Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of KT-333, a Targeted Protein Degrader of STAT3, in Patients with Relapsed or Refractory Lymphomas, Leukemia, and Solid Tumors

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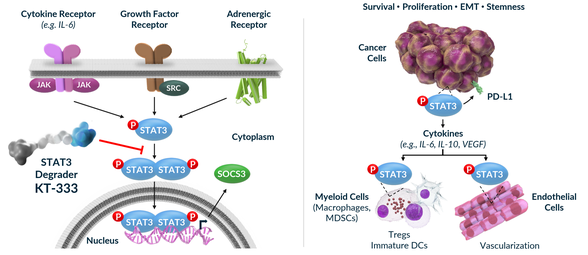
INTRODUCTION

- STAT3, a transcription factor in the JAK/STAT signaling pathway, regulates expression of genes involved in a variety of cellular functions including survival, proliferation, stemness and immunosuppression.
- Aberrant activation of STAT3 resulting from genetic aberrations or deregulated cytokine signaling underlies various hematological malignancies, notably, different subtypes of T-cell lymphomas and classic Hodgkin lymphoma (cHL).
- Characteristically for cHL, in addition to PD-L1/PD-L2 copy number amplifications, chromosome 9p24.1 alterations also underlie Janus kinase 2 (JAK2) overexpression resulting in constitutive STAT3 signaling in tumor cells as well as within the immunosuppressive tumor micro-environment.
- As a master regulator of tumor cell intrinsic and extrinsic mechanisms including expression of PD-1 ligands, STAT3 is central to cHL pathogenesis.
- Among treatment options, while PD-1 blockade is highly efficacious in R/R cHL, blocking JAK/STAT signaling has been shown to reinvigorate responses to anti-PD1 in patients whose tumors fail to respond or eventually develop resistance.
- Targeted protein degraders offer 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 that has been evaluated in hematological malignancies as well as solid tumors in a Phase 1 study.

Figure 1. STAT3 Signaling in Cancer

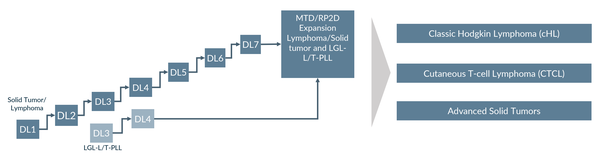


METHODS

Phase 1a
Dose Escalation & MTD/RP2D Expansion

Phase 1b
Dose Expansion Opportunities

KT-333 IV Weekly in 28-day Cycles



MTD=maximum tolerated dose; RP2D=recommended phase 2 dose; IV=intravenous; DL=dose level; T-PLL=T-cell prolymphocytic leukemia

STUDY DESIGN AND OBJECTIVES

Primary Objective:
- **Phase 1a.** Overall safety profile of escalating doses of KT-333 and determination of the maximum tolerated dose through evaluation of dose limiting toxicity (DLT) to determine MTD/RP2D.

Secondary Objective:
- PK and preliminary clinical activity.

Exploratory: STAT3 degradation and STAT3-regulated circulating biomarkers in peripheral blood; STAT3/pSTAT3 expression and immune TME profiling in baseline and on-treatment tumor biopsies; Gene expression in peripheral blood and tumor biopsy; STAT3 mutational analyses.

KEY ELIGIBILITY CRITERIA

Inclusion Criteria:
- **Phase 1a.**
  - Lymphomas (including cHL, B-, T- and NK-Cell lymphoma) or solid tumors relapsed/refractory (R/R) to at least two prior treatments or with no available standard therapy.
  - LGL-L/T-PLL: R/R to one prior systemic treatment.
- ECOG of 0-2.
- Adequate liver/kidney (all patients) 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.
- Allogenic hematopoietic or bone marrow transplant less than 6 months prior to 1st dose.
- Diagnosis of Chronic Lymphocytic Leukemia or small lymphocytic leukemia.

