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Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma

Updated Results From a Phase 1/2 Open-label Study

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IMPORTANCE The data reported herein were accepted for assessment by the US Food and Drug Administration for Biologics License Application under priority review to establish the clinical benefit of durvalumab as second-line therapy for locally advanced or metastatic urothelial carcinoma (UC), resulting in its recent US approval.

OBJECTIVE To report a planned update of the safety and efficacy of durvalumab in patients with locally advanced/metastatic UC.

DESIGN, SETTING, AND PARTICIPANTS This is an ongoing phase 1/2 open-label study of 191 adult patients with histologically or cytologically confirmed locally advanced/metastatic UC whose disease had progressed on, were ineligible for, or refused prior chemotherapy from 60 sites in 9 countries as reported herein.

INTERVENTION Patients were administered durvalumab intravenous infusion, 10 mg/kg every 2 weeks, for up to 12 months or until progression, starting another anticancer therapy, or unacceptable toxic effects.

MAIN OUTCOMES AND MEASURES Primary end points were safety and confirmed objective response rate (ORR) per blinded independent central review (Response Evaluation Criteria In Solid Tumors [RECIST], version 1.1).

RESULTS A total of 191 patients with UC had received treatment. As of October 24, 2016 (90-day update), the median follow-up was 5.78 months (range, 0.4-25.9 months). The median age of patients was 67.0 years and most were male (136 [71.2%]) and white (123 [71.1%]). All patients had stage 4 disease, and 190 (99.5%) had prior anticancer therapy (182 [95.3%] postplatinum). The ORR was 17.8% (34 of 191; 95% CI, 12.7%-24.0%), including 7 complete responses. Responses were early (median time to response, 1.41 months), durable (median duration of response not reached), and observed regardless of programmed cell death ligand-1 (PD-L1) expression (ORR, 27.6% [n = 27; 95% CI, 19.0%-37.5%] and 5.1% [n = 4; 95% CI, 1.4%-12.5%] in patients with high and low or negative expression of PD-L1, respectively). Median progression-free survival and overall survival were 1.5 months (95% CI, 1.4-1.9 months) and 18.2 months (95% CI, 8.1 months to not estimable), respectively; the 1-year overall survival rate was 55% (95% CI, 44%-65%), as estimated by Kaplan-Meier method. Grade 3/4 treatment-related adverse events (AEs) occurred in 13 patients (6.8%); grade 3/4 immune-mediated AEs occurred in 4 patients (2.1%); and treatment-related AEs led to discontinuation of 3 patients (1.6%), 2 of whom had immune-mediated AEs that led to death (autoimmune hepatitis and pneumonitis).

CONCLUSIONS AND RELEVANCE Durvalumab, 10 mg/kg every 2 weeks, demonstrates favorable clinical activity and an encouraging and manageable safety profile in patients with locally advanced/metastatic UC.

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Supplemental content

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Outcome for patients who relapse after chemotherapy for stage 4 urothelial carcinoma (UC) is poor. Optimal second-line chemotherapy remains undefined.[1] As such, there is a significant unmet need for therapies that are well tolerated and confer clinical benefit in this population. Recent encouraging data with immune checkpoint inhibitors have resulted in positive randomized phase 3 studies and regulatory approvals.

The presence of tumor-infiltrating mononuclear cells is associated with longer overall survival (OS) in patients with locally advanced or metastatic UC.[2] However, UC tumors may evade immune detection by exploiting inhibitory checkpoint pathways that suppress T-cell responses, such as the programmed cell death-1 (PD-1)–programmed cell death ligand-1 (PD-L1) pathway.[3-5] Moreover, UCs demonstrate relatively high PD-L1 expression compared with other tumors.[6] Although the relationship between PD-L1 expression and outcome is complex and likely dependent on assessment methods (as evidenced in the nivolumab phase 2 and pembrolizumab phase 3 trials),[2,7,8] PD-L1 blockade may overcome this immune checkpoint, resulting in prolonged T-cell activation and possible tumor rejection.[9] Indeed, several anti-PD-1/PD-L1 agents have shown preliminary activity with acceptable safety in patients with locally advanced/metastatic UC.[7,8,10-14] For example, treatment with the anti-PD-1 antibody pembrolizumab was associated with a 27% reduction in risk of death vs chemotherapy among previously treated patients with UC.[8]

Durvalumab is a selective, high-affinity, engineered human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 (half-maximal inhibitory concentration [IC_{50}], 0.1 nM) and CD80 (IC_{50}, 0.04 nM).[15] An ongoing, multicenter, phase 1/2 open-label study (NCT01693562) is evaluating the safety and antitumor activity of durvalumab monotherapy in patients with advanced solid tumors, including locally advanced /metastatic UC. An interim analysis of 61 patients with UC in this study indicated that durvalumab was well tolerated and associated with antitumor activity, particularly in patients with PD-L1-high disease (≥25% of tumor cells [TCs] or tumor-infiltrating immune cells expressing PD-L1),[16] resulting in its breakthrough therapy designation by the US Food and Drug Administration (FDA).

We report a planned analysis of the safety and efficacy of durvalumab in patients with locally advanced/metastatic UC from this phase 1/2 study. These data were accepted for assessment by the FDA for Biologics License Application under priority review, resulting in recent US approval of durvalumab for postplatinum, locally advanced/metastatic UC. They include, for the first time, results for progression-free survival (PFS) and OS. In addition, safety findings for the overall population of patients with any solid tumor from this study are reported.

