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ORIGINAL REPORT

Safety and Efficacy of Durvalumab (MEDI4736), an Anti–Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer

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ABSTRACT

Purpose
To investigate the safety and efficacy of durvalumab, a human monoclonal antibody that binds programmed cell death ligand-1 (PD-L1), and the role of PD-L1 expression on clinical response in patients with advanced urothelial bladder cancer (UBC).

Methods
A phase 1/2 multicenter, open-label study is being conducted in patients with inoperable or metastatic solid tumors. We report here the results from the UBC expansion cohort. Durvalumab (MEDI4736, 10 mg/kg every 2 weeks) was administered intravenously for up to 12 months. The primary end point was safety, and objective response rate (ORR, confirmed) was a key secondary end point. An exploratory analysis of pretreatment tumor biopsies led to defining PD-L1–positive as ≥ 25% of tumor cells or tumor-infiltrating immune cells expressing membrane PD-L1.

Results
A total of 61 patients (40 PD-L1–positive, 21 PD-L1–negative), 93.4% of whom received one or more prior therapies for advanced disease, were treated (median duration of follow-up, 4.3 months). The most common treatment-related adverse events (AEs) of any grade were fatigue (13.1%), diarrhea (9.8%), and decreased appetite (8.2%). Grade 3 treatment-related AEs occurred in three patients (4.9%); there were no treatment-related grade 4 or 5 AEs. One treatment-related AE (acute kidney injury) resulted in treatment discontinuation. The ORR was 31.0% (95% CI, 17.6 to 47.1) in 42 response-evaluable patients, 46.4% (95% CI, 27.5 to 66.1) in the PD-L1–positive subgroup, and 0% (95% CI, 0.0 to 23.2) in the PD-L1–negative subgroup. Responses are ongoing in 12 of 13 responding patients, with median duration of response not yet reached (range, 4.1+ to 49.3+ weeks).

Conclusion
Durvalumab demonstrated a manageable safety profile and evidence of meaningful clinical activity in PD-L1–positive patients with UBC, many of whom were heavily pretreated.

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INTRODUCTION

Urothelial bladder cancer (UBC), which accounts for > 90% of all bladder cancers,[1] is one of the 10 predominant malignancies worldwide.[2] Systemic platinum-based chemotherapy, introduced nearly 30 years ago, remains the standard of care for untreated patients with inoperable or advanced metastatic UBC and is associated with median overall survival of 14 to 15 months and a 5-year survival rate of ≤ 15%.[3-5] The prognosis for patients who fail standard platinum-containing chemotherapy is dismal (median overall survival ranging from 5 to 7 months).[6] No established standard of care exists, and participation in clinical trials is currently recommended.[7] Therefore, new therapies are needed for this patient population.

Novel immunotherapies that can interrupt signals generated by immune checkpoint proteins can effectively enhance antitumor T-cell immunity. One such checkpoint protein, programmed

cell death-1 (PD-1, CD279), is a key receptor expressed on activated T cells that when bound by its ligand, programmed cell death ligand-1 (PD-L1, B7 homolog 1, CD274), suppresses T-cell–mediated immune responses.[8-11] Tumor cells (TC) often hijack the PD-1/PD-L1 pathway to protect themselves from tumor-specific T cells.[12] Moreover, immune cells (IC) in the tumor microenvironment may also express PD-L1 and similarly inhibit T-cell responses at the tumor site.[13] To date, PD-1 monoclonal antibodies nivolumab and pembrolizumab have been approved for the treatment of advanced melanoma, non–small-cell lung cancer, and renal cell carcinoma (nivolumab only).[14,15] Blockade of immune checkpoints activated by the PD-1/PD-L1 pathway has also shown promising early clinical activity in UBC.[2,11,12,16-19]

Durvalumab is a selective, high-affinity, human immunoglobulin G1 κ monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80 (B7.1), allowing T cells to recognize and kill tumor cells. A phase 1/2 dose-escalation and dose-expansion study is evaluating the safety and antitumor activity of durvalumab monotherapy in adult patients with advanced solid tumors. Previous reports from this study in other tumor types demonstrated that durvalumab has a tolerable safety profile and durable antitumor activity.[20-22] Herein, we report safety and efficacy of durvalumab in the expansion cohort of patients with UBC. A biomarker subset analysis was conducted to determine the activity of durvalumab on the basis of PD-L1 expression on TC or IC to select the most appropriate PD-L1 definition that enriches for patients most likely to respond to durvalumab.

