5th Annual TPD Targeted Protein Degradation

Discovery of a First in Class MDM2 Degrader for the Treatment of Relapsed/Refractory TP53 Wt AML & Solid Tumors

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October 26, 2022

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Outline of Presentation

- Kymera's pipeline
- MDM2 is key regulator of p53
- Profile of MDM2 degrader KT-253
- KT-253 *in vivo* efficacy in ALL and AML xenograft models
- MDM2 dependency across large subset of tumor types
- Summary and outlook

Founded
2016

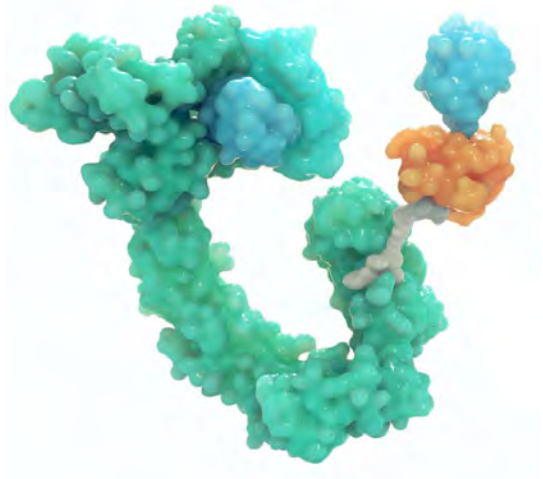
KYMERA

Recognition

Partnerships

Introduction to Kymera

KYMERA



OUR VISION

To be a disease- and technology-agnostic, fully integrated global biopharmaceutical company, using targeted protein degradation to deliver medicines that will transform patients' lives

- **Leader** in Targeted Protein Degradation (TPD)
- Building a **fully-integrated**, global biotech company
- Initial focus in **Immunology/Inflammation and Oncology**, but already a **disease-agnostic platform**
- Accelerating forward integration through **key strategic partnerships**
- Executed **many "firsts"** for TPD with initial clinical programs
- Three clinical stage programs and **a deep pipeline positioned to deliver ≥1 IND/year**
- Focused on **continued innovation** in platform and discovery
- Well capitalized with over **$600 million of cash** as of 8/31/22

Kymera's Pipeline of Novel Protein Degraders

Pathway	Program	Indication(s)	Discovery	IND Enabling	Phase 1	Phase 2	Next Milestones	Rights*
IL-1R/TLR	IRAK4	Immuno-inflammatory Diseases: HS, AD, RA, others	KT-474 Multiple molecules staged as potential back ups if needed				HS/AD Patient Data 4Q22	KYMERA sanofi
	IRAKIMiD (IRAK4, Ikaros, Aiolos)	MYD88^{MT} Tumors	KT-413				POM 4Q22	KYMERA
JAK/STAT	STAT3	Liquid & Solid Tumors	KT-333				POM 4Q22	KYMERA
	STAT3	Autoimmune & Fibrotic Diseases						KYMERA
p53	MDM2	Liquid & Solid Tumors	KT-253				IND 2H22	KYMERA
Collaboration	*Confidential*	*Confidential*						KYMERA sanofi
Discovery Pipeline	Several Discovery Programs			Multiple programs in immune-inflammatory and oncology indications to deliver ≥ 1 IND/year			≥ 1 DC: 2H22	KYMERA
Collaboration	6 Undisclosed Programs		6 targets in 5 disease areas outside of immunology-inflammation and oncology					K VERTEX

● = Oncology ● = Immunology-Inflammation

*Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US

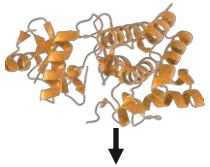
We Want to Drug All Target Classes

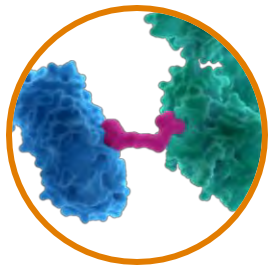
Expanding the Druggable Proteome with TPD

ID — Inadequately Drugged Targets with Clear Degrader Advantage

Small molecule binders exist but unable to drug target fully

e.g. IRAK4, MDM2…



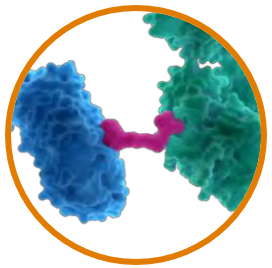


Heterobifunctional Degraders

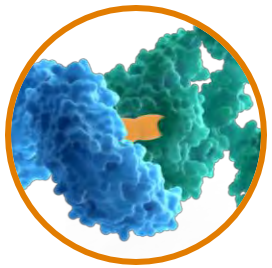
UD — Undrugged Targets

No other technology can drug

Ligandable Proteins	Un-ligandable Proteins
e.g. STAT3…	e.g. other transcription factors



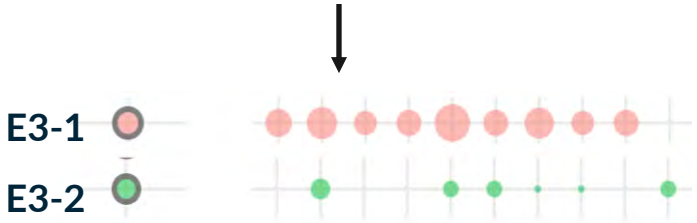
Heterobifunctional Degraders



Molecular Glues

TR — Clinically Validated Targets Enabled by E3 Ligase Tissue Restricted Expression

