IP36-06

Association of Genomic Disease Burden Markers and Programmed Death-Ligand 1 with Clinical Outcomes in Patients with Muscle-Invasive Bladder Cancer Treated with Gemcitabine Intravesical System + Cetrelimab or Cetrelimab Alone in the Phase 2 SunRISe-4 Trial

Felix Guerrero-Ramos,[1*] Andrea Necchi,[2] Neal Shore,[3] Paul L. Crispen,[4] Bernadett Szabados,[5,6] Evangelos Xylinas,[7] Karen Urtishak,[8] Sebastiano Battaglia,[8] Flavia Pinho,[9] Mohamad Hasan,[8] Cinty Gong,[10] Hind Stitou,[11] Sumeet Bhanvadia,[8] Sarah P. Psutka[12]

[1]Department of Urology, Hospital Universitario 12 de Octubre, Madrid, Spain; [2]IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; [3]START Carolinas/Carolina Urologic Research Center, Myrtle Beach, SC, USA; [4]Department of Urology, University of Florida, Gainesville, FL, USA; [5]Barts Experimental Cancer Medicine Centre, Barts Cancer Institute, Queen Mary University of London, London, UK; [6]Department of Urology, University College London Hospital NHS Foundation Trust, London, UK; [7]Department of Urology, Bichat-Claude Bernard Hospital, Assistance Publique-Hôpitaux de Paris, Université de Paris Cité, Paris, France; [8]Johnson & Johnson, Spring House, PA, USA; [9]Johnson & Johnson, San Diego, CA, USA; [10]Johnson & Johnson, Raritan, NJ, USA; [11]Johnson & Johnson, Issy-les-Moulineaux, France; [12]University of Washington, Fred Hutchinson Cancer Center, WA, USA

*Presenting author

Key Takeaway

High genomic disease burden markers (TMB, GDB) and PD-L1 expression at baseline were associated with high pathologic overall response to neoadjuvant gem-iDRS + CET or CET alone in patients with MIBC; further investigation in a larger study is warranted to further evaluate the predictive utility of these biomarkers

Conclusions

High baseline TMB, GDB, and PD-L1 were associated with pathologic overall response rates in the overall SunRISe-4 trial population (of patients with MIBC treated with neoadjuvant gem-iDRS + CET or CET alone)

No baseline biomarkers were associated with pCR or RFS with neoadjuvant gem-iDRS + CET or CET alone in the SunRISe-4 trial

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Introduction

- The standard of care for muscle-invasive bladder cancer (MIBC) is radical cystectomy (RC) with neoadjuvant cisplatin-based chemotherapy (NAC); however, up to 50% patients may be ineligible for or refuse cisplatin[1,2]
- Effective and better tolerated neoadjuvant treatment options are needed for patients with MIBC who are candidates for RC but not for NAC
- In the SunRISe-4 trial, neoadjuvant treatment with gemcitabine intravesical system (gem-iDRS) + cetrelimab (CET) demonstrated high pathologic complete response (pCR, 37.5% [95% CI, 27.4–48.5]), pathologic overall response (pOR, 53.4% [95% CI, 42.5–64.1]), and 1-year recurrence-free survival (RFS, 77.4% [95% CI 66.6–85.1]) in patients with MIBC[3]