METHODS

Study Design and Participants

This phase 1/2 first-in-human, multicenter, open-label dose-escalation and dose-expansion study is being conducted at 70 centers worldwide. Approximately 60 patients with UBC were planned to be enrolled in the expansion cohort.

Eligible patients were ≥ 18 years of age with histologically or cytologically confirmed inoperable or metastatic transitional-cell urothelial carcinoma and who had progressed on, been ineligible for, or refused any number of prior therapies. Patients had an Eastern Cooperative Oncology Group performance status score of 0 or 1, adequate organ and hematologic functions, and fresh tumor biopsy and/or archival tumor tissue available for PD-L1 testing. Key exclusion criteria were active autoimmune disease or inflammatory bowel disease, prior severe or persistent immune-related adverse events (AEs), previous exposure to anti–PD-1 or anti–PD-L1 therapy, requirement for > 10 mg/d of prednisone or equivalent, and untreated CNS metastases. The study protocol was reviewed and approved by the institutional review board of each participating center, and informed consent was obtained from all patients.

Procedures

Patients were treated with durvalumab (10 mg/kg every 2 weeks) via intravenous infusion in the dose-expansion phase.[23] Durvalumab was administered for 12 months or until confirmed disease progression, initiation of alternative anticancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons for study drug discontinuation.[22] Patients with confirmed disease progression could continue to receive durvalumab if they did not have clinical deterioration and were deriving clinical benefit from treatment. Treatment interruptions, but not dose reductions, were permitted. Patients were offered one 12-month retreatment course if disease progression was noted during follow-up and the patient had not received other anticancer treatment and had not met criteria for discontinuation.

Safety assessments were performed from study start through 90 days after the last durvalumab dose in accordance with the National Cancer Institute Common Terminology Criteria, version 4.03. Measurable target and nontarget lesions were assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and documented before treatment initiation. Patients underwent tumor assessments with cross-sectional imaging at study sites at weeks 6, 12, and 16 and then every 8 weeks during treatment. After treatment discontinuation, tumor assessments were performed every 2 months for 1 year and then every 3 months.

Biomarker Analysis for Patient Eligibility

Pretreatment tumor tissue samples were assessed centrally (Ventana Medical Systems, Tucson, AZ) for PD-L1 expression by immunohistochemistry with the analytically validated Ventana SP263 assay optimized for use on the automated BenchMark ULTRA platform (Ventana).[24] PD-L1 expression for both TC and IC in the tumor microenvironment was determined by the percentage of cells expressing PD-L1 at any intensity above background staining.

The initial 20 patients with UBC were enrolled regardless of PD-L1 expression. However, preliminary data suggested that PD-L1 may be expressed more commonly on IC than on TC.[13] Therefore, to ensure the ability to assess the contribution of PD-L1–expressing TC on response to durvalumab, subsequent patients were required to have a minimum of 5% PD-L1 expression on TC.

Biomarker Cutoff Selection

After review of PD-L1 expression in the initial 20 patients enrolled and followed for a minimum of 12 weeks, a 25% cutoff for defining TC- or IC-dependent status was chosen for response analysis because each seemed to enrich for response. This cutoff was also selected, in part, because a 25% TC-only criterion has been optimized for selection of patients with non–small-cell lung cancer and squamous cell carcinoma of the head and neck treated with durvalumab, as previously described.[24] In addition to TC- or IC-independent definitions, a combined TC/IC algorithm was developed and applied to all patients to potentially separate responding and nonresponding groups. For the combined algorithm, PD-L1 was defined as positive if either ≥ 25% of TC or ≥ 25% of IC expressed PD-L1, and PD-L1 was defined as negative if both < 25% of TC and < 25% of IC expressed PD-L1. Unless noted otherwise, PD-L1–positive refers to positive staining of either TC or IC as defined above. Because of the potential for a change in PD-L1 status over time and/or in response to anticancer therapies, the PD-L1 status for a given patient was derived only from the most recent evaluable tumor biopsy sample.