Key Points

Question Does durvalumab provide clinical benefit to patients with locally advanced or metastatic urothelial carcinoma (UC)?

Findings In a phase 1/2 open-label study of 191 patients with locally advanced/metastatic UC, confirmed objective response rate with durvalumab, 10 mg/kg every 2 weeks, was 17.8%, including 7 complete responses, and median progression-free survival and overall survival were 1.5 and 18.2 months, respectively. Grade 3/4 treatment-related and immune-mediated adverse events occurred in 13 patients (6.8%) and 4 patients (2.1%), respectively.

Meaning Durvalumab shows favorable efficacy and an excellent safety profile in patients with locally advanced/metastatic UC.

Methods

Study Design and Participants

For the overall study population, patients with solid tumors ages 18 years or older with histologically and/or cytologically confirmed disease were eligible for inclusion. Eligible patients could have disease that progressed on prior therapy or be treatment-naïve, had Eastern Cooperative Oncology Group performance status 0/1, and had adequate organ and bone marrow function. Patients were not eligible if they had received any immunotherapy or investigational anticancer therapy within the past 4 weeks (6 weeks for monoclonal antibodies) or if they were receiving any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer. Patients who met these criteria and had locally advanced/metastatic UC and whose disease had progressed while they were receiving prior therapy or were ineligible for or refused any number of prior therapies were eligible for inclusion in the UC cohort.[16]

This study was conducted according to the Declaration of Helsinki and approved by the independent ethics committee or institutional review board at each participating center, with written informed consent obtained from all patients. Study participants were not compensated. See Supplement 1 for the trial protocol and the statistical analysis plan.

Procedures

Durvalumab was administered by intravenous infusion, 10 mg/kg every 2 weeks (Q2W), for up to 12 months, or until confirmed progressive disease, initiation of another anticancer therapy, unacceptable toxic effects, consent withdrawal, or other reasons for discontinuation. For patients with disease progression during follow-up who had not received another anticancer therapy and had not met criteria for discontinuing study treatment, a 12-month course of durvalumab retreatment was allowed. Safety was assessed from start of study with monitoring continued through 90 days after the last durvalumab dose or until initiation of another anticancer therapy. Toxic effects were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Tumor assessments occurred at 6, 12, and 16 weeks, and every 8 weeks thereafter during treatment. Following discontinuation, tumor assessments were performed every 2 months for 1 year and then every 3 months thereafter.

Outcomes

Primary safety end points included AEs, serious AEs, laboratory evaluations, vital signs, and physical examinations. Also

assessed were AEs of special interest (AESIs) and immune-mediated adverse events (imAEs [AESIs requiring systemic steroids, endocrine therapy, or other immunosuppressants within 30 days of onset and prior to resolution that were consistent with an immune-mediated mechanism and had no clear alternate etiology]). The primary efficacy end point was objective response rate (ORR; proportion with confirmed complete response or partial response by blinded independent central review using Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1).[17] Key secondary end points included duration of response, time to response, change in target lesion size, disease control rate (confirmed complete response or partial response or stable disease for ≥6 weeks), PFS (time from first dose until documented disease progression per RECIST, version 1.1, or death), and OS (time from first dose until death).

PD-L1 expression was evaluated by immunohistochemical analysis in tumor tissue obtained prior to treatment, using the SP-263 anti-PD-L1 antibody assay (Ventana Medical Systems), as described previously.[16] With respect to patient eligibility for the trial, the first 20 patients were enrolled regardless of PD-L1 expression[16]; however, preliminary data suggested that PD-L1 may be expressed more commonly on immune cells than on TCs.[11] Therefore, to ensure assessment of the contribution of PD-L1-expressing TCs to response with durvalumab, subsequently enrolled patients (n = 43) were required to have PD-L1 expression of at least 5% on TCs. However, an interim analysis showed that ORRs in patients with less than 5% PD-L1 expression (n = 86) were similar to ORRs in all patients. Therefore, a protocol amendment removed this requirement. For purposes of biomarker analyses, a 25% cutoff for defining TC- or immune cell–dependent expression status was chosen, as previously described,[16] because this cutoff seemed to enrich for response, based on review of PD-L1 expression in the first 20 enrolled patients who were followed for a minimum of 12 weeks. This exploratory analysis also suggested the optimal scoring algorithm to be a unique combined assessment of PD-L1 staining of TCs and immune cells (PD-L1 "high,"≥25% of either TCs or immune cells staining for PD-L1, and PD-L1 "low or negative,"<25% of both TCs and immune cells staining for PD-L1).

Statistical Analysis

This planned study update is based on more than 3 times as many patients and increased follow-up compared with the initial report of this study,[16] and its timing was predicated by regulatory interactions. In addition, we examined time to onset of treatment-related AEs and AESIs, which was defined as the time from the first dose of study treatment to the onset date of the AE. All patients who received their first dose of durvalumab at least 30 days before July 24, 2016 (data cutoff for the interim analysis), were included in the safety and efficacy analyses ("as-treated" population). A total of 191 patients with UC would provide a width between the observed ORR and its lower limit of the exact 2-sided 95% CI ranging from 6% to 7%, when the ORR was expected to be in the 20% to 30% range.