RESULTS

DEMOGRAPHICS

	Dose Levels 1 to 4 0.05 – 0.4 mg/kg (n=31)	Dose Level 5 0.7 mg/kg (n=10)	Dose Level 6 1.1 mg/kg (n=9)	Dose Level 7 1.5 mg/kg (n=6)	Overall (N=56)
Age					
Median (min, max)	66 (40, 81)	65.5 (30, 75)	47 (24, 73)	61.5 (50, 73)	62 (24, 81)
Gender at Birth					
Male	21 (67.7)	7 (70.0)	5 (55.6)	1 (16.7)	34 (60.7)
ECOG					
0	10 (32.3)	4 (40.0)	6 (66.7)	2 (33.3)	22 (39.3)
1	21 (67.7)	5 (50.0)	2 (22.2)	4 (66.7)	32 (57.1)
2	-	-	1 (11.1)	-	1 (1.8)
Missing	-	1 (10.0)	-	-	1 (1.8)
Prior Anti-cancer Regimens					
≥4	10 (32.3)	3 (30.0)	5 (55.6)	3 (50.0)	21 (37.5)
Primary Diagnosis					
Solid Tumor‡	17 (54.8)	3 (30.0)	-	1 (16.7)	21 (37.5)
Classic Hodgkin Lymphoma (cHL)	2 (6.5)	2 (20.0)	5 (55.6)	3 (50)	12 (21.4)
CTCL	5 (16.1)	2 (20.0)	4 (44.4)	-	11 (19.6)
T-Cell LGL-L	3 (9.7)	2 (20.0)	-	-	5 (8.9)
PTCL	2 (6.5)	-	-	1 (16.7)	3 (5.4)
T-PLL	2 (6.5)	-	-	-	2 (3.6)
NK-Cell Lymphoma	-	-	-	1 (16.7)	1 (1.8)
B-Cell Lymphoma	-	1 (10.0)	-	-	1 (1.8)

‡ = colorectal (4); head and neck (3); pancreatic (2); anal; appendiceal; cervical; cholangiocarcinoma; colon adenocarcinoma; duodenal; endometrial; gallbladder; ovarian, peritoneal, rectal and renal (n=1 each)

EXPOSURE AND DISPOSITION

- As of 23 October 2024, fifty-six patients received a mean 10 doses (range 4, 17) across the first seven dose levels in patients with solid tumors, lymphomas and LGL-L/T-PLL. This included backfill enrollment at DL2 through DL6.
- Ten patients remain active (DL3, n=2; DL4, n=1; DL5, n=2; DL6, n=2; DL7, n=3) and 46 patients discontinued KT-333. Primary reasons for discontinuation of treatment were disease progression, n=23; discretion of the investigator n=9; withdrawal by patient, n=7; adverse event, n=3; clinical progression, n=3.

OVERALL SAFETY

Number of Patients with Adverse Event Occurring in >15% Patients (n, (%)) – Regardless of Causality

Preferred Term	Dose Levels 1 to 4 0.05 to 0.4 mg/kg (n=31)		Dose Level 5 0.7 mg/kg (n=10)		Dose Level 6 1.1 mg/kg (n=9)		Dose Level 7 1.5 mg/kg (n=6)		Overall (n=56)	
	All	≥Grade 3	All	≥Grade 3	All	≥Grade 3	All	≥Grade 3	All	≥Grade 3*
Stomatitis	7 (22.6)	-	6 (60.0)	1 (10)	8 (88.9)	2 (22.2)	3 (50.0)	-	24 (42.9)	3 (5.4)
Fatigue	9 (29)	1 (3.2)	1 (10)	-	4 (44.4)	-	2 (33.3)	1 (16.7)	16 (28.6)	2 (3.6)
Nausea	9 (29)	-	2 (20)	-	3 (33.3)	-	1 (16.7)	-	15 (26.8)	-
ALT increased	7 (22.6)	1 (3.2)	2 (20)	-	4 (44.4)	-	1 (16.7)	-	14 (25)	1 (1.8)
Constipation	6 (19.4)	-	2 (20)	-	5 (55.6)	1 (11.1)	-	-	13 (23.2)	1 (1.8)
AST increased	5 (16.1)	1 (3.2)	2 (20)	-	3 (33.3)	-	1 (16.7)	-	11 (19.6)	1 (1.8)
Pyrexia	2 (6.5)	-	4 (40)	-	3 (33.3)	-	2 (33.3)	-	11 (19.6)	-
Diarrhea	6 (19.4)	-	1 (10)	-	1 (11.1)	-	1 (16.7)	-	9 (16.1)	-

