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Abstract CT262: Efficacy and safety of the combination PKMYT1-inhibitor lunresertib and ATR-inhibitor camonsertib in patients with ovarian and endometrial cancers: Phase I MYTHIC study (NCT04855656) FREE

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Abstract

Background:

Lunresertib (lunre), a first-in-class PKMYT1 inhibitor, in combination with the ATR inhibitor, camonsertib (cam), is synthetic lethal with *CCNE1* amplification, and/or deleterious *FBXW7* or *PPP2R1A* mutations (mut). Here we report updated safety in all patients (pts) treated at an individualized RP2D schedule and efficacy in pts with ovarian (OC) and endometrial cancer (EC) treated at RP2D.

Methods:

Safety of lunre + cam was analyzed in pts from MYTHIC treated at the RP2D of 80mg BID lunre + 80mg QD cam given 3d on/4d off after individualized schedule optimization, determined by baseline hemoglobin levels (weekly or 2w on/1w off). Efficacy evaluable pts with OC or EC were treated at RP2D and had measurable disease and ≥1 post-baseline scan. Endpoints were response rate (RECISTv1.1 unconfirmed+confirmed), clinical benefit rate (CBR; response per RECISTv1.1 or treatment for ≥16w w/o PD), progression-free survival (PFS), and molecular response rate (MRR; ≥50% decline in circulating tumor DNA). Target and pathway engagement were evaluated by IHC in paired tumor biopsies.

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Results:

As of November 2024, 67 pts received combination lunre + cam at the RP2D after schedule optimization. The most frequent Gr3 TRAE was anemia (26.9%); the only other Gr3+ TRAE occurring in >10% of pts was neutropenia (11.9%). No treatment-related deaths were reported. For pts with platinum-resistant or -ineligible OC (n=24; 100% p53 mut; 71% high-grade serous OC; 54% with ≥3 prior lines of therapy), the response rate was 38%. Tumor shrinkage occurred in 75% of pts. Median time to response [mTTR] was 7w (range: 5-18w) with 44% (4/9) occurring at or after the 2nd assessment. Overall, CBR was 79% with a median (mPFS) of 21w (95%CI: 17-27w). Pts with EC (n=27; 85% p53 mut; none MSI high; 19% carcinosarcoma, 48% serous; 78% with prior ICI; 59% with ≥3 prior lines of therapy), the response rate was 26%. Overall, 70% had reductions in tumor burden. The mTTR was 6w (range: 5-21w) with 29% (2/7) occurring at or after the 2nd assessment, while one pt achieved a CR 12w after initial PR. CBR was 48%, with mPFS of 17w (95%CI: 11-27w). Paired tumor analysis confirmed target engagement (-50% CDK1-Thr14 relative change) in 75% pts (9/12) and DNA damage induction (≥100% γ-H2AX increase) in 43% (6/14). MRR was 57.6% (19/33) across all patients.

Conclusions:

Lunre + cam is a tolerable and effective oral combination therapy of two novel targeted agents in molecularly-selected OC and EC with poor prognostic features and no approved targeted therapies. Enrollment closed in Dec 2024, the presentation will provide updated data for potential late-stage clinical development.

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