Patient-Reported Outcomes and Inflammatory Biomarkers in Patients With Locally Advanced/Metastatic Urothelial Carcinoma Treated With Durvalumab in Phase 1/2 Dose-Escalation Study 1108

Running Head: Durvalumab in Urothelial Carcinoma; PROs

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CONFLICT OF INTERESTS DISCLOSURES

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*Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools.

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PRECIS

In patients with locally advanced/metastatic urothelial carcinoma treated with durvalumab, improvements in patient-reported outcomes correlated not only with objective tumor response but also with reduction in markers of systemic inflammation. These findings provide insight into potential links between attenuation of inflammation in cancer and patient-reported outcomes.

ABSTRACT

Background: Durvalumab showed meaningful clinical activity in patients with metastatic urothelial carcinoma (mUC) in Study 1108 (NCT01693562). An important focus in treatment is health-related quality of life (HRQoL). Here, patient-reported outcomes (PROs) from Study 1108 and their relationship with inflammatory biomarkers are explored.

Methods: Disease-related symptoms, functioning, and HRQoL were assessed using the FACT-Bl and EORTC-QLQ-C30. Relationships between PRO improvement and best changes in tumor size, albumin level, and neutrophil-lymphocyte ratio (NLR) were assessed by Spearman's correlation analysis.

Results: Mean (SD) FACT-Bl total score improved from 107.5 (23.0) at baseline to 115.4 (22.6) on day 113, with similar increases in trial outcome index (TOI) and bladder cancer subscale (BLCS) scores. Mean FACT-Bl total scores improved over time and FACT-Bl TOI scores significantly improved by day 113 ($P < .05$). Mean (SD) EORTC-QLQ-C30 global health status/QoL score improved from 57.1 (24.8) at baseline to 69.0 (21.4) on day 113; functional scale and symptom scores (day 113) were higher than baseline ($P < .05$) for EORTC social functioning. FACT-Bl total, BLCS, and TOI scores improved in 32.6%, 34.9%, and 32.6% of patients at day 113; 26.3% to 37.8% of patients exhibited improvements in EORTC-QLQ-C30 functional scores. Best tumor shrinkage and in serum albumin and NLR posttreatment improvements correlated ($P < .05$) with increases in FACT-Bl total, TOI, BLCS, EORTC physical functioning, and role functioning scores.

Conclusion: Durvalumab was associated with improvements in disease-related symptoms, functioning, and HRQoL in mUC patients. Improvements in systemic inflammation may contribute to PRO improvements in these patients.

Key words: urothelial carcinoma, durvalumab, patient-reported outcome measures, health-related quality of life, biomarkers, tumor, inflammation.

INTRODUCTION

The historic 5-year survival rate of patients with locally advanced or metastatic (stage IV) urothelial carcinoma (mUC) is 15%.[1] Platinum-based chemotherapy, which is associated with median survival of 9 to 15 months, remains the standard of care for first-line treatment. In patients ineligible for platinum-based chemotherapy, first-line options include pembrolizumab and atezolizumab.[2] Most patients experience disease progression. Second-line treatment options include vinflunine, taxanes, and the immune checkpoint inhibitors pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab.

A key focus of management for patients with mUC is prolonging survival while maintaining functioning and health-related quality of life (HRQoL); treatment should aim to achieve palliation of symptoms without additional drug-related toxicity.[2,3] As novel treatments for mUC emerge, it is equally important to evaluate changes in disease-related symptoms, functioning, and HRQoL using patient-reported outcome (PRO) measures alongside efficacy and safety data.[4,5]

Cancer-related symptoms can have a marked impact on HRQoL, are linked with poorer clinical outcomes, and are now recognized to be associated with a systemic inflammatory response.[6] Increased systemic inflammation portends a poor prognosis in many malignancies, including UC,[7] and it is correlated with worsening of HRQoL/functioning parameters in patients with advanced cancer.[8] An elevated

neutrophil-lymphocyte ratio (NLR), which is an index of systemic inflammation, has shown significant association with adverse oncologic and survival outcomes in patients with UC[9-11] and improvements in NLR have been shown to predict response across different tumors, including UC.[12] Additionally, serum albumin levels can reflect disease severity, progression and prognosis as inflammation and malnutrition in chronic disease lead to suppression of albumin synthesis.[10] Reduction in such inflammatory biomarkers may be linked to improvements in HRQoL in patients with cancer.[6]

