Vertical inhibition of the MAPK pathway as potential treatment strategy in NRAS-mutant melanoma

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Background

- Metastatic melanoma is the most aggressive form of skin cancer. Worldwide incidences of melanoma continue to rise, with 100,000 new cases estimated in the United States during 2023, ranking melanoma as the sixth most common cancer.
- A large proportion of melanomas carry mutations in the mitogen-activated protein kinase (MAPK) signaling pathway leading to hyper-activation and proliferation of the mutated cells. Driver mutations in BRAF V600 (50%) and NRAS Q61 (20%) are the most common mutations found in melanoma.
- Newly developed FDA-approved kinase inhibitors that directly target BRAFV600E-mutated tumours have shown dramatic and long-lasting clinical efficacy, but relapses do occur.
- Treatment of tumours containing NRAS mutations have relied on inhibition of MEK, a downstream target of NRAS, as no current therapies that directly target mutant NRAS are available.
- Importantly, previous experiments using the pan-RAF dimer inhibitor Lifirafenib and the selective MEK inhibitor Mirdametinib showed striking antitumor activity after combination treatment in RAS-mutated solid tumours. Collectively, these data suggest that vertical inhibition of the MAPK in mutated melanoma tumours could result in synergistic benefits.

Results

Pan-RAFi (BGB-3245) and MEKi (Mirdametinib) have inhibitory effects on primary patient-derived NRAS mutated melanoma cell lines in vitro

Therapeutic strategy

- Mirdametinib (PD-0325901) is an investigational, oral, potent, and selective inhibitor of MEK that has demonstrated monotherapy clinical activity in certain tumours driven by overactivation of the MAPK pathway.
- BGB-3245 is an investigational, oral, and potent second-generation RAF dimer inhibitor. It is being investigated in an ongoing clinical study (NCT02499811) in participants with advanced or refractory solid tumors harboring BRAF or NRAS mutations.

Combination of BGB-3245 and Mirdametinib induced greater frequencies of apoptosis at clinical relevant concentrations

BGB-3245 and Mirdametinib treatment resulted in dose-dependent MAPK pathway inhibition in vitro

In vivo combination of BGB-3245 and Mirdametinib resulted in tumour regression and survival benefit in Xenograft models

Conclusion

- This study showed significant therapeutic effects on primary patient-derived NRAS Q61 mutated melanoma cell lines, both in vitro and in vivo, using the combination of BGB-3245 and Mirdametinib at clinically relevant doses.
- Mechanistically, the combination of BGB-3245 and Mirdametinib treatment resulted in greater apoptosis of treated cell lines in vitro. This correlated with dose-dependent inhibition of the MAPK pathway proteins pMEK1/2, pERK, and Cyclin D1.
- NRAS Q61 may serve as a prospective biomarker for patient stratification in trials assessing the combination of pan-RAF and MEK inhibitors in mutant melanoma.
- Overall, these data support the clinical investigation of MAPK pathway vertical inhibition through combination treatment with BGB-3245 and Mirdametinib in patients with RAS mutations.

References


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