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Efficacy and Tolerability of Tremelimumab in Locally Advanced or Metastatic Urothelial Carcinoma Patients Who Have Failed First-Line Platinum-Based Chemotherapy

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ABSTRACT

Purpose: Patients with advanced urothelial carcinoma who fail platinum-containing chemotherapy (treatment fails) have a poor prognosis and limited treatment options. Recent approvals of immune-checkpoint inhibitors confirmed the value of immunomodulatory therapy in urothelial carcinoma. Tremelimumab is a selective human immunoglobulin G2 (IgG2) monoclonal antibody against cytotoxic T-lymphocyte–associated antigen 4 with demonstrated durable response rate in metastatic melanoma. This is the first study to report the efficacy and safety of tremelimumab in urothelial carcinoma.

Patients and Methods: We report the results of the urothelial carcinoma cohort from a phase II, open-label, multicenter study of patients with advanced solid tumors (NCT02527434). Patients with locally advanced/metastatic urothelial carcinoma were treated with tremelimumab monotherapy (750 mg via intravenous infusion every 4 weeks for seven cycles, then every 12 weeks for two additional cycles) for up to 12 months or until disease progression, initiation of other anticancer therapy, unacceptable toxicity, or consent withdrawal.

Results: In 32 evaluable patients with metastatic urothelial carcinoma, objective response rate was 18.8% (95% confidence interval, 7.2–36.4), including complete response (CR) in 2 (6.3%), and partial response in 4 patients (12.5%). Median duration of response has not been reached. Stable disease of $\geq$12 months was reported in 1 patient (3.1%), yielding a disease control rate at 12 months of 21.9%. Overall, tremelimumab was generally well tolerated; safety results were consistent with the known safety profile.

Conclusions: Tremelimumab monotherapy demonstrated clinical activity and durable responses in patients with metastatic urothelial carcinoma. This study is the first in which CR has been observed with tremelimumab as a single agent in urothelial carcinoma.

Introduction

Bladder cancer is the ninth most common cancer diagnosis worldwide, with approximately 430,000 new cases diagnosed each year (1); over 90% of bladder cancers are urothelial carcinoma (2). Systemic platinum-based chemotherapy is the standard of care for untreated patients with metastatic urothelial carcinoma (3). Prior to the advent of immunomodulatory agents as second-line therapy, patients who failed standard platinum-containing chemotherapy had a poor prognosis, with a median overall survival (OS) of 6 to 7 months. Patients treated with pembrolizumab in the KEYNOTE-045 trial experienced a median OS of 10.3 months, demonstrating the value of immune-checkpoint inhibitors targeting programmed cell death-1 (PD-1) and its ligand programmed cell death ligand-1 (PD-L1) in this setting (4).

The cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a coinhibitory receptor expressed on T cells (5). The natural ligands for CTLA-4, which are present on immune cells, are CD80 (B7.1) and CD86 (B7.2; ref. 6). By competitively binding to CD80 and CD86 ligands, CTLA-4 reduces the amplitude of CD28-mediated T-cell activation (5). CTLA-4 blockade leads to enhanced cellular immune responses such as enhanced T-cell activation (6); therefore, blockade of CTLA-4 can restore immune control and limit tumor development (5).

Tremelimumab is a selective human immunoglobulin G (IgG2) monoclonal antibody against CTLA-4 (7). Anti–CTLA-4 appears to primarily act on effector T cells rather than regulatory T cells based on published data from murine and human studies (8–12). Tremelimumab blocks binding of CTLA-4 to the CD80 (B7.1) and CD86 (B7.2) ligands, which in turn enhances T-cell activation and antitumor immunity (5, 13). Tremelimumab (15 mg/kg every 90 days) has been shown to induce antitumor activity in first-line metastatic melanoma (13), in second-line refractory/relapsed melanoma (14), advanced malignant mesothelioma (15, 16), and recurrent or metastatic head and neck squamous cell carcinoma (HNSCC; ref. 17). Across indications, the safety profile of tremelimumab is consistent with the known safety profile of CTLA-4 inhibitors (17–19).

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Translational Relevance

Current treatment options for advanced urothelial carcinoma are limited, with only modest clinical and survival benefits resulting from chemotherapy. In addition, patients with advanced urothelial carcinoma who fail platinum-containing chemotherapy have poor prognosis and limited treatment options; therefore, new treatment strategies are needed for this group of patients. Immunotherapy has emerged as a new treatment strategy that has demonstrated efficacy in urothelial carcinoma. However, although single-agent immunotherapies have shown antitumor activity, patients will progress and eventually die from disease progression, which opens up an opportunity for further improvements with this therapy. For example, combination regimens utilizing two drugs targeting nonredundant pathways may lead to enhanced activity compared with a single-agent regimen. This article provides important data on the activity of single agent tremelimumab as monotherapy, with promising long-term, durable disease control observed in patients with advanced urothelial carcinoma, and provides support for its evaluation in combination with other immunotherapy agents.

The PD-L1 inhibitors atezolizumab, durvalumab, and avelumab and the PD-1 inhibitors nivolumab and pembrolizumab are approved by the U.S. Food and Drug Administration for the treatment of locally advanced or metastatic urothelial carcinoma that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (3). Atezolizumab and pembrolizumab are also approved as a first-line option for patients with locally advanced or metastatic urothelial carcinoma whose tumors express high levels of PD-L1 and who are not eligible for cisplatin-containing chemotherapy.

As PD-L1 and CTLA-4 regulate immune responses by different mechanisms (6), targeting both checkpoints provides the potential for additive or synergistic effects. Given that CTLA-4 blockade can induce PD-L1 expression (20, 21), combining anti–CTLA-4 with anti–PD-L1 agents may be an effective therapeutic strategy, with promising results in urothelial carcinoma as recently reported (22).