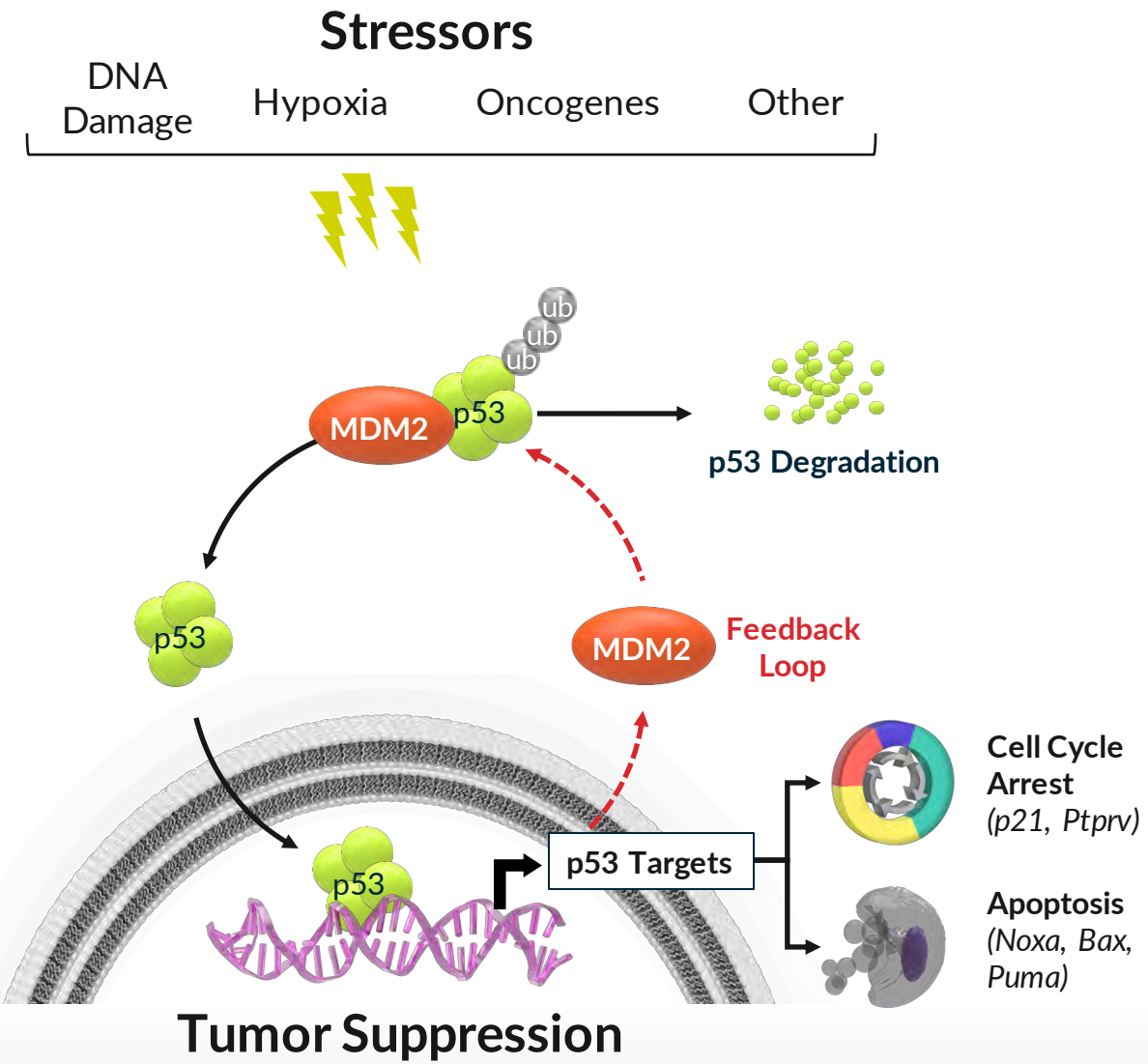
On target unwanted pharmacology limits clinical application



Tissue sparing or selective E3 ligases eliminate unwanted toxicity and allow full clinical potential

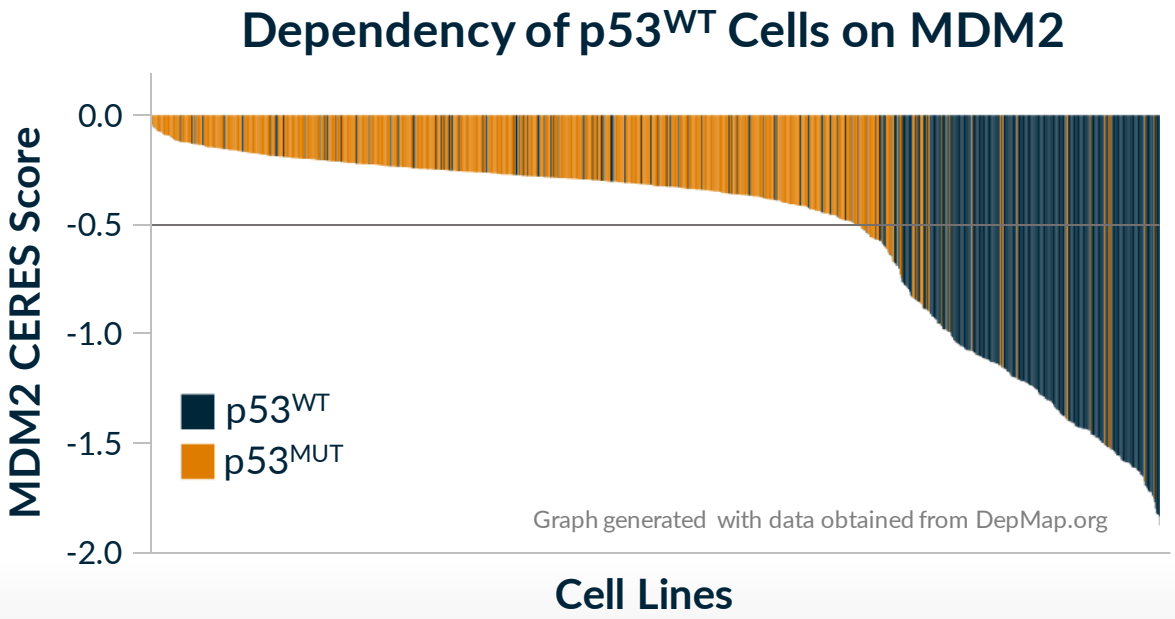
MDM2 (KT-253)

