RAS(ON) G12C-selective and multi-selective doublet combination overcomes clinical resistance mechanisms to KRAS G12C(OFF) inhibitors and sensitizes to immune checkpoint blockade in preclinical models

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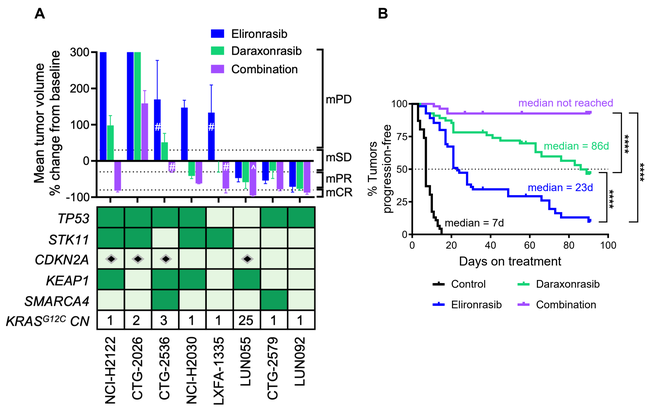
Introduction

Oncogenic RAS promotes carcinogenesis by sustaining cell proliferation and driving evasion of immune surveillance by tumor cells. Clinical data have shown that most patients treated with KRAS G12C(OFF) inhibitors develop resistance through reactivation of the RAS pathway, underlining the need for combination therapeutic approaches that improve durability.

Elironrasib, a mutant-selective covalent inhibitor of the GTP-bound RAS(ON) form of RAS G12C and daraxonrasib, a noncovalent RAS(ON) multi-selective inhibitor of both mutant and wild-type variants of canonical RAS isoforms have shown profound antitumor activity as monotherapies in preclinical models and, more recently, showed promising clinical activity in patients with RAS-driven tumors at exposures that were well tolerated.

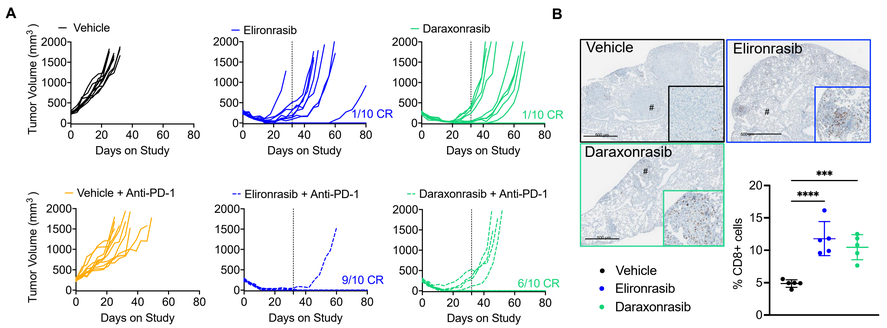
Here we tested the RAS(ON) doublet combination of elironrasib (RMC-6291) with daraxonrasib (RMC-6236) in KRAS G12C NSCLC PDX, CDX and murine preclinical models harboring alterations driving clinically relevant resistance mechanisms to KRAS G12C(OFF) mutant-selective inhibitors and evaluated if it can sensitize an immune-refractory syngeneic NSCLC model to anti-PD-1.

The RAS(ON) inhibitor doublet leads to deep and durable responses in KRAS G12C NSCLC models



A. Tumor response waterfall plot of 8 KRAS G12C NSCLC xenograft models upon daily treatment of elironrasib at 30^, 100 or 200# mg/kg and daraxonrasib at 25 mg/kg as single agents or in combination (n = 3-15 per model). B. Kaplan-Meier analysis of time to tumor doubling on treatment in individual tumor-bearing animals from 8 KRAS G12C NSCLC xenograft models upon daily treatment of vehicle (n = 46), elironrasib at 30, 100 or 200 mg/kg (n = 55), daraxonrasib at 25 mg/kg (n = 55) or doublet combination (n = 54) for up to 90 days.

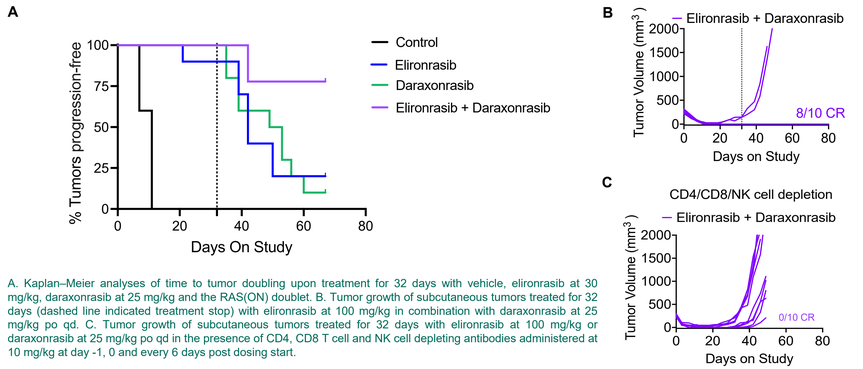
Elironrasib and daraxonrasib increase T cell infiltration and synergize with anti-PD-1 in the immunogenic KPAR1.3 NSCLC model



The KPAR 1.2 model is T cell infiltrated and partially responsive to immunotherapy due to the expression of a derepressed endogenous retroviral antigen

