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

#3081

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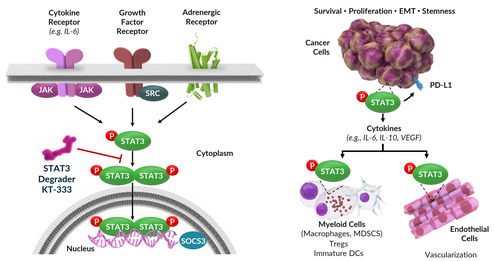
INTRODUCTION

STAT3

- 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

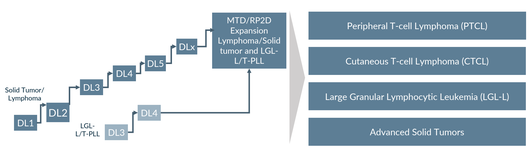
- Targeted protein degraders are a new therapeutic class of compounds that utilize the ubiquitin proteasome system to target degradation of specific proteins.
- KT-333 is a first-in-class, potent, highly selective, heterobifunctional small molecule degrader of STAT3.
- In preclinical studies, proof of 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). STAT3 degradation also led to an IFNγ response and TME remodeling in a syngeneic solid tumor model sensitizing to PD-1 blockade.

METHODS

Phase 1a
Dose Escalation & MTD/RP2D Expansion (n=~45)

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 (MTD)/recommended Phase 2 dose (RP2D).
- **Phase 1b.** Safety and tolerability of KT-333 at the RP2D in patients with PTCL, LGL-L, CTCL and solid tumors.

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 Hodgkin, B- and T-cell) 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.
- **Phase 1b.** PTCL, CTCL, LGL-L (T-cell 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.
- 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 Level 1 0.05 mg/kg (n=4)	Dose Level 2 0.1 mg/kg (n=4)	Dose Level 3 0.2 mg/kg (n=5)	Dose Level 4 0.4 mg/kg (n=11)	Dose Level 5 0.7 mg/kg (n=5)	Overall (N=29)
Age (years)						
Median (min, max)	64.5 (57, 70)	63.5 (59, 74)	69.0 (40, 76)	66.0 (42, 81)	61.0 (30, 69)	65.0 (30, 81)
Sex (n, (%))						
Male	3 (75.0)	1 (25.0)	3 (60.0)	9 (81.8)	5 (100)	21 (72.4)
ECOG (n, (%))						
0	1 (25.0)	-	2 (40.0)	4 (36.4)	3 (60.0)	10 (34.5)
1	3 (75.0)	4 (100)	3 (60.0)	7 (63.6)	2 (40.0)	19 (65.5)
Prior Anti-Cancer Therapy						
≥3	4 (100)	4 (100)	5 (100)	9 (81.8)	4 (80.0)	25 (86.2)
Tumor Type						
Solid Tumor‡	3 (75.0)	2 (50.0)	5 (100)	7 (63.6)	2 (40.0)	19 (65.5)
PTCL^	-	1 (25.0)	-	-	-	1 (3.4)
CTCL	1 (25.0)	1 (25.0)	-	3 (27.3)	-	5 (17.2)
T-Cell LGL-L	-	-	-	-	2 (40.0)	2 (6.9)
B-Cell Lymphoma	-	-	-	-	1 (20.0)	1 (3.4)
Hodgkin's	-	-	-	1 (9.1)	-	1 (3.4)

‡ = anal; appendiceal; cholangiocarcinoma; colon adenocarcinoma; colorectal (4); duodenal; endometrial; head and neck (3); ovarian, pancreatic (2), peritoneal, rectal and renal; ^ = anaplastic T-cell lymphoma; Data cut-off: 18 October 2023

Overall Safety

Number of Patients with Adverse Event Occurring in ≥15% Patients Overall (n, (%)) – All Causality and Related to KT-333

