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

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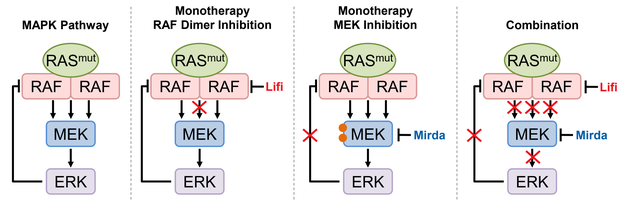
Background

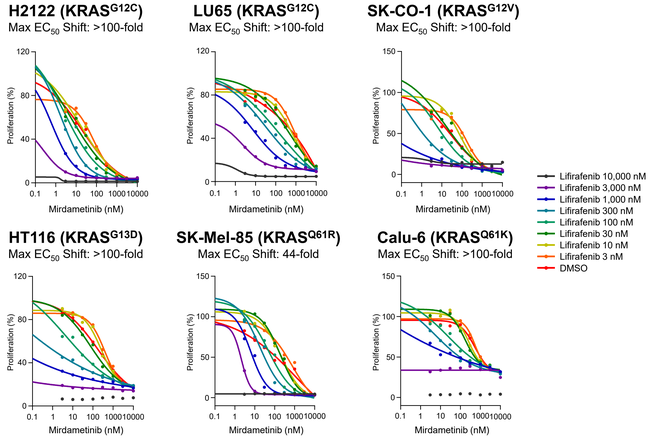
- RAS proteins occupy a critical position in the mitogen-activated protein kinase (MAPK) pathway and play a key role in its signal transduction cascade.
- Diverse mutations in RAS genes, particularly those in *KRAS*, have been described in up to 25% of solid tumors and have been shown to be driver oncoproteins in cancers such as non-small cell lung cancer (NSCLC), endometrial cancer, and colorectal cancer.
- Monotherapy approaches targeting RAF dimers have had limited clinical success in *KRAS*-mutated cancers owing to an inability to adequately suppress MAPK signaling as single agents.
- Monotherapy approaches targeting MEK have had limited clinical success in *KRAS*-mutated cancers owing to feedback phosphorylation of MEK and reactivation of MAPK signaling via RAF dimers.
- These limitations have been shown to be addressable in *KRAS*-mutated cancer models using a vertical inhibition strategy centered upon inhibiting RAF dimers in order to suppress RAF-dependent MEK reactivation while simultaneously inhibiting MEK to directly block ERK activation.
- **Lifirafenib** (BGB-283) is an oral, potent, and reversible pan-RAF inhibitor that has demonstrated monotherapy clinical activity in *BRAF* and certain *KRAS* mutated solid tumor patients.
- **Mirdametinib** (PD-0325901) is an oral, potent, and selective inhibitor of MEK that has demonstrated monotherapy clinical activity in certain tumors driven by overactivation of the MAPK pathway.

Therapeutic Strategy



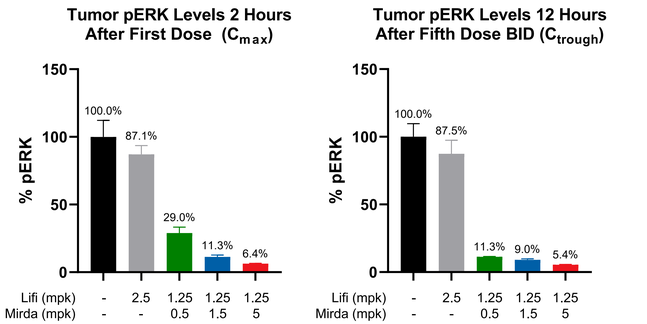
Treatment of *KRAS* mutated tumors with monotherapy **lifirafenib** inhibits RAF dimers but is unable to fully suppress signaling through ERK. Treatment of *KRAS* mutated tumors with monotherapy **mirdametinib** leads to increased RAF dimerization, increased MEK phosphorylation, and elevated ERK activity. Combination treatment disrupts RAF dimers and inhibits the MEK inhibitor-induced feedback reactivation, thereby inhibiting MAPK signaling.

Lifirafenib and Mirdametinib Demonstrate Synergistic Antiproliferative Effects in Cell Lines Harboring a Variety of *KRAS* Mutations



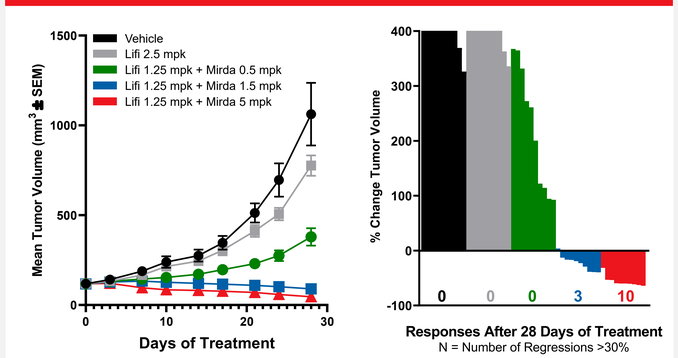
Lifirafenib and mirdametinib demonstrated statistically significant synergistic inhibition in cancer cell lines harboring a variety of *KRAS* mutations. The synergistic effect of lifirafenib and mirdametinib was evaluated in 22 *KRAS* mutant cancer cell lines using an 8×8 dose matrix with a luminescent cell viability assay readout. For each dose combination, the Biochemically Intuitive Generalized Loewe method with Highest Single Agent null model was utilized to evaluate synergy between the two agents. P-values < 0.05 were scored as having a statistically significant synergistic effect and 14 of the 22 cell lines achieved this threshold. Statistically significant synergistic activity was observed in cell lines harboring a variety of *KRAS* mutant alleles, including G12C, G12V, G13D, Q61R, and Q61K. Example cell lines are shown above.