MDM2 is the E3 Ligase that Modulates P53, the Largest Tumor Suppressor

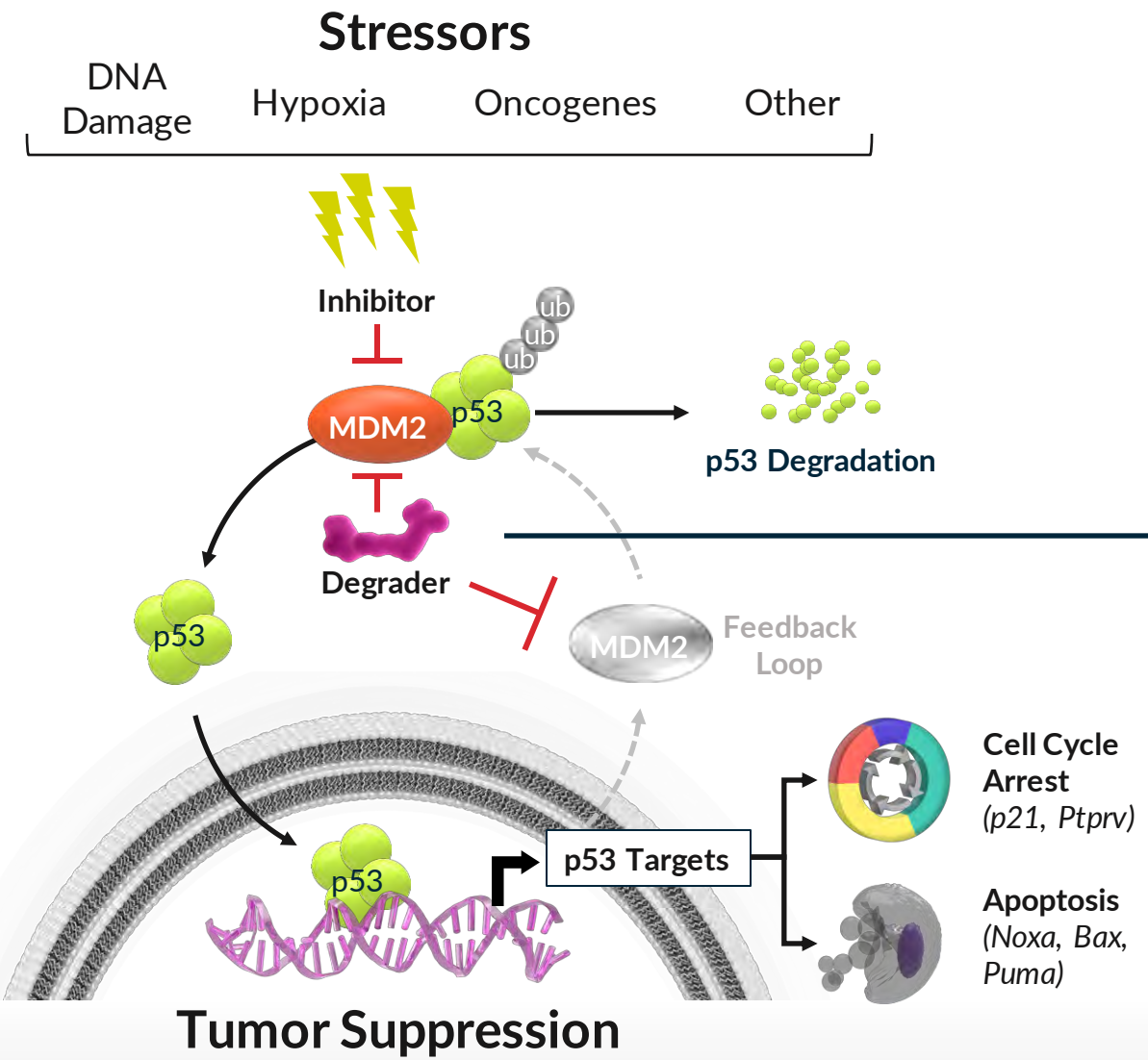


Cancer Genetics

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



MDM2 Degradation, Not Inhibition, Efficiently Restores p53



Clinical Validation

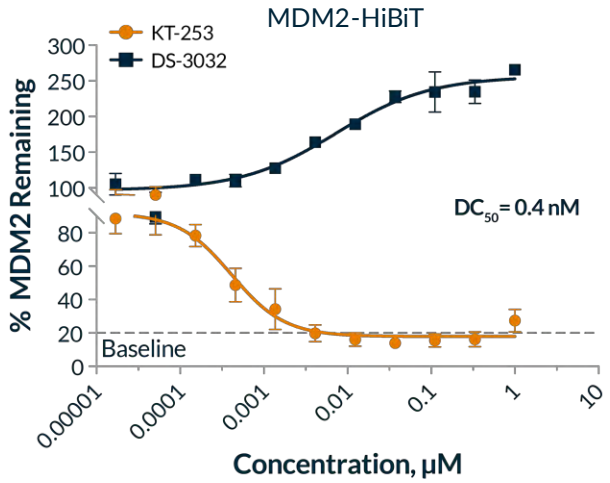
- **MDM2 small molecule inhibitors** of MDM2/p53 interaction **show activity in the clinic**..
- **...but they induce MDM2 feedback loop** resulting in limited impact on pathway

Degrader Advantage

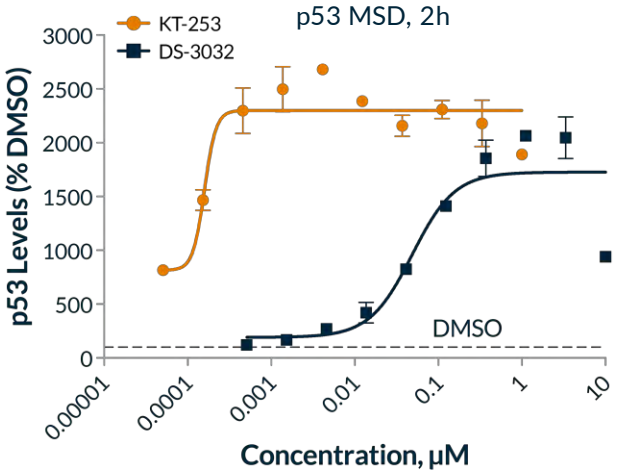
- **MDM2 degraders**, by removing the protein, **can overcome the p53-dependent feedback loop that upregulates MDM2**
- MDM2 degrader can induce an acute apoptotic response in tumor cells, **increasing efficacy and therapeutic index vs a small molecule inhibitor**

Kymera's MDM-2 Degrader Development Candidate, KT-253 is Superior to MDM2/p53 Small Molecule Inhibitors