This phase II study sought to evaluate tremelimumab as monotherapy in patients with urothelial bladder cancer, triple-negative breast cancer, or pancreatic ductal adenocarcinoma (NCT02527434). Here we report the analysis of efficacy and safety in the cohort of patients with unresectable, stage IV urothelial bladder cancer with documented transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra), who have failed first-line platinum-based chemotherapy in the metastatic setting. This study aims to provide important data on the activity of single-agent tremelimumab in patients with advanced urothelial carcinoma and seeks to provide support for its evaluation in combination with other immunotherapy agents.

Patients and Methods

Study design and treatment

Patients received tremelimumab [750 mg via intravenous (i.v.) infusion every 4 weeks for seven cycles, then every 12 weeks for two additional cycles) for up to 12 months or until disease progression, initiation of other anticancer therapy, unacceptable toxicity, or withdrawal of consent (**Fig. 1A**). At the discretion of the investigator, eligible patients who had completed the initial course of tremelimumab monotherapy, or during the follow-up period, with confirmed disease progression were given the option of tremelimumab monotherapy retreatment or receiving either durvalumab monotherapy or durvalumab + tremelimumab combination therapy. Patients receiving durvalumab monotherapy were given 1.5 g via i.v. infusion every 4 weeks for up to 12 months, and patients receiving the durvalumab + tremelimumab combination therapy were given durvalumab 1.5 g via i.v. infusion every 4 weeks + tremelimumab 75 mg via i.v. infusion every 4 weeks for up to four cycles each, followed by durvalumab via i.v. infusion every 4 weeks for up to 8 months (up to 12 months total) or until disease progression (whichever occurred first). Based on the results of a previous study (23), it was decided to administer a lower dose of tremelimumab when given in combination with durvalumab. The retreatment arms of durvalumab monotherapy and durvalumab + tremelimumab combination therapy are reported in the Supplementary Material.

The study was performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation/Good Clinical Practice. The Clinical Study Protocol and the Informed Consent Form were approved by each participating site's Independent Ethics Committee or Institutional Review Board. All patients provided informed written consent.

Patient population

This study was conducted in adult patients (aged $\geq$18 years) with advanced or metastatic solid tumors, including but not limited to, histologically or cytologically documented urothelial carcinoma, who progressed on, were ineligible for, or refused standard first-line platinum-based chemotherapy. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 (indicating no symptoms) or 1 (indicating mild symptoms), presence of $\geq$1 lesion, not previously irradiated, $\geq$10 mm at the longest diameter at baseline ($\geq$15 mm short axis for lymph nodes) with computed tomography (CT; preferred) or magnetic resonance imaging scans suitable for assessments per Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST 1.1) guidelines. Patients who had prior surgery, localized radiation, and/or neoadjuvant/adjuvant chemotherapy for muscle-invasive disease were also permitted.

Key exclusion criteria were prior exposure to immune-mediated therapy, including but not limited to other anti–CTLA-4, anti–PD-1, anti–PD-L1, or anti–PD-L2 antibodies, anticancer vaccines, and use of any concurrent chemotherapy, biological, or hormonal therapy for cancer treatment. Also excluded were patients with unresolved toxicity from previous anticancer therapy; current or prior use of immunosuppressive medication within 14 days before first study dose; history of allogenic organ transplantation; patients with active or prior autoimmune or inflammatory disorders; any condition that would interfere with evaluation of investigational product or interpretation of patient safety or study results, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, and serious chronic gastrointestinal conditions associated with diarrhea.

Study objectives and endpoints

Tremelimumab monotherapy

The primary objective of the study was to assess the efficacy of tremelimumab monotherapy in terms of confirmed investigator-assessed objective response rate (ORR) according to RECIST v1.1. A secondary objective was to further assess the efficacy of

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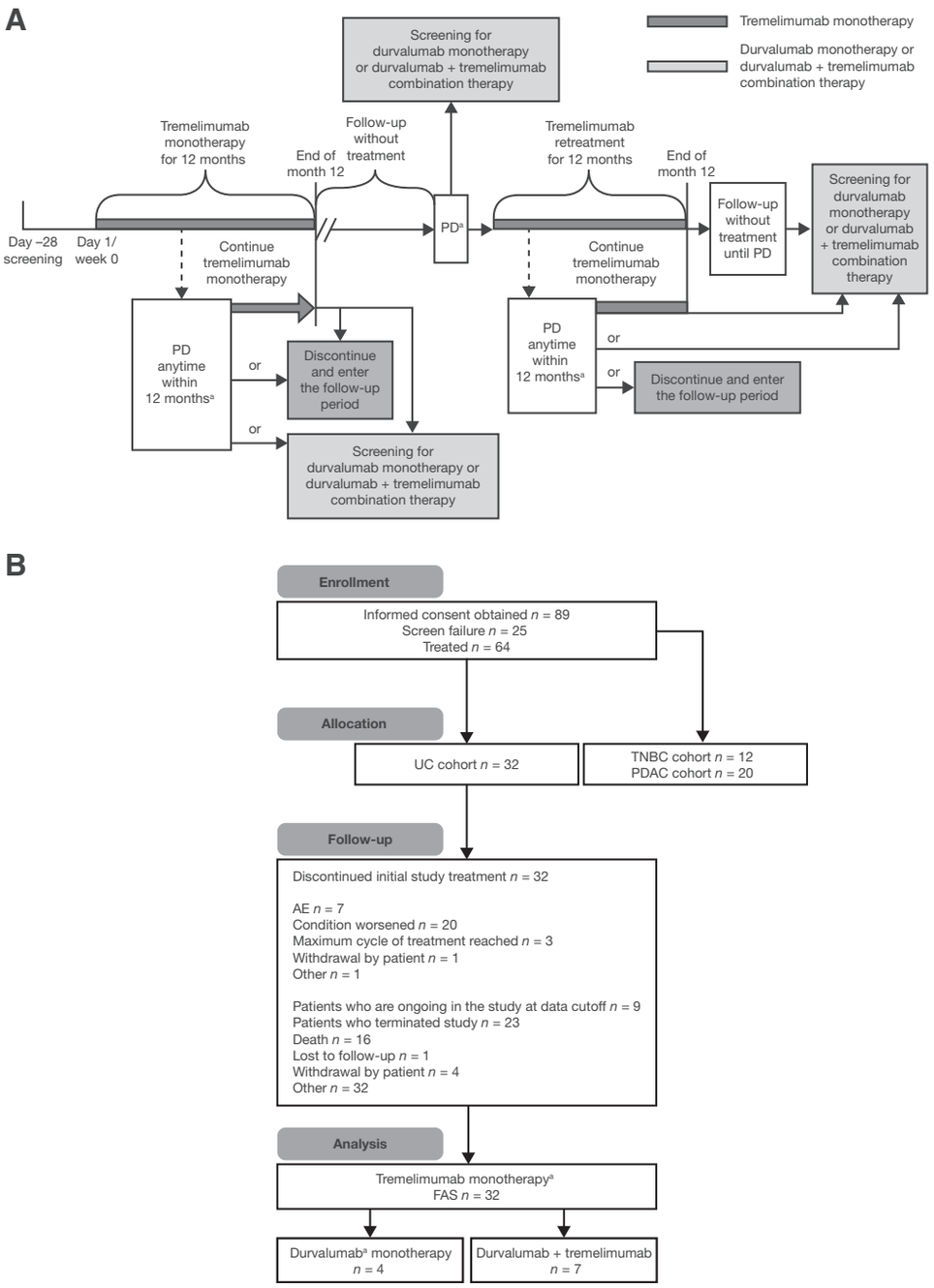

