Predictive Markers of Response to the MDM2 Degrader KT-253

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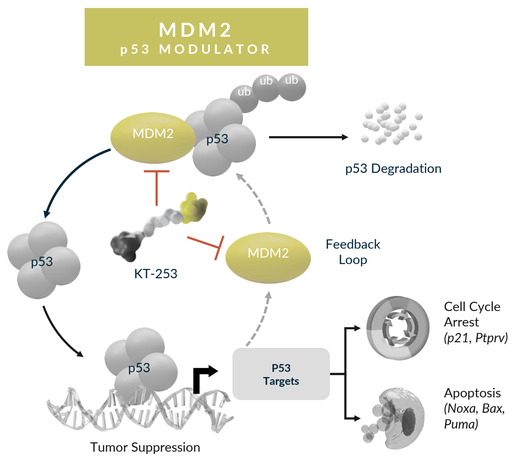
INTRODUCTION

Murine double minute 2 (MDM2) is an E3 ligase that regulates the tumor suppressor p53. Clinical trials employing small-molecule MDM2/p53 interaction inhibitors (SMIs) have demonstrated limited activity, underscoring an unmet need for a better approach to target MDM2.

We have developed a highly potent and selective heterobifunctional degrader of MDM2, KT-253, that overcomes the MDM2 feedback loop seen with SMIs and induces acute apoptosis in a range of hematologic and solid tumor lines. KT-253 is being evaluated in a Phase 1 clinical trial in adult patients with advanced solid tumors, lymphoma, myelofibrosis, high-grade myeloid malignancies and acute lymphocytic leukemias (NCT05775406).

The objective of this work was to identify a patient selection strategy that enriched for tumor types where KT-253 induces an acute apoptotic response and robust antitumor activity with Q3W dosing. We incorporated our understanding of biologic mechanisms, *in vitro* and *in vivo* studies, expression profiling, and machine learning to define biomarkers associated with response.

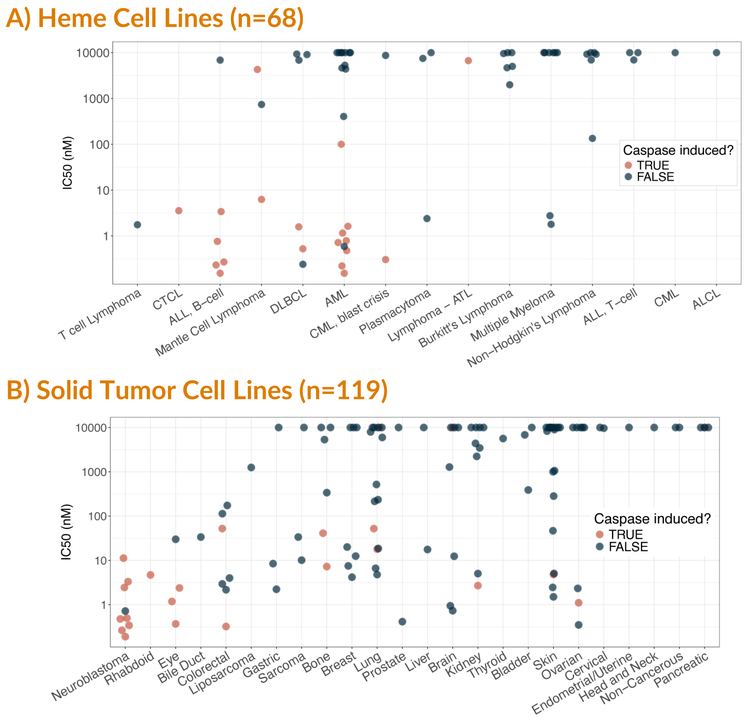


METHODS

We explored the activity of KT-253 *in vitro* in a panel of 350 p53 wild-type cell lines spanning 48 indications. The combination of both cell growth inhibition and apoptosis was evaluated using CTG (Promega) and Caspase-Glo 3/7 assays in 187 lines. Twenty-four pediatric patient-derived xenograft (PDX) models representing 6 tumor types (Ewing sarcoma, rhabdomyosarcoma, rhabdoid tumor, Wilms tumor, hepatoblastoma, and neuroblastoma) and 101 adult PDX models representing 5 solid tumor types (breast, lung, colorectal, gastric, melanoma) were evaluated using a single mouse trial design. KT-253 was administered intravenously every 3 weeks (Q3W). Baseline expression profiles of the adult PDX models were used in a machine learning framework to build a predictive signature of response to KT-253. The signature was validated in 19 prospectively selected PDX models.

