available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Urothelial Cancer

# Atezolizumab in Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma: Clinical Experience from an Expanded Access Study in the United States

*Sumanta Kumar Pal*[a,*], *Jean Hoffman-Censits*[b], *Hanzhe Zheng*[c], *Constanze Kaiser*[c], *Darren Tayama*[c], *Joaquim Bellmunt*[d,*]

[a] *City of Hope Comprehensive Cancer Center, Duarte, CA, USA;* [b] *Sidney Kimmel Cancer Center at Jefferson, Philadelphia, PA, USA;* [c] *Genentech, Inc., South San Francisco, CA, USA;* [d] *Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA*

**Article info**

***Article history:***
Accepted February 8, 2018

***Associate Editor:***
James Catto

***Keywords:***
Atezolizumab
Expanded access program
Immunotherapy
Urothelial carcinoma

**Abstract**

***Background:*** Atezolizumab (anti–programmed death-ligand 1) was approved in the USA, Europe, and elsewhere for treatment-naive and platinum-treated locally advanced/metastatic urothelial carcinoma (mUC).
***Objective:*** To report efficacy and safety from an atezolizumab expanded access study.
***Design, setting, and participants:*** This single-arm, open-label study enrolled 218 patients at 36 US sites. Key eligibility criteria included progression during/following ≥1 platinum-based chemotherapy for mUC or in perioperative setting (progression within 12 mo) and Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2.
***Intervention:*** Patients received atezolizumab1200 mg intravenously every 3 wk until loss of clinical benefit, unacceptable toxicity, consent withdrawal, decision to discontinue, death, atezolizumab commercial availability, or study closure.
***Outcome measurements and statistical analysis:*** Key end points reported herein included Response Evaluation Criteria in Solid Tumors v1.1 objective response rate and duration, disease control rate (DCR; response or stable disease), and safety.
***Results and limitations:*** All patients received prior systemic therapy (68% mUC; 27% adjuvant; and 26% neoadjuvant). At baseline, 57% of 214 treated patients had ECOG PS ≥1, 19% had hemoglobin <10 g/dl, and 25% had liver metastases. Median treatment duration was 9 wk (interquartile range [IQR], 6–12 wk). Median follow-up duration was 2.3 mo (IQR, 1.6–3.4 mo) overall and 2.7 mo (IQR, 2.0–3.5 mo) in patients not known to have died. Seventeen of 114 evaluable patients (15%) had objective responses (16 ongoing at study termination). DCR was 49%. Treatment-related adverse events (mostly fatigue) occurred in 98 of 214 treated patients.
***Conclusions:*** The benefit/risk profile of atezolizumab was consistent with that observed in previous studies, despite pretreatment and poor prognostic factors. These results suggest a potential role for atezolizumab in a broader patient range than typically eligible for phase 1–3 studies.
***Patient summary:*** In this expanded access study, atezolizumab was active and tolerable in a range of patients with platinum-treated metastatic urothelial carcinoma.

* Corresponding author. City of Hope Comprehensive Cancer Center, Department of Medical Oncology and Therapeutics Research, 1500 East Duarte Road, Duarte, CA 91010, USA. Tel. +1 626 2564673; Fax: +1 626 3018233 (S.K. Pal); Dana-Farber Cancer Institute, Department of Medicine, Da 1061, 44 Binney St, Boston, MA 02115, USA. Tel. +1 617 6323237 (J. Bellmunt).
E-mail addresses: spal@coh.org (S.K. Pal), joaquim_bellmunt@dfci.harvard.edu (J. Bellmunt).

https://doi.org/10.1016/j.eururo.2018.02.010


Please cite this article in press as: Pal SK, et al. Atezolizumab in Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma: Clinical Experience from an Expanded Access Study in the United States. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.02.010

## 1. Introduction

Patients with advanced urothelial carcinoma (UC) have poor prognoses and low overall survival (OS) rates of >5 yr. Although cisplatin- or carboplatin-based chemotherapy can prolong OS, progression is typically inevitable [1–6]. No global treatment standard exists in postplatinum setting, with vinflunine approved in Europe and taxanes commonly used in the USA [2,3], with modest survival outcomes [7,8]. More recently, cancer immunotherapy approvals have altered advanced and metastatic UC (mUC) management [2,9–13]. Data from diverse study settings can collectively help shape the evolving body of immunotherapy data, helping inform treatment decisions and making treatments more accessible to a wider range of patient populations.

Atezolizumab, a humanized engineered monoclonal antibody, selectively targets anti–programmed death-ligand 1 (PD-L1) [14]. By preventing PD-L1 from binding to its receptors programmed death-1 (PD-1) and B7.1, atezolizumab can reinvigorate and enhance anticancer immunity [14,15]. Additionally, atezolizumab leaves the PD-L2/PD-1 interaction intact, potentially preserving immune homeostasis [15]. In patients with inoperable locally advanced UC or mUC, atezolizumab has demonstrated durable objective responses and good tolerability in phase 1–3 studies [16–19], leading to US and European approvals for the treatment of patients who have progressed during or following platinum-based chemotherapy and those ineligible for cisplatin-containing chemotherapy [9,20]. Atezolizumab has also demonstrated clinical benefit in other cancers and has been approved for non–small cell lung cancer [9,14].