Lifirafenib and Mirdametinib Drive MAPK Pathway Inhibition in Calu-6 KRAS^{Q61K} NSCLC Xenograft Model Using Clinically Relevant Doses



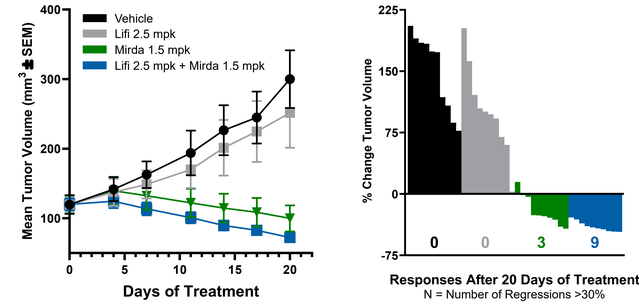
The addition of mirdametinib to lifirafenib led to potent and sustained inhibition of MAPK pathway activity, as measured by tumor pERK levels. Calu-6 cells were inoculated subcutaneously in BALB/c Nude mice and mice were treated once tumor volumes reached ~325 mm^3. Tumors were snap frozen 2 hours following the first dose (left) and 12 hours following the fifth dose (right). pERK levels were assessed using the Surefire AlphaScreen kit and MAPK pathway inhibition was confirmed with Western blot analysis of pMEK, MEK, pERK, ERK, and GAPDH levels (not shown).

Lifirafenib and Mirdametinib Demonstrate Tumor Regressions in Calu-6 KRAS^{Q61K} NSCLC Xenograft Model Using Clinically Relevant Doses



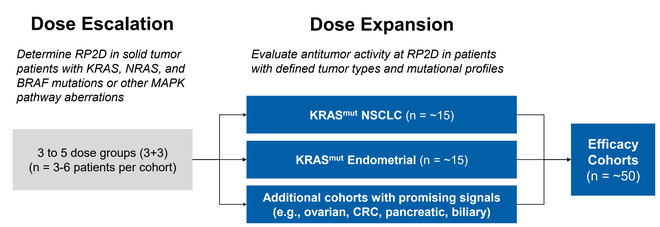
Combination of lifirafenib and mirdametinib exhibited enhanced antitumor activity in human NSCLC KRAS^{Q61K} xenograft model. Calu-6 cells were inoculated subcutaneously in BALB/c Nude mice and mice were randomized and treated as indicated once tumor volumes reached ~120 mm^3 (N=10 per group).

Lifirafenib and Mirdametinib Demonstrate Tumor Regressions in NCI-H358 KRAS^{G12C} NSCLC Xenograft Model Using Clinically Relevant Doses



Combination of lifirafenib and mirdametinib exhibited enhanced antitumor activity in human NSCLC KRAS^{G12C} xenograft model. NCI-H358 cells were inoculated subcutaneously in BALB/c Nude mice and mice were randomized and treated as indicated once tumor volumes reached ~120 mm^3 (N=10 per group).

Design of Ongoing Phase 1b/2 Clinical Trial



Conclusions

- We have demonstrated evidence for potent activity of lifirafenib and mirdametinib across preclinical models driven by a variety of *KRAS* mutations, including KRAS^{Q61K} and KRAS^{G12C} xenografts
- PD analysis showed strong synergistic activity *in vivo* against pERK using clinically relevant doses of each compound, supporting the antitumor activity of this vertical inhibition strategy
- Lifirafenib and mirdametinib are currently being evaluated in an ongoing Phase 1b/2 combination clinical trial (ID: NCT03905148)

References:

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Disclosures: **XY**, **XZ**, **RD**, **SC**, **XW**, **BJ**, **ZT**, **MW**, **CZ**, and **LW** are employees of and hold stocks and shares in BeiGene. **TS**, **BE**, and **LMS** are employees of and hold stocks and shares in SpringWorks. **ZY** is an SAB member of MapKure. **NR** is an SAB member of AstraZeneca, Chugai, BeiGene, Zai Laboratories, Ribon, and MapKure (jointly owned by BeiGene and SpringWorks), is a consultant to Tarveda, Boehringer Ingelheim (BI), Concello, Novartis, and Jubilant, reports receiving commercial research grants from BI and Chugai, and has ownership interest (including patents) in BeiGene, Kura, and Zai Laboratories. **LL** is an employee of and holds stocks and shares in BeiGene and holds shares in MapKure.

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