The ORR, disease control rate, and their respective exact 2-sided 95% CIs were estimated using the Clopper-Pearson method and by PD-L1 expression status (although the study was not designed to perform formal statistical comparisons of PD-L1 subgroups). Time-to-event end points, such as duration of response (in patients with objective response), PFS, OS, time to response, landmark PFS and OS rates, and cumulative incidences of AEs, were estimated by Kaplan-Meier method (relevant censoring times are defined in the eMethods in Supplement 2) with 2-sided 95% CIs provided by Brookmeyer and Crowley method. SAS statistical software (version 9.3 or higher) was used for all statistical analyses.

Results

Patients in the UC Cohort

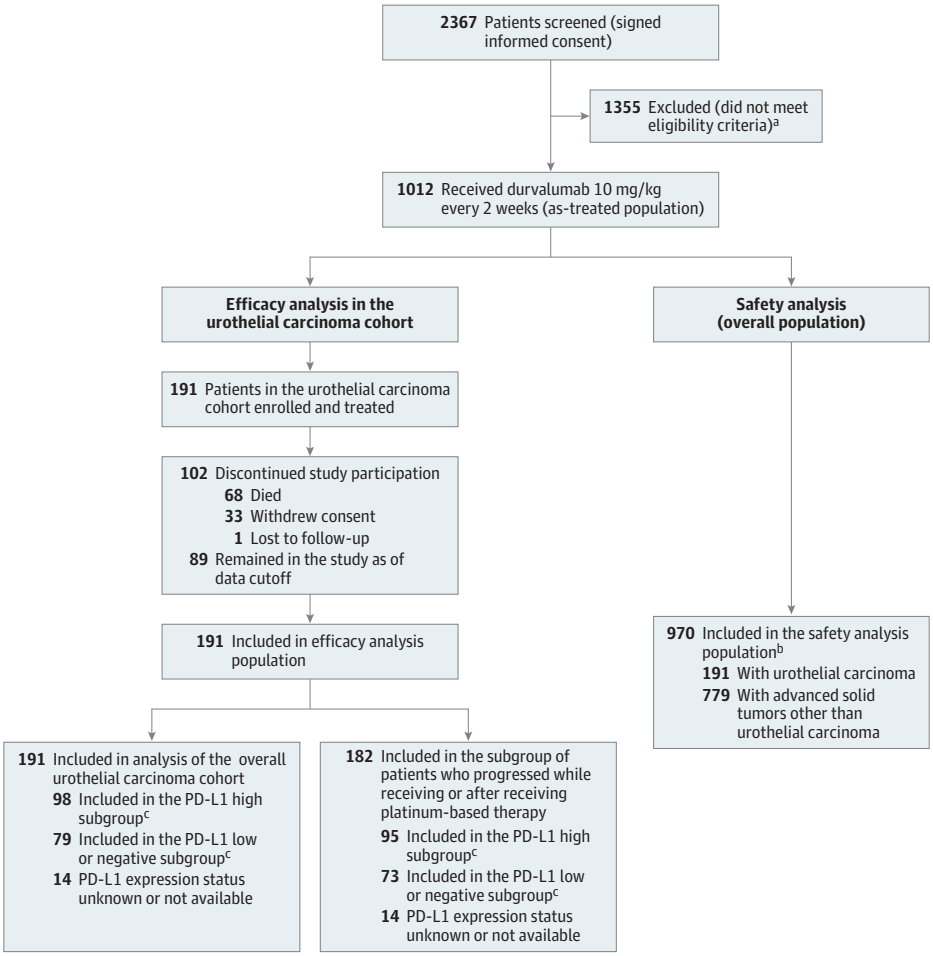
A total of 191 patients with locally advanced/metastatic UC from 60 sites across 9 countries had received treatment (as-treated population) (**Figure 1**). The median exposure duration in the as-treated UC population was 2.8 months (range, 0.4-12.5 months), and the median follow-up was 5.78 months (range, 0.4-25.9 months). As of the data cutoff of October 24, 2016 (90-day update), 44 patients (23.0%) were still receiving durvalumab.

Demographic and baseline characteristics of the patients with UC are summarized in **Table 1** (eTable 1 in Supplement 2 summarizes baseline characteristics for all patients who received durvalumab, 10 mg/kg Q2W [n = 970]). The median age of patients with UC was 67.0 years and most patients were male (136 [71.2%]) and white (123 [71.1%]). All patients with UC had stage 4 disease, and 190 (99.5%) had received prior anticancer therapy; 64 (33.5%) had received at least 2 prior regimens, and 188 (98.4%) had received prior platinum-based treatment. Overall, 182 of 191 patients (95.3%) whose disease had progressed while receiving or after receiving a platinum-based therapy or within 12 months of receiving therapy in a neoadjuvant or adjuvant setting (hereinafter referred to as second-line or greater postplatinum subgroup). The other 9 patients (4.7%) were either treatment naïve or designated as first-line patients who had received platinum-based therapy in the neoadjuvant/adjuvant setting and whose disease progressed more than 12 months after the last dose of therapy. At study entry, 177 of 191 patients (92.7%) had visceral metastases; 82 of 191 (42.9%), liver metastases; and 14 of 191 (7.3%), lymph node–only disease; PD-L1 expression was high in 98 of 191 (51.3%), low or negative in 79 of 191 (41.4%), and unknown in 14 of 191 (7.3%).

