Safety and Dose Selection for LYC-55716, a First-in-Class ROR-γ Agonist to Treat Solid Tumors: Phase 1 Results from an Open-Label, Multicenter Phase 1/2a Trial

Abstract #CT132

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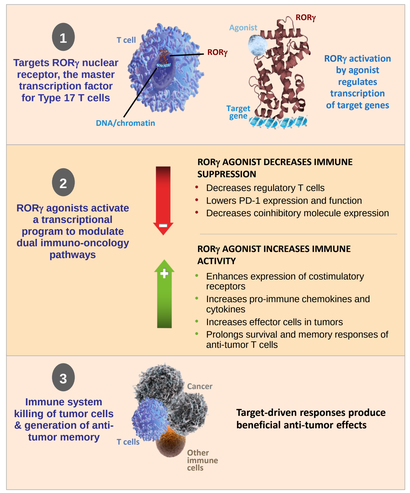
BACKGROUND

- Retinoic acid receptor–related orphan receptor γ (RORγ) is the master transcription factor responsible for type 17 effector T cell differentiation and function.
- Synthetic RORγ agonists can modulate immune cell gene expression by enhancing Type 17 helper (Th17) and cytokine (Tc17) T cells, stimulating a potent antitumor response that includes increased immune activity and decreased immune suppression based on preclinical models (**Figure 1**).[1]
- RORγ agonists have shown promise as monotherapy and combination therapy in syngeneic tumor models.
- LYC-55716 is a first-in-class, oral, small-molecule investigational agent that selectively activates RORγ.
- Phase 1 clinical testing of LYC-55716 identified a pharmacodynamically active dose and demonstrated that this agent was well tolerated in cancer patients.
- The ARGON trial (Trial of RORγ 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 investigational agent LYC-55716 and assess objective response rate in adults with relapsed or refractory metastatic cancer who failed to respond to standard therapies.
  - Results of the Phase 1 portion of the study are presented herein.

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



METHODS

Key Eligibility Criteria

- The study enrolled 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, and
  - Karnofsky Performance Status (KPS) score ≥70 or Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.
- Subjects were excluded from the study if any of the following conditions were present:
  - Receiving standard therapies (eg, chemotherapy, immunotherapy, radiation therapy, systemic/topical corticosteroids, surgery),
  - Unresolved adverse reaction to prior treatment,
  - 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,
  - History of HIV or chronic hepatitis B or C infection, or
  - 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, with additional enrollment in some cohorts based on the recommendation of the study safety review committee.
  - Patients underwent a 28-day Screening period, then received LYC-55716 in 28-day treatment cycles.
  - After the first patient in each 3-patient cohort began treatment, no additional patients in that cohort were treated until the first patient completed 3 treatment days with no treatment-related AEs.
  - If no maximum tolerated dose was identified prior to the dose at which pharmacokinetic (PK) and pharmacodynamic data indicated a plateau in target-mediated effect, then the dose at which effect plateaued was considered the recommended Phase 2a dose.
- 150 mg BID was chosen as a starting dose based on nonclinical toxicology and biochemical studies. For dose escalation, dose and dosing regimen were determined according to observed PK profile and safety.

Study Endpoints

- Primary endpoints were safety and the incidence of dose-limiting toxicities during the first 28-day treatment cycle.
  - Safety outcomes included monitoring of adverse events (AEs), physical examination, and clinical lab results, and 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.
  - Tumor response rate was analyzed using summary statistics.
  - PK results were calculated based on nonparametric methods.
- Pharmacodynamic markers of RORγ activation were also evaluated.

RESULTS

Cohort Selection and Patient Characteristics

- Thirty-two patients (median age, 62 y; 38% male) were enrolled into five cohorts, receiving doses ranging from 150 mg BID to 450 mg BID (**Figure 2**, **Table 1**).
- Across cohorts, patients had received a median of 3-5 (range, 1-10) prior cancer therapies (**Table 2**).

Figure 2. Dose escalation and cohort selection

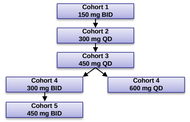


Table 1. Patient enrollment and characteristics

	Cohort 1	Cohort 2	Cohort 3	Cohort 4a	Cohort 4b	Cohort 5
	150 mg BID	300 mg QD	450 mg QD	300 mg BID	600 mg QD	450 mg BID
Enrolled, n	5	6	4	4	4	9
Discontinued, n	5	6	4	3	3	8
Primary reason for discontinuation, n						
Progression	4	6	4	3	3	6
AE	0	0	0	0	0	0
Patient decision	0	0	0	0	0	2
PI decision	1	0	0	0	0	0
Median age, y (range)	63 (39, 77)	56.5 (51, 77)	58.5 (44, 75)	65.5 (23, 73)	59.5 (55, 68)	62 (57, 79)
Sex, male/female, n	1 / 4	3 / 3	2 / 2	3 / 1	1 / 3	2 / 7
ECOG/KPS score						
ECOG 0	1	0	1	1	1	2
ECOG 1	4	4	3	2	3	6
KPS 80	0	1	0	0	0	0
KPS 90	0	1	0	1	0	0

PI, primary investigator.