Preferred Term	Dose Level 1 0.05 mg/kg (n=4)		Dose Level 2 0.1 mg/kg (n=4)		Dose Level 3 0.2 mg/kg (n=5)		Dose Level 4 0.4 mg/kg (n=11)		Dose Level 5 0.7 mg/kg (n=5)[a]		Overall (N=29)	
	All	Related	All	Related	All	Related	All	Related	All	Related	All	Related
Nausea	1 (25.0)	-	1 (25.0)	-	3 (60.0)	-	3 (27.3)	1 (9.1)	-	-	8 (27.6)	1 (3.4)
ALT increased	-	-	-	-	2 (40.0)	-	4 (36.4)	3 (27.3)	2 (40.0)	-	8 (27.6)	3 (10.3)[b]
AST increased	-	-	-	-	2 (40.0)	-	3 (27.3)	2 (18.2)	2 (40.0)	-	7 (24.1)	2 (6.9)[b]
Constipation	2 (50.0)	-	1 (25.0)	-	-	-	3 (27.3)	-	1 (20.0)	1 (20.0)	7 (24.1)	1 (3.4)
Fatigue	2 (50.0)	-	1 (25.0)	-	2 (40.0)	1 (20.0)	2 (18.2)	1 (9.1)	-	-	7 (24.1)	2 (6.9)
Stomatitis	-	-	-	-	1 (20.0)	-	3 (27.3)	3 (27.3)	3 (60.0)	3 (60.0)	7 (24.1)	6 (20.7)
Anemia	-	-	2 (50.0)	-	1 (20.0)	-	2 (18.2)	1 (9.1)	1 (20.0)	-	6 (20.7)	1 (3.4)
Abdominal pain	2 (50.0)	1 (25.0)	-	-	-	-	1 (9.1)	-	2 (40.0)	-	5 (17.2)	1 (3.4)

a) At the time of data cut off DL5 was still open to enrollment in patients with Solid Tumors and Lymphoma diagnosis with an expected enrollment total of n=6
b) All Grade 1

Data cut-off: 18 October 2023

Safety Summary

- Grade 3 and 4 Adverse Events (no Grade 5 (n=patients))
  - Unrelated to KT-333:
    - Grade 3: abdominal pain (3), acute kidney injury (1), ALT increase (1), anemia (2), AST increase (1), fatigue (1), febrile neutropenia (1), hypertension (1), neutropenia (2), ANC decrease (1); pyrexia (1)
    - Grade 4: neutropenia (1)
  - Related to KT-333: Grade 3: stomatitis (1), arthralgia (1), weight decreased (1)
- Dose Limiting Toxicities: Grade 3 stomatitis (single KT-333 related SAE) and Grade 3 arthralgia (occurred in 2 different LGL-L patients treated in DL5).
- The MTD was exceeded in leukemia patients based on the DLTs observed in the LGL-L patients treated at DL5; therefore, the protocol was revised to evaluate dose escalation separately in patients with LGL-L/T-PLL from those with solid tumors or lymphomas.
- LGL-L/T-PLL patient enrollment continuing at DL3 with potential escalation limited to DL4.
- Solid tumor and lymphoma patients enrolling at DL5 with potential escalation to DL6 and beyond per 3+3.

Exposure, Duration on Treatment and Disposition

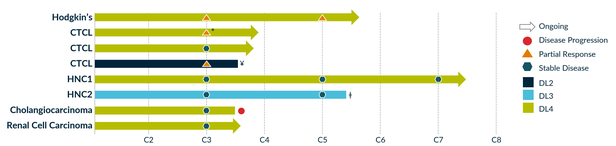
- As of 18 October 2023, Twenty-nine patients received a mean of eight doses across the first five dose levels (range 4, 9.4).
- Seven patients remain active (DL3, 1; DL4, 5; DL5, 1) and 22 patients discontinued KT-333. Primary reasons for discontinuation were adverse event (2: Gr. 2 squamous cell carcinoma of skin in CTCL pt, probably related to KT-333 and Gr. 1 stomatitis, probably related/Gr1 pyrexia, unlikely related to KT-333), withdrawal by subject (2), disease progression (11), clinical progression (1), pt no longer acceptable (1), and discretion of investigator (5).

