 2nd line therapy
- No more than 3 prior regimens

Squamous Cell Head and Neck Cancer:
- Stage III-IV SCCHN (nasopharynx, salivary, and non-squamous excluded)
- Post platinum and CPI; no more than 3 prior regimens

Ovarian cancer:
- Epithelial ovarian cancer post platinum-based regimens (no further benefit expected based on clinician assessment)
- No more than 3 prior regimens

Renal Cell Carcinoma:
- Advanced/metastatic disease after failure of SOC (clear cell histology must have had prior VEGF therapy)
- No more than 4 prior regimens

Urothelial carcinoma:
- Advanced (unresectable) or metastatic urothelial cancer
- Post CPI; no more than 3 prior regimens

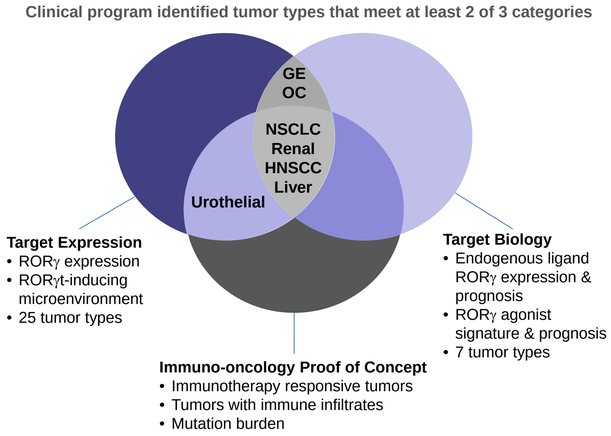
SOC, standard of care; CPI, checkpoint inhibitor therapy

- Washout periods of at least 7-28 days are required for prior treatments.
- Select eligibility exclusions include:
  - Symptomatic brain metastases/leptomeningeal involvement.
  - Evidence of bowel obstruction, uncontrolled malabsorption syndrome, or total gastrectomy.
  - Uncontrolled cardiac condition or abnormality, including NYHA Class III-IV heart disease, active ischemia, myocardial infarction ≤12 weeks of screening.
  - Receiving topical steroid Class I or II agents, systemic steroids, or immunosuppressive agents.

Tumor Selection

- Bioinformatic analyses were conducted using The Cancer Genome Atlas (TCGA) dataset.
- Phase 2 tumor types were selected based on RORγ expression, RORγ biology, and immune profile criteria (Figure 3).

Figure 3. Factors considered in tumor selection



Study Design

- The Phase 2a portion of the study will enroll patients with 6 tumor types considered most likely to be responsive to a RORγ agonist (Table 2).[3]

Table 2. Tumor indications and study cohorts

Cohort	Indication	Planned Number of Patients
1	Non–small cell lung cancer	14-19 patients/cohort, with optional biopsies in first 14 patients; mandatory biopsies (up to n=5) beginning with 15th patient
2	Esophageal / gastric / gastroesophageal junction cancer	
3	Squamous cell head and neck cancer	
4	Ovarian cancer	~9/cohort
5	Renal cell carcinoma	
6	Urothelial carcinoma	

Study Intervention

- Following a 28-day screening period, patients will receive 28-day treatment cycles of LYC-55716 (450 mg BID).
- Patients may continue to receive treatment as long as they do not have clinically significant progressive disease.

Assessments

- Patients will attend study visits at screening (≤28 days of treatment day 1); once weekly during the first two 28-day treatment cycles; and on days 1 and 15 of subsequent treatment cycles.
  - AEs and serious AEs will be monitored throughout the study.
  - Safety assessments (eg, vitals, ECG) will be performed during study visits for treatment cycle 1 and on day 1 of subsequent cycles.
  - Immune biomarker blood samples will be obtained at baseline, days 1 and 15 of treatment cycle 1, and day 1 of subsequent cycles.
  - Tumor measurements (RECIST v1.1) will be performed every 8 weeks.
  - Plasma pharmacokinetics (PK) will be assessed on days 1, 2, and 15 of treatment cycle 1 and day 1 of all subsequent cycles.
- Tumor biopsies will be obtained at screening and after 4-12 weeks of treatment for immune biomarker analyses.
  - In Cohorts 1-3, biopsies will be optional for the first 14 patients enrolled. Biopsies will be mandatory beginning with the 15th patient, until a total of 5 patients with biopsies have ben enrolled.
  - In Cohorts 4-6, biopsies will be optional for all enrolled patients.

Study Endpoints

- The primary endpoint is the objective response rate according to RECIST v1.1.
- Secondary endpoints are as follows:
  - Duration of response
  - Progression-free and overall survival at one year
  - Safety and tolerability (measured via lab results, ECG, and adverse events [AEs])
  - LYC-55716 plasma PK
- As an exploratory endpoint, immune-related biomarkers will be analyzed using blood and tumor tissue obtained pre- and post-treatment.

Study Status

- The study is recruiting patients. A total of 56 patients are currently enrolled (Table 3).

Table 3. Enrollment Status

Tumor Type	No. of Patients Enrolled
Non–Small Cell Lung Cancer	15
Gastroesophageal Adenocarcinoma	12
Squamous Cell Head and Neck Cancer	4
Ovarian Cancer	14
Renal Cell Carcinoma	4
Urothelial Carcinoma	7

CONCLUSION

This Phase 2a trial will evaluate the efficacy of the novel, small-molecule RORγ agonist LYC-55716 in treating advanced non–small cell lung, gastroesophageal, head and neck, ovarian, renal cell, and urothelial cancers.

REFERENCE

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