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Urothelial Cancer

Atezolizumab in Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma: Outcomes by Prior Number of Regimens

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Abstract

Background: Patients with metastatic urothelial carcinoma (mUC) who progress after platinum-based chemotherapy have had few treatment options and uniformly poor outcomes. Atezolizumab (anti-programmed death-ligand 1) was approved in the USA for cisplatin-ineligible and platinum-treated mUC based on IMvigor210, a phase 2, single-arm, two-cohort study.
Objective: To evaluate the efficacy and safety of atezolizumab by the number of prior lines of systemic therapy in patients with pretreated mUC.
Design, setting, and participants: IMvigor210 enrolled 315 patients with mUC with progression during or following platinum-based therapy at 70 international sites between May 2014 and November 2014. Key inclusion criteria included age ≥18 yr, creatinine clearance ≥30 ml/min, and Eastern Cooperative Oncology Group performance status 0–1, with no limit on prior lines of treatment.
Intervention: Patients in this cohort received atezolizumab 1200 mg intravenously every 3 wk until loss of clinical benefit.
Outcome measurements and statistical analysis: Centrally assessed Response Evaluation Criteria In Solid Tumors v1.1 objective response rate (ORR), median duration of response, overall survival (OS), and adverse events were evaluated by prior treatment. Potential differences between subgroups were evaluated using log-rank (for OS) and chi-square (for ORR and adverse events frequencies) testing.
Results and limitations: Three hundred and ten patients were efficacy and safety evaluable (median follow-up, 21 mo). Objective responses and prolonged OS occurred across all prespecified subgroups; median duration of response was not reached in most subgroups. In patients without prior systemic mUC therapy (first-line subgroup), ORR was 25% (95% confidence interval: 14–38), and median OS was 9.6 mo (95% confidence interval: 5.9–15.8). No significant differences in efficacy or toxicity by therapy line were observed.
Conclusions: Atezolizumab demonstrated comparable efficacy and safety in previously treated patients with mUC across all lines of therapy evaluated.
Patient summary: We investigated effects of previous treatment in patients with metastatic urothelial carcinoma that progressed after platinum-based therapy. Atezolizumab was active and tolerable no matter how many treatment regimens patients had received. ClinicalTrials.gov, NCT02108652.

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1. Introduction

Platinum-based chemotherapy is the standard initial approach for treating metastatic urothelial carcinoma (mUC) [1,2]. However, effective therapies for patients who progress after first-line (1L) therapy are needed, as overall survival (OS) remains short [3–6], and progression on platinum is typically inevitable. Furthermore, cisplatin ineligibility presents a challenge, especially among elderly patients [7,8]. A wide variety of chemotherapies and targeted therapies have failed to show significant improvement of clinical outcomes in clinical trials, leaving a lack of effective options [9]. In Europe, vinflunine is the only approved agent for the second-line (2L) treatment of mUC [6], and until recently, no treatments were approved for patients with mUC who progressed on or after platinum-based chemotherapy.

Atezolizumab is a humanized engineered monoclonal antibody that selectively targets programmed death-ligand 1 (PD-L1) to reinvigorate and enhance anticancer activity [10,11]. Atezolizumab has demonstrated efficacy and safety in a range of cancers [10]. Approval was granted by the US Food and Drug Administration for the use of atezolizumab in patients with mUC, both in the cisplatin-ineligible and platinum-treated settings [12], based on results from the phase 2 IMvigor210 study, and European approval has also been granted following results from the phase 3 IMvigor211 study [13,14]. The platinum-treated cohort of IMvigor210 showed that among a population including heavily pretreated patients, atezolizumab provided durable activity and tolerability in an overall population unselected for PD-L1 expression [15].