Overall Response in Evaluable Patients*

	Non-CTCL Lymphoma/ Hodgkin's (n=3)	CTCL (n=5)	Solid Tumor (n=12)
Partial Response	1	2	0
Stable Disease	0	1	4
Progression of Disease	2	2	8

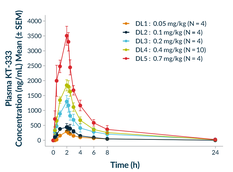
* Two LGL-L patients at DL5 not included as they were not evaluable for response assessment at time of KT-333 discontinuation

Figure 1: Duration on Treatment for Patients with Response of SD or Better



* Received steroids during 1st week of C1 to treat symptoms arising from Sezary Syndrome
¥ Discontinued d/t AE (Gr. 2 squamous cell carcinoma of skin)
ǂ Discontinued d/t PI discretion (stable disease at discontinuation)
HNC1 = Mucoepidermoid carcinoma of parotid gland
HNC2 = Sinonasal adenocarcinoma

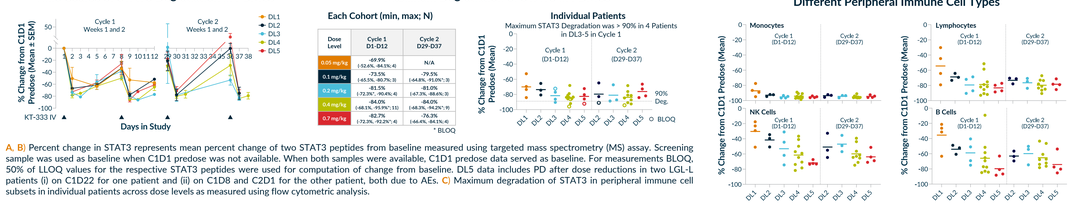
Figure 2: Cycle 1, Day 1 Pharmacokinetic Profile and Parameters



PK Parameter	0.05 mg/kg (n=4)	0.1 mg/kg (n=3)	0.2 mg/kg (n=4)	0.4 mg/kg (n=10)	0.7 mg/kg (n=4)
C_{max} (ng/mL)	307 (30.5%)	443 (24.4)	1360 (31.2)	1940 (25.7)	3690 (14.4)
AUClast (ng.h/mL)	1550 (66.0%)	1930 (18.6)	6460 (59.7)	8860 (46.6)	15200 (18.3)
Vd (L/kg)	0.277 (17.1%)	0.263 (35.2)	0.283 (42.9)	0.294 (36.1)	0.257 (11.9)
CL (L/h/kg)	0.0447 (62.7%)	0.0531 (20.9)	0.0421 (59.3)	0.0532 (39.7)	0.0475 (20.7)
$t_{1/2}$ (h)	6.25 (78.8%)	3.42 (28.5)	5.14 (22.9)	4.09 (30.4)	3.84 (19.0)

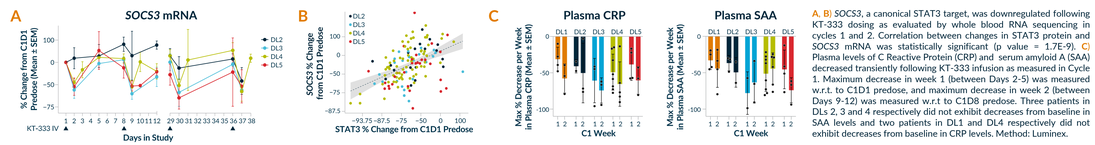
Mean (%CV) are presented; subject 103-001 (DL2) excluded from calculation of PK parameters due to inconsistency in PK profile

