FMC-376 a dual inhibitor of on off states of KRAS^{G12C} is broadly active in PDX models of resistance

Poster # 5948

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Background

KRAS is the most frequently mutated oncogene in human cancer with activating mutations occurring in approximately 25% of NSCLC. Of these, KRAS^{G12C} occurs in approximately 14% of adenocarcinomas and in 0.5 to 4% of squamous NSCLCs. This mutation impairs GTPase activity and GTP-hydrolysis leading to an increase in the active, GTP-bound (ON), state. While the first generation of KRAS^{G12C} inhibitors has demonstrated clinical response, many cancers do not respond, and acquired resistance is common.

FMC-376 is a next-generation dual inhibitor of both ON+OFF states of KRAS^{G12C}. FMC-376 was discovered through the Frontier™ platform, which integrates chemoproteomics, machine-learning, and covalent fragment-based drug discovery.

Here we report the anti-tumor activities of FMC-376 in a broad panel of patient derived xenograft (PDX) models derived from NSCLC, CRC and PDAC cancer patients.

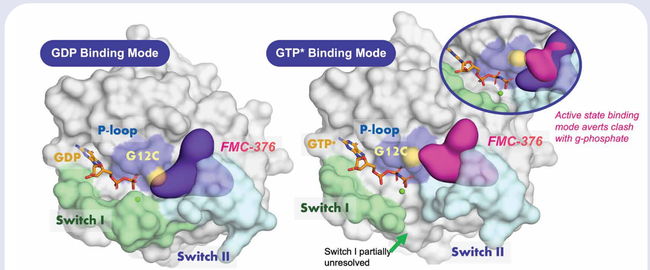

Figure 1: The Frontier™ Platform enabled FMC-376 to adopt two low energy confirmations and bind both ON and OFF states of KRAS^{G12C}

Dual ON + OFF inhibition overcomes resistance

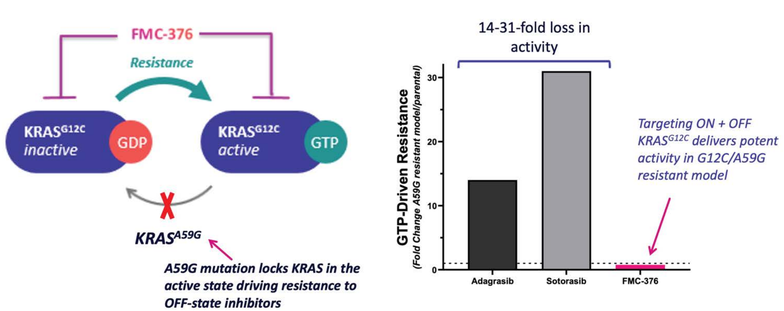

Figure 2: FMC-376 a dual ON+ OFF-state inhibitor, maintains potent activity against resistant cells with the A59G mutation. MCF10A cells stably overexpressing KRAS^{G12C} or KRAS^{G12C}/A59G were treated with adagrasib, sotorasib, and FMC-376. Cell viability was determined in both the double mutant KRAS^{G12C}/A59G and KRAS^{G12C} MCF10A cells and the ratio of IC50s is presented.

FMC-376 demonstrates anti-tumor activity in PDX models derived from heavily-pretreated patients

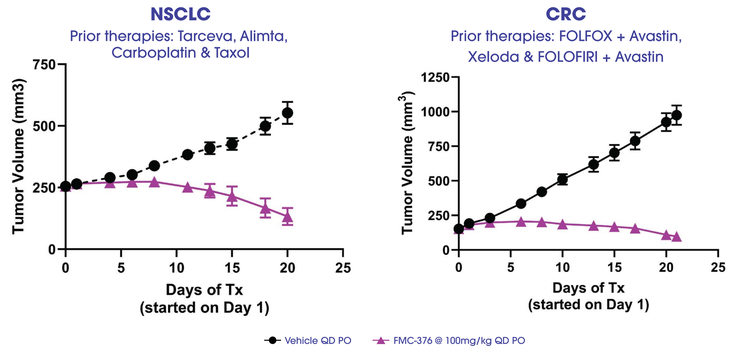

Figure 3: Robust anti-tumor activity of FMC-376. Tumor fragments derived from heavily-pretreated patients are inoculated into the flank of BALB/c nude or NOD/SCID mice. When the mean tumor size reached approximately 100-200 mm^3, mice are randomized to receive either vehicle control or FMC-376 (100 mg/kg, QD) for 21 days.