ALT = alanine aminotransferase; AST = aspartate aminotransferase
*Two Grade 4 events were observed: DL6 CTCL patient with Grade 4 Toxic epidermal necrolysis and an LGL-L patient in DL5 with Grade 4 Neutropenia, both considered not related to KT-333. No Grade 5 events.

SAFETY SUMMARY

- Overall, KT-333 was well tolerated with primarily Grade 1-2 Adverse Events (AEs).
- The most common AEs related to KT-333 (incidence >15%) were stomatitis, fatigue and ALT increase.
- Grade 3 AEs related to KT-333 were stomatitis (n=3), acute kidney injury (n=1), arthralgia (n=1), fatigue (n=1), hematuria (n=1), neutropenia (n=2), platelet count decreased (n=1), and weight decreased (n=1) (there were no Grade >3 AEs related to KT-333).
- Leukemia patients:
  - DLTs: Grade 3 arthralgia and Grade 3 stomatitis in 2/2 LGL-L patients at DL5
  - Protocol revised to evaluate dose escalation separately in leukemia patients only at DL3-DL4 and enrollment completed without DLTs.
- Solid Tumor/Lymphoma patients:
  - DLTs: Grade 3 fatigue (lymphoma pt/DL7), Grade 2 stomatitis (cHL pt/DL6 backfill) and Grade 3 stomatitis (cHL pt/DL6 backfill).

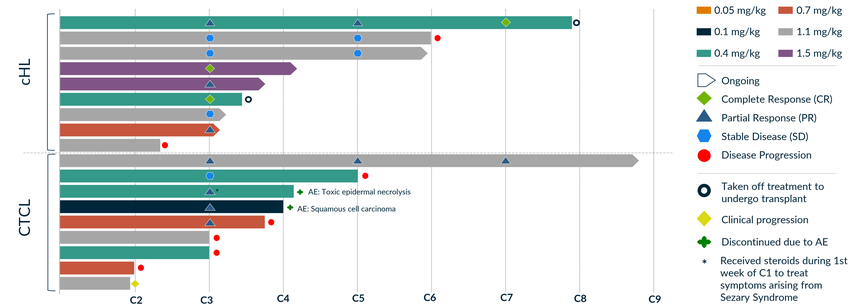
CLINICAL RESPONSES

Best Overall Response[1]

	Hodgkin Lymphoma (cHL) (n=9)	CTCL (n=9)	B-cell NHL[3] (n=1)	PTCL[4] (n=3)	NK-Cell Lymphoma (n=1)	LGL-L/ T-PLL[6] (n=3/n=1)	Solid Tumor (n=15)
Complete Response	3	-	-	-	1[2]	-	-
Partial Response	2[3]	4	-	-	-	-	-
Stable Disease	3	1	-	-	-	3/-	4
Progressive Disease	1	4[4]	1	3	-	-/1	11
Overall Response (%)	5 (55.6)	4 (44.4)	-	-	1 (100.0)	-	-

