

Neoadjuvant gemcitabine intravesical system (TAR-200) + cetrelimab or cetrelimab alone in patients with muscle-invasive bladder cancer: SunRISe-4 primary analysis and biomarker results

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Disclosure of interests

- Andrea Necchi has received grants or institutional research funding from AstraZeneca, Bristol Myers Squibb, Gilead, Ipsen, and Merck; has received consulting or advisory fees from Astellas, AstraZeneca, Bristol Myers Squibb, Catalym, Gilead, Johnson & Johnson, Samsung Bioepis, Bicycle Therapeutics, and Merck; serves in a leadership role for the Global Society of Rare Genitourinary Tumors (GSRGT); and serves as an associate editor for the *Journal of Clinical Oncology*

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Unmet need for patients with MIBC who refuse or are ineligible for cisplatin-based chemotherapy

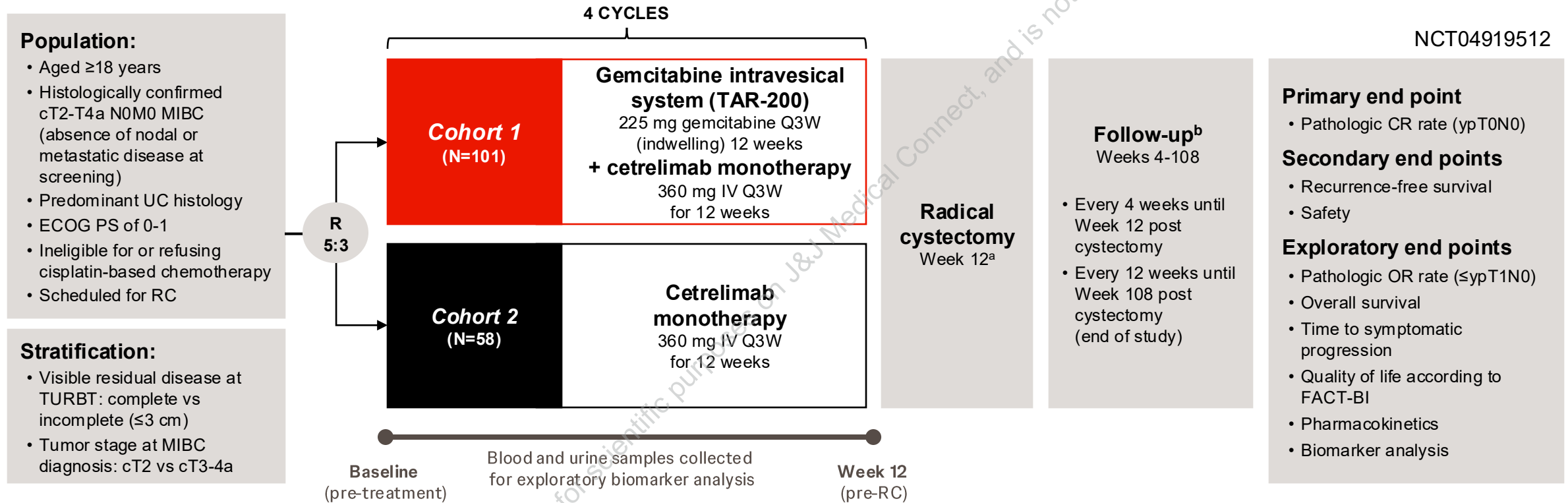
- Standard of care for MIBC (T2-T4a N0M0) is RC with NAC, or chemoradiation for select patients^{1,2}
 - However, many patients are ineligible for (up to 50%) or refuse cisplatin³⁻⁶
 - For these patients, standard of care is immediate RC^{1,2}
- In patients with MIBC undergoing RC, pathologic stage is a prognostic factor for survival⁷⁻¹⁰
 - pCR rates with RC alone, with NAC, and with neoadjuvant checkpoint inhibitors are 10-15%, 26-42%, and 31-37%, respectively^{9,11-18}
 - pCR in patients who have received NAC is associated with 55% lower risk of death and 81% lower risk of recurrence compared with patients with residual disease⁸
- There is need for effective and more tolerable treatment options for patients with MIBC who are candidates for RC but not candidates for NAC

MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant cisplatin-based chemotherapy; RC, radical cystectomy.

