

Baseline and On-Treatment Urinary Tumor DNA Molecular Residual Disease (utDNA MRD) and Clinical Response to Gemcitabine Intravesical System (Gem-iDRS) in SunRISe-1 (SR-1): Updated Analysis

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Key Takeaway

Despite the established poor prognosis generally associated with utDNA MRD positivity, gem-iDRS demonstrated clinically meaningful activity across both MRD+ and MRD- patients with high-risk NIMBC with CIS +/- papillary disease, differentiating it from other therapies

Conclusions

Unlike in prior studies of other agents, gem-iDRS demonstrated benefit regardless of baseline MRD status

Despite detectable utDNA at Week 12 and higher GDB scores in non-CR patients, MRD+ vs MRD- patients had similar long term-benefit

These findings corroborate the broad activity of gem-iDRS monotherapy in BCG-unresponsive CIS +/- papillary disease



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Disclosures

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Introduction

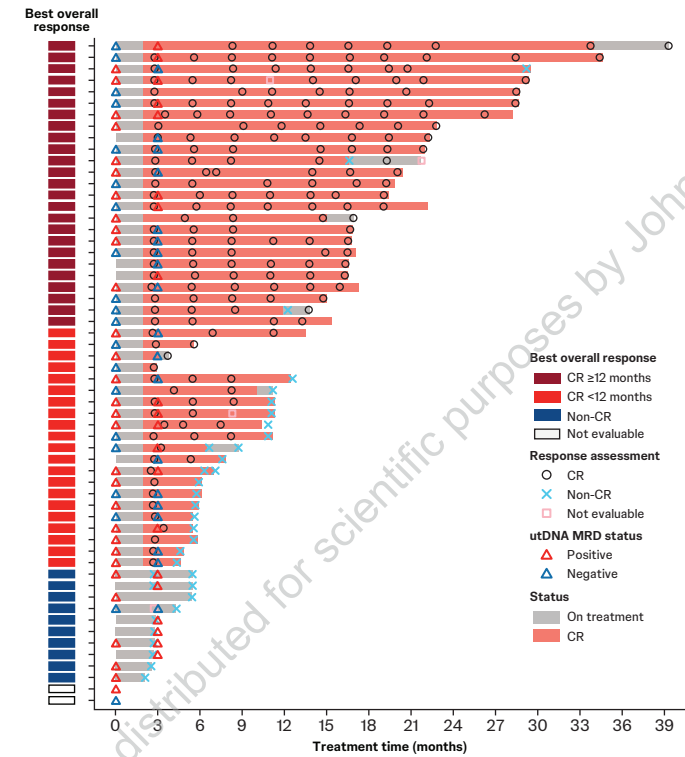
- Prior studies report baseline utDNA MRD+ rates of 40% to 70% in patients with high-risk non-muscle-invasive bladder cancer (HR NMIBC), with MRD+ status associated with significantly poorer prognosis¹⁻⁴
- Gem-iDRS is an intravesical drug-releasing system that provides prolonged gemcitabine in the bladder, approved by the US Food and Drug Administration to treat patients with bacillus Calmette-Guérin (BCG)-unresponsive HR NMIBC with carcinoma in situ (CIS) ± papillary disease^{5,6}
 - SR-1 (NCT04640623) is a phase 2b study assessing the efficacy and safety of gem-iDRS monotherapy in patients with BCG-unresponsive HR NMIBC with CIS ± papillary disease (Cohort 2) or with BCG-unresponsive papillary-only HR NMIBC (Cohort 4) (Figure 1)⁵
 - In Cohort 2, gem-iDRS showed an overall complete response (CR) rate of 82% and a favorable benefit-risk profile in patients with BCG-unresponsive CIS⁵
- We assessed baseline and Week 12 utDNA MRD status in relation to clinical outcomes with gem-iDRS treatment

Results

Overview of patients included in utDNA analysis

- This analysis included 58 patients treated with gem-iDRS monotherapy in SunRISe-1 Cohort 2 who had available utDNA MRD results at baseline or Week 12 (Figure 2)
 - 46 of 58 patients (79%) achieved a CR at any time
 - Of 46 responders, 25 had CR ≥12 months
- MRD status was available in 50 of 58 patients (86.2%) at baseline and 39 of 58 patients (67.2%) at Week 12
 - 19 patients had MRD status available at both visits

Figure 2: Response to gem-iDRS monotherapy in SunRISe-1 Cohort 2 among patients who had sequenced urine samples (N=58)



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Methods

- Pretreatment and Week 12 urine pellets (residual cytology) from SR-1 Cohort 2 were tested using UroAmp assay (Convergent Genomics)⁷
 - utDNA MRD status was classified using a locked logistic regression model with mutation profiles as input features
 - Genomic disease burden (GDB) was defined as the percentile rank of the sum of variant allele frequency of all somatic mutations in a sample among the empirical distributions of NMIBC utDNA samples
- Correlations of **MRD status** and **GDB scores** with CR, duration of response (DOR), and event-free survival (EFS) were assessed
 - CR** was defined as either (1) negative cystoscopy and negative (including atypical) urine cytology or (2) positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative (including atypical) urine cytology
 - DOR** was defined as the time from first CR to first evidence of recurrence or progression or death, whichever occurs first
 - EFS** was defined as the time from first dose to persistence/recurrence of HR NMIBC, progression, or death from any cause, whichever occurred first

Patient characteristics

- The subset of patients with available utDNA MRD results (N=58) were representative of the Cohort 2 intention-to-treat set (N=85) (Table 1)
 - Most patients were male and had CIS only (no papillary disease)

