COMBINING KRAS\textsuperscript{G12C(ON)} INHIBITOR WITH SHP2 AND/OR IMMUNE CHECKPOINT BLOCKADE TO OVERCOME ADAPTIVE RESISTANCE AND ENHANCE ANTI-TUMOUR IMMUNITY IN LUNG CANCER

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Background The approval of mutant-specific KRAS\textsuperscript{G12C} inhibitors (G12C) has changed the clinical practice for lung cancer patients harbouring KRAS\textsuperscript{G12C} mutations. However, responses to G12Ci are short-lived as a result of rapid resistance development.\(^1\)\(^2\) Combinations with immune checkpoint blockade (ICB), such as anti-PD-1/CTLA-4, which generate long term responses in non-small cell lung cancer patients (NSCLC) present an opportunity for combination with G12Ci as they could potentially enhance the anti-tumour immune responses induced by KRAS inhibition. Recent evidence suggests that these combinations would only be effective in inflamed tumours underlining the necessity for development of further combinatorial approaches to sensitise even immune exclusive/cold tumours.\(^3\)

Methods In this study we use a novel, covalent tri-complex KRAS\textsuperscript{G12C(ON)} inhibitor, RM-029, which targets KRAS\textsuperscript{G12C} in the active state in combination with the SHP2 inhibitor RMC-4550 (both preclinical tool compounds), and studied their in vivo anti-tumor activity on transplantable KRAS-mutant lung cancer mouse models of varying immunogenicities. Furthermore, immunoblotting, qPCR and multiplex Flow Cytometry were performed to study both the intrinsic effects and the effects on the tumour microenvironment (TME) of these combinations.

Results In vitro, RM-029 exhibited higher potency for inhibition of cell viability than the KRAS\textsuperscript{G12C(OFF)} inhibitor MRTX849 in both human and murine NSCLC cell lines. However, treatment with a KRAS\textsuperscript{G12C(ON)} inhibitor RM-029 still resulted in RAS pathway reactivation. In an inflamed, anti-PD-1 sensitive mouse model of NSCLC, KRAS\textsuperscript{G12C(ON)} and SHP2 inhibitors alone and in combination profoundly remodel the TME to drive durable responses by suppressing tumour relapse and inducing development of immune memory. However, tumour rejections are driven through the combination of G12Ci and anti-PD-1 immunotherapy. In contrast, combined KRAS and SHP2 inhibition is essential for sensitizing an anti-PD-1 resistant, immune exclusive/cold mouse model of NSCLC to ICB and generate tumour rejection. This is accompanied by significant TME reorganization, including depletion of immunosuppressive innate immune cells and recruitment and activation of T and NK cells.

Conclusions Overall, our preclinical results demonstrate the potential of the combination of KRAS\textsuperscript{G12C(ON)} inhibitors with SHP2 inhibitors and/or immune checkpoint blockade not only by targeting KRAS-driven proliferation in tumour cells but by stimulating anti-tumour immunity.

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REFERENCES


Ethics Approval All studies were performed under a UK Home Office-approved project license and in accordance with institutional welfare guidelines.

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