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Exploratory analysis of molecular subtypes and association with treatment outcomes in patients (pts) with muscle-invasive bladder cancer (MIBC) from NIAGARA

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Background

MIBC is molecularly heterogeneous with known genomic drivers and transcriptome-defined subtypes that influence prognosis and therapy response. In NIAGARA (NCT03732677), perioperative durvalumab (D) + neoadjuvant chemotherapy (NAC) significantly improved event-free survival (EFS) and overall survival vs NAC alone in MIBC. Here, we report exploratory analyses of MIBC molecular drivers and subtypes in relation to treatment benefit.

Methods

1063 cisplatin-eligible pts with MIBC (cT2–T4aN0/1M0) planned for radical cystectomy (RC) were randomised 1:1 to receive perioperative D + gemcitabine-cisplatin NAC + RC or NAC + RC alone. EFS was a primary endpoint. Dual DNA/RNA was extracted from baseline tumours for WES (n=407) and RNA-seq (n=402), analysis by *Natera, Inc.* Exploratory, non-alpha-controlled analysis of molecular drivers and outcomes was conducted.

Results

Baseline WES and RNA-seq captured the landscape of key mutational drivers and transcriptome-based subtypes, characteristic of MIBC. D + NAC consistently improved EFS across mutation-defined subgroups, with increased magnitude of benefit vs intent-to-treat population (ITT) observed in pts whose tumours carried mutations in *TP53* or *FGFR3* (largely mutually exclusive), cell cycle or RTK/RAS/PI3K pathways (80% of pts) or that were tumour-mutational burden (TMB) high (Table). Excepting luminal papillary, D + NAC appeared to improve EFS across transcriptional subtypes (83% of pts) (Table). Pts with basal-squamous subtype, characterised by enriched *TP53* mutation (60% vs ≤50% for others), high immune infiltration gene signature and higher prevalence of variant histology (26% vs ≤15% for others) exhibited the greatest apparent benefit with D.

Conclusions

Exploratory integrated baseline genomics and transcriptomics from NIAGARA suggest a broad benefit for perioperative D + NAC in MIBC, with consistent EFS improvement across a diverse molecular landscape.Table: 4741R0

	Pts, % D + NAC EFS 24 mo*, % NAC EFS 24 mo*, % D + NAC vs NAC EFS HR*, 95% CI		
ITT, N=1063	-	68	60
Mutated genes/pathways (n=407)			0.68, 0.56–0.82

	Pts, % D + NAC EFS 24 mo*, % NAC EFS 24 mo*, % D + NAC vs NAC EFS HR*, 95% CI			
<i>TP53</i> , n=204	50	77	64	0.51, 0.32–0.81
<i>FGFR3</i> , n=44	11	90	66	0.24, 0.07–0.87
Cell cycle pathway (<i>TP53/RB1/CDKN2A/B</i>), n=254	62	76	67	0.58, 0.38–0.88
RTK/RAS/PI3K pathway, n=168	41	80	73	0.49, 0.28–0.85
TMB high, n=161	40	84	62	0.44, 0.25–0.76
Transcriptome-based subtypes [#] (n=402)				
Basal-squamous, n=91	23	83	68	0.47, 0.20–1.11
Luminal, n=139	34	79	66	0.52, 0.28–0.94
Luminal-papillary, n=68	17	70	78	1.35, 0.64–2.87
Luminal-infiltrated, n=77	19	63	67	0.67, 0.35–1.31
Neuronal, n=27	7	78	44	Not calculated

*Kaplan-Meier analysis. [#]The Cancer Genome Atlas classification.

Clinical trial identification

NCT03732677.

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Disclosure

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