Preclinical development of PKMYT1 and WEE1 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
- Lunresertib (RP-6306) is a clinical stage, potent and selective oral inhibitor of PKMYT1
- Histone H3 phosphorylation (H3-pS10) in EdU-incorporating cells marks premature mitotic entry in S-phase
- CCNE1-amp and FBXW7-LOF are associated with high levels of replication stress and depend on the inhibitory phosphorylation of CDK1 at Thr14 (CDK1-pT14) by PKMYT1 to prevent premature mitosis
- 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 WEE1 kinase through phosphorylation of CDK1 at Tyr15 (CDK1-pY15), we evaluated the potential synergy between lunresertib and a WEE1 inhibitor (WEE1i: Debio-0123).

Lunresertib + WEE1i synergy is observed across PKMYT1i-sensitizing alterations

- The synthetic lethal window for lunresertib between CCNE1-high and parental FT282 cells is enhanced by addition of WEE1i
- Maximal synergy is observed at doses below the monotherapy EC100

CDK1 activation is achieved by deep reduction of both inhibitory phosphorylations

- CDK1 activation is monitored by Cyclin B phosphorylation (CyclinB-pS126)
- Cyclin E phosphorylation (CCNE1-pS126) and premature mitotic entry in S-phase
- Lunresertib + WEE1i induces faster and stronger CDK1 activation and premature mitosis in CCNE1-high cells compared to parental counterparts at doses with minimal single-agent activity in either background

Lunresertib + WEE1i synergize to induce CDK1 activation and premature mitosis in CCNE1-high cells

- Lunresertib + WEE1i drive tumor regressions on an intermittent schedule

Conclusions

- Lunresertib + WEE1i show strong synergy in cell lines harboring PKMYT1i-sensitizing alterations
- Lunresertib + WEE1i enhances lunresertib-induced DNA damage
- Lunresertib + WEE1i show strong synergy in cell lines harboring PKMYT1i-sensitizing alterations
- Lunresertib + WEE1i synergize to induce CDK1 activation and premature mitosis in CCNE1-high cells

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