Antitumor Activity in the UC Cohort

In the as-treated population (n = 191), the ORR was 17.8% (34 of 191; 95% CI, 12.7%-24.0%), including 7 complete responses (3.7%; see the eResults and eTable 4 in Supplement 2 for additional details of the complete responses), and was consistent with that seen in the second-line or greater postplatinum subgroup (32 of 182 [17.6%] [95% CI, 12.3%-23.9%]); ORRs were 27.6% (n = 27; 95% CI, 19.0%-37.5%) in PD-L1 high patients and 5.1% (n = 4; 95% CI, 1.4%-12.5%) in PD-L1 low or negative patients (**Table 2**). The complete response rates did not numerically differ by PD-L1 status, and responses in both

Figure 1. Study Profile



The overall population included 17 different tumor-specific cohorts; 2367 patients were screened, of whom 1355 were screen failures. ≥2L indicates second-line or greater; Q2W, every 2 weeks; PD-L1, programmed cell death ligand-1.

[a] A large portion of screen failures were based on their PD-L1 status and eligibility criteria requiring a specific PD-L1 status for enrollment.

[b] These included 6 patients from the dose-escalation phase of the study.

[c] PD-L1 expression status was unknown (owing to insufficient tumor in biopsy) or unavailable (as testing had not been processed at data cutoff) for 14 patients.

subgroups were durable (Table 2). Objective responses were observed across all subgroups, including subsets with poor prognosis: ORRs in patients with visceral metastases and liver metastases were 15.3% (27 of 177; 95% CI, 10.3%-21.4%) and 7.3% (6 of 82; 95% CI, 2.7%-15.2%), respectively; the ORR in patients with baseline lymph node–only disease was 50.0% (7 of 14; 95% CI, 23.0%-77.0%).

The disease control rate by blinded independent central review assessment was 36.6% (95% CI, 29.8%-43.9%) in the as-treated population and 36.3% (95% CI, 29.3%-43.7%) in the second-line or greater postplatinum subgroup. The disease control rates were numerically greater in PD-L1 high vs low or negative subgroups (44.9% vs 21.5% in the as-treated population; 44.2% vs 20.5% in the second-line or greater postplatinum population) (Table 2).

Responses occurred early and were durable (**Figure 2**A). Median time to response was 1.41 months (range, 1.2-7.2), coinciding with the first protocol-specified imaging assessment. Time to response did not numerically differ by PD-L1 expression status and was similar in the second-line or greater postplatinum subgroup (data not shown). Median duration of response in the as-treated population had not been reached at data cutoff (range, ≥0.9 to ≥19.9 months). Seventeen of 34 responders (50.0%) had a response lasting at least 6 months (Figure 2A, Table 2), and 26 (76.5%) had an ongoing response at data cutoff (see the eResults in Supplement 2 for additional details regarding patients without an ongoing response at data cutoff).

Among the 159 patients with target lesions at baseline and at least 1 postbaseline scan, 51 (32.1%) experienced a target lesion reduction of at least 30% from baseline (Figure 2B). Tumor shrinkage and deep durable changes were seen in both PD-L1 subgroups (Figure 2B; eFigure 1 in Supplement 2).

Survival in the UC Cohort

Given limited follow-up, OS data were considered immature at data cutoff. The median PFS was 1.5 months (95% CI, 1.4-1.9) in the as-treated population and 2.1 months (95% CI, 1.4-2.8) and 1.4 months (95% CI, 1.3-1.5) in PD-L1 high and low or negative patients, respectively. The PFS rates at 6, 9, and 12 months were 22% (95% CI, 16%-28%), 18% (95% CI, 12%-25%), and 16% (95% CI, 10%-23%), respectively, in the as-treated population (eFigure 2 in Supplement 2). The median OS was 18.2 months (95% CI, 8.1 to not estimable) in the as-treated population and 20.0 months (95% CI, 11.6 to not estimable) and 8.1 months (95% CI, 3.1 to not estimable) in PD-L1

Table 1. Demographic and Baseline Characteristics of the Cohort With Urothelial Carcinoma (UC), Including the ≥2L Postplatinum Subgroup

Characteristic	UC Cohort, No. (%)	
	As-Treated Population (n = 191)	≥2L Postplatinum (n = 182)
Age, median (range), y	67.0 (34-88)	67.0 (34-88)
Sex		
No.	191	182
Female	55 (28.8)	51 (28.0)
Male	136 (71.2)	131 (72.0)
Race[a]		
Asian	36 (20.8)	15 (17.4)
Black or African American	8 (4.6)	4 (4.7)
White	123 (71.1)	65 (75.6)
Other	5 (2.9)	2 (2.3)
Multiple categories checked	1 (0.6)	0
ECOG performance status		
0	64 (33.5)	61 (33.5)
1	127 (66.5)	121 (66.5)
Baseline hemoglobin concentration[b]		
≥10 g/dL	145 (78.4)	137 (77.8)
<10 g/dL	40 (21.6)	39 (22.2)
Stage 4 at study entry	191 (100)	182 (100)
Sites of disease at baseline[c]		
Visceral	177 (92.7)	168 (92.3)
Liver	82 (42.9)	78 (42.9)
Lymph node only	14 (7.3)	14 (7.7)
PD-L1 expression status[d]		
High	98 (51.3)	95 (52.2)
Low or negative	79 (41.4)	73 (40.1)
Prior line of systemic therapy for inoperable metastatic disease		
0	9 (4.7)	0
1	118 (61.8)	118 (64.8)
2	48 (25.1)	48 (26.4)
3	10 (5.2)	10 (5.5)
≥4	6 (3.1)	6 (3.3)
Previous therapy with platinum-based regimen		
Carboplatin	56 (29.3)	54 (29.7)
Cisplatin	131 (68.6)	127 (69.8)
Other platinum combination[e]	1 (0.5)	1 (0.5)

Abbreviations: ≥2L, second-line or greater; BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group.

