Combination of RAS(ON) Mutant-Selective and Multi-Selective Inhibitors Sensitizes Immune-Refractory, RAS-Driven Preclinical Models to Immunotherapy

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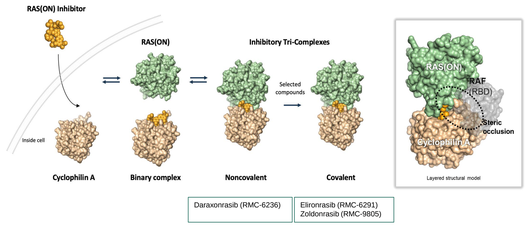
Introduction

- Oncogenic RAS promotes carcinogenesis by sustaining cell proliferation and orchestrating immune escape
- We and others have shown that RAS inhibition combined with immune checkpoint blockade (ICB) prolongs durability of response in immunogenic, RAS-driven preclinical models[1,2]
- Clinical data have shown that most patients treated with KRAS G12C(OFF) inhibitors develop resistance through reactivation of the RAS pathway
- We have previously demonstrated that the RAS(ON) doublet combinate ion of a RAS(ON) G12C-selective inhibitor with a RAS(ON) multi-selective inhibitor can overcome mechanisms of intrinsic and acquired resistance in an immune-refractory preclinical NSCLC model[1]
- Here we evaluated if the RAS(ON) doublet combination of elironrasib (RMC-6291) or zoldonrasib (RMC-9805), a RAS(ON) G12C-selective inhibitor and a RAS(ON) G12D-selective inhibitor, respectively, with the RAS(ON) multi-selective inhibitor daraxonrasib (RMC-6236) can sensitize traditionally hard to treat, immune-refractory preclinical models of RAS mutant NSCLC and PDAC to anti-PD-1

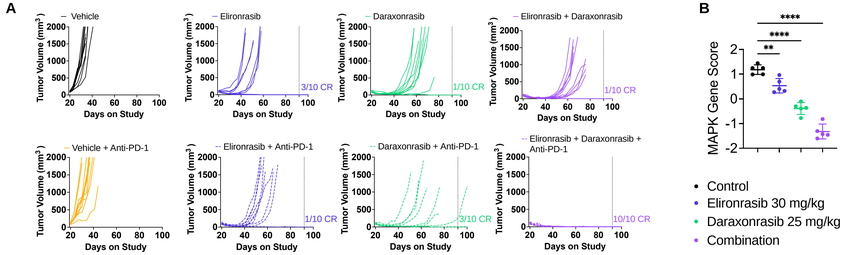
Revolution Medicines' Tri-Complex Inhibitor Platform to Target Oncogenic RAS



Preclinical strategy to test the combination of RAS(ON) doublet + CPI in immuno-refractory tumor models

Key Results

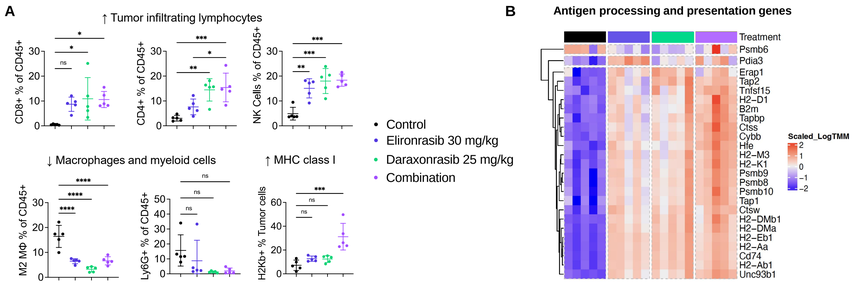
Elironrasib plus daraxonrasib RAS(ON) doublet maximizes RAS pathway suppression and sensitizes an immune refractory NSCLC model to anti-PD-1



- All mice with complete regressions established immunological memory and rejected the tumors upon rechallenge

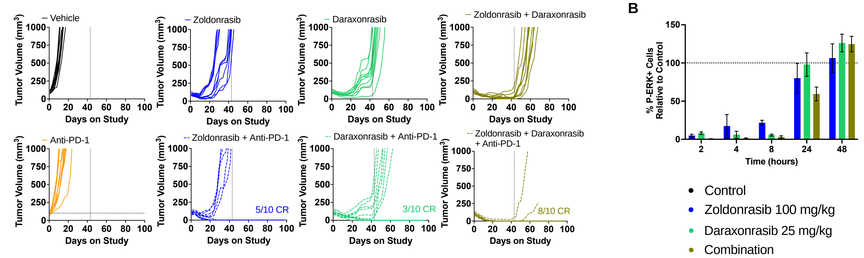
A. 3LL ΔNRAS tumors treated with elironrasib at 30 mg/kg po qd, daraxonrasib at 25 mg/kg po qd and anti-PD-1 at 10 mg/kg ip biw; dotted line indicates treatment stop; days on study represent days post tumor inoculation B. PROGENy score of bulk RNAseq data from 3LL ΔNRAS tumors treated with elironrasib at 30 mg/kg po qd, daraxonrasib at 25 mg/kg po qd or the combination at 24 hours post 7 days of treatment.

