Abstract #TPS9111

A Phase 1b Trial of RORγ Agonist LYC-55716 in Combination with Pembrolizumab to Evaluate Safety, Efficacy, and Immune Biomarker Profiles in Patients with Metastatic Non–Small Cell Lung Cancer

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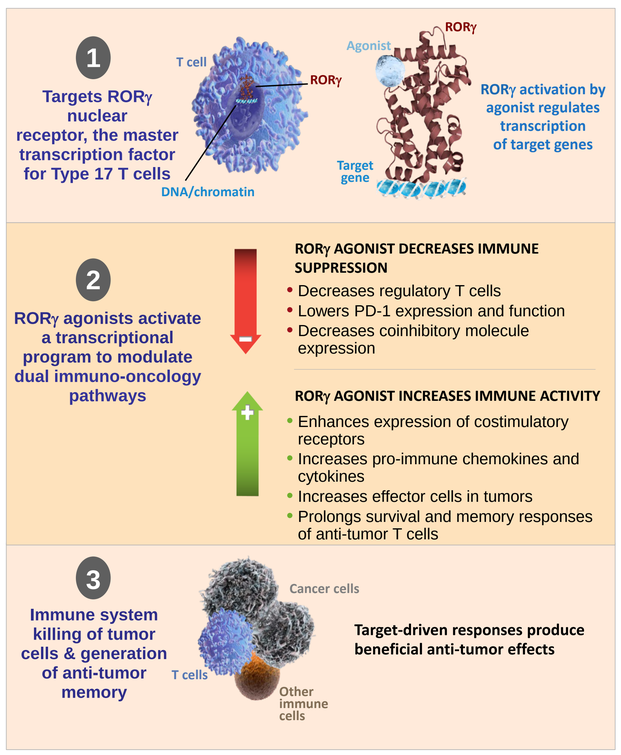
BACKGROUND

- 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]
- LYC-55716 is a first-in-class oral, small-molecule RORγ agonist being developed as an immuno-oncology agent for solid tumors.
- In the Phase 1 portion of an ongoing Phase 1/2a trial, monotherapy LYC-55716 was well tolerated, with no dose-limiting toxicities (DLTs) in 32 patients.[2]
  - A confirmed partial response was observed in a NSCLC patient refractory to anti-PD-1 and carboplatin/pemetrexed.
- RORγ agonist treatment decreases expression of PD-1 and other co-inhibitory receptors, which may diminish checkpoint inhibition within the tumor microenvironment (TME).
- Additionally, in syngeneic tumor models, the addition of RORγ agonists enhances the activity of PD-1/PD-L1 inhibitors, which is associated with increased number and activation of tumor-infiltrating lymphocytes and decreased immune suppression.[3]
- An open-label, multicenter Phase 1b trial (NCT03396497) is ongoing to assess the safety and tolerability of combining the investigational agent LYC-55716 and pembrolizumab (L+P) to treat patients with non–small cell lung cancer (NSCLC).

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



Objective

- The objectives of this study are to assess the safety and tolerability of L+P for treating patients with metastatic NSCLC, and to assess the combination of L+P for biologic and clinical activity in NSCLC.

METHODS

Key Eligibility Criteria

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

Table 1. Minimum laboratory values required 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. Eligibility criteria for NSCLC patient population

TPS score ≥50%; have begun pembrolizumab as single agent without complete or partial response, or with disease progression ≤6 pembrolizumab treatment cycles

OR

TPS score ≥50%; have begun pembrolizumab as single agent and have stable disease or disease progression after ≥6 pembrolizumab treatment cycles

OR

TPS score ≥1%; disease progression on/after platinum-containing chemotherapy and are beginning pembrolizumab as single agent