Durvalumab has been granted accelerated approval for patients with mUC progressing on platinum-based chemotherapy, based on results from the phase 1/2 Study 1108 (data cutoff [DCO]: October 24, 2016) (NCT01693562).[13,14] In patients with mUC receiving durvalumab, tumor shrinkage, and overall survival (OS) have been shown to correlate with changes in inflammatory biomarkers, while decreased tumor size and longer OS have been shown to correlate with increased albumin and decreased NLR.[15] Durvalumab may therefore be associated with a decrease in systemic inflammation in patients with mUC.[15]

Here, in a post hoc analysis of Study 1108, we report the impact of durvalumab on PROs, and assess the relationship between inflammatory biomarkers and PROs.[14]

METHODS

Study Design and Treatment

Study 1108 (NCT01693562) was a phase 1/2, single-arm, dose-escalation study in patients with advanced solid tumors. Patients with mUC were enrolled in the expansion cohort (n = 191) and received durvalumab 10 mg/kg every 2 weeks for up to 12 months or until confirmed progressive disease or discontinuation, as previously described.[14,16] PRO analyses were carried out in patients (n = 182) who had experienced disease progression after prior platinum-based therapy for metastatic disease.[14]

Procedures for PRO Assessments

Disease-related symptoms, functioning and HRQoL were assessed using the Functional Assessment of Cancer Therapy-Bladder (FACT-Bl), a bladder cancer-specific instrument; European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC-QLQ-C30), a general cancer-specific instrument; and a single-item pain questionnaire (details provided in supporting materials). All PRO instruments were administered before other procedures at scheduled study visits (Figure 1) with change in baseline defined as the mean difference between absolute postbaseline score and baseline score.

Procedures for Assessment of Biomarkers and Tumor Size

Inflammatory biomarkers (NLR, serum albumin) were obtained from standard serum chemistry and hematology panels. Tumor measurements (sum of longest diameter) were scheduled at days 1, 43, 85, 113, and every 56 days thereafter.

Statistical Analysis

Questionnaire completion/compliance was assessed. Domain scores for EORTC-QLQ-C30 and FACT-Bl were calculated based on the scoring manuals when at least 50% of the items were completed by the patient. Primary outcomes for the PRO analyses were: FACT-Bl total score, FACT-Bl trial outcome index (TOI), and FACT-Bl BLCS; and EORTC-QLQ-C30 functional scales (physical, role, cognitive, emotional, and social), multi-item symptom scales (fatigue and pain), and global health status/QoL.

Analyses were conducted for the overall study population and for subgroups stratified by clinical tumor response; responders were defined as patients who achieved an objective response per Response Evaluation Criteria In Solid Tumors (RECIST 1.1). Additional analyses compared mean change from baseline in FACT-Bl scores (total, TOI BLCS) and EORTC-QLQ-C30 functional scale and Global Health Status/QoL scores over time in 3 subgroups: responders, patients with stable disease, and others (patients not meeting criteria for objective response or stable disease including nonresponders).

Changes in PROs for all patients were analyzed descriptively at all timepoints; statistical analyses (paired *t*-test) were also performed for the differences in mean FACT-Bl and mean EORTC-QLQ-C30 functioning scores between baseline and days

43, 57, and 113. *P* values were not adjusted for multiple comparisons. Data beyond day 113 are not reported owing to low sample sizes (Table 1).

