CoREST inhibition by TNG260 increases expression of immunomodulatory genes in STK11-mutant cancer and sensitizes to immune checkpoint blockade

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INTRODUCTION

Loss of function mutations in STK11 drive immune evasion and cause resistance to immune checkpoint blockade. TNG260 is a small molecule that inhibits the CARM1/COP9/CoREST complex (CoREST). CoREST inhibition increases expression of immunomodulatory genes that enhance checkpoint blockade. TNG260 also increases expression of immunomodulatory genes in STK11-deficient cell lines and sensitizes to immune checkpoint blockade.

CoREST inhibition by TNG260 reverses anti-PD1 resistance caused by loss of STK11

Figure 1. STK11 loss decreases anti PD-1 resistance and anti PD-1 sensitivity. (A) Loss of STK11 increases T cell killing. (B) T cell killing of STK11-null tumors and wild-type tumors. (C) Costimulation index (Stimulation index) of STK11-null tumors and wild-type tumors.

Figure 2. TNG260 increases expression of T cell attracting cytokines and stimulates T cell migration. (A) Expression of cytokines in STK11 cells. (B) Migration assay of T cells in STK11-null cells.

Figure 3. TNG260 increases expression of T cell attracting cytokines and increases CD38+ T cell migration. (A) Relative mRNA levels of cytokines in STK11-null cells compared to wild-type cells. (B) CD38+ T cell migration in STK11-null cells.

Figure 4. TNG260 increases expression of T cell attracting cytokines and increases T cell migration. (A) Relative mRNA levels of cytokines in STK11-null cells compared to wild-type cells. (B) T cell migration in STK11-null cells.

TNG260 increases expression of immunomodulatory genes in STK11-deficient cell lines and sensitizes to T cell killing

Figure 5. TNG260 increases expression of immunomodulatory genes in STK11-deficient cell lines and sensitizes to T cell killing. (A) Relative mRNA levels of immunomodulatory genes in STK11-null cells compared to wild-type cells. (B) T cell killing of STK11-null cells and wild-type cells.

TNG260 decreases intratumoral Treg recruitment in combination with anti-PD1

Figure 6. TNG260 decreases intratumoral Treg recruitment in combination with anti-PD1. (A) Treg recruitment in STK11-null tumors with and without TNG260. (B) Treg recruitment in STK11-null tumors with and without anti-PD1.

TNG260 inhibits effector T cell suppression by regulatory T cells

Figure 7. TNG260 inhibits effector T cell suppression by regulatory T cells. (A) Relative mRNA levels of immunomodulatory genes in regulatory T cells. (B) T cell suppression by regulatory T cells.

Figure 8. TNG260 inhibits effector T cell suppression by regulatory T cells. (A) T cell suppression by regulatory T cells in the presence of TNG260.

TNG260 outperforms AXL inhibitor in combination with anti-PD1 in STK11-null cancer model

Figure 9. TNG260 outperforms AXL inhibitor in combination with anti-PD1 in STK11-null cancer model. (A) Comparison of TNG260 and AXL in STK11-null and wild-type models.

ALK1 inhibition is not redundant for TNG260 when combined with anti-PD1 in STK11-mutant cancer

Figure 10. ALK1 inhibition is not redundant for TNG260 when combined with anti-PD1 in STK11-mutant cancer. (A) Survival of TNG260 and ALK1 inhibitor. (B) Survival of TNG260 and ALK1 inhibitor in combination with anti-PD1.

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REFERENCES


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