Characterization of CCNE1 amplifications and associated genomic features in ovarian and uterine cancers

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Clinical relevance of CCNE1

Cyclin E1 protein encoded by the CCNE1 gene is a core component of cell cycle in normal cells. In conjunction with Cyclin Dependent Kinase 2 (CDK2), it promotes G1-S transition through phosphorylation of specific substrates. Cyclin E plays an important role in cell cycle progression and DNA replication. Oncogenic activation of the Cyclin E/CDK2 complex mediated by CCNE1 amplification causes replication stress and DNA damage leading to genomic instability and contributing to carcinogenesis[1]. Cyclin E is not a canerogeneically actionable target, therefore therapeutic approaches to selectively target CCNE1 amplified tumors are being pursued by inhibiting its cell cycle interaction partners CDK2, WEHI, and PKMYT1[2]. Clinical success of these therapeutic strategies would benefit from a thorough understanding of how DNA damage and replication stress caused by CCNE1 amplification alters the genomic landscape of tumors.

RP-6306 is a first-in-class, highly potent and selective PKMYT1 inhibitor currently being investigated in clinical trials as a single agent (NCT04477562) and in combination with other agents including gemcitabine (NCT05147272), lonetocin (NCT05147350), or camozemib (NCT04456886), in patients with solid tumors harboring CCNE1 amplification[3]. In pre-clinical models, correlation between CCNE1 copy number, cyclin E1 expression and sensitivity to PKMYT1 inhibition is imperfect. Thus, a deep understanding of genomic changes associated with CCNE1 amplification is critical for strengthening our understanding of the mechanism of action. These learnings will be applied to clinical trials evaluating RP-6306.

In this study, we used whole exome sequencing (WES) data from TCGA and whole genome sequencing (WGS) data from the PCAWG consortium to describe the genomic landscape of CCNE1-amplified ovarian and uterine tumors (endometrial carcinoma and uterine carcinomas). Our analysis included 361 ovarian and 580 uterine cancer exomes, and 113 ovarian and 51 uterine cancer genomes. Copy Number (CN) calls were made by ASCAT[4], dominantly by non-clustered 100Kb-1Mb deletions (median=20, p=0.002). Back inversion calls were made by the Hartwig pipeline, and all CN calls included 361 ovarian and 580 uterine cancer exomes, and 113 ovarian and 51 uterine cancer genomes. Whole genome duplication (WGD) is a common genetic abnormality that occurs in about 30% of cancers and is associated with genome instability. WGD was detected significantly more frequently in ovarian and uterine tumors with CCNE1 amplification as compared to non-amplified tumors (ovarian: 90.9% vs 48.3%, p = 6.4e-10; uterine: 78.7% vs 21.9%, p = 7.7e-15).

Co-mutation landscape of CCNE1 amplifications

A review of the co-mutation landscape using WES revealed that TP53 mutations frequently co-occurred with CCNE1 amplifications in both ovarian and uterine tumors (ovarian: 98.9% vs 97.6%, OR = 3.24, p<0.01; uterine: 89.6% vs 36.0%, OR = 15.2, p = 2.14e-13) and BRCA1 alterations are mutually exclusive with CCNE1 amplifications (16% vs 7.9%, OR = 2.02, p = 3.1e-3). In addition, mutations in ARID1A (0% vs 45.9%, OR = 0, p = 1.3e-10) and PTEN (4.2% vs 60.1%, OR = 0.03, p = 2.7e-15) were mutually exclusive with CCNE1 amplifications in uterine tumors.

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WGD in tumors with CCNE1 amplification

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Evidence for BFB cycle in CCNE1 amplification

Breakage fusion bridge (BFB) cycle is a mechanism of chromosomal instability that leads to the occurrence of BFB cycle that leads to the occurrence of chromosomal arrangements and eventual amplification of genes in those arrangements[5]. Certain genomic characteristics such as fold-back inversions (FBI) and segment copy number patterns suggest the occurrence of BFB cycle.

In pre-clinical models, correlation between CCNE1 copy number, cyclin E1 expression and sensitivity to PKMYT1 inhibition is imperfect. Thus, a deep understanding of genomic changes associated with CCNE1 amplification is critical for strengthening our understanding of the mechanism of action. These learnings will be applied to clinical trials evaluating RP-6306.

Conclusions

CCNE1 amplification leads to genome instability in ovarian and uterine cancer patients. TP53 frequently co-occurs with CCNE1 amplification in ovarian and uterine cancers. BRCA1 alterations are mutually exclusive with CCNE1 amplification in ovarian cancer. PTEN and ARID1A mutations are mutually exclusive with CCNE1 amplifications in uterine cancer. WGD, FBIs, and specific SV signatures such as large tandem duplications, deletions and translocations are enriched in the tumors with CCNE1 amplification.

There is evidence for breakage fusion bridge being the mechanism of CCNE1 amplification in about 38% of patients.

References