Neoadjuvant Therapy with Durvalumab + Tremelimumab in Patients with High-Risk, Cisplatin-Ineligible Muscle-Invasive Urothelial Carcinoma

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Disclosures

- Jianjun Gao has served as a consultant/advisor for
  - ARMO Biosciences
  - AstraZeneca
  - CRISPR Therapeutics
  - Jounce
  - Nektar
  - Polaris
  - Pfizer
  - Symphogen

Background

- **For muscle invasive bladder cancer, Neoadjuant chemotherapy increases survival.**
- **Neoadjuant chemotherapy with Gem/Cis and MVAC has pCR rate 20-40%.**
- **However, about 50% patients are ineligible for cisplatin-based neoadjuant chemotherapy due to: 1) renal failure; 2) neuropathy; 3) hearing loss; 4) heart failure.**

Background

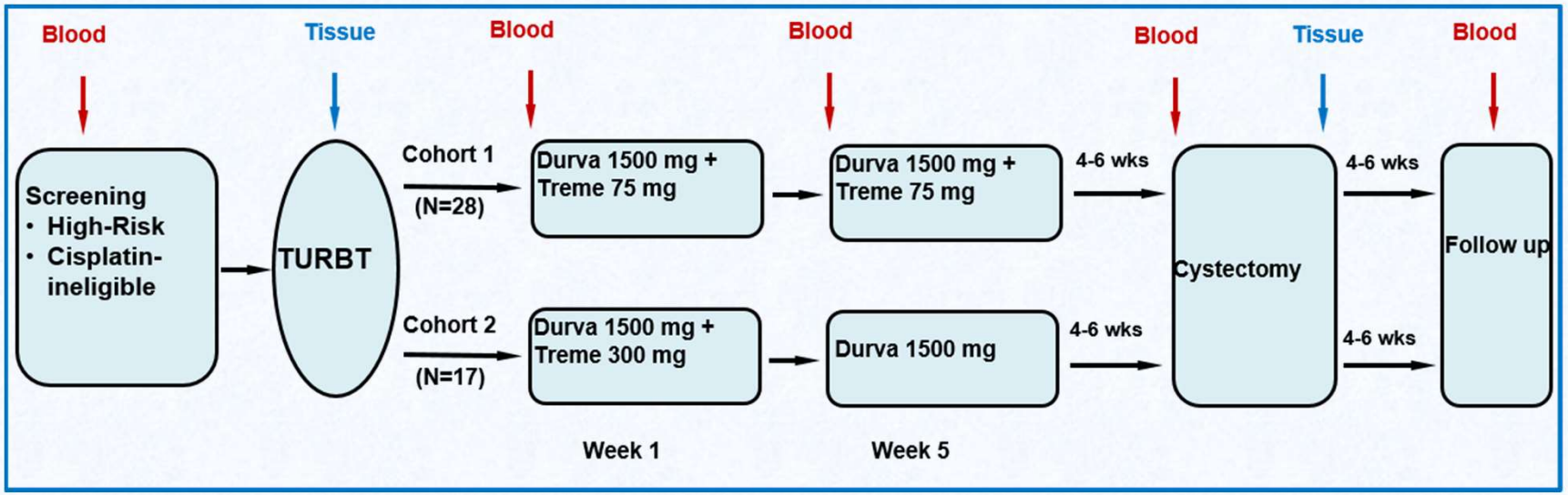
- **Bladder cancer:**
  - **Anti-CTLA-4**
    - **Ipilimumab: RR-25% (3/12)**
  - **Anti-PD-L1:**
    - **Atezolizumab: RR-15% (2nd line); RR-23.5% (1st line)**
    - **Durvalumab: RR-17% (2nd line)**
    - **Avelumab: RR-16.1% (2nd line)**
  - **Anti-PD1:**
    - **Nivolumab: RR-19.6% (2nd line)**
    - **Pembrolizumab: RR-21.1% (2nd line); RR-29% (1st line)**

Hypothesis

- **Anti-CTLA-4 plus anti-PD-L1 will have an acceptable safety profile as neoadjuvant therapy for patients with localized bladder cancer ineligible for cisplatin-based chemotherapy.**

- **Lead to measurable immunologic changes, with identification of novel biomarkers that can be used for immune monitoring and clinical correlation in the setting of metastatic disease.**

Durvalumab/Tremelimumab Trial Schema (NCT02812420)



- **Total accrual: 28 patients on cohort 1(Median follow up: 19.2 mos)**
- **Primary endpoint: Safety**
- **Secondary endpoints: Biomarker; pathologic T0 rate; RFS, OS**

Patient Baseline Characteristics

Characteristics	(N=28)
Age	
Median	71
Range	24-83
sex - no. (%)	
Male	20 (71%)
Female	8 (29%)
Histology	
UC with squamous cell carcinoma component	2 (7%)
UC with Micropapillary component	2 (7%)
UC with small cell component	1 (4%)
UC with spindle sarcomatoid features	1 (4%)
Pure UC	22 (78%)
Clinical Stage at Baseline (%)	
T1[a]	1 (4%)
T2	12 (43%)
T3	12 (43%)
T4	3 (11%)
High risk features (%)[b]	
Exam under anesthesia showing 3-D mass	12 (43%)
Hydronephrosis	6 (21%)
Lymphovascular invasion	4 (14%)
Variant histology	6 (21%)
T4a	3 (11%)
High grade upper tract UC	2 (7%)
Reasons for cisplatin ineligibility (%) [c]	
CrCl per Cockcroft Gault <60 mL/min	18 (64%)
Cardiac dysfunction	4 (14%)
Neuropathy	2 (7%)
Hearing impairment	5 (17%)
Patients declining chemotherapy	3 (10%)

