KRAS alterations combined with TP53 mutations as novel synthetic lethal genomic lesions for PKMYT1 inhibition

Marc L. Hyer1, Jimmy Fourtounis1, David Gallo2, Vivek Bhaskaran1, Rino Stocco1, Rosie Kryczka1, Sai Save1, Helen Burston1, Olivier Nicolas1, Sunantha Sethuraman1, Stephen J. Mann, Anne Roulston1, Jordan T. F. Young2, Michal Zimmermann2, C. Gary Marshall1, Artur Veloso, Elsa Aguado-Fraile1

1Repare Therapeutics, Cambridge, MA, USA; 2Repare Therapeutics, St.-Laurent, QC, Canada

Introduction

- Membrane-associated brinjal and brinjal sarcosid (C48H) inhibitory kinase (PKMYT1) is a cell cycle regulatory kinase that inhibits CDK1/Cyclin B activity, delaying mitotic entry in tumor cells expressing replication stress (RS).
- RS is frequently induced by genetic alterations that drive pre-mitotic transition from G2 to S phase, promoting genomic instability and a synthetic lethal (SL) relationship between these specific alterations and PKMYT1 inhibition. This relationship has been demonstrated preclinically and clinically with CDK1 inhibitor and PKMYT1 activity, in common alterations in ovarian and colorectal cancers, respectively.
- Oncogenic KRAS gain-of-function (GOF) mutations are bona fide drivers of RS. Oncogenic KRAS promotes alterations in the number of active replicators and replication fork progression, which leads to DNA damage and genomic instability. In the current context, mutations to TP53 compromise checkpoint regulation, enabling cells to proceed through the cell cycle prior to DNA damage repair.
- Here we investigate the relationship between KRAS/TP53 alterations and PKMYT1 inhibition, mediated by the Rac-family, p38a and selective PKMYT1 inhibitor lunresertib (RF626), alone or in combination with RS-inducing agents.

Lunresertib mechanism of action

- Lunresertib is a cell cycle regulatory kinase that inhibits CDK1/Cyclin B activity, regulating entry into mitosis and promoting cell cycle arrest at the G2/M checkpoint.
- Lunresertib’s reduced kinase activity results in decreased tumor cell proliferation and cell cycle arrest, which may lead to apoptosis.
- Lunresertib’s mechanism of action is consistent with the known mechanism of action of CDK1 inhibitors, which target the G2/M checkpoint.

Results

KRAS/TP53 mutations sensitize cell lines to PKMYT1 inhibition

- Lunresertib induces premature mitosis and catastrophic DNA damage in KRAS TP53 mutant cells

Sensitivity to PKMYT1 inhibition is observed in different KRAS activating mutation alleles

- Results

Conclusions

- GFP, KRAS/TP53, combined with TP53 alterations, show a strong SL relationship with PKMYT1 inhibition, alone and in combination with RS-inducing antitumor agents.
- The SL phenotype is observed across multiple tumor indications and KRAS/TP53 mutant combinations, suggesting a potential broad scope of clinical utility beyond approved KRAS inhibitors.
- KRAS/TP53 mutations enhance G1/S transition driving replication stress and heightened dependence on PKMYT1 mediated CDK1/Cyclin B inhibition.
- Cell-based and PDX confirm efficacy studies demonstrate robust cell growth inhibition and tumor activity in pancreatic and colorectal settings, with durable tumor regressions and complete responses.
- These data establish scientific rationale to evaluate PKMYT1 inhibition in KRAS/TP53 altered tumors, supporting further exploration in the clinic.

Lunresertib in combination with VSELIR and pemetrexed is currently being evaluated in patients with advanced solid tumors (NCT05065090), including KRAS/TP53 mutant CRC

Poster number: C183

References


Presented at the 2023 AACR-NCI-EORTC (AHE) Conference, October 11–15, Boston, MA.