Repotrectinib Increases Effectiveness of KRAS-G12C Inhibitors in KRASG12C Mutant Cancer Models via Simultaneous SRC/FAK/JAK2 Inhibition

INTRODUCTION

- KRAS regulates a complex signaling network with multiple downstream pathways that promote survival, proliferation, and cytokine secretion in cancer cells.[1]
- Resistance via feedback reactivation, bypass signaling, and cytokine-mediated tumor immunity limit the efficacy of KRAS inhibitors (AMG10, MITRX49) as single-agents.[2]
- SRC, FAK, and JAK2 play important roles in the KRAS signaling network and operate in a compensatory manner to affect both tumor cell intrinsic and extrinsic processes.[3]
- Simultaneous inhibition of SRC/FAK/JAK2 by repotrectinib has the potential to improve the effectiveness of KRAS inhibitors[4]

EVALUATION OF REPOTRECTINIB IN BIOCHEMICAL ASSAYS

- Repotrectinib (1 µM ATP) inhibits SRC/FAK/JAK2 in biochemical assays (Figure 1).
- Repotrectinib potently inhibits SRC/FAK/JAK2 and therefore modulates a broader signaling network (Figure 2).

Figure 1: Repotrectinib kinase selectivity at 10 nM.

EVALUATION OF REPOTRECTINIB/AMG510 IN CELL-BASED ASSAYS

- Repotrectinib/AMG510 combination suppresses more KRAS signaling nodes than AMG10 combinations with dasatinib, defactinib, or ruxolitinib in H122 KRASG12C NSCLC cells and therefore modulates a broader signaling network (Figure 3).
- Repotrectinib/AMG510 combination leads to a decrease in H128 KRAS-NSCLC cell viability (Figure 4A) compared to single-agent treatment. Similar results were observed in other KRASG12C cell lines (H122, H23, H1792, H1793).
- Repotrectinib/AMG510 combination is synergistic in H122 KRAS-NSCLC cells (Figure 4B).

Figure 3: Repotrectinib/AMG510 combination vs AMG510 combination with Dasatinib, Defactinib or Ruxolitinib in H122 KRASG12C NSCLC Cells.

- Repotrectinib/AMG510 combination enhances apoptosis (increased cleaved PARP) and decreases total PARP compared to single-agent treatment (Figure 5A).
- Repotrectinib/AMG510 combination is more effective at inducing apoptosis in H122 KRASG12C NSCLC cells than AMG10 combined with multiple inhibitors that have a subset of repotrectinib activities (Figure 5B).

Figure 5: Evaluation of SRC/FAK/JAK2 Signaling in In-Vivo Assays.

- Repotrectinib inhibits cytokine secretion and enhances AMG510 effects in KRASG12C NSCLC cells (Figure 6).

Figure 6: Cytokine Secretion and Enhanced AMG510 Effects in KRASG12C Cells.

- At clinically relevant repotrectinib exposure, repotrectinib/AMG510 combination potently inhibits SRC, FAK, STAT3, ERK, and AKT phosphorylation in an H1650 (NSCLC) cell-derived xenograft tumor model (Figure 7).

Figure 7: Evaluation of SRC/FAK/JAK2 Signaling in In-Vivo Assays.

- Repotrectinib demonstrates single agent and enhanced combination efficacy in H183 xenograft model (Figure 8).
- Repotrectinib/AMG510 combination is efficacious in the LU1693 PDX model which is resistant to AMG510 single agent treatment (Figure 9).

Figure 8: waterfall plot of anti-tumor effect of Repotrectinib/AMG510 in H183 NSCLC KRASG12C xenograft tumor model.

CONCLUSIONS

- Repotrectinib inhibits SRC/FAK/JAK2 in vivo and in vivo models.
- STAT3 and AKT phosphorylation is suppressed by repotrectinib in vivo and in vivo models.

REFERENCES & DISCLOSURES

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