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SunRISe-4: open-label, multicenter, parallel cohort phase 2 study of neoadjuvant TAR-200 + cetrelimab or cetrelimab alone in MIBC



- Here we report **(1)** the primary analysis of SunRISe-4 and **(2)** exploratory biomarker analyses of utDNA and ctDNA MRD
- Side-by-side descriptive summary of efficacy was conducted; no statistical hypotheses were tested to compare cohorts

CR, complete response; ctDNA, circulating tumor DNA; FACT-BI, Functional Assessment of Cancer Therapy – Bladder; IV, intravenous; OR, overall response; Q3W, every 3 weeks; TURBT, transurethral resection of bladder tumor; UC, urothelial carcinoma; utDNA, urinary tumor DNA.

^a Protocol specified window of Week 11 to Week 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.



Patient characteristics in SunRISe-4

Characteristic	Cohort 1: TAR-200 + cetrelimab (N = 101)	Cohort 2: Cetrelimab monotherapy (N = 58)
Age, years, median (IQR)	74 (69-77)	69 (64-74)
Sex, male, No. (%)	86 (85.1)	46 (79.3)
Race, No. (%)		
White	72 (71.3)	43 (74.1)
Asian	18 (17.8)	11 (19.0)
Other	11 (10.9)	4 (6.9)
Geographic region, No. (%) ^a		
America	40 (39.6)	21 (36.2)
Asia	20 (19.8)	12 (20.7)
Western Europe	41 (40.6)	25 (43.1)
Nicotine use, No. (%)		
Current	26 (25.7)	12 (20.7)
Former	51 (50.5)	34 (58.6)
Never	1 (1.0)	0
Unknown	23 (22.8)	12 (20.7)
ECOG performance status, No. (%)		
0	83 (82.2)	45 (77.6)
1	18 (17.8)	13 (22.4)
Tumor stage at initial diagnosis, No. (%)		
T2	79 (78.2)	49 (84.5)
T3	19 (18.8)	8 (13.8)
T4a	3 (3.0)	1 (1.7)

Characteristic	Cohort 1: TAR-200 + cetrelimab (N = 101)	Cohort 2: Cetrelimab monotherapy (N = 58)
Prior intravesical therapy, No. (%)	12 (11.9)	9 (15.5)
Residual disease (visibly incomplete TURBT), No. (%)	19 (18.8)	8 (13.8)
PD-L1 status, No. (%) ^b		
Low	33 (50.8)	23 (74.2)
High	32 (49.2)	8 (25.8)
Urothelial carcinoma with variant histology, No (%)	22 (21.8)	16 (27.6)
Reason for not receiving neoadjuvant cisplatin-based chemotherapy, No. (%)		
Ineligible	46 (45.5)	22 (37.9)
Glomerular filtration rate <60 mL/min	29 (28.7)	15 (25.9)
Grade ≥2 audiometric hearing loss	11 (10.9)	3 (5.2)
Grade ≥2 peripheral neuropathy	4 (4.0)	3 (5.2)
Multiple	2 (2.0)	1 (1.7)
Refused	55 (54.5)	36 (62.1)
Quality of life	34 (33.7)	32 (55.2)
Age	10 (9.9)	2 (3.4)
Patient comorbidity	3 (3.0)	1 (1.7)
Patient decision	6 (5.9)	1 (1.7)
Other	2 (2.0)	0