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

RESULTS

Study 1108 Baseline Characteristics and Clinical Outcome

Baseline characteristics of the 182 patients in the mUC cohort of Study 1108 have been previously published.[14] Primary safety and efficacy results were based on DCO October 24, 2016. The objective response rate in this cohort was 17.6% (32/182 patients; 6 complete responses and 26 partial responses). Median time to response was 1.41 months (range, 1.2-7.2).[14]

Questionnaire Compliance

The full analysis set for the PRO analysis included 182 patients; PRO data were unavailable for 1 patient (a nonresponder). Questionnaire completion data are shown in Table 1. Overall completion rate (patients who completed at least 1 questionnaire at baseline and the same questionnaire at 1 or more postbaseline visits) was 146/181 (81% [31/32 responder, 97%; 115/149 nonresponder, 77%]) and 136/181 (75%) for FACT-Bl (29/32 responder, 91%; 107/149 nonresponder, 72%); 88/181 (49%) for

EORTC-QLQ-C30 (23/32 responder, 72%; 65/149 nonresponder, 44%); and 142/181 (78%) for the pain questionnaire (30/32 responder, 94%; 112/149 nonresponder, 75%).

Baseline Data and Changes in PRO Scores Over Time

1. FACT-Bl

Mean (SD) FACT-Bl total score at baseline for all patients was 107.5 (23.0), 107.7 (24.1) for responders and 107.4 (22.9) for nonresponders (Figure 2). Changes from baseline in FACT-Bl total score, FACT-Bl BLCS and FACT-Bl TOI over time are reported in Figure 3. Mean (SD) FACT-Bl total scores for all patients improved over time with ($P < .05$) for FACT-Bl TOI scores at day 113 (Figure 3); responders showed better FACT-Bl scores over time than patients with no response or stable disease (data not shown).

The proportion of patients reporting improvement, no change or deterioration in FACT-Bl total score, FACT-Bl BLCS, and FACT-Bl TOI over time are shown in Figure 4. At day 43, FACT-Bl total score was improved in 23.9% of patients (56.3% no change, 19.7% deterioration); 31.0% showed improvement in FACT-Bl BLCS (49.0% no change, 19.7% deterioration) and 21.1% in FACT-Bl TOI (60.6% no change, 18.3% deterioration) (Figure 4). FACT-Bl total score was improved at day 113 in 32.6% of patients (48.8% no change, 18.6% deterioration); 34.9% showed improvement in FACT-Bl BLCS (44.2% no change, 20.9% deterioration) and 32.6% in FACT-Bl TOI (55.8% no change, 11.6% deterioration) at this timepoint (Figure 4). Responders were more likely

to have significant improvements versus deterioration in FACT-Bl scores versus nonresponders at the majority of timepoints when statistical comparisons could be performed (Figure 4).[17-19]

2. EORTC-QLQ-C30

The mean (SD) baseline score for EORTC-QLQ-C30 Global Health Status/QoL was 57.1 (24.8) (Figure 2). Corresponding values were 71.2 (23.8) for responders and 53.3 (23.8) for nonresponders. Baseline values for EORTC-QLQ-C30 subscales suggested responders had numerically better functioning and less severe symptoms (Figure 2). Mean (SD) EORTC-QLQ-C30 Global Health Status/QoL score improved over time, from 57.1 (24.8) at baseline, through 61.3 (20.9) on day 43, to 69.0 (21.4) on day 113. Mean functional EORTC scores at day 113 were numerically higher than at baseline; the difference was significant ($P < .05$) for EORTC social functioning. Numerical difference between responders and nonresponders were greatest for physical and role functioning scores (Figure 5). Mean symptom EORTC scores for fatigue and pain were improved at day 113 in all groups (Figure 5), with changes from baseline being numerically greatest in responders.

Analysis of EORTC functional scale scores by patient response status suggested responders and patients with stable disease showed better scores over time in physical and role functioning than other patients (data not shown).

Improvements in EORTC-QLQ-C30 functional domains were seen in 10.9% to 29.6% of patients at day 43 and in 26.3% to 37.8% of patients at day 113 (Figure 6).[17-19] Most patients reported improvement in EORTC-QLQ-C30 pain score by day 43 (56.4%) and in EORTC-QLQ-C30 fatigue score by day 85 (53.5%). Improvements in fatigue and pain scores were reported at day 113 by 57.6% and 73.1% of the total population, 66.7% and 92.3% of responders, and 50.0% and 53.9% of nonresponders, respectively.

3. Pain Questionnaire

Baseline values (SD) for the pain questionnaire were well balanced between responders and nonresponders (Figure 2). Changes in mean pain scores are shown in Figure 7. Improvements in pain scores were similar in responders and nonresponders.