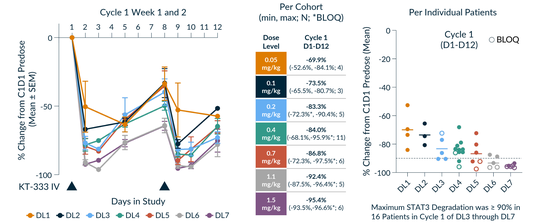
CTCL = Cutaneous T-Cell lymphoma; NHL = Non-Hodgkin's lymphoma; PTCL = Peripheral T-Cell lymphoma; LGL-L = Large granular lymphocytic leukemia; T-PLL = T-cell polymorphic leukemia
[1]The patient totals listed above represent the number of patients enrolled that were disease evaluable for response assessment at the time of cut-off; [2]PET CR; [3]One PR noted after data cut off; [4]Includes one patient with clinical progression

Figure 2. Duration of Time on Treatment – Response Evaluable cHL and CTCL Patients



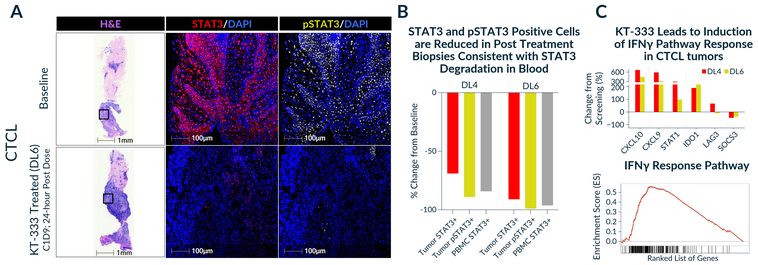
PHARMACODYNAMICS

Figure 3. KT-333 Leads to Robust STAT3 degradation with Mean Maximum of 95% in Peripheral Blood Mononuclear Cells at Dose Level 7 Demonstrating Proof-of-Mechanism



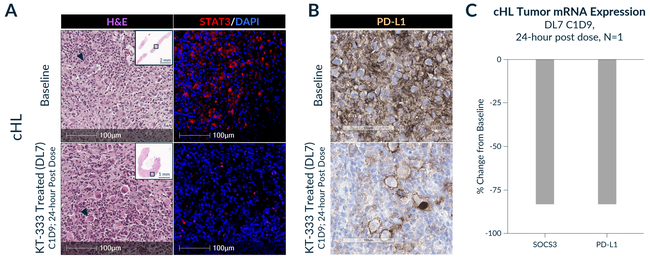
A, B) Percent change in STAT3 represents mean percent change of two STAT3 peptides from baseline measured using targeted mass spectrometry (MS) assay. Screening sample was used as baseline when C1D1 predose was not available. When both samples were available, C1D1 predose data served as baseline. For measurements BLOQ, 50% of LLOQ values for the respective STAT3 peptides were used for computation of change from baseline. DL5 data includes PD after dose reductions in two LGL-L patients (i) on C1D22 for one patient and (ii) on C1D8 and C2D1 for the other patient, both due to AEs.

Figure 4. KT-333 Leads to Marked Reductions in STAT3, pSTAT3 and STAT3 target, SOCS3 with Concomitant Induction of IFNγ Stimulated Genes in CTCL Tumors



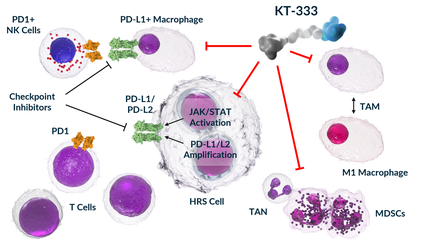
A) Representative ROIs from histological sections of a pair of pre (baseline) & post treatment (C1D9, 24 hr ±3 hr post dose) CTCL tumor biopsies from DL6 (N=1 patient) are shown. Multiplex immunofluorescence (mIF) for STAT3, pSTAT3 were conducted. Images include epidermal region, dermal region and tumor infiltrate. DAPI was used as nuclear counterstain. **B)** HALO image analysis platform was used for analysis of mIF data from a DL4 and above DL6 pre/post treatment CTCL biopsies. Intensity-based thresholds were set to derive classifiers for STAT3+, STAT3/pSTAT3 double+ that delineated biomarker positive versus negative DAPI+ cells in both Screening and C1D9 [t = 24 (±3) hours post 2nd KT-333 dose] biopsies. The epidermis was excluded from quantitative analysis. PBMC STAT3 from matched blood draws was measured by Targeted MS. **C)** Gene expression profiling of the DL4 and DL6 pre/post-treatment biopsies using RNA sequencing. Plots show biomarkers that constitute the IFNγ stimulated gene signature [Ayers, et al. (2017)], STAT3 canonical target SOCS3, and enrichment of the IFNγ response pathway as determined by GSEA.

