EFFICACY AND SAFETY OF ATEZOLIZUMAB CONCURRENT WITH RADIOTHERAPY IN PATIENTS WITH MUSCLE-INVASIVE BLADDER CANCER: AN INTERIM ANALYSIS OF THE ATEZOBLADDERPRESERVE PHASE II TRIAL (SOGUG-2017-A-IEC(VEJ)-4)

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BACKGROUND

- Bladder cancer is the ninth most diagnosed cancer in the world, with around 614,000 new cases and 220,000 deaths in 2022[1]. While radical cystectomy (RC) remains the standard of care for patients with **muscle-invasive bladder cancer** (MIBC), the 5-year survival rate following RC remains suboptimal, standing at 50% [2, 3].
- **Combined-modality treatments (CMTs)** are bladder-preserving alternatives for patients who are not candidates for RC due to medical reasons, refusal, or patient's choice (4). CMTs combine maximal transurethral resection (TUR) of bladder tumor, radiotherapy (RT), and concurrent chemotherapy[4, 5]. Emerging immune therapies seem to enhance tumor-specific immune responses induced by RT[6, 7].
- **Atezolizumab**, a monoclonal antibody, targets programmed death-ligand 1 (PD-L1), blocking its immune-suppressive effect. The combination of RT with anti-PD-1/PD-L1 shows promising efficacy with acceptable toxicity in invasive BC[8].
- Here, we present an **interim analysis** of the ongoing **ATEZOBLADDERPRESERVE** study evaluating the **efficacy and safety of atezolizumab concurrent with external beam RT** (EBRT) for treating MIBC as bladder preservation therapy.

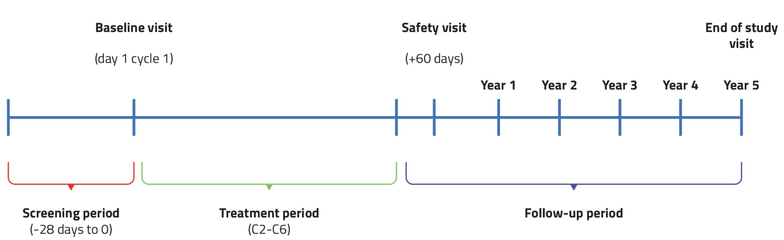
OBJECTIVES

- The **primary objective** of the study is to evaluate the efficacy of atezolizumab with concurrent EBRT in terms of the pathological complete response (pCR).
- The **secondary objectives** include the assessment of atezolizumab safety profile and the evaluation of the cystectomy rate.

METHODS

- **ATEZOBLADDERPRESERVE** is an open, multicenter, phase II trial conducted in 10 sites in Spain.
- **Inclusion/exclusion criteria:** this study enrolled consenting adults (≥18 years) diagnosed with MIBC in clinical stages cT2-T4a N0 M0 and with ECOG performance status 0 to 2 who were not candidates for RC due to medical reasons, refusal, or patient's choice, and who were unfit to receive cisplatin-based chemotherapy. Patients were excluded if they had received prior RT at the bladder, systemic chemotherapy, or immune checkpoint inhibitors.
- The study comprises a 28-day screening period, a treatment phase, and a five-year post-treatment follow-up, including a safety visit involving a biopsy one to two months after the last administration of atezolizumab (**Figure 1**).
- **Treatment** entails six doses of **atezolizumab** (1200 mg intravenously every three weeks) from day 1 of **EBRT** and 60 Gy of EBRT in 30 fractions over six weeks at 2 Gy/day.
- An **interim analysis** (data cut-off: October 2023) on the primary endpoint encompassing data from the screening to the safety visits has been conducted. The primary endpoint is pCR, defined as a grade 5 response according to Miller and Payne criteria one to two months after the last dose of atezolizumab. The incidence of adverse events (AEs) and serious AE (SAEs) and the cystectomy rate have been secondarily assessed.

Figure 1. Study design overview



RESULTS

- Between September 2019 and October 2023, 59 patients were screened, of whom 20 were excluded for non-compliance with eligibility criteria (15 patients), consent withdrawal (6 patients), and AE (1 patient). Thus, the evaluable population consisted of 39 patients.
- Baseline demographics and clinical characteristics are outlined in **Table 1**. Notably, **84.6% of patients were ≥75 years old, 94.9% had at least one previously diagnosed clinically significant condition, 61.5% had prior surgery, and all of them were receiving concomitant medication**.