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.0.

[a] Each race category counts patients who selected only that category. There are missing values for patients enrolled in France owing to local regulations. In total, race data are available for 173 and 86 patients in the UC cohort and ≥2L postplatinum subgroup, respectively.

[b] Baseline hemoglobin concentration data are available for 185 and 176 patients in the UC cohort and ≥2L postplatinum subgroup, respectively.

[c] Site of disease at baseline was derived from the baseline disease assessment by the investigator and BICR. Visceral metastases defined as liver, lung, bone, or any non–lymph node or soft-tissue metastases.

[d] PD-L1 expression status was unknown (owing to insufficient tumor in biopsy) or unavailable (as testing had not been processed at data cutoff) for 14 patients in both the UC cohort and ≥2L postplatinum subgroup.

[e] Type of platinum was unspecified.

high and low or negative patients, respectively (Figure 2C). The OS rates at 6, 9, and 12 months were 64% (95% CI, 56%-71%), 57% (95% CI, 47%-66%), and 55% (95% CI, 44%- 65%), respectively, in the as-treated population (Figure 2C).

Safety in the UC Cohort

Any-grade treatment-related AEs were reported in 60.7% (**Table 3**). With a median time to onset of 6.1 weeks (range, 4.1-10.1 weeks), the cumulative incidence of treatment-related AEs occurred early, was highest during the first 8 weeks, and subsequently seemed to plateau at around 32 weeks (eFigure 3 in Supplement 2). The most common AEs were fatigue (19.4%), decreased appetite (9.4%), diarrhea (8.4%), and rash (7.3%). Grade 3 or 4 treatment-related AEs occurred in 6.8% (Table 3).

Treatment-related AEs leading to death occurred in 2 of 191 patients (1.0%), 1 each due to autoimmune hepatitis (in a man in his 70s with no history of autoimmune disease, liver disease, or liver abnormalities, but who had elevated liver enzyme levels at baseline prior to dosing) and pneumonitis (in a man in his 50s with a history of untreated grade 1 dyspnea and remote tobacco use); see the eResults in Supplement 2 for additional details regarding the treatments and events that led to both deaths. There were no clinically meaningful differences in AE rates between PD-L1 high and low or negative subgroups (data not shown). Serious treatment-related AEs were reported in 4.7%. Autoimmune hepatitis occurred in 2 patients, whereas other serious AEs only occurred in 1 patient each. Treatment-related AEs required infusion interruption or

Table 2. Antitumor Activity of Durvalumab per Blinded Independent Central Review in the UC Cohort, Including the ≥2L Postplatinum Subgroup

Parameter[a]	All UC			≥2L Postplatinum UC[b]		
	Total (n = 191)[c]	PD-L1 High (n = 98)[d]	PD-L1 Low or Negative (n = 79)[d]	Total (n = 182)	PD-L1 High (n = 95)[d]	PD-L1 Low or Negative (n = 73)[d]
Confirmed ORR, No. (%) [95% CI]	34 (17.8) [12.7 to 24.0]	27 (27.6) [19.0 to 37.5]	4 (5.1) [1.4 to 12.5]	32 (17.6) [12.3 to 23.9]	26 (27.4) [18.7 to 37.5]	3 (4.1) [0.9 to 11.5]
CR, No. (%)	7 (3.7)	4 (4.1)	2 (2.5)	6 (3.3)	4 (4.2)	1 (1.4)
PR, No. (%)	27 (14.1)	23 (23.5)	2 (2.5)	26 (14.3)	22 (23.2)	2 (2.7)
Nonevaluable, No. (%)[e]	33 (17.3)	11 (11.2)	22 (27.8)	31 (17.0)	11 (11.6)	20 (27.4)
Responses ongoing at time of DCO, No. (%)	26 (76.5)	20 (74.1)	3 (75.0)	24 (75.0)	19 (73.1)	2 (66.7)
DoR, median (range), mo	NR (≥0.9 to ≥19.9)	NR (≥0.9 to ≥19.9)	12.25 (≥1.9 to ≥12.3)	NR (≥0.9 to ≥19.9)	NR (≥0.9 to ≥19.9)	12.25 (≥1.9 to 12.3)
≥6 mo, No. (%)	17 (50.0)	15 (55.6)	2 (50.0)	15 (46.9)	14 (53.8)	1 (33.3)
DCR, No. (%) [95% CI]	70 (36.6) [29.8 to 43.9]	44 (44.9) [34.8 to 55.3]	17 (21.5) [13.1 to 32.3]	66 (36.3) [29.3 to 43.7]	42 (44.2) [34.0 to 54.8]	15 (20.5) [12.0 to 31.6]

Abbreviations: ≥2L, second-line or greater; CR, complete response; DCO, data cutoff; DCR, disease control rate including CR, PR, or SD≥6 weeks; DoR, duration of response; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand-1; PR, partial response; SD, stable disease; UC, urothelial carcinoma.

[a] Based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

[b] The ≥2L postplatinum subgroup includes patients who had progressed while on or after a platinum-based therapy, including those patients whose disease progressed within 12 mo of receiving therapy in a neoadjuvant/adjuvant setting.

