1. 100% (5/5) 83% (5/6) 60% (3/5)

2. Addition of VS-6766 to AMG 510 increases depth & duration of inhibition of p-ERK relative to AMG 510 alone across a panel of KRAS G12C mutant NSCLC cell lines

3. VS-6766 & FAKi potentiate AMG 510 efficacy in KRAS G12C mutant NSCLC in vivo

4. Strong synergy observed between VS-6766 and agents targeting other nodes in the RAS pathway (vertical blockade), including pan-HER, SHP2, SOS1 and ERK1/2 inhibitors

CONCLUSIONS

- VS-6766 is a dual RAF/MEK inhibitor that uniquely confers vertical inhibition of the MAPK pathway with a single drug
- Synergy of VS-6766 + G12C observed across KRAS G12C mutant NSCLC, pancreatic cancer & CRC cell lines
- VS-6766 combination confers better ERK pathway blockade relative to G12C alone
- Both VS-6766 & FAKi enhance efficacy of G12C in H2122 & H358 xenograft models, triple combination of G12C + VS-6766 + FAKi yields tumor regression in all mice in both models.
- These results support the clinical evaluation of VS-6766 ± FAKi (or defactinib) in combination with a G12C inhibitor for treatment of KRAS G12C mutant cancers

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