Development of KT-253, a Highly Potent and Selective Heterobifunctional MDM2 Degrader for the treatment of Acute Myeloid Leukemia

#2776

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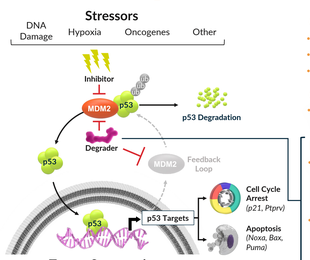
INTRODUCTION

The murine double minute 2 (MDM2) oncoprotein is a key E3 ubiquitin ligase that degrades and thereby inactivates the tumor-suppressor p53. Targeting of the MDM2/p53 interaction with reversible small molecule inhibitors (SMI) to stabilize p53 and induce apoptosis in wildtype (WT) p53 tumors has been an emerging therapeutic approach in AML and in other WT p53 hematologic and solid tumor malignancies. However, recent clinical trials with MDM2 inhibitors, especially in R/R AML, have resulted in suboptimal clinical activity, highlighting the need for novel therapeutic approaches.

KT-253 is a novel, highly potent heterobifunctional MDM2 degrader that suppresses p53-dependent MDM2 protein upregulation that is known to be triggered by the MDM2 SMIs and thereby limits their clinical activity. Previously, we have shown that KT-253 has superior activity compared to MDM2 SMIs, demonstrating >200-fold improvements in both in vitro cell growth inhibition and apoptosis. Because of its superior pharmacological profile, a single dose of KT-253 was sufficient to induce rapid apoptosis and sustained tumor regression in the MV4;11 AML and RS4;11 ALL cell line-derived (CDX) mouse xenograft models, supporting an intermittent dosing schedule of KT-253.

MDM2 Degradation Effectively Induces p53 Signaling



Cancer Genetics

- p53 is **NOT mutated** in almost 50% of tumors
- MDM2 overexpression and amplification can inactivate p53
- Large opportunity in wide variety of cancers

Clinical Validation

- **Small molecule inhibitors** of the MDM2/p53 are active but are limited due to narrow therapeutic index

Degrader Advantage

- **MDM2 degraders**, because of their catalytic and not occupancy driven mechanism can lead to more efficient p53 stabilization and induction of an acute apoptotic response in tumor cells
- The distinct degrader pharmacology enables an intermittent dosing schedule that gives normal cells more time to recover and may increase the therapeutic index vs a small molecule inhibitor

Proteome Editing with Targeted Protein Degradation

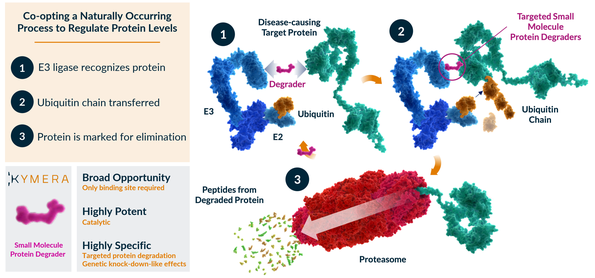
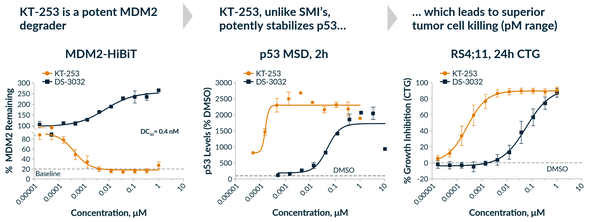


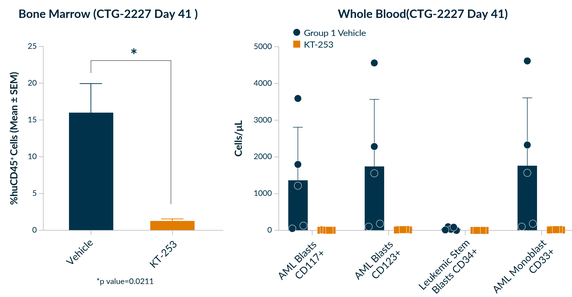
Figure 1: KT-253 is Superior to MDM2/p53 Small Molecule Inhibitors



