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Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer

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ABSTRACT

BACKGROUND

Neoadjuvant chemotherapy followed by radical cystectomy is the standard treatment for cisplatin-eligible patients with muscle-invasive bladder cancer. Adding perioperative immunotherapy may improve outcomes.

METHODS

In this phase 3, open-label, randomized trial, we assigned, in a 1:1 ratio, cisplatin-eligible patients with muscle-invasive bladder cancer to receive neoadjuvant durvalumab plus gemcitabine–cisplatin every 3 weeks for four cycles, followed by radical cystectomy and adjuvant durvalumab every 4 weeks for eight cycles (durvalumab group), or to receive neoadjuvant gemcitabine–cisplatin followed by radical cystectomy alone (comparison group). Event-free survival was one of two primary end points. Overall survival was the key secondary end point.

RESULTS

In total, 533 patients were assigned to the durvalumab group and 530 to the comparison group. The estimated event-free survival at 24 months was 67.8% (95% confidence interval [CI], 63.6 to 71.7) in the durvalumab group and 59.8% (95% CI, 55.4 to 64.0) in the comparison group (hazard ratio for progression, recurrence, not undergoing radical cystectomy, or death from any cause, 0.68; 95% CI, 0.56 to 0.82; P<0.001 by stratified log-rank test). The estimated overall survival at 24 months was 82.2% (95% CI, 78.7 to 85.2) in the durvalumab group and 75.2% (95% CI, 71.3 to 78.8) in the comparison group (hazard ratio for death, 0.75; 95% CI, 0.59 to 0.93; P=0.01 by stratified log-rank test). Treatment-related adverse events of grade 3 or 4 in severity occurred in 40.6% of the patients in the durvalumab group and in 40.9% of those in the comparison group; treatment-related adverse events leading to death occurred in 0.6% in each group. Radical cystectomy was performed in 88.0% of the patients in the durvalumab group and in 83.2% of those in the comparison group.

CONCLUSIONS

Perioperative durvalumab plus neoadjuvant chemotherapy led to significant improvements in event-free survival and overall survival as compared with neoadjuvant chemotherapy alone. (Funded by AstraZeneca; NIAGARA ClinicalTrials.gov number, NCT03732677; EudraCT number, 2018-001811-59.)

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*A complete list of the NIAGARA investigators is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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Standard treatment for cisplatin-eligible patients with muscle-invasive bladder cancer involves neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy with pelvic-lymph-node dissection.[1-3] Approximately 50% of patients with muscle-invasive bladder cancer have recurrence within 3 years.[4,5]

Several phase 1–2 studies and phase 2 studies have assessed the safety and feasibility of combining immunotherapy with platinum-based chemotherapy as neoadjuvant treatment for muscle-invasive bladder cancer,[6-11] and a systematic review showed that the percentage of patients with a response was higher with neoadjuvant immunochemotherapy than with neoadjuvant chemotherapy alone.[12] In the adjuvant setting, two phase 3 trials showed the benefit of immune-checkpoint inhibitors as monotherapy in muscle-invasive bladder cancer: disease-free survival after surgery for high-risk disease was significantly improved with adjuvant nivolumab as compared with placebo and with adjuvant pembrolizumab as compared with observation.[13,14] Perioperative immunotherapy regimens may improve patient outcomes but need to be safe and feasible to deliver.

Durvalumab is a selective, high-affinity, human IgG1 kappa monoclonal antibody that binds to programmed death ligand 1 (PD-L1) and blocks the interaction of PD-L1 with programmed death 1 and CD80. In a single-group, phase 2 trial involving cisplatin-eligible patients with operable muscle-invasive bladder cancer, perioperative durvalumab in combination with neoadjuvant gemcitabine–cisplatin followed by radical surgery appeared to be safe and efficacious.[15] Here, we report the results of the phase 3 NIAGARA trial, which was conducted to evaluate the efficacy and safety of perioperative durvalumab in combination with neoadjuvant gemcitabine–cisplatin followed by radical cystectomy, as compared with neoadjuvant gemcitabine–cisplatin followed by radical cystectomy alone, in cisplatin-eligible patients with muscle-invasive bladder cancer.

Methods

Trial Oversight

The trial was designed by the steering committee in conjunction with the sponsor (AstraZeneca). The protocol (available with the full text of this article at NEJM.org) and all amendments were approved by the institutional review boards at the trial sites. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Before enrollment, patients provided written informed consent to participate in the trial. All the investigators were responsible for data collection and providing the data to the sponsor; data analyses were performed by employees of the sponsor. The authors, along with clinical trial personnel and statisticians employed by the sponsor, interpreted the data. An independent data monitoring committee provided oversight of the trial and performed interim assessments of the data. The sponsor was unaware of the trial-group assignments and patient-level efficacy data before unblinding.

The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All authors had full access to the data in the trial. The first draft of the manuscript was written by the first author. The authors reviewed and edited the first draft, contributed to all subsequent drafts, and provided final approval to submit the manuscript for publication.

No previous agreements concerning the confidentiality of the data were made between the sponsor and the authors or the authors' institutions. Medical writing assistance, including development of the initial draft of the manuscript, was funded by the sponsor.

