Preclinical development of PKMYT1 and ATR inhibitor combinations

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Introduction

• PKMYT1 is a negative regulator of the cyclin-dependent kinase CDK1 and a compelling therapeutic target due to its established synthetic lethal relationship with CCNE1 amplification or FBXW7 loss-of-function* (found in ~20% ovarian, ~15% uterine, ~17% stomach, ~14% colorectal cancer)

• ATR activation (through CHK1-mediated inhibition of CDC25)

Lunresertib + camonsertib synergize in CCNE1-amp and FBXW7 LOF models

• Lunresertib (RP-6306) is a clinical stage, potent and selective oral inhibitor of PKMYT1, with single agent activity in CCNE1-amp preclinical models

• As CDK1 activity is also restricted by the activity of the ATR kinase through inhibition of the CDK25 family of phosphatases, we evaluated the potential synergy between lunresertib and camonsertib (RP-3500), a clinical stage inhibitor of ATR

Camonsertib enhances CDK1 activation and premature mitosis in lunresertib-treated cells

• CDK1 activation is monitored by Cyclin B phosphorylation (CyclinBpS126)

• Histogram H3 phosphorylation (H3-pS10) in EdU-incorporating cells marks premature mitotic entry

• Lunresertib-camonsertib shows encouraging synergy and efficacy, including tumor regressions, at sub-efficacious single-agent doses in pre-clinical models harboring PKMYT1-sensitizing alterations

Conclusions

• Lunresertib-camonsertib helps lower CDK1, leading to combination sensitivity

• In OVCAR3 cell line-derived xenografts (CDX) lunresertib+camonsertib achieve tumor growth inhibition on an intermittent schedule at well tolerated doses that have sub-efficacious single-agent activity

• Addition of camonsertib to lunresertib triggers faster and stronger CDK1 activation and premature mitotic entry from S-phase than lunresertib single-agent

PKMYT1i + ATRi drive tumor regressions, reduction of CDK1-pT14, and DNA damage in vivo

• Lunresertib-treated CCNE1-high cells activate ATR-CHK1, which limit CDC25B activity and CDK1 activation

• Addition of camonsertib de-represses CDC25B, allowing further CDK1 dephosphorylation and activation

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• Camonsertib helps lower CDK1, leading to combination sensitivity

• The combination is being evaluated clinically

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*Gallo, Young, Fourtounis et al., 2022, Nature 604(7907):749-756

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