Baseline Urinary Tumor DNA, Minimal Residual Disease and Genomic Disease Burden in Relation to Clinical Response to TAR-200 in the Phase 2b SunRISe-1 Trial

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Key Takeaway

Gem-iDRS (previously TAR-200) monotherapy showed broad clinical activity in patients with BCG-unresponsive HR NMIBC with CIS independent of utDNA MRD status or GDB score

Conclusions

Baseline utDNA MRD status and genomic disease burden score were independent of patient demographics and tumor characteristics

CR rate and durability of CR were consistent in subgroups of patients who were utDNA MRD+ or utDNA MRD− at baseline

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Introduction

- For patients with high-risk non-muscle invasive bladder cancer (HR NMIBC), intravesical therapy with bacillus Calmette-Guérin (BCG) is the standard-of-care treatment[1]
  - However, one third of patients become unresponsive to BCG, with >50% experiencing recurrence and progression during long-term follow-up[2,3]
- Gemcitabine intravesical system (gem-iDRS; TAR-200) is an intravesical drug-releasing system designed to provide sustained local delivery of gemcitabine in the bladder
- Cohort 2 of the ongoing phase 2b SunRISe-1 study is assessing the efficacy and safety of gem-iDRS monotherapy in patients with BCG-unresponsive HR NMIBC with carcinoma in situ (CIS) ± papillary disease (Figure 1)
  - The primary analysis of SunRISe-1 Cohort 2 demonstrated clinically significant efficacy and a positive benefit-risk profile for gem-iDRS monotherapy[4]
- Urinary tumor DNA (utDNA) status detects minimal residual disease (MRD) with high sensitivity in patients with BCG-unresponsive NMIBC[5,6]

Objective

- To assess the baseline utDNA status and its association with response to gem-iDRS monotherapy in patients with BCG-unresponsive HR NMIBC with CIS ± papillary disease

Methods

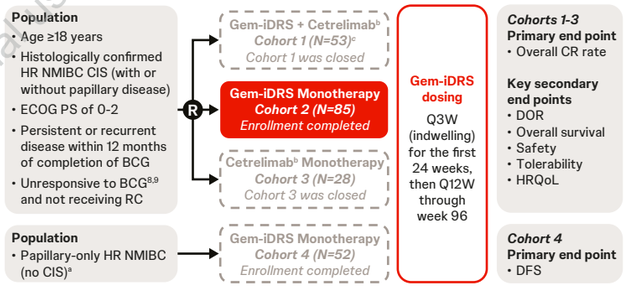
Urine-based genomic profiling:

- Urinary MRD analysis was conducted for the gem-iDRS monotherapy cohort
- Pretreatment residual urine cytology pellets were tested using UroAMP assay (Convergent Genomics, South San Francisco, CA)[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
- Genomic data from baseline urine samples were available from 41 of 85 patients in Cohort 2

Correlation with clinical outcomes:

- ***Complete response (CR)*** was defined as at least 1 of the following: (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
- Correlations of ***MRD status and GDB scores*** with CR, duration of response (DOR), and CR ≥12 months were assessed

Figure 1: SunRISe-1 study design (NCT04640623)



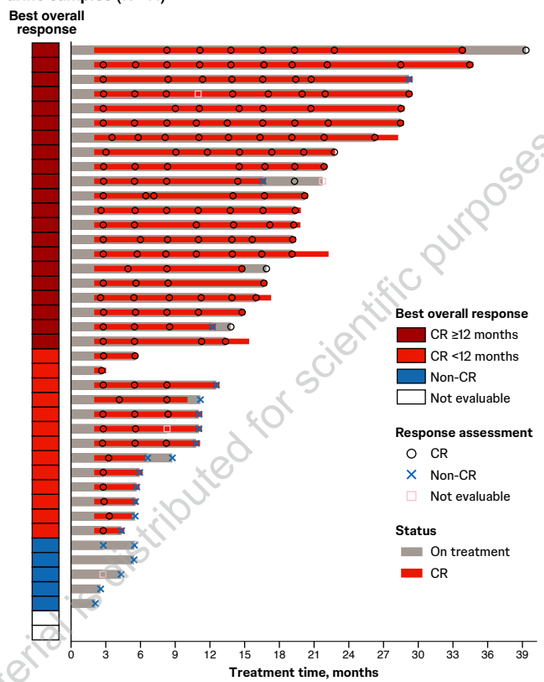
[a]Patients with BCG-unresponsive papillary-only HR NMIBC (high-grade Ta, any T1) per protocol amendment 4. [c]Cetrelimab is an anti–programmed cell-death-1 protein; cetrelimab dosing was Q3W through week 78. [c]Number of patients enrolled in Cohort 1: N=55, number of patients treated: N=53. DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRQoL, health-related quality of life; Q3W, every 3 weeks; Q12W, every 12 weeks; R, randomization; RC, radical cystectomy.