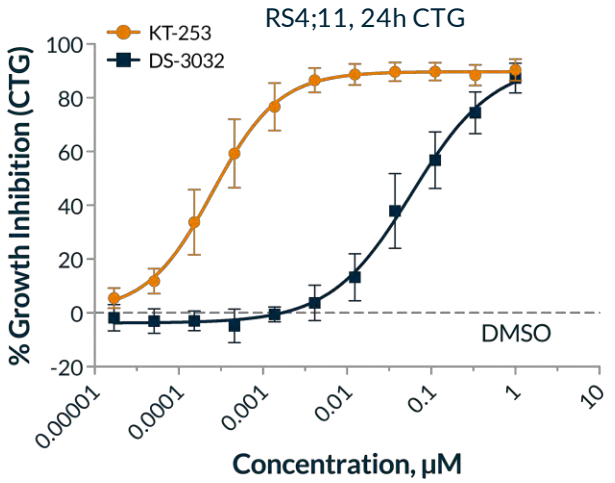
KT-253 is a potent MDM2 degrader



KT-253, unlike SMI's such as DS-3032, strongly stabilizes p53…



… which leads to superior tumor cell killing (pM range)

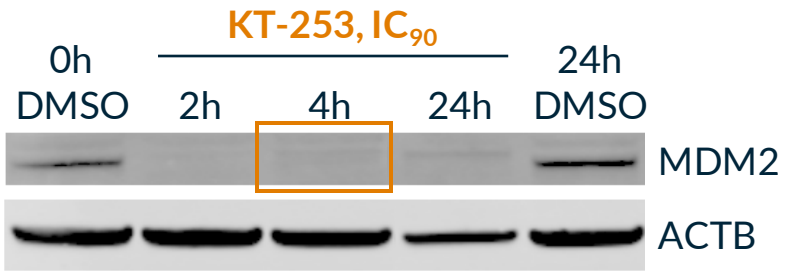


Compound	KT-253	DS-3032	RG7388	SAR405838	HDM201	AMG-232
Company	Kymera	Sankyo/Rain	Roche	Sanofi	Novartis	Amgen/Kartos
Clinical stage	IND enabling	Ph II / combo AML	Ph II / III	Paused	Ph I / II	Multiple Ph II; combo AML
RS4-11 IC_{50} (nM) (CTG)	0.3	67	220	620	163	280
MDM2-HiBiT, DC_{50} (nM) (Degradation)	0.4	-	-	-	-	-

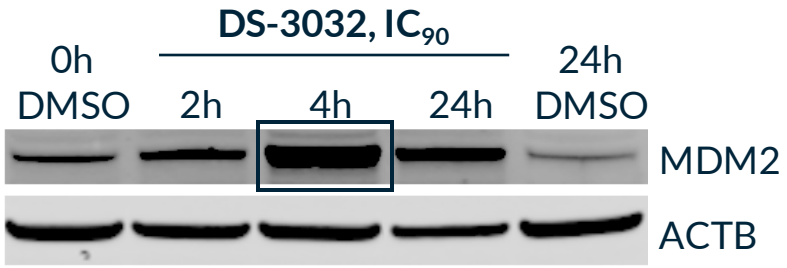
- KT-253 is **>200-fold more potent** in tumor cell killing assays than SMI's due to to its mechanism of action
- Proteomics show selective degradation of KT-253

KT-253, Unlike Small Molecule Inhibitors, Overcomes the MDM2 and p53 Autoregulatory Feedback Loop