Figure 1.

A, Study design. PD, progressive disease; Q4W, every 4 weeks; Q12W, every 12 weeks. [a]At the discretion of the investigator, patients who achieve or maintain disease control through to the end of the 12-month treatment period may restart their assigned treatment upon evidence of PD (according to RECIST 1.1, with or without confirmation). **B,** CONSORT diagram. PDAC, pancreatic ductal adenocarcinoma; TNBC, triple-negative breast cancer. [a]Following confirmed progressive disease, patients were given the option for retreatment with tremelimumab monotherapy or be sequenced to durvalumab monotherapy (durvalumab) or durvalumab + tremelimumab combination therapy. Full analysis set (FAS): All treated patients in the urothelial cancer (UC) cohort (i.e., received at least one dose of tremelimumab monotherapy). The SAS comprised all patients who received at least one dose of investigational product. The PK analysis set included all patients who received at least one dose of investigational product, per the protocol for whom any postdose PK data were available. The ADA-evaluable set was defined as patients in the SAS who had ADA results at baseline and at ≥1 post-baseline time point. Durvalumab analysis set: All patients who were treated with tremelimumab, received at least one dose of durvalumab monotherapy, and who had a baseline tumor assessment prior to durvalumab monotherapy dosing in the urothelial carcinoma cohort. Durvalumab + tremelimumab combination analysis set: All patients who were treated with tremelimumab, received at least one dose of durvalumab + tremelimumab combination therapy, and had a baseline tumor assessment prior to durvalumab + tremelimumab combination therapy dosing in the urothelial carcinoma cohort.

tremelimumab monotherapy in terms of duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), best objective response (BOR), and OS.

The safety and tolerability profile of tremelimumab monotherapy was assessed. Safety outcomes were assessed by physical examination, laboratory findings, vital signs, and electrocardiogram. Adverse events (AE) were graded by Common Terminology Criteria for Adverse Events v4.03. Adverse event categories included treatment-related AEs (TRAE) and immune-mediated AEs (imAE). TRAEs were considered possibly related to treatment, as assessed by the investigator and imAEs were defined as an AE of special interest that was associated with drug exposure and was consistent with an immune-mediated mechanism of action, where there is no clear alternate etiology. Exploratory endpoints included the assessment of immunogenicity and pharmacokinetics (PK) to define biological responses to tremelimumab monotherapy.

Durvalumab monotherapy and durvalumab + tremelimumab combination therapy

Additional secondary objectives (reported in the Supplementary Material) were to assess the safety and efficacy of durvalumab monotherapy and durvalumab + tremelimumab combination therapy after

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confirmed progressive disease on tremelimumab monotherapy using the criteria as set for tremelimumab monotherapy. Exploratory endpoints included the PK assessment of durvalumab monotherapy and durvalumab + tremelimumab combination therapy, and to investigate the immunogenicity of tremelimumab and durvalumab.

Assessments

Patients were assessed for tumor response according to RECIST v1.1 at baseline, then every 8 weeks until confirmed disease progression. Safety assessments occurred at each clinic visit.

Analyses

The statistical analyses were to be descriptive, and no inferential analyses were to be performed based on statistical tests. All evaluations were exploratory in nature. A total of 38 patients with urothelial carcinoma were screened to ensure that 32 evaluable patients were enrolled.

All analysis sets for the urothelial carcinoma cohort are described in **Fig. 1B**.

Objective response rate, DCR, and BOR are presented as patient number *n* (%), with a Clopper–Pearson 95% confidence interval (CI). ORR was defined as the number *n* (%) of patients with a confirmed complete response (CR) or confirmed partial response (PR) among all treated patients with measurable disease at baseline. DCR at 4 or 12 months was defined as the percentage of patients who had a BOR of CR or PR in the first 4 or 12 months, respectively, or who demonstrated stable disease for a minimum interval of 11 or 15 weeks, respectively, following the start of study treatment. DoR was measured at 4 and 12 months and presented as median with a 95% CI for patients who achieved a response. PFS and OS are presented as median with a 95% CI.