Tumor Size and Biomarker Changes

Baseline absolute values and best percent (%) change in tumor size and improvements in biomarkers (ie, increase in serum albumin and decrease in NLR) from baseline in patients treated with durvalumab are shown in Table 2. The best increase in serum albumin and the best decrease in NLR from baseline were both significantly greater in responders than nonresponders ($P < .0001$) (Table 2A).

PRO-Biomarker Correlations

FACT-Bl total scores, FACT-Bl TOI, and FACT-Bl BLCS were correlated significantly with decreased tumor size ($P < .0001$), increased albumin ($P = .004$ to .03), and

decreased NLR (*P* = .006 to .04) (Table 2B). EORTC-QLQ-C30 physical functioning improvement was correlated significantly with decreased tumor size (*P* < .0001), increased albumin (*P* = .0007), and decreased NLR (*P* = .03) (Table 2B). EORTC-QLQ-C30 role functioning was correlated significantly with decreased tumor size (*P* = .003) and decreased NLR (*P* = .008); there was no significant correlation with albumin level (Table 2B).

Multiple regression analysis showed that decreased tumor size is the most significant factor in association with improvement of the five PRO measurements. After adjustment of tumor size and albumin changes, decreased NLR remained significantly correlated with increased FACT-TOI (P =.02) and FACT-BLCS (P =.03). Total FACT-Bl and role functioning improvement also showed trends of correlation with NLR change after adjustment of tumor size and albumin changes (Table 2C).

DISCUSSION

A previous analysis of data from Study 1108 identified prognostic and predictive biomarkers of clinical outcomes with a population-based modeling approach.[20] Here, we provide the first report of the effects of durvalumab on cancer-related symptoms, functioning, and HRQoL in patients with mUC progressing following platinum-based chemotherapy, and, to our knowledge, the first study to use a bladder cancer-specific PRO measure, the FACT-Bl, in patients with mUC treated with immunotherapy.

Overall, improvements in scores over time were seen with FACT-Bl total scores, FACT-Bl BLCS, and FACT-Bl TOI, together with improvements in EORTC-QLQ-C30 functional domains, global health status, and symptom scores (pain and fatigue). HRQoL improvements in patients with stable disease do not represent a response, but they do signify potential clinical benefit. Overall, responders had improved scores over time compared with nonresponders, though no formal statistical testing was performed. The fact that improvements in HRQoL outcomes were seen in nonresponders suggests that durvalumab may have HRQoL-related benefits, even in patients not meeting the RECIST criteria for objective response; however, the lack of a blinded control arm limits this interpretation.

The information available regarding PROs in patients with mUC progressing after platinum-based chemotherapy is predominantly based on EORTC-QLQ-C30, a general instrument for patients with cancer.[21] Interestingly, the largest differences in patients with UC versus general population were observed in the EORTC-QLQ-C30 symptom domains: fatigue, role and physical functioning in multivariate regression analysis;[3] this is consistent with the present study showing the largest numerical differences from baseline in these domains with durvalumab.

The EORTC-QLQ-C30 is perhaps the best validated PRO measure in patients with locally advanced/metastatic UC, and, overall, the baseline EORTC-QLQ-C30 scores observed in this study were similar to those reported in previous studies.[3,22] Multiple prospective studies have suggested that HRQoL may remain stable or deteriorate in

patients receiving chemotherapy,[4,5,23,24] but remain stable or improve in patients treated with immune checkpoint inhibitors.[15,25] While no assessments in this study were made after day 113 due to decreasing sample sizes, our results are in line with this trend; additional prospective evidence, including longer follow-up time, from randomized trials comparing chemotherapy and immunotherapy may better confirm these findings.

Correlations observed between improvements in HRQoL with durvalumab and improvements in inflammatory biomarkers are consistent with the association previously observed between inflammatory biomarkers and survival in patients with mUC treated with durvalumab.[15,20] Increased systemic inflammation is known to be correlated with worsening of HRQoL/functioning parameters in patients with advanced cancer (independent of performance status).[8] In the current study, multiple regression analysis showed that, after adjusting for tumor size and albumin changes, decreased NLR remained significantly associated with increases in TOI and BLCS. Total FACT-BI and role functioning improvement also showed trends towards correlation with change in NLR after adjustment for tumor size and albumin changes. These results suggest a direct association between NLR change and improvement of PROs; however, it is unknown whether attenuation of cancer inflammation (as indicated by decreased NLR) is causal with respect to improved HRQoL or simply a reflection of reduced tumor burden and generally improved health in patients responding to treatment[8] Detailed research in this regard is a potential direction for future study.

There were some limitations that should be acknowledged for our study. This was an open-label study with no control or standard therapy comparator arm. This is a post-hoc analysis and, regarding comparisons between nonresponders versus responders, these groups were not predefined at baseline. In addition, across all the PRO measures utilized, the overall completion rate was higher in responders than nonresponders. Given the open-label study design, both patients and providers were aware of the clinical benefit or lack thereof, which may have driven the significant change from baseline in PROs. Also, day 43 is not a specified protocol data collection timepoint and, as such, includes smaller patient numbers than day 56. Finally, the small sample size at some visits should be considered when interpreting the results.

CONCLUSIONS

Patients with mUC treated with durvalumab as second-line therapy reported improvement from baseline in symptoms, functioning, and HRQoL based on FACT-Bl total score, FACT-Bl BLCS, FACT-Bl TOI, EORTC-QLQ-C30 functional domains, and global health status/QoL scales to day 113. Improvements in many of the FACT-Bl and EORTC-QLQ-C30 scores were correlated significantly with posttreatment improvements in inflammatory biomarkers.

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TABLE 1. Number of Patients With Evaluable PRO per Visit, FACT-Bl, and EORTC QLQ-C30 Functioning Scales[a]

Study visit day		D1	D29	D43	D57	D85	D113	D169	D225	D281	D337
FACT-Bl Total score	All	169	121	72	91	61	44	22	14	8	10
	R	29	25	19	25	21	18	9	8	6	7
	NR	140	96	53	66	40	26	13	6	2	3
FACT-Bl BLCS	All	169	121	72	92	62	44	22	14	8	10
	R	29	25	19	26	21	18	9	8	6	7
	NR	140	96	53	66	41	26	13	6	2	3
FACT-Bl TOI	All	169	121	72	91	61	44	22	14	8	10
	R	29	25	19	25	21	18	9	8	6	7
	NR	140	96	53	66	40	26	13	6	2	3
EORTC-QLQ-C30[b]	All	113	85	57	65	53	39	21	12	8	9
Physical functioning	R	24	20	14	24	18	18	11	8	5	6
	NR	89	65	43	41	35	21	10	4	3	3
EORTC-QLQ-C30	All	113	84	57	64	53	38	21	12	8	9
Role functioning	R	24	20	14	24	18	18	11	8	5	6
	NR	89	64	43	40	35	20	10	4	3	3
EORTC-QLQ-C30	All	113	85	56	65	53	39	21	12	8	9
Emotional	R	24	20	13	24	18	18	11	8	5	6
functioning	NR	89	65	43	41	35	21	10	4	3	3
EORTC-QLQ-C30	All	113	85	56	65	53	39	21	12	8	9
Cognitive	R	24	20	13	24	18	18	11	8	5	6
functioning	NR	89	65	43	41	35	21	10	4	3	3
EORTC-QLQ-C30	All	113	85	56	65	53	39	21	12	8	9
Social functioning	R	24	20	13	24	18	18	11	8	5	6
	NR	89	65	43	41	35	21	10	4	3	3
EORTC-QLQ-C30	All	113	84	56	65	53	39	21	12	8	9
Global health	R	24	20	13	24	18	18	11	8	5	6
status/QoL	NR	89	64	43	41	35	21	10	4	3	3

[a]A domain score was calculated when at least half of the items for that domain were filled in by the patient.
[b]Number of patients filling in the EORTC-QLQ-C30 questionnaire (113 of 182 at baseline) is lower than for FACT-Bl (169 of 182 at baseline) as this instrument was added to the protocol after study start and was not administered at all scheduled visits.
Abbreviations: BLCS, bladder cancer subscale; D, study day; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; EOT, end of treatment; QoL, quality of life; TOI, trial outcome index.

TABLE 2. PROs, Tumor Size, and Biomarker Improvement After Durvalumab Treatments

A. Baseline Values and Best Improvement in tumor Size, Albumin, and NLR

	All		R		NR		*P*
	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	(R vs NR)
Baseline tumor size (mm)	72.8 ± 49.4	186	60.1 ± 54.9	34	68.6 ± 42.1	121	NS
Tumor size,[a] min % change	–5.6 ± 40.9	159	–69.6 ± 15.2	33	11.6 ± 40.9	121	< .0001
Tumor size,[a] min absolute change (mm)	–2.4 ± 36.7	159	–42.7 ± 38.6	33	8.5 ± 28.5	121	< .0001
Baseline Albumin (g/L)	37.5 ± 5.3	184	40.5 ± 3.3	35	37.4 ± 5.1	119	< .0001
Albumin,[b] max % change	3.4 ± 9.8	174	10.1 ± 7.2	33	3.2 ± 9.3	118	< .0001
Baseline NLR	6.2 ± 7.9	183	3.2 ± 1.2	33	5.9 ± 8.0	121	< .001
NLR,[a] min % change	–14.4 ±35.9	173	–35.1 ± 20.8	31	–14.3 ± 33.5	118	< .0001

B. Correlation Between PRO Improvement and Biomarker Changes

	FACT-BI max increase			EORTC QLQ-C30 max increase	
Parameter	Total, ρ (*P*)	TOI, ρ (*P*)	BLCS, ρ (*P*)	Physical functioning, ρ (*P*)	Role functioning, ρ (*P*)
Tumor size,[a] min % change	−0.44 (< .0001)	−0.49 (< .0001)	−0.42 (< .0001)	−0.5 (< .0001)	−0.32 (.003)
Tumor size,[a] min absolute change	–0.46 (< .0001)	–0.53 (< .0001)	–0.44 (< .0001)	–0.55 (< .0001)	–0.41 (.0001)
Albumin,[b] max % change	0.26 (.004)	0.21 (.02)	0.2 (.03)	0.36 (.0007)	NS
NLR,[a] min % change	−0.19 (.04)	−0.25 (.006)	−0.21 (.02)	−0.24 (.03)	−0.29 (.008)

C. Multiple regression analysis of PRO improvement based on biomarker changes

	FACT-Bl max increase			EORTC QLQ-C30 max increase	
Parameter	Total, β (*P*)	TOI, β (*P*)	BLCS, β (*P*)	Physical functioning, β (*P*)	Role functioning, β (*P*)
Tumor size,[a] min % change	−0.12 (< .001)	−0.1 (< .0001)	–0.04 (< .001)	−0.18 (< .001)	−0.16 (.02)
Albumin,[b] max % change	0.12 (.5)	0.02 (.9)	0.03 (.6)	0.13 (.6)	–0.59 (.14)
NLR,[a] min % change	–0.09 (.06)	−0.08 (.02)	–0.04 (.03)	–0.009 (.9)	–0.17 (.06)

[a]Decrease indicates improvement.
[b]Increase indicates improvement.

Abbreviations: BLCS, bladder cancer subscale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-Bl, Functional Assessment of Cancer Therapy-Bladder; max, maximum; min, minimum. NLR, neutrophil/lymphocyte ratio; NR, nonresponder; NS, nonsignificant. PRO, patient-reported outcome; R, responder; TOI, trial outcome index; ρ, Spearman's rank correlation coefficient.

Figure 1. Study 1108 design.
Durvalumab (10 mg/kg) was administered every 2 weeks for up to 12 months. PRO questionnaires (pain questionnaire, FACT-Bl, and EORTC QLQ-C30) were administered during screening and then before other procedures at study visits on days 1, 29 (±3), 43 (±7), 57 (±7), 85 (±7), and 113 (±7), then every 8 weeks (±7 days) thereafter. Patients with disease progression during follow-up who had not received another anticancer therapy and had not met criteria for discontinuing study treatment were allowed a 12-month course of durvalumab retreatment.

Abbreviations: D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; FACT-Bl, Functional Assessment of Cancer Therapy-Bladder; PRO, patient-reported outcome; Q2W, every 2 weeks.

Figure 2. Mean baseline values FACT-Bl, EORTC QLQ-C30, and pain scores.
Abbreviations: BLCS, bladder cancer subscale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; FACT-Bl, Functional Assessment of Cancer Therapy-Bladder; NR, non-responder; R, responder.

Figure 3. Mean change from baseline in FACT-Bl total, FACT-Bl BLCS, and FACT-Bl TOI scores over time.
Error bars indicate standard deviation. Changes from baseline in scores for All Patients were analyzed descriptively at all timepoints; statistical analyses (paired *t*-test) of difference in mean FACT-Bl between baseline and days 43, 57, and 113 were performed with significant *P*-values shown as **P* < .05; ***P* < .005; ****P* < .001 on the figure. Statistical analysis of responder versus nonresponders were not performed.

Abbreviations: BLCS, bladder cancer subscale; FACT-Bl, Functional Assessment of Cancer Therapy-Bladder; NR, non-responder. R, responder; SD, standard deviation; TOI, trial outcome index.

Figure 4. FACT-Bl total, FACT-Bl BLCS, and FACT-Bl TOI responses over time.
Figures show the proportion of patients reporting improvement, no change, or deterioration at each study visit. The proportion of patients with an improvement or deterioration from day 1 was assessed by using a threshold based on minimum important difference (MID) in change from baseline, defined as half baseline standard deviation (SD) for FACT-Bl and as a 10-point difference for EORTC QLQ-C30. The half SD estimate for the MID is a general recommendation in HRQoL scores, Norman et al,[18] while a 10-point threshold is widely accepted for EORTC QLQ questionnaires, Osoba et al and Cocks et al.[17,19]

P-values for Fisher exact tests for Responder status x Change were calculated for all timepoints; significant *P*-values (shown as **P* < .05; ***P* < .005; ****P* < .001) indicate proportions within R and NR differ. Pairwise odd ratios were calculated to determine which group comparison (no change vs deterioration [a] or improvement versus deterioration [b] was significantly different (*P* < .05); [c] indicates that 1 of the groups had 0 patients precluding the calculation of an odds ratio and associated *P*-value.

Figure 5. Mean change from baseline in EORTC-QLQ-C30 functional scale, Global Health Status/QoL (increase indicates improvement), and symptom scale (pain and fatigue; decrease indicates improvement) scores over time.
Error bars indicate standard deviation (SD). Changes from baseline in scores for All Patients were analyzed descriptively at all timepoints; statistical analyses (paired *t*-test) of difference in mean FACT-

Bl between baseline and days 43, 57, and 113 were performed with significant *P*-values shown as **P* < .05; ***P* < .005; ****P* < .001 on the figure. Statistical analyses of responders versus nonresponders were not performed.

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; NR, non-responder; QoL, quality of life; R, responder.

Figure 6. **EORTC QLQ-C30 total, functional, and symptom score responses over time.**
Figures show the proportion of patients reporting improvement, no change, or deterioration at each study visit. The proportion of patients with an improvement or deterioration from day 1 was assessed by using a threshold based on minimum important difference (MID) in change from baseline, defined as half baseline standard deviation (SD) for FACT-Bl and as a 10-point difference for EORTC QLQ-C30. The half SD estimate for the MID is a general recommendation in HRQoL scores, Norman et al,[18] while a 10-point threshold is widely accepted for EORTC QLQ questionnaires, Osoba et al and Cocks et al.[17,19]

P-values for Fisher Exact tests for Responder status x Change were calculated for all timepoints; significant *P*-values (shown as **P* < .05; ***P* < .005; ****P* < .001) indicate proportions within R and NR differ. Pairwise odd ratios were calculated to determine which group comparison (no change versus deterioration [a] or improvement versus deterioration [b] was significantly different (*P* < .05); [c] indicates that 1 of the groups had 0 patients precluding the calculation of an odds ratio and associated *P*-value.

Figure 7. Mean change from baseline in pain questionnaire scores over time (decrease indicates improvement).