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Association of Molecular Markers With Clinical Response to TAR-200 in the Phase 2b SunRISe-1 Trial in Patients With BCG-Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC) With Carcinoma In Situ (CIS), With or Without Papillary Disease

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Key Takeaway

TAR-200 monotherapy demonstrated robust clinical efficacy in BCG-unresponsive HR-NMIBC with CIS, with outcomes largely independent of baseline genomic alterations, PD-L1 expression, or utDNA MRD status.

Conclusions

Genomic alterations, PD-L1 expression, TMB, microsatellite stability, and utDNA MRD status did not significantly influence CR or DOR to TAR-200.

The treatment showed consistent efficacy across molecular subgroups, supporting its potential as a bladder-sparing option for patients with BCG-unresponsive HR-NMIBC with CIS, with or without papillary tumors, ineligible for or refusing RC.

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Background

- TAR-200 is a novel intravesical drug-releasing system designed to provide sustained, localized delivery of gemcitabine within the bladder.[1]
- TAR-200 has been approved by the United States Food and Drug Administration (FDA) for the treatment of adult patients with Bacillus Calmette–Guérin (BCG)-unresponsive, non–muscle-invasive bladder cancer (NMIBC) presenting with carcinoma in situ (CIS), with or without papillary tumors.[1–4]
- TAR-200 is currently being evaluated in the Phase 2b SunRISe-1 study (Cohort 2; **Figure 1**), involving patients with BCG-unresponsive high-risk (HR) NMIBC, with CIS, for which radical cystectomy (RC) is not an option.[5]
- Primary analysis results showed a complete response (CR) rate of 82.4% in Cohort 2, supporting TAR-200's potential as an effective bladder-sparing therapy.[5]
- Here we evaluated baseline molecular subsets in response to TAR-200 monotherapy.

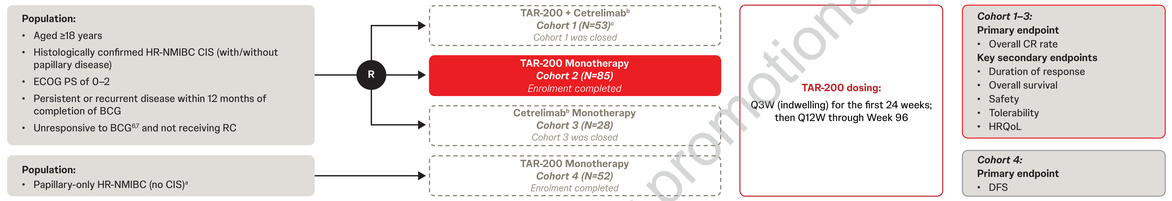
Objective

- To evaluate the association between baseline molecular and immune biomarkers (including genomic alterations, programmed death-ligand 1 [PD-L1] expression, tumor mutational burden [TMB], microsatellite instability [MSI], and urine tumor DNA [utDNA] minimal residual disease [MRD]) and clinical response to TAR-200 monotherapy in patients with BCG-unresponsive HR-NMIBC (Cohort 2 of SunRISe-1 study).

Methods

Study Design

Figure 1: SunRISe-1 study design (NCT04640623)



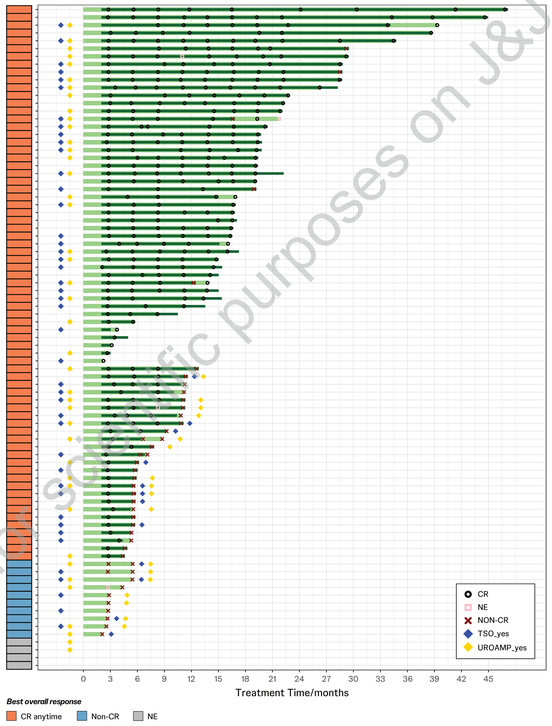
[a]Patients with BCG-unresponsive papillary-only HR-NMIBC (high-grade Ta, any T1) per protocol amendment 4. [b]Cetrelimab is an anti-programmed cell death-1; cetrelimab dosing was Q3W through Week 78. [c]Number of patients enrolled in Cohort 1 was N=55 and number of patients treated was N=53. BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; CR, complete response; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; HR-NMIBC, high-risk non-muscle-invasive bladder cancer; Q3W, every 3 weeks; Q12W, every 12 weeks; R, randomization; RC, radical cystectomy.