Figure 5. KT-333 Mediated STAT3 Degradation Results in Downregulation of STAT3 Target Genes, SOCS3 and PD-L1 in a cHL Tumor



A) Representative ROI from histological sections of a pair of pre (baseline screening) & post treatment (C1D9, 24 hr ±3 hr post dose) cHL tumor biopsies from DL7 (N=1 patient), are shown. Arrows show representative Hodgkin Reed Sternberg (HRS) cells in the H&E images. Multiplex immunofluorescence (mIF) for STAT3 was performed on serial sections; representative ROIs are shown. DAPI was used as nuclear counterstain. **B)** Representative ROI from histological sections of the cHL paired biopsies (A) were analyzed using immunohistochemistry (IHC) for PD-L1 (Dako 22C3). Hematoxylin was used as counterstain. **C)** Gene expression profiling of paired pre/post treatment cHL biopsy specimens from a DL7 patient (Fig. 5A) 24 hrs post KT-333, using RNA sequencing.

Figure 6. Proposed Model for KT-333 Mechanism of Action in cHL



A schematic representation of KT-333 mechanism of action in classic Hodgkin lymphoma (cHL), addressing tumor- immune microenvironment interactions where STAT3 plays key tumor cell intrinsic and cell-extrinsic roles. Adapted from Calabretta et al. *Int. J. Mol. Sci.* (2019).

CONCLUSIONS

- KT-333 was well tolerated with primarily Grade 1 and 2 adverse events. Two DLTs occurred in LGL-L patients at DL5, one DLT was observed in a lymphoma patient treated at DL7, and two DLTs at DL6 (backfill), both observed in cHL patients.
- Dose escalation was completed in September 2024 and 10 patients remain ongoing including 5 cHL patients at DL5-7. The MTD was not reached and RP2D is 1.1-1.5 mg/kg (DL6-7) for ST/lymphoma patients based on safety/tolerability and PD.
- Among response-evaluable patients, objective responses observed in 5 of 9 cHL patients including 3 CRs (all having received prior BV and at least one regimen containing a checkpoint inhibitor and two of which subsequently proceeded to transplant) and 2 PRs; 4 of 9 CTCL patients with 4 PRs; and 1 of 1 NK-Cell Lymphoma (STAT3mut +) with CR by PET.
- KT-333 exposure increased approximately dose proportionally between the 0.05 mg/kg to 1.5 mg/kg doses, with a half-life of 4-7 hours.
- Mean maximum STAT3 degradation in peripheral blood mononuclear cells ranged from 87% at DL5 to 95% at DL7.
- In CTCL and cHL patient tumors, KT-333 resulted in substantial reduction of STAT3, pSTAT3 and SOCS3.
- Induction of IFNγ-stimulated genes (ISG) in CTCL tumors suggests a favorable immunomodulatory response.
- Checkpoint protein and STAT3 target PD-L1, overexpression of which is a hallmark of cHL pathogenesis, was markedly reduced by KT-333 in a cHL patient tumor.
- The robust STAT3 knockdown and favorable immunomodulation seen at doses that were well-tolerated support further development of KT-333 as monotherapy in cHL and CTCL and in combination with anti-PD1 therapy in cHL and solid tumors.

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