Combination of tipifarnib with KRAS<sup>G12C</sup> inhibitors to prevent adaptive resistance

Hetika Vora Patel<sup>1</sup>, Alison Smith<sup>1</sup>, Stacia Chan<sup>1</sup>, Linda Kessler<sup>1</sup>, Francis Burrows<sup>1</sup>, and Shivani Malik<sup>1</sup>

<sup>1</sup>Kura Oncology, Inc, San Diego, CA

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**BACKGROUND**

Selective, irreversible KRAS<sup>G12C</sup> inhibitors, including MRTX849 (adagrasib) and AMG510 (sotorasib), exhibit clinical activity with response rates of 45% and 37%, respectively, in patients with KRAS<sup>G12C</sup>-NSCLC<sup>1,2</sup>. However, feedback reactivation of mTOR signaling pathways seems to limit therapeutic efficacy of single agent KRAS<sup>G12C</sup> inhibitors, warranting rational combination strategies<sup>1,2</sup>. We have shown tipifarnib, a farnesyltransferase inhibitor, blocks compensatory feedback reactivation through inhibition of mTOR signaling<sup>3</sup>. Based on our previous work, we hypothesize that tipifarnib in combination with KRAS<sup>G12C</sup> inhibitors could potentially inhibit mTOR pathway reactivation, thus enhancing single agent efficacy and durability in KRAS<sup>G12C</sup>-NSCLC. In this study, we utilize xenograft models to evaluate the therapeutic effects of the combination of tipifarnib with a KRAS<sup>G12C</sup> inhibitor, including adagrasib and sotorasib, in KRAS<sup>G12C</sup>-NSCLC.

**RESULTS**

Combination of tipifarnib and KRAS<sup>G12C</sup> inhibitors decrease spheroid growth of KRAS<sup>G12C</sup> NSCLC cell lines in a dose-dependent manner.

**CONCLUSIONS**

• Combination of tipifarnib with KRAS<sup>G12C</sup> inhibitors, such as adagrasib and sotorasib, leads to significant tumor regression in KRAS<sup>G12C</sup>-NSCLC CDX and PDX models.

Tipifarnib suppresses the feedback reactivation of mTOR signaling at the level of p-S6 (S235/236) that occurs after single-agent KRAS<sup>G12C</sup> inhibitor treatment.

Further in vivo and in vitro mechanistic studies are ongoing to determine MOA of tipifarnib in the context of combination with KRAS<sup>G12C</sup> inhibitors in KRAS<sup>G12C</sup>-NSCLC.

**REFERENCES**


**Figure 1.** Tipifarnib and KRAS<sup>G12C</sup> inhibitors, adagrasib and sotorasib, inhibit the spheroid growth of KRAS<sup>G12C</sup>-NSCLC cell lines. A-D. NSCLC H122 KRAS<sup>G12C</sup>-NSCLC cell line was treated with tipifarnib and (A) adagrasib or (D) sotorasib, and NCI-H1792 KRAS<sup>G12C</sup>-NSCLC cell line was treated with tipifarnib and (B) adagrasib or (E) sotorasib. A549 KRAS<sup>G12C</sup>-NSCLC cell line was used as a control for KRAS<sup>G12C</sup> inhibitor treatment, and this control cell line was treated with tipifarnib and (C) adagrasib or (F) sotorasib.

**Figure 2.** Anti-tumor efficacy in KRAS<sup>G12C</sup>-NSCLC xenograft models with combination of tipifarnib with KRAS<sup>G12C</sup> inhibitors. LUS122 KRAS<sup>G12C</sup>-NSCLC PDX model had significant tumor regressions with (A) tipifarnib, 60 mg/kg, BID + adagrasib, 100 mg/kg, OD and (B) tipifarnib, 60 mg/kg, BID + sotorasib, 100 mg/kg, OD compared to vehicle control. NCI-H122 KRAS<sup>G12C</sup>-NSCLC CDX model had significant tumor regressions with (C) tipifarnib, 60 mg/kg, BID + adagrasib, 100 mg/kg, OD and (D) tipifarnib, 60 mg/kg, BID + sotorasib, 100 mg/kg, OD compared to vehicle control and single-agent treatment groups. (E) Immunoblot analysis was done for the NCI-H122 KRAS<sup>G12C</sup>-NSCLC CDX tumors. Combination of tipifarnib with adagrasib caused an increase in the apoptotic marker cleaved caspase 3 (CC3) as well as decreases in the mTOR signaling pathway markers, p-S6 and p-4EBP1, compared to single-agent treatments.

**Figure 3.** Combination of tipifarnib with a KRAS<sup>G12C</sup> inhibitor suppresses mTOR signaling reactivation and promotes cell apoptosis. Combination of tipifarnib with sotorasib treatment suppresses mTOR signaling more potently and durably than single agent sotorasib. Immunoblot of p-4EBP1, p-akt and total mTOR showed in NCI-H122 KRAS<sup>G12C</sup>-NSCLC xenograft model had significant tumor regressions with (C) tipifarnib, 60 mg/kg, BID + adagrasib, 100 mg/kg, QD compared to vehicle control and single-agent treatment groups. (D) tipifarnib, 60 mg/kg, BID + sotorasib, 100 mg/kg, QD compared to vehicle control. NCI-H1792 KRAS<sup>G12C</sup>-NSCLC xenograft model had significant tumor regressions with (A) tipifarnib, 60 mg/kg, BID + adagrasib, 100 mg/kg, QD and (B) tipifarnib, 60 mg/kg, BID + sotorasib, 100 mg/kg, QD compared to vehicle control and single-agent treatment groups. (E) Statistical significance (p<0.05; *p<0.01; **p<0.001; ***p<0.0001).