First Results from the Dose Escalation Part of the Phase 1 Study of KTX-1001, an Oral, First-in-class, Potent Inhibitor of MMSET/NSD2 for Relapsed/Refractory Multiple Myeloma (RRMM)

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To learn more about this trial

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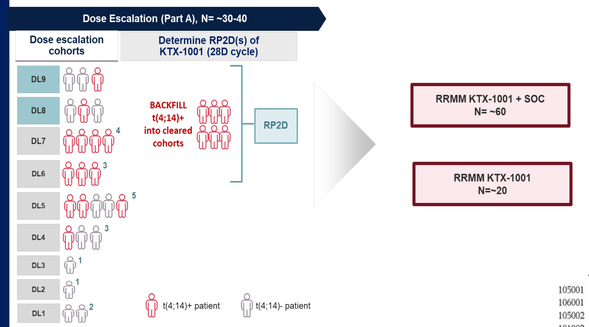
SUMMARY

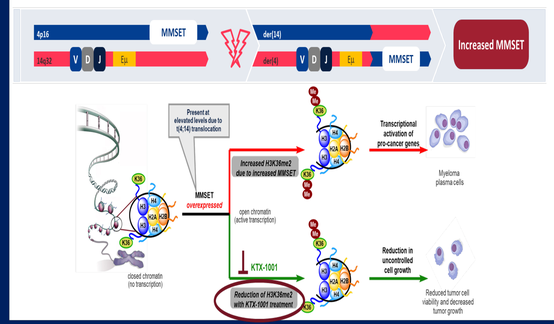
- KTX-1001 (p.o.) is being studied in a Phase 1 trial to investigate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in patients with **relapsed/refractory multiple myeloma** (RRMM), including in those who have translocation of chromosomes 4 and 14 [t(4;14)] (NCT05651932)[1]
- KTX-1001 shows excellent **tolerability** to date
- PK have demonstrated **increasing exposure with dose**
- On-target PD effects were observed in peripheral blood as measured by decrease in **H3K36me2** level
- Dose-escalation ongoing to finalize determination of **recommended phase 2 dose** (RP2D)

INTRODUCTION

- KTX-1001 is an oral, first-in-class, selective and potent small molecule inhibitor of MMSET (also know as NSD2 / WHSC1), and is the first investigational drug that targets the t(4;14) MM patient population
- Despite recent major advances, multiple myeloma (MM) remains incurable using currently available therapies
- There are no available/approved targeted therapies for MM that allow for individualized therapeutic approaches to the disease
- Fifteen to 20% of newly diagnosed MM patients have a t(4;14) translocation which is associated with poor clinical prognosis[2] significant gap remains in outcomes of these patients with current standard of care
- T(4;14) puts transcription of the gene encoding Multiple Myeloma SET domain-containing protein (MMSET or NSD2), a histone 3 lysine 36 methyltransferase, under the control of the IgH super enhancer[3]
- Overexpression of MMSET results in an abnormal histone code that promotes myelomagenesis
  - KTX-1001 breaks this abnormal histone code



KTX-1001: MOA

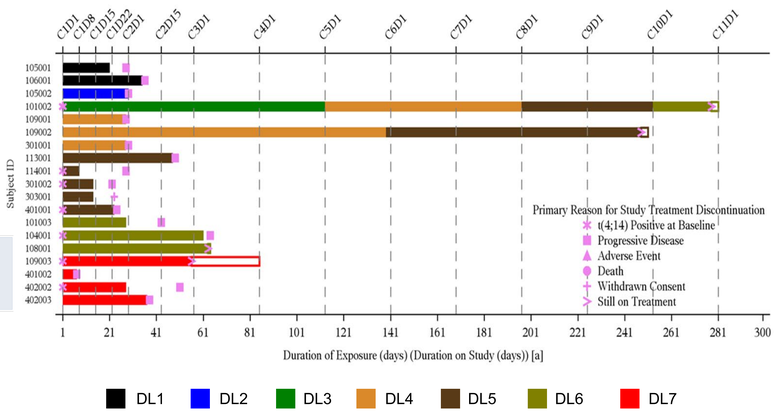


PATIENT DEMOGRAPHICS

Demographic Characteristic (Data cutoff Sept 4th)		Total Patients (N=19)
Median Age, years (range)		69 (50-83)
Sex, n (%)	Male	10 (52.6)
	Female	9 (47.4)
Median Time from MM Diagnosis to Screening, years (range)		8 (1-14)
Cytogenetic Abnormality, n (%)	13q deletion	1 (5.3)
	17p deletion	1 (5.3)
	t(4;14) translocation	**12 (63)**
	t(11;14) translocation	0
	t(14;16) translocation	0
	t(14;20) translocation	1 (5.3)
	1q21 amplification	3 (15.8)
Presence of EMP, n (%)		7 (36.8)
Median Number of Prior Regimens (range)		**5 (3–17)**
Prior therapy by Drug Class, n (%)	IMiD	19 (100)
	PI	19 (100)
	Anti-CD38	19 (100)
	BCMA CART	7 (36.8)
	BCMA Targeted Drugs	7 (36.8)
	Non-BCMA Bispecific	6 (31.6)
	Chemotherapy	10 (52.6)
	ASCT	12 (63.2)
	Experimental and Other Approved Drugs	8 (42.1)

