Gemcitabine Intravesical System (Gem-iDRS) in Combination With Cetrelimab Versus Chemoradiotherapy in Muscle-Invasive Bladder Cancer: SunRISe-2 Final Results

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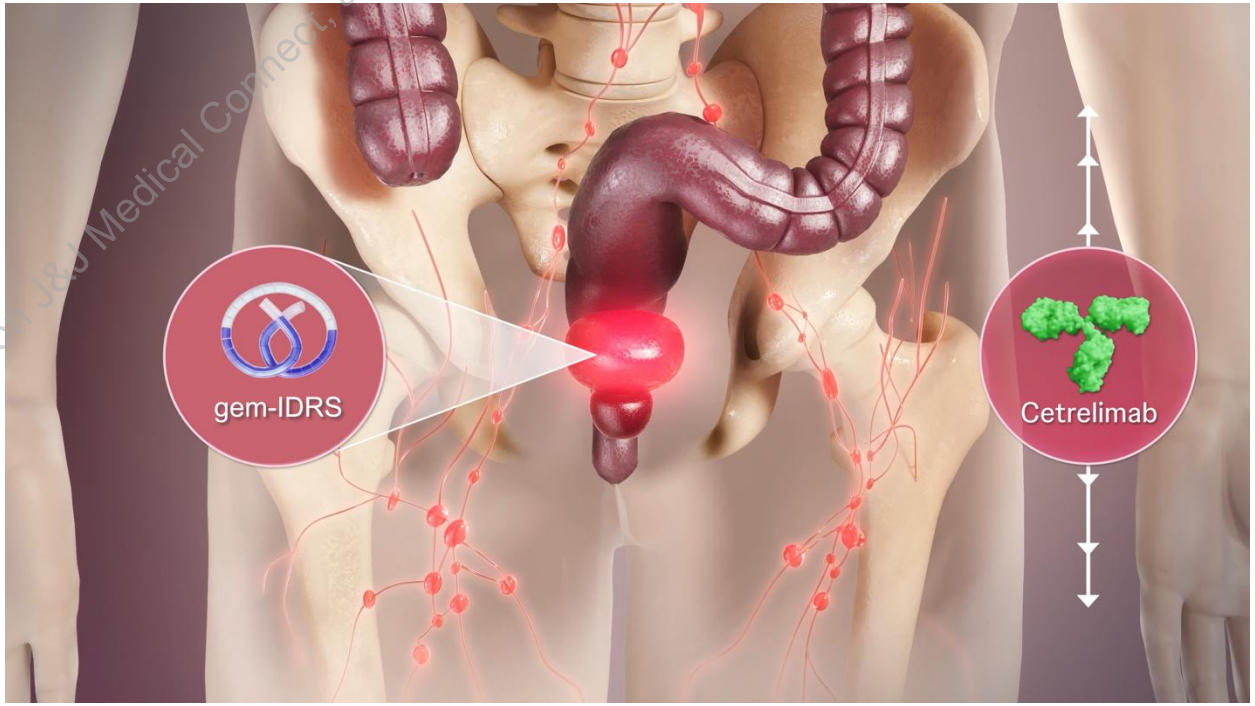
High Unmet Medical Need for Bladder-Sparing Treatments for Patients With MIBC Who Are Not Candidates for RC

- The treatment landscape of MIBC is evolving with the use of novel agents, providing new therapeutic options for cisplatin-eligible/-ineligible patients[1-3]
- However, the role of new therapies with regard to the established standard of care, CRT, is unknown
- Neoadjuvant gem-iDRS + cetrelimab demonstrated activity in the randomized phase 2 SunRISe-4 study of cisplatin-ineligible patients with MIBC[4,5]
- We report final analysis of SunRISe-2, a phase 3 superiority study of gem-iDRS + IV cetrelimab versus concurrent CRT in patients with MIBC who declined or were ineligible for RC

Gem-iDRS (gemcitabine intravesical system; previously TAR-200)

provides prolonged delivery of gemcitabine within the bladder. Gem-iDRS is approved for BCG-unresponsive HR NMIBC with CIS with or without papillary tumors[6]



Gem-iDRS is placed using a urinary placement catheter in a **brief in-office procedure**

BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; CRT, chemoradiotherapy; HR NMIBC, high-risk non–muscle-invasive bladder cancer; IV, intravenous; MIBC, muscle-invasive bladder cancer; RC, radical cystectomy.