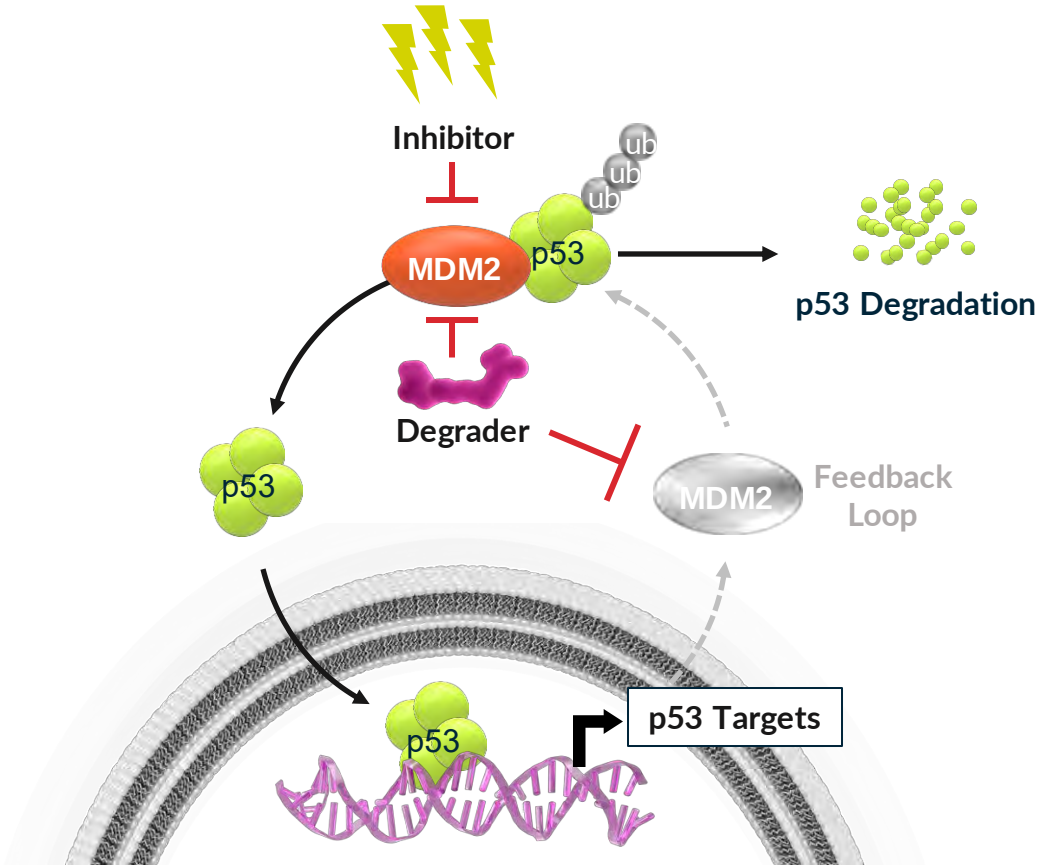
Degrader Overcomes MDM2 Feedback Loop



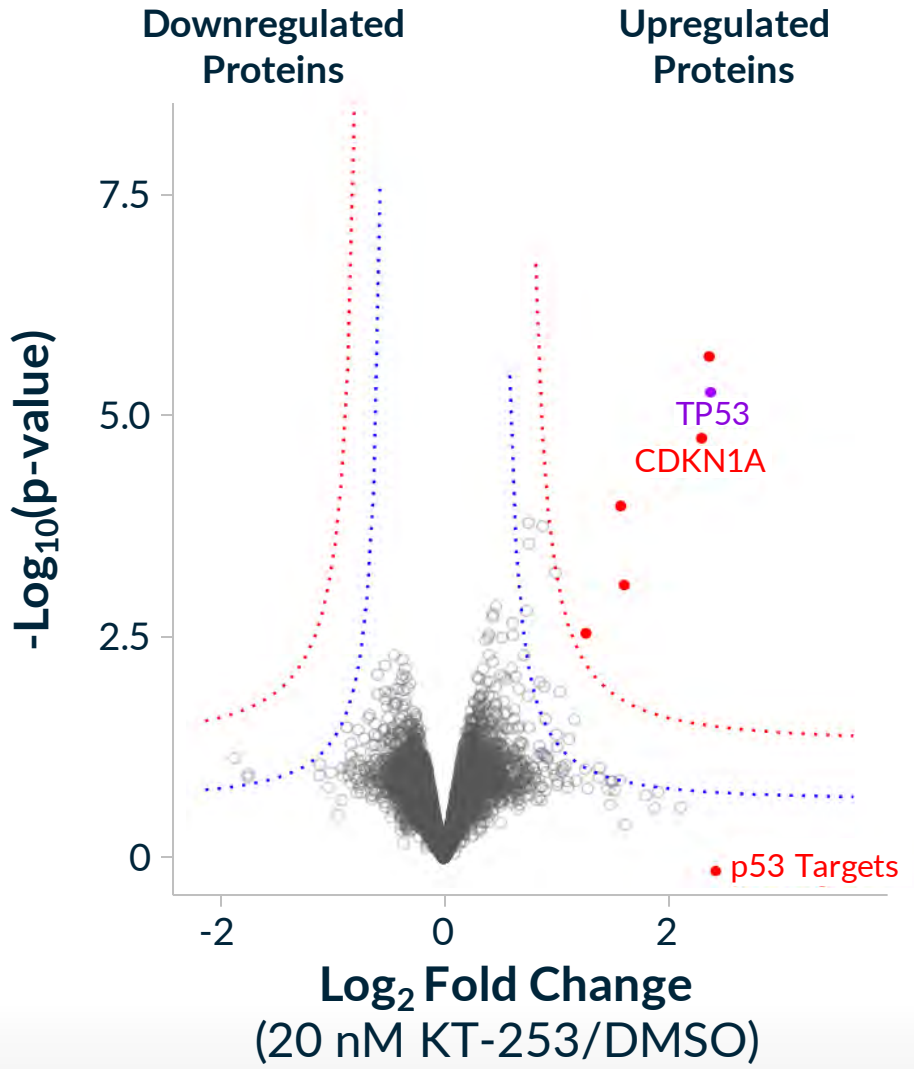
MDM2 levels are kept at undetectable levels with MDM2 degrader KT-253, leading to p53 stabilization



MDM2 levels are increased by the small molecule inhibitor (feedback loop), impairing p53 stabilization