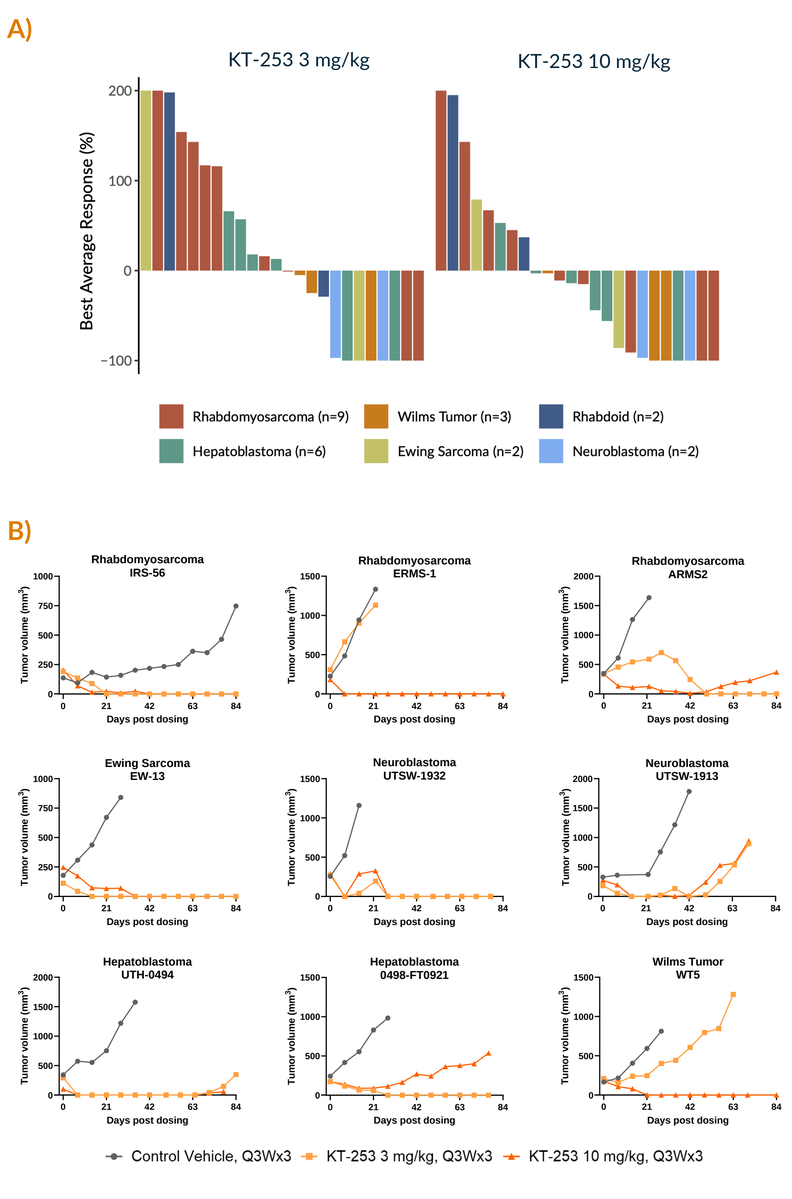
RESULTS

Figure 1: KT-253 is Active in Multiple p53 WT Hematological and Solid Tumor Cell Lines *In Vitro*



