COREST INHIBITION BY TNG260 INCREASES EXPRESSION OF IMMUNOMODULATORY GENES IN STK11-MUTANT CANCER AND SENSITIZES TO IMMUNE CHECKPOINT BLOCKADE

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Background Loss of function mutations in STK11 drive immune evasion and cause resistance to immune checkpoint blockade. TNG260 is a small molecule inhibitor of the CoREST complex that increases the expression of immune-related genes in STK11-deficient cancer cells. TNG260 reverses the immune evasion phenotype caused by STK11 loss and induces tumor regressions in STK11-deficient models in combination with anti-PD1.

Methods We discovered and developed TNG260, a small molecule which selectively inhibits the CoREST complex and spares the other Class I HDAC complexes, NCoR, NuRD, and Sin3 (with 500-fold selectivity). Previous reports have shown that combining an LSD1 inhibitor with anti-PD1 results in improved antitumor responses. Since LSD1 is a member of the CoREST complex, the combination of an LSD1 inhibitor with anti-PD1 was evaluated to determine if an LSD1 inhibitor can replicate the effects of TNG260 in an STK11-deficient mouse model that is typically resistant to anti-PD1 monotherapy. We also profiled an AXL inhibitor, which is currently in development for STK11-mutant cancer as a combination approach with pembrolizumab. To determine the mechanism of the TNG260 immunomodulatory effect on tumors, we performed RNA-sequencing and cytokine profiling of STK11-mutant cancer cell lines after treatment with TNG260.

Results TNG260 with anti-PD1 induced tumor regressions in 75% of animals with STK11-deficient tumors. In contrast, an LSD1 inhibitor in combination with anti-PD1 provided limited tumor growth inhibition compared to anti-PD1 alone in an STK11-deficient syngeneic model. Similarly, the AXL inhibitor, bemcentinib, provided a minor enhancement to the tumor growth inhibition seen with anti-PD1 as a single agent in this model. These data suggest that TNG260 outperforms other anti-PD1-based combination therapies in development for STK11-deficient cancer. TNG260 causes transcriptional changes in STK11-mutant cancer cells such as up-regulation of genes involved in antigen presentation and interferon gamma pathway signaling. These results are consistent with cytokine profiling studies which show that TNG260 causes an increase in T cell activity when tumor cells are co-cultured with PBMCs. These findings support previous experiments which demonstrate that TNG260 is an immunomodulatory compound.

Conclusions TNG260 alters expression of immunomodulatory genes in STK11-deficient cancer cells via inhibition of the CoREST complex. Unlike other small molecules being combined with anti-PD1 for STK11-deficient NSCLC, the combination of TNG260 with anti-PD1 drives tumor regressions in STK11-deficient models that are typically resistant to anti-PD1 monotherapy. TNG260 is under investigation in a Phase 1/2 study as a single agent and in combination with pembrolizumab for patients with STK11-mutated, advanced solid tumors.

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