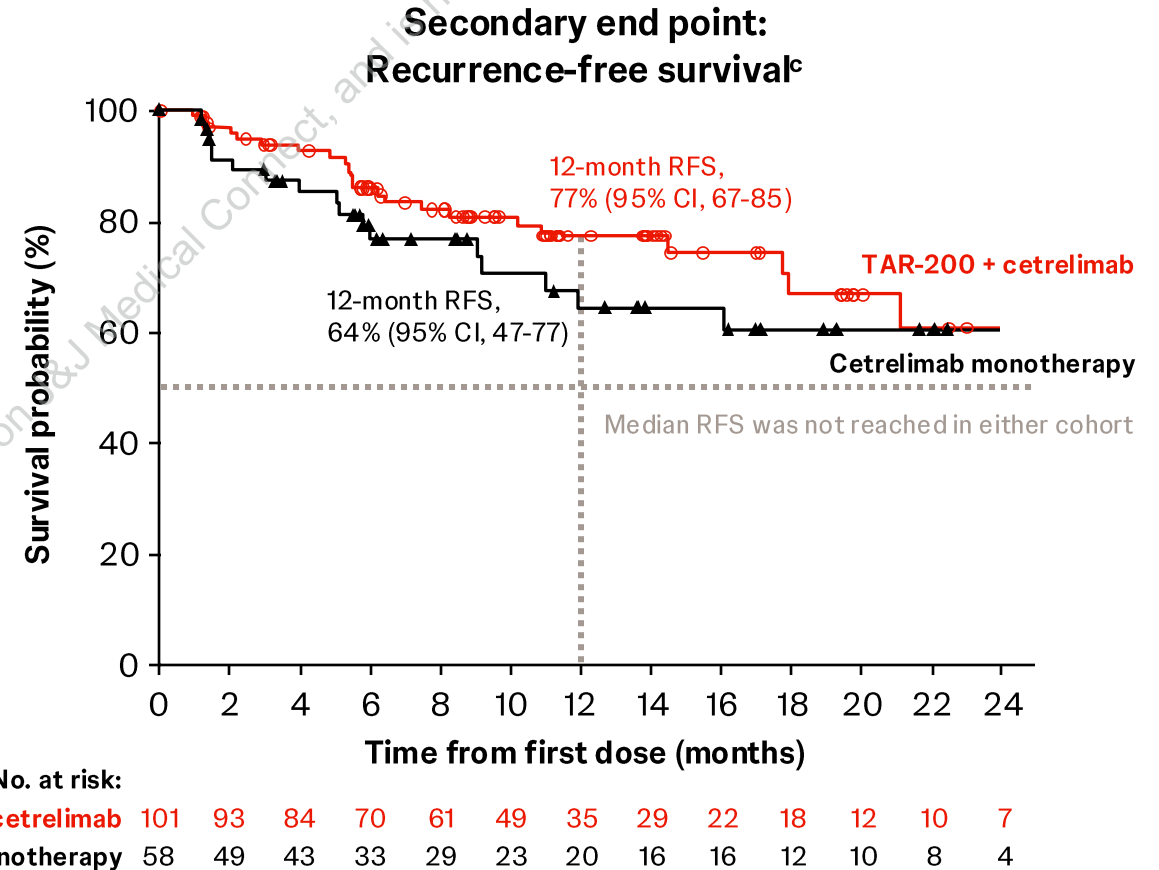
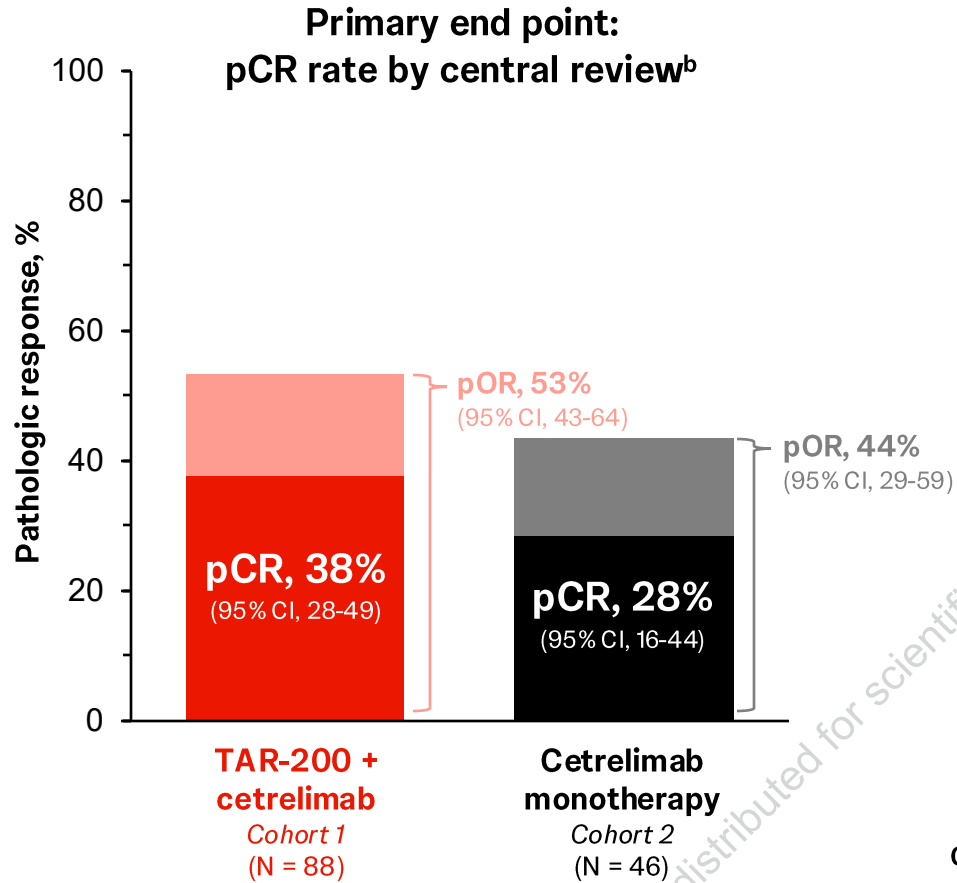
ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD-L1, programmed death-ligand 1; TURBT, transurethral resection of bladder tumor.