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SunRISe-2 Study: Randomized, Controlled Superiority Design

NCT04658862

Population:
- Aged ≥18 years
- Histologically confirmed cT2-T4a, N0, M0 MIBC
- ECOG PS of 0-2
- Declined/ineligible for RC
- Adequate organ function

- Screening re-TURBT: tumor ≤3 cm; no diffuse CIS

Stratification:
- Screening re-TURBT: visibly complete vs incomplete
- Tumor stage at screening re-TURBT: T0 vs Ta/T1/Tis vs T2-T4a

R 1:1

Gem-iDRS + IV cetrelimab *Arm 1*

Gem-iDRS Q3W (21-day indwelling) for 18 weeks, followed by Q12W from Week 24 until Week 144
+ cetrelimab IV Q3W until Week 78

Concurrent CRT *Arm 2*

Investigator's choice of cisplatin (QW for 4-6 weeks) **or gemcitabine** (Q2W for 4-6 weeks) **+ RT**[a]

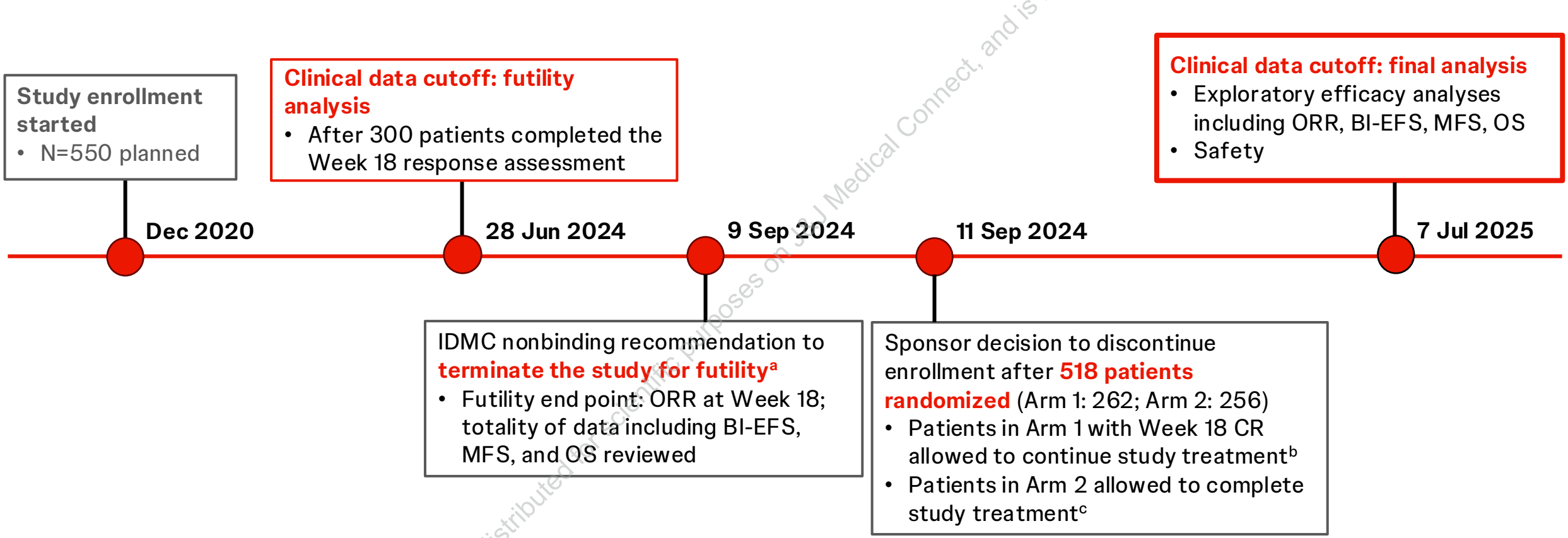
Primary end point
- BI-EFS[b]

Secondary end points
- ORR at Week 18[c]
- MFS
- OS
- Safety

- Median follow-up: 11.3 (range, 0.03-43.2) months
- The study was designed assuming a 12% absolute improvement in the 2-year BI-EFS rate, providing 90% power to detect an HR of 0.65 between treatment vs control arms using a 2-sided alpha of 0.05[d]