Outcomes

The primary end point of this study was safety on the basis of assessment of AEs and serious AEs. A key secondary end point was objective response rate (ORR, defined as confirmed complete or partial response) on the basis of investigator-assessed RECIST v1.1.[25] Another efficacy end point was disease control rate at 12 weeks (DCR12, defined as confirmed complete or partial response, or stable disease for ≥ 12 weeks) according to RECIST v1.1. Exploratory analyses included the assessment of biomarkers (eg, PD-L1) that were hypothesized to potentially correlate with clinical activity and could, in the future, be used prospectively to identify patients most likely to respond to durvalumab.

Statistical Analysis

Safety analysis was performed on the as-treated population, defined as all enrolled patients who received one or more doses of durvalumab. ORR was assessed in the response-evaluable population, defined as patients who initiated study treatment ≥ 12 weeks before data cutoff, had

measurable disease at baseline, and had one or more postbaseline scans or experienced disease progression or death. Analyses of duration of response were performed on the subset of patients who achieved an objective response. ORR, DCR12, and accompanying 95% CIs were estimated using the exact binomial method for all patients with UBC and by PD-L1 status. Duration of response was estimated using the Kaplan-Meier method.[26] SAS (version 9.1) was used for all statistical analyses. This study is registered with ClinicalTrials.gov, number NCT01693562, and EudraCT, number 2012-002206-52.

RESULTS

Patient Characteristics

Between August 28, 2014 and November 10, 2015, 61 patients (40 PD-L1–positive, 21 PD-L1–negative) were enrolled in the UBC expansion cohort of the study. At data cutoff on November 20, 2015, median duration of follow-up was 4.3 months (range, 0.3 to 14.8 months), and follow-up duration was similar between PD-L1–positive and PD-L1–negative patients. All 61 patients were included in the safety analysis, and 42 patients were evaluable for response. Nineteen patients were not response evaluable because they either had initiated treatment < 12 weeks before data cutoff (n = 17) or discontinued before first postbaseline disease assessment because of withdrawal of consent (n = 2).

Overall, the majority of patients were men (68.9%) and white (65.6%), with a median age of 66.0 years (Table 1). Most patients (93.4%) had received one or more prior lines of systemic therapy for advanced disease, and 31.1% had received three or more prior lines of systemic therapy. Many patients had adverse prognostic risk factors, including liver metastases (29.5%) and baseline hemoglobin concentration < 10 g/dL (23.0%). Patient characteristics were well balanced between the PD-L1–positive and PD-L1–negative subgroups, although the PD-L1–negative subgroup had a higher proportion of patients with non–lymph-node-only metastases.

On the basis of fresh tumor biopsies obtained during screening or archival tumor tissue taken before study entry from all screened patients (n = 183), the prevalence of PD-L1–positive staining was estimated to be 59% on the basis of TC or IC staining, 19% on the basis of TC staining only, and 45% on the basis of IC staining only. Figure 1 illustrates representative immunohistochemical staining patterns for PD-L1 on TC and/or IC.

Safety and Tolerability

The median duration of exposure was 8.0 weeks (range, 1.6 to 54.0 weeks) in the overall UBC population and 9.2 and 6.0 weeks in PD-L1–positive and PD-L1–negative subgroups, respectively (Table 1). Thirty-nine patients (63.9%) reported a treatment-related AE of any grade (Table 2). The most frequently reported events were fatigue, diarrhea, and decreased appetite. A similar proportion of PD-L1–positive (65.0%) and PD-L1–negative (61.9%) patients reported treatment-related AEs.

The majority of the treatment-related AEs were low grade (Table 2). Grade 3 treatment-related AEs (acute kidney injury,