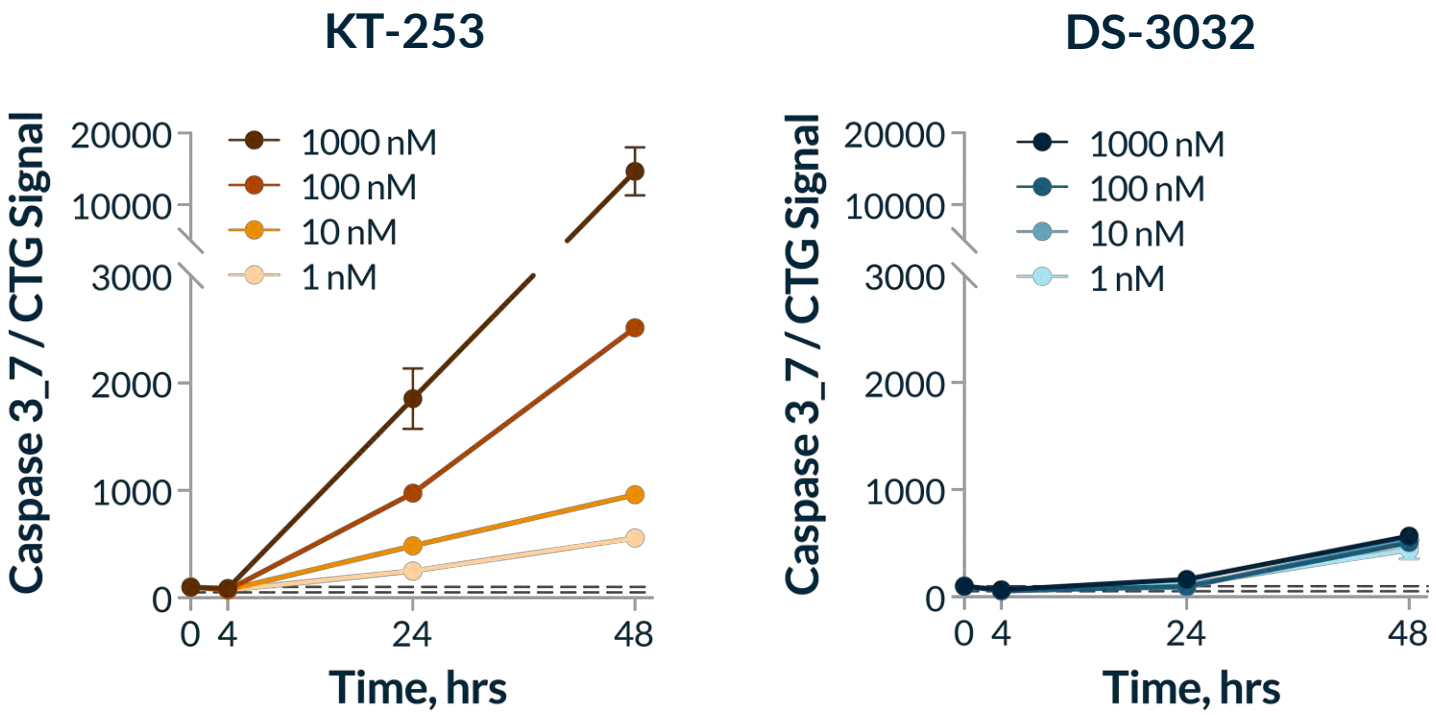


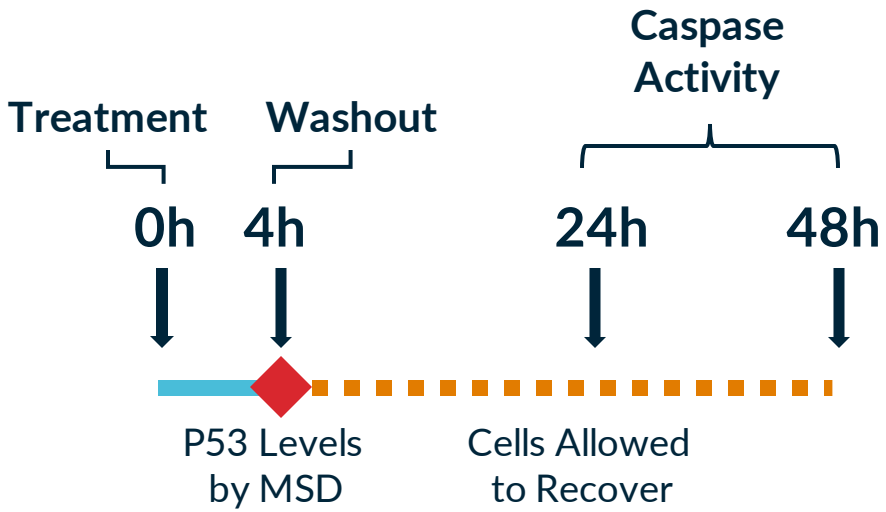
KT-253 is Highly Selective MDM2 Degrader that Leads to MDM2 Degradation-Dependent Downstream Activation of p53 Targets



- Deep Tandem Mass Tag proteomics analysis at 8h post KT-253 treatment showed **no off-target degradation** in RS4;11 cells at 10x IC_{90} concentration
- ~9000 Proteins were monitored
- All upregulated proteins are **downstream targets of p53 stabilization**
- Due to its very low abundance in RS4;11, MDM2 itself could not be monitored in this study
- Highly sensitive targeted mass spec has been developed to detect MDM2

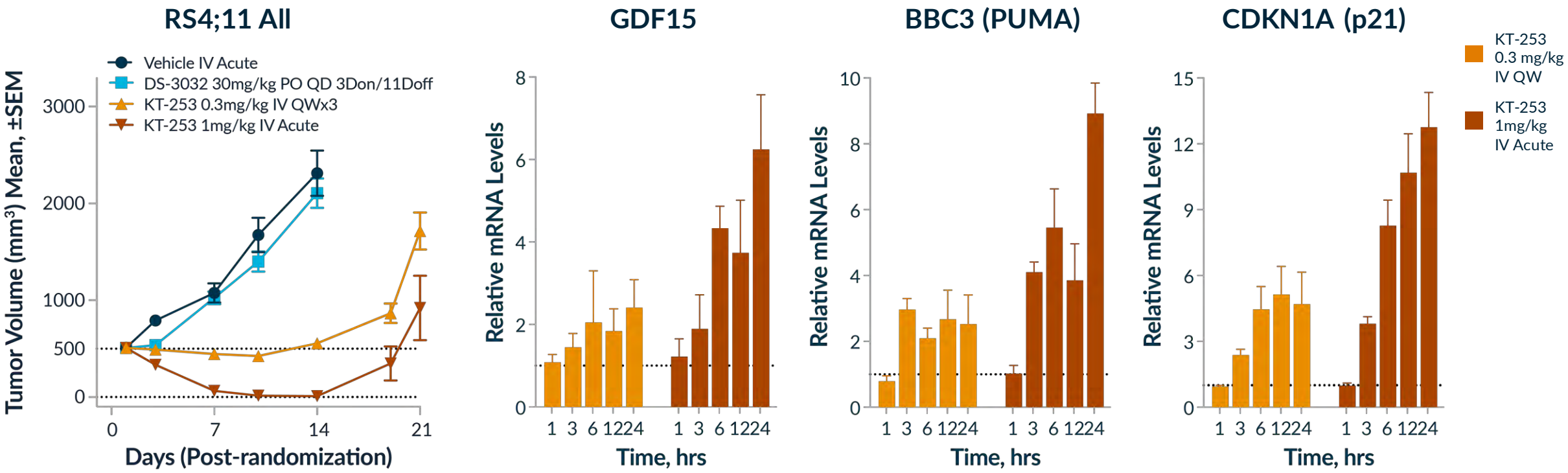
Short Term Exposure to MDM2 Degrader, but not SMI, is Sufficient to Commit Cells to Undergo Apoptosis