[a]RT was either conventional (64 Gy, bladder only) for up to 6.5 weeks or hypofractionated (55 Gy, bladder only) for up to 4 weeks. [b]Defined as any of the following: histologically proven presence of MIBC, clinical evidence of nodal or metastatic disease, RC, or death due to any cause. [c]A futility analysis based on ORR was conducted after 300 patients completed the Week 18 disease assessment. [d]Assumes a 34-month accrual, 24 months of additional follow-up, and a 5% annual dropout rate.
BI-EFS, bladder-intact event-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; MFS, metastasis-free survival; ORR, overall response rate; OS, overall survival; QW, every week; Q2W, every 2 weeks; Q3W, every 3 weeks; Q12W, every 12 weeks; R, randomization; RT, radiation therapy; TURBT, transurethral resection of bladder tumor.

SunRISe-2: Key Time Points



[a]The IDMC recommendation to continue the study was contingent on whether ORR with gem-iDRS + CET was higher vs CRT or lower vs CRT by ≤15% points. If the ORR with gem-iDRS + CET was lower vs CRT by >15% points, the IDMC would review the risks and benefits of gem-iDRS + CET to inform the nonbinding recommendation for futility. The totality of data was examined to inform the decision on termination for futility including the primary and key secondary end points. The HRs, confidence intervals around the HRs, and trends in the Kaplan-Meier curves for the efficacy end points of BI-EFS, MFS, and OS were considered to inform the decision.
[b]Participants in Arm 1 continuing on study treatment transitioned to the long-term extension phase of the study following implementation of Protocol Amendment 5.
[c]After completing study treatment, participants in Arm 2 discontinued study after the 100-day safety follow-up period.
CR, complete response; IDMC, independent data monitoring committee.

SunRISe-2: Demographics and Baseline Characteristics Were Balanced Across Treatment Arms

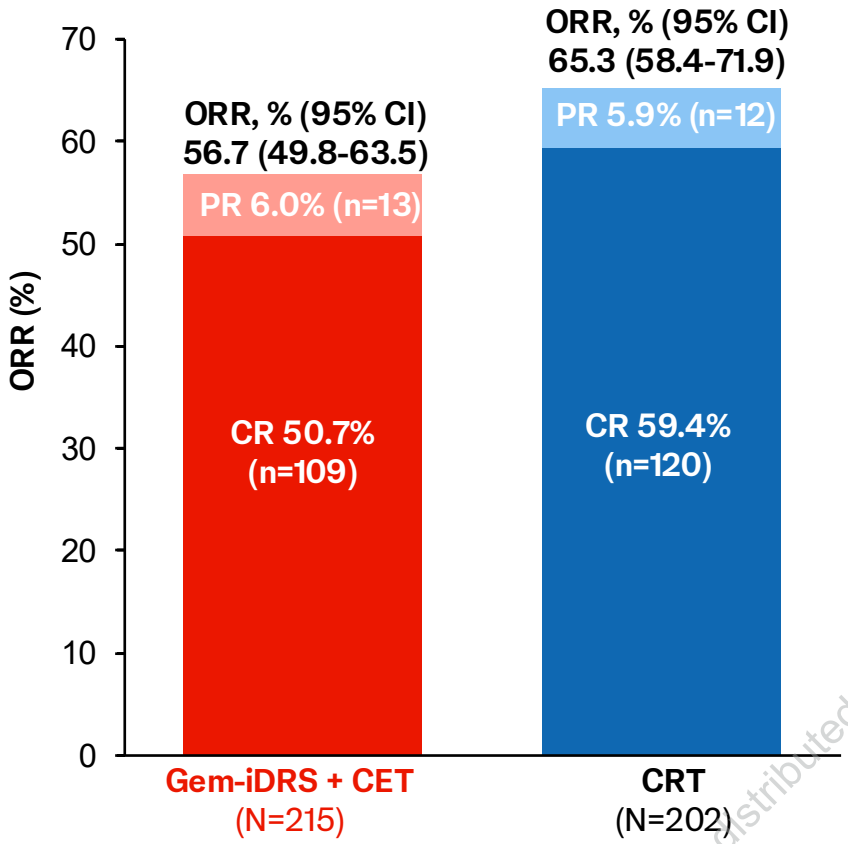
Characteristic, n (%) unless stated	Gem-iDRS + CET (N=262)	CRT (N=256)
Median age (range), years	71.0 (46-91)	72.0 (36-90)
Male	205 (78.2)	196 (76.6)
Race		
White	153 (58.4)	154 (60.2)
Asian	86 (32.8)	80 (31.3)
Other[a]	10 (3.8)	10 (3.9)
Not reported/unknown	13 (5.0)	12 (4.7)
Region		
North and South America	92 (35.1)	89 (34.8)
Europe	84 (32.1)	89 (34.8)
Asia	86 (32.8)	78 (30.5)
Nicotine use history		
Current	49 (18.7)	43 (16.8)
Former	123 (46.9)	117 (45.7)
Never	90 (34.4)	96 (37.5)
Visibly complete re-TURBT[b]	225 (85.9)	223 (87.1)

