LYC-55716, a First-in-Class RORγ Agonist: Rationale and Preclinical Data to Support Clinical Combinations with Established Immunotherapies

Abstract #5566

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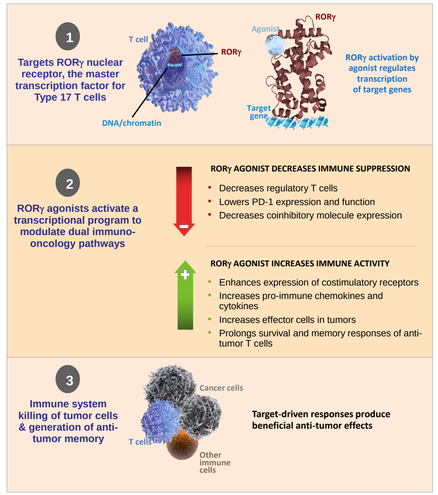
BACKGROUND & STRATEGY

- Retinoic acid receptor–related orphan receptor γ (RORγ) is the master transcription factor regulating type 17 effector T cell differentiation and function.
- Synthetic RORγ agonists can modulate gene expression in immune cells 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 in preclinical models (Figure 1).[1]
- LYC-55716 is a selective, 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. A Phase 2a expansion trial of LYC-55716 in patients with select solid tumors (NCT02929862) is ongoing.

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



PRIORITIZATION OF COMBINATION PARTNERS

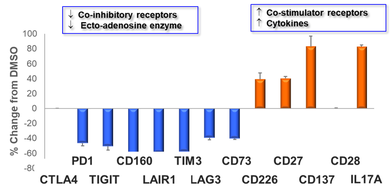
- RORγ agonists affect multiple anti-tumor mechanisms; these compounds have the potential to combine with other agents to enhance tumor immunity.
- To identify and prioritize potential clinical combinations for LYC-55716:
  - Combination partners with partially overlapping biologic profiles were identified.
  - Literature was evaluated to identify potential combination therapies.
  - Preclinical data were generated to support a biological rationale for candidate agents.
- Prioritized combination partners include:
  - PD-1, PD-L1, CTLA4, ICOS, OX40, etc. as key immunotherapy agents
  - Doxorubicin, platinum, etc. as key chemotherapy agents
  - Radiotherapy

COMBINATION WITH IMMUNOTHERAPY

Rationale:

- RORγ agonists modulated expression of genes that promote immune responses (Figure 2).

Figure 2. RORγ agonist reduced expression of co-inhibitory receptors and increased expression of co-stimulatory receptors



- Lycera is testing RORγ agonists in preclinical models in combination with other IO agents such as vaccine and OX40 (see posters 3762/12, 3773/23, 3777/27).

Combination with anti–PD-1

Rationale:

- Type 17 T cells express reduced PD-1 vs other T cells.[1]
- RORγ agonist reduces PD-1 expression in vitro (Figure 2) and in vivo after adoptive cell transfer.[1]
- RORγ agonist relieves PD-1/PD-L1 inhibition of proliferation and IFNγ.[1]

Table 1. Established syngeneic tumors treated for 1 week with anti–PD-1 + RORγ agonist combination therapy showed decreased tumor growth over anti–PD-1 alone

	% Tumor Growth Inhibition[a]		
Model	Anti–PD-1	RORγ agonist	RORγ agonist + anti-PD-1
H22 (liver)	++	+	+++[b]
Pan02 (pancreas)	–	–	+[b]
CT26 (colon)	+	–	–
B16F10 (melanoma)	+	+	+
A20 (lymphoma)	–	+	++
Renca (renal)	–	++[b]	++[b]

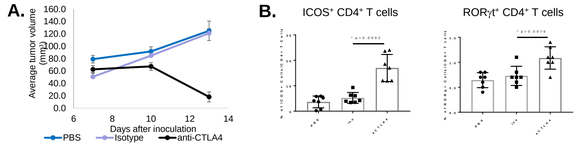
+++, >50% TGI; ++, 30-50% TGI; +, 10-30% TGI; –, <10% TGI.
[a]Mice treated when tumors ≥300mm^3 for 1 week (CrownBio 12-model panel); %TGI calculated vs vehicle control group.
[b]P<.05 vs vehicle.

