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Blood and Urine Liquid Biopsy for Molecular Monitoring in Muscle-Invasive Bladder Cancer Under Bladder-Preserving Therapy

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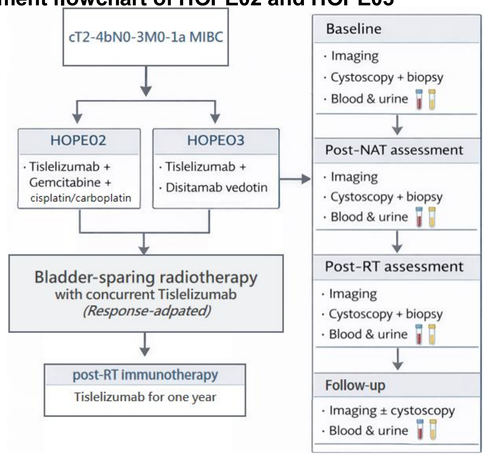
INTRODUCTION

While trimodal therapy is the current standard for organ preservation in muscle-invasive bladder cancer (MIBC), its clinical efficacy remains limited, and there is a critical need for noninvasive biomarkers to support real-time treatment decisions. This study explores a novel bladder-sparing approach combining immunotherapy-based neoadjuvant treatment with radiotherapy in patients with locally advanced MIBC. To enable dynamic monitoring of treatment response, a next-generation sequencing (NGS)-based liquid biopsy assay was utilized to assess molecular changes in both urine and blood.

METHODS

In this exploratory analysis, 29 patients were enrolled from two Phase II clinical trials (HOPE02: ChiCTR2100045213; HOPE03: ChiECRCT20210564). Patients received neoadjuvant tislelizumab combined with gemcitabine plus cisplatin/carboplatin (HOPE02) or disitamab vedotin (HOPE03), followed by bladder-sparing radiotherapy based on treatment response. Tumor response was assessed through radiographic imaging and cystoscopy with biopsy. Concurrently, longitudinal liquid biopsy analyses were conducted to evaluate circulating tumor DNA (ctDNA) and urinary tumor DNA (utDNA). Urine and blood samples were collected at multiple time points. The PredicineCARE targeted NGS assay was employed to detect somatic alterations and quantify tumor fractions in both ctDNA and utDNA.

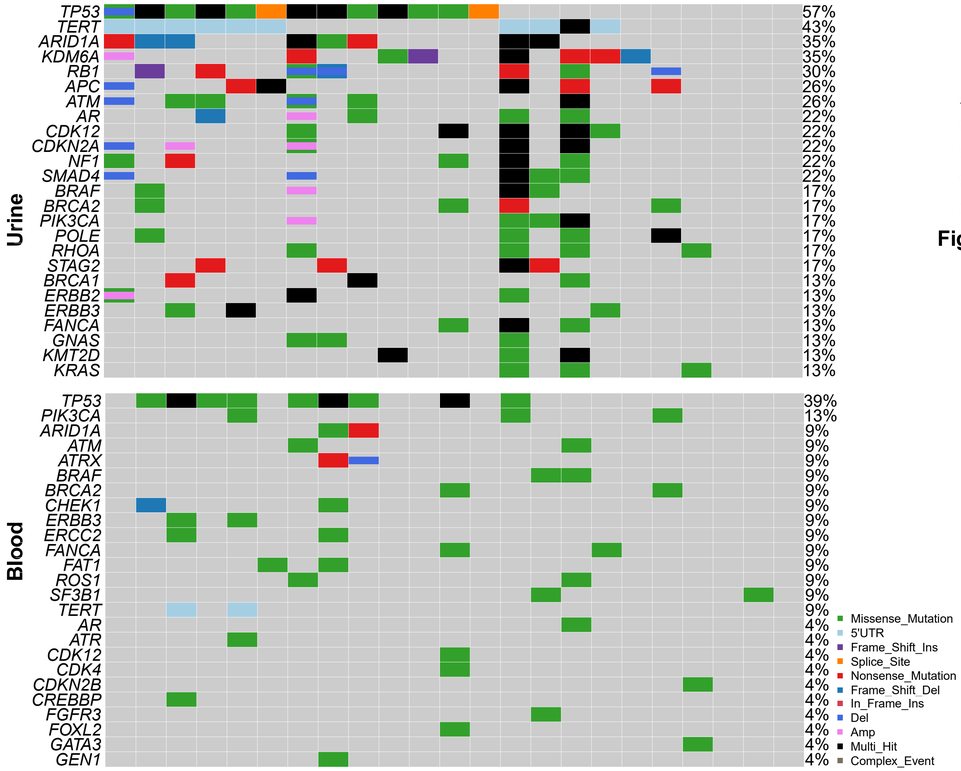
Fig 1. Treatment flowchart of HOPE02 and HOPE03



RESULTS

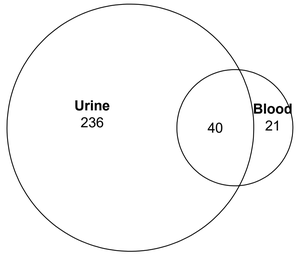
A total of 29 patients had eligible blood samples and 28 had eligible urine samples for molecular analysis, among whom 23 had paired blood and urine samples available from baseline. The most frequently mutated genes in urine were TP53 (57%), TERT (43%), ARID1A (35%), KDM6A (35%), and RB1 (30%). In blood, the most prevalent mutations were observed in TP53 (39%), PIK3CA (13%), ARID1A (9%), ATM (9%), and BRCA2 (9%).

Fig 2. Molecular profiling of baseline urine & blood samples



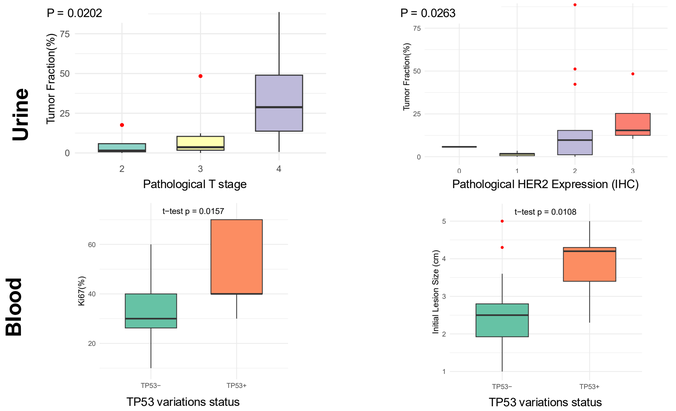
Urine samples yielded a higher number of somatic mutations compared to blood. At baseline, 276 mutations were detected in urine and 61 in blood, with 40 overlapping mutations identified across both sample types.

Fig 3. Baseline mutation counts and overlap between blood and urine samples



At baseline, tumor fraction levels derived from the NGS assay in urine were significantly associated with pathological T stage (p = 0.0202) and HER2 expression levels determined by immunohistochemistry (p = 0.0263). In blood samples, TP53 mutations were significantly correlated with higher Ki67 expression (p = 0.0157) and larger baseline tumor size (p = 0.0108).

Fig 4. Correlations between baseline profiles and clinical characteristics



CONCLUSIONS

Our study demonstrates the feasibility of a bladder-preserving strategy involving neoadjuvant immunotherapy combinations and radiotherapy in MIBC patients. NGS-based liquid biopsy using both urine and blood samples enabled dynamic monitoring of treatment response and showed strong correlations with clinical risk factors, underscoring its potential as a noninvasive tool to guide personalized therapy.