Characteristic, n (%) unless stated	Gem-iDRS + CET (N=262)	CRT (N=256)
ECOG performance status		
0	184 (70.2)	180 (70.3)
1-2	78 (29.8)	76 (29.7)
Reason for not receiving RC		
Refused	223 (85.1)	218 (85.2)
Ineligible	39 (14.9)	38 (14.8)
Tumor stage at screening re-TURBT[b,c]		
T0	107 (44.4)	91 (38.6)
Ta/T1/Tis	64 (26.6)	75 (31.8)
≥T2	70 (29.0)	70 (29.7)
Variant histology[d]	8 (3.1)	17 (7.1)
Type of radiation therapy received[e]		
Conventional (64 Gy)	N/A	156 (64.7)
Hypofractionated (55 Gy)		85 (35.3)

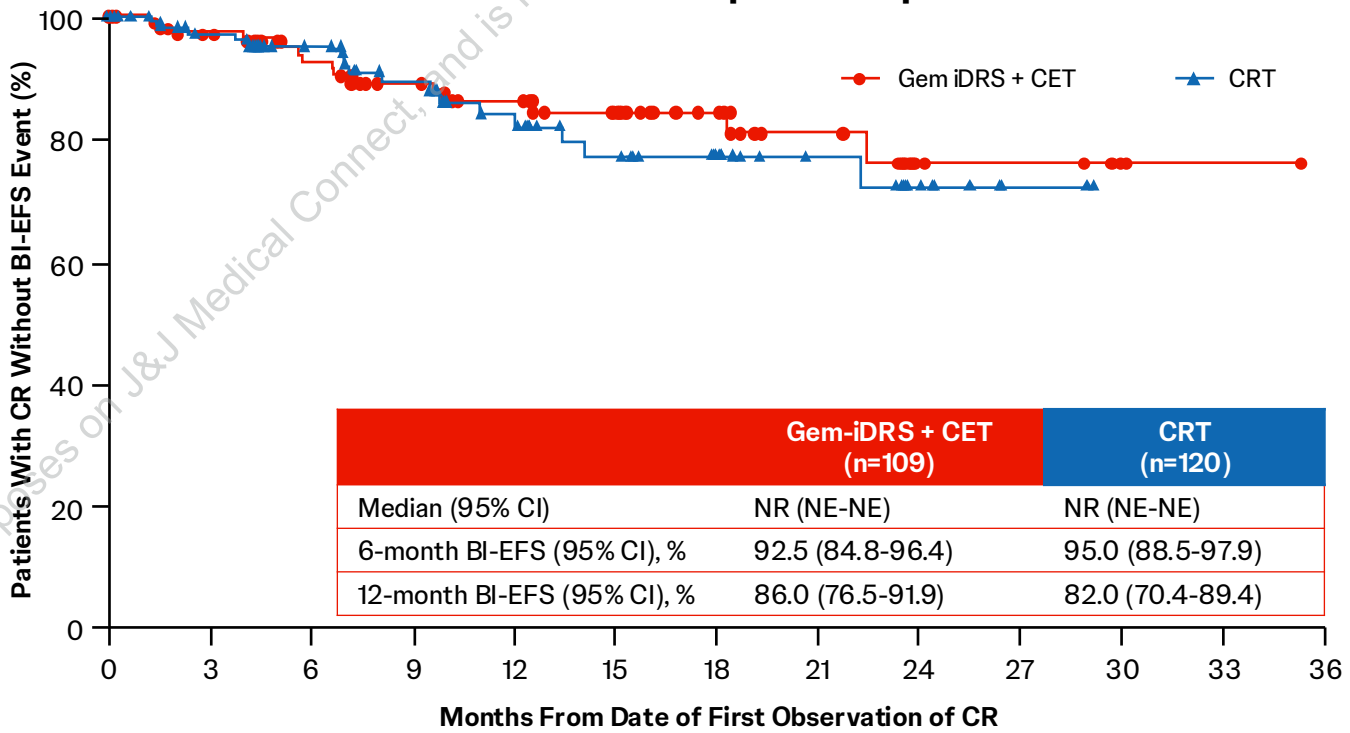
Clinical cutoff date July 7, 2025. [a]Other race includes American Indian or Alaska native, Black or African American, Native Hawaiian or Other Pacific Islander and those who reported multiple race categories.
[b]TURBT was conducted at prescreening and screening. The screening TURBT was used for stratification. [c]N=241 for gem-iDRS + CET and N=236 for CRT. [d]N=254 for gem-iDRS + CET and N=240 for CRT. [e]N=241 for CRT-treated patients.
CET, cetrelimab.