Serum concentrations of tremelimumab were measured using a validated quantitative enzyme-linked immunosorbent assay with a lower limit of quantitation of 156 ng/mL. The PK data were analyzed based on the PK analysis set. (Further information is provided in the Supplementary Material.)

A validated electrochemiluminescence, solution-phase bridging immunoassay that uses Meso Scale Discovery technology was used to detect anti-tremelimumab in human serum. All immunogenicity analyses were conducted on the antidrug antibody (ADA)–evaluable set.

Results

Patient characteristics

As of the data cutoff on February 17, 2018, 32 patients from eight sites in five countries had received tremelimumab monotherapy for urothelial carcinoma [final analysis set (FAS)]. The mean total treatment duration of tremelimumab monotherapy was 3.5 months [standard deviation (SD), 3.8; minimum 0.2 to maximum 14.8; safety analyses set (SAS)]. Although patients with locally advanced urothelial carcinoma were eligible for the study, all patients enrolled had metastatic disease. Most ($n = 29$; 90.6%) had received prior cytotoxic chemotherapy (**Table 1**). Following initial tremelimumab monotherapy, 4 patients were treated with durvalumab monotherapy and 7 patients received tremelimumab + durvalumab (**Fig. 1B**). Results for these latter two groups are reported in the Supplementary Material; however, no efficacy or safety conclusions can be drawn due to the small size of these cohorts.

At primary data cutoff (February 17, 2018), all patients had discontinued initial tremelimumab monotherapy treatment. The most common reason for initial treatment discontinuation was condition under investigation worsened ($n = 20$; 62.5%), followed by AEs ($n = 7$, 21.9%). In 9.4% of patients ($n = 3$), the maximum cycle of treatment was reached.

Table 1. Patient baseline characteristics (FAS, $n = 32$)[a].

Characteristic	*n* (%)
Median age, years (range)	66.5 (44–81)
≥18 to <65	13 (40.6)
≥65 to <88	19 (59.4)
Sex	
Male	26 (81.3)
Female	6 (18.8)
Race	
Caucasian	21 (65.6)
Black or African American	0
Asian	10 (31.3)
Other	1 (3.1)
ECOG PS	
0	19 (59.4)
1	13 (40.6)
Previous disease-related treatment modalities	
Cytotoxic chemotherapy	29 (90.6)
Neoadjuvant	3 (9.4)
Adjuvant	4 (12.5)
First line	22 (68.8)
Second line[b]	3 (9.4)
Palliative	4 (12.5)
Not applicable[b]	2 (6.3)
Radiotherapy	13 (40.6)
Adjuvant	2 (6.3)
Definitive	1 (3.1)
Palliative	10 (31.3)
Not applicable	2 (6.3)
Primary tumor location	
Bladder	26 (81.3)
Ureter	3 (9.4)
Renal pelvis	2 (6.3)
Unknown	1 (3.1)
Metastatic disease[c]	32 (100)
Lymph nodes	24 (75.0)
Respiratory	16 (50)
Bone and locomotor	12 (37.5)
Hepatic (liver and gallbladder)	11 (34.4)
Genitourinary	10 (31.3)
Other	6 (18.8)
Gastrointestinal	1 (3.1)
Pericardial effusion	1 (3.1)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set; UC, urothelial carcinoma.

[a]FAS comprises all enrolled patients.

[b]Important protocol deviations were recorded for 2 patients with second-line chemotherapy in the urothelial carcinoma cohort. One patient received first-line treatment with methotrexate, vinblastine, doxorubicin, and cisplatin, which was recorded in error as second-line treatment. Another patient, E7801006 in the urothelial carcinoma cohort, did not receive any prior chemotherapy; this was not recorded as an important protocol deviation due to error; however, it will be documented during the final analysis.

[c]Patients with an overall disease classification of metastatic may have sites with locally advanced disease.

Antitumor activity

Confirmed ORR was 18.8% ($n = 6$; 95% CI, 7.2–36.4; **Table 2**), including two (6.3%) CR and four (12.5%) PR. The most common

Table 2. Tremelimumab antitumor activity FAS ($n = 32$).

Response	*n*	% (95% CI)
Confirmed ORR	6	18.8 (7.2–36.4)
Duration of response	Not reached	N/A
Time to response (median)	99.5 days	
Best objective response:		
Complete response	2	6.3
Partial response	4	12.5
Stable disease[a]	3	9.4
Progressive disease (RECIST 1.1)	22	68.8
Not evaluable[b]	1	3.1

Abbreviations: CI, confidence interval; FAS, full analysis set; N/A, not applicable; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria In Solid Tumors, Version 1.1.
[a]Stable disease for ≥15 weeks.
[b]Incomplete postbaseline assessments.

BOR was progressive disease (68.8%), followed by PR (12.5%), stable disease (≥15 weeks; 9.4%), and CR (6.3%; **Table 2**).

The median follow-up was 9.3 months. The median time to response during tremelimumab monotherapy was ∼3.5 months (99.5 days). Median DoR was not reached; all responders remained in response at 4 months, and 83.3% remained in response at 12 months from baseline (**Table 2**; **Fig. 2A**). DCR at 4 months was 25% ($n = 8$; 95% CI, 11.5–43.4) and was 21.9% ($n = 7$; 95% CI, 9.3–40.0) at 12 months.

The median OS (95%) was 10.3 months (range, 5.9–not evaluable; **Fig. 2B**). The estimated survival rate at 12 months was 36.0%. Twenty patients (62.5%) had a PFS event (9 patients progressed and 11 died). The median PFS was 2.63 months (**Fig. 2C**). Patients who responded to treatment saw decreases in target lesion size, ranging from 30% to 100%, and durable changes over a period of 24 months. In patients with PD, however, increases in target lesion size between 20% and 150% were recorded over 13 months (**Fig. 2D**).