Treatment Related Adverse Events

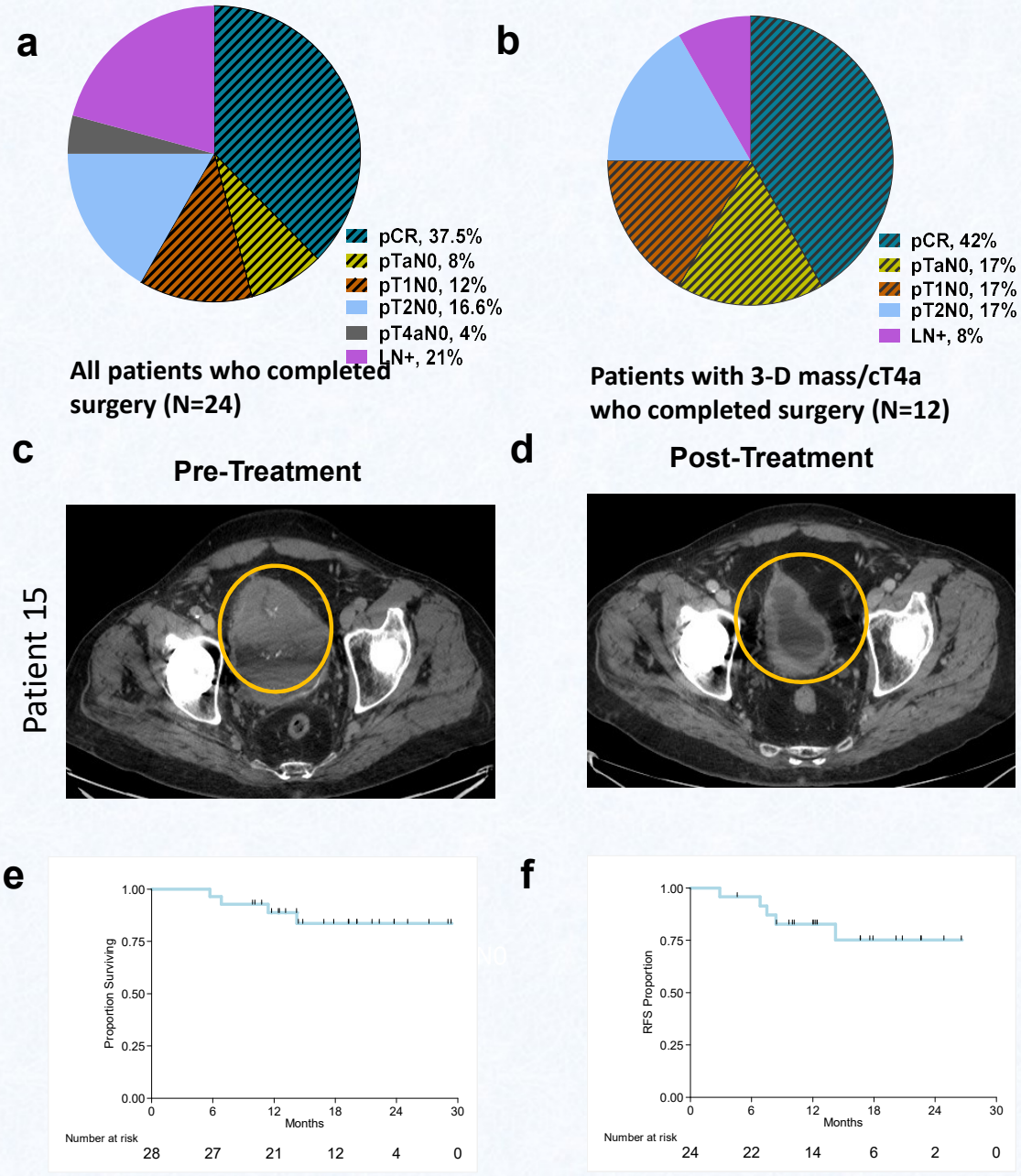
Treatment Related Adverse Events (N=28)	Any Grade N (%)	Grade >/= 3 N (%)
Any adverse events	26 (93%)	6 (21%)
Lipase increased	5 (18%)	4 (14%)
Alanine aminotransferase increased	6 (21%)	3 (11%)
Aspartate aminotransferase increased	6 (21%)	3 (11%)
Blood bilirubin increased	3 (11%)	2 (7%)
Amylase increased	8 (29%)	1 (4%)
Hyponatremia	4 (14%)	1 (4%)
Colitis	3 (11%)	1 (4%)
Rash	8 (29%)	0
Pruritus	7 (25%)	0
Fatigue	5 (18%)	0
Hyperthyroidism	5 (18%)	0
Anemia	4 (14%)	0
Hyperkalemia	4 (14%)	0
Hypomagnesemia	4 (14%)	0
INR increased	4 (14%)	0
Nausea	4 (14%)	0
Alkaline phos increased	3 (11%)	0
Constipation	3 (11%)	0
Hypoalbuminemia	3 (11%)	0
Hypocalcemia	3 (11%)	0