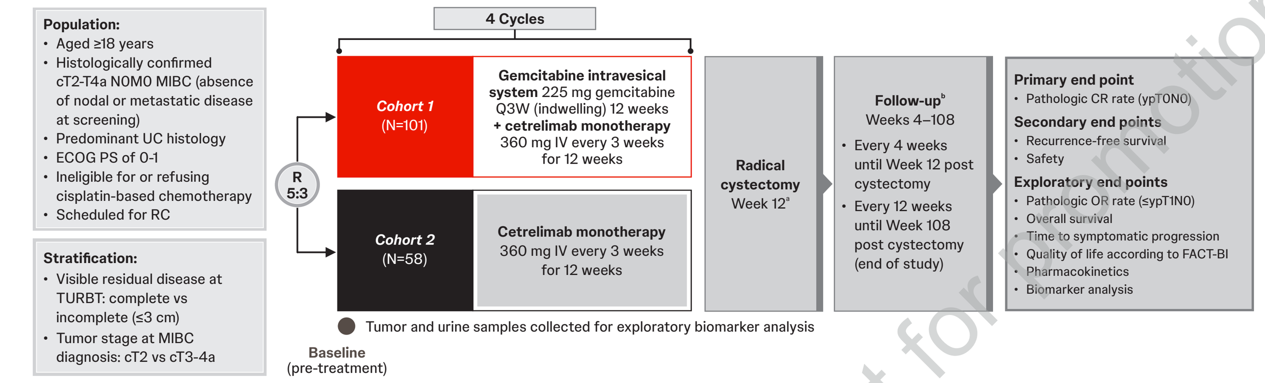
Objective

- To evaluate the association between baseline tumor mutational burden (TMB), mismatch repair deficiency (MMRd), genomic disease burden (GDB), and programmed death-ligand 1 (PD-L1) status and clinical outcomes with neoadjuvant gem-iDRS + CET or CET alone in the SunRISe-4 trial

Methods

- SunRISe-4 is a phase 2, open-label, randomized controlled trial (**Figure 1**)

Figure 1: SunRISe-4 trial design (NCT04919512)



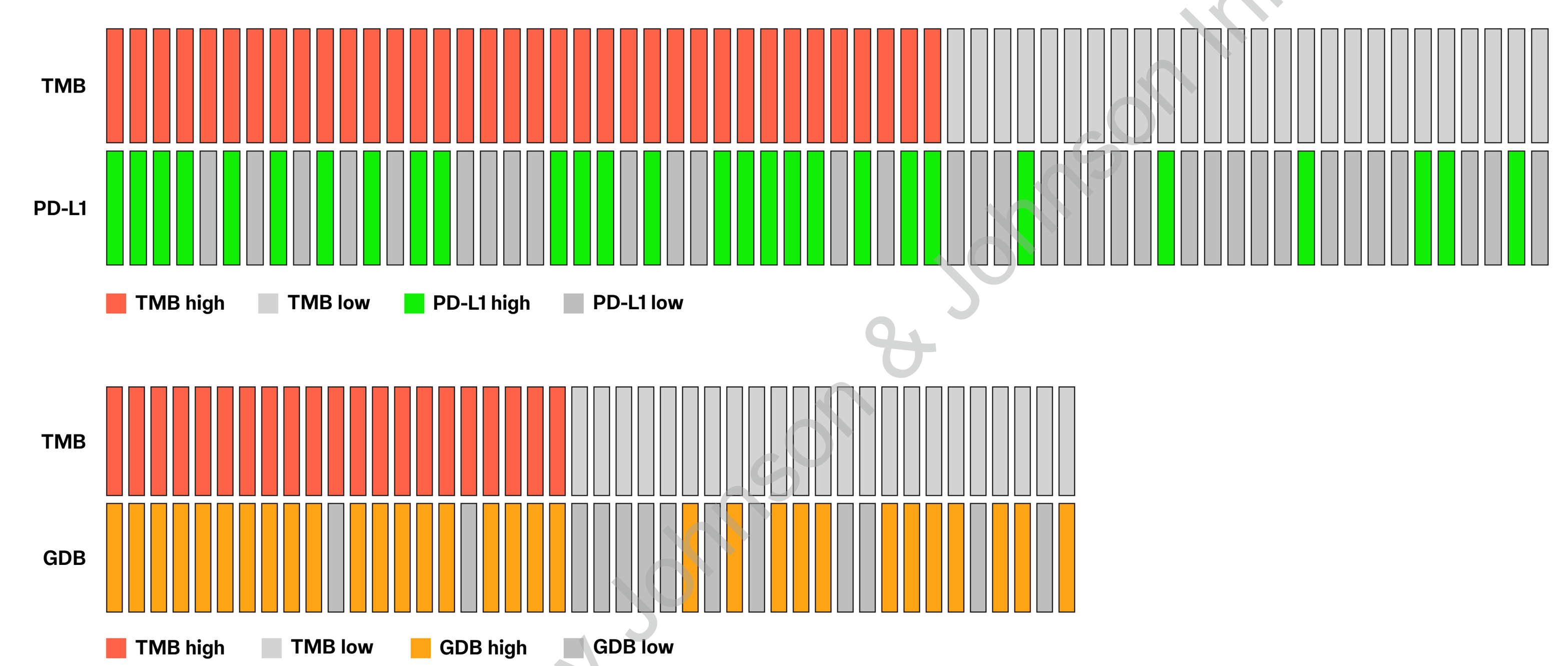
[a]Protocol-specified window of Weeks 11–15. [b]Clinical follow-up visits and laboratory tests, including urine culture at all visits. Cross-sectional imaging (CT/MRI of chest, abdomen, and pelvis) was performed at Week 6 during treatment and Week 12 post-RC.
CR, complete response; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; FACT-BI, Functional Assessment of Cancer Therapy-Bladder; IV, intravenous; MIBC, muscle-invasive bladder cancer; OR, overall response; RC, radical cystectomy; TURBT, transurethral resection of bladder tumor; UC, urothelial carcinoma; utDNA, urinary tumor DNA.