- Patient demographics reflect heavily treated population with median prior therapy of 5 lines and up to 17 lines
- Population consistent with late-stage, heavily pretreated RRMM population

PATIENT TREATMENT STATUS



- Three heavily pre-treated patients [two known to be t(4;14)+] have achieved long-lasting stable disease and clinical benefit at 13, 12, and 6 months respectively (as of Nov 01, 2024).
- Two of the three patients have been intra-patient dose escalated.

SAFETY

Worst Per Patient Cycle 1 TEAEs Grade ≥ 2 by Dose Level and SOC

System Organ Class	DL 1 (N=2)	DL 2 BID (N=1)	DL 3 (N=1)	DL 4 (N=3)	DL 5 (N=5)	DL 6 (N=3)	DL 7 (N=4)	Total (N=19)
Maximum Severity	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Gastrointestinal disorders	1 (50.0)	1 (100)	0	2 (66.7)	2 (40.0)	3 (100)	0	9 (47.4)
Grade 2 (Moderate)	0	1 (100)	0	1 (33.3)	2 (40.0)	2 (66.7)	0	6 (31.6)
General disorders and administration site conditions	1 (50.0)	0	1 (100)	2 (66.7)	3 (60.0)	2 (66.7)	1 (25.0)	10 (52.6)
Grade 2 (Moderate)	1 (50.0)	0	0	0	2 (40.0)	1 (33.3)	1 (25.0)	5 (26.3)
Musculoskeletal and connective tissue disorders	2 (100)	0	1 (100)	2 (66.7)	2 (40.0)	1 (33.3)	0	8 (42.1)
Grade 2 (Moderate)	1 (50.0)	0	0	0	1 (20.0)	0	0	2 (10.5)
Grade 3 (Severe)	1 (50.0)	0	0	1 (33.3)	1 (20.0)	1 (33.3)	0	4 (21.1)
Investigations	1 (50.0)	1 (100)	0	2 (66.7)	1 (20.0)	0	2 (50.0)	7 (36.8)
Grade 3 (Severe)	0	1 (100)	0	0	1 (20.0)	0	0	2 (10.5)
Grade 4[a] (Life-threatening)	1 (50.0)	0	0	1 (33.3)	0	0	0	2 (10.5)
Blood and lymphatic system disorders	1 (50.0)	0	0	1 (33.3)	3 (60.0)	0	0	5 (26.3)
Grade 2 (Moderate)	1 (50.0)	0	0	0	0	0	0	1 (5.3)
Grade 3 (Severe)	0	0	0	0	3 (60.0)	0	0	3 (15.8)
Nervous system disorders	0	0	0	2 (66.7)	1 (20.0)	1 (33.3)	1 (25.0)	5 (26.3)
Grade 2 (Moderate)	0	0	0	0	0	1 (33.3)	0	1 (5.3)
Grade 3 (Severe)	0	0	0	1 (33.3)	0	0	0	1 (5.3)
Metabolism and nutrition disorders	0	0	0	1 (33.3)	1 (20.0)	2 (66.7)	0	4 (21.1)
Grade 2 (Moderate)	0	0	0	0	1 (20.0)	1 (33.3)	0	2 (10.5)
Grade 4[b] (Life-threatening)	0	0	0	1 (33.3)	0	0	0	1 (5.3)
Endocrine disorders	0	0	0	0	0	0	1 (25.0)	1 (5.3)
Grade 2 (Moderate)	0	0	0	0	0	0	1 (25.0)	1 (5.3)
Renal and urinary disorders	0	0	0	1 (33.3)	0	1 (33.3)	1 (25.0)	3 (15.8)
Grade 3 (Severe)	0	0	0	1 (33.3)	0	1 (33.3)	0	2 (10.5)
Infections and infestations	0	0	0	0	2 (40.0)	0	0	2 (10.5)
Grade 2 (Moderate)	0	0	0	0	1 (20.0)	0	0	1 (5.3)
Respiratory, thoracic and mediastinal disorders	1 (50.0)	0	0	0	0	0	1 (25.0)	2 (10.5)
Grade 5[c] (Death)	0	0	0	0	0	0	1 (25.0)	1 (5.3)
Vascular disorders	0	0	0	1 (33.3)	1 (20.0)	0	0	2 (10.5)
Grade 2 (Moderate)	0	0	0	1 (33.3)	0	0	0	1 (5.3)
Injury, poisoning and procedural complications	0	0	0	0	1 (20.0)	0	0	1 (5.3)
Grade 2 (Moderate)	0	0	0	0	1 (20.0)	0	0	1 (5.3)