Clinical to Pathologic Staging Changes

Patient #	Clinical Stage at Baseline	Pathologic Stage
2	cT2	pT0N0
3	cT2	pT0N0
4	cT2	pT4aN0
5	cT4a	pT0N0
8	cT3b, 3-D mass on EUA	pT0N0
9	cT2	pT4N2
10	cT2	pT1N0
11	cT4a	pT1N0
12	cT2	pT0N0
13	cT3b, 3-D mass on EUA	pT2aN0
15	cT3b, 3-D mass on EUA	pTaN0
16	cT3b, 3-D mass on EUA	pT2N0
18	cT2	pT3bN1
22	cT2	pT2N0
23	cT3b, 3-D mass on EUA	pT0N0
24	cT3b, 3-D mass on EUA	pTisN0
25	cT3b, 3-D mass on EUA	pTis & TaN0
31	cT2	pT4aN2
32	cT3b, 3-D mass on EUA	pT2N1
34	cT2	pT2N0
35	cT2	pT2pN1
36	cT3b, 3-D mass on EUA	pT2pN0
37	cT1*	pT0N0

* cT1: diffuse bladder tumors with high grade histology and high-risk feature of micropapillary disease

Pathologic Responses to Durvalumab + Tremelimumab



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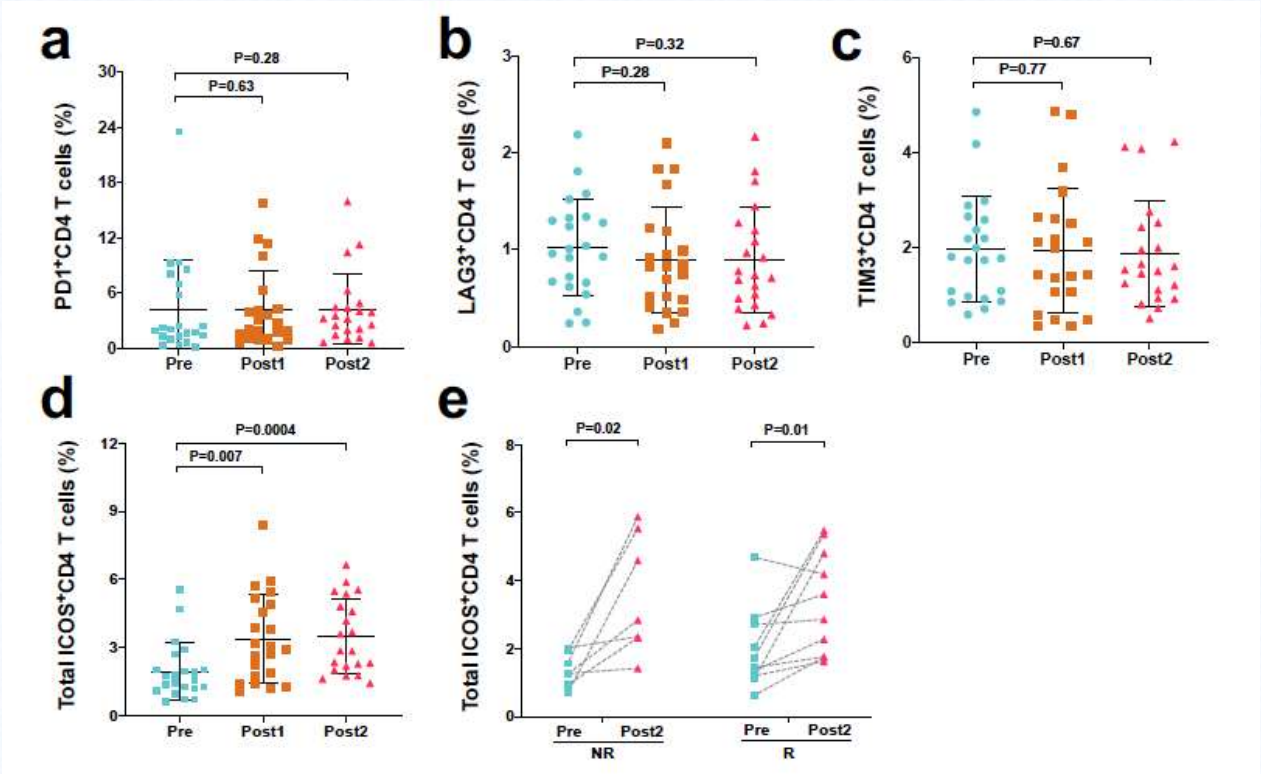
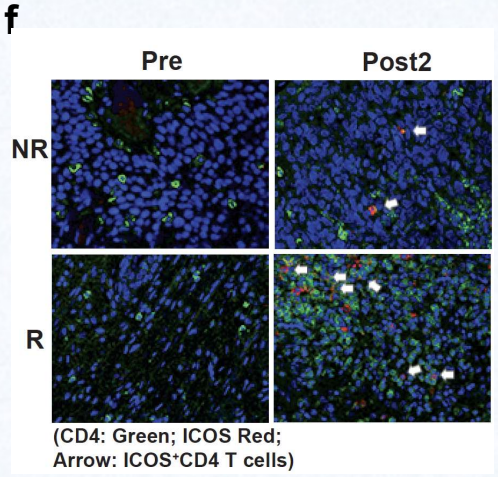
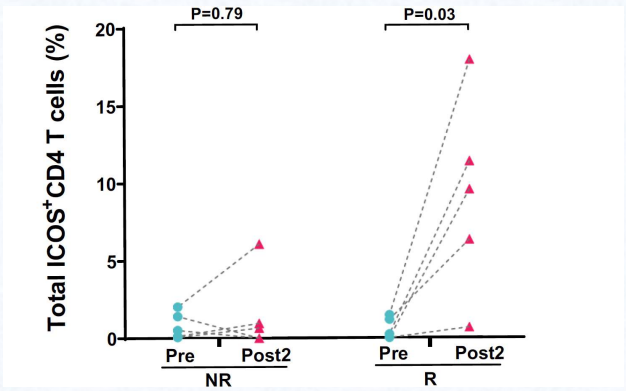
Durva/Treme Caused Significant Increase of ICOS+CD4 T Cells in Peripheral Blood and Tumor Tissues