- Our analysis included biomarker-evaluable patients from Cohorts 1 and 2 combined (overall cohort) and from Cohort 1 alone. Cohort 2 was not analyzed separately due to small sample size
- Baseline patient samples were analyzed via whole exome sequencing (WES) for tissue using Signatera (Natera™) and for urine using UroAMP (Convergent Genomics™)
- TMB was calculated from WES as the number of nonsynonymous mutations/patient divided by coding region size, and by corresponding % mutated genes in urine. MMRd was determined using WES from tumor tissue. GDB was assessed in urine. PD-L1 was assessed by immunohistochemistry with clone SP263 (Roche®)
- Biomarker thresholds were: TMB high ≥10 mutations/Mb; MMRd=mutation in MLH1, MSH2, MSH6, or PMS2; GDB high ≥42; PD-L1 high per manufacturer's guidelines
- Associations between biomarkers and pCR/pOR and RFS were calculated with Fisher's exact test and Cox hazard ratios, respectively. Logistic regression and cox proportional hazards analyses are univariable

Results

- At the data cutoff of May 9, 2025, our biomarker-evaluable overall cohort comprised 88 patients from SunRISe-4: 61 patients from Cohort 1 (gem-iDRS + CET) and 27 patients from Cohort 2 (CET monotherapy)
- 73 tissue samples and 67 urine samples were collected; biomarker frequency in evaluable samples was TMB high: 58% (51/88), MMRd: 41% (19/46), GDB high: 75% (50/67), and PD-L1 high 42% (29/69)
- High baseline TMB, GDB, and PD-L1 were associated with pathologic overall response rates in the overall SunRISe-4 trial population (in patients with MIBC treated with neoadjuvant gem-iDRS + CET or CET alone)
- No other pairwise comparisons between TMB, GDB, PD-L1, or MMRd were significant
- Similar pairwise association was observed in the neoadjuvant gem-iDRS + CET (Cohort 1) for baseline TMB (OR 3.52 [95% CI; 1.02–12.89]; p=0.02) and baseline PD-L1 (OR 3.89 [0.96–18.18]; p=0.04)

Figure 2: Pairwise associations between biomarker-defined subgroups at baseline in the overall cohort



GDB, genomic disease burden; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden.