[a]One event of platelet count decreased Grade 4 was observed in the context of disease progression at DL 1, and similarly, two events of Grade 4 platelet count decreased and Grade 4 white blood cell count decreased were observed in the same patient at DL 4 in the context of disease progression and were not suspected to be related to KTX-1001

[b]One event of Grade 4 hypercalcemia was observed in a patient at DL 4 in the context of disease progression and was not suspected to be related to KTX-1001

[c]One event of Grade 5 respiratory failure was observed in a patient at Dose Level 7 due to disease progression, and was not suspected to be related to KTX-1001

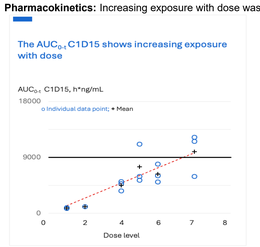
Worst Per Patient Grade ≥ 2 TEAEs (All Cycles) by Preferred Term [a]

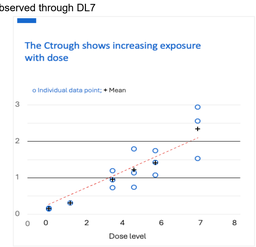
TEAE	Grade 2	Grade 3	Grade 4	Total (N=19)
	n(%)	n(%)	n(%)	n(%)
Back pain	3 (15.8)	2 (10.5)	0	5 (26.3)
Fatigue	4 (21.1)	1 (5.3)	0	5 (26.3)
Anemia	1 (5.3)	2 (10.5)	0	3 (15.8)
Diarrhea	3 (15.8)	0	0	3 (15.8)
Hyponatremia	2 (10.5)	1 (5.3)	0	3 (15.8)
Neutrophil count decreased	1 (5.3)	2 (10.5)	0	3 (15.8)
Platelet count decreased	1 (5.3)	0	2 (10.5)	3 (15.8)
White blood cell count decreased	1 (5.3)	1 (5.3)	1 (5.3)	3 (15.8)
Acute kidney injury	0	2 (10.5)	0	2 (10.5)
Arthralgia	0	2 (10.5)	0	2 (10.5)
Asthenia	2 (10.5)	0	0	2 (10.5)
Bone pain	0	2 (10.5)	0	2 (10.5)
Constipation	2 (10.5)	0	0	2 (10.5)
Hypercalcemia	1 (5.3)	0	1 (5.3)	2 (10.5)
Hyperphosphataemia	2 (10.5)	0	0	2 (10.5)
Hypertension	2 (10.5)	0	0	2 (10.5)
Nausea	2 (10.5)	0	0	2 (10.5)
Neutropenia	0	2 (10.5)	0	2 (10.5)
Pleural effusion	1 (5.3)	1 (5.3)	0	2 (10.5)
Pulmonary embolism	1 (5.3)	1 (5.3)	0	2 (10.5)
Urinary tract infection	2 (10.5)	0	0	2 (10.5)

[a]For any TEAE occurring more than once

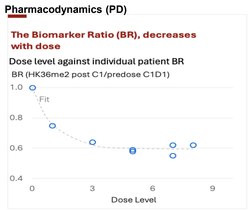
PK AND PD

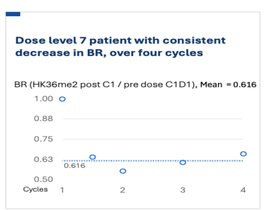
- **Pharmacokinetics:** Increasing exposure with dose was observed through DL7





Pharmacodynamics (PD)





- Reduction of histone 3 Lysine 36 di-methylation (H3K36me2) is the primary PD readout for KTX-1001
- The biomarker ratio (BR) is the level of H3K36me2 at Cycle 2 / pre-dose level in T, B, NK, monocytes, and CD38+ cells in peripheral blood
- Consistent decrease in H3K36me2 observed across dose levels (left) with an example of sustained PD effect (right)

As of the data cut-off date of September 04, 2024:

- Frequency and/or severity of TEAEs have not increased with escalating doses nor treatment duration
- No patients have discontinued due to an AE
- Most TEAEs have been of Grade 1 or 2 severity

CONCLUSIONS

- Dose escalation of oral KTX-1001 is ongoing, with increasing exposure by dose
- Excellent safety profile to date; no discontinuation due to an AE
- Three heavily pre-treated patients have completed >6 cycles, with 2 of these patients remaining on treatment for at least 12 cycles
- On-target PD have been observed which will help inform the RP2D(s)
- PD data support the targeted mechanism of action of KTX-1001 to selectively inhibit MMSET and break the t(4;14) histone code
- Single-agent and combination expansion cohorts with standard-of-care MM agents/classes will begin in 2025 to further optimize doses and provide proof of concept in Part B of the Phase 1 study

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