^a America includes the United States; Asia includes Israel and South Korea; Western Europe includes Belgium, France, Germany, Italy, Netherlands, Poland, Spain, and the United Kingdom.

^b Percentages are based on number of patients with available PD-L1 status data. N = 65 patients with available data in Cohort 1; N = 31 patients with available data in Cohort 2.



Efficacy: pCR rate was higher and RFS was longer with the addition of TAR-200 to cetrelimab^a



CI, confidence interval; pCR, pathologic complete response (defined as ypT0N0); pOR, pathologic overall response (defined as ≤ypT1N0); RFS, recurrence-free rate.

^a Median duration of follow-up, 14.1 months (range, 1.2-32).

^b Data are shown for the efficacy evaluable set (N = 134) defined as patients who underwent cystectomy and had available centrally review histopathology.

^c RFS was defined as the time from first dose of any study treatment to first radiologic evidence of nodal or metastatic disease that precludes RC, first radiologic evidence of nodal or metastatic disease after RC, or death due to any cause. Data are shown for each timepoint with ≥5 patients in either cohort.



No new safety signals for TAR-200, cetrelimab, or the combination were observed

Patients with ≥1 event, No. (%)	Cohort 1: TAR-200 + cetrelimab (N = 101)		Cohort 2: Cetrelimab monotherapy (N = 58)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TRAE ^{a,b}	82 (81.2)	16 (15.8)	30 (51.7)	6 (10.3)
Dysuria	31 (30.7)	0	1 (1.7)	0
Pollakiuria	31 (30.7)	1 (1.0)	0	0
Micturition urgency	18 (17.8)	0	0	0
Fatigue	13 (12.9)	2 (2.0)	7 (12.1)	0
Hematuria	13 (12.9)	2 (2.0)	0	0
Hypothyroidism	11 (10.9)	1 (1.0)	4 (6.9)	0
Hyperthyroidism	11 (10.9)	0	3 (5.2)	0
Urinary tract infection	11 (10.9)	3 (3.0)	0	0
Pruritus	5 (5.0)	0	7 (12.1)	0
Immune-related TRAE	48 (47.5)	8 (7.9)	29 (50.0)	5 (8.6)

Patients with ≥1 event, No. (%)	Cohort 1: TAR-200 + cetrelimab (N = 101)		Cohort 2: Cetrelimab monotherapy (N = 58)	
	Any grade	Any grade	Any grade	Any grade
Serious TRAE ^c	14 (13.9)	3 (5.2)		
TRAE leading to death	0	1 (1.7) ^d		
TRAE leading to treatment discontinuation ^e	21 (20.8)	0		
TRAE leading to TAR-200 discontinuation	18 (17.8)	—		
TRAE leading to cetrelimab discontinuation ^g	11 (10.9)	0		

TRAE, treatment-related adverse event.

^a AE was categorized as related if assessed by investigator as possibly, probably, or very likely related to study treatment. Patients were counted only once for any given AE, regardless of the number of times the AE occurred.