Results

Overview of patients included in utDNA analysis

- This analysis included 41 patients treated with gem-iDRS monotherapy in SunRISe-1 Cohort 2 who had available utDNA MRD results (Figure 2)
  - 34 of 41 patients (83%) achieved a CR at any time
  - Of 34 responders, 21 had CR ≥12 months

Figure 2: Gem-iDRS (Cohort 2) response in patients with sequenced urine samples (N=41)



Patient characteristics

- At baseline, 23/41 (56%) patients were utDNA MRD positive (+) and 18/41 (44%) were MRD negative (−) (Table 1)
  - Of both MRD+ and MRD− patients, the majority were male and had CIS only (no papillary disease)
  - Baseline utDNA MRD status was independent of patient demographics and disease characteristics
- Baseline GDB scores were significantly different between MRD+ vs MRD− patients (Figure 3)
  - Mean (SD) GDB scores were 58.4 (22.1) in utDNA MRD+ patients and 10.0 (12.8) in MRD− patients

Table 1: Baseline demographics and disease characteristics by utDNA MRD status and median GDB

Characteristic[a]	MRD− (N=18)	MRD+ (N=23)	GDB Score, Median (Range)
Sex, n (%)			
Male	13 (72.2)	21 (91.3)	35 (0-93.9)
Female	5 (27.8)	2 (8.7)	16 (0-75.9)
Nicotine use history, n (%)			
Current	3 (16.7)	2 (8.7)	29 (0-76.7)
Former	10 (55.6)	10 (43.5)	23 (0-93.9)
Never	5 (27.8)	11 (47.8)	50 (0-88)
ECOG PS, n (%)			
0	16 (88.9)	21 (91.3)	33 (0-93.9)
1	2 (11.1)	2 (8.7)	29 (0-82.8)
Tumor stage, n (%)			
CIS only	11 (61.1)	16 (69.6)	35 (0-90.8)
CIS + papillary	7 (38.9)	7 (30.4)	30 (0-93.9)
Total doses of prior BCG, n (%)			
≤14	15 (83.3)	13 (56.5)	29 (0-93.9)
>14	3 (16.7)	10 (43.5)	40 (3.4-2.8)
BCG strain subgroup, n (%)			
Tice	13 (72.2)	17 (73.9)	30 (0-90.8)
Non-Tice	5 (27.8)	6 (26.1)	40 (0-93.9)

[a]Across all characteristics, Fisher exact test showed no statistically significant differences between MRD+ and MRD− patients or between GDB scores (all p values >0.05).

Efficacy outcomes by baseline utDNA MRD status and GDB scores

- CR rate was 78% (18/23) in patients who were utDNA MRD+ and 89% (16/18) in patients who were utDNA MRD− (Fisher exact test, p=0.4376)
- Baseline GDB scores were not significantly different between patients with CR and those with non-CR or who were non-evaluable (mean [SD], 36.0 [30.4] vs 48.7 [32.3]) (Figure 4)
- Baseline MRD status and GDB scores were not predictive of best overall response

Figure 3: Baseline GDB vs MRD status

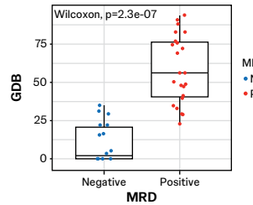
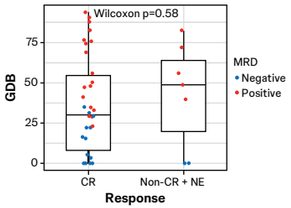


Figure 4: Baseline GDB vs response



- MRD status and GDB scores were similar between patients with CR ≥12 months vs those with CR <12 months or non-CR (Figure 5)
- 1-year DOR rate was 61.1% (95% CI, 35.3-79.2) in utDNA MRD+ patients and 64.6% (95% CI, 34.7-83.5) in utDNA MRD− patients (Figure 6)

Figure 5: Baseline GDB vs CR ≥12 months or CR <12 months/non-CR

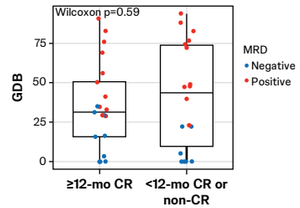
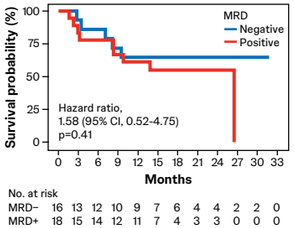


Figure 6: DOR by baseline MRD status



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