Retrospective baseline biomarker analyses in a first-in-human Phase 1 trial of the PKMYT1 inhibitor lunresertib (RP-6306) in patients with advanced solid tumors harboring CCNE1 amplification and/or deleterious alterations in FBXW7 or PPP2R1A

Introduction

- Lunresertib (RP-6306) is a novel PARP inhibitor that disrupts the G2A checkpoint leading to premature mitosis and catastrophic DNA damage in cells harboring synthetic lethal genomic alterations.
- The safety and tolerability of lunresertib alone and in combination with cam bendos (RP-3105) is being investigated in the Phase 1 MYTHIC trial in patients with advanced solid tumors with either CCNE1 amplifications or deleterious alterations in FBXW7 or PPP2R1A (NCT04854585).
- Preliminary results from the MYTHIC trial show that lunresertib is safe and well tolerated as a monotherapy or in combination with cam bendos.
- Robust PROOF proof-of-concept for synthetic lethality needs of PARP in cancer medicine.

Here, we present a comprehensive retrospective biomarker analysis aimed at understanding: concordance between detected loci, cancer type-specific patient samples, and unamplified NGS results. The correlation between CCNE1 copy number assessed by NGS and FISH and the relationship between CCNE1 and cyclin E1 protein levels were investigated.

Methods

- MYTHIC study: Summary of enrollment and data availability

- Patient selection based on CCNE1 amplification enriches for tumors with high cyclin E1 levels.

Results

- CCNE1 amplification is highly concordant between FISH and tissue NGS.

- Patient selection based on CCNE1 amplification enriches for tumors with high cyclin E1 levels.

Conclusions

- Pre-approved local NGS tests were a reliable method to identify biomarker-defined patients for MYTHIC Phase 1 trial.
- FISH and NGS are both appropriate methods to evaluate CCNE1 copy number. Cyclin E1 protein overexpression has been shown to be enriched in CCNE1 amplified tumors.
- Plasma ctDNA detected 85% of FBXW7 and PPP2R1A enrichment alterations and is not confounded by CHIP.
- CCNE1 amplification had a high falsenegative detection rate in ctDNA, therefore, tissue testing is preferable.
- The retrospective analysis of lunresertib baseline biomarkers (CCNE1, FBXW7, and PPP2R1A) provides an understanding of framework for interpretation of clinical data from MYTHIC trial and informs future patient selection strategies.

Abbreviations

- ANC: absolute neutrophil count
- CA-125: cancer antigen-125
- CDK: cyclin-dependent kinase
- CHIP: clonal hematopoiesis of indeterminate potential
- Chr: chromosome
- CN: copy number
- ctDNA: cell-free DNA
- EA: European American
- EB: East Asian
- EAM: educational achievement
- FDR: false discovery rate
- FISH: fluorescence in situ hybridization
- FO: female on
- HPV: human papillomavirus
- IHC: immunohistochemistry
- RB: retinoblastoma
- ROC: receiver operating characteristics
- SC: sex chromosome
- TP53: tumor protein p53
- WHO: World Health Organization