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Poster Abstract Form

Title: The Effect of Nutrient Availability and KRAS Mutations on Daraxonrasib Treatment in PDAC Cell Lines

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Introduction

Daraxonrasib is the first FDA approved pan-RAS(ON) inhibitor allowing for treatment of previously untargetable KRAS mutations in PDAC [1]. However, its effects on PDAC metabolism remain poorly understood. Defining metabolic responses to Daraxonrasib may reveal vulnerabilities that could improve efficacy.

Methods

Half-maximal inhibitory concentration (IC_{50}) of Daraxonrasib were determined in PDAC cell lines with different KRAS mutations AsPC1 (G12D), Mia-Paca-2 (G12C) and BxPC3 (Wildtype) using crystal violet cell viability assays in either standard culture media (RPMI) or human plasma-like media (HPLM). Western blotting assessed downstream KRAS signalling (e.g. ERK and mTOR). Untargeted metabolomics was performed in AsPC1 cells following 4 or 24 hours of Daraxonrasib treatment at $\sim IC_{25}$.

Results

IC_{50} in AsPC1 (2.2nM and 0.5nM) and Mia-Paca-2 (0.5nM and 0.3nM) cells (RPMI and HPLM respectively) showed differing sensitivities, whereas BxPC3 cells were insensitive to Daraxonrasib. Western blotting supported IC_{50} , as downstream KRAS-dependent pathways including ERK and mTOR showed decreased activation in the same dose-dependent manner. Untargeted metabolomic data showed significant increases in 30 metabolites (including many amino acids), while 12 metabolites were significantly reduced at 4hr. These metabolic changes were attenuated after 24 hours.

Conclusion

We show that media nutrient availability and KRAS mutation status have an impact on Daraxonrasib effectiveness. Untargeted metabolomic data reveals potential KRAS-mediated metabolic pathways that may be disrupted after 4 hours of Daraxonrasib treatment, highlighting the specificity of the treatment. Attenuation of metabolic changes by 24 hours suggests potential metabolic adaptation or compensatory responses. Identifying these mechanisms may reveal metabolic vulnerabilities that could enhance Daraxonrasib efficacy in PDAC.

References:

1. Wolpin, B.M., et al., *Daraxonrasib in Previously Treated Advanced RAS -Mutated Pancreatic Cancer*. New England Journal of Medicine, 2026. **394**(18): p. 1790-1802.