Table 1. Baseline Characteristics

Characteristic	PD-L1–Positive (n = 40)	PD-L1–Negative (n = 21)	Total (N = 61)
Median (range) age, years	67.0 (34-79)	62.0 (52-81)	66.0 (34-81)
Male sex	30 (75.0)	12 (57.1)	42 (68.9)
Race			
Asian	4 (10.0)	2 (9.5)	6 (9.8)
Black or African American	3 (7.5)	1 (4.8)	4 (6.6)
White	26 (65.0)	14 (66.7)	40 (65.6)
Other	2 (5.0)	1 (4.8)	3 (4.9)
Unknown	5 (12.5)	3 (14.3)	8 (13.1)
No. of prior systemic therapies for advanced disease			
0	1 (2.5)	3 (14.3)	4 (6.6)
1	19 (47.5)	7 (33.3)	26 (42.6)
2	9 (22.5)	3 (14.3)	12 (19.7)
≥ 3	11 (27.5)	8 (38.1)	19 (31.1)
ECOG PS			
0	13 (32.5)	4 (19.0)	17 (27.9)
1	27 (67.5)	17 (81.0)	44 (72.1)
Baseline hemoglobin, g/dL	(n = 36)	(n = 19)	(n = 55)
≥ 10	30 (75.0)	11 (52.4)	41 (67.2)
< 10	6 (15.0)	8 (38.1)	14 (23.0)
Metastatic sites at baseline*	(n = 39)	(n = 21)	(n = 60)
Liver	13 (32.5)	5 (23.8)	18 (29.5)
Lymph node			
Lymph node only	10 (25.0)	3 (14.3)	13 (21.3)
Non–lymph node only	10 (25.0)	12 (57.1)	22 (36.1)
Both lymph and non–lymph node	19 (47.5)	6 (28.6)	25 (41.0)
Median (range) duration of exposure, weeks	9.2 (1.6-54.0)	6.0 (2.0-54.0)	8.0 (1.6-54.0)

NOTE. Data presented as No. (%) unless otherwise noted. PD-L1–positive was defined as either ≥ 25% of TC or ≥ 25% of IC expressing PD-L1, and PD-L1–negative was defined as both < 25% of TC and < 25% of IC expressing PD-L1.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IC, tumor-infiltrating immune cells; PD-L1, programmed cell death ligand-1; TC, tumor cells.
*Site of metastases at baseline was derived from the baseline disease assessment.

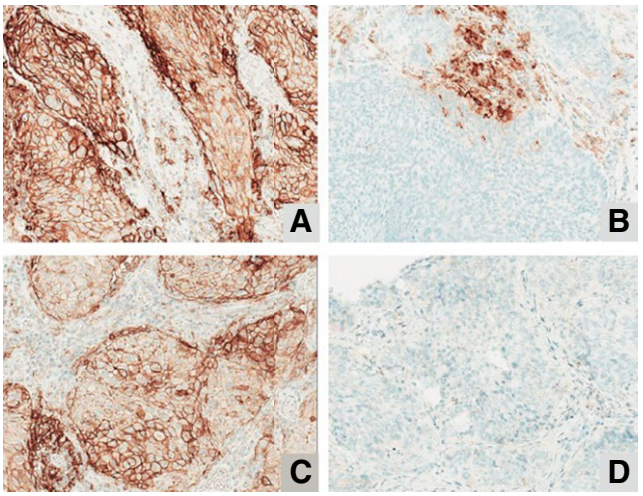

Fig 1. Representative photomicrographs of urinary bladder cancer biopsy specimens from patients, illustrating immunohistochemical staining for programmed cell death ligand-1 (PD-L1) on tumor cells (TC) and tumor-infiltrating immune cells (IC). (A) Tumor biopsy with ≥ 25% TC and ≥ 25% IC (TC-positive/IC-positive) PD-L1 staining; (B) < 25% TC and ≥ 25% IC (TC-negative/IC-positive) PD-L1 staining; (C) ≥ 25% TC and < 25% IC (TC-positive/IC-negative) PD-L1 staining; and (D) < 25% TC and < 25% IC (TC-negative/IC-negative) PD-L1 staining.

infusion-related reaction, tumor flare) occurred in three patients (4.9%). These events were serious (the only treatment-related serious AEs reported); however, they were manageable by standard guidelines. The patient with treatment-related grade 3 acute kidney injury (biopsy-proven nephritis) discontinued study drug because of the event, which improved to grade 1 with steroid treatment and was ongoing at data cutoff. The other treatment-related grade 3 AEs resolved. There were no grade 4 or 5 treatment-related AEs and no reports of pneumonitis or colitis.

Treatment-related AEs of special interest (AESIs) of any grade were reported in 14 of 61 patients (23.0%). The most frequently reported AESIs were diarrhea (9.8%), pruritus, and infusion-related reaction (3.3% each). All other events were reported in one patient (1.6%) each. Because of limited follow-up, not all potential late-emergent immune-related AEs may have been captured.

