Phase 1 trial of KT-333, a STAT3 degrader, in patients with relapsed or refractory lymphomas, large granular lymphocytic leukemia and solid tumors


Introduction/Background

- STAT3 promotes tumor cell-intrinsic expression of genes involved with survival, proliferation, stemness, and metastasis.
- STAT3 also promotes differentiation and activity of immunosuppressive cells in the tumor microenvironment.

**KT-333**
- Targeted protein degraders are a new therapeutic class of compounds that utilize the ubiquitin proteasome system to target degradation of specific proteins.
- KT-333 is a first-in-class, potent, highly selective, heterobifunctional small molecule degrader of STAT3.
- In preclinical studies, proof of concept antitumor activity was seen with KT-333 monotherapy in mouse xenograft models of STAT3-dependent peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL) and with KT-333 in combination with anti-PD-1 in syngeneic mouse colorectal cancer model.

Methods

**Study Design and Objectives**

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<th>Phase</th>
<th>Study Design &amp; Objectives</th>
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<td>Phase 1</td>
<td>Dose Escalation &amp; MTDRP2D Expansion (n=45)</td>
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<td>Phase 1b</td>
<td>Dose Expansion (n=20 each)</td>
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**Phase 333 IV Weekly in 28-day Cycles**

- Peripheral T-cell lymphoma (PTCL)
- Cutaneous T-cell lymphoma (CTCL)
- Large granular lymphocytic leukemia (LGL-L)
- Advanced Solid Tumors

**Primary Objective:** Safety, tolerability and determine the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) (Phase 1a).

**Secondary:** PK, preliminary efficacy.

**Exploratory:** STAT3 mutational status; STAT3 pathway gene expression including pSTAT3 expression at baseline; immune TME profiling & correlations with anti-tumor activity.

Key Eligibility Criteria

**Inclusion Criteria**
- Phase 1a:
  - Lymphomas (including Hodgkin's, B- and T-cell) or solid tumors relapsed/refractory (R/R) to at least two prior treatments or no available standard therapy.
- LGL-L R/R to one prior systemic treatment.
- Phase 1b: PTCL, CTCL, LGL-L or CLPD-NK or solid tumors R/R to at least one prior systemic treatment or with no available standard therapy.
- ECOG of 0-2, adequate liver/kidney and bone marrow function (except for LGL-L).

**Exclusion Criteria**
- Radiation, anti-cancer therapy or major surgery within 4 weeks.
- Autologous hematopoietic stem cell transplant less than 3 months prior to first dose of study drug.
- Prior allogeneic hematopoietic or bone marrow transplant.

Conclusions

- KT-333 achieved up to 88% mean maximum STAT3 degradation in peripheral blood mononuclear cells with evidence of STAT3 pathway inhibition (decrease in SOCS3) and downregulation of inflammatory biomarkers in peripheral blood.
- Most common treatment-emergent adverse events were Grade 1-2 fatigue, anemia and gastrointestinal symptoms, with no DLTs or drug-related SAEs.
- Phase 1a dose escalation ongoing, with continued enrollment onto Dose Level 4.

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