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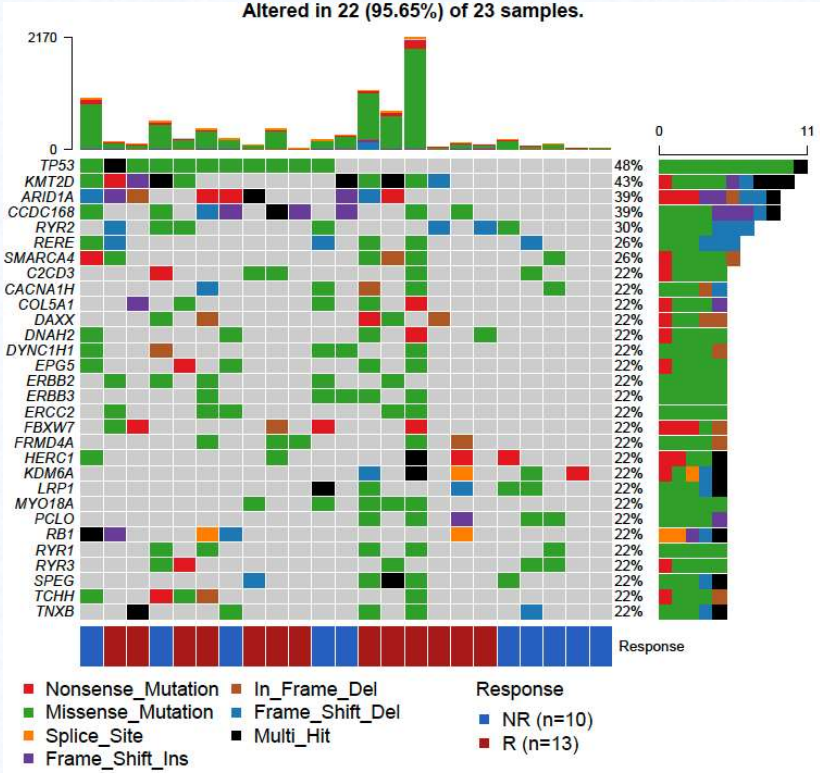
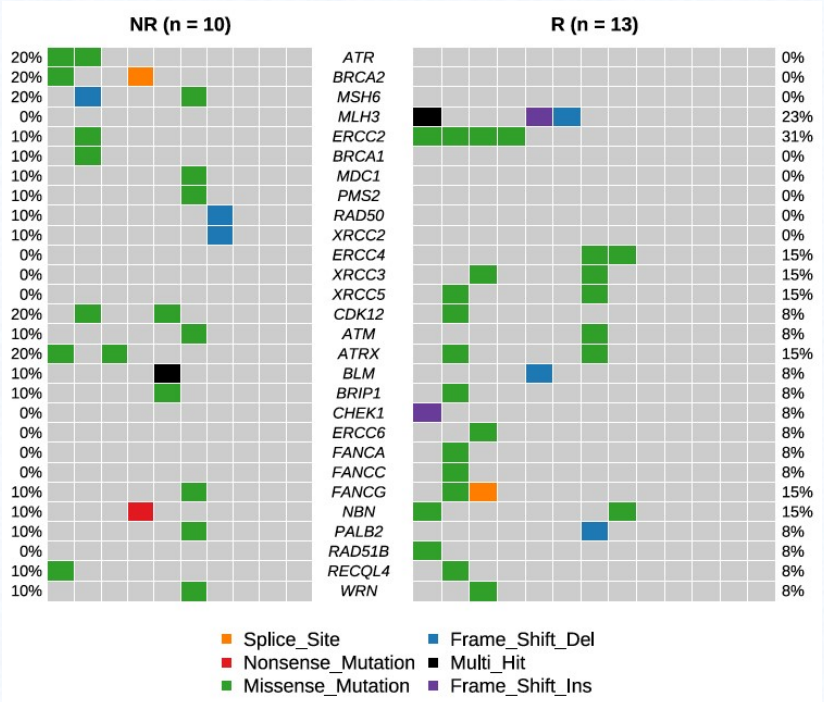