Due to the lack of treatment options for mUC, a large proportion of patients are not treated with any 2L chemotherapy, and far fewer receive post-2L treatment [16,17]. Although retrospective data do not suggest different prognostic effects based on the number of prior lines of therapy [17], precise impacts remain unclear because patients receiving later lines of therapy have historically been under-represented or excluded from clinical trials. The platinum-treated cohort of the IMvigor210 study included patients who had multiple lines of treatment for metastatic disease, providing an opportunity to assess outcomes as a function of the extent of pretreatment. Here, we describe the efficacy and safety in an updated analysis based on the number of systemic treatments administered in the metastatic setting prior to study enrollment.

2. Patients and methods

2.1. Patients, study design, and procedures

The study population for this analysis included patients with mUC who were enrolled in the platinum-treated cohort of IMvigor210 (ClinicalTrials.gov identifier, NCT02108652). Details on this two-cohort phase 2 study and patient populations have been reported previously [15,18]. The protocol was approved by institutional review boards or independent ethics committees at participating study sites. All patients provided written informed consent before entry into the study, which was performed in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines.

Key eligibility criteria specific to this cohort included locally advanced or metastatic urothelial carcinoma of the bladder, renal pelvis, ureter, or urethra (herein referred to as mUC), creatinine clearance $\geq$30 ml/min, and Eastern Cooperative Oncology Group performance status of 0–1. Patients were required to have experienced disease progression during or following $\geq$1 prior platinum-based regimen for metastatic disease or in the neoadjuvant or adjuvant setting if progression occurred within 12 mo. There were no restrictions on the maximum number of prior therapies. Patients received atezolizumab 1200 mg intravenously every 3 wk until loss of clinical benefit as defined by the treating investigator. Objective response rates (ORRs) per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 were reviewed by an independent facility (BioClinica, Princeton, NJ, USA). Central evaluation of PD-L1 expression (HistoGeneX, Brussels, Belgium) was performed prospectively using the VENTANA SP142 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ, USA), with samples scored as IC2/3, IC1, or IC0 based on the percentage of tumor-infiltrating immune cells with PD-L1 expression [15]. Safety was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

2.2. Treatment definitions, assessments, and statistical details

The IMvigor210 study protocol defined atezolizumab treatment in the metastatic setting as 2L and above (2L+) for patients who met the above-described inclusion criteria. For the current analysis, treatment definitions were assessed as follows: atezolizumab treatment was considered 1L when administered to patients who had only received prior platinum therapy perioperatively, as described above. Atezolizumab treatment was considered 2L, third line (3L), fourth line (4L), or fifth line and beyond (5L+) for patients with one, two, three, or at least four prior regimens, respectively, specific to the metastatic setting (regardless of perioperative chemotherapy).

The protocol-defined primary analysis [15] evaluated coprimary endpoints of ORR based on centrally assessed, confirmed RECIST v1.1, and investigator-assessed immune-modified RECIST [19], and the former are reported here. Secondary endpoints included duration of response (DOR) and progression-free survival (by both RECIST v1.1 per independent review facility and immune-modified RECIST per investigator assessment), OS, and safety. In this post hoc analysis, centrally assessed RECIST v1.1 ORR and DOR, in addition to OS and adverse event (AE) frequencies, were evaluated based on the number of prior treatment regimens as defined above. The Kaplan-Meier approach was used to estimate median DOR and OS along with 95% confidence intervals (CIs) [20]. Exploratory analyses were conducted to investigate potential differences between subgroups for key endpoints; these analyses were performed using log-rank test (for OS) and chi-square test (for ORR and AE frequencies). The p values from these tests are presented without multiple-testing adjustment. The data cut-off date used in this analysis was July 4, 2016.

3. Results

3.1. Baseline and prior treatment characteristics

Overall, 310 eligible patients were included in this analysis (Table 1). The median age was 66 yr, and the majority were men and had visceral metastases (both 78%). Thirty-eight percent of patients had liver metastases, and 62% had Eastern Cooperative Oncology Group performance status of 1. Fifty-six patients received only perioperative

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