Table 1: Baseline demographics and disease characteristics

Characteristic	SunRISe-1 Cohort 2 ITT population (N=85)	Patients with utDNA MRD results (N=58)
Age, y, median (range)	71.0 (40-88)	69.5 (40-88)
Sex, male, %	80.0	82.8
Race		
White	87.1	84.5
Asian	9.4	10.3
Black or African American	2.4	3.4
Not reported/unknown	1.2	1.7
Nicotine use, %		
Current	8.2	8.6
Former	58.8	56.9
Never	32.9	34.5
ECOG PS 0, %	91.8	89.7
Tumor stage, %		
CIS only	67.1	67.2
CIS + papillary disease	32.9	32.8
Total doses of prior BCG, no., median (range)	12 (7-42)	12 (7-42)
Time from last BCG dose to CIS diagnosis, months, median (range)	3.2 (0-22.0)	3.2 (0.1-15.1)

Efficacy outcomes by baseline GDB scores and baseline utDNA MRD status

- Baseline GDB scores were not predictive of best overall response (Figure 3)
- Baseline utDNA MRD status was not statistically associated with DOR or EFS (Figure 4)

Figure 3: CR by baseline GDB scores and with baseline MRD status

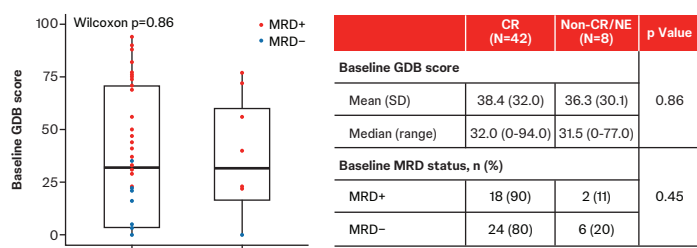
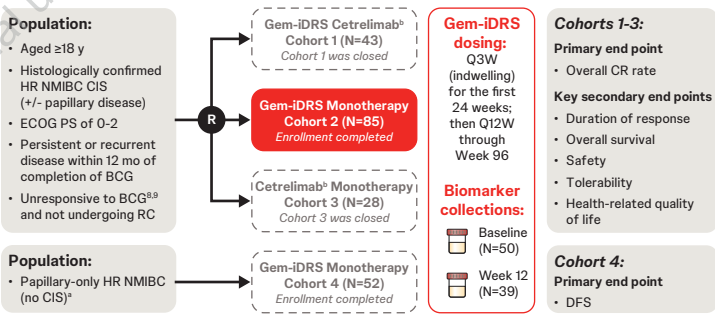
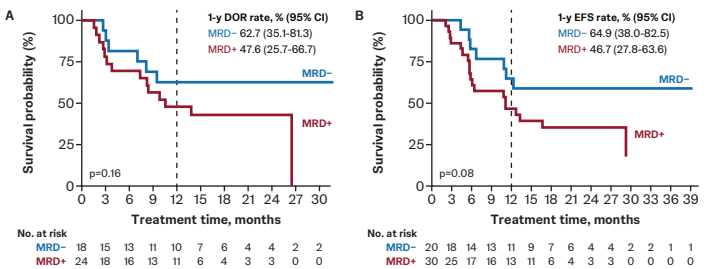


Figure 1: SunRISe-1 study design (NCT04640623)



DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; Q3W, every 3 weeks; Q12W, every 12 weeks; RC, radical cystectomy.
*Patients with BCG-unresponsive papillary-only HR NMIBC (high-grade Ta, any T1) per protocol amendment 4. *Cetrelimab is an anti-programmed cell death-1 antibody¹⁰; cetrelimab dosing was Q3W through Week 78.

Figure 4: Association of (A) DOR and (B) EFS with baseline MRD status



Efficacy outcomes by Week 12 GDB scores and Week 12 utDNA MRD status

- Week 12 GDB scores were significantly higher in patients with non-CR or in those who were not evaluable (Figure 5)
- Week 12 utDNA MRD status was not statistically associated with DOR or EFS (Figure 6)

Figure 5: CR by Week 12 GDB scores and by Week 12 MRD status

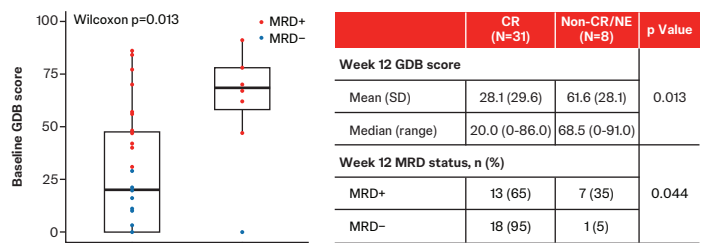
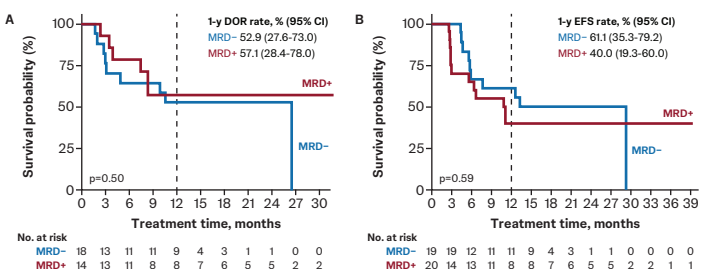


Figure 6: Association of (A) DOR and (B) EFS with Week 12 MRD status



Urothelial Cancer