Table 2. Treatment-Related Adverse Events in All Patients (N = 61)

Adverse Events	Any Grade	Grade 3*
Any	39 (63.9)	3 (4.9)
Treatment-related AEs reported in ≥ 5% of patients		
Fatigue	8 (13.1)	0
Diarrhea	6 (9.8)	0
Decreased appetite	5 (8.2)	0
Arthralgia	4 (6.6)	0
Asthenia	4 (6.6)	0
Nausea	4 (6.6)	0
Pyrexia	4 (6.6)	0
Treatment-related grade ≥ 3 AEs reported in one or more patient		
Acute kidney injury	1 (1.6)	1 (1.6)
Infusion-related reaction	1 (1.6)	1 (1.6)
Tumor flare	1 (1.6)	1 (1.6)
Treatment-related AESIs reported in two or more patients		
Diarrhea	6 (9.8)	0
Infusion-related reaction	2 (3.3)	1 (1.6)
Pruritus	2 (3.3)	0

NOTE. Data presented as No. (%).
Abbreviations: AE, adverse event; AESI, adverse event of special interest.
*There were no grade 4 or 5 treatment-related AEs.

Efficacy

Among 42 response-evaluable patients, the ORR was 31.0% (95% CI, 17.6 to 47.1) overall (Table 3). The ORR was 46.4% in the PD-L1–positive subgroup and 0% in the PD-L1–negative subgroup, and DCR12 was 57.1% and 28.6%, respectively. In addition, there were three unconfirmed responses (two in the PD-L1–positive subgroup and one in the PD-L1–negative subgroup) that were ongoing at the data cutoff.

Response was also assessed by subgroups. By TC-only status, the ORR was 46.7% in the PD-L1–positive subgroup and 22.2% in the PD-L1–negative subgroup (Table 3). By IC-only status, the ORR was 55.6% and 12.5% in the PD-L1–positive and PD-L1–negative subgroups, respectively. By metastatic site at baseline, the ORR was 25.0% (95% CI, 5.5 to 57.2) in all patients (n = 12) and 37.5% (95% CI, 8.5 to 75.5) in the PD-L1–positive subgroup (n = 8) with liver metastases, and 50.0% (95% CI, 15.7 to 84.3) in all patients (n = 8) and 66.7% (95% CI, 22.3 to 95.7) in the PD-L1–positive subgroup (n = 6) with lymph-node-only disease.

The greater antitumor activity observed in the PD-L1–positive subgroup was particularly apparent for best change in tumor size compared with baseline (Fig 2A). (Note: Not all reductions in tumor size met RECIST response criteria). In the PD-L1–positive subgroup with available postbaseline scans, 19 of 25 (76.0%) response-evaluable patients had some reduction in tumor size, whereas 17 (68.0%) experienced a ≥ 30% target lesion reduction from baseline. In the PD-L1–negative subgroup, four of 11 patients (36.4%) had some reduction in tumor size, of whom one (9.1%) had a ≥ 30% target lesion reduction from baseline. Plots of change in tumor size over time compared with baseline demonstrated unique patterns of radiographic changes (Figs 2B and 2C). Notably, a subgroup of PD-L1–positive patients demonstrated rapid decreases in tumor burden at the first disease assessment at 6 weeks. Other patients, in both the PD-L1–positive and PD-L1–negative subgroups, demonstrated more gradual decreases in tumor burden. In addition, two unconventional responses were observed in the PD-L1–positive subgroup; these patients continued treatment through initial radiographic progression and subsequently experienced tumor regression.

Assessment of time to response and duration of response demonstrated rapid and durable responses in the PD-L1–positive subgroup (Fig 3). Median follow-up of response-evaluable patients was 6.5 months (range, 0.8 to 14.8 months). The median time to response was 6.3 weeks (95% CI, 5.6 to 12.1 weeks) in the 13 responding patients, and median duration of response has not been reached (range, 4.1+ to 49.3+ weeks). Among these patients, 12 of 13 (92.3%) had an ongoing response at last follow-up (ie, the patient is alive, is progression free, and has not started alternative anticancer therapy). Only one responding patient had subsequent

Table 3. Clinical Activity of Durvalumab by PD-L1 Status in Response-Evaluable Patients

