# The clinical dual KRAS$^{G12C}$ inhibitor FMC-376 has demonstrated potential as both a monotherapy and in combination for the treatment of patients with KRAS$^{G12C}$ mutation positive NSCLC

Poster # 5949

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## Background

KRAS$^{G12C}$ mutation 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 first generation of KRAS$^{G12C}$ inhibitors have 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$^{TM}$ platform, which integrates chemoproteomics, machine-learning, and covalent fragment-based drug discovery.

Here we demonstrate FMC-376 is highly active across a panel of NSCLC PDX models, including those that carry co-mutations that are associated with both primary and acquired resistance to OFF-state inhibitors in NSCLC. Furthermore, FMC-376 is active in a model of NSCLC CNS metastasis and in combination with immune checkpoint inhibition.

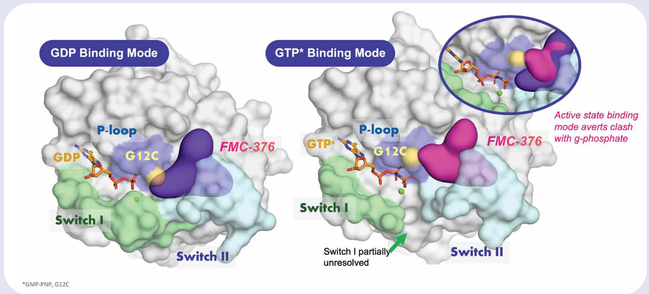


**Figure 1:** The Frontier$^{TM}$ Platform enabled FMC-376 to adopt two low energy confirmations and bind both ON and OFF states of KRAS$^{G12C}$

## FMC-376 overcomes innate and acquired resistance mechanisms in PDX models

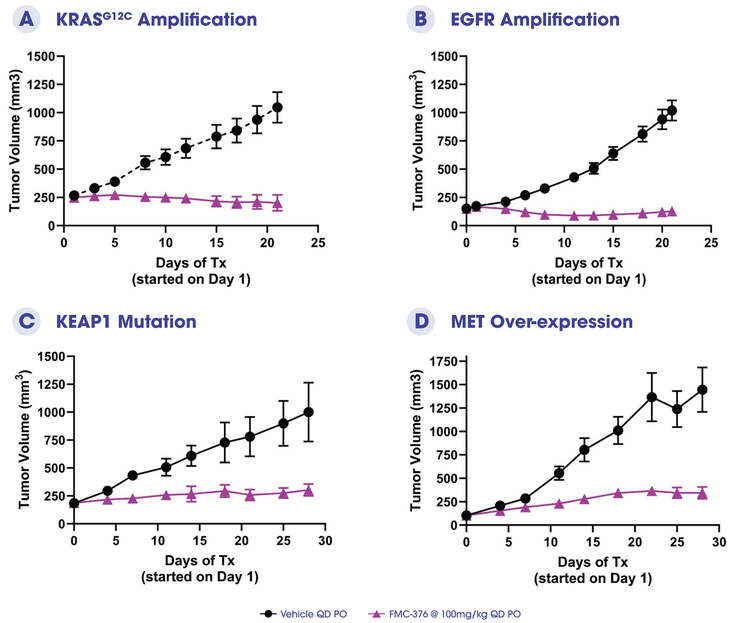


**Figure 3:** All PDX models are derived from NSCLC patient tumors and carry a KRAS$^{G12C}$ mutation plus additional mutation known to drive innate and acquired clinical resistance to OFF state inhibitors. Panel A) KRAS$^{G12C}$ amplification; Panel B) EGFR amplification; Panel C) KEAP1 mutation; Panel D) MET overexpression