- **Tumor Tissue Genomic Sequencing**
  - Baseline tumor tissue samples were collected via transurethral resection of bladder tumor during screening. Genomic data were available for 44 baseline tissue samples from Cohort 2 (**Figure 1**).
  - Genomic profiling was performed using the TruSight Oncology 500 (TSO-500) panel (Omniseq Inc., USA).
- **Urine-Based Genomic Profiling**
  - Pre-treatment residual urine cytology pellets were submitted to Convergent Genomics (USA), where genomic profiling was conducted using the UroAmp assay, which evaluates 60 bladder cancer–related genes and detects MRD.
  - Genomic data were available for 41 baseline urine samples.
- **DNA profiles were available from a total of 63 baseline samples (tissue or urine), including 43 samples from CIS-only cases and 20 from cases with CIS with papillary tumors**
- **PD-L1 Expression Analysis**
  - PD-L1 expression was assessed using the 22C3 clone via immunohistochemistry at LabCorp CLS, Los Angeles and PD-L1 positivity was defined as a combined positive score ≥1.
- **Correlation With Clinical Outcomes**
  - Molecular data from tissue and urine samples were correlated with CR (primary endpoint) and duration of response (DOR) (secondary endpoint).

Results

- In Cohort 2, the CR rate was 82.4% (70/85; 95% confidence interval [CI]: 72.6%, 89.8%).
- The median duration of response (mDOR) was 25.8 months (33/70; 95% CI: 8.3, not estimable [NE]).
- Among patients with available DNA sequencing data (n=63), the CR rate was 84.1% (53/63; 95% CI: 72.7%, 92.1%) and mDOR was 25.8 months (25/51; 95% CI: 8.31, NE) (**Figure 2**).

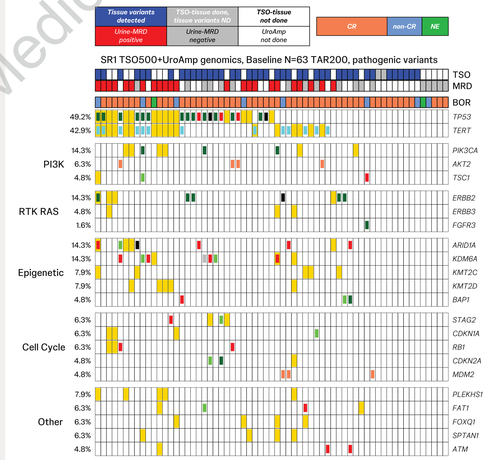
Figure 2: Overview of TAR-200 (Cohort 2) response and samples sequenced



CR, complete response; NE, not evaluable; Non-CR, non-complete response; TSO, TruSight Oncology; UroAmp, urothelial cancer molecular analysis program.

- Genomic alterations were identified in 85.7% (54/63) of tumors (**Figure 3**).
- The most frequently altered genes included:
  - *TP53*: 49.2%
  - *TERT*: 42.9%
  - *ERBB2*: 14.3%
  - *PIK3CA*: 14.3%
- All evaluable tumors (n=41) were microsatellite stable.
- High TMB (≥10 mutations/megabase) was observed in 19.5% (8/41) of tumors.

Figure 3: Genomic alterations detected



BOR, best overall response; CR, complete response; MRD, minimal residual disease; NE, not evaluable; ND, Non-CR, non-complete response; TSO, TruSight Oncology; UroAmp, urothelial cancer molecular analysis program.

- No statistically significant differences in CR or mDOR were observed across genomic subgroups (all *P*>0.05) or between PD-L1 positive vs negative groups (CR: *P*=0.64 and mDOR: *P*=0.88, respectively; **Table 1**).
- Among TMB-high tumors, the CR rate was 62.5% (5/8; 95% CI: 24.4%, 91.5%), and mDOR was not estimable (1/5).
- TMB-low tumors had a CR rate of 94% (31/33; 95% CI: 79.8%, 99.3%) and mDOR of 13.8 months (16/28; 95% CI: 7.89, NE).