Following the primary data cutoff (February 17, 2018), follow-up by the investigators has been undertaken and documented out of protocol. Additional encouraging evidence for durable response has been demonstrated. One patient, evaluated by CT scan, has a DoR of ∼35 months and has been in CR for 30 months ongoing as of May 2019. A second patient had been in CR for ∼13 months before death; cause of death was not considered to be related to the disease under study. A third patient, with stable disease by RECIST assessment due to residual abnormality visible on CT, had a negative positron emission tomography examination performed during the last assessment before data cutoff (outside of study protocol). The patient showed a clinical benefit of 26 months, which was ongoing as of May 2019.

Adverse events

Most patients experienced an AE of any grade ($n = 30$; 93.8%). Grade ≥3 AEs were reported for more than half of these patients ($n = 19$; 59.4%), most commonly colitis ($n = 3$; 9.4%) and anemia ($n = 3$; 9.4%). Approximately one third of patients had an AE leading to discontinuation of tremelimumab monotherapy ($n = 10$; 31.3%).

AEs that were considered by the investigators to be related to treatment (TRAEs) occurred in 18 patients (56.3%) treated with tremelimumab monotherapy; the most commonly reported TRAEs of any grade were fatigue ($n = 9$; 28.1%), colitis ($n = 8$; 25.1%), pruritis ($n = 7$; 21.9%), diarrhea ($n = 6$; 18.8%), and nausea ($n = 6$; 18.8%; **Table 3**). Grade ≥3 TRAEs occurred in 9 patients (28.1%), most commonly colitis ($n = 4$; 12.5%), diarrhea ($n = 3$; 9.4%), and anemia ($n = 3$; 9.4%). Treatment-related serious AEs occurred in 9 patients (28.1%; **Table 3**). Nine patients (28.1%) discontinued tremelimumab due to a TRAE; 7 (21.9%) due to colitis, 1 (3.1%) due to hepatotoxicity, and 1 (3.1%) due to pruritus.

Immune-mediated AEs (imAE) were reported in 11 patients (34.4%; **Table 3**). Grade ≥3 imAEs occurred in 5 patients (15.6%), serious imAEs in 6 (18.8%), and imAEs leading to discontinuation of tremelimumab in 5 patients (15.6%; **Table 3**). Among those with an imAE, treatment with a high-dose steroid/systemic corticosteroid, endocrine therapy, or other immunosuppressive therapy was required in 65.7%, 12.5%, and 9.4% patients, respectively. imAEs resolved in 5 patients (15.6%) but did not resolve in 6 patients (18.8%).

No deaths were considered related to treatment by the investigator, and the most common reason for death was related to disease under study (34.4%).

Immunogenicity

Immunogenicity data were available for 26 ADA-evaluable urothelial carcinoma patients. There were 4 ADA-positive patients (ADA prevalence was 15.4%), but only one was classified as treatment-emergent ADA-positive (ADA incidence was 3.8%). The latter was the only patient who tested positive for the presence of neutralizing antibody at any visit (prevalence was 3.8%; Supplementary Table S1).

Pharmacokinetics

Figure 3 displays the observed serum concentrations of tremelimumab in urothelial carcinoma patients (PK analysis set, $n = 32$) following a dose of 750 mg every 4 weeks via i.v. infusion at nominal visits [$n = 25$, maximum serum concentration at the start of the first cycle treatment ($C_{max,1}$); $n = 24$, minimum serum concentration after the first cycle treatment ($C_{min,1}$); $n = 8$, minimum serum concentration after the third treatment cycle ($C_{min,w12}$); and $n = 7$, maximum serum concentration at the start of the fourth treatment cycle ($C_{max,w12}$)]. A comparison of observed PK data following administration of tremelimumab monotherapy from this study was made with simulated PK data at the same dose regimen based on the final population PK model of tremelimumab and a virtual population of 100 solid tumor patients. Overall, the tremelimumab concentrations observed in this study are consistent with the range of exposure predicted by the model that was built on PK data from a pool of 746 patients from solid tumors [including patients with non–small cell lung cancer (NSCLC), HNSCC, and bladder cancer], suggesting that the PK profile of tremelimumab is comparable across tumor indications.

Discussion

In this phase II, multicenter, open-label study of tremelimumab monotherapy (750 mg via i.v. infusion every 4 weeks) in patients with metastatic urothelial carcinoma, tremelimumab monotherapy demonstrated durable antitumor response and an acceptable safety profile. Median DoR was not reached, and all patients with confirmed CR (6.3%) or PR (12.5%) had disease control at 12 months from baseline. Although CR with tremelimumab has previously been observed in metastatic melanoma (13), this is the first study in which durable CR has been observed with tremelimumab monotherapy in urothelial carcinoma. Overall, tremelimumab demonstrated an acceptable safety profile, and results were consistent with the known safety profile of immuno-oncology (IO) therapy with rates of grade ≥3 TRAEs higher with CTLA-4 inhibition than with anti–PD-1/PD-L1 therapies.