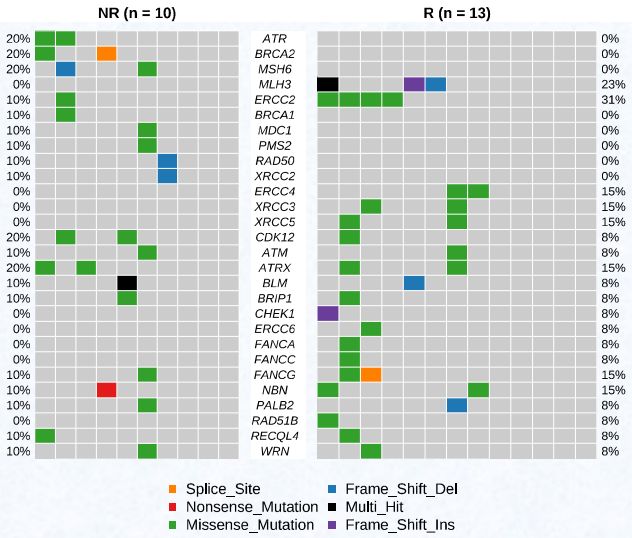
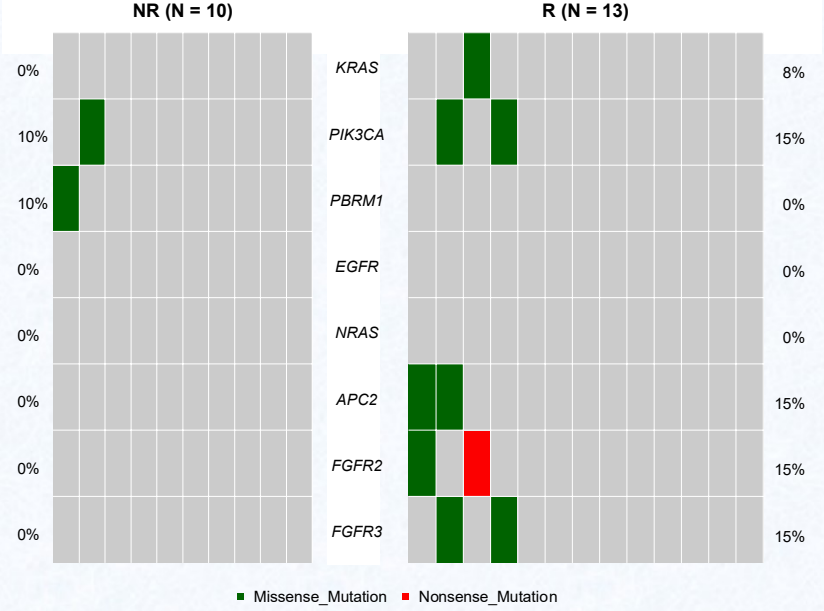
Pathologic Responses Did Not Correlate with Specific Mutations

