Safety, Pharmacokinetics (PK), Pharmacodynamics (PD) and Efficacy of KT-253, a Targeted Protein Degrader of MDM2, in Patients with Relapsed/Refractory (R/R) Solid Tumors, Lymphoma, High Grade Myeloid Malignancies and Acute Lymphoblastic Leukemia (ALL)

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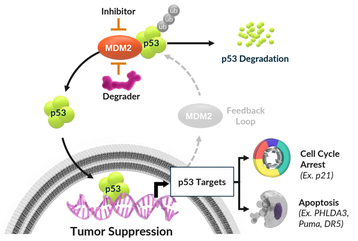
INTRODUCTION

MDM2

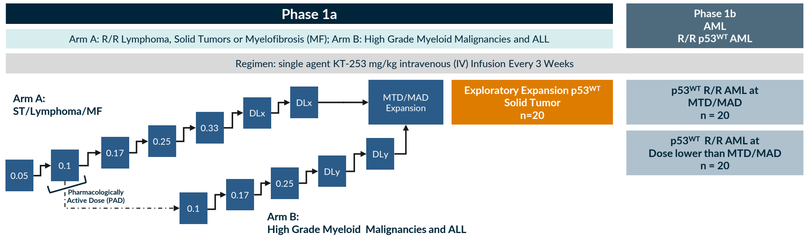
- The tumor suppressor p53 is mutated in approximately 50% of cancers.
- In cancers with wild-type p53, its activity is controlled by mouse double minute 2 (MDM2), an E3 ligase that tags p53 for degradation.
- MDM2 overexpression and amplification can inactivate p53
- MDM2 degraders, due to their catalytic rather than occupancy driven pharmacology, can lead to more efficient p53 stabilization and induction of an acute apoptotic response in tumor cells.



KT-253

- Targeted protein degraders are a new therapeutic class of compounds that utilize the ubiquitin proteasome system to target degradation of specific proteins.
- KT-253 is a novel, highly potent heterobifunctional MDM2 degrader that upregulates p53 activity and overcomes the p53-MDM2 feedback loop, resulting in >200-fold higher potency compared to MDM2 inhibitors.
- In preclinical PDX models of sensitive $p53^{WT}$ solid tumors, acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), KT-253 robustly activates p53, induces apoptosis, and results in tumor regressions with Q3-week dosing.

METHODS



Study Design/Objectives

Primary Objectives:

- **Phase 1a:** To evaluate overall safety of KT-253 and to determine the maximum tolerated dose (MTD)/maximum administered dose (MAD) in patients with R/R high grade myeloid malignancies, ALL, and separately, in patients with myelofibrosis (MF), lymphomas and advanced solid tumors.
- **Phase 1b:** To evaluate the safety and tolerability of KT-253 in patients with R/R AML.

Exploratory Objectives:

- To assess pharmacodynamic effects of KT-253 and the relationship between baseline MDM2 expression, p53 status, and tumor genotype and response to KT-253.

Key Eligibility Criteria

Phase 1a:

Arm A

- Lymphomas or solid tumors (ST) with measurable disease that is relapsed/refractory (R/R) to ≥2 prior treatments or MF following discontinuation of prior JAKi due to intolerance or refractory/resistant disease.
- No autologous or allogeneic hematopoietic stem cell transplant (HSCT) within 6 months.
- Adequate bone marrow function.

Exploratory ST Expansion

- Pathologically confirmed ST with documented $p53^{WT}$ by local assessment.

Arm B

- R/R AML, High/very high-risk Myelodysplastic Syndromes (MDS), Myelodysplastic/myeloproliferative neoplasms (MDS/MPN), Myeloproliferative neoplasms in blast phase (MPN-BP) or accelerated phase (MPN-AP) or ALL
- No allogeneic HSCT<12 weeks or autologous HSCT <4 weeks prior to dosing.

Phase 1b:

- R/R AML with documented $p53^{WT}$ status by local assessment.
- Life expectancy of ≥12 weeks.
- No allogeneic HSCT<12 weeks or autologous HSCT <4 weeks prior to dosing.

All Patients:

- ECOG 0-2.
- Adequate liver and kidney function.