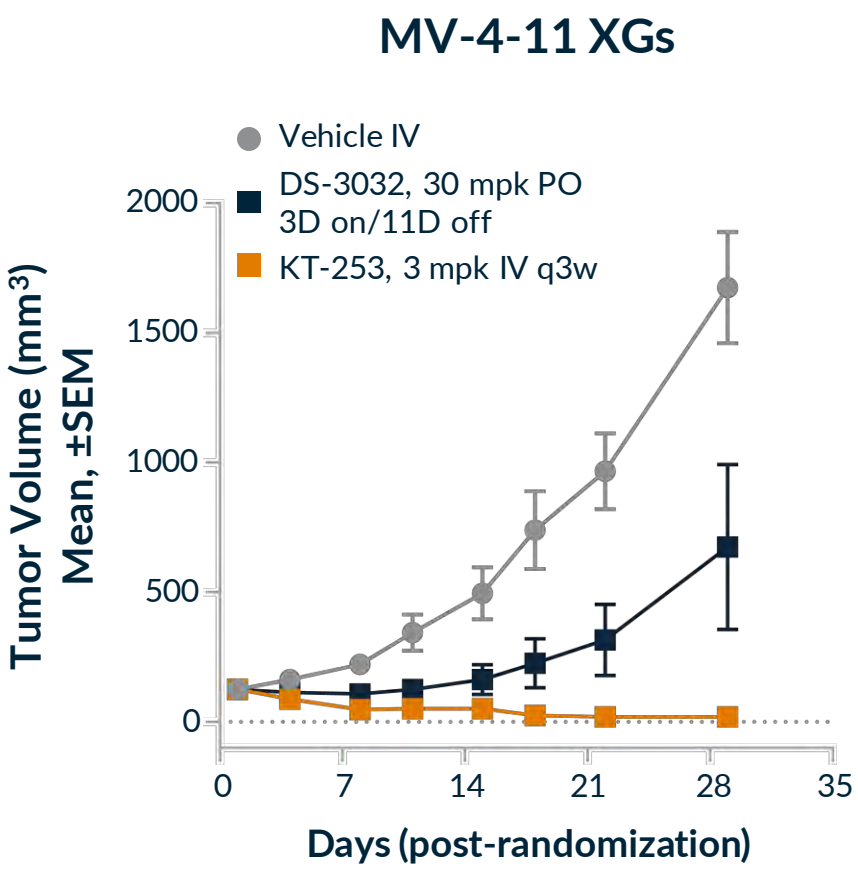
- 4 hr target coverage by KT-253 is sufficient to induce apoptosis in contrast to SMIs
- Supports hypothesis that intermittent dosing schedule of KT-253 can drive efficacy while increasing therapeutic index

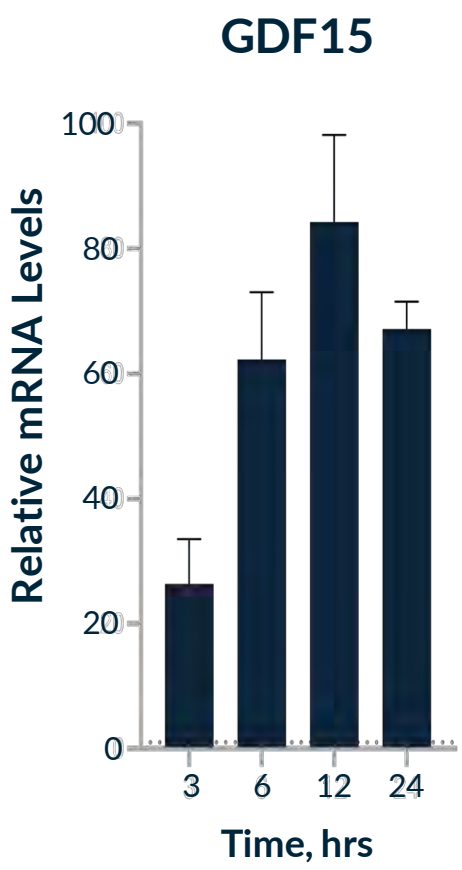
High Acute Exposures of KT-253 Trigger Acute Apoptotic Response and Tumor Regression in RS4;11 (ALL) Xenograft Model

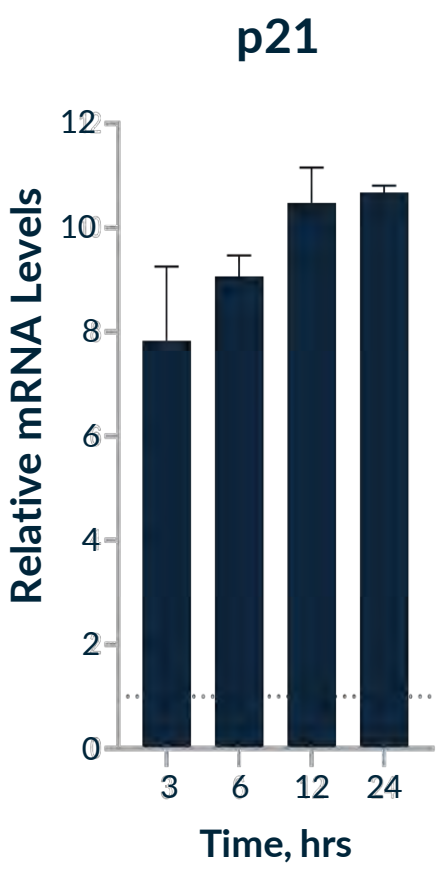


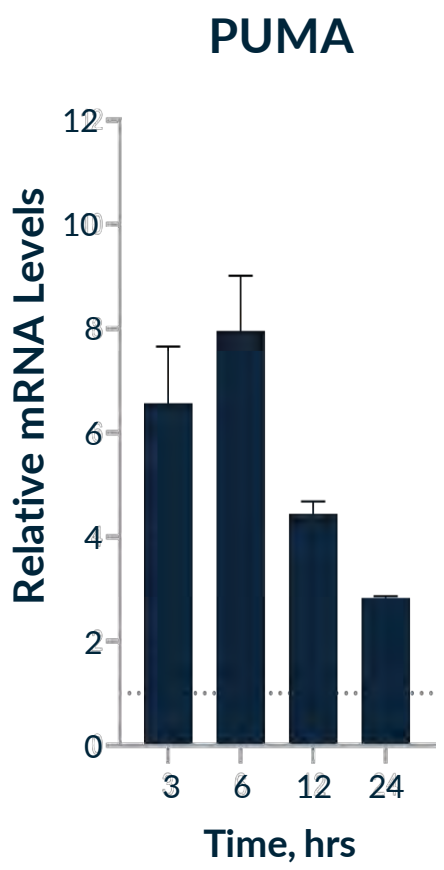
- Short term high exposures of KT-253 induce apoptosis and cause sustained tumor regression
- DS-3032 MDM2 inhibitor dosed at clinically relevant dose/schedule shows inferior efficacy vs KT-253 at expected tolerated human dose/schedule

