POSTER
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A First-in-human, Open-label, Multicenter Phase 1/2a Study to Evaluate the Safety and Efficacy of Increased Repeated Doses of the First-in-class RORγ Agonist LYC-55716 in Treating Locally Advanced or Metastatic Solid Tumors

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LYCERA

BACKGROUND

- Nuclear transcription factor RORγt (retinoic acid–related orphan receptor γt) acts as a T cell master control switch
- RORγ drives the function of Th17 (helper T) and Tc17 (cytotoxic T) cells
  - Th17/Tc17 cytokines and chemokines can boost immune response to cancer cells
  - Th17/Tc17 chemokines recruit cytotoxic CD8+ T cells, neutrophils, and natural killer cells into the tumor microenvironment
  - Th17 cells inhibit regulatory T cell (Treg) development in the tumor microenvironment
- The first-in-class, oral, small-molecule LYC-55716 is a selective RORγ agonist
- In *in vivo* preclinical models, LYC-55716 reprogrammed immune cells and downregulated immunosuppressive mechanisms, resulting in decreased tumor growth and enhanced survival (**Figure 1**, **Figure 2**)
  - LYC-55716 increased production of antitumor cytokines in murine and human cells
  - LYC-55716 elicited favorable changes in T effector cell/Treg ratios and reduced PD-1 expression and sensitivity to checkpoint inhibition
  - LYC-55716 modulated expression of genes operating in pathways that enhance immunity (*GMCSF*, *CD137*, *CD27*) and that decrease immune suppression (*CD39/CD73*, *TIM3*, *LAG3*, *TIGIT*, *PD1*)

Figure 1. RORγ agonist alters immune suppression and activation

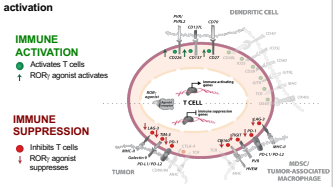


Figure 2. RORγ agonist enhances antitumor T cell response by shifting the co-stimulation/co-inhibition balance

- The ARGON trial (Trial of RORgamma Agonist LYC-55716 in Advanced Cancer) is a first-in-human, single-arm, open-label multicenter Phase 1/2a study (NCT02929862) to evaluate the safety and tolerability of LYC-55716 and assess objective response rate in adults with relapsed or refractory metastatic cancer who failed to respond to standard therapies
  - Details of Cohorts 1–3 of the Phase 1 portion of the study are presented herein

METHODS

Key Eligibility Criteria

- Males and non-pregnant females ≥18 y old with ≥1 measurable lesion according to response evaluation criteria in solid tumors (RECIST) v1.1 criteria and histologic or cytologic confirmation of advanced unresectable solid tumor
- Eastern Cooperative Oncology Group (ECOG) score of 0 or 1, or Karnofsky Performance Status Score of ≥70
- No longer receiving standard therapies (eg, chemotherapy, immunotherapy, radiation therapy, systemic/topical corticosteroids, surgery), and no unresolved adverse reaction to prior treatment
- No symptomatic brain metastases/leptomeningeal involvement
- No evidence of bowel obstruction, uncontrolled malabsorption syndrome, or total gastrectomy
- No uncontrolled cardiac condition or abnormality, including NYHA Class III-IV heart disease, active ischemia, myocardial infarction ≤12 weeks of Screening
- No history of HIV or chronic hepatitis B or C infection
- No active autoimmune disease requiring systemic steroids or immunosuppressive agents