^b TRAEs by preferred term are listed if events of any grade were reported in ≥10% of patients in either cohort. Most frequent grade ≥3 TRAEs in Cohort 1 were urinary tract infection (n=3 [3.0%]), fatigue (n=2 [2.0%]), and hematuria (n=2 [2.0%]). Most frequent grade ≥3 TRAEs in Cohort 2 were hyponatremia (n=2 [3.4%]) and acute kidney injury (n=2 [3.4%]).

^c The most frequent serious TRAEs (reported in ≥2 patients) were hyponatremia (Cohort 1, n = 1 [1.0%]; Cohort 2, n = 2 [3.4%]), tubulointerstitial nephritis (Cohort 1, n = 2 [2.0%]; Cohort 2, n = 0), and urinary tract infection (Cohort 1, n = 2 [2.0%]; Cohort 2, n = 0).

^d Case of hyperglycemic hyperosmolar nonketotic syndrome.

^e TRAE leading to discontinuation of TAR-200, cetrelimab, or both.

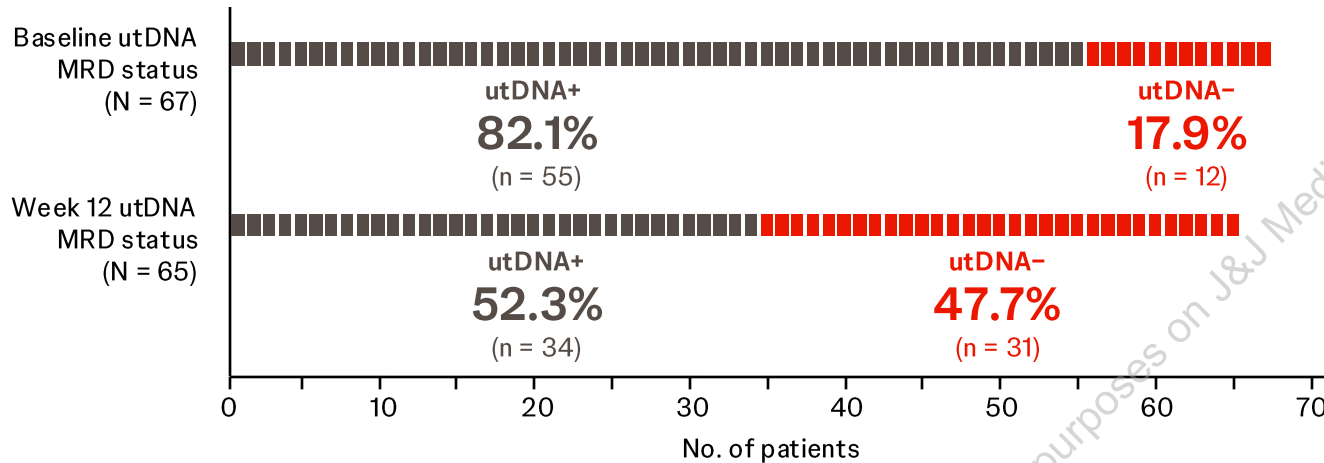
^f The most frequent TRAEs leading to TAR-200 discontinuation were pollakiuria (n = 4 [4.0%]), noninfective cystitis (n = 3 [3.0%]), and bladder pain (n = 2 [2.0%]). All other TRAEs leading to TAR-200 discontinuation occurred in one patient each.

^g All TRAEs leading to cetrelimab discontinuation occurred in one patient each.



utDNA MRD was reduced after 12 weeks of neoadjuvant treatment

Prevalence of utDNA+ at baseline and Week 12^a



- The proportion of patients who were utDNA+ was reduced from baseline to Week 12 **irrespective of treatment**
 - In Cohort 1, 77.8% and 50.0% of patients were utDNA+ at baseline and Week 12, respectively^d
 - In Cohort 2, 90.9% and 55.6% of patients were utDNA+ at baseline and Week 12, respectively^e
 - No meaningful differences were observed between cohorts, though sample sizes were limited

- At baseline, **81.8%** of patients with visibly complete^b and **83.3%** with visibly incomplete TURBT^c were utDNA+

MRD, minimal residual disease.

^a utDNA MRD was assessed by UROAmp assay (Convergent Genomics, South San Francisco, CA, USA).

^b N = 55 patients across both cohorts who had available utDNA results and visibly complete TURBT.