FMC-376 overcomes mechanisms of innate and acquired resistance in NSCLC

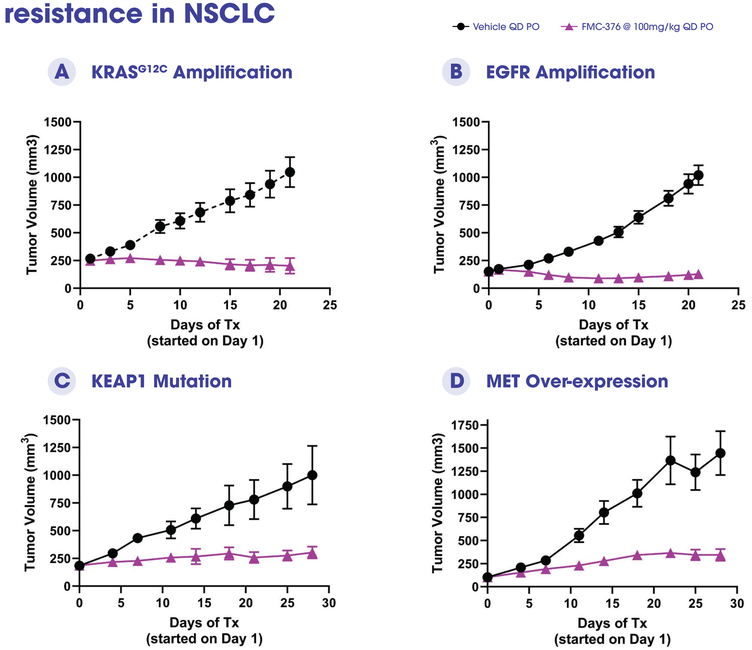

Figure 4: FMC-376 is highly efficacious in PDX models of NSCLC. All PDX models are derived from NSCLC patient tumors and carry a KRAS^{G12C} mutation plus additional mutation known to drive innate and acquired clinical resistance to OFF state inhibitors. Panel A) KRAS^{G12C} amplification; Panel B) EGFR amplification; Panel C) KEAP1 mutation; Panel D) MET overexpression

FMC-376 demonstrates anti-tumor activity in KRAS^{G12C} models derived from CRC and PDAC Patients

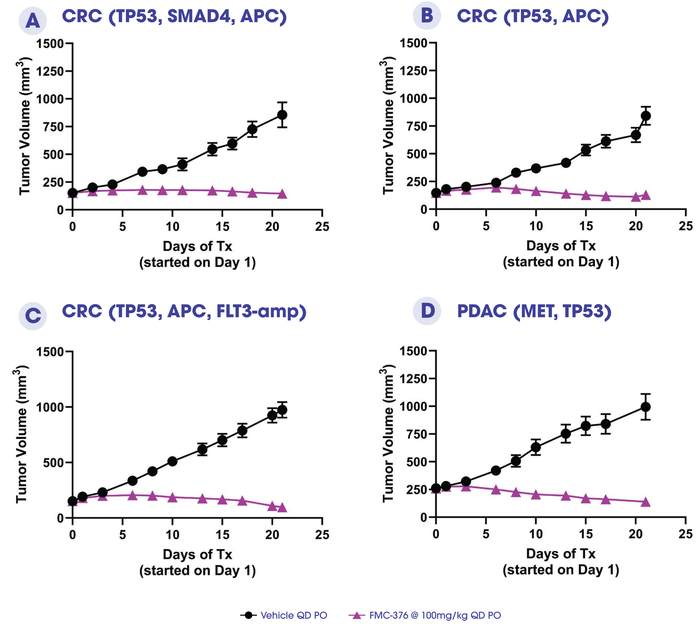

Figure 5: Robust anti-tumor activity of FMC-376 in PDX models of CRC and PDAC. All PDX models are derived from CRC and PDAC patient tumors and carry a KRAS^{G12C} mutation. Panels A-C) CRC PDX models, Panel D) PDAC PDX model.

Conclusions

- The Frontier™ Platform has enabled discovery of FMC-376, a first-in-class dual inhibitor of ON+OFF KRAS^{G12C}
- FMC-376 is highly active in models of G12Ci resistance where ON state KRAS^{G12C} is upregulated
- FMC-376 is efficacious in KRAS^{G12C} mutant containing PDX models derived from CRC, NSCLC and PDAC patients including tumors derived from heavily treated patients, with the potential to deliver best-in-class treatment outcomes
- The Phase 1/2 PROSPER clinical trial (NCT06244771) is currently recruiting to evaluate FMC-376 in participants with KRAS G12C cancers, regardless of prior KRAS^{G12C} inhibitor therapy