- In the overall cohort, pOR rates with neoadjuvant gem-iDRS + CET or CET alone were significantly higher in patients with high baseline TMB, GDB, or PD-L1 than in patients with low baseline TMB, GDB, or PD-L1, respectively (Table 1)
- Baseline genomic burden and PD-L1 status did not appear to influence pCR rates with neoadjuvant gem-iDRS + CET or CET alone in the overall cohort

Table 1: pCR and pOR rates by baseline genomic burden and PD-L1 in the overall cohort

Biomarker status at baseline (N=total BM+)	Response endpoint	% Response (BM+ responders/patients evaluable)	OR [95% CI]	p-value
TMB high (N=46)	pCR	25% (20/79)	1.75 [0.62–5.13]	0.25
	pOR	41% (32/79)	3.92 [1.41–11.52]	**0.01**
MMRd (N=18)	pCR	11% (5/44)	0.73 [0.15–3.17]	0.74
	pOR	18% (8/44)	0.69 [0.17–2.69]	0.76
GDB high (N=43)	pCR	33% (19/58)	2.10 [0.52–10.76]	0.36
	pOR	50% (29/58)	4.03 [1.02–18.13]	**0.03**
PD-L1 high (N=28)	pCR	19% (12/62)	1.55 [0.49–5.02]	0.44
	pOR	32% (20/62)	3.10 [0.97–10.64]	**0.04**

BM, biomarker; CI, confidence interval; GDB, genomic disease burden; MMRd, mismatch repair deficiency; OR, odds ratio; pCR, pathologic complete response; PD-L1, programmed death-ligand 1; pOR, pathologic overall response; TMB, tumor mutational burden.

- In the gem-iDRS + CET cohort, pOR rates were significantly higher in patients with high baseline TMB or PD-L1 than in patients with low baseline TMB or PD-L1, respectively (**Table 2**)

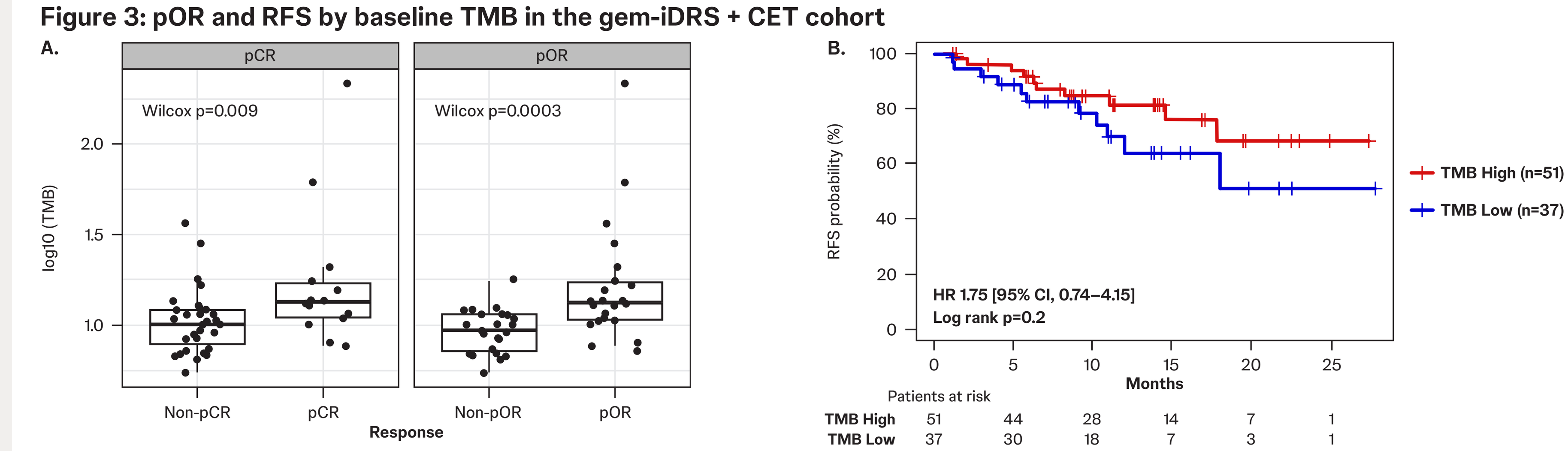
Table 2: pCR and pOR rates by baseline genomic burden and PD-L1 in the gem-iDRS + CET cohort

