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ADVANCED-1: Phase 1a Dose-finding, Open-label Study to Evaluate Safety and Toxicity of Intravesical Instillation of TARA-002 in Adults with High-grade Non-muscle Invasive Bladder Cancer

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INTRODUCTION

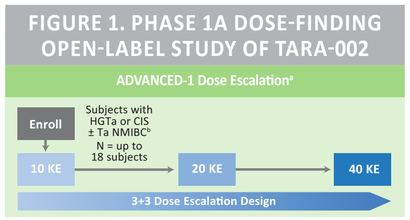
- Bladder cancer is the most common malignancy involving the urinary system, resulting in approximately 18,000 deaths each year[1]
- Bladder cancer is the 6th most common cancer in the United States, with non-muscle invasive bladder cancer (NMIBC) representing approximately 80% of bladder cancer diagnoses[2,3]
- With the current Bacillus Calmette-Guérin (BCG) shortage and limited effective alternative therapies, there remains a significant unmet need for treatment options for patients with NMIBC
- TARA-002 is a lyophilized biological preparation for instillation containing cells of *Streptococcus pyogenes* (Group A, type 3) Su strain treated with benzylpenicillin and is being developed for the treatment of high-grade NMIBC
- TARA-002 is manufactured using the same master cell bank as OK-432
- OK-432 is approved in Japan and Taiwan for the treatment of several oncology indications[4]
- The antitumor activity of TARA-002 and OK-432 is thought to occur by direct cytotoxicity and by stimulation of immunocompetent cells (including T cells and natural killer cells) through the induction of helper T-cell type-1 cytokines (including interferon gamma and various interleukins), which then recruit cytotoxic T lymphocytes to tumor cells[3,5]
- Nonclinical toxicology studies with TARA-002 support the starting dose of the Phase 1a dose-finding study (ADVANCED-1)

STUDY OBJECTIVES/ ENDPOINTS

- The purpose of this ADVANCED-1 study is to evaluate the safety and toxicity of TARA-002 and to establish the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) in the treatment of HGTa or CIS NMIBC (including CIS with concomitant Ta)
- Primary Endpoints: ADVANCED-1 Dose Escalation
  - Incidence of dose limiting toxicity (DLT) adverse events (AEs) in subjects with HGTa or CIS NMIBC (including CIS with concomitant Ta)
  - MTD and RP2D of TARA-002 in subjects with HGTa or CIS NMIBC (including CIS with concomitant Ta)

METHODS

FIGURE 1. PHASE 1A DOSE-FINDING OPEN-LABEL STUDY OF TARA-002



Abbreviations: BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; HGTa, high-grade Ta; KE, Klinische Einheit; NMIBC, non-muscle invasive bladder cancer.
[a]Subjects will receive weekly intravesical doses of TARA-002 instillation for 6 weeks.
[b]Subjects with HGTa or CIS ± Ta NMIBC who are unable to obtain intravesical BCG, received ≥ 1 dose of intravesical BCG, or received ≥ 1 dose of intravesical chemotherapy.

- ADVANCED-1 is a Phase 1a, dose-finding, open-label study of TARA-002 in adults ≥ 18 years with high-grade NMIBC (HGTa or CIS [including CIS with concomitant Ta])
- Three subjects were enrolled and treated in 3 cohorts of increasing dose levels: 10 KE, 20 KE and 40 KE (**Figure 1**)
  - Across the 3 cohorts, 9 subjects with high-grade NMIBC who were unable to receive intravesical BCG or have received ≥ 1 dose of intravesical BCG or chemotherapy, were included
- The overall study duration for each subject was 12-14 weeks (28 days of screening period; 6-week treatment period; 6-week follow-up period)
- During the study, eligible subjects received weekly intravesical doses of TARA-002 instillation for 6 weeks
  - Up to 3 dose levels were tested sequentially with 6 weekly intravesical doses, starting with the lowest dose using a 3+3 design in a dose escalation manner until the RP2D was established
- Urinary symptoms and AEs were collected throughout the study duration
- The dose escalation remains ongoing in exploratory cohorts

RESULTS

TABLE 1. OVERVIEW OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF STUDY ADVANCED-1

	TARA-002 10 KE (N=3)	TARA-002 20 KE (N=3)	TARA-002 40 KE (N=3)	Total (N=9)
Age (years) [a]				
n	3	3	3	9
Mean (SD)	72.7 (7.02)	62.0 (17.78)	76.7 (5.51)	70.4 (11.92)
Median	72.0	68.0	77.0	72.0
Min, Max	66, 80	42, 76	71, 82	42, 82
Age category n (%) [a]				
> 75	1 (33.3)	1 (33.3)	2 (66.7)	4 (44.4)
≤ 75	2 (66.7)	2 (66.7)	1 (33.3)	5 (55.6)
Sex n (%)				
Male	1 (33.3)	2 (66.7)	2 (66.7)	5 (55.6)
Female	2 (66.7)	1 (33.3)	1 (33.3)	4 (44.4)
Race n (%)				
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	3 (100.0)	3 (100.0)	3 (100.0)	9 (100.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity n (%)				
Hispanic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Hispanic	3 (100.0)	3 (100.0)	3 (100.0)	9 (100.0)
BMI (kg/m^2)				
n	3	3	3	9
Mean (SD)	30.87 (6.385)	26.80 (4.531)	27.93 (2.916)	28.53 (4.555)
Median	30.10	24.70	26.30	26.30
Min, Max	24.9, 37.6	23.7, 32.0	26.2, 31.3	23.7, 37.6
ECOG PS at Baseline n (%) [a]				
0	2 (66.7)	3 (100.0)	3 (100.0)	8 (88.9)
1	1 (33.3)	0 (0.0)	0 (0.0)	1 (11.1)
Prior Doses of Non-BCG Bladder Cancer Therapies				
Yes	2 (66.7)	2 (66.7)	1 (33.3)	5 (55.6)
No	1 (33.3)	1 (33.3)	2 (66.7)	4 (44.4)
Prior Doses of BCG Therapy				
Yes	1 (33.3)	2 (66.7)	2 (66.7)	5 (55.6)
No	2 (66.7)	1 (33.3)	1 (33.3)	4 (44.4)

