Poster LP166

VOLGA: Results From the Phase 3 Safety Run-In With Durvalumab (D) + Tremelimumab (T) + Enfortumab Vedotin (EV) for Cisplatin-Ineligible Muscle-Invasive Bladder Cancer (MIBC)

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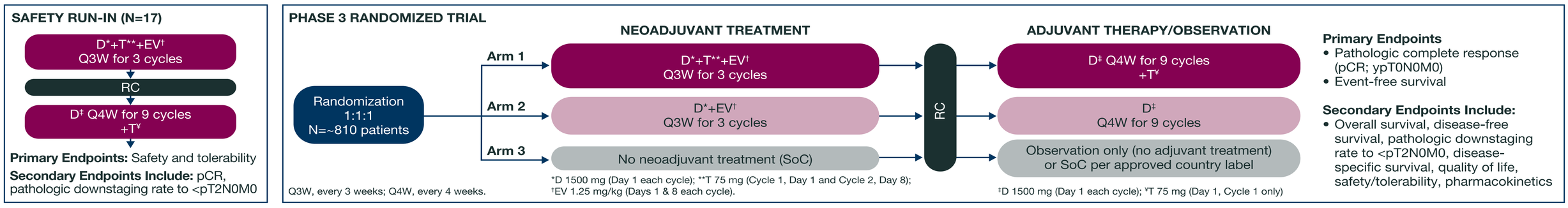
Introduction and Objective

- The standard management of MIBC involves neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (RC) and pelvic lymph node dissection.[1]
- Approximately 40% of patients with MIBC are cisplatin-ineligible[2–4]; in this patient population, RC alone remains the standard of care (SoC).[5]
- For patients who are at high risk of recurrence after radical resection, only nivolumab has been approved as adjuvant treatment[6]; therefore, to provide choice for patients and clinicians, additional treatment options are required.
- VOLGA is the first international Phase 3 study examining the novel triplet combination of D (anti-programmed death ligand-1 [PD-L1]) + T (anti-cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) + EV (antibody-drug conjugate directed against nectin-4) for cisplatin-ineligible MIBC.
- Here, we present preliminary results from the safety run-in phase of VOLGA (NCT04960709).

VOLGA Safety Run-In and Phase 3 Study Design



Q3W, every 3 weeks; Q4W, every 4 weeks.

*D 1500 mg (Day 1 each cycle); **T 75 mg (Cycle 1, Day 1 and Cycle 2, Day 8); †EV 1.25 mg/kg (Days 1 & 8 each cycle).

‡D 1500 mg (Day 1 each cycle); ¥T 75 mg (Day 1, Cycle 1 only)

Eligibility Criteria

Key Inclusion Criteria

- Aged ≥18 years, with histologically or cytologically documented MIBC (urothelial and mixed urothelial histology).
- Clinical stage of T2–4aN0-N1M0 including T1N1M0.
- Cisplatin-ineligible, as defined by Galsky et al 2011[7] criteria OR refused cisplatin-based chemotherapy (documented in medical records).
- Medically fit for cystectomy and able to receive neoadjuvant therapy.
- No prior systemic chemotherapy or immunotherapy for treatment of MIBC.
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or 2.
- Availability of tumor sample prior to study entry.

Key Exclusion Criteria

- Evidence of lymph node (N2+) or metastatic disease.
- Active infection or uncontrolled intercurrent illness.
- Prior exposure to immune-mediated therapy (bacillus Calmette-Guérin excluded), including but not limited to other anti–CTLA-4, anti–PD-1, anti–PD-L1, or anti–PD-L2 antibodies.
- Current/prior use of immunosuppressives within 14 days before the first dose of investigational product.

Participating Countries in VOLGA Trial

- Argentina
- Austria
- Brazil
- Canada
- Chile
- Columbia
- France
- Germany
- Greece
- Hong Kong
- Israel
- Italy
- Japan
- Mexico
- The Netherlands
- Poland
- Portugal
- Republic of Korea
- Russian Federation
- Serbia
- **Spain***
- Taiwan
- Thailand
- Turkey
- Ukraine
- United Kingdom
- **United States***
- Vietnam

*Safety run-in participant countries.

Results

- At the data cutoff, August 2022, 17 patients had participated in the safety run-in (**Table 1**).

Table 1. Demographic and Baseline Characteristics

Baseline characteristics (N=17)*	n (%), unless otherwise stated
Age, median (range), y	75 (50–83)
Male	16 (94.1)
ECOG PS	
0	8 (47.1)
1	8 (47.1)
2	1 (5.9)
Tumor stage	
T2	7 (41.2)
T2a	3 (17.6)
T2b	3 (17.6)
T3	2 (11.8)
T4a	2 (11.8)
Regional lymph nodes	
N0	15 (88.2)
N1	2 (11.8)
Metastases	
M0	17 (100)
Cisplatin ineligibility	
Hearing loss only	12 (70.6)
Creatinine clearance <60 mL/min	4 (23.5)
ECOG PS 2	1 (5.9)

*Patients from the safety run-in who had been treated with D+T+EV.