Majority of Patients in Both Arms Achieved CR at Week 18; BI-EFS Rates Were Similar in Patients With Week 18 CR

ORR at Week 18[a]



BI-EFS in complete responders



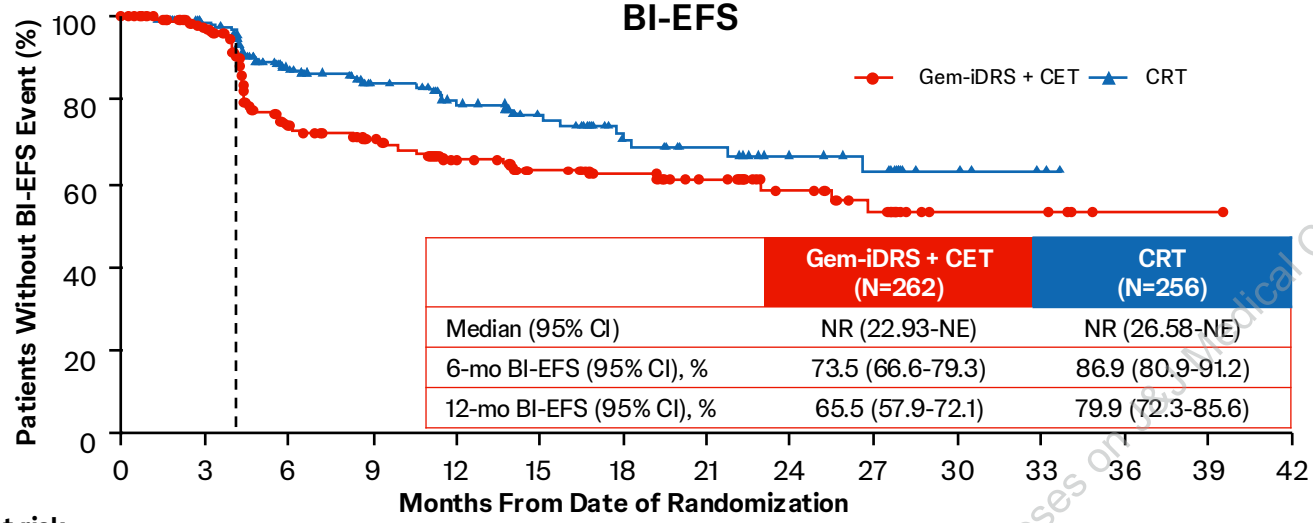
	Gem-iDRS + CET (n=109)	CRT (n=120)
Median (95% CI)	NR (NE-NE)	NR (NE-NE)
6-month BI-EFS (95% CI), %	92.5 (84.8-96.4)	95.0 (88.5-97.9)
12-month BI-EFS (95% CI), %	86.0 (76.5-91.9)	82.0 (70.4-89.4)

Patients at risk

Gem-iDRS + CET	109	94	79	64	54	44	32	19	8	7	2	1	0
CRT	120	94	74	58	40	32	25	15	7	2	0	0	0