NCT05775406

RESULTS

Demographics – ARM A

	Dose Level A1 0.05 mg/kg (n=3)	Dose Level A2 0.1 mg/kg (n=4)	Dose Level A3 0.17 mg/kg (n=3)	Dose Level A4 0.25 mg/kg (n=5)	Dose Level A5 0.33 mg/kg (n=1)	Overall (N=16)
Age (years)						
Median (min, max)	64.0 (42, 66)	64.0 (55, 74)	52.0 (43,57)	66.0 (43, 81)	54.0 (54, 54)	62.5 (42, 81)
Sex (n, (%))						
Male	1 (33.3)	2 (50.0)	2 (66.7)	3 (60.0)	1 (100)	9 (56.3)
ECOG (n, (%))						
0	-	1 (25.0)	2 (66.7)	3 (60.0)	NA[a]	6 (37.5)
1	3 (100)	3 (75.0)	1 (33.3)	2 (40.0)		9 (56.3)
2	-	-	-	-		0
Prior Anti-Cancer Therapy Regimens						
≥3	3 (100)	4 (100)	2 (66.7)	4 (80)	NA[a]	13 (81.2)
Tumor Type						
Merkel Cell Carcinoma	1 (33.3)	-	-	2 (40.0)	-	3 (18.8)
Adenoid Cystic Carcinoma	-	1 (25.0)	-	1 (20.0)	-	2 (12.5)
Melanoma	-	-	1 (33.3)	1 (20.0)	-	2 (12.5)
Uveal Melanoma	1 (33.3)	1 (25.0)	-	-	-	2 (12.5)
Colorectal Cancer	-	-	-	-	1 (100.0)	1 (6.3)
Fibromyxoid sarcoma	1 (33.3)	-	-	-	-	1 (6.3)
Oropharyngeal	-	-	-	1 (20.0)	-	1 (6.3)
Osteosarcoma	-	-	1 (33.3)	-	-	1 (6.3)
Prostate Cancer	-	1 (25.0)	-	-	-	1 (6.3)
Rectal Cancer	-	1 (25.0)	-	-	-	1 (6.3)
Renal Cell	-	-	1 (33.3)	-	-	1 (6.3)

[a]Data not available at time of data cut

Demographics – ARM B

	Dose Level B1[b] 0.1 mg/kg (n=3)	Dose Level B2 0.17 mg/kg (n=4)	Dose Level B3 0.25 mg/kg (n=1)	Overall (N=8)
Age (years)				
Median (min, max)	66.0 (60, 70)	62.0 (41, 79)	35.0 (35, 35)	63.0 (35, 79)
Sex (n, (%))				
Male	3 (100)	4 (100)	NA[a]	7 (87.5)
ECOG (n, (%))				
0	-	-	-	-
1	2 (66.7)	3 (75.0)	1 (100.0)	6 (75.0)
2	1 (33.3)	1 (25.0)	-	2 (25.0)
Prior Anti-Cancer Therapy Regimens				
≥4	2 (66.7)	3 (75.5)	1 (100.0)	6 (75.0)
Tumor Type				
AML	2 (66.7)	3 (75.0)	1 (100.0)	6 (75.0)
Post-MPN[c] AML	1 (33.3)	1 (25.0)	-	2 (25.0)

[a]Data not available at time of data cut; [b]Patients in Arm B started at the dose level identified as the pharmacologically active dose in Arm A; [c]Myeloproliferative neoplasm

Overall Safety

Number of Patients with AE by Grade Occurring in >15% Patients Overall (n, (%)) – All Causality
Dose Levels including Arm A and Arm B patients