PD-L1 Expression by Location	PD-L1 Status Definition	ORR*		DCR12†	
		n/N (%)	95% CI	n/N (%)	95% CI
Unselected		13/42 (31.0)	17.6 to 47.1	20/42 (47.6)	32.0 to 63.6
TC or IC	PD-L1–positive (≥ 25% TC or IC)	13/28 (46.4)	27.5 to 66.1	16/28 (57.1)	37.2 to 75.5
	PD-L1–negative (< 25% TC and IC)	0/14 (0.0)	0.0 to 23.2	4/14 (28.6)	8.4 to 58.1
TC	PD-L1–positive (≥ 25%)	7/15 (46.7)	21.3 to 73.4	8/15 (53.3)	26.6 to 78.7
	PD-L1–negative (< 25%)	6/27 (22.2)	8.6 to 42.3	12/27 (44.4)	25.5 to 64.7
IC	PD-L1–positive (≥ 25%)	10/18 (55.6)	30.8 to 78.5	12/18 (66.7)	41.0 to 86.7
	PD-L1–negative (< 25%)	3/24 (12.5)	2.7 to 32.4	8/24 (33.3)	15.6 to 55.3

Abbreviations: DCR12, disease control rate at 12 weeks; IC, tumor-infiltrating immune cells; ORR, objective response rate; PD-L1, programmed cell death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cells.
*ORR was defined as confirmed complete or partial response per RECIST version 1.1.
†DCR12 was defined as confirmed complete or partial response or stable disease for ≥ 12 weeks per RECIST version 1.1.

disease progression. This patient achieved initial response after 12.1 weeks and then discontinued treatment at 14.9 weeks because of grade 3 acute kidney injury. After discontinuation of durvalumab in this patient, additional follow-up scans demonstrated a radiographic response persisting until 48 weeks even in the absence of additional therapy.