[c] Includes 14 patients who had unknown and/or unavailable PD-L1 status and who are not included in either the PD-L1 high or PD-L1 low or negative subgroups.

[d] PD-L1 expression status was unknown (owing to insufficient tumor in biopsy) or unavailable (as testing had not been processed at data cutoff) for 14 patients.

[e] Nonevaluable patients were those without postbaseline scans owing to death, PD, or withdrawal of consent prior to the first on-treatment disease assessment or had a postbaseline scan that did not meet the minimum required interval for SD.

dose delay in 11.0% and led to permanent treatment discontinuation in 3 patients (1.6%), including the 2 patients with imAEs that led to death.

Any-grade treatment-related AESIs occurred in 34.6%, most of which were grade 1 or 2 (eTables 2 and 3 in Supplement 2); their cumulative incidence seemed to plateau at around 32 weeks (eFigure 3 in Supplement 2); 4.7% experienced treatment-related grade 3/4 AESIs. Within this population, imAEs occurred in 11.5%; most had grade 1 or 2 events (eTable 3 in Supplement 2). The most common imAEs were hypothyroidism (5.2%), diarrhea (2.1%), and selected hepatic events (2.1%; including increased aspartate aminotransferase level, increased alanine aminotransferase level, increased transaminase levels, and autoimmune hepatitis). Grade 3 or 4 imAEs occurred in 4 patients (2.1%) and were reported in the categories of selected hepatic events (1.0%), and rash and selected renal events (0.5% each). Among patients with any-grade treatment-related AESIs, 7.3% were administered concomitant systemic steroids.

Safety in the Overall Population Receiving Durvalumab, 10 mg/kg Q2W

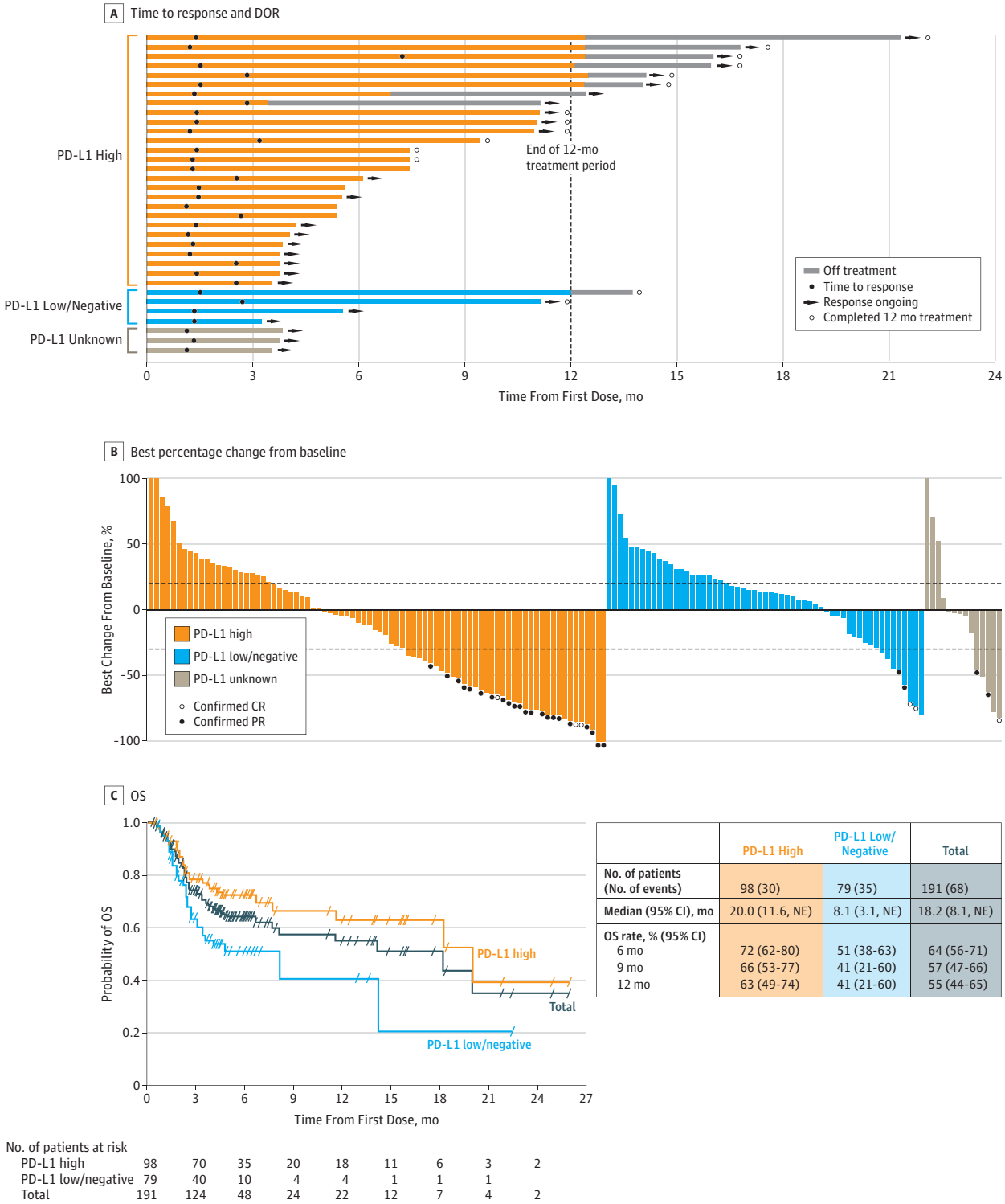
The types and frequencies of any-grade and grade 3 or 4 treatment-related AEs in all patients who received durvalumab, 10 mg/kg Q2W (ie, patients with any solid tumor; n = 970), were similar to those of patients with UC (Table 3). In addition, time to onset of treatment-related AEs was similar (8.1 weeks; range, 6.1-10.1 weeks) and the cumulative incidences of treatment-related AEs and AESIs also seemed to be highest during the first 8 weeks, plateauing at around 32 weeks (eFigure 3 in Supplement 2). See the eResults in Supplement 2 for further details regarding the safety of durvalumab in this population.