Figure 3: KT-333 leads to Mean Maximum STAT3 Degradation of Up to 84% in Peripheral Blood Mononuclear Cells at Dose Levels 4-5 Demonstrating Proof-of-Mechanism



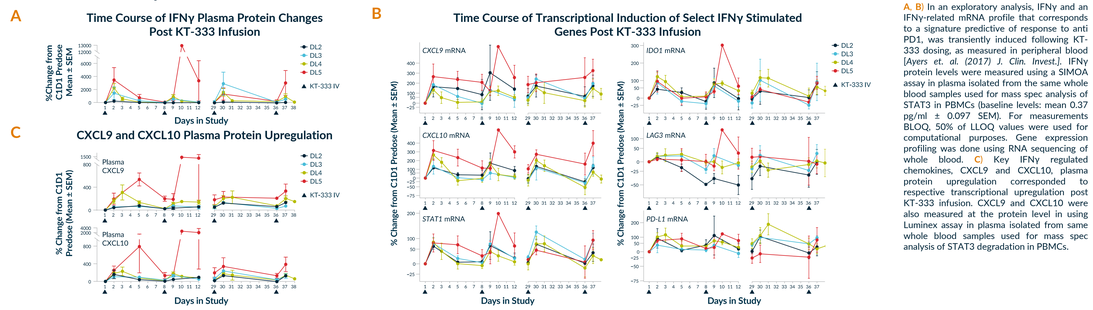
A, B) Percent change in STAT3 represents mean percent change of two STAT3 peptides from baseline measured using targeted mass spectrometry (MS) assay. Screening sample was used as baseline when C1D1 predose was not available. When both samples were available, C1D1 predose data served as baseline. For 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. C) Maximum degradation of STAT3 in peripheral immune cell subsets in individual patients across dose levels as measured using flow cytometric analysis.

Figure 4: KT-333 Achieves STAT3 Pathway Inhibition and Acute Downregulation of Inflammatory Biomarkers in Peripheral Blood



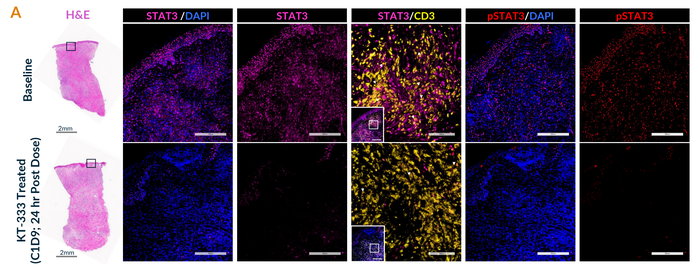
A, B) *SOCS3*, a canonical STAT3 target, was downregulated following KT-333 dosing as evaluated by whole blood RNA sequencing in cycles 1 and 2. Correlation between changes in STAT3 protein and *SOCS3* mRNA was statistically significant (p value = 1.7E-9). C) Plasma levels of C Reactive Protein (CRP) and serum amyloid A (SAA) decreased transiently following KT-333 infusion as measured in Cycle 1. Maximum decrease in week 1 (between Days 2-5) was measured w.r.t. to C1D1 predose, and maximum decrease in week 2 (between Days 9-12) was measured w.r.t to C1D8 predose. Three patients in DLs 2, 3 and 4 respectively did not exhibit decreases from baseline in SAA levels and two patients in DL1 and DL4 respectively did not exhibit decreases from baseline in CRP levels. Method: Luminex.