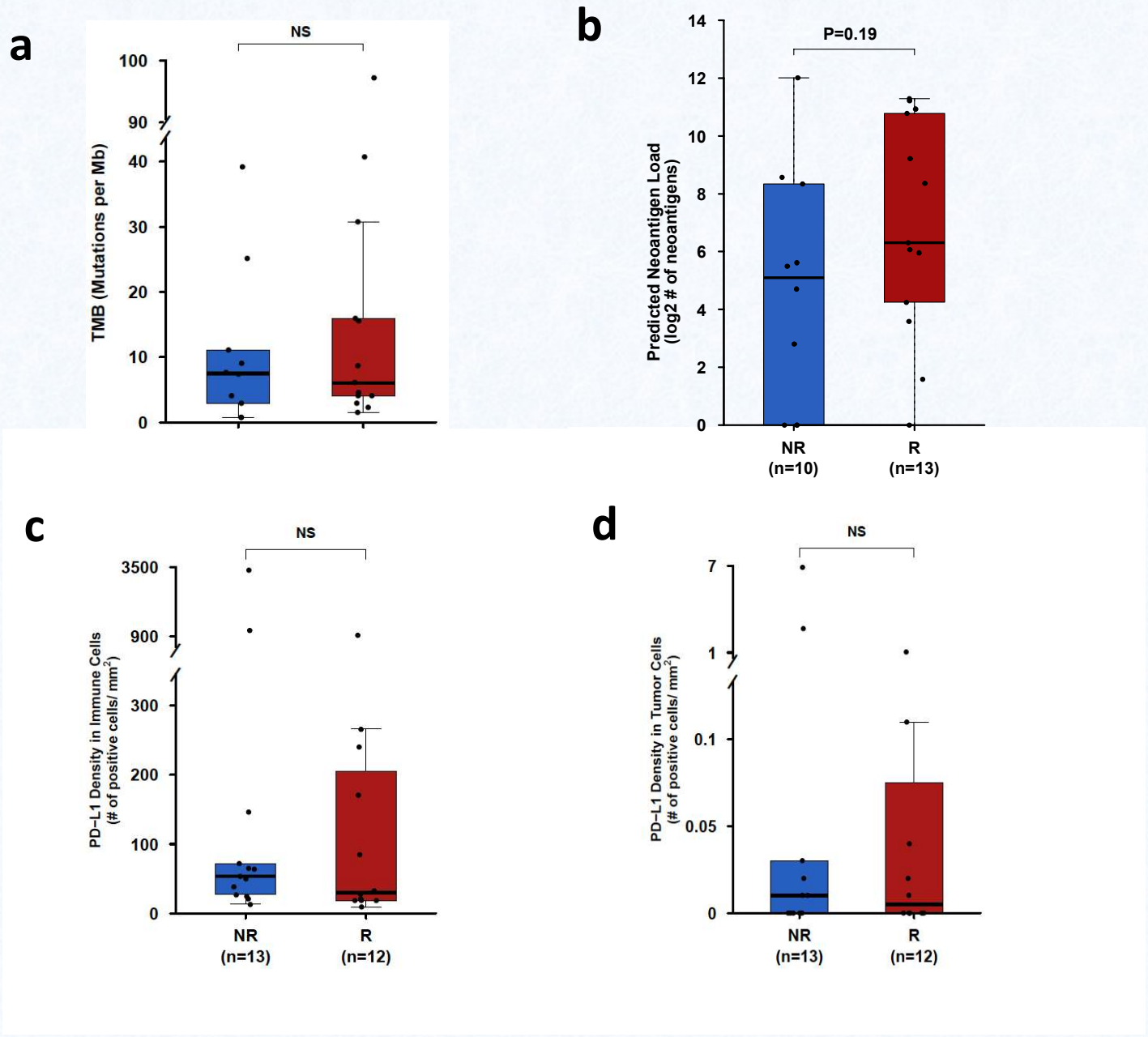




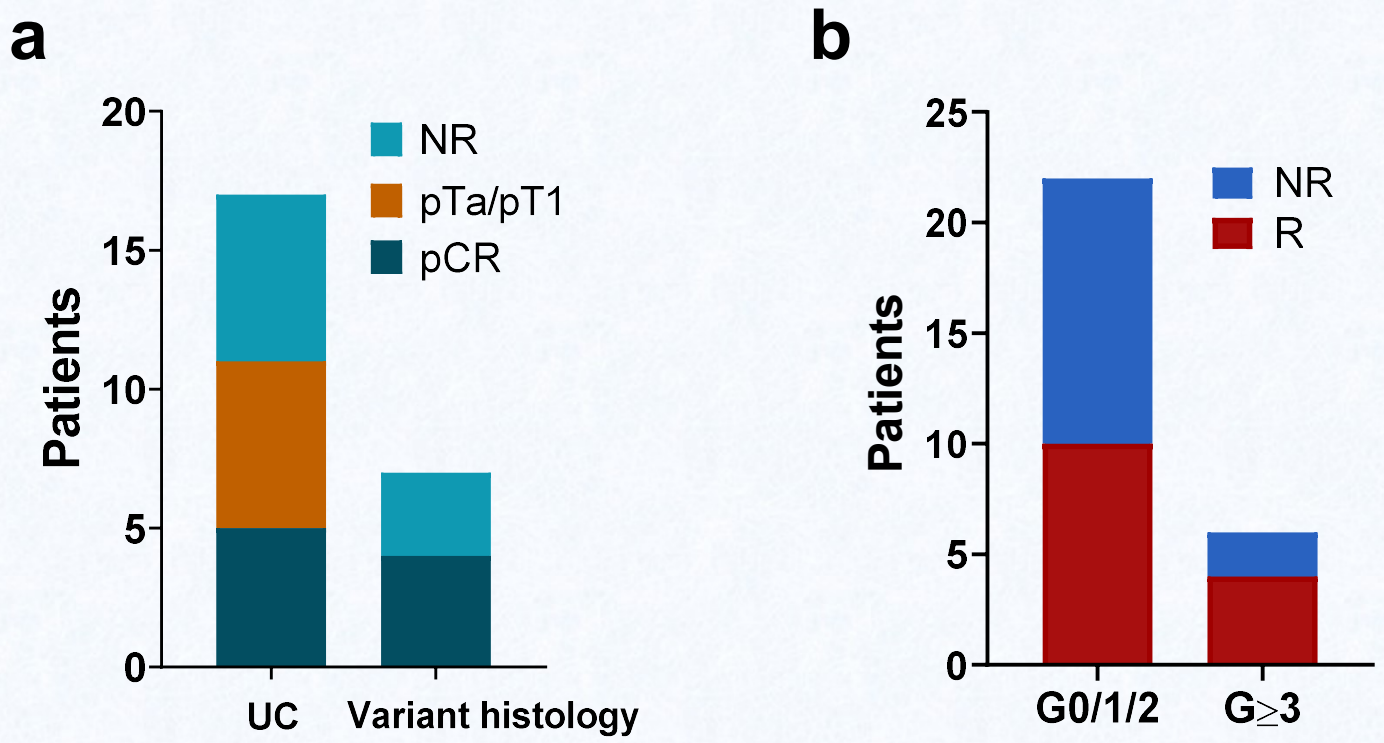




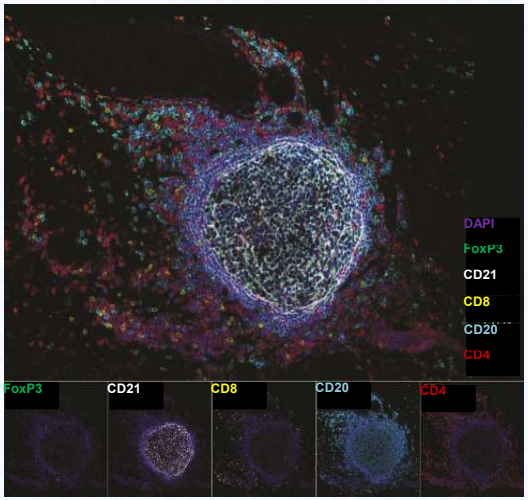
Pathologic Responses Did Not Correlate with TMB, Neoantigen or PD-L1