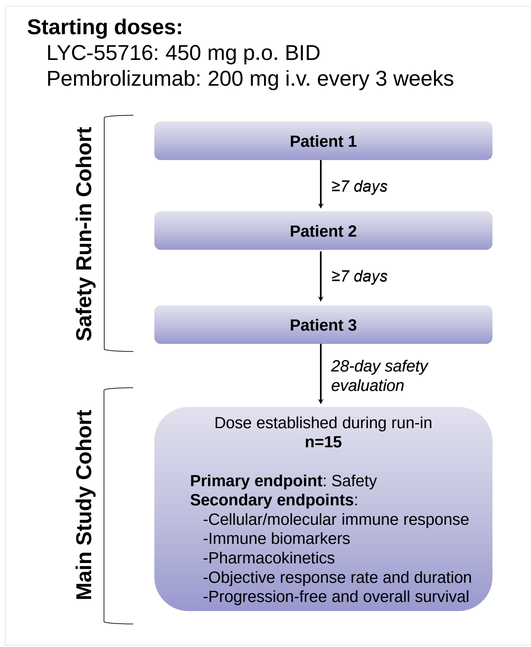
TPS, tumor-proportion score.

- 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.

Study Design

- The study will begin with a run-in cohort of 3 patients, enrolled at intervals of ≥7 days to monitor for adverse reactions to treatment (Figure 3).
  - If no patients in the run-in cohort experience a dose-limiting toxicity (DLT), the study will proceed to the main study cohort (n=15).
  - If 1 patient in the run-in cohort experiences a DLT, the cohort will be expanded to 6 patients.
  - If ≥2 patients in the 3-patient run-in cohort experiences a DLT, then recruitment will be stopped and a second run-in cohort will be started at a reduced LYC-55716 dose (if approved by a Safety Review Committee [SRC]).
  - Due to expected toxicities of pembrolizumab, all DLTs will be adjudicated by the SRC.

Figure 3. Study flow



- Following a 28-day screening period, patients will receive 28-day treatment cycles of LYC-55716 (450 mg p.o. BID) and will be administered pembrolizumab (200 mg i.v. infusion over 30 minutes) every 3 weeks.
- Patients will receive combination treatment until disease progression or unacceptable toxicity, or a maximum of 24 months.
- Patients will attend study visits at Screening (≤28 days of treatment day 1); on treatment days 1, 2, 8, 15, and 22 of the first LYC-55716 treatment cycle; on days 1, 15, and 22 of the second treatment cycle; and on day 1 of all subsequent LYC-55716 treatment cycles.
  - For patients in the safety run-in cohort, DLT assessments will be performed at all study visits during the first treatment cycle.
  - For all patients, safety assessments (eg, vital signs, physical exam, clinical labs) will be performed at weekly study visits.
  - Immune biomarker blood samples will be taken every 2 weeks.
  - Tumor measurements (RECIST v1.1) will be performed every 8 weeks (± 7 days).
  - Fresh tumor biopsies will be obtained at screening and after ≥4 weeks of treatment for all patients in the main study cohort.

Study Endpoints

Primary Endpoints

- Safety and tolerability will be assessed throughout the study via monitoring of adverse events (AEs), vital signs, lab results, and electrocardiogram.
- Incidence of DLTs will be monitored throughout the study.

Secondary Endpoints

- The following secondary endpoints will be assessed for the main study cohort:
  - Cellular and molecular immune response, as measured by tumor-infiltrating lymphocytes in paired biopsy samples.
  - Immune biomarkers characterized in peripheral blood samples (Figure 4).
  - Pharmacokinetics.
  - Objective response rate and response duration, determined according to RECIST v1.1.
  - One-year progression-free and overall survival.

Figure 4. Immune biomarker monitoring

Study Status

- Enrollment is ongoing for patients in the run-in cohort.
- Immunohistochemistry assay validation for RORγ and other immune markers is complete.

CONCLUSION

This Phase 1b trial will evaluate the occurrence of DLTs and determine the recommended Phase 2 dose of L+P in adults with metastatic NSCLC receiving pembrolizumab treatment.

REFERENCE

1. Hu X, et al. *Oncoimmunology*. 2016;5:e1254854.
2. Mahalingam D, et al. Poster CT132. Presented at AACR Annual Meeting 2018; Chicago, IL.
3. Hu X, et al. Poster 5566. Presented at AACR Annual Meeting 2018; Chicago, IL.

DISCLOSURE: LYC-55716 is an investigational agent not yet approved by FDA: the safety and efficacy of LYC-55716 have not been established in patients.

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