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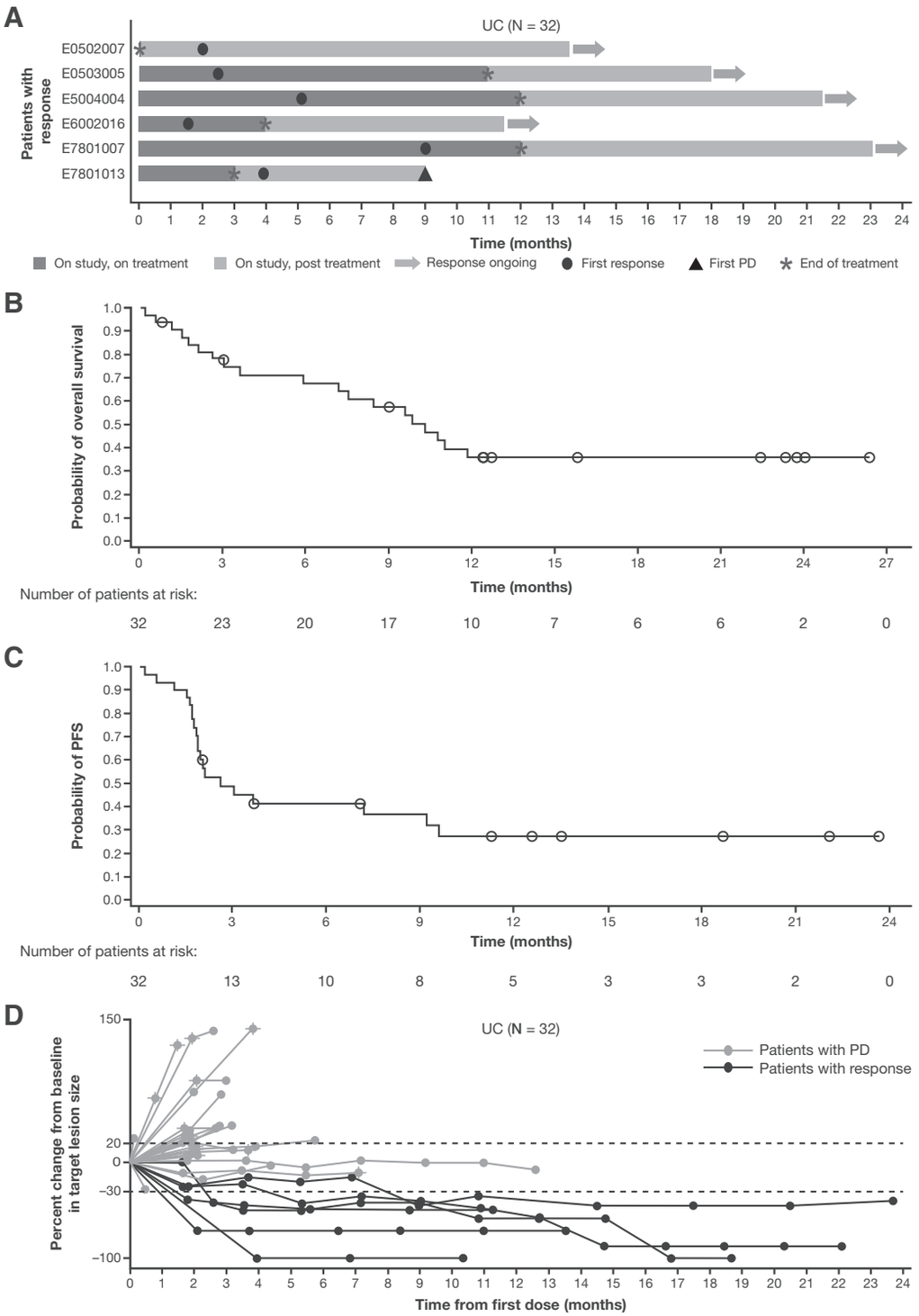

Figure 2.

A, Continuation/duration of response for tremelimumab monotherapy (FAS) in patients with urothelial carcinoma. ● Initial response. Arrows indicate ongoing response for 6 patients from the FAS (n = 32) who showed response. **B,** Kaplan–Meier estimates of overall survival at 12 months (FAS, *n* = 32). **C,** Kaplan–Meier estimates for PFS at 12 months (FAS, *n* = 32). **D,** Target lesion size, percentage change of target lesion size (FAS). FAS, full analysis set; PFS, progression-free survival.

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Table 3. Adverse events tremelimumab monotherapy (SAS).

	Overall AE *n*[a] (%)
Any AE	30 (93.8)
AE grade 3/4	19 (59.4)
Any SAE	18 (56.3)
Any AE leading to discontinuation of tremelimumab	10 (31.3)
Any AE leading to death	0
TRAEs[b]	18 (56.3)
TRAE grade 3/4	9 (28.1)
TRAE SAE	9 (28.1)
TRAE leading to discontinuation of tremelimumab	9 (28.1)
TRAE leading to death	0
imAEs	11 (34.4)
imAE grade 3/4	5 (15.6)
imSAE	6 (18.8)
imAE leading to discontinuation of tremelimumab	5 (15.6)
imAE leading to death	0
Most common ($n = \geq 2$; $\geq 5\%$ patients) TRAEs reported	
Fatigue	9 (28.1)
Colitis[c]	8 (25.1)
Pruritis	7 (21.9)
Diarrhea	6 (18.8)
Nausea	6 (18.8)
Dry skin	4 (12.5)
Decreased appetite	3 (9.4)
Headache	3 (9.4)
Hypothyroidism	3 (9.4)
Lipase increased	3 (9.4)
Vomiting	3 (9.4)
Amylase increased	2 (6.3)
Anemia	2 (6.3)
Hypokalemia	2 (6.3)
Muscular weakness	2 (6.3)
Pruritis generalized	2 (6.3)
Pyrexia	2 (6.3)
Rash	2 (6.3)
Rash maculopapular	2 (6.3)

Abbreviations: AE, adverse event; imAE, immune-mediated adverse event; imSAE, immune-mediated serious adverse event; SAE, serious adverse event; SAS, safety analyses set; TRAE, treatment-related adverse event.
[a]Patients with multiple events in the same category are counted only once in that category.
[b]As assessed by the investigator.
[c]Colitis and autoimmune colitis combined.

