Abstract #: 552

Longitudinal personalized urinary tumor DNA analysis in muscle invasive bladder cancer from the neoadjuvant immunotherapy trial RJBLC-I2N003.

Ruiyun Zhang[1], Jingyu Zang[1], Feng Xie[2], Yue Zhang[2], Akezhouli Shahatiaili[1], Yiqiu Wang[1], Pan Du[2], Shidong Jia[2], Guanglei Zhuang[1], Yiran Huang[1], Haige Chen[1]
[1]Department of Urology, Ren Ji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China and [2]Huidu Shanghai Medical Sciences Ltd, Shanghai, China

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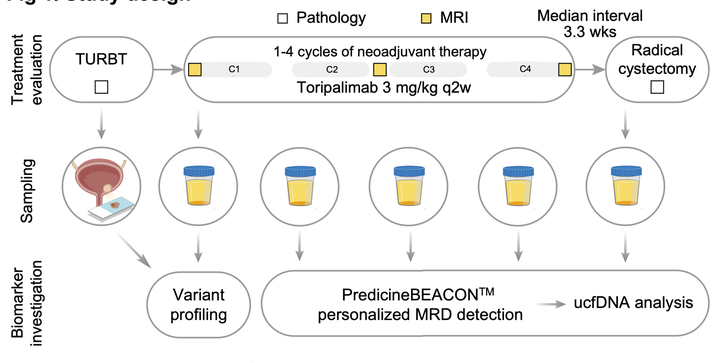
INTRODUCTION

RJBLC-I2N003 is an investigator-initiated study to evaluate the clinical activity and predictive biomarkers for neoadjuvant immunotherapy with toripalimab (anti-PD-1) in muscle invasive bladder cancer (MIBC). Here we present the evaluation of the PredicineBEACON™ personalized MRD assay to monitor response to therapy in this trial. Twenty patients were enrolled in this study. Sixteen patients (80%) completed all 4 cycles of neoadjuvant treatment. Grade 3-4 immune-related adverse events occurred in two patients (10%). Eight patients (40%) achieved a pathological complete response (pCR). Thirteen patients (65%) had no remaining invasive disease (pCR or pTisN0/pTaN0). On-treatment urinary tumor DNA (utDNA) clearance was associated with objective responses. Preliminary concordance was observed between molecular and pathological MRD status.

METHODS

Twenty patients with pathologically confirmed MIBC were enrolled and received toripalimab (3 mg/kg Q2W, 4 cycles) before radical cystectomy. The safety and efficacy of neoadjuvant toripalimab were assessed. Serial urinary cell-free DNA (ucfDNA) and blood cell-free DNA (bcfDNA) were obtained at baseline and after each cycle of toripalimab treatment. The PredicineBEACON™ personalized MRD assay was used for therapy monitoring, which includes whole exome sequencing of baseline urine and/or tissue samples collected before neoadjuvant therapy, followed by ultra-deep sequencing of urine samples to track 50 personalized mutations and 500 actionable/hotspot variants, in combination with low-pass whole genome sequencing (LP-WGS) to assess copy number burden (CNB).

Fig 1. Study design



RESULTS

Clinical response of MIBC patients undergoing neoadjuvant immunotherapy with toripalimab (anti-PD-1).

- Three patients (15%) achieved complete response (CR), and eleven patients (55%) achieved partial response (PR). The overall response rate (ORR, CR or PR) was 70% (Fig 2 and Fig 3).
- Grade 3-4 immune-related adverse events occurred in two patients (10%) (Fig 2).
- Eight patients (40%) achieved a pathological complete response (pCR) (Fig 3).

Fig 2. Treatment and imaging evaluation of patients.