Table 2. Number of prior cancer therapies

	Cohort 1	Cohort 2	Cohort 3	Cohort 4a	Cohort 4b	Cohort 5
	150 mg BID	300 mg QD	450 mg QD	300 mg BID	600 mg QD	450 mg BID
Median	5	4	3	3	3	3
Range	2-6	1-9	3-5	2-4	1-3	1-10

[a]Data not available for one patient in cohort 3.

LYC-55716 Safety & Tolerability

Adverse Events and Laboratory Findings

- Most treatment-related AEs were Grade 1-2; none were Grade 4 (**Table 3**). Grade 3 treatment-related anemia, elevated GGT, and hypophosphatemia were reported in one patient each.
- Preclinical toxicity studies had suggested that diarrhea/loose stools might be observed clinically, and high RORγ expression has been documented in the GI system, liver, and kidney.
  - In Cohorts 1-5, 13/32 (41%) patients experienced diarrhea, of which 11 events were considered treatment related (**Table 3**).
- No significant trends were observed in clinical laboratory measurements.
- No dose-limiting toxicities were observed.

Table 3. Treatment-related AEs occurring in more than one patient[a]

Adverse Event	Total No. of Patients With Event	No. of Treatment-Related Events
Diarrhea	13	11
Fatigue	12	7
Anemia[b]	10	4
Vomiting	10	2
Anorexia	8	4
Nausea	7	4
Dry mouth	5	3
Hypokalemia	6	1
Dehydration	4	1
Elevated GGT[b]	2	2
Dysgeusia	2	2
Weakness	2	2
Drowsiness	2	2

[a]Unless otherwise noted, AEs were Grade 1 or 2.
[b]Grade 3 was highest treatment-related AE.

Serious Adverse Events

- A total of 17 serious AEs were reported for 12 patients. None of the serious AEs were considered by the investigators to be related to treatment.

Patient Deaths

- Eight deaths were reported during the Phase 1 portion and 30-day follow-up period. None of the deaths were considered treatment related by the investigators. Seven of the deaths were due to disease progression, and 1 was attributed to an unknown cause.

LYC-55716 Pharmacokinetics

- LYC-55716 demonstrated an estimated elimination half-life of ~12 h.
- Exposures increased roughly linearly at doses between 150 and 450 mg BID (**Figure 3**, **Table 4**).
  - Exposures overlapped at doses of 150 mg and 300 mg BID.
- At the highest dose tested (450 mg BID; Cohort 5), the median C_{min} exceeded by ~24-fold the 50% effective concentration (EC_{50}) and exceeded by 3-fold the EC_{90} that preclinical studies had indicated were required for target gene regulation.
- Twice-daily dosing resulted in minimum plasma concentrations that were consistently higher than once-daily dosing, providing better coverage of the EC_{50} and EC_{90} targets.

Figure 3. Median LYC-55716 concentration at Day 29, by cohort

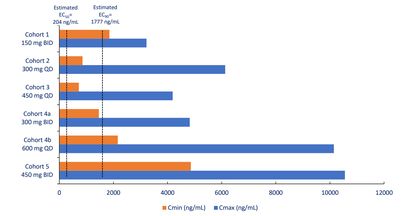


Table 4. Pharmacokinetic results at Day 29, by cohort

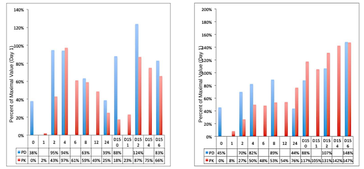
Cohort	C_{max} (ng/mL)	C_{min} (ng/mL)[a]	AUCτ (ng.h/mL)[b]
Cohort 1 (150 mg BID)	3,220 (1,790-8,760)	1,850 (1,250-5,070)	32,837 (19,577-78,797)
Cohort 2 (300 mg QD)	6,130 (1,660-23,500)	858 (228-15,400)	57,719 (19,160-45,1475)
Cohort 3 (450 mg QD)	4,190 (2,710-8,550)	721 (307-2,360)	47,163 (32,413-11.2610)
Cohort 4a (300 mg BID)	4,820 (1,520-5,660)	1,460 (544-2,750)	38,567 (10,532-48,335)
Cohort 4b (600 mg QD)	10,145 (8360-11,700)	2,160 (1,060-3,080)	100,520 (79,650-130,500)
Cohort 5 (450 mg BID)	10,550 (5,600-12,200)	4,860 (11.50-9,250)	87,009 (40,125-128,917)

Data are median (range).
[a]Lowest concentration measured. May not be C_{ss}.
[b]AUC_{0-12} for cohorts with BID dosing. AUC_{0-24} for cohorts with QD dosing.