In the absence of a direct comparator, evaluation across studies suggests that tremelimumab monotherapy showed comparable efficacy, confirmed ORR of 18.8% (95% CI, 7.2–36.4), to that observed in patients treated with other immunotherapy agents used as second-line therapy in locally advanced/metastatic urothelial carcinoma (22). In the KEYNOTE-045 study, the ORR of patients with advanced or metastatic urothelial carcinoma treated with pembrolizumab as second-line therapy was 21.1% (95% CI, 16.4–26.5; ref. 4). In the CheckMate 275 study, in which nivolumab was given to patients with metastatic or unresectable urothelial carcinoma whose disease progressed or recurred following platinum-based chemotherapy, the ORR was 19.6% (95% CI, 15.0–24.9) with a CR rate of 2% (24). In a multicenter, open-label, phase III, randomized, controlled trial (IMvigor211), atezolizumab was compared with investigators' choice of chemotherapy in patients with metastatic urothelial carcinoma who progressed after platinum-based chemotherapy. ORR for the overall population was 13.4% (95% CI, 10.5–16.9) with a CR achieved in 3% and a PR in 10% of patients (25). In a pooled analysis of avelumab from two cohorts of the phase I, dose-expansion Javelin Solid Tumor study, patients with locally advanced or metastatic urothelial carcinoma that had progressed after at least one previous platinum-based chemotherapy were assessed. A BOR of CR was achieved in 6% of patients and PR in 11% (26). In a phase I/II, open-label study (Study 1108) in patients with advanced solid tumors, patients with locally advanced/metastatic urothelial carcinoma who had disease progression during or following platinum-containing chemotherapy given durvalumab, the ORR was 17.8% (95% CI, 12.7–24.0) for the overall population (27).

Tremelimumab has proven durable tumor responses in melanoma (13, 14, 19). In the subsequent, phase III, randomized trial, tremelimumab did not demonstrate a statistically significant improvement in OS over first-line treatment with standard-of-care (SoC) chemotherapy, although the durable responses observed suggest that a subset of patients with metastatic melanoma may benefit from treatment with tremelimumab (13). The lack of statistically significant improvement in OS with tremelimumab over SoC chemotherapy, and the similar rate of responses seen in both treatment arms, may be explained by the high rate of crossover from SoC to ipilimumab treatment observed in the control arm (13) following the approval of ipilimumab during the course of the study. Crossover from SoC to tremelimumab in the control arm was not permitted.

In two investigator-sponsored, phase II trials of patients with previously treated advanced malignant mesothelioma, tremelimumab monotherapy demonstrated preliminary antitumor activity compared with placebo (15, 16). However, these findings were not corroborated in a randomized, double-blind, placebo-controlled, phase IIb trial (NCT01843374) in patients with unresectable malignant mesothelioma, where tremelimumab did not significantly prolong the primary endpoint of OS compared with placebo (18). In patients with recurrent or metastatic HNSCC, tremelimumab monotherapy resulted in clinical benefit in patients with low or no PD-L1 tumor cell expression (17).

It is known that patients with urothelial carcinoma develop resistance to most therapies. Urothelial carcinoma, like many other cancers, can evade the immune system by downregulating tumor antigen presentation, inactivating cytotoxic T cells, upregulating immune checkpoints, and maintaining an immunosuppressive environment (28, 29). The lack of response to single-agent, antibody-based therapies may, in part, be due to the heterogeneity in lymphocyte infiltration and the low frequency of antitumor-reactive T cells in tumor lesions. A combination strategy that targets nonredundant pathways (i.e., CTLA-4 and PD-1/PD-L1) has the potential to release multiple brakes on the adaptive immune response. The potential benefit of combination immunotherapy has been demonstrated over single-agent therapy (22, 30), supporting the additional study of these combinations.

PD-L1 is an important immune checkpoint that negatively regulates T-cell function by binding to the receptor PD-1 on activated T lymphocytes and other immune cells. PD-L1 is expressed across a wide range of malignancies, including urothelial carcinoma, and blockade of the PD-L1/PD-1 pathway has been shown to produce an OS benefit in metastatic urothelial carcinoma, NSCLC, melanoma, and renal cell carcinoma, leading to the approval of anti–PD-1 and anti–PD-L1 agents in metastatic urothelial carcinoma. Anti–PD-L1 antibodies have demonstrated compelling clinical activity in patients with urothelial carcinoma who progressed on or after platinum-based therapy (4, 24–27) and, therefore, could be considered suitable options in combination therapy. Trials of PD-L1 and CTLA-4 coinhibition are ongoing in urothelial carcinoma.

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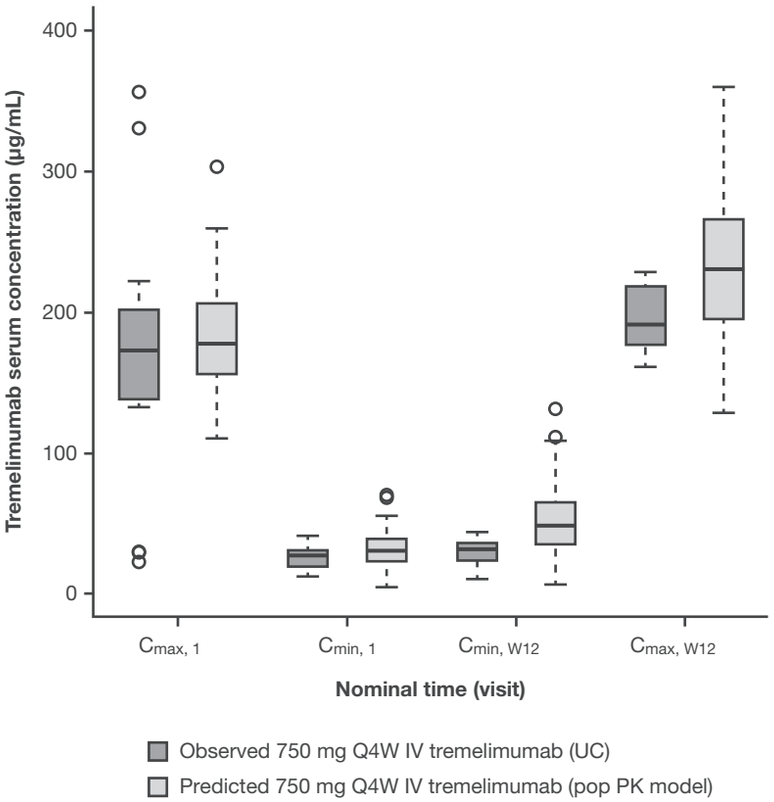

Figure 3.