Clinical cutoff date July 7, 2025. [a]ORR was for the evaluable analysis set that consisted of all patients who had at least 1 Week 18 efficacy assessment, had disease progression prior to or in Week 18, or discontinued the study without the Week 18 assessment. Nonresponse was reported in 93 (43.3%) patients in the gem-iDRS + CET arm and 70 (34.7%) patients in the CRT arm. BI-EFS event is defined as any of the following: histologically proven presence of MIBC, clinical evidence of nodal or metastatic disease (as assessed by RECIST 1.1 criteria), RC, or death due to any cause. Patients last known to be BI-EFS event-free were censored at the date of last assessment.
BI-EFS, bladder-intact event-free survival; CI, confidence interval; CR, complete response; CRT, chemoradiotherapy; MIBC, muscle-invasive bladder cancer; NE, not estimable; NR, not reached; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors.

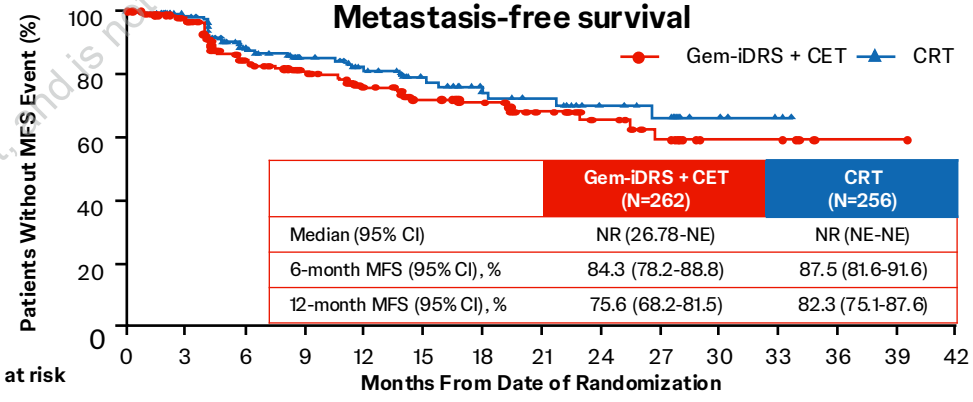
Gem-iDRS + Cetrelimab Did Not Result in Superior BI-EFS, MFS, or OS, Compared With CRT



	Gem-iDRS + CET (N=262)	CRT (N=256)
Median (95% CI)	NR (22.93-NE)	NR (26.58-NE)
6-mo BI-EFS (95% CI), %	73.5 (66.6-79.3)	86.9 (80.9-91.2)
12-mo BI-EFS (95% CI), %	65.5 (57.9-72.1)	79.9 (72.3-85.6)

Patients at risk

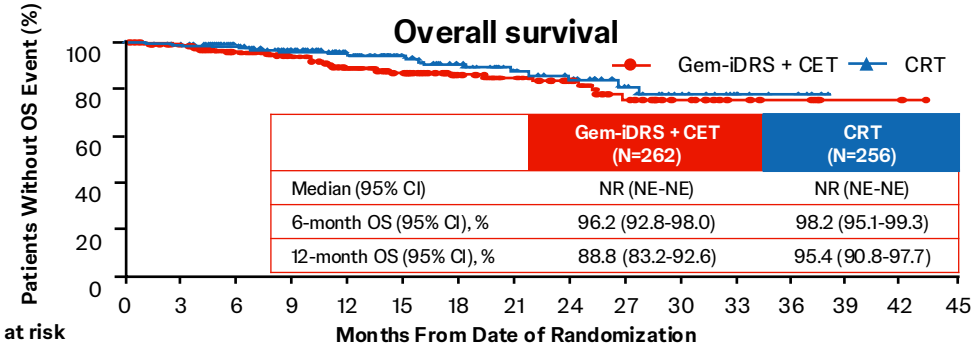
Gem-iDRS + CET	262	198	122	104	82	67	55	41	24	18	8	8	1	1	0
CRT	256	183	123	92	75	55	42	34	20	17	6	2	0	0	0