## FMC-376 is effective in a model of NSCLC CNS metastasis

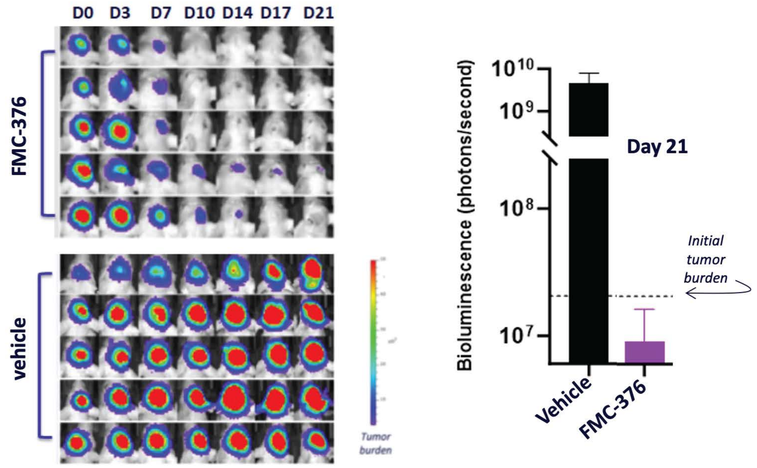


**Figure 5:** FMC-376 achieves tumor regression in a NSCLC brain metastasis model. NCI-H1373-Luc tumor cells were inoculated intracranially at the right frontal lobe of the mice. Bioluminescence intensity, an indicator of the tumor burden, was measured by Xenogen instrument. Tumor-bearing mice were randomized and treated with either vehicle or 100 mg/kg FMC-376 QD PO.

## Robust suppression of MAPK signaling in the presence of high growth factor signaling

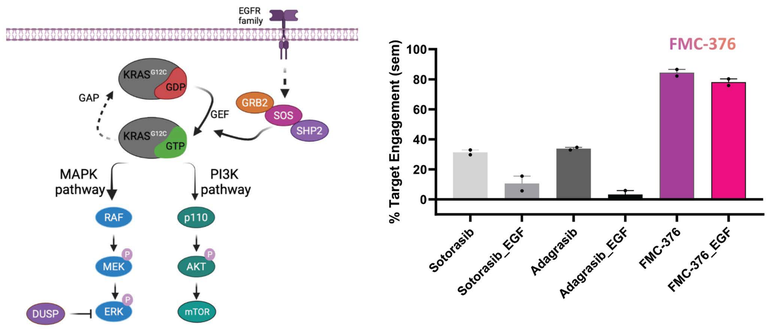


**Figure 2:** FMC-376 maintains rapid and durable target engagement in the presence of high growth factor signaling. In brief, Lu65-B cells were treated with drug for 30min, +/- EGF stimulation. KRAS$^{G12C}$ target engagement was quantified by mass spectrometry.

## Addition of FMC-376 to a checkpoint inhibitor leads to increased survival

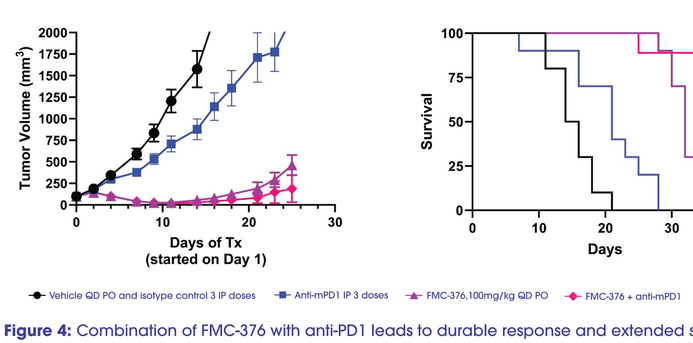


**Figure 4:** Combination of FMC-376 with anti-PD1 leads to durable response and extended survival. The CT26 tumor cell line was engineered to express KRAS$^{G12C}$. Established tumors were treated with either vehicle control, FMC-376 (100 mg/kg, QD), anti-mPD1 (10 mg/kg on Days 1, 4 and 7, ip), or combination of FMC-376 and anti-mPD1 for 25 days.

## Conclusions

- The Frontier$^{TM}$ Platform has enabled discovery of FMC-376, a first-in-class dual inhibitor of ON+OFF states of KRAS$^{G12C}$
- FMC-376 overcomes drivers of innate and acquired clinical resistance to OFF state inhibitors of KRAS$^{G12C}$ as demonstrated by robust anti-tumor activity across a broad panel of NSCLC PDX models, to potentially drive best-in-class treatment outcomes
- Combination of FMC-376 with an immune checkpoint inhibitor leads to increased response and survival in a preclinical model
- FMC-376 is highly effective in a model of NSCLC CNS metastasis
- 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