^c N = 12 patients across both cohorts who had available utDNA results and visibly incomplete TURBT (residual tumor ≤3 cm).

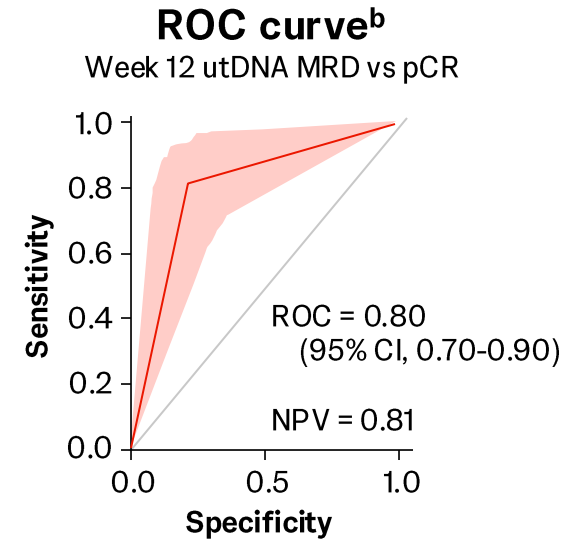
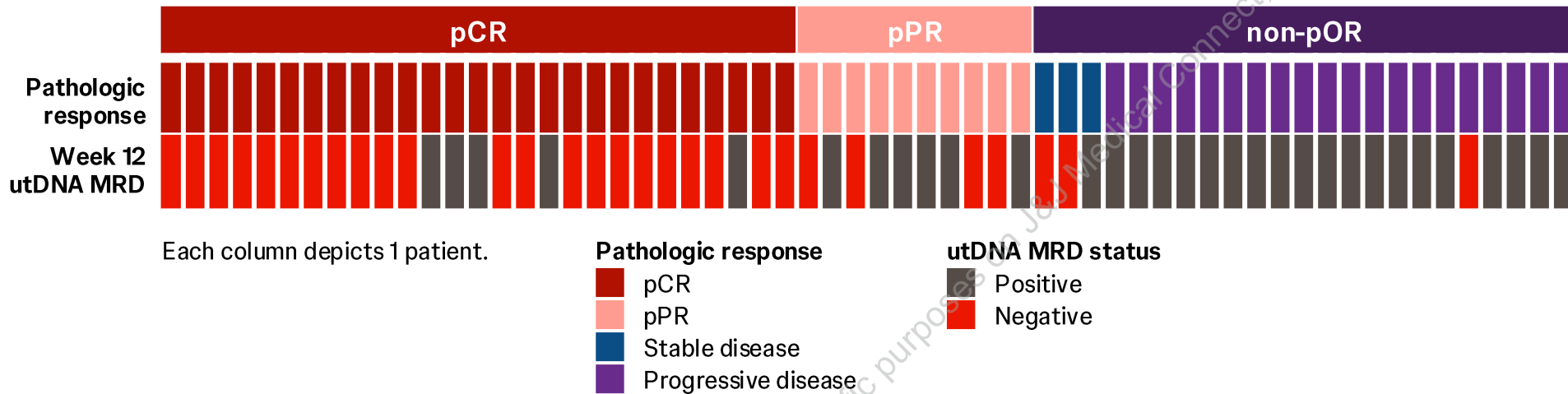
^d N = 45 and 38 patients in Cohort 1 who had available utDNA results at baseline and Week 12, respectively.

^e N = 22 and 27 patients in Cohort 2 who had available utDNA results at baseline and Week 12, respectively.



utDNA negative status at Week 12 was associated with pCR

Week 12 utDNA MRD status^a and pathologic response (N = 60)



- 22 of 27 patients (**81.5%**) who achieved pCR were utDNA- at Week 12 compared with 7 of 33 (**21.2%**) who did not achieve pCR (Fisher's test, $p = 5.4 \times 10^{-6}$)

NPV, negative predictive value; pPR, pathologic partial response; ROC, receiver operating characteristic.