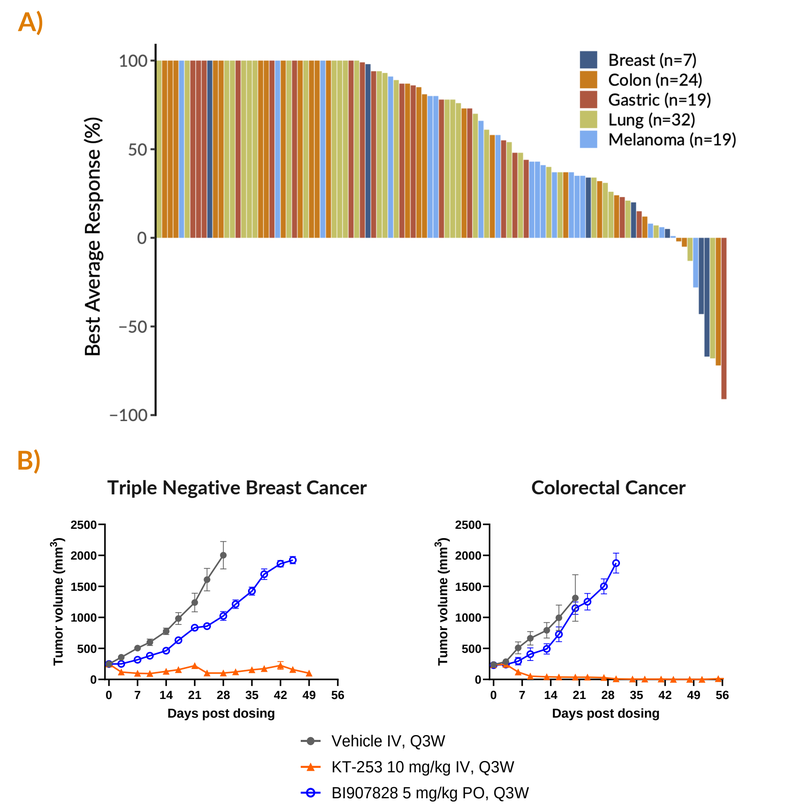
In vitro screening indicates a wide range of **A)** heme and **B)** solid tumor cell lines show sub-nanomolar growth inhibition (CTG assay, 96h) and induction of apoptosis (caspase 3/7 activity, 48h) in response to KT-253. AML, ALL and solid tumor indications that include small round blue cell tumor (**SRBCT**) types were among the most sensitive. These data demonstrate the potential for KT-253 development across a wide variety of heme and solid tumor indications. See Poster PB032 which demonstrates that KT-253 shows robust antitumor activity in Merkel Cell Carcinoma, a neuroendocrine SRBCT.

Figure 2: 38% of Pediatric Solid Tumors Show Complete and Durable Responses to KT-253



A) Waterfall plot of best average response to KT-253 relative to baseline tumor volume at start of treatment in a single mouse trial of 24 pediatric PDX models representing 6 tumor types that include neuroendocrine and SRBCT types. Tumors were established subcutaneously in the hind flank of SCID mice. Complete responses were achieved in 9 of 24 models. Best average response is defined as the average of the best percent change in tumor volume over the course of 5 weeks.
B) Tumor growth curves for 9 models that showed complete response to KT-253 (n=1/group). Mice were dosed intravenously on day 0, 21, and 42.

