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

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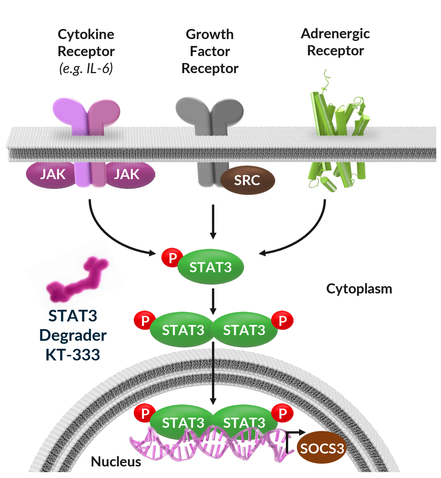
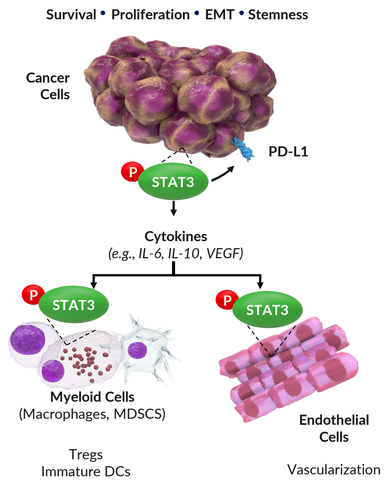
Introduction/Background

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) and with KT-333 in combination with anti-PD-1 in syngeneic mouse colorectal cancer model.

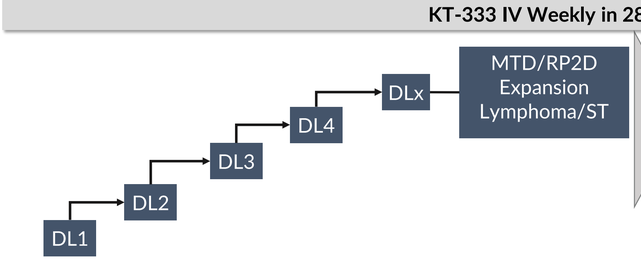
Methods

Study Design and Objectives

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

Phase 1b
Dose Expansion (n=20 each)

KT-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

DL=dose level; MTD=maximum tolerated dose; RP2D=recommended phase 2 dose; ST=solid tumor

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 (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.
- Prior allogenic hematopoietic or bone marrow transplant.

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=3)	Dose Level 4 0.4 mg/kg (n=2*)	Overall (N=13)
Age (years)					
Median (min, max)	64.5 (57, 70)	63.5 (59, 74)	52.5 (40, 76)	74.5 (72, 77)	65.0 (40, 77)
Sex (n, (%))					
Male	3 (75)	1 (25)	1 (33.3)	2 (100)	7 (53.8)
Race (n, (%))					
Black or African American	-	2 (50)	1 (33.3)	1 (50)	4 (30.8)
White	4 (100)	2 (50)	2 (66.7)	-	8 (61.5)
Unknown (patient did not disclose)	-	-	-	1 (50)	1 (7.7)
ECOG (n, (%))					
0	1 (25)	0	2 (66.7)	0	3 (23.1)
1	3 (75)	4 (100)	1 (33.3)	2 (100)	10 (76.9)
Number of prior systemic therapies					
≥3	4 (100)	4 (100)	2 (66.7)	2 (100)	12 (92.3)
Tumor type					
Solid Tumor‡	3 (75)	2 (50)	3 (100)	2 (100)	10 (76.9)
PTCL⌂	-	1 (25)	-	N/A*	1 (7.7)
CTCL	1 (25)	1 (25)	-	N/A*	2 (15.4)

‡ = appendiceal; colorectal (2); pancreatic; endometrial; peritoneal; ovarian; head and neck; anal and intrahepatic cholangiocarcinoma
⌂ = anaplastic T-cell lymphoma
* = DL4, at time of data cut off, two patients were enrolled, and accrual was ongoing. N/A = data not available.

Exposure and Disposition

- As of 01 May 2023, Thirteen patients received a mean of five doses across four dose levels.
- Five patients remain active, and eight patients discontinued between Cycle 1, Day 1 and C3, Day 22. Primary reasons for discontinuation were disease progression (3); withdrawal by subject (2); PI decision (2); and Adverse event (1; Gr. 2 squamous cell carcinoma of skin in CTCL patient with prior history of UVB treatment and recurrent SCCs of skin, possibly related to KT-333 per investigator assessment).

Overall Safety

Number of Patients with Adverse Event Occurring in ≥2 Patients (n, (%))

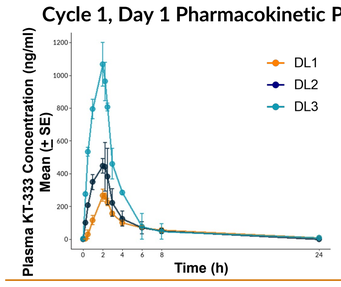
Preferred Term	Dose Level 1 0.05 mg/kg (n=4)		Dose Level 2 0.1 mg/kg (n=4)		Dose Level 3 0.2 mg/kg (n=3)		Dose Level 4 0.4 mg/kg (n=2[c])		Overall [a, b] (N=13)	
	All	Related	All	Related	All	Related	All	Related	All	Related[d]
Fatigue	2 (50)	-	1 (25)	-	1 (33.3)	-	-	-	4 (30.8)	-
Anemia	-	-	2 (50)	-	1 (33.3)	-	-	-	3 (23.1)	-
Constipation	2 (50)	-	1 (25)	-	-	-	-	-	3 (23.1)	-
Nausea	1 (25)	-	1 (25)		1 (33.3)	-	-	-	3 (23.1)	-
Dehydration	1 (25)	-	1 (25)		-	-	-	-	2 (15.4)	-
Dizziness	1 (25)	-	1 (25)		-	-	-	-	2 (15.4)	-
Skin infection	1 (25)	-	1 (25)		-	-	-	-	2 (15.4)	-