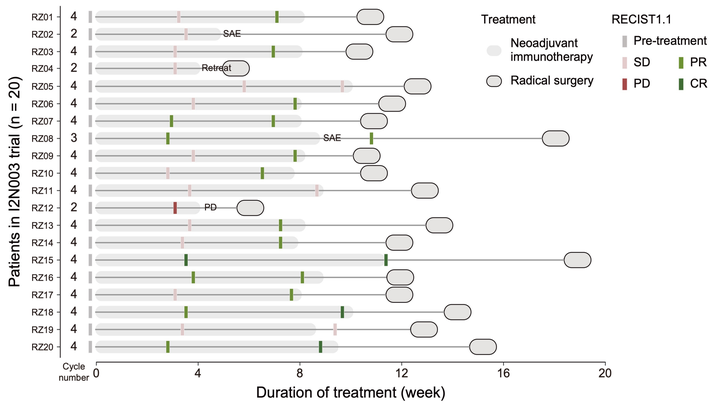
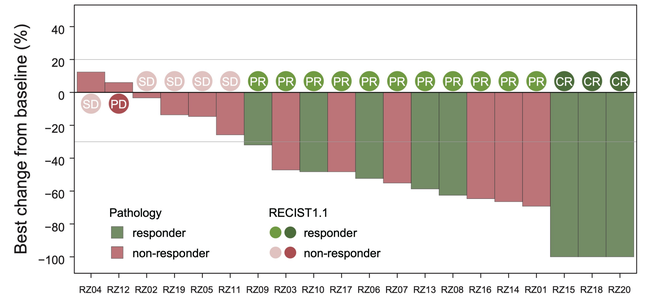


Fig 3. Best percentage change in tumor size from baseline. Green and red color in circles indicate responder and non-responder assessed by the RECIST 1.1. Green and red color in rectangles indicate responder and non-responder assessed by the pathology.



20 patients with MIBC in the I2N003 trial

PredicineBEACON™ - personalized MRD assay for therapy monitoring.

Pre- and post-neoadjuvant immunotherapy urine samples were collected from eighteen patients and tested with the PredicineBEACON™, the personalized MRD assay. MRD positive was called when two or more mutations were detected or copy number burden (CNB) above defined threshold.

Fig 4. PredicineBEACON™ MRD-based urinary tumor DNA (utDNA) clearance was associated with objective responses. Cancer cell fraction (CCF) inferred from personalized mutation tracking was significantly lower in the responder group (*P < 0.036*) after neoadjuvant immunotherapy, and a similar trend was observed for CNB (*P < 0.060*).

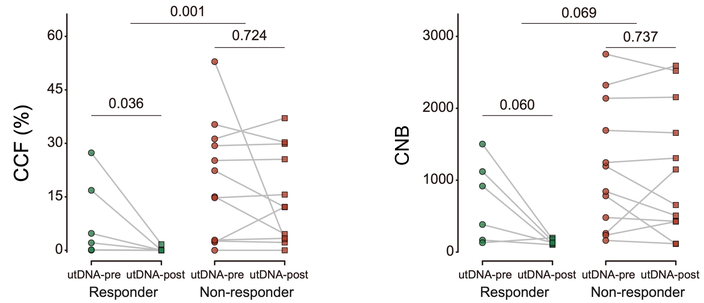


Fig 5. MRD status post-neoadjuvant immunotherapy correlates with clinical response. Fifteen MRD+ (83.3%) and three MRD- (16.7%) were detected from the urine samples collected from post-neoadjuvant immunotherapy. Under RECIST1.1 criteria, 2/2 (100%) patients in CR group were detected as MRD-, 9/10 (90%) patients in PR group were detected as MRD+, and all (100%) patients in SD and PD were detected as MRD+. Under pathology assessment criteria, 3/6 (50%) patients in CR group were detected as MRD-, and all (100%) patients in non-CR group were detected as MRD+.

	RZ20	RZ18	RZ15	RZ08	RZ13	RZ06	RZ10	RZ09	RZ01	RZ14	RZ16	RZ07	RZ17	RZ03	RZ11	RZ05	RZ19	RZ02	RZ12	RZ04
RECIST1.1	CR	CR	CR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	SD	SD	SD	SD	PD	SD
Pathology	CR	CR	CR	CR	CR	CR	CR	CR	non-CR	non-CR	non-CR	non-CR	non-CR	non-CR	non-CR	non-CR	non-CR	non-CR	non-CR	non-CR
MRD	-	NA	-	+	+	NA	-	+	+	+	+	+	+	+	+	+	+	+	+	+

NA: sample not available.

CONCLUSIONS

These findings suggest that neoadjuvant administration of PD-1 blockade followed by surgical resection represents a feasible and efficacious approach to treat MIBC. PredicineBEACON™-based urine MRD biomarker assessment identified MRD-positive patients that achieved pCR, demonstrating the potential clinical utility of longitudinal personalized utDNA analysis to complement existing trial endpoints. This study suggests that urine-based MRD test could be used to identify MRD-negative MIBC patients after neoadjuvant therapy who could potentially avoid radical cystectomy.