Figure 5: KT-333 Leads to Induction of IFNγ, a Central Cytokine Involved in Anti-Tumor Immunity, and IFNγ Stimulated Genes as Detected in Peripheral Blood

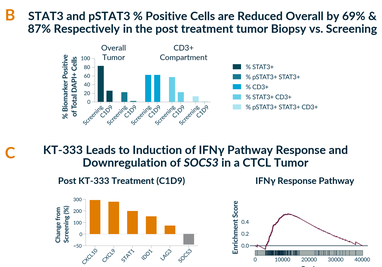


A, B) In an exploratory analysis, IFNγ and an IFNγ-related mRNA profile that corresponds to a signature predictive of response to anti PD1, was transiently induced following KT-333 dosing, as measured in peripheral blood [*Ayers et. al. (2017) J. Clin. Invest.*]. IFNγ protein levels were measured using a SIMOA assay in plasma isolated from the same whole blood samples used for mass spec analysis of STAT3 in PBMCs (baseline levels: mean 0.37 pg/ml ± 0.097 SEM). For measurements BLOQ, 50% of LLOQ values were used for computational purposes. Gene expression profiling was done using RNA sequencing of whole blood. C) Key IFNγ regulated chemokines, CXCL9 and CXCL10, plasma protein upregulation corresponded to respective transcriptional upregulation post KT-333 infusion. CXCL9 and CXCL10 were also measured at the protein level in using Luminex assay in plasma isolated from same whole blood samples used for mass spec analysis of STAT3 degradation in PBMCs.

Figure 6: KT-333 Leads to Marked Reductions in STAT3, pSTAT3 and SOCS3 Levels with Concomitant Induction of IFNγ Stimulated Genes Including Chemokines, CXCL9 and CXCL10 in Tumor Tissue from a CTCL Patient



t = 24 (±3) hours post 2nd dose of KT-333 (C1D9); CTCL patient treated in DL4; Maximum STAT3 degradation in PBMCs by MS: 86% (C1); 91% (C2)



t = 24 (± 3) hours post 2nd KT-333 infusion; CTCL patient was treated in DL4

A) Representative ROIs from histological sections of tumor biopsies analyzed using multiplex immunofluorescence (mIF) for STAT3, pSTAT3 and CD3. Images include epidermal region, dermal region and CD3+ tumor infiltrate. DAPI was used as nuclear counterstain. Scale bars: 2 mm for H&E; 300 µm for mIF and 80 µm for high magnification ROI showing STAT3/CD3 co-stain. White arrows indicate STAT3+CD3+ cells. B) HALO image analysis platform was used for analysis of mIF data. Intensity-based thresholds were set to derive classifiers for CD3, STAT3, pSTAT3 that delineated biomarker positive versus negative DAPI+ cells in both the screening and C1D9 biopsies. The epidermis was excluded from quantitative analysis. C) Gene expression profiling of FFPE specimen from screening and C1D9 CTCL biopsy using RNA sequencing.

CONCLUSIONS

- KT-333 was well tolerated with primarily Grade 1 and 2 adverse events. Two DLTs occurred in LGL-L patients at DL5 and no DLTs observed in solid tumor/lymphoma patients. Dose escalation is ongoing at DL5 in solid tumor/lymphoma patients and at DL3 in leukemia patients.
- Partial response (PR) observed in one patient with Hodgkin's lymphoma at DL4, and among the five CTCL patients treated to date, two PRs and one stable disease (3 of 5 with clinical benefit) were observed at DLs 2 and 4. Ongoing stable disease observed in four patients with advanced solid tumors; one at DL3 and three at DL4.
- KT-333 achieved up to 84% mean maximum STAT3 degradation in peripheral blood mononuclear cells at DL4-5 and maximum degradation up to 96% with evidence of STAT3 pathway inhibition (decrease in SOCS3) and downregulation of inflammatory biomarkers in peripheral blood.
- Key cytokine involved in anti-tumor immunity, IFNγ, as well as IFNγ-stimulated genes were induced in peripheral blood showing functional engagement of the JAK/STAT pathway.
- KT-333 resulted in substantial reduction of STAT3, pSTAT3 and SOCS3 in a CTCL patient tumor with concomitant induction of IFNγ-stimulated genes, including chemokines CXCL9 and CXCL10, suggestive of favorable immunomodulatory response in the TME.

ACKNOWLEDGMENT

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