Study Design

- The Phase 1 portion of the study followed a 3 + 3 dose-escalation design:
  - Following a 28-day screening period, patients received 28-day treatment cycles of LYC-55716
  - After the first patient in each 3-patient cohort started treatment, no additional patients were treated until the first patient completed 3 treatment days with no treatment-related AEs
  - During Phase I dose escalation, a minimum of 3 and up to 6 evaluable patients were enrolled per dose level
  - If no MTD was defined at the dose at which pharmacokinetic (PK) and pharmacodynamic data indicated a plateau in target-mediated effect, then that dose was considered the recommended Phase 2a dose
- A starting dose of 150 mg BID was chosen based on nonclinical toxicology and biochemical studies; for dose escalation, dose and dosing regimen were determined according to PK profile and safety
- Primary endpoints were safety (monitoring of adverse events [AEs], physical examination, clinical lab results) and incidence of dose-limiting toxicities during the first 28-day treatment cycle
  - Safety outcomes were assessed using descriptive statistics
- Secondary endpoints included objective tumor response rate (assessed via RECIST v1.1 at scans performed every 8 weeks) and PK results
  - Summary statistics were used to analyze tumor response rate
  - PK results were calculated based on nonparametric methods and are presented in summary tables

RESULTS

Cohort Selection & Patient Characteristics

Figure 3. Dose escalation and cohort selection

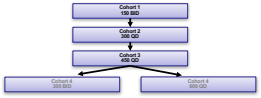


Table 1. Patient enrollment and characteristics

	Dose Cohort		
	Cohort 1 150 mg BID	Cohort 2 300 mg QD	Cohort 3 450 mg QD
Enrolled, n	5	6	4
Discontinued, n	3	5	0
Primary reason for discontinuation, n			
Progression	3	3	0
AE	0	1	0
Patient Decision	0	1	0
Median age, y (range)	63 (39, 77)	56.5 (51, 77)	58.5 (44, 75)
Sex, male/female, n	1 / 4	3 / 3	2 / 2
ECOG/Karnofsky performance status			
ECOG 0	1	0	1
ECOG 1	4	4	3
KPS 80	0	1	0
KPS 90	0	1	0

Table 2. Tumor type and number of prior cancer therapies, by patient

Tumor Type	No. of Prior Cancer Therapies	Median No. of Prior Therapies
Cohort 1: LYC-55716 150 mg BID		
Adenoid cystic head and neck	2	5
Mucosal melanoma	6	
Colorectal	5	
Small intestinal adenocarcinoma	3	
Leiomyosarcoma	6	
Cohort 2: LYC-55716 300 mg QD		
Colorectal	4	4
Vulvar	1	
Small-cell lung	3	
Breast	7	
Colorectal	4	
Colorectal	9	
Cohort 3: LYC-55716 450 mg QD		
Ovarian	5	4
Sarcomatoid mesothelioma	3	
Pancreatic	NAV	
Soft tissue sarcoma	NAV	

NAV indicates data not available.

LYC-55716 Safety & Tolerability

Adverse Events and Laboratory Findings

- Preclinical toxicity studies suggested that diarrhea/loose stools might be observed clinically. Additionally, high RORγ expression has been documented in the GI system, liver, and kidney. In Cohorts 1–3, 6/15 (40%) patients reported Grade 1 diarrhea, 4 of which were considered treatment related (**Table 3**).
- No significant changes or abnormalities were observed in clinical laboratory measurements
- No dose-limiting toxicities were observed

Table 3. AEs occurring in more than one patient in Cohorts 1–3[ab]

AE	Total No. of Patients with Event	No. of Treatment-related Events
Fatigue	7	3
Diarrhea	6	4
Anorexia (Poor Appetite)	3	2
Dry Mouth	3	2
Anemia	3[c]	1
Anxiety	3	0
Lower Extremity Edema	3	0
Drowsiness	2	2
Nausea	2	1
Insomnia	2	1

[a]Unless otherwise noted, all adverse events were Grade 1 or 2.
[b]Events that occurred in two patients are listed if one of the events was treatment-related.
[c]Includes Grade 3 AE unrelated to LYC-55716.