Preferred Term	0.05 mg/kg (n=3) All Grades	0.05 mg/kg (n=3) ≥Gr 3	0.1 mg/kg (n=7) All Grades	0.1 mg/kg (n=7) ≥Gr 3	0.17 mg/kg (n=7) All Grades	0.17 mg/kg (n=7) ≥Gr 3	0.25 mg/kg (n=6) All Grades	0.25 mg/kg (n=6) ≥Gr 3	Overall (N=24[d]) All Grades	Overall (N=24[d]) ≥Gr 3
Nausea	2 (66.7)	-	3 (42.9)	1 (14.3)	5 (71.4)	-	2 (33.3)	-	12 (50.0)	1 (4.2)
Fatigue	1 (33.3)	-	3 (42.9)	-	2 (28.6)	-	2 (33.3)	-	8 (33.3)	-
Vomiting	2 (66.7)	-	1 (14.3)	1 (14.3)	2 (28.6)	-	3 (50.0)	-	8 (33.3)	1 (4.2)
Hypotension	1 (33.3)	1 (33.3)	2 (28.6)	-	3 (42.9)	-	1 (16.7)	-	7 (29.2)	1 (4.2)
Blood creatinine increased	1 (33.3)	-	1 (14.3)	-	2 (28.6)	-	1 (16.7)	-	5 (20.8)	-
Cough	1 (33.3)	-	2 (28.6)	-	2 (28.6)	-	-	-	5 (20.8)	-
Dyspnoea	1 (33.3)	-	1 (14.3)	-	3 (42.9)	1 (14.3)	-	-	5 (20.8)	1 (4.2)
Headache	1 (33.3)	-	1 (14.3)	-	3 (42.9)	-	-	-	5 (20.8)	-
Hypokalaemia	-	-	2 (28.6)	1 (14.3)	2 (28.6)	-	1 (16.7)	1 (16.7)	5 (20.8)	2 (8.3)
Decreased appetite	-	-	1 (14.3)	-	1 (14.3)	-	2 (33.3)	-	4 (16.7)	-
Diarrhoea	2 (66.7)	-	-	-	2 (28.6)	-	-	-	4 (16.7)	-
Dizziness	1 (33.3)	-	-	-	3 (42.9)	-	-	-	4 (16.7)	-
Hypocalcaemia	-	-	1 (14.3)	-	2 (28.6)	-	1 (16.7)	-	4 (16.7)	-

[d]At time of data cut off one patient in Arm A was enrolled in 0.33 mg/kg and one patient in Arm B was enrolled in 0.25 mg/kg and no AEs were reported. No Grade 5 events reported.

Summary

Adverse Events:

- There were no observable differences in safety between Arm A and Arm B patients.
- Most common AEs related to KT-253 observed in >15% patients, n (%): nausea 8 (33.3), fatigue 6 (25.0), decreased appetite 4 (16.7)

Dose Limiting Toxicities:

- Arm A - DL4: Gr. 2 fatigue and Gr. 2 arthralgia leading to KT-253 discontinuation in 1 patient
- Arm B - none

Related Serious Adverse Events

- Arm A - Gr. 3: hypotension (n=1; DL1) in a patient with decreased oral intake; ventricular tachycardia (VT) leading to treatment discontinuation (n=1; DL3)
- Arm B - none

Exposure, Duration on Treatment and Disposition

- As of 09 April 2024, Twenty-four patients received a mean of 3.2 doses across the first five dose levels in Arm A and 2.6 doses the first three dose levels in Arm B.
- Eight patients remain active across both arms (0.1 mg/kg, n=2; 0.17 mg/kg, n=2; 0.25 mg/kg, n=3; 0.33 mg/kg, n=1) and 16 patients discontinued KT-253. Primary reasons for discontinuation were disease progression (n=8), adverse event (n=2), patient decision to discontinue (n=2), clinical progression (n=1), investigator discretion (n=1), protocol non-compliance (n=1) and patient death due to disease progression (n=1).

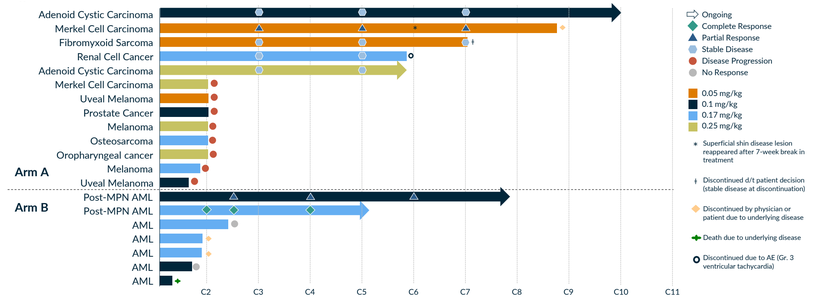
Clinical Responses

ARM A (n=13[1], n (%))		ARM B (n=7[1], n (%))	
Complete Response	-	Complete Response	1[5] (14.3)
Partial Response	1[2] (7.7)	Partial Response	1[5] (14.3)
Stable Disease	4[3] (30.8)	No Response	2 (28.6)
Progressive Disease	8[4] (60.2)	Treatment Failure-Refractory Disease	-
		Non-Evaluable	3[6] (42.9)