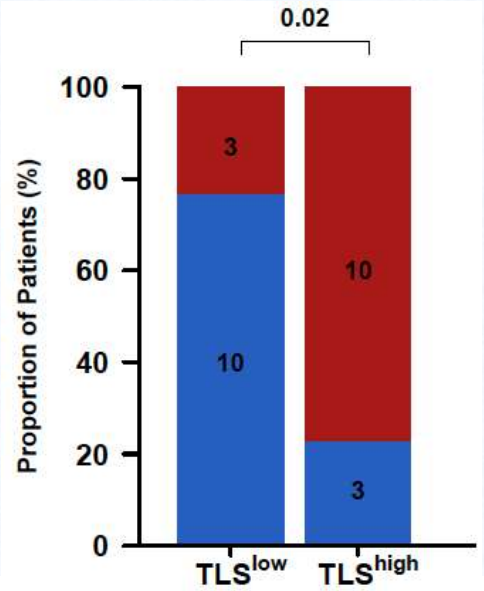


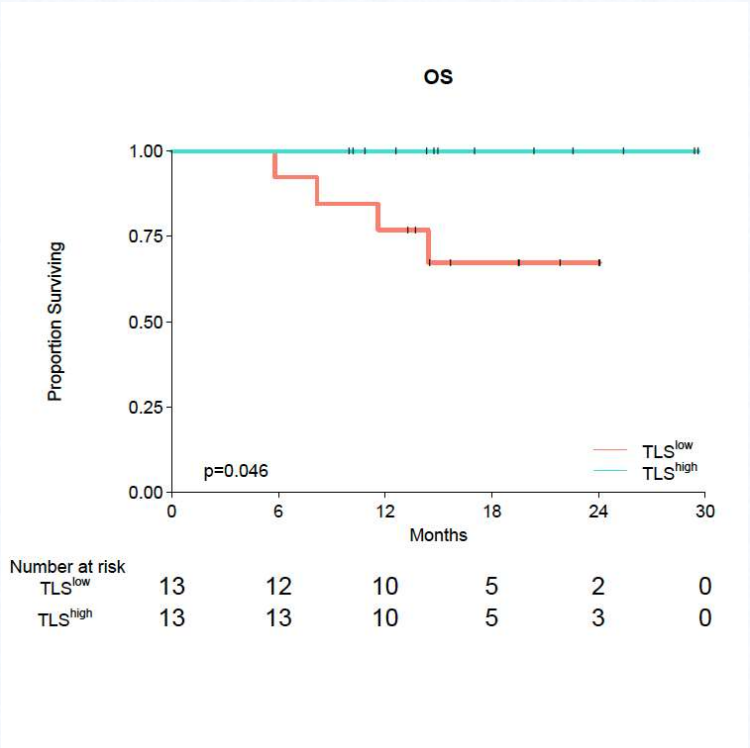
Histology and irAEs Did not Significantly Correspond to Pathologic Responses