Serious Adverse Events and Patient Deaths

- No treatment-related serious AEs occurred
  - Two patients (both Cohort 2) had 3 non–treatment-related serious AEs: 1 with 2 hospitalizations, 1 with sepsis
- Three non-treatment related deaths occurred: 2 patients died from PD after discontinuing study treatment; 1 patient died from complications of acute dyspnea and possible pulmonary embolism after developing deep vein thrombosis while on study

LYC-55716 Pharmacokinetics

- Steady-state exposure to LYC-55716 was reached by Day 15 (**Table 4**)
- PK modeling of the Cohort 1 data indicated an elimination half-life ($t_{1/2}$) of ~20 h; as a result, a QD dosing schedule was explored in subsequent cohorts

Table 4. Pharmacokinetic results

Treatment Day	Median Values			
	C_{max} (ng/mL)	T_{max} (hr)	C_{min} (ng/mL)	AUC_τ (ng.h/mL)[a]
Cohort 1: LYC-55716 150 mg BID				
1	1030	4	710	8243
15	3530	4	2260	30,307
29	3220	4	2450	32,837
Cohort 2: LYC-55716 300 mg QD				
1	4495	5	793	36,560
15	6620	3	947	62,197
29	6130	3	1100	57,719
Cohort 3: LYC-55716 450 mg QD				
1	2390	5	734	39,157
15	5265	3	715	58,759
29	4190	3	721	47,163

[a]$AUC_{0\text{-}12}$ for Cohort 1 (150 mg BID); $AUC_{0\text{-}24}$ shown for Cohorts 2-3 (300 mg QD and 450 mg QD).
AUC, indicates area under the concentration-time curve through the dosing interval, at steady state; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; T_{max}, time of maximum plasma concentration on Day 29.

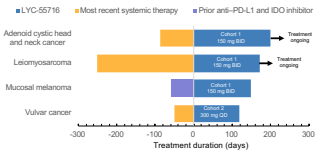
LYC-55716 Efficacy

Table 5. Objective tumor response assessment

Best Response	Cohort 1 (n=5)	Cohort 2 (n=6)	Cohort 3 (n=4)
Stable disease; study participation ongoing			Too early to assess
>24 weeks	2	0	
Stable disease; off study	1[a]	1[b]	
Disease progression	2	3[c]	
Other	0	2[d]	

[a]Patient discontinued at 21 weeks due to progressive disease
[b]Patient discontinued at 17 weeks due to progressive disease
[c]One patient had PD by RECIST, but remains on treatment under irRECIST
[d]One patient discontinued due to non–treatment-related AE leading to death, 1 patient withdrew consent

Figure 4. Treatment duration among patients with disease stabilization[a]



[a]Cohorts 1 and 2 only; data not yet available for Cohort 3.

PHASE 2A EXPANSION

Phase 2a Expansion Planning

- After selection of a recommended dose for Phase 2, expansion into the Phase 2a portion of the trial is planned for 6 tumor targets in ~60 patients with relapsed/refractory solid tumors (**Table 6**)
- Tumor targets for Phase 2a testing have been selected based on RORγ expression, bioinformatics, and demonstrated clinical proof of concept with T cell–directed therapy

Table 6. Phase 2a expansion planning

	Indication	Phase 2A Single Agent (Target N)
Signal Seeking	Non–small-cell lung cancer	14–19 patients per cohort with optional initial biopsies (n=14) stopping rule at n=14 for efficacy with mandatory biopsy (up to n=5)
	Esophageal / gastric / gastroesophageal junction cancer	
	Squamous cell head and neck cancer	
Exploratory	Ovarian cancer	~9 per cohort
	Renal cell carcinoma	
	Urothelial carcinoma	

CONCLUSIONS

- ***LYC-55716 is well tolerated, with no dose-limiting toxicities observed to date, in doses up to 450 mg QD***
- ***Observed AEs (Grade 1–2) are consistent with observations from preclinical toxicology testing***
- ***PK data demonstrated high systemic exposure following BID or QD regimens with steady state achieved by day 15***
- ***Four of 11 patients experienced disease stabilization (range 102–200 days); 2 patients with stable disease continue on treatment***
- ***Dose expansion to LYC-55716 600 mg daily is ongoing to establish a recommended Phase 2 dose***

REFERENCES

1. Hu X, et al. *Oncolmmunology.* 2016;5(12):e1254854.
2. Hu X, et al. *Nat Chem Biol.* 2015;11(2):141–147.

Study sponsored by Lycera Corp. 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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