444 TNG260, A COREST-SELECTIVE DEACETYLASE INHIBITOR, REVERSES ANTI-PD1 RESISTANCE DRIVEN BY LOSS OF STK11

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Background Histone deacetylase 1 (HDAC1) was identified from a novel *in vivo* CRISPR screening platform as a target gene whose inhibition reverses α-PD1 resistance driven by loss of STK11. Histone deacetylases are a well-studied class of oncology drug targets, but existing non-isoform-selective HDAC inhibitors have few approved clinical applications due to toxicities that limit sufficient exposure in solid tumors. Our data suggest that HDAC3, an essential gene, is a primary driver of bone marrow toxicity caused by HDAC inhibitors that target multiple isoforms.

Methods We discovered and developed TNG260, a small molecule which inhibits HDAC1 with 10-fold selectivity over HDAC3 in cells, and 500-fold selectivity for the CoREST complex over the other HDAC1-containing complexes, NuRD and Sin3. Due to its CoREST-selective deacetylase inhibition, we have termed TNG260 a CoreDAC inhibitor.

Results Treatment of an α-PD1 resistant STK11-mutant MC38 syngeneic tumor model with TNG260 re-sensitizes this model to treatment with α-PD1. The combination of TNG260 and α-PD1 led to durable complete tumor regressions in the majority of treated animals. All mice with complete responses remained tumor-free until tumor rechallenge (21 days) and rejected engraftment of tumor cells. Unlike previously developed HDAC inhibitors designed for tumor cell cytotoxicity, TNG260 has no anti-tumor efficacy in immunocompromised mice, indicating the tumor cell killing with TNG260 is immune-mediated and not due to direct cell killing. Immune profiling of tumors following treatment with TNG260 and α-PD1 showed a decoupling of $T_{effector}$ and $T_{regulatory}$ cell recruitment caused by α-PD1 monotherapy, leading to a more active immune microenvironment. TNG260 also decreased intratumoral infiltration of neutrophils, an immune suppressive cell type associated with STK11-mutant NSCLC. Toxicity profiling of TNG260 shows it has less viability impact on erythroid and myeloid cells *in vitro* than other HDAC inhibitors, and *in vivo* toxicity studies showed bone marrow suppression only at TNG260 doses that are no longer selective for HDAC1/2.

Conclusions TNG260 is a potent, highly selective small molecule CoreDAC inhibitor with good drug-like properties. It reverses the immune evasion phenotype caused by loss of STK11 and induces tumor regressions in an STK11-mutant model in combination with α-PD1. The TNG260 clinical development plan will be among the first to combine the power of genetic patient selection and immunotherapy, evaluating patients with STK11 mutant cancers in a trial combining TNG260 and a checkpoint inhibitor.

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