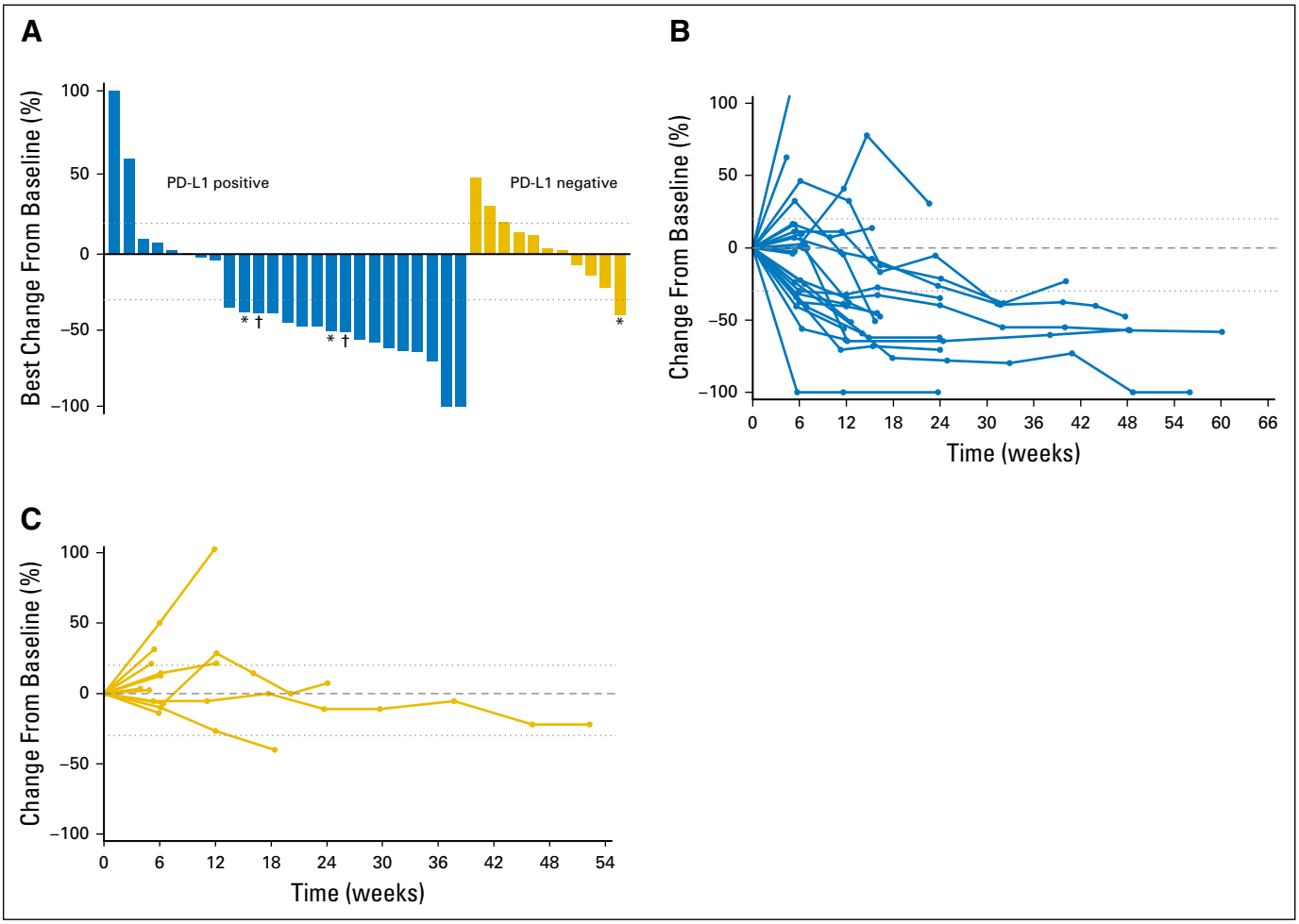

Fig 2. (A) Best change from baseline in tumor size over time by programmed cell death ligand-1 (PD-L1) status; (B) tumor size change from baseline by PD-L1–positive status (response-evaluable population with one or more postbaseline scans); (C) tumor size change from baseline by PD-L1–negative status (response-evaluable population with one or more postbaseline scans). Note: PD-L1–positive was defined as either ≥ 25% of tumor cells or ≥ 25% of tumor-infiltrating immune cells expressing PD-L1, and PD-L1–negative was defined as both < 25% of tumor cells and < 25% of tumor-infiltrating immune cells expressing PD-L1. *Unconventional response. †Unconfirmed response at data cutoff, awaiting confirmation (with the exception of patients with unconventional responses, all other patients with best tumor shrinkage ≥ 30% had confirmed responses).

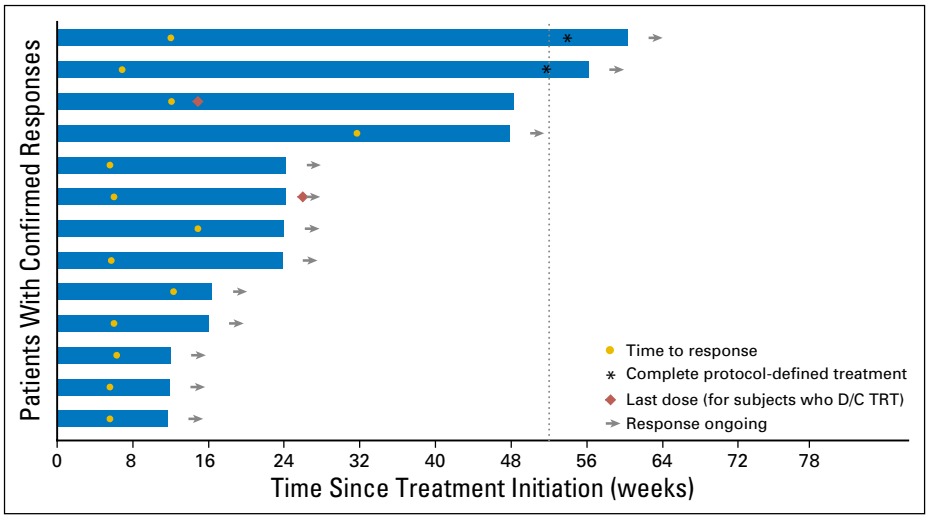

Fig 3. Time to response and duration of response. Note: programmed cell death ligand-1–positive was defined as either ≥ 25% of tumor cells or ≥ 25% of tumor-infiltrating immune cells expressing programmed cell death ligand-1. This figure includes only response-evaluable patients who had confirmed responses. Abbreviations: D/C, discontinued; TRT, treatment.

