BACKGROUND

- Nuclear transcription factor RORγ (retinoid-related orphan receptor γ) acts as a T cell master control switch
- RORγ drives the function of Th17 (Th17) cells, producing cytokines such as IL-17A
- Th17 cells secrete IL-17A cytokine, which plays a role in immune responses to viral and bacterial infections

METHODS

- The Phase I portion of the study consisted of a 3 + 3 dose-escalation design
- After the first patient in each 3-patient cohort started treatment, additional patients were enrolled until the first patient in the next cohort discontinued treatment
- During Phase I dose escalation, a minimum of 3 up to 6 evaluable patients were enrolled per dose level
- If no MTD was defined at the dose at which pharmacokinetics (PK) and pharmacodynamics data indicated a plateau in target-related effects, then that dose was considered the recommended Phase II dose
- A starting dose of 100 mg BID was chosen based on nonclinical efficacy

RESULTS

CoHort Selection & Patient Characteristics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Number of patients</th>
<th>Median Age (yr)</th>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>6</td>
<td>55–71</td>
<td>EOCO</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>15</td>
<td>55–71</td>
<td>EOCO</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>6</td>
<td>55–71</td>
<td>EOCO</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>6</td>
<td>55–71</td>
<td>EOCO</td>
</tr>
</tbody>
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LYC55716 Safety & Tolerance

- Pharmacological studies suggested that dose-limiting toxicity might be observed clinically
- Additional, high RORγ expression has been documented in the gut system, liver, and skin. In mice, it mediates an immunosuppressive effect, then that dose was considered the recommended Phase II dose
- No significant changes or abnormalities were observed in clinical laboratory measurements

Adverse Events and Laboratory Findings

- Cohort 1: LYC55716 150 mg BID
- Cohort 2: LYC55716 300 mg QD
- Cohort 3: LYC55716 450 mg QD
- Cohort 4: LYC55716 600 mg QD

LYC55716 Pharmacokinetics

- Steady-state exposure to LYC55716 was reached by Day 15

Table 5. Objective tumor response assessment

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LYC55716 Efficacy

- Disease progression stabilization
- Disease progression

CONCLUSIONS

- LYC55716 is well tolerated with dose-limiting toxicities observed in 1 in 2 patients
- Observed AEs (Grade 2–3) are consistent with observations from preclinical toxicology testing
- PK data demonstrated high systemic exposure following 300 or 600 mg daily with steady state achieved by Day 15
- Four of 17 patients experienced disease stabilization (range 130–230 days); 2 patients with stable disease
- Dose expansion to LYC55716 600 mg daily is ongoing to establish a recommended Phase 2 dose

REFERENCES