LYC-55716 Pharmacodynamics

- Patient blood samples collected at the time points shown in **Figure 4** (hours post-dose) were stimulated with PMA/ionomycin and incubated for 24 hours.
  - IL-17A, IL-17F, and IFNγ protein were measured by MSD/ELISA.
  - IL-17A, IL-17F, and IL-22 transcripts were assessed by qPCR.
- High intra- and inter-patient variability was observed, likely due to differences in baseline lymphocyte counts and levels of RORγ expression.
- Pharmacodynamic data indicated target engagement and qualitative evidence of pharmacodynamic response (**Figure 4**), consistent with evidence of LYC-55716 exposure levels in the predicted efficacious range.

Figure 4. Post-treatment changes in IL-17A and PK Profile*



Mean IL-17A and PK Values, Cohort 4a (600 mg QD) (hours post-dose)

Mean IL-17A and PK Values, Cohort 4b (300 mg BID) (hours post-dose)

* All data normalized to maximal IL-17A value and LYC-55716 concentration on Day 1

LYC-55716 Efficacy

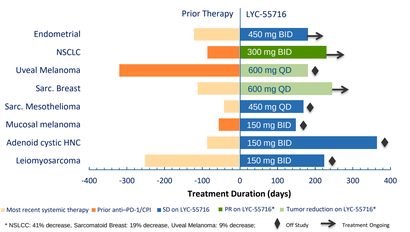
- Twelve patients had disease stabilization (range, 60-364 days) on LYC-55716 therapy; treatment is ongoing for 3 patients (**Table 5**, **Figure 5**).

Table 5. Best response for overall study population

	Number of patients (N=32)
Partial Response	1 (4%)
Stable Disease	12 (46%)
Treated >4 months	7 (27%)
Progressive Disease	13 (50%)
Evaluable for response	26
Not evaluable[a]	6

[a]PD within 6 weeks, no scans available (n=5); patient withdrew (n=1).

Figure 5. Patients with treatment duration >4 months



PHASE 2A EXPANSION

- Tumor targets for Phase 2a testing were selected based on RORγ expression, bioinformatics, and demonstrated clinical proof of concept with T cell–directed therapy.[2]
- The Phase 2a part of the trial (NCT02929862) is underway in ~70 patients with advanced non-small cell lung, head and neck, gastroesophageal, renal cell, urothelial, and ovarian cancers.

Table 6. Phase 2a expansion

Indication	Phase 2A Single Agent
Non-small cell lung cancer	14-19 patients per cohort with optional biopsies in first 14 patients; mandatory biopsies (up to n=5) beginning with 15th patient
Esophageal / gastric / gastroesophageal junction cancer	
Squamous cell head and neck cancer	
Ovarian cancer	~9 per cohort
Renal cell carcinoma	
Urothelial carcinoma	

CONCLUSIONS

- **LYC-55716 is well tolerated, with no dose-limiting toxicities observed with doses up to 450 mg BID. Treatment-related AEs (mainly Grade 1-2) are consistent with those expected based on preclinical toxicology testing.**
- **Plasma LYC-55716 concentrations exceeded estimates for EC_{50} and EC_{90}. The C_{min} values of BID dosing were more consistently above the estimated EC_{90} compared to QD dosing.**
- **Pharmacodynamic assessments demonstrated qualitative evidence of a PD effect based on increases in target cytokine markers following LYC-55716 dosing.**
- **Clinical activity of LYC-55716 has been documented.**
  - **A confirmed PR has been observed in a NSCLC patient refractory to both anti-PD1 and pemetrexed/carboplatin.**
  - **Twelve patients had disease stabilization, including 7 for >4 months. Three patients continue on treatment.**
- **These data support the safety of LYC-55716 and selection of a 450 mg BID dosing regimen for the ongoing Phase 2a study in patients with non-small cell lung, head and neck, gastroesophageal, renal cell, urothelial, and ovarian cancers.**

REFERENCES

1. Hu X, et al. *Oncoimmunology.* 2016;5:e1254854.
2. Hu X, et al. *J Immunother Cancer.* 2017;5:P253.

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