	Gem-iDRS + CET (N=262)	CRT (N=256)
Median (95% CI)	NR (26.78-NE)	NR (NE-NE)
6-month MFS (95% CI), %	84.3 (78.2-88.8)	87.5 (81.6-91.6)
12-month MFS (95% CI), %	75.6 (68.2-81.5)	82.3 (75.1-87.6)

Patients at risk

Gem-iDRS + CET	262	200	136	112	86	70	58	41	24	18	8	8	1	1	0
CRT	256	186	125	93	75	55	42	34	20	17	6	2	0	0	0



	Gem-iDRS + CET (N=262)	CRT (N=256)
Median (95% CI)	NR (NE-NE)	NR (NE-NE)
6-month OS (95% CI), %	96.2 (92.8-98.0)	98.2 (95.1-99.3)
12-month OS (95% CI), %	88.8 (83.2-92.6)	95.4 (90.8-97.7)

Patients at risk

Gem-iDRS + CET	262	239	193	156	126	106	82	67	49	33	20	11	9	2	1	0
CRT	256	236	167	127	105	82	67	51	40	28	18	10	5	0	0	0

Clinical cutoff date July 7, 2025.
BI-EFS: Vertical line at Week 18 indicates response assessment timepoint. BI-EFS event is defined as any of the following: histologically proven presence of MIBC, clinical evidence of nodal or metastatic disease (as assessed by RECIST 1.1 criteria), radical cystectomy, or death due to any cause. Patients last known to be BI-EFS event-free were censored at the date of last assessment.

MFS is defined as the time from randomization to first radiologic (as assessed by RECIST 1.1 criteria) evidence of metastatic disease or death due to any cause. Evidence of metastatic disease was determined by imaging results showing progression. Patients known to be alive and free of metastatic disease were censored at the date of last assessment.

OS is defined as the time from randomization to death from any cause. Patients who did not have an OS event were censored at the date when they were last known to be alive.

Summary of Treatment-Related Adverse Events

Patients with events, n (%)	Gem-iDRS + CET (N=254)		CRT (N=241)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
≥1 TRAE[a]	203 (79.9)	68 (26.8)	212 (88.0)	77 (32.0)
Most frequent TRAEs (reported in ≥10% of patients)				
Dysuria	66 (26.0)	1 (0.4)	47 (19.5)	1 (0.4)
Urinary tract infection	63 (24.8)	16 (6.3)	18 (7.5)	4 (1.7)
Pollakiuria	53 (20.9)	0	28 (11.6)	1 (0.4)
Hematuria	32 (12.6)	1 (0.4)	18 (7.5)	2 (0.8)
Hypothyroidism	27 (10.6)	1 (0.4)	0	0
Anemia	12 (4.7)	1 (0.4)	54 (22.4)	9 (3.7)
Fatigue	11 (4.3)	2 (0.8)	27 (11.2)	1 (0.4)
Diarrhea	11 (4.3)	1 (0.4)	69 (28.6)	5 (2.1)
Constipation	6 (2.4)	0	28 (11.6)	1 (0.4)
Asthenia	6 (2.4)	1 (0.4)	22 (9.1)	2 (0.8)
Nausea	5 (2.0)	0	49 (20.3)	0
Lymphopenia	5 (2.0)	0	21 (8.7)	19 (7.9)
Thrombocytopenia	4 (1.6)	0	67 (27.8)	7 (2.9)
Neutropenia	4 (1.6)	1 (0.4)	41 (17.0)	21 (8.7)
Decreased appetite	4 (1.6)	1 (0.4)	28 (11.6)	0
Leukopenia	0	0	41 (17.0)	15 (6.2)

