

# Phase 1 Study of KT-333, a Targeted Protein Degradator of STAT3, in Patients with Relapsed or Refractory Lymphomas, Large Granular Lymphocytic Leukemia, and Solid Tumors

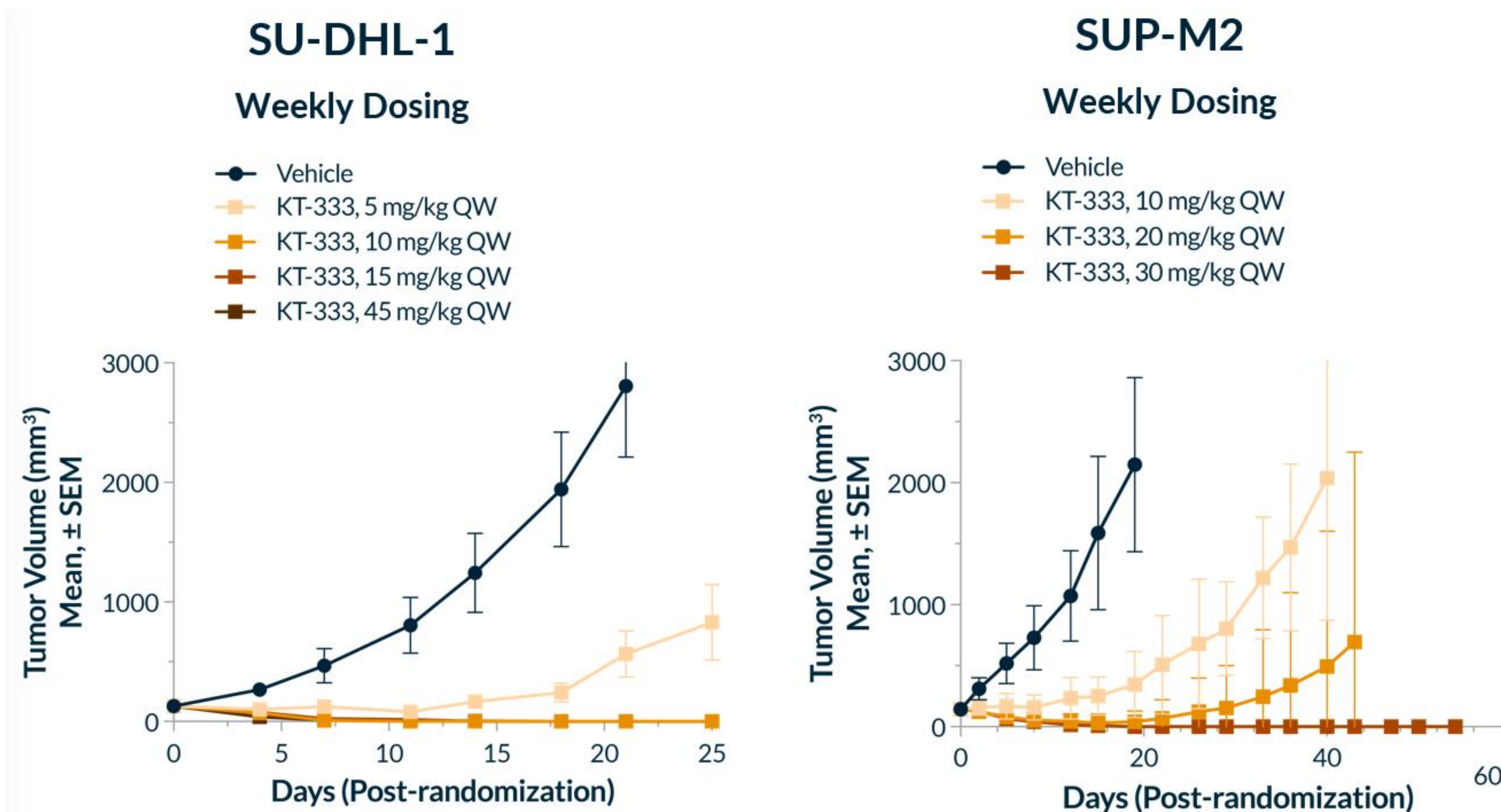
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## BACKGROUND

- The signal transducer and activator of transcription 3 (STAT3) protein is aberrantly activated by oncogenic mutations or upstream signaling through cytokines and growth factors, resulting in tumor growth and promotion and hindering antitumor immunity.
- Approximately 70% of human hematological malignancies and solid tumors exhibit increased STAT3 signaling.
- There is evidence of constitutive activation of STAT3 in large granular lymphocytic leukemia (LGL-L), peripheral T-cell lymphoma (PTCL), and cutaneous T-cell lymphomas (CTCL). Hyperactivation of STAT3 has been reported in a variety of solid tumors.
- Selective inhibition of STAT3 has been proven to be difficult with conventional therapeutic approaches.
- Targeted protein degraders represent a new therapeutic class of compounds that utilize the ubiquitin proteasome system to target the degradation of specific proteins.

