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The oligoclonal anti-EGFR antibody MM-151 synergizes with trametinib in KRAS wildtype and mutant colorectal cancer models resistant to conventional monoclonal anti-EGFR antibodies

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Background: EGFR is a key driver of tumor growth in colorectal cancer (CRC). Many CRC patients initially derive benefit from anti-EGFR-based treatment regimens, but eventually develop resistance. Resistance can arise through acquisition or selection of mutations in KRAS, NRAS, or BRAF. We hypothesized that this mechanism could be overcome by combining MM-151, a potent oligoclonal EGFR inhibitor, with MEK inhibitor trametinib. For tumors that do not develop mutations in RAS or RAF, resistance may emerge through upregulation of ligands like heregulin (HRG) and insulin-like growth factor-1. These ligands activate prosurvival signaling through PI3K/Akt. We postulated that a biomarker-driven approach could determine which investigational agent to pair with MM-151 to overcome resistance in CRC models. In parallel, we have initiated a Phase 1, biomarker-directed open-label study evaluating the safety, pharmacology and preliminary activity of MM-151 in combination with MM-121, trametinib, or MM-141 in CRC, squamous cell carcinoma of the head and neck, and non-small cell lung cancer (NCT02538627).

Materials and Methods: We evaluated combinations of MM-151 with trametinib or MM-121 in a panel of KRAS mutant, BRAF mutant, or KRAS/BRAF-wildtype CRC cell lines using an optimized in vitro culture system to measure cell viability and treatment effect on cell signaling. The screen was performed in the presence or absence of exogenous ligands. Cetuximab was used as a monoclonal anti-EGFR antibody comparator in the same treatment settings. Using these data, we selected xenograft models for in vivo analysis of combination efficacy. We also used engineered CRC xenograft models with altered biomarker profiles, including varying levels of HRG, to investigate the treatment effects of MM-151, MM-121, cetuximab, trametinib and their combinations. Animal experiments were approved by the IACUC.

Results: We found that MM-151 and trametinib exhibit additive effects on decreasing cell viability in RAS mutant, RAF mutant, and RAS/RAF wild-type CRC cell lines in the presence of EGFR ligands. In contrast, cetuximab and trametinib do not. Notably, HRG compromises the effect of both MM-151 and trametinib on cell viability in both KRAS-mutant and KRAS-wildtype cell lines. The addition of MM-121 can restore sensitivity to the MM-151/trametinib combination in vitro.

Although the effects of MM-151 and trametinib are additive in vitro, they are clearly synergistic in several CRC xenograft models, leading to potent anti-tumor activity. Synergy was observed regardless of KRAS mutation status. Mechanistically, synergy depends on the oligoclonality of MM-151, as cetuximab failed to synergize with trametinib in vivo.

Conclusions: CRC models that do not respond to treatment regimens based on monoclonal anti-EGFR antibodies may benefit from combination treatment with MM-151 and trametinib.

Conflict of interest: *Ownership: All authors are employees of Merrimack Pharmaceuticals, Inc.*