(a) All Grade 1 and 2 events except the following: 1 patient with Gr. 3 abdominal pain and 1 patient with Gr. 3 fatigue that were not related to KT-333.
(b) No Grade 4 or Grade 5 events.
(c) At time of data cut off, DL4 had enrolled two patients and no AEs had been reported.
(d) AEs related to KT-333 (n=1 each): Gr. 1: abdominal pain upper, LDH increase, and rash. Gr. 2: diarrhea, hypothyroidism and squamous cell carcinoma of the skin.

Safety Summary: At the time of the data cut off, KT-333 was well tolerated, with no dose limiting toxicity observed and no serious adverse events considered related to KT-333.

Pharmacodynamics and Pharmacokinetics

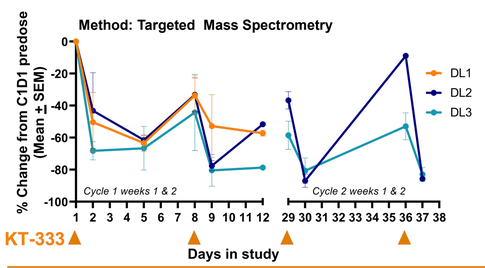
Cycle 1, Day 1 Pharmacokinetic Profile and Parameters



PK Parameter	Dose Level 0.05 mg/kg (n=4)	0.1 mg/kg (n=2)	0.2 mg/kg (n=2)
C_{max} (ng/mL)	307 (30.5%)	382 (405, 359)	1020 (1130, 902)
AUClast (ng.h/mL)	1550 (65.7%)	1820 (2120, 1520)	3150 (3050, 3250
Vd (L/kg)	0.277 (17.1%)	0.315 (0.293, 0.337)	0.388 (0.374, 0.401)
CL (L/h/kg)	0.0447 (62.7%)	0.0565 (0.047, 0.0659)	0.0636 (0.0656, 0.0616)
$t_{1/2}$ (h)	6.25 (78.8%)	3.93 (4.32, 3.55)	4.23 (3.95, 4.51)

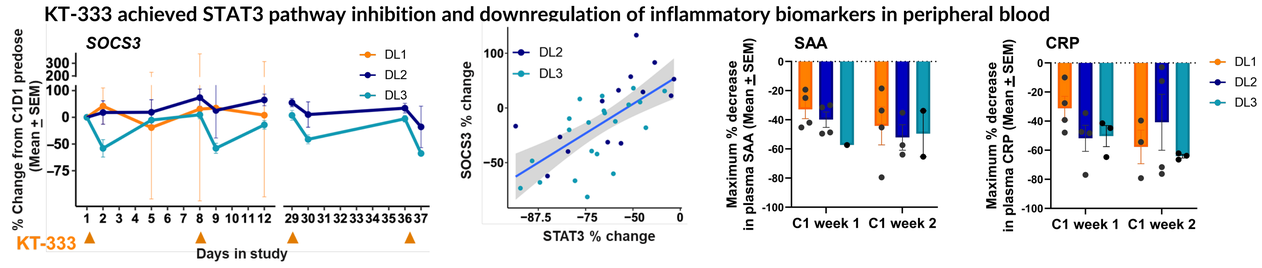
Mean (%CV) shown for DL1; Mean (individual values) shown for DL2 and DL3

Proof-of-mechanism for KT-333 demonstrated with up to 88% mean max degradation of STAT3 in peripheral blood mononuclear cells



Dose Level	Patient ID	Cycle 1 Maximum Degradation mean** (weekly max)	Cycle 1 Average	Cycle 2 Maximum Degradation mean** (weekly max)	Cycle 2 Average
0.05 mg/kg (n=4)	105-001	-79.8 % (-75.6 %, -84.1 %)	-66.4 %	N/A	N/A
	105-002	-67.8 % (-73.5 %, -62.0 %)		N/A	
	102-001	-50.0 % (-47.4 %, -52.6 %)		N/A	
	105-003	-67.8 % (-66.1 %, -69.5 %)		N/A	
0.1 mg/kg (n=3)	105-004	-65.5 % (-65.5 %, *missing*)	-70.2 %	-82.8 %	-85.6 %
	103-001	-74.4 % (-68.1 %, -80.7 %)		-88.4 % (-91.0# %, -85.7#%)	
	180-004	-70.6 % (-66.9 %, -74.4 %)		*pending*	
0.2 mg/kg (n=2)	180-001	-75.5 % (-73.9 %, -77.0 %)	-80.5 %	-83.6 % (-88.6 %, -78.6 %)	-81.8 %
	180-002	-85.4 % (-80.3 %, -90.4 %)		-80.0 % (-72.7 %, -87.2 %)	
		** post doses 1 & 2; # = BLOQ		** post doses 5 & 6; # = BLOQ	

KT-333 achieved STAT3 pathway inhibition and downregulation of inflammatory biomarkers in peripheral blood



- Dose-dependent reduction in *SOCS3* mRNA during Cycles 1 and 2
- Correlation between changes in STAT3 protein and SOC3 mRNA
- Reductions in plasma SAA and CRP during Cycle 1

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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