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-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).
- Synthmic RORγ agonists can modulate immune cell gene expression in Type 17 cells, potentially mitigating a potent antimurine response that includes increased immune activity and decreased immune suppression based on preclinical models (Figure 1).
- LYC-55716 is a first-in-class small molecule RORγ agonist that has been developed as an immune-oncology agent for solid tumors.
- In a 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. 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 agonist 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.
- An open-label, multicenter Phase 1b trial (NCT03936497) 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

1. Targets RORγ nuclear receptor, the master transcription factor for Type 17 T cells
2. RORγ agonists activate a transcriptional program to modulate dual immune-oncology pathways
3. Immune system killing of tumor cells & generation of anti-tumor memory

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.

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 ≥8 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.

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 the second run-in cohort will be started at a reduced LYC-55716 dose (if approved by a Safety Review Committee [SRC]).

Figure 3. Study flow

Table 1. Minimum laboratory values required for study eligibility

<table>
<thead>
<tr>
<th>Laboratory Value</th>
<th>Level Required for Study Eligibility</th>
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</thead>
<tbody>
<tr>
<td>Absolute neutrophils</td>
<td>≥5,000/mmc (≥1.5 x 10^9/L)</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100,000/mm (≥100 x 10^9/L)</td>
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<tr>
<td>Lymphocytes</td>
<td>≥0.5 x 10^9/L</td>
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<tr>
<td>Hemoglobin</td>
<td>≥9 g/dL</td>
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<tr>
<td>Serum creatinine or creatinine clearance</td>
<td>≤1.5 x ULN or &gt;50 mL/min</td>
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<tr>
<td>Total serum bilirubin</td>
<td>≤1.5 x ULN (&lt;3.0 mg/dL if patient has Gilbert’s syndrome)</td>
</tr>
<tr>
<td>Liver transaminases (ALT/AST)</td>
<td>≤2.5 x ULN (≤5.0 x ULN if liver metastases present)</td>
</tr>
<tr>
<td>ALT, aspartate aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal. *Without ongoing growth factor or transfusion support.</td>
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<tr>
<td>Calculated using Cockroft and Gault’s formula.</td>
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</tbody>
</table>

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

- BLOOD SAMPLE: Screening; 2, 4, 6, 8 wk post-C1D1; and end of treatment
  - NanoString PanCancer Immune Profiling Panel + 30 RORγ-Related Genes
  - C1D1, treatment cycle 1, day 1.

- TISSUE SAMPLE: FFPE; Baseline; 4-12 wk post-C1D1
  - Immunohistochemistry RORγ, CD3, CD4, CD8, FOXP3, PD-L1, CD163, K67
  - NanoString PanCancer Immune Profiling Panel + 30 RORγ-Related Genes

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


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. Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO® and the authors of this poster.

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