Preclinical data shows that adaptive up-regulation of signaling through SHP2 inhibitor drives anti-tumor activity and immunity. KRASG12C(OFF) inhibitors drive anti-tumor activity and immunomodulation. Preclinical data have demonstrated that SHP2 inhibition has activity against KRASG12C NSCLC. However, recent clinical data show that the majority of NSCLC tumors escaping from KRASG12C therapy have no identifiable genomic cause. As a result, the immunosuppressive tumor microenvironment is an important component of KRAS inhibitor resistance. Additional studies are required to further characterize efficacy of RMC-4630 in combination with sotorasib as monotherapy for subjects with KRASG12C mutant NSCLC after failure of prior standard therapy.

Methods
- Dose escalation from Dose Level 1 to Dose Level 2 will be guided by a modified toxicity probability interval algorithm and decision made by the Dose Committee.
- Safety run-in phase: up to 6 subjects will be enrolled during the safety run-in portion of the study. An additional 6 subjects may be enrolled during the safety run-in if no DLTs occur. A dose expansion at Dose Level 2 may be initiated after the DLT-free run-in.

Conclusion
- Combination of SHP2 and KRASG12C(OFF) inhibitor shows anti-tumor activity and acceptable safety and tolerability in locally advanced or metastatic NSCLC subjects with KRASG12C mutation with and without co-existing genetic aberrations in specific genes after failure of prior standard therapy.

Acknowledgements
- A phase 2, open-label, multicenter study of the combination of RMC-4630 and Sotorasib for non-small cell lung cancer subjects with KRASG12C mutation. The phase 2 RMC-4630-03 study evaluating efficacy and safety of RMC-4630 as monotherapy or in combination with sotorasib is open for enrollment and recruiting in 10 countries.

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