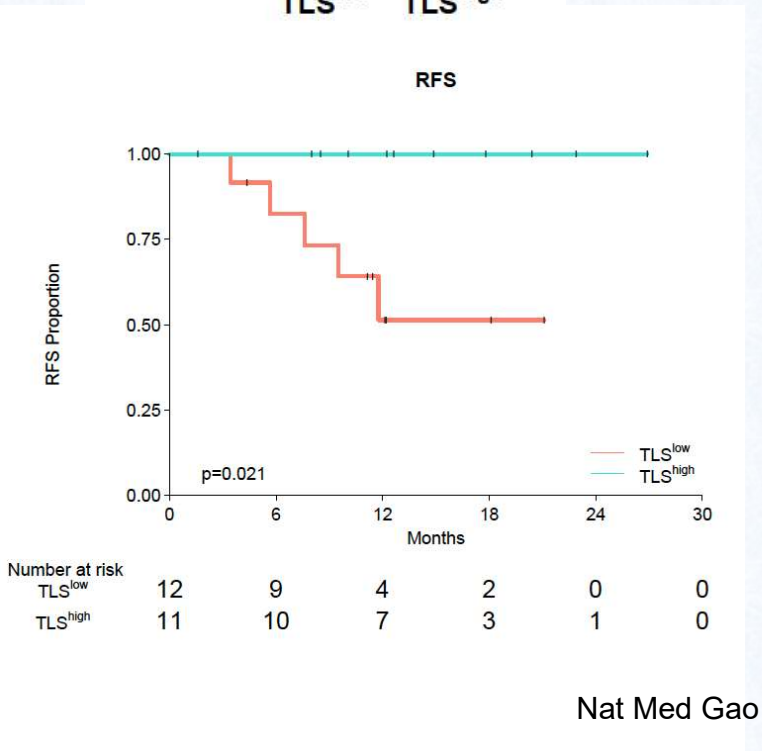


Baseline Tumor TLS Density Corresponds to Pathologic Responses, OS and RFS









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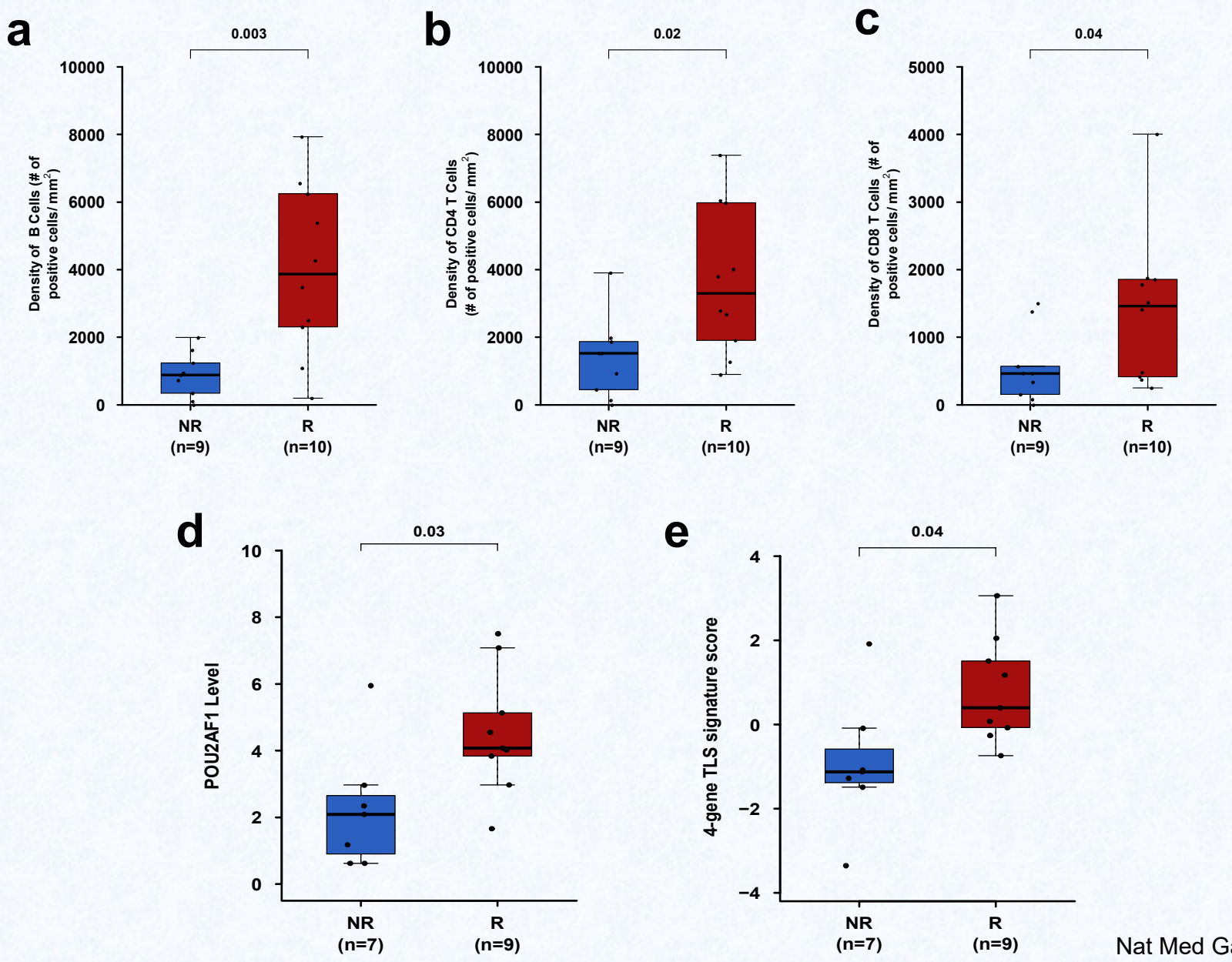
Baseline Tumor B Cells, T cells, and TLS Signature Corresponds to Pathologic Responses



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Summary

1. Durvalumab plus tremelimumab have an acceptable safety profile as neoadjuvant therapy for patients with high-risk MIBC ineligible for cisplatin-based chemotherapy.

2. Durvalumab plus tremelimumab lead to promising pathologic response rates that can be confirmed in larger trials.

3. Correlated data indicate that TLS is a promising biomarker that can be used for clinical correlation in the setting of localized disease.

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