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-isooform-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.