Combination with anti-CTLA4

Rationale:

- Anti-CTLA4 induces inducible T cell costimulator (ICOS) expression.
- Successful treatment with the anti-CTLA4 antibody ipilimumab is associated with increased ICOS$^+$CD4$^+$ T cells in bladder cancer and melanoma.[2-6]
- ICOS signaling induces and sustains RORγ expression.[7]

Figure 3. Anti-CTLA4 treatment (A) decreased MC38 tumor volume and (B) increased ICOS and RORγ expression in splenic CD4$^+$ T cells



- The above in vivo data also supported the possibility for combination with agonistic anti-ICOS antibody.

Table 2. Established syngeneic tumors treated for 1 week with anti-CTLA4 + RORγ agonist combination therapy showed decreased tumor growth over anti-CTLA4 alone

	% Tumor Growth Inhibition[a]		
Model	Anti-CTLA4	RORγ agonist	RORγ agonist + anti-CTLA4
H22 (liver)	+++[b]	+	+++[b]
Pan02 (pancreas)	+	–	+[b]
CT26 (colon)	–	–	++
B16F10 (melanoma)	+/–	+	++
A20 (lymphoma)	–	+	+/–
Renca (renal)	+	++[b]	++[b]

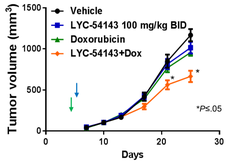
+++, >50% TGI; ++, 30-50% TGI; +, 10-30% TGI; +/–, 10% TGI; –, <10% TGI.
[a]Mice treated when tumors ≥300mm^3 for 1 week (CrownBio 12-model panel); %TGI calculated vs vehicle control group.
[b]P≤.05 vs vehicle.

COMBINATION WITH CHEMOTHERAPY

Rationale:

- Cytotoxic chemotherapy has immunomodulatory effects, which may be enhanced by RORγ agonists.[8]
  - Doxorubicin has an IL-17–dependent anti-tumor effect.[9]
  - IL-17 predicts responses to platinum chemotherapies.[10,11]

Figure 4. Combination treatment with LYC-54143 significantly augmented anti-tumor activity of doxorubicin in an orthotopic 4T1 breast cancer model

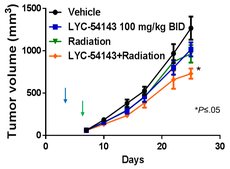


COMBINATION WITH RADIOTHERAPY

Rationale:

- Large-field radiation reduces the number of lymphocytes. RORγ agonist is expected to enhance thymocyte and T cell survival and T cell receptor repertoire.[1]
- Targeted radiation generates tumor antigens and immune changes in the tumor microenvironment. RORγ agonists would enhance the formation of Type 17 anti-tumor T cells.[12,13]

Figure 5. Combination treatment with LYC-54143 and radiotherapy in an orthotopic breast cancer 4T1 model resulted in significantly greater tumor growth inhibition compared with either treatment alone



CONCLUSIONS

- **Preclinical studies suggest that in some tumor models, a combination of RORγ agonist with another immuno-oncology agent or with standard of care therapy showed superior anti-tumor activity.**
- **A phase 1 clinical trial of single-agent RORγ agonist LYC-55716 demonstrated a well-tolerated safety profile, leading to a Phase 2A clinical trial that is currently enrolling patients across 6 selected solid tumor types (NCT02929862).**
- **These clinical and preclinical results support the combination of LYC-55716 with other immunotherapy agents and other established treatment modalities. A Phase 1b study of LYC-55716 and pembrolizumab in patients with non-small cell lung cancer is ongoing (NCT03396497).**

REFERENCES

1. Hu X, et al. *Oncoimmunology*. 2016;5:e1254854.
2. Tang DN, et al. *Canc Immunol Res*. 2013;1:229-34.
3. Wang W, et al. *J Transl Med*. 2012;10;146.
4. Chen H, et al. *Cancer Immunol Res*. 2014;2:167-76.
5. Liakou CI, et al. *Proc Natl Acad Sci USA*. 2008;105:14987-92.
6. Carthon BC, et al. *Clin Cancer Res*. 2010;16:2861.
7. Paulos CM, et al. *Sci Transl Med*. 2010;2:55ra78.
8. Wargo JA, et al. *Semin Oncol*. 2015;42:601-16.
9. Mattarollo SR, et al. *Cancer Res*. 2011;71:4809-20.
10. Droeser RA, et al. *BMC Cancer*. 2016;16:639.
11. Droeser RA, et al. *J Cancer Res Clin Oncol*. 2013;139:1295-1302.
12. Sridharan V, Schoenfeld JD. *Discov Med*. 2015;19:219-28.
13. Loi M, et al. *Crit Rev Oncol Hematol*. 2017;112:1-10.

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