Discussion

Durvalumab, 10 mg/kg Q2W, showed compelling clinical activity in the as-treated population with UC based on ORR (17.8%), disease control rate (36.6%), and median OS (18.2 months [95% CI, 8.1 to not estimable]), which is promising compared with the median OS of historical controls.[1] Responses were early, durable, and observed regardless of PD-L1 expression. The onset of AEs was characterized as occurring fairly early and then plateauing after approximately 32 weeks. These outcomes are notable for a population comprised mainly of heavily pretreated patients, including those with poor prognoses (visceral and liver metastases). These results build on previous findings from this study[16] and represent one of the first studies to test response durability following 12 months of PD-L1 inhibition in patients with UC. This study limited treatment to 1 year. Although patients who had responded continued to respond after 1 year of treatment, it is unclear if continuous suppression of tumor defense is needed. Future studies randomizing patients to continuous vs limited therapy may be warranted to understand this further.

The ORR with durvalumab reported herein for all patients in the UC cohort (n = 191), 17.8% (95% CI, 12.7%-

Figure 2. Antitumor Activity and Kaplan-Meier Estimates of Overall Survival in the Cohort With Urothelial Carcinoma by PD-L1 Expression Status



	PD-L1 High	PD-L1 Low/ Negative	Total
No. of patients (No. of events)	98 (30)	79 (35)	191 (68)
Median (95% CI), mo	20.0 (11.6, NE)	8.1 (3.1, NE)	18.2 (8.1, NE)
OS rate, % (95% CI)			
6 mo	72 (62-80)	51 (38-63)	64 (56-71)
9 mo	66 (53-77)	41 (21-60)	57 (47-66)
12 mo	63 (49-74)	41 (21-60)	55 (44-65)

Programmed cell death ligand-1 (PD-L1) expression status was unknown (owing to insufficient tumor in biopsy) or unavailable (as testing had not been processed at data cutoff) for 14 patients. A, Time to response and duration of response (DoR) by blinded independent central review (BICR). B, Best percentage change from baseline in tumor size by BICR (patients with target lesions at baseline and ≥1 postbaseline scan). One patient in the PD-L1 high subgroup with confirmed complete response was excluded from the figure owing to lack of a target lesion at baseline per BICR. For patients with lymph nodes included in their target lesions, complete response may not equate with a 100% decrease from baseline according to Response Evaluation Criteria in Solid Tumors, version 1.1. C, Overall survival (OS). Given limited follow-up, OS data were considered immature at the time of data cutoff. CR indicates complete response; NE, not evaluable; neg, negative; PR, partial response.

Table 3. Treatment-Related Adverse Effects in the UC Cohort and in the Overall Population Receiving Durvalumab, 10 mg/kg Q2W[a]

	No. (%)			
	UC Cohort (As-Treated Population) (n = 191)		Overall Population Receiving Durvalumab, 10 mg/kg Q2W (n = 970)[b]	
Adverse Event	All Grades[c]	Grade 3/4	All Grades[c]	Grade 3/4
Any	116 (60.7)	13 (6.8)	565 (58.2)	92 (9.5)
Occurring in ≥5% of patients in either population or with grade ≥3 severity in ≥1 patient in the UC cohort				
Fatigue	37 (19.4)	0	185 (19.1)	16 (1.6)
Decreased appetite	18 (9.4)	0	69 (7.1)	3 (0.3)
Diarrhea	16 (8.4)	1 (0.5)	80 (8.2)	5 (0.5)
Rash	14 (7.3)	0	64 (6.6)	1 (0.1)
Nausea	13 (6.8)	0	82 (8.5)	2 (0.2)
Arthralgia	11 (5.8)	0	49 (5.1)	2 (0.2)
Pyrexia	11 (5.8)	0	31 (3.2)	0
Pruritus	10 (5.2)	0	69 (7.1)	1 (0.1)
Increased ALT level	8 (4.2)	2 (1.0)	36 (3.7)	9 (0.9)
Increased AST level	6 (3.1)	3 (1.6)	38 (3.9)	11 (1.1)
Increased GGT level	6 (3.1)	2 (1.0)	22 (2.3)	8 (0.8)
Increased blood ALP level	4 (2.1)	1 (0.5)	15 (1.5)	2 (0.2)
Hypertension	3 (1.6)	2 (1.0)	8 (0.8)	3 (0.3)
Anemia	2 (1.0)	1 (0.5)	21 (2.2)	2 (0.2)
Maculopapular rash	2 (1.0)	1 (0.5)	19 (2.0)	2 (0.2)
Infusion-related reaction	2 (1.0)	1 (0.5)	11 (1.1)	2 (0.2)
Increased transaminases	2 (1.0)	1 (0.5)	5 (0.5)	2 (0.2)
Autoimmune hepatitis	2 (1.0)	1 (0.5)	4 (0.4)	3 (0.3)
Tumor flare	2 (1.0)	1 (0.5)	2 (0.2)	1 (0.1)
Acute kidney injury	1 (0.5)	1 (0.5)	4 (0.4)	1 (0.1)
Atrial fibrillation	1 (0.5)	1 (0.5)	2 (0.2)	1 (0.1)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; Q2W, every 2 weeks; UC, urothelial carcinoma.

