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Abstract CT127: Pre-operative abemaciclib in localized cisplatin-ineligible MIBC with tissue and ctDNA molecular response validation (CLONEVO) FREE

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Abstract

Background:

Up to 40% of patients with muscle-invasive bladder cancer (MIBC) are ineligible to receive standard-of-care neoadjuvant cisplatin-based chemotherapy, creating a significant unmet need for effective neoadjuvant therapies. Based on our prior findings of the high prevalence of somatic cell cycle alterations in MIBC, we conducted the first window-of-opportunity investigator-initiated trial of the CDK4/6 inhibitor abemaciclib (abema) followed by radical cystectomy (RC) in MIBC (CLONEVO, NCT03837821).

Methods:

Eligibility included MIBC appropriate for RC and cisplatin-ineligibility or refusal. Planned treatment was abema (200mg BID PO) for 4-8 weeks prior to RC. We planned to enroll 20 patients (accounting for 20% attrition). With 16 evaluable patients, this provided 80% power to detect an effect size of 0.75 (α=0.05 and r=0.5 between pairs). Planned Whole-exome (WES) and RNA sequencing of pre- and post-abema tissues and serial evaluation of ctDNA WES were performed using Caris Life Sciences assays.

Results:

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20 patients were enrolled and received abema for a median of 36 days. Median age was 73, 16/20 (80%) were males, and 5/20 (25%) had cT4 stage. 3 patients didn't undergo RC, and 1 withdrew consent. Abema resulted in pathologic complete response in 18.8% (3/16) and

pathologic downstaging in 31.3% (5/16) of 16 evaluable patients. No unexpected safety signals were detected. Grade 3 abema-related adverse events included anemia (4/20), diarrhea (1/20), abdominal pain (1/20), neutropenia (1/20), and leukopenia (1/20). Variant allele frequency of somatic mutations significantly decreased after abema by 20.5% (p =0.04), confirming its efficacy in reducing tumor burden. Serial ctDNA showed a significant reduction in tumor fraction (TF) following abema by 11.7% (p =0.03). Post-TURBT ctDNA TF increased prior to initiating abema but rapidly decreased within 2 weeks of starting abema (19.3%), confirming that responses were driven by abema, not TURBT. Patients with *CCND1* amplification had the most significant decrease in ctDNA TF (45% vs. 1.1% p=0.001). The higher response in *CCND1*-amplified tumors aligns with its role as a driver of CDK4/6-dependent cell cycle progression, identifying a potential response biomarker. Abema significantly downregulated the expression of MKI67, CCNA2, and PCNA proliferation markers with log-fold changes of -1.2, -0.7, and -0.6 (p=0.001). Gene set enrichment analysis of matched pre- and post-abema samples showed significant downregulation of E2F targets and G1/S transition pathways. Patients who achieved pathologic downstaging had a significant decrease in E2F target scores (-1.6 vs. -0.4, p=0.01). These data confirm that abema suppressed E2F-dependent cancer cell proliferation, validating on-target drug activity. Interestingly, abema significantly inhibited the homologous recombination pathway of double-strand DNA breaks (DSB) repair (FDR=0.001), particularly TOPBP1 and RAD51.

Conclusion:

This first trial of short-term pre-operative abema in MIBC demonstrated favorable efficacy and tolerability while modulating cell cycle-dependent pathways, including DSB repair. Our findings support future trials investigating sequential therapy combining abema with antibody-drug conjugates such as enfortumab vedotin, where abema's effects on DSB repair enhance treatment responses.

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