## KT-333

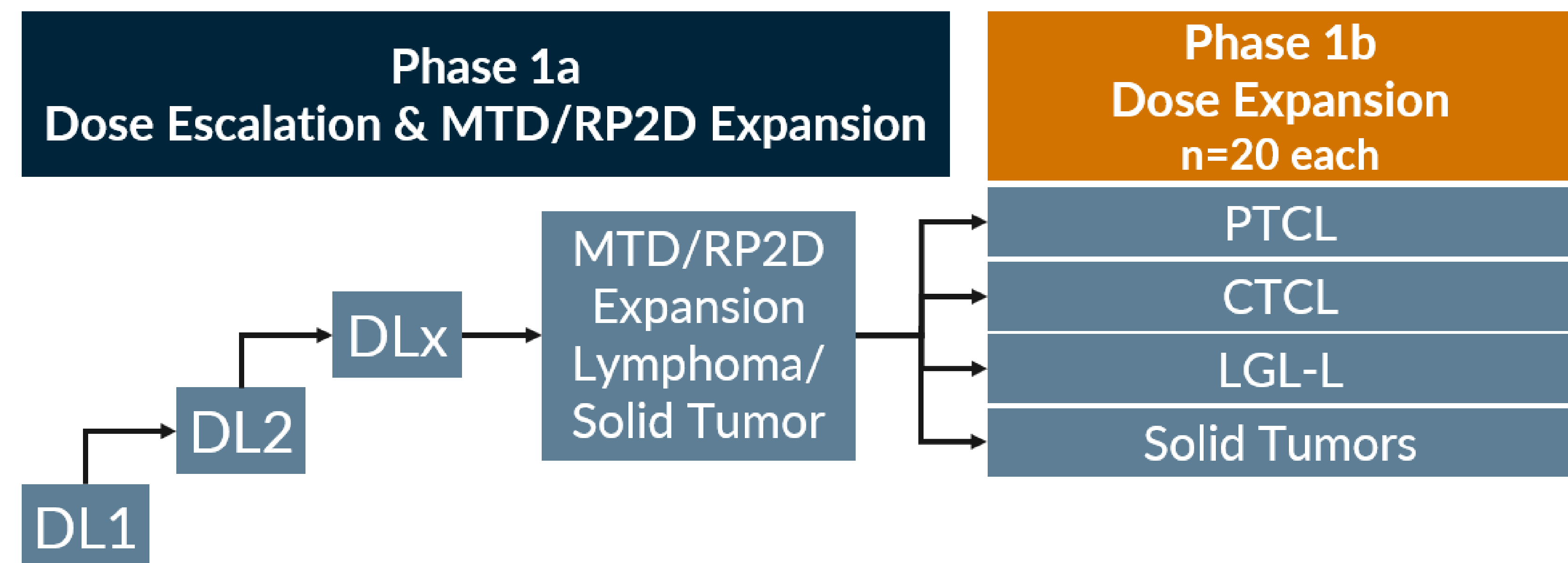
- KT-333 is a potent, highly selective, heterobifunctional small molecule degrader of STAT3.
- In preclinical studies, durable tumor regressions were seen with weekly intravenous (IV) dosing of KT-333 in STAT3-dependent T-cell lymphomas (ALK + ALCL).



## METHODS

- This is an open-label, Phase 1a (dose escalation) and Phase 1b (expansion) first-in-human study in patients with relapsed/refractory (R/R) lymphomas and advanced solid tumors.
- The Phase 1 RP2D determined in R/R lymphoma and solid tumor patients will be evaluated further during Phase 1b in patients with PTCL, CTCL, LGL-L or advanced solid tumors.
- In Phase 1a, ascending doses of IV KT-333 given once weekly in 28-day cycles will be evaluated in an accelerated dose titration design followed by the 3+3 design.
- In Phase 1b, KT-333 will be administered at the RP2D determined during Phase 1a.
- Treatment with KT-333 will continue until disease progression, unacceptable toxicity, or patient refusal.

## TRIAL DESIGN



**Primary Objective:** To evaluate safety, tolerability and PK/PD of KT-333 in patients with relapsed or refractory lymphomas, solid tumors, PTCL, CTCL, and LGL-L (Phase 1b only).

### Study Endpoints:

**Primary:** Safety, tolerability, MTD/RP2D (Phase 1a).

**Secondary:** PK, preliminary efficacy.

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

## KEY ELIGIBILITY CRITERIA

### Inclusion Criteria

- Phase 1a:** Lymphomas (including Hodgkin's, B-cell, T-cell, Small Lymphocytic, or NK-cell Lymphomas) or solid tumors R/R to at least 2 prior systemic treatments or in cases where there is no standard therapy available.
- Phase 1b:** PTCL, CTCL, LGL-L (T-cell LGL-L or CLPD-NK) or solid tumors R/R to at least 1 prior systemic treatment or in cases where there is no standard therapy available.
- LGL-L (Phase 1b only):** Severe neutropenia  $<500/\text{mm}^3$ , or neutropenia associated with recurrent infection, or symptomatic anemia and/or transfusion-dependent anemia.
- PTCL and Solid Tumors:** Measurable disease (Phase 1a allows non-measurable disease for solid tumor patients).
- Eastern Cooperative Oncology Group performance status of 0-2.
- Adequate bone marrow function (except for patients with LGL-L), adequate liver/kidney organ function for all patients.

### Exclusion Criteria

- History or suspicion of central nervous system (CNS) metastases.
- Not recovered from clinically significant AEs of previous treatments to a pretreatment baseline or Grade 1.
- Radiation treatment or major surgery requiring general anesthesia within 4 weeks prior to first dose of KT-333.
- Autologous hematopoietic stem cell transplant less than 3 months prior to first dose of study drug.
- Prior allogeneic hematopoietic or bone marrow transplant.

## Acknowledgments

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