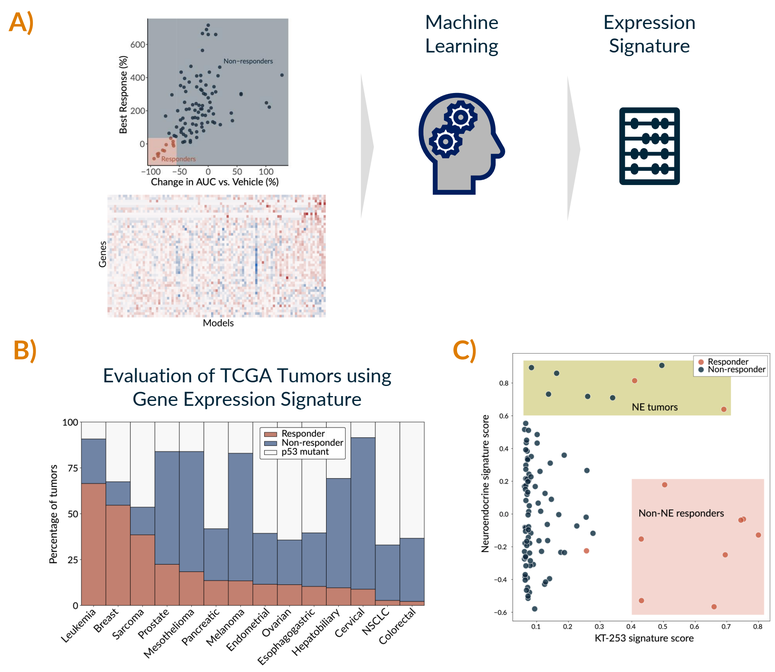
Figure 3: KT-253 is Active in Multiple Adult Solid Tumor Types including Tumors that are Insensitive to an MDM2 Small Molecule Inhibitor



A) Waterfall plot of best average response to KT-253 relative to baseline tumor volume at start of treatment in a single mouse trial of 101 adult PDX models representing 5 different tumor types. Responders were observed in each tumor type. Best average response is defined as the average of the best percent change in tumor volume over the course of 5 tumor measurements.

B) Tumor growth curves comparing the activity of KT-253 to the MDM2 SMI, BI907828 in a triple negative breast cancer model and a colorectal cancer model that expresses the neuroendocrine marker synaptophysin. BI907828 was administered at the clinically relevant dose (n=3/group).

Figure 4: Finding a Gene Expression Signature that Predicts Response to KT-253

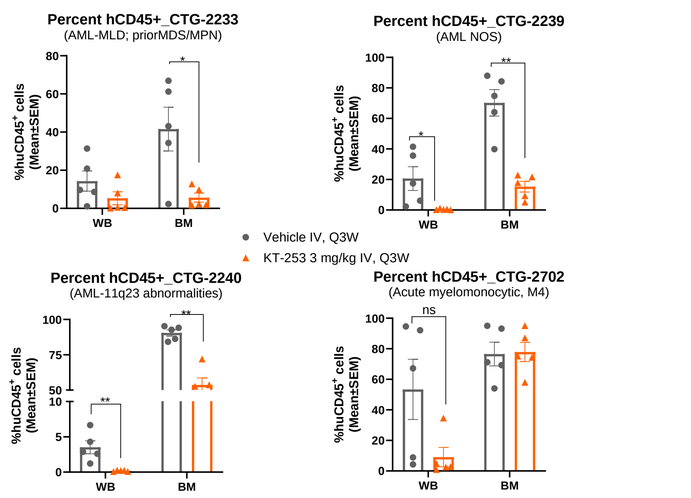


A) To identify a broader pan-cancer responder signature, baseline expression profiles of the adult PDX models were used in a machine learning framework to build a predictive signature.

B) The signature was applied to The Cancer Genome Atlas (TCGA) pan-cancer dataset and identified AML and a subset of solid tumors as sensitive, consistent with our preclinical and early clinical findings.