Preliminary Summary of Safety

- Overall, 17 patients experienced an adverse event (AE) (**Table 2**). The most common AEs were dry mouth, fatigue, or maculopapular rash (each n=9 [52.9%]), dysgeusia (n=8 [47.1%]), and pruritus (n=7 [41.2%]).
- Grade 3 or 4 AEs were experienced by 12 patients (70.6%) (**Table 2**).
- In total, 16 patients (94.1%) experienced ≥1 treatment-related AE (TRAE) (**Table 2**) — 8 patients (47.1%) had Grade 3 or 4 TRAEs, and no Grade 5 TRAEs occurred.

Table 2. Adverse Events

All values reported are n (%)	N=17
Any grade AE	17 (100)
Any grade 3/4 AE	12 (70.6)
Any serious AE	10 (58.8)
Any serious TRAE	5 (29.4)
Any D/T AE of special/possible interest	14 (82.4)
Immune-mediated AE	12 (70.6)
Any AE leading to discontinuation of any study medication	2 (11.8)
Any AE leading to dose interruption of any study medication	4 (23.5)
AE leading to dose delay	
Durvalumab	5 (29.4)
Enfortumab vedotin	6 (35.5)
AE leading to dose reduction	
Enfortumab vedotin	5 (29.4)
AE leading to death	0
Any TRAE (possibly related to any study medication)	16 (94.1)
TRAEs occurring in ≥15% of patients	
Fatigue	9 (52.9)
Maculopapular rash	9 (52.9)
Dysgeusia	8 (47.1)
Dry mouth	7 (41.2)
Pruritus	6 (35.3)
Alopecia	5 (29.4)
Peripheral sensory neuropathy	5 (29.4)
Aspartate aminotransferase increased	4 (23.5)
Constipation	4 (23.5)
Hyperthyroidism	4 (23.5)
Nausea	4 (23.5)
Hypothyroidism	3 (17.6)

Preliminary Summary of Activity

Neoadjuvant phase

- A total of 13 patients completed the 3 cycles of neoadjuvant treatment.
- Median treatment duration was 66 days for durvalumab, 57 days for tremelimumab, and 69 days for enfortumab vedotin.
- RC was performed in 14 patients; all RC procedures were completed in the protocol-specified time frame of ≥14 days to 56 days after last dose of neoadjuvant therapy.
- 3 patients did not undergo RC due to either experiencing an AE (n=2) or progression prior to RC (n=1).

Post-RC

- At the time of data cutoff, no evidence of systemic disease was shown in 13 of 14 patients post-cystectomy.
- pCR was achieved in 6 patients, and 9 patients achieved pathologic non-muscle invasive response <pT2N0M0 (**Table 3**).

Table 3. Pathologic State at Radical Cystectomy

Patient	Baseline clinical stage	RC	Pathologic stage	pCR	Pathologic non-muscle invasive response (<pT2 N0 M0)
1	T2 N0 M0	YES	pT0 pN0 M0	YES	YES
2	T2 N0 M0	YES	pT0 pN0 M0	YES	YES
3	T2 N0 M0	YES	pT0 pN0 M0	YES	YES
4	T2 N0 M0	YES	pTis pN0 M0	–	YES
5	T2 N0 M0	YES	pT1 pN0 M0	–	YES
6	T2 N0 M0	YES	pT2b pN0 M0	–	–
7	T2a N0 M0	YES	pT0 pN0 M0	YES	YES
8	T2a N0 M0	YES	pT3b pN2 M0	–	–
9	T2b N0 M0	YES	pT0 pN0 M0	YES	YES
10	T2b N0 M0	YES	pTa pN0 M0	–	YES
11*	T2b N1 M0	YES	pTa pN1 M0	–	–
12	T3 N0 M0	YES	pT3b pN0 M0	–	–
13	T4a N0 M0	YES	pT2a pN1 M0	–	–
14	T4a N1 M0	YES	pT0 pN0 M0	YES	YES
15	T2 N0 M0	NO	–		–
16	T2a N0 M0	NO	–		–
17	T3 N0 M0	NO	–		–

*Patient had pathologic downstaging but did not achieve <pT2N0M0.

Conclusions

- The results from the VOLGA safety run-in support continued evaluation of the triplet regimen of D+T+EV in patients with cisplatin-ineligible MIBC.
- 3 neoadjuvant cycles were completed by 13/17 patients, and among patients undergoing cystectomy, no delays in time to RC were experienced.
- The safety profile of 3 cycles of neoadjuvant D+T+EV, followed by D+T post cystectomy, was manageable.
  - The most common TRAEs occurring in >30% of patients were fatigue, maculopapular rash, dysgeusia, dry mouth, and pruritus.
  - Grade 3/4 AEs were experienced by 12 patients; no Grade 5 events were reported; 2 patients experienced AEs leading to treatment discontinuation.
- Preliminary activity was observed, with 6/17 patients achieving pCR and 9/17 patients achieving pathologic non-muscle invasive response—though given the small population, results should be interpreted with care.
- Enrollment has opened for the randomized Phase 3 portion of VOLGA, for patients with MIBC who are ineligible for, or refuse, cisplatin-based chemotherapy.

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