KT-253 Achieves Tumor Regression in MV-4-11 (AML) Xenograft Model







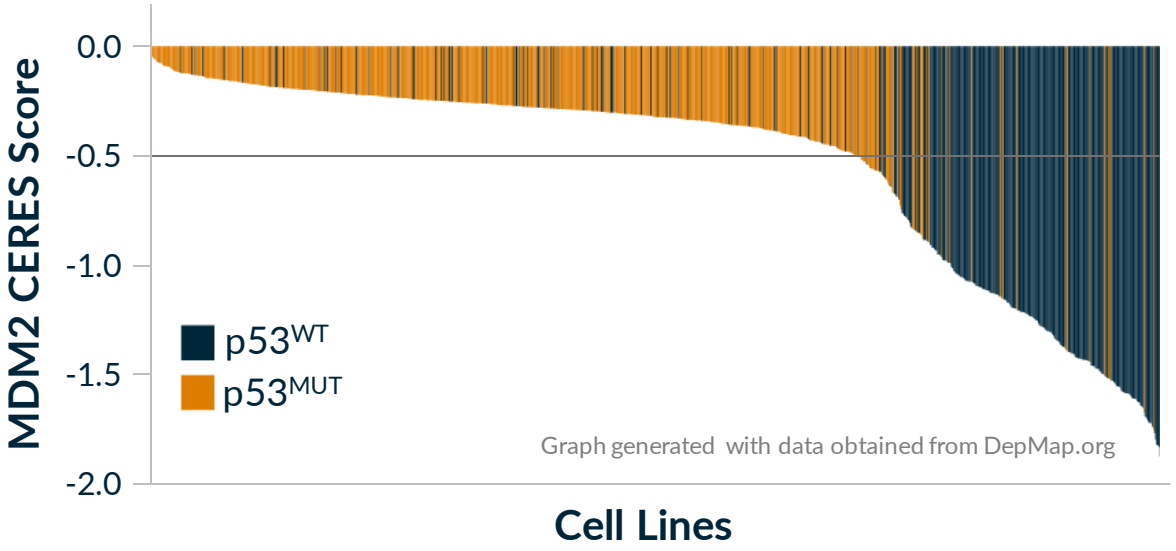


- KT-253 achieves sustained tumor regression in MV-4-11 xenograft model
- MDM2 degradation (KT-253, 3 mg/kg) leads to rapid upregulation of p53 downstream targets

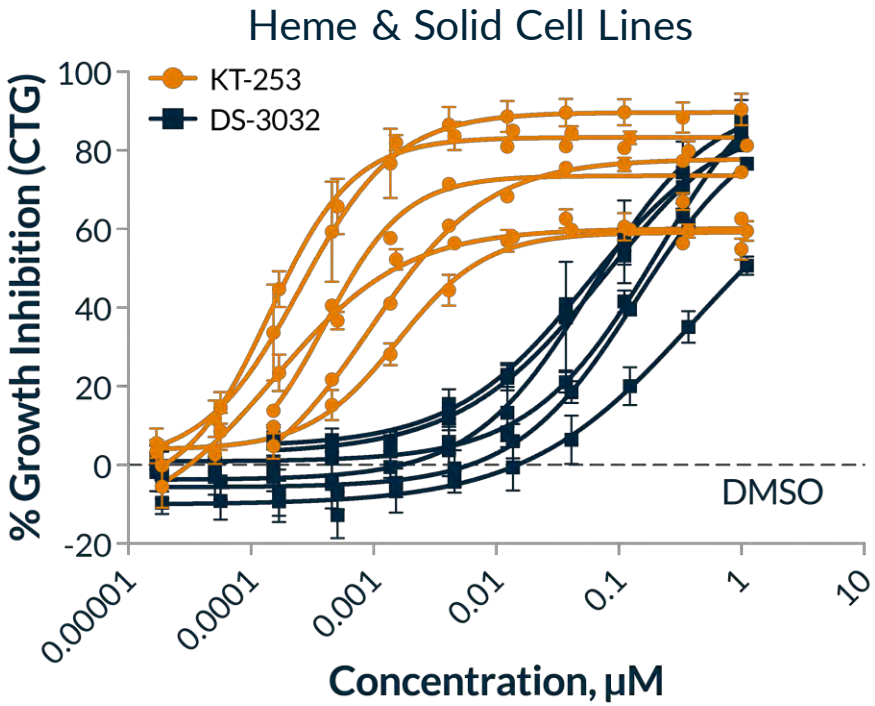
MDM2 Dependency Seen Across a Large Subset of Tumor Types

Large Franchise Potential in Liquid and Solid Tumors

Dependency of p53^{WT} Cell Lines on MDM2



MDM2 Degrader Superior to SMI Across Cell Line Panel



Tumor Types: Uveal melanoma, Bile Duct, Bladder, Bone, Brain, Breast, Colon, Endometrial/Uterine, Gastric, Kidney, Liver, Lung, Ovarian, Pancreatic, Rhabdoid, Sarcoma, Leukemia, Lymphoma

p53WT cell lines sensitive: ALL, AML, DLBCL, Uveal Melanoma p53 mutant cell lines were not sensitive to KT-253 or DS-3032 as expected

KT-253 Summary

- KT-253 is a potent MDM2 degrader and a best-in-class p53 stabilizer with potential to treat numerous p53 WT tumors
- KT-253 inhibits tumor cell growth with **picomolar potency** and is **>200-fold more potent** than clinically active MDM2 small molecule inhibitors
- KT-253, unlike small molecule inhibitors, **blocks the feedback loop** which up-regulates MDM2 production and in doing so more effectively stabilizes the tumor suppressor p53
- **Short term high exposures of KT-253** are enough to induce apoptosis in cell lines and cause sustained tumor regression in ALL and AML xenograft models, which ensures high activity and improved therapeutic index vs SMI's
- Broad franchise opportunities available for this mechanism (p53 WT is present in >50% tumors); Kymera is focused on indications with **specific sensitivity to degrader mechanism**, such as AML, uveal melanoma and other solid and liquid tumors through a biomarker selection strategy
- Projected IND filing in **2022**

KYMERA

Thank You!

Summer 2022