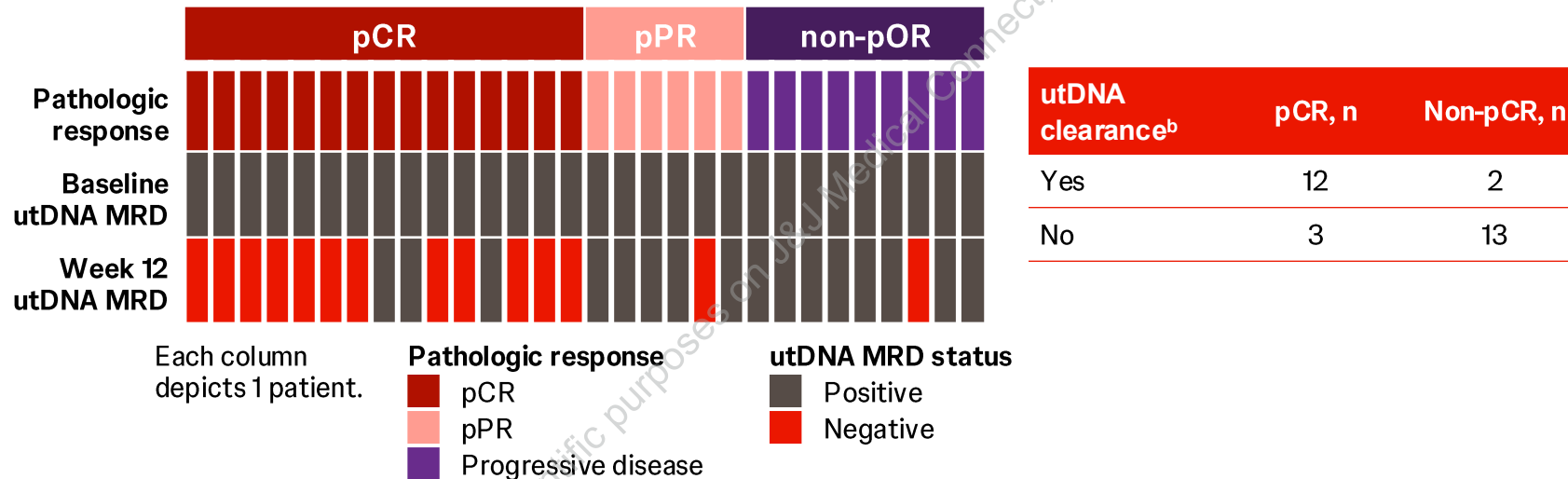
^a utDNA MRD was assessed by UROamp assay (Convergent Genomics, South San Francisco, CA, USA).

^b Light red shading depicts 95% CI for area under the ROC curve.



utDNA clearance from baseline to Week 12 was associated with pCR

utDNA clearance at Week 12^{a,b} and pathologic response in patients that were utDNA+ at baseline and had matched week 12 utDNA results (N = 30)



- Of 30 patients who were utDNA+ at baseline and had matched Week 12 utDNA results, 14 (**46.7%**) had utDNA clearance at Week 12^{b,c}
- 12 of 15 patients (**80.0%**) who were utDNA+ at baseline and achieved pCR had utDNA clearance at Week 12, compared with 2 of 15 (**13.3%**) who did not achieve pCR (Fisher's test, p=0.0006)

^a utDNA MRD was assessed by UROAmp assay (Convergent Genomics, South San Francisco, CA, USA).

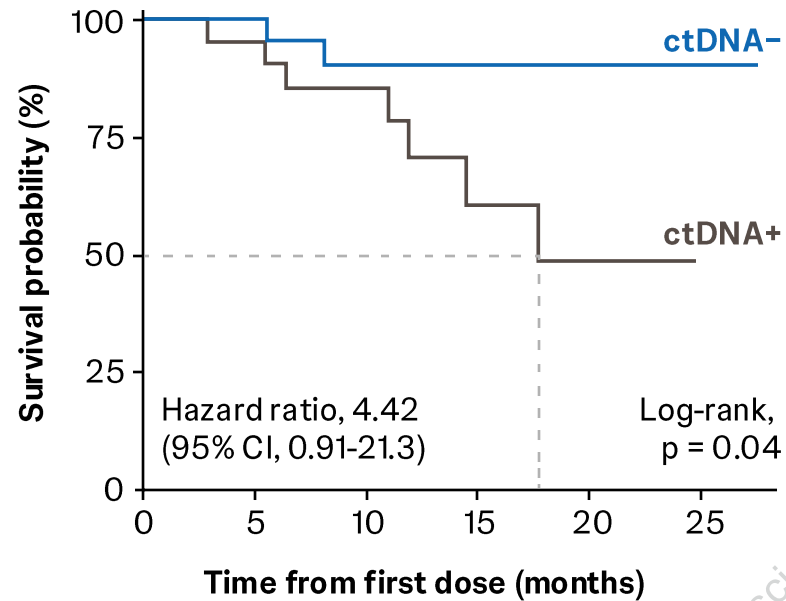
^b utDNA clearance was defined as utDNA+ status at baseline and utDNA- at week 12.