Following initial phase 1 and 2 data demonstrating encouraging clinical benefit for atezolizumab in mUC, an expanded access study was initiated in the USA. The objective of this program was to grant patients with platinum-treated mUC access to atezolizumab before US Food and Drug Administration (FDA) approval for this indication. The study ended upon approval. Here, we describe initial clinical activity and safety findings.

## 2. Patients and methods

### 2.1. Study design, patients, and procedures

This expanded access study (ClinicalTrials.gov identifier NCT02589717) was designed to provide atezolizumab to patients with mUC that had progressed during or following platinum-based chemotherapy. This single-arm, open-label study was designed to enroll approximately 200 patients at 40 US centers and was conducted in accordance with the Declaration of Helsinki and International Conference of Harmonisation Good Clinical Practice guidelines. The protocol was approved by institutional review boards or independent ethics committees at participating sites. All patients provided written informed consent before enrollment.

Patients were screened over 28 d and enrolled based on eligibility, screening date, and atezolizumab availability. Key eligibility criteria included mUC (stage T4b [any N], any T [N 2 – 3], or M1) of the bladder, renal pelvis, urethra, or ureters with dominant transitional cell histology. Eligible patients had disease progression during or following ≥1 platinum-based regimen for advanced disease or within 12 mo following completion of a platinum-based adjuvant or neoadjuvant regimen. A regimen was defined as ≥2 cycles of platinum-containing chemotherapy, but patients who received one cycle and discontinued due to grade 4 hematologic or grade 3–4 nonhematologic toxicity were potentially eligible. The maximum number of prior therapies was not restricted. Patients were required to have Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2. Initially, study entry was restricted to PD-L1–selected patients but was subsequently extended to allow for enrollment regardless of PD-L1 status, with optional collection of tumor tissue for PD-L1 testing.

PD-L1 expression on tumor-infiltrating immune cells (ICs) was centrally evaluated using the VENTANA SP142 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ, USA). Baseline PD-L1 expression was scored based on the percentage of ICs with PD-L1 expression: IC2/3 (≥5%) and IC0/1 (<5%). Patients received atezolizumab 1200 mg intravenously every 3 wk. As responses to immune checkpoint inhibitors can manifest as delayed or nonclassical responses [21], patients could continue treatment past Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 disease progression until the earliest of the following events: loss of clinical benefit per investigator, unacceptable toxicity, withdrawal of consent, patient or physician decision to discontinue treatment, death, commercial availability of atezolizumab following FDA approval, or study closure. The last possible enrollment date was the day of commercial availability of atezolizumab in the USA. Afterward, patients could receive one cycle of atezolizumab before their treatment discontinuation visit (30 ± 7 d after the last dose of study drug). Following study termination, optional long-term follow-up was initiated (ongoing until 2019) to assess survival of patients who provided consent. Patients could continue on commercially available atezolizumab treatment as appropriate but not as part of the study.

### 2.2. Study objectives and assessments

The primary objective of this study was to provide access to atezolizumab as treatment for patients with mUC who had progressed on or were intolerant of platinum-based chemotherapy. The efficacy objectives were objective response rate (ORR), disease control rate (DCR), duration of response (DOR), time to treatment failure, and OS. Safety and tolerability were also evaluated. The study was terminated on May 18, 2016, and clinical database lock date used in this analysis was October 5, 2016.

Key efficacy end points reported in this analysis were evaluated in patients who received ≥1 dose of atezolizumab and had a postbaseline tumor response assessment (as per investigator-assessed RECIST v1.1). DOR, analyzed for the subset of patients with an objective response, was defined between the date of the first occurrence of either a complete response (CR) or a partial response (PR) and the date of first documented progressive disease or death. Tumor assessments were planned to occur approximately every 9 wk for 54 wk from the start of study treatment and, if applicable, every 12 wk thereafter until disease progression or treatment discontinuation (for patients who continued to receive atezolizumab following disease progression), or per local standard of care. Patients who had not progressed or died by the database lock date were censored at the time of last tumor assessment date. DOR was censored at the first occurrence of a CR or PR plus 1 d, if no tumor assessments were performed after the date of the first occurrence of a CR or PR. OS was assessed by the Kaplan-Meier method, and for patients who are still alive at database lock date, data were censored at the date they were last known to be alive. Descriptive summaries of these analyses are presented for this single-arm study. Follow-up duration was defined between treatment initiation and death or last date known to be alive.

Safety-evaluable patients were defined as patients who received ≥1 dose of atezolizumab. Adverse events (AEs) were monitored on or after

Please cite this article in press as: Pal SK, et al. Atezolizumab in Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma: Clinical Experience from an Expanded Access Study in the United States. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.02.010