RAF Dimer Inhibitor Lifirafenib Enhances the Antitumor Activity of MEK Inhibitor Mirdametinib in *RAS* Mutant Tumors

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K-RAS mutation represents one of the most frequent genetic alterations in cancers. Monotherapy approaches targeting RAS downstream effectors such as MEK and ERK have had limited clinical success in patients with *K-RAS*-mutated cancers. The reduced sensitivity of *K-RAS*-mutated cells to certain MEK inhibitors is associated with feedback phosphorylation of MEK and reactivation of mitogen-activated protein kinase (MAPK) signaling. Herein, we report that RAF dimer inhibitor lifirafenib (BGB-283) shows strong synergistic effect with MEK inhibitor mirdametinib (PD-0325901) in suppressing proliferation of *K-RAS*-mutated cancer cell lines. This synergistic effect was not observed using vemurafenib, a first-generation B-RAF^{V600E} selective inhibitor. Mechanistic analysis revealed that RAF dimer inhibition could suppress RAF-dependent MEK reactivation and led to sustained inhibition of MAPK signaling in *K-RAS*-mutated cells. Furthermore, combination synergy was observed in *K-RAS* mutant xenograft models. Pharmacodynamic analysis supported the role of synergistic phospho-ERK blockade in enhancing the antitumor activity in the *K-RAS* mutant models. These findings support the rationale to combine a RAF dimer inhibitor and a MEK inhibitor to treat *K-RAS*-mutated cancers and led to the ongoing a Phase 1b/2 clinical trial of lifirafenib and mirdametinib in patients with *K-RAS* mutations or other MAPK pathway aberrations (Clinical Trial ID: NCT03905148).