Compound	KT-253	DS-3032	RG7388	SAR405838	HDM201	AMG-232
Company	Kymera	Sankyo/Rain	Roche	Sanofi	Novartis	Amgen/Kartos
RS4-11 IC_{50} (nM) (ALL Cell Killing)	0.3	67	220	620	163	280
MDM2-HiBiT, DC_{50} (nM) (Degradation)	0.4	-	-	-	-	-

- KT-253 is **>200-fold more potent** in tumor cell killing assays than SMI's due to its mechanism of action

Figure 2: KT-253 (1mg/kg, Q3W) Achieves Tumor Regression in CTG-2227 AML Patient-Derived Xenograft (PDX) Model and Partial Response in CTG-2240 and CTG-2700 AML PDX Models



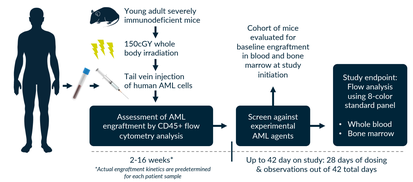
- KT-253 1 mg/ kg, Q3W dosing significantly reduces hCD45+ cells in bone marrow
- KT-253 1 mg/ kg, Q3W dosing significantly reduces AML blasts

CTG-2227 Characteristics:

- R/R AML, M4 (myelomonocytic)
- Mutations: IDH1, FLT3 ITD, DNMT3A, NPM1, ASXL1
- **Animals received 2 doses; Takedown and assessment at Day 41 post-implant**

Model	FAB Classification/ WHO Subtype	p53 Status	Diagnosis	Treatment History	Response in Peripheral Blood
CTG-2227	M4 (myelomonocytic)	WT	Relapsed	Pretreated	Complete Response
CTG-2240	AML (11q23 abnormalities)	WT	De novo	Naïve	Partial Response
CTG-2700	M2 (with maturation)	WT	De novo	Pretreated	Partial Response

- Three AML PDX models respond to KT-253 (1mg/kg, Q3W)
- One complete response and two partial responses

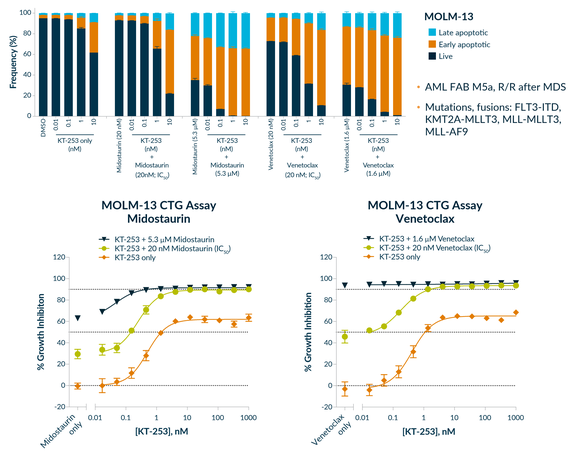


*Response Criteria by Champions Oncology

<25% decrease or increase	No response
25-50% decrease	Partial response
>50% decrease	Complete response

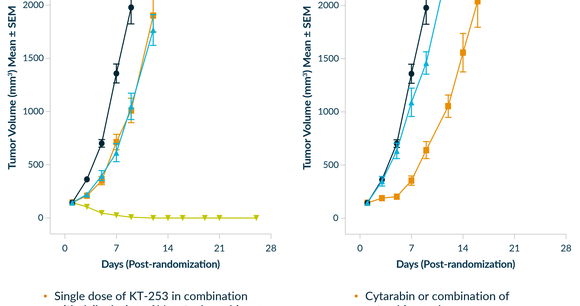
- Workflow for AML PDX model development, figure adopted from Champions Oncology
- Primary patient samples (never passaged) from leukapheresis was directly used for PDX engraftment
- CTG-2227, CTG-2240, CTG-2700 AML models were developed by Champions Oncology