Abbreviations: BCG, Bacillus Calmette-Guérin; BMI = Body Mass Index; ECOG = Eastern Cooperative Oncology Group; KE = Klinische Einheit; n = number; PS = performance status; SD = standard deviation.

- The study screened 15 participants, of which 9 participants enrolled (HGTa: 6; CIS ± Ta: 3) within 3 cohorts of increasing dose levels (10 KE, 20 KE and 40 KE), with 3 subjects per cohort (**Table 1**)
  - Median age of the participants was 72 years
  - Four participants (44.4%) were female
  - All participants were non-Hispanic and White

TABLE 2. ACTIVITY OUTCOMES OF STUDY ADVANCED-1

	Cohort 1 (10 KE, n=3)	Cohort 2 (20 KE, n=3)	Cohort 3 (40 KE, n=3)	Total (N=9)
No. of evaluable subjects	3	3	3	9
No. of HGTa	3	1	2	6
No. of CIS ± Ta	0	2	1	3
High-grade CR rate in CIS ± Ta at Week 12	NA	50% (1/2)	0% (0/1)	33% (1/3)
HGRFS in HGTa at Week 12	67% (2/3)	100% (1/1)	100% (2/2)	83% (5/6)

Abbreviations: CIS = carcinoma in situ; CR = complete response; HGTa = high-grade Ta; HGRFS = high-grade recurrence free survival; KE = Klinische Einheit; NA = not applicable.

- Three subjects with CIS reached the three-month (Week 12) activity assessment (**Table 2**)
- In Cohort 2 (20 KE cohort), 1 heavily pre-treated BCG-unresponsive participant with CIS ± Ta achieved complete response
  - In the other 2 CIS ± Ta subjects, visible tumor regression was observed
- Five of 6 subjects with HGTa achieved high-grade recurrence free survival at Week 12

TABLE 3. OVERVIEW OF INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS THROUGHOUT THE STUDY DURATION

	Cohort 1 (10 KE, n=3)	Cohort 2 (20 KE, n=3)	Cohort 3 (40 KE, n=3)	Total (N=9)
Any DLTs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAEs	3 (100.0)	2 (66.7)	3 (100.0)	8 (88.9)
Any TEAEs with CTCAE Severity Grade ≥3	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)
Any TEAEs Related to TARA-002	3 (100.0)	2 (66.7)	2 (66.7)	7 (77.8)
Any TEAEs Leading to Treatment Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAEs Leading to Study Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any Serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any Serious TEAEs Related to TARA-002	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAEs with Outcome of Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAEs Leading TARA-002 Dose Interruption	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Event; DLT = Dose Limiting Toxicity; KE = Klinische Einheit; TEAE = treatment emergent adverse event.

- Across all 3 cohorts, 8 of 9 (88.9%) subjects experienced at least one treatment emergent AE (TEAE, **Table 3**)
  - One subject experienced a TEAE with a maximum severity of Grade 3 (hypoxia after TURBT), which was not related to TARA-002
- The most commonly reported AEs were general disorders and administration site conditions (including fatigue, chills, influenza-like illness, and pyrexia) and renal and urinary disorders (bladder spasm, micturition urgency, pollakiuria, urinary tract pain, dysuria, and urinary retention)
  - These events spontaneously resolved without treatment or after the use of antipyretics/ analgesics
- No serious TEAEs, study discontinuations, or deaths occurred
- No DLTs were observed; MTD was not established

CONCLUSIONS

- In the ADVANCED-1 study, TARA-002 was generally well tolerated at all three evaluated dose levels
  - TARA-002 demonstrated a favorable safety profile for the treatment of high-grade NMIBC
- Because no DLTs were observed, an MTD was not established for TARA-002
  - Therefore, higher doses are currently being explored
    - Dose escalation remains ongoing in exploratory Phase 1a cohorts
- No serious TEAEs were observed
  - Most TEAEs resolved by the end of the study
- RP2D was determined at 40 KE for the treatment of high-grade NMIBC
- Additionally, anti-tumor activity was observed at 20 KE and 40 KE suggest that 40 KE, suggesting a therapeutically active dose at the RP2D of 40 KE

FUTURE DIRECTIONS

- Enrollment is ongoing in the open-label expansion trial (ADVANCED-1EXP) to evaluate intravesical TARA-002 at the 40 KE dose in 12 CIS ± Ta patients
- A Phase 2 study (ADVANCED-2) is ongoing to assess the anti-tumor activity and safety of TARA-002 at 40 KE in subjects with high-grade CIS NMIBC ± Ta/T1 based on prior BCG experience
  - Cohort A: BCG naive CIS ± Ta/T1 unable to access BCG or BCG exposed > 24 months prior to CIS diagnosis
  - Cohort B: BCG unresponsive CIS ± Ta/T1

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DISCLOSURE: This study is funded by Protara Therapeutics, Inc.