[a] Patients with any solid tumor.

[b] Includes patients in the UC cohort.

[c] Grade 5 treatment-related AEs occurred in 2 UC patients (1 each due to autoimmune hepatitis and pneumonitis) and 4 patients in the overall population receiving durvalumab, 10 mg/kg Q2W (pneumonia in the setting of pneumonitis in a patient with non–small-cell lung cancer, autoimmune hepatitis and pneumonitis in patients with UC, and immune thrombocytopenic purpura in a patient with triple-negative breast cancer).

24.0%), was lower than that reported previously for the interim analysis (n = 61), 31.0% (95% CI, 17.6%-47.1%).[16] However, the 95% CIs overlap, and such findings are not unexpected. Reduced ORR from one clinical development phase to the next has been observed in studies of other immunotherapies (eg, for the anti-PD-L1 antibody atezolizumab).[11,12]

Durvalumab, 10 mg/kg Q2W, was well tolerated in patients with locally advanced/metastatic UC (n = 191). Treatment-related AEs were mostly grade 1 or 2, with cumulative incidences plateauing after early onset; only 6.8% had grade 3 or 4 AEs. The incidences of treatment-related SAEs (4.7%), treatment-related AEs leading to discontinuation (1.6%), and imAEs (11.5%) were also low; imAEs were mostly grade 1 or 2; only 2 patients discontinued treatment owing to imAEs. Only 7.3% with treatment-related AESIs were concomitantly administered systemic steroids.

Cross-trial comparison can be confounding; however, these safety results are compelling when indirectly compared with other trials in this setting. The rates of grade 3 or 4 treatment-related AEs and discontinuation due to treatment-related AEs with durvalumab are favorable compared with those related to other agents.[7,8,10,11,13,14] Each antibody is structurally unique and potentially generates different host immune responses, and, while the most likely explanation for observed differences are study design, patient population, reporting, and duration of follow-up, potentially different safety signals between these agents cannot be excluded.

Similarly, durvalumab, 10 mg/kg Q2W, was well tolerated in patients with any solid tumor, comprising the overall population (n = 970). Only 2.8% discontinued this therapy owing to treatment-related AEs; imAEs occurred in 11.5%, systemic steroids were concomitantly administered to 6.2% with treatment-related AESIs, and 0.4% had treatment-related AEs leading to death. Finally, while the frequencies of AEs and AESIs are widely reported, the timing of their onset has not, to our knowledge, been studied in detail. The work presented herein shows that the frequency is highest during the first 8 weeks, with a plateau occurring by week 32. In addition, onset of AEs and AESIs runs in parallel over time.

Limitations

Notwithstanding inherent limitations of cross-trial comparisons, the antitumor activity of durvalumab was consistent with those of other, previously studied immunotherapies.[7,8,10,11,13,14] In addition, despite different methodologies, most of these studies also showed better outcomes in PD-L1 high patients. Although clinical activity with durvalumab was observed in both PD-L1 high and low or negative patients, ORR was numerically higher in PD-L1 high patients. The combined

algorithm therefore supports the effectiveness of the VENTANA PD-L1 (SP263) assay to identify patients most likely to respond to durvalumab, as internally validated using the first 20 enrolled patients to establish the algorithm and the remaining patients in the UC cohort to validate the approach (data not shown); however, external validation is warranted before this approach can be used extensively. In addition, this aligns with the biology of response to immunotherapy and is consistent with external UC data, since PD-L1 expression on either TCs or tumor-associated immune cells can inhibit antitumor immunity. However, while optimal, this approach does not completely exclude patients who may respond. The high negative predictive value of the assay (94.9%) may be especially helpful in educating patients on the likelihood of response to durvalumab; however, it should not be used to exclude patients from therapy, especially because there is no single standard of care in the second-line or greater UC setting, such that some PD-L1 low or negative patients may be better candidates for single-agent durvalumab vs commonly used chemotherapy.

Conclusions

This study supports the manageable safety and tolerability of durvalumab, 10 mg/kg Q2W, as monotherapy in patients with solid tumors and confirms its favorable clinical activity in previously treated patients with locally advanced/metastatic UC for whom prognosis is poor. Based on these findings, durvalumab seems to be an attractive alternative to chemotherapy, irrespective of biomarker status. Further UC studies, including DANUBE (NCT02516241), BISCAY (NCT02546661), and Study 10 (NCT02261220), are evaluating durvalumab as monotherapy and in combination with other agents (tremelimumab, AZD4547, olaparib, AZD1775, and vistusertib). In conclusion, these are the most robust and encouraging safety data yet reported for durvalumab in locally advanced/metastatic UC and, together with the efficacy data, have formed the basis for its recent regulatory approval and positioning as a standard of care (alongside atezolizumab and nivolumab) in this setting.

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