Biomarker status at baseline (N=total BM+)	Response endpoint	% Response (BM+ responders/patients evaluable)	OR [95% CI]	p-value
TMB high (N=35)	pCR	28% (16/57)	1.78 [0.52–6.55]	0.40
	pOR	44% (25/57)	3.52 [1.02–12.89]	**0.02**
MMRd (N=15)	pCR	16% (5/32)	0.57 [0.10–2.90]	0.49
	pOR	25% (8/32)	0.63 [0.11–3.21]	0.72
GDB high (N=29)	pCR	29% (12/41)	1.40 [0.28–7.87]	0.73
	pOR	49% (20/41)	3.02 [0.62–15.86]	0.16
PD-L1 high (N=22)	pCR	22% (10/46)	1.38 [0.37–5.29]	0.76
	pOR	37% (17/46)	3.89 [0.96–18.18]	**0.04**

BM, biomarker; CI, confidence interval; GDB, genomic disease burden; MMRd, mismatch repair deficiency; OR, odds ratio; pCR, pathologic complete response; PD-L1, programmed death-ligand 1; pOR, pathologic overall response; TMB, tumor mutational burden.

- Using baseline TMB on a continuous scale from WES data, TMB was significantly higher in patients achieving a pCR or pOR compared with those patients who did not (**Figure 3A**). A similar trend was seen for the gem-iDRS + CET cohort
- Patients with high basline TMB trended toward longer recurrence free survival (RFS) compared with patients with low baseline TMB, (p=0.2; **Figure 3B**). No trends were seen between RFS and baseline PD-L1, MMRd, or GDB

Figure 3: pOR and RFS by baseline TMB in the gem-iDRS + CET cohort



HR, hazard ratio; pCR, pathologic complete response; pOR, pathologic overall response; RFS, recurrence-free survival; TMB, tumor mutational burden.

- Mutational data from WES and utDNA were assessed to determine whether gene alterations were predictive of TMB-high status at baseline in the overall cohort
- *TP53 or ATM* alterations were significantly associated with high TMB at baseline in the overall cohort (**Table 3**)

Table 3: Association between gene alterations and TMB status at baseline in the overall cohort

Gene	TMB High (n=51)	TMB Low (n=37)	OR [95% CI]	p-value
	% Altered (n/N)	% Altered (n/N)		
TP53	**75% (38/51)**	**43% (16/37)**	**3.8 [1.4–10.5]**	**0.004**
RB1	22% (11/51)	13% (5/37)	1.7 [0.5–7.1]	0.409
PIK3CA	25% (13/51)	24% (9/37)	1.1 [0.4–3.2]	1
ATM	**24% (12/51)**	**5% (2/37)**	**5.3 [1.1–52.0]**	**0.036**
TSC1	22% (11/51)	13% (5/37)	1.7 [0.5–7.1]	0.409
ERCC2	14% (7/51)	11% (4/37)	1.3 [0.3–6.6]	0.754
FGFR3	12% (6/51)	16% (6/37)	0.7 [0.2–2.9]	0.549
POLE	8% (4/51)	3% (1/37)	3.0 [0.3–154.9]	0.393

CI, confidence interval; OR, odds ratio; TMB, tumor mutational burden.

Limitations

- The limitations for the SunRISe-4 trial include the open-label, noncomparative design and the exclusion of patients with residual tumors >3 cm
- The number of evaluable patients was limited, which may affect the generalizability of the findings
- Data from the CET monotherapy cohort could not be analyzed due to limited sample size

References

1. Holzbeierlein J, et al. *J Urol* 2024;212:3-10. **2.** Witjes JA, et al. *Eur Urol* 2024;85:17-31. **3.** Necchi A, et al. *J Clin Oncol* 2026;44:586-597.

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