Best Overall Response by Arm

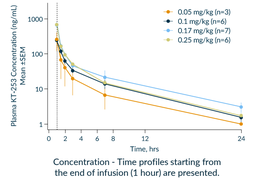
[1]Thirteen of the sixteen Arm A and seven of eight Arm B patients enrolled were evaluable for response assessment at the time of cut-off; [2]MCC; [3]Fibromyxoid sarcoma (n=1), adenoid cystic carcinoma (n=2); renal (n=1); [4]Includes one patient with uveal melanoma assessed as clinical progression; [5]Post-MPN AML; [6]Off treatment from death due to underlying disease (n=1) or clinical deterioration (n=2) prior to first response assessment; Arm A responses assessed per RECIST 1.1; Arm B by ELN 2022

Figure 1. Duration of Time on Treatment – Disease Evaluable Patients



Pharmacokinetics – Arm A and Arm B Combined

Figure 2. Cycle 1, Day 1 Pharmacokinetic Profile



Concentration - Time profiles starting from the end of infusion (1 hour) are presented.

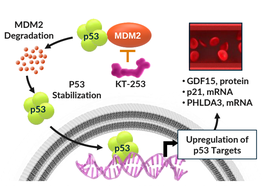
Parameter	PK Parameters by Dose Level 0.05 mg/kg (n = 3)	0.1 mg/kg (n = 6)	0.17 mg/kg (n = 7)	0.25 mg/kg (n = 6)
C_{max} (ng/mL)	180 (111%)	300 (36.4%)	1530 (152%)	844 (24.5%)
AUC_{inf} (ng.h/mL)	353 (116%)	573 (27.6%)	1460 (64.3%)	1230 (21.4%)
Vd (L/kg)	2.65 (114%)	1.69 (45.0%)	4.30 (74.0%)	3.30 (45.7%)
CL (L/h/kg)	0.335 (83.9%)	0.188 (33.1%)	0.147 (42.3%)	0.211 (20.9%)
$t_{1/2}$ (h)	6.91 (77.9%)	7.0 (55.3%)	22.0 (66.6%)	10.8 (40.4%)

For Arm B, Cycle 2 data is shown for patients 105-001 and 105-002 instead of Cycle 1 as they had lower than expected exposures. Patient 109-001 (Arm B: 0.1 mg/kg) did not have sufficient PK data and was excluded from PK analysis.

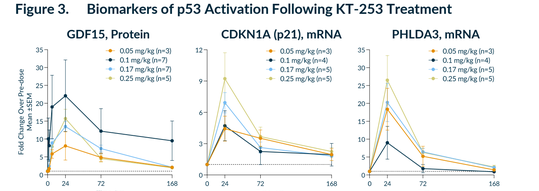
- PK was linear with a half-life of less than 24 hours and approximately dose proportional increase in exposure.

Pharmacodynamics – p53 Pathway Activation in Blood

Figure 3. Biomarkers of p53 Activation Following KT-253 Treatment



Schematic showing upregulation of PD biomarkers by MDM2 degradation-mediated p53 pathway activation



Fold-change over pre-dose baseline for Cycle 1. Pre-dose baseline indicated by dotted line

- Biomarkers of p53 activation expected to increase with MDM2 degradation showed peak upregulation at 24-hour post start of treatment, with levels recovering towards baseline by Day 8

CONCLUSIONS

- Initial clinical proof of concept in tumor types shown to be sensitive to KT-253 in preclinical models was demonstrated, including responses in one of two evaluable patients with MCC (PR) and two of two patients with Post-MPN AML (CR and PR).
- KT-253 treatment resulted in upregulation of p53 pathway activation biomarkers even at the lowest dose levels in solid tumor and AML patients, providing proof of mechanism for MDM2 target engagement.
- KT-253 was well tolerated with no significant myelosuppression or thrombocytopenia typical of MDM2 small molecule inhibitors observed to date.
- Phase 1a dose escalation is ongoing in patients with solid tumor/lymphoma/MF (Arm A) and high-grade myeloid malignancies and ALL (Arm B).

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