Table 1. Baseline sociodemographic and clinical characteristics of evaluable patients (N=39)

Patient characteristics	Value
Age, median (IQR), years	79.7 (76.5-85.4)
≥75 years old, n (%)	33 (84.6)
Gender, female, n (%)	14 (35.9)
Race, Caucasian, n (%)	38 (97.4)
Smoking habits, n (%)[1]	
Current smoker	7 (19.4)
Ex-smoker	18 (50.0)
Non-smoker	11 (30.6)
Age at diagnosis, median (IQR), years[2]	79.6 (76.5-85.3)
Histological grade, n (%)	
G2	9 (23.1)
G3	20 (51.3)
Gx	4 (10.3)
ECOG, n (%)[3]	
0	18 (47.4)
1	10 (26.3)
2	10 (26.3)
TNM classification, n (%)[3]	
T2a N0 M0	23 (59.0)
T2b N0 M0	10 (25.6)
T3a N0 M0	3 (7.7)
T3b N0 M0	1 (2.6)
T4a N0 M0	1 (2.6)
Patients with previous clinically significant condition, n (%)	37 (94.9)
Patients with prior surgery, n (%)	24 (61.5)
Patients receiving concomitant medication, n (%)	39 (100.0)

ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range. Data at screening period unless otherwise stated; [1]missing data, n=3; [2]missing data, n=2; [3]missing data, n=1.

Efficacy

- **All 26 (100%) patients with pathological assessment at the safety visit achieved pCR.**
  - From the remaining 13 patients, seven patients did not undergo pathological assessment during the safety visit, and six patients did not attend the safety visit: three patients withdrew, one patient did not attend the safety visit on time, one died due to an SAE, and another died due to an SAE related to atezolizumab (acute kidney injury).
- At the safety visit, cystectomy was not performed in any patient with available data.

Safety

- Thirty-seven (94.9%) patients experienced at least one AE. The most frequently observed adverse events were asthenia (21 patients), diarrhea (17 patients), and dysuria (13 patients).
- AEs related to EBRT occurred in 24 (61.5%) patients and those related to atezolizumab in 21 (53.8%).
- Thirteen (33.3%) patients experienced at least one SAE, including renal failure in three patients and bacteremia, COVID-19 infection, respiratory infection, urosepsis, acute kidney injury, general physical health deterioration, pyrexia, hepatic ischemia, hepatotoxicity, ischemic cardiomyopathy, rectal hemorrhage, and prostatitis in one. One (2.6%) patient had at least one SAE related to EBRT, and three (7.7%) patients reported SAEs related to atezolizumab.
- AEs leading to treatment discontinuation occurred in one (2.6%) patient and AEs leading to death in two (5.1%), in one of them related to atezolizumab (acute kidney injury).

Table 2. Safety of atezolizumab concurrent with EBRT (N=39 patients)

Safety variables	N (%)
Patients with at least one AE	37 (94.9)
Related to atezolizumab	21 (53.8)
Grade 1	16 (41.0)
Grade 2	13 (33.3)
Grade 3	2 (5.1)
Grade 5	1 (2.6)
Related to EBRT	24 (61.5)
Grade 1	17 (43.6)
Grade 2	15 (38.5)
Grade 3	1 (2.6)
Patients with at least one SAE	13 (33.3)
Related to atezolizumab	3 (7.7)
Related to EBRT	1 (2.6)
Patients with at least one AE of special interest	2 (5.1)
Patients with at least one AE leading to treatment discontinuation	1 (2.6)
Patients with at least one AE leading to death	2 (5.1)
Related to atezolizumab	1 (2.6)

AE: adverse event; EBRT: external beam radiotherapy; SAE: serious adverse event. Data is expressed in number of patients.

CONCLUSIONS

- Interim results in a sample of Spanish patients suggest that atezolizumab combined with EBRT seems to be effective in achieving pCR in a **vulnerable elderly population with multiple comorbidities**. The safety profile appears manageable.
- The final analysis of this study will provide valuable insights into the effect of atezolizumab with EBRT on clinical outcomes, such as survival, in addition to updated safety data.

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