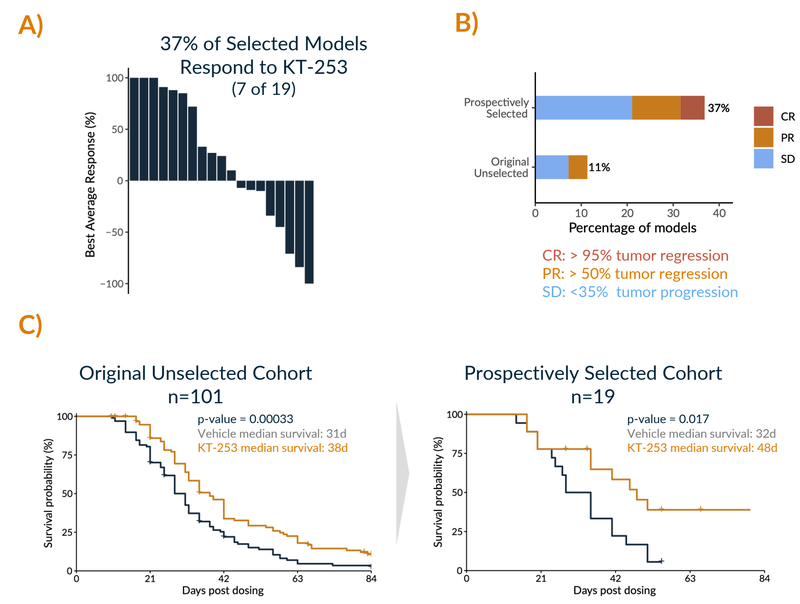
C) Plot of a neuroendocrine (NE) signature (PMID: 29017058) vs. KT-253 predictive signature highlighting that the predictive signature identifies both neuroendocrine and non-endocrine tumors that respond to KT-253. The neuroendocrine tumors include 4 SCLC, 2 poorly differentiated gastric cancers, 1 melanoma and 1 synaptophysin positive CRC.

Figure 5: Disseminated AML PDX Models Show Complete Responses to KT-253



Bar graphs of the percent human CD45+ cells in whole blood (WB) and bone marrow (BM) after treatment with KT-253. Sub-lethally irradiated NOG-EXL mice were inoculated with $2x10^8$ primary AML cells. Treatment was initiated when tumor engraftment levels in the bone marrow of surrogate animals were 68% (CTG-2233), 39% (CTG-2239), 21% (CTG-2240), 50% (CTG-2702). Mice were dosed on day 0, 21 and 42 and tumor burden was quantified by flow cytometry 24h after the last dose. Statistical analysis was conducted using a Student's t-test. Complete responses were achieved in 3 of the 4 models evaluated.

Figure 6: Prospectively Selected PDX Models Demonstrate Improved Response Rates and Survival



A) Waterfall plot of best average response to KT-253 relative to baseline tumor volume at start of treatment in 19 adult PDX models selected using our predictive gene signature. 37% of prospectively selected models responded to KT-253 vs. 11% of unselected models.

B) Bar graph of response calls. Response is defined as the combination of 1) Best response after 14 days of SD or better, 2) Best average response over the course of 5 timepoints of SD or better, and 3) Less than -0.45 change in AUC relative to control. In unselected cohort, we observed 4 PR and 7 SD (11 of 101). In prospectively selected cohort, we observed 1 CR, 2 PR, 4 SD (7 of 19). CR: complete response, PR: partial response, SD: stable disease.

C) Kaplan-Meier curves comparing time to endpoint (tumor volume = 1500 mm^3) in control vs. KT-253 treated animals. Median survival was longer in the prospective models than in the original cohort (48d vs 38d). Odds ratio is 4.7 with 95% CI (1.29, 16.6). p-value= 0.0089.

CONCLUSIONS

- Single mouse trials show that KT-253 has the potential to induce durable complete responses in both pediatric and adult solid tumor types.
- We have used a machine learning framework to build a predictive signature of response to KT-253 that is distinct from published signatures.
- The resulting signature identifies AML and solid tumors with neuroendocrine characteristics as sensitive, consistent with our preclinical and early clinical findings. Importantly, it also identifies non-neuroendocrine tumors that respond to KT-253.
- Application of the responder signature for tumor model selection increased the KT-253 response rate in adult solid tumors from ~10 to 37% and prospectively selected models demonstrated prolonged median survival.
- The signature can be further refined using emerging clinical data to enrich for patients in future trials.

DISCLOSURES

This study was funded by Kymera Therapeutics. Dumont, Karnik, Chutake, Dey, Breitkopf, Howarth, Meeske, Fasciano, Mosher, Gollob and Williams are Kymera Therapeutics employees and equity owners.

The safety and efficacy of this investigational agent has not been established. This agent is not approved by any regulatory body for any indication.