Figure 3: KT-253 Shows Combinatorial Benefit with Venetoclax and Midostaurin in MOLM-13 Cell Line



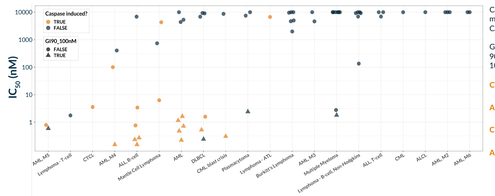
- AML FAB M5a, R/R after MDS
- Mutations, fusions: FLT3-ITD, KMT2A-MLLT3, MLL-MLLT3, MLL-AF9
- KT-253 combination with Midostaurin or Venetoclax enhances induction of apoptosis and cell killing in MOLM-13 AML cell line

Figure 4: Significant Combination Benefit of KT-253 with SoC in AML *in vivo* model



- Single dose of KT-253 in combination with daily dosing of Venetoclax achieves sustained tumor regression in MOLM-13 xenograft model
- Cytarabin or combination of cytarabine and venetoclax demonstrate no significant anti-tumor activity

Figure 5: KT-253 is Active Across Multiple Heme Indications



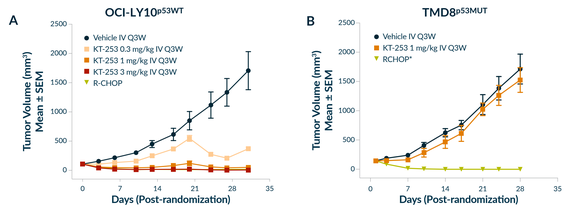
Caspase induction was measured at 48 hr with the Caspase-Glo assay

GI90_100nM indicates 90% growth inhibition at 100nM dose

CTCL: Cutaneous T cell lymphoma
ALL: Acute lymphocytic leukemia
CML: Chronic myelogenous leukemia
ALCL: Anaplastic large cell lymphoma

- Multiple hematological cancer cell lines were sensitive to KT-253 treatment *in vitro*
- AML, T cell lymphomas, mantle cell lymphoma, DLBCL were the most sensitive indications

Figure 6: KT-253 is Highly Active in p53WT ABC-Subtype DLBCL



- KT-253 highly active in OCI-LY10 p53 WT ABC-subtype DLBCL xenograft model (A) but not TMD8 p53 MUT ABC-subtype DLBCL xenograft model (B)

METHODS

In vitro Assays

All cell lines were cultured according to recommended procedures unless otherwise noted. For growth inhibition assays, cells were treated with compounds for indicated time points. Viability was assessed using Promega® CellTiter-Glo® assay, and apoptosis was assessed using Promega® Caspase-Glo® 3/7 assay. Cell cycle arrest and/or apoptosis in response to single agent or combination treatment was assessed using flow cytometry analysis on cells treated for 24h.

In vivo Experiments

AML patient cells from leukapheresis were intravenously (IV) injected and established in immunocompromised host strain mice. Surrogate animals were used to determine the level of engraftment targeting a threshold of ~20% huCD45+ cells in BM. Mice were randomized on study and treatment was initiated. Vehicle and KT-253, 1 mg/kg were administered IV, every three weeks for six weeks (total of two doses of KT-253). At study end, whole blood, bone marrow and spleen were assessed by flow cytometry.

CONCLUSIONS

- KT-253 is a Potent MDM2 Degrader and a Best-in-Class p53 Stabilizer that inhibits tumor cell growth with picomolar potency and is >200-fold more potent than clinically active MDM2 small molecule inhibitors.
- KT-253 dosed intermittently is highly active resulting in responses and complete regression in AML PDX xenograft models.
- KT-253 shows combinatorial benefit with SoC agents in AML in-vitro and in-vivo model, suggesting that KT-253 combination can be used for larger patient population.
- Preclinical data suggest potential for KT-253 to be active in additional hematological malignancies, such as DLBCL.
- Kymera is focused on indications with specific sensitivity to degrader mechanism, such as AML, other heme and solid tumors through a biomarker selection strategy.
- Anticipated IND clearance in 2022

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