Elironrasib and daraxonrasib favorably modulate the tumor microenvironment, and the combination additionally increases antigen presentation in a NSCLC model



A. Flow cytometric analysis and B. Bulk RNAseq analysis of 3LL ΔNRAS tumors treated with elironrasib at 30 mg/kg po qd, daraxonrasib at 25 mg/kg po qd or the combination at 24 hours post 7 days of treatment. N = 5 mice/group. One-way ANOVA (*P<0.05, **P <0.01, ***P <0.001, ****P<0.0001).

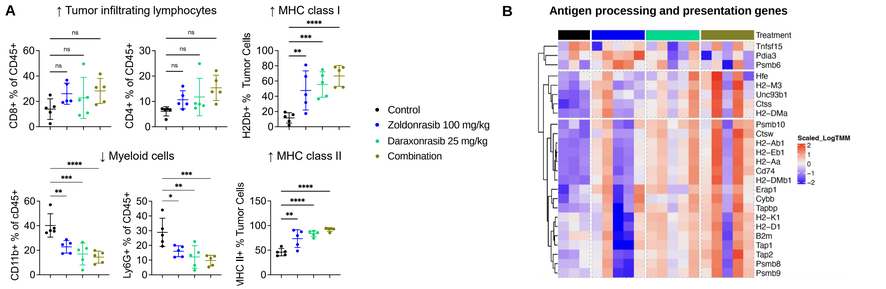
Zoldonrasib plus daraxonrasib RAS(ON) doublet maximizes RAS pathway suppression and sensitizes an immune-refractory GEM-derived PDAC model to anti-PD-1



- Zoldonrasib and Daraxonrasib as single agents achieve combination benefit with anti-PD-1

KPCY 2838c3 tumors treated with zoldonrasib at 100 mg/kg po qd, daraxonrasib at 25 mg/kg po qd and anti-PD-1 at 10 mg/kg ip biw; dotted line indicates treatment stop for the RAS(ON) inhibitors; days on study represent days on treatment. B. IHC quantification of p-ERK N = 3 mice/group of tumors treated with zoldonrasib at 100 mg/kg po qd, daraxonrasib at 25 mg/kg po qd or the combination at indicated time points.

The combination of zoldonrasib and daraxonrasib achieves favorable transformation of the tumor microenvironment and increase in antigen presentation in a PDAC model



A. Flow cytometric analysis and B. Bulk RNAseq analysis of tumors treated with zoldonrasib at 100 mg/kg po qd, daraxonrasib at 25 mg/kg po qd or the combination at 24 hours post 7 days of treatment at 24 hours post 8 days of treatment. N = 5 mice/group. One-way ANOVA (*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001).

Conclusion

- RAS(ON) doublet combination of RAS(ON) mutant-selective and multi-selective inhibitors achieved deeper and more durable pathway suppression and prolonged durability of response in preclinical models of RAS mutant NSCLC and PDAC
- The RAS(ON) doublet reversed the immune-evasion mechanisms governed by oncogenic RAS, decreasing myeloid derived suppressor cells and favoring the infiltration with T cells
- The RAS(ON) doublet upregulated MHC class I expression, increasing the probability of antigen presentation and recognition of the tumor by T cells and sensitized immune-refractory tumors to ICB to induce durable CRs and immunological memory
- Collectively, these preclinical data support the clinical evaluation of the RAS(ON) doublets in combination with ICB in patients with RAS-driven cancers
- Clinical evaluation of RAS(ON) inhibitors with pembrolizumab is ongoing (NCT06162221)

Abbreviations:

ANOVA, analysis of variance; anti-PD-1, anti-programmed cell death protein 1; biw, biweekly; CRs, complete regressions; CPI, checkpoint inhibitor; ENA, European Network of Addiction; GEM, genetically engineered mouse; ICB, immune checkpoint blockade; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma virus oncogene; MHC, major histocompatibility complex; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; PROGENy, pathway respiration and organo-genic influenced network lysing network phenotype; RAS, rat sarcoma virus oncogene; RNAseq, rna sequencing

References:

1. Blaj et al, ENA, [Poster Abstract #PB044] (2022)
2. Anastasiou et al, Nature Communications 15(1):8146 (2024)

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