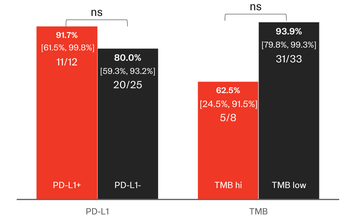
Table 1: Association of genomic findings with response

	CR rate (Event/N; [95% CI])	mDOR (Event/N; [95% CI])	
All Cohort 2	82.4% (70/85; [72.6%, 89.8%])	25.8 mo (33/71; [8.31, NE])	
DNAseq set	84.1% (53/63; [72.7%, 92.1%])	25.8 mo (25/51; [8.31, NE])	
Gene Alteration	**CR rate among altered patients (Event/N; [95% CI])**	**mDOR among altered patients (Event/N; [95% CI])**	**DOR between ALT vs WT *P* value**
TERT	81.5% (22/27; [61.9%, 93.7%])	26.5 mo (9/21; [8.34, NE])	0.24
TP53	83.9% (26/31; [66.3%, 94.5%])	26.5 mo (12/25; [8.31, NE])	0.56
ERBB2	77.8% (7/9; [40%, 97.2%])	26.5 mo (4/7; [2.92, NE])	0.68
RB1	100% (4/4; [39.8%, 100%])	26.5 mo (2/4; [9.82, NE])	0.82
ARID1A	88.9% (8/9; [51.8%, 99.7%])	8.15 mo (5/8; [2.27, NE])	0.14
KDM6A	77.8% (7/9; [40%, 97.2%])	8.28 mo (5/8; [2.27, NE])	0.55
PIK3CA	88.9% (8/9; [51.8%, 99.7%])	9.49 mo (4/7; [2.27, NE])	0.86
PD-L1 positive	91.7% (11/12; [61.5%, 99.8%])	26.5 mo (5/11; [2.79, NE])	0.88
PD-L1 negative	80.0% (20/25; [59.3%, 93.2%])	NE (8/20; [7.06, NE])	
TMB-high	62.5% (5/8; [24.4%, 91.5%])	NE (1/5; [7.06, NE])	0.81
TMB-low	94% (31/33; [79.8%, 99.3%])	13.8 mo (16/28; [7.89, NE])	

ALT, altered; CI, confidence interval; DOR, duration of response; CR, complete response; mDOR, median duration of response; mo, months; NE, not estimable; PD-L1, programmed death ligand 1; TMB, tumor mutational burden; WT, wild-type.

- Of the 37 patients tested for PD-L1 expression, 12 (32%) were PD-L1 positive, and among 41 patients with available TMB status, 8 (20%) were classified as TMB-high (**Figure 4**).
- No statistically significant differences in CR rates were observed between PD-L1 positive vs negative groups or between TMB-high vs TMB-low groups.

Figure 4: PD-L1 and TMB status and association with response

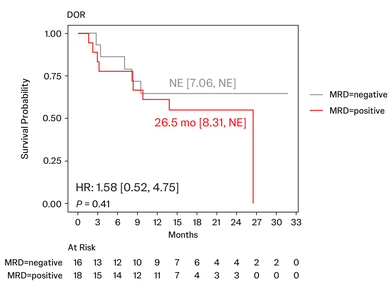


CR, complete response; hi, high; ns, not significant; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden.

- Among patients with available utDNA MRD data (n=41), MRD-positive patients (n=23) demonstrated a CR rate of 78.2% (95% CI: 56.3%, 92.5%) and a 1-year DOR rate of 64.6% (95% CI: 34.7%, 83.5%).
- In comparison, MRD-negative patients (n=18) had a CR rate of 88.9% (95% CI: 65.3%, 98.6%) and a 1-year DOR rate of 61.1% (95% CI: 35.3%, 79.2%).
- Median DOR was 26.5 months (95% CI: 8.31 mo, NE) for MRD-positive patients and NE (95% CI: 7.06 mo, NE) for MRD-negative patients.
- No statistically significant differences were observed in CR or mDOR between the two groups (*P* values: 0.82 and 0.41, respectively; **Figure 5**), with a hazard ratio for mDOR of 1.58 (95% CI: 0.52, 4.75).

Figure 5: Association of MRD status with response

	CR rate [95% CI]	*P* value	1 yr DOR rate (%) [95% CI]	*P* value
MRD-positive	78.2% [56.3%, 92.5%]	0.820	64.6% [34.7%, 83.5%]	0.41
MRD-negative	88.9% [65.3%, 98.6%]		61.1% [35.3%, 79.2%]	



CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; mo, months; MRD, minimal residual disease; NE, not estimable; yr, year.

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