DISCUSSION

In this expansion cohort that included heavily pretreated patients with UBC, durvalumab demonstrated a manageable safety profile and evidence of meaningful clinical activity, primarily in the PD-L1–positive subgroup. The ORR and durability of responses observed in patients with PD-L1–positive tumors (as defined by TC or IC expression using the SP263 assay) compares favorably with the outcomes provided with currently available therapies for this population.[6]

The safety profile of durvalumab in patients with UBC was consistent with previous reports in other tumor types[20-22] and generally consistent with the known safety profile of anti–PD-1/PD-L1 antibodies.[13,14,27] No unique AEs were reported in the UBC population, and there were no treatment-related deaths. The three grade 3 serious AEs were manageable by standard guidelines. Of note, the grade 3 acute kidney injury rapidly improved to grade 1 with steroid treatment and was ongoing at the data cutoff. A low incidence of AESIs was observed, and most were grade 1 or 2 in severity. Mild to moderate diarrhea was the most common treatment-related event. Importantly, there were no reports of pneumonitis or colitis in this study, which might be attributed to effective AE monitoring and management strategies provided in the study protocol. However, the absence of these typical immune-mediated events could also be explained, in part, by the small sample size and limited follow-up in this study.

The totality of the emerging data suggests that PD-L1 expression may be a valuable biomarker for selecting patients most likely to benefit from treatment with PD-1/PD-L1 inhibitors.[20,28-30] However, a lack of standardized assays and metrics for defining PD-L1 positivity has resulted in inconsistencies in the literature and confusion regarding how best to select patients for treatment. Recently, a variety of assays to assess PD-L1 expression and thresholds to define PD-L1–positive status have been used, and expression on TC, IC, or both has been considered. For example, the phase 2 study of atezolizumab, a humanized PD-L1 monoclonal antibody, in 310 patients with UBC analyzed ORR on the basis of PD-L1 expression on IC only.[19] That study showed that PD-L1 positivity (classified as IC2/3 and defined as ≥ 5% PD-L1 expression on IC) was associated with improved response to atezolizumab (26% ORR in 100 IC2/3 patients) compared with an 8% ORR in 210 IC0/1 PD-L1–negative patients (subsets IC0 and IC1 were defined as < 1% expression or ≥ 1% and < 5% expression, respectively). An exploratory analysis of TC staining was also completed. However, TC staining using the SP142 assay did not seem to enrich for responders. Response rates were similar at all tested thresholds of PD-L1 expression on TC.

In the current study, defining PD-L1 status on the basis of expression on TC or IC, independently, did not cleanly separate responders from nonresponders. In contrast, defining PD-L1 status on the basis of its expression on either TC or IC differentiated responding and nonresponding subgroups. By this definition, ORR was 46.4% in the PD-L1–positive subgroup compared with 0% in the PD-L1–negative subgroup, and patients with PD-L1–positive tumors had rapid, durable, and deep responses to durvalumab compared with the PD-L1–negative subgroups. These findings are consistent with an emerging body of evidence supporting the hypothesis that PD-L1 expression on either TC or IC may be associated with improved response to PD-1/PD-L1 antibodies in UBC, in particular.[19,20,28,29,31] Moreover, these findings suggest that PD-L1 expression on either TC or IC may be considered for treatment decisions, given that expression on either TC or IC is likely to be biologically relevant, both TC and IC independently correlated with response, and assessing both TC and IC in a combined definition of PD-L1 status seems to show the clearest dichotomy between responding and nonresponding subgroups.

The apparent discrepancy regarding the predictive role of PD-L1 expression on TC between the current findings using the SP263 assay and those recently published highlight the ongoing debate regarding the criteria that should be used to define PD-L1 expression in the tumor microenvironment to select patients for treatment with PD-1 or PD-L1 antibodies. Follow-up studies to clinically validate the current findings using the SP263 assay are ongoing. Comparative analyses between the two assays may be necessary to illuminate why there seem to be discrepant results between studies.

In conclusion, durvalumab had a manageable safety profile and meaningful clinical activity in patients with UBC, many of whom were heavily pretreated. All RECIST responses occurred in the PD-L1–positive subgroup on the basis of combined TC or IC expression. Responses occurred early and seem durable, given the current follow-up. Other studies of durvalumab in UBC are ongoing.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Safety and Efficacy of Durvalumab (MEDI4736), an Anti–Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer

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