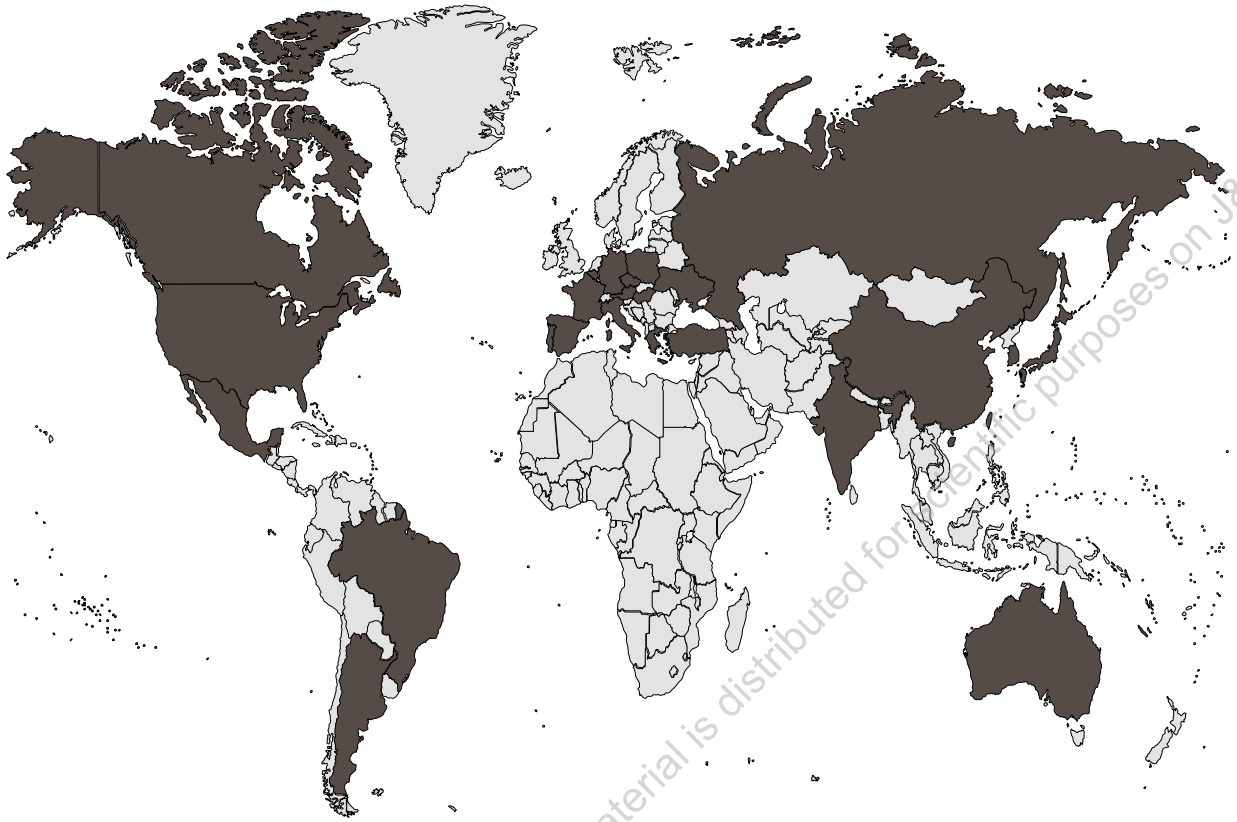
- Median (range) duration of exposure was 18.2 (1-151) weeks for gem-iDRS, 22.7 (0-82) weeks for CET, and 6.4 (0-15) weeks for CRT
- TRAEs leading to treatment discontinuation were observed in:
  - 15.0% with gem-iDRS + CET[b]
  - 9.5% with CRT[b]
- There were no treatment-related deaths with gem-iDRS + CET; 1 treatment-related death was reported in the CRT arm

Clinical cutoff date July 7, 2025.
[a]An AE is categorized as related if the investigator determines that there is a possible, probable, or causal relationship between the AE and the study treatment(s), insertion procedure, removal procedure, or the urinary placement catheter. Patients were counted only once for any given AE, regardless of the number of times they actually experienced the event. [b]The most frequent TRAEs leading to treatment discontinuation were dysuria and adrenal insufficiency (1.2% each) with gem-iDRS + CET and thrombocytopenia (1.7%) with CRT.
AE, adverse event; TRAE, treatment-related adverse event.

Conclusions

- The SunRISe-2 trial was stopped early for futility based on Week 18 ORR assessment, and the totality of efficacy data including BI-EFS, MFS, and OS
- The final analysis of SunRISe-2 showed CR rates >50% in the gem-iDRS + CET and CRT arms
  - The CR rate achieved in the gem-iDRS + CET arm is notable given the lack of a systemic cytotoxic agent utilized in that arm
  - BI-EFS rates in participants with Week 18 CRs were comparable between the 2 arms (>80% at 12 months in both arms)
- There were no unexpected safety findings

https://www.congresshub.com/Oncology/GU2026/Gem-iDRS/Necchi



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