^c In Cohort 1, 7 of 18 patients (38.9%) had utDNA clearance at Week 12. In Cohort 2, 7 of 12 patients (58.3%) had utDNA clearance at Week 12.



ctDNA negative status at baseline and week 12 was associated with longer RFS

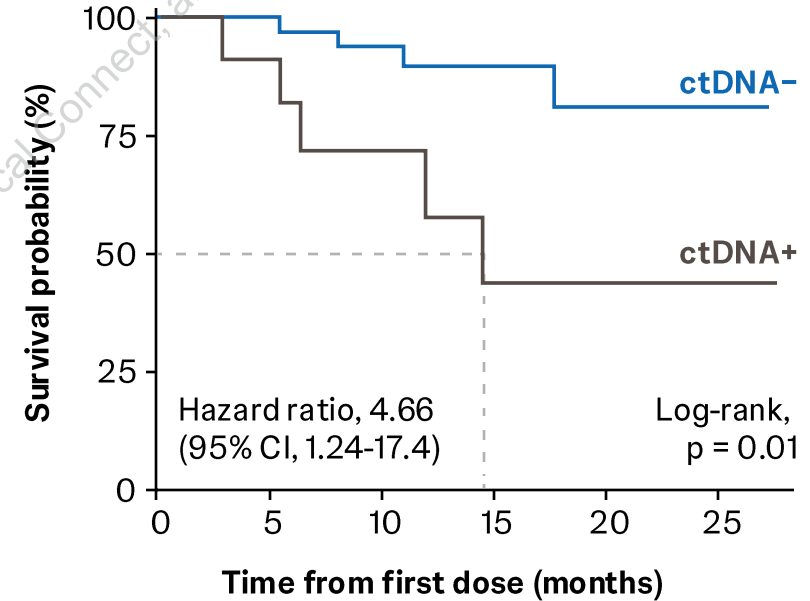
RFS by baseline ctDNA MRD status^a (N = 44)



No. at risk:

ctDNA-	22	22	17	11	5	2
ctDNA+	22	20	14	6	4	0

RFS by Week 12 ctDNA MRD status^a (N = 44)



No. at risk:

ctDNA-	32	32	25	14	7	1
ctDNA+	12	10	6	3	2	1

- Week 12 ctDNA MRD status and ctDNA clearance at Week 12 were not significantly associated with pCR (p = 0.12 and 0.15, respectively)

^a ctDNA MRD was assessed by Natera Signatera assay (Natera, Inc., Austin, TX, USA).



Conclusions

- At the primary analysis of SunRISe-4, neoadjuvant **gemcitabine intravesical system + cetrelimab** showed a high pCR rate (**38%**) and 12-month RFS rate (**77%**), supporting further investigation of the combination in MIBC
- **Cetrelimab monotherapy** showed a pCR rate (**28%**) and 12-month RFS rate (**64%**) consistent with previous studies of neoadjuvant checkpoint inhibitor monotherapy¹⁻³
- No new safety signals were observed in either treatment cohort
- Exploratory utDNA/ctDNA MRD results support further investigation as predictive biomarkers for residual disease after neoadjuvant therapy in MIBC
 - At baseline, 82% of patients with visibly complete TURBT were utDNA positive
 - **utDNA negative status** at week 12, as a potential marker of local disease, was strongly associated with **pCR**
 - **ctDNA negative status**, as a potential marker of non-local disease, was strongly associated with **longer RFS**, but not associated with pCR



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- We thank the patients who participated in the study, their families, and the investigators and clinical research staff from the study centers
- Editorial support was provided by Benjamin Ricca, PhD, of Johnson & Johnson
- This study is sponsored by Janssen Research & Development, LLC, a Johnson & Johnson company