Observed PK exposure following 750 mg Q4W i.v. infusion of tremelimumab in urothelial carcinoma patients at nominal visits of study NCT02527434 versus predicted exposure levels from a final population PK model of tremelimumab developed based on data from solid tumor patients. For observations, the *n* numbers were used ($n = 25$, $C_{max,1}$; $n = 24$, $C_{min,1}$; $n = 8$ $C_{min,w12}$; $n = 7$ $C_{max,w12}$) whereas for simulations, $n = 100$ virtual patients were utilized. $C_{max,1}$, maximum serum concentration following the first dose; $C_{max,w12}$, maximum serum concentration at week 12 (fourth administration); $C_{min,1}$, minimum serum concentration following the first dose (taken predose at week 4); $C_{min,w12}$, minimum serum concentration at week 12. i.v., intravenous; *n*, number of patients; PK, pharmacokinetic; popPK, population pharmacokinetics; Q4W, every 4 weeks; UC, urothelial cancer.

Combination therapy using agents that target both CTLA-4 and PD-1/PD-L1 has shown significantly improved clinical efficacy in metastatic urothelial carcinoma, untreated melanoma, and metastatic renal cell carcinoma. CheckMate 032 is an open-label, phase I/II study of nivolumab alone or nivolumab with ipilimumab (in two dose regimens) in metastatic urothelial carcinoma. The combination including the higher dose of ipilimumab produced higher rates of response and median OS than the lower dose or monotherapy (22). CheckMate 067 is a randomized, double-blind, phase III study of nivolumab alone or combined with ipilimumab versus ipilimumab alone in advanced melanoma in which the nivolumab-containing groups showed significantly improved PFS when compared with ipilimumab, suggesting complementary activity between PD-1 and CTLA-4 blockade (30). In the randomized, open-label Checkmate 214 study (NCT02231749), patients with previously untreated metastatic renal cell carcinoma who received nivolumab plus ipilimumab demonstrated significant improvements in OS and ORR versus sunitinib (31); this combination has also been recently approved by the U.S. Food and Drug Administration for this indication (32). Additionally, in a multicenter, nonrandomized, open-label, phase Ib, dose-escalation study to investigate the safety and tolerability of the combination of durvalumab + tremelimumab in locally advanced or metastatic NSCLC, the combination demonstrated a manageable tolerability profile, and evidence of antitumor activity was observed (23).

The tolerability of combination therapies appears dose- and schedule-dependent, highlighting the need for optimal dose selection to minimize the toxicity of combination regimens while maintaining clinical activity. Based on findings from a previous study (23), the dose utilized in this study for tremelimumab monotherapy (750 mg, nine doses) was higher than in the durvalumab + tremelimumab group (75 mg, four doses). Although a higher incidence of AEs and high-grade AEs is seen in IO–IO combination therapies, IO-specific toxicities are generally manageable using standard guidelines.

There are some limitations to the study that should be considered when interpreting the results, including the small sample size, lack of a control group, and cross trial comparisons. Additionally, the ORR was assessed by the investigator, rather than by a blinded independent reviewer. The study aimed to include patients with both locally advanced and metastatic urothelial carcinoma; however, only those with metastatic disease were ultimately enrolled. At study initiation, the validated tool for measuring response to treatment was RECIST version 1.1. However, as tumors respond differently to immunotherapies compared with chemotherapeutic drugs, a modified guideline specific to cancer immunotherapy, iRECIST, has since been developed. iRECIST allows the different response patterns with immunotherapy versus chemotherapy to be assessed, and its use in upcoming studies of tremelimumab could improve protocol development and facilitate the ongoing comparison of trial data across cancer immunotherapy trials (33).

This study has shown the favorable and durable clinical results of single-agent tremelimumab in patients with metastatic urothelial carcinoma who have progressed on, were ineligible for, or refused platinum-based therapy. The results reported here support the rationale of tremelimumab as a component of combination therapy with an anti–PD-1/PD-L1 agent in bladder cancer as enhanced activity may occur when combining two drugs targeting nonredundant pathways when compared with single agents. Phase III studies such as DANUBE (NCT02516241) and NILE (NCT03682068) will investigate the efficacy and safety of durvalumab with or without tremelimumab in comparison with SoC in patients with unresectable stage IV urothelial carcinoma in various settings.

Disclosure of Potential Conflicts of Interest

P. Sharma is an employee/paid consultant for Constellation, Jounce, Neon, BioAtla, Pieris, Oncolytics, Forty-Seven, Polaris, Apricity, Marker, Codiak, ImaginAb, Hummingbird, Dragonfly, Lytix, Bristol-Myers Squibb, and Tvardi, and holds ownership interest (including patents) in Jounce, Neon, Constellation, Oncolytics, BioAtla, Forty-Seven, Apricity, Polaris, Marker, Codiak, ImaginAb, Hummingbird, Dragonfly, Lytix, Tvardi, Merck, and Bristol-Myers Squibb. J. Sohn reports receiving commercial research grants from MSD, Roche, Norvatis, AstraZeneca, Lilly, Pfizer, Bayer, GlaxoSmithKline, CONTESSA, and Daiichi Sankyo. E. Kalinka reports receiving commercial research grants from AstraZeneca, Bristol-Myers Squibb, Roche, and MSD. D. Ruscica, P. Baverel, C. C.-K. Chen, and N. Morsli are employees/paid consultants for AstraZeneca. S. Ferro is an employee/paid consultant for and holds ownership interest (including patents) in AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

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Efficacy and Tolerability of Tremelimumab in Locally Advanced or Metastatic Urothelial Carcinoma Patients Who Have Failed First-Line Platinum-Based Chemotherapy

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