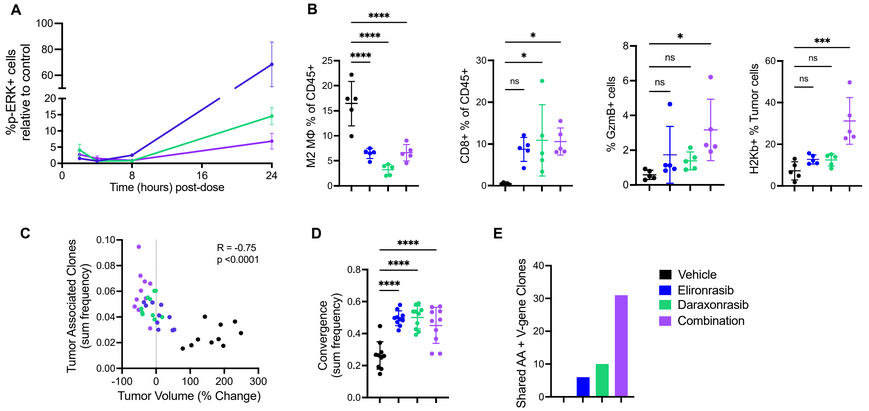
A. KPAR1.3 tumors treated with elironrasib at 100 mg/kg po qd, daraxonrasib at 25 mg/kg po qd and anti-PD-1 at 10 mg/kg ip biw; B. KPAR1.3 tumors treated with elironrasib at 100 mg/kg po qd in combination with daraxonrasib at 25 mg/kg po qd in the presence of CD4, CD8 and NK cell depleting antibodies administered at 20 mg/kg ip at day -1, 0, and every 6 days post dosing start. Dashed lines represent treatment stop; days on study represent days post dosing start. B. Representative lung IHC images and quantification of CD8+ T cells as percentage of all cells within the tumor region in orthotopic lung tumors at 4 hours post 4 days of treatment with elironrasib at 30 mg/kg, daraxonrasib at 25 mg/kg po qd. # represents enlarged areas.

Elironrasib and daraxonrasib synergize and drive immune-dependent complete regressions in the KPAR1.3 tumors



A. Kaplan–Meier analyses of time to tumor doubling upon treatment for 32 days with vehicle, elironrasib at 30 mg/kg, daraxonrasib at 25 mg/kg and the RAS(ON) doublet. B. Tumor growth of subcutaneous tumors treated for 32 days (dashed line indicated treatment stop) with elironrasib at 100 mg/kg in combination with daraxonrasib at 25 mg/kg po qd. C. Tumor growth of subcutaneous tumors treated for 32 days with elironrasib at 100 mg/kg or daraxonrasib at 25 mg/kg po qd in the presence of CD4, CD8 T cell and NK cell depleting antibodies administered at 10 mg/kg at day -1, 0 and every 6 days post dosing start.

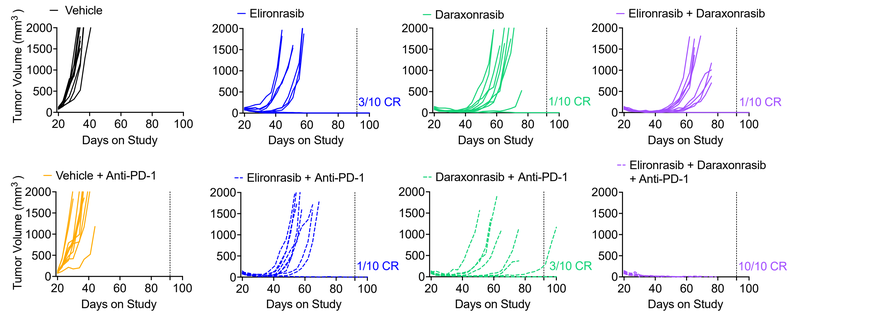
The RAS(ON) doublet maximizes RAS pathway suppression and increases tumor immune recognition in the T cell excluded 3LL-ΔNRAS NSCLC model



In the 3LL-ΔNRAS model mutant NRAS was knocked out in order to increase the dependency on oncogenic KRAS.

A. PD of single dose elironrasib at 30 mg/kg, daraxonrasib at 25 mg/kg and the RAS(ON) doublet in subcutaneous 3LL-ΔNRAS tumors shown as relative change in pERK expression in tumor cells. Tumors were collected at indicated time points. B. Frequency of M2 macrophages (CD11b+, F4/80+, CD206+) and CD8 T cells based on live, CD45+ cells and H2K^b cell surface expression on tumor cells (large CD45-, Periostin-) identified by multiparameter spectral flow cytometry in tumors collected at 24 hours post 8 days of treatment. C-E Immuno-sequencing (TCRB assay) of gDNA extracted from tumors collected at 24 hours post 8 days of treatment C. Correlation of percent change in tumor. D. Sum frequency of convergent clones in the tumors. E. Number of share clones within each treatment group that were found in each treated tumor/group.

The RAS(ON) doublet sensitizes the immuno-refractory 3LL-ΔNRAS model to anti-PD-1



Tumor growth of subcutaneous tumors treated for 72 days (dashed line represents treatment stop) with vehicle, elironrasib at 30 mg/kg or daraxonrasib at 25 mg/kg po qd in combination with mouse IgG2a (isotype control) or anti-PD-1 at 10 mg/kg ip biw

Conclusion

- The RAS(ON) inhibitor doublet induced profound and sustained tumor regression preclinically in KRAS G12C NSCLC models, including in resistant settings, by doubling down on mutant KRAS while concomitantly inhibiting wild-type RAS proteins
- RAS(ON) inhibitors favorably remodeled the tumor microenvironment and drove immune-dependent complete regressions in an immunogenic syngeneic NSCLC model
- The RAS(ON) doublet enhanced tumor immune recognition by boosting antigen presentation, increasing the convergence of the TCR repertoire and sensitizing an immuno-refractory, T cell-excluded NSCLC model to immune checkpoint blockade
- The combination of elironrasib, daraxonrasib and pembrolizumab is undergoing clinical evaluation as a potential chemotherapy-sparing option for patients with previously untreated metastatic KRAS G12C-mutated NSCLC (NCT06162221)

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