Patients

Eligible patients were 18 years of age or older who had histologically or cytologically documented muscle-invasive bladder cancer; had a clinical tumor stage of T2, T3, or T4a, N0 or N1, and M0 (according to the eighth edition of the American Joint Committee on Cancer *AJCC Cancer Staging Manual*[16]); were eligible for cisplatin-based chemotherapy; had a creatinine clearance of at least 40 ml per minute per 1.73 m^2 of body-surface area; and were medically fit to undergo radical cystectomy. Patients who had previously received systemic chemotherapy or immunotherapy for muscle-invasive bladder cancer and those

with pure nonurothelial carcinoma or any small-cell histologic features were excluded. Patients with conventional urothelial carcinoma and those with urothelial carcinoma with divergent differentiation (squamous or glandular) or other histologic subtypes were eligible. A tumor-biopsy specimen obtained at screening was needed for the assessment of tumor PD-L1 expression. The complete eligibility criteria are listed in the protocol.

TRIAL DESIGN AND TREATMENTS

In this phase 3, global, open-label, randomized trial, we used an interactive voice-response system to assign patients, in a 1:1 ratio, to the durvalumab or comparison group. Randomization was stratified on the basis of clinical tumor stage (T2N0 or higher than T2N0), renal function (creatinine clearance of 40 to <60 ml per minute per 1.73 m^2 or ≥60 ml per minute per 1.73 m^2), and tumor PD-L1 expression level (high expression or low or no expression). Patients with T2N0 disease were limited to approximately 40% of the total enrollment, and patients with a creatinine clearance of at least 40 but less than 60 ml per minute per 1.73 m^2 were limited to up to 20% of the total enrollment.

In the durvalumab group, patients received four cycles of neoadjuvant durvalumab (at a dose of 1500 mg) with gemcitabine–cisplatin (gemcitabine at a dose of 1000 mg per square meter of body-surface area and cisplatin at a dose of 70 mg per square meter were given on day 1, and gemcitabine at a dose of 1000 mg per square meter was given on day 8) administered intravenously every 3 weeks, followed by radical cystectomy and then up to eight cycles of adjuvant durvalumab (at a dose of 1500 mg) administered intravenously every 4 weeks. In the comparison group, patients received the same neoadjuvant regimen of gemcitabine–cisplatin followed by radical cystectomy alone.

Patients with a creatinine clearance of at least 40 but less than 60 ml per minute per 1.73 m^2 received a split dose of cisplatin, in which a dose of 35 mg per square meter was administered intravenously on day 1 and day 8 every 3 weeks.[17] Radical cystectomy had to be performed within 2 to 8 weeks after the last dose of neoadjuvant chemotherapy. Adjuvant therapy had to start between 42 and 120 days after radical cystectomy.

END POINTS AND ASSESSMENTS

The dual primary end points were pathological complete response (as assessed by blinded central pathology review) and event-free survival (as assessed by blinded independent central review or by central pathology review if a biopsy was needed for analysis of a suspected new lesion). The key secondary end point was overall survival as assessed with an alpha-allocation approach. Other secondary end points included event-free survival at 24 months and safety. The full list of end points is provided in the protocol.

Central pathology review of specimens obtained during radical cystectomy was performed according to the eighth edition of the *AJCC Cancer Staging Manual*[16] to assess the pathological stage. Pathological complete response was defined as a pathological stage of T0N0M0.

Event-free survival was defined as the time from randomization to progressive disease that precluded radical cystectomy, the first recurrence of disease after radical cystectomy, the expected date of surgery (in patients who did not undergo radical cystectomy), or death from any cause. Radiologic tumor assessments were completed according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Additional information about tumor assessments is provided in the Supplementary Appendix, available at NEJM.org. Overall survival was defined as the time from the date of randomization until death from any cause regardless of whether the patient had been withdrawn from the trial therapy or had received subsequent anticancer therapy.

Adverse events were monitored and graded throughout the trial according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Treatment-related adverse events were assessed by the investigator and defined as adverse events related to durvalumab or gemcitabine–cisplatin and did not include adverse events related to surgery. Immune-mediated adverse events were defined as adverse events of special interest that were consistent with an immune-mediated mechanism of action with no clear alternative cause and resulted in the use of systemic glucocorticoids, other immunosuppressants, or endocrine therapy.

Patients were stratified according to the PD-L1 expression level in baseline tumor samples on

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Durvalumab (N=533)	Comparison (N=530)
Age — yr		
Median (range)	65 (34–84)	66 (32–83)
≥75 — no. %	58 (10.9)	63 (11.9)
Sex — no. (%)		
Male	437 (82.0)	433 (81.7)
Female	96 (18.0)	97 (18.3)
Race — no. (%)†		
White	354 (66.4)	358 (67.5)
Asian	152 (28.5)	145 (27.4)
Black	6 (1.1)	4 (0.8)
Other	7 (1.3)	1 (0.2)
Missing data	14 (2.6)	22 (4.2)
Region — no. (%)		
Europe	265 (49.7)	287 (54.2)
Asia	151 (28.3)	143 (27.0)
North America and Australia	66 (12.4)	62 (11.7)
South America	51 (9.6)	38 (7.2)
ECOG performance-status score — no. (%)‡		
0	418 (78.4)	415 (78.3)
1	115 (21.6)	115 (21.7)
Smoking status — no. (%)		
Current	122 (22.9)	130 (24.5)
Former	255 (47.8)	269 (50.8)
Never	144 (27.0)	120 (22.6)
Missing data	12 (2.3)	11 (2.1)
Histologic type — no. (%)§		
Invasive urothelial carcinoma, not otherwise specified	457 (85.7)	441 (83.2)
Urothelial carcinoma with squamous differentiation	38 (7.1)	49 (9.2)
Urothelial carcinoma with glandular differentiation	10 (1.9)	15 (2.8)
Urothelial carcinoma with other histologic subtype	28 (5.3)	25 (4.7)
Tumor stage — no. (%)§¶		
T2N0	215 (40.3)	213 (40.2)
Higher than T2N0	318 (59.7)	317 (59.8)
Regional lymph-node stage — no. (%)§		
N0	505 (94.7)	500 (94.3)
N1	28 (5.3)	30 (5.7)
Creatinine clearance — no. (%)		
≥60 ml/min/1.73 m^2	432 (81.1)	430 (81.1)
40 to <60 ml/min/1.73 m^2	101 (18.9)	100 (18.9)
Tumor PD-L1 expression level — no. (%)‖		
High	389 (73.0)	388 (73.2)

Table 1. (Continued.)

Characteristic	Durvalumab (N = 533)	Comparison (N = 530)
Low or none	144 (27.0)	142 (26.8)

* Shown are data for the intention-to-treat population, which included all the patients who were randomly assigned to receive neoadjuvant chemotherapy plus durvalumab, followed by adjuvant durvalumab after cystectomy (durvalumab group), or neoadjuvant chemotherapy followed by cystectomy alone (comparison group). Percentages may not sum to 100 because of rounding.
† Race was reported by the patient.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
§ Histologic type, tumor stage, and regional lymph-node stage were assessed by the investigator on the basis of a pathological tumor assessment of a sample obtained during transurethral resection of the bladder tumor, an examination of the patient under anesthesia after the transurethral resection of the bladder tumor, and findings on computed tomography or magnetic resonance imaging.
¶ Tumor staging was performed according to the eighth edition of the American Joint Committee on Cancer *AJCC Cancer Staging Manual*.[16]
‖ Baseline samples were assessed with the Ventana PD-L1 (SP263) assay (Ventana Medical Systems) according to the TC/IC25% algorithm, in which a high expression level was defined as PD-L1 expression on at least 25% of tumor cells, at least 25% of immune cells if immune cells were present in more than 1% of the tumor area, or 100% of immune cells if immune cells were present in 1% of the tumor area.

immunohistochemical staining (Ventana PD-L1 [SP263] assay; Ventana Medical Systems) with the use of a TC/IC25% algorithm. According to the algorithm, a high expression level was defined as PD-L1 expression on at least 25% of tumor cells, at least 25% of immune cells if immune cells were present in more than 1% of the tumor area, or 100% of immune cells if immune cells were present in 1% of the tumor area (see the Supplementary Appendix). Examination of the tumor cell and immune cell components of the TC/IC25% algorithm showed that the reported prevalence of PD-L1 expression on tumor cells was consistent among the central laboratories but that the reported prevalence of PD-L1 expression on immune cells varied by more than 25%. To assess the effect of the variation in the reported prevalence of immune cells on the estimate of the treatment effect in the primary analysis of event-free survival, additional subgroup analyses of event-free survival were prespecified and conducted with the use of algorithms for PD-L1 expression that included tumor cells only (see the Supplementary Appendix).

STATISTICAL ANALYSIS

We calculated that the enrollment of 525 patients in each group would provide the trial with at least 95% power, at a two-sided alpha level of 0.001, to detect a significant between-group difference in the percentage of patients with a pathological complete response, under the assumption that the underlying percentage of patients with such a response would be 50% in the durvalumab group and 35% in the comparison group. We estimated that 451 events of progression, recurrence, not undergoing radical cystectomy, or death from any cause would provide the trial with 90% power to detect a significant between-group difference in event-free survival, with an underlying hazard ratio of 0.73 and a two-sided alpha level of 0.049. A multiple testing procedure with a gatekeeping strategy was used for the analysis of the dual primary end points and the secondary end points of overall survival and overall survival at 5 years, with an alpha-exhaustive recycling strategy.[18] Alpha allocation was controlled with the use of the Lan–DeMets O'Brien–Fleming spending function.

To comply with *Journal* guidelines, pathological complete response in the two trial groups was compared with the use of log-binomial regression (adjusted for the stratification factors), and the result of the analysis is reported as a risk ratio with a corresponding 95% confidence interval and P value. Patients with a missing assessment of pathological complete response were considered to have had no response.

For the comparison of event-free survival and overall survival in the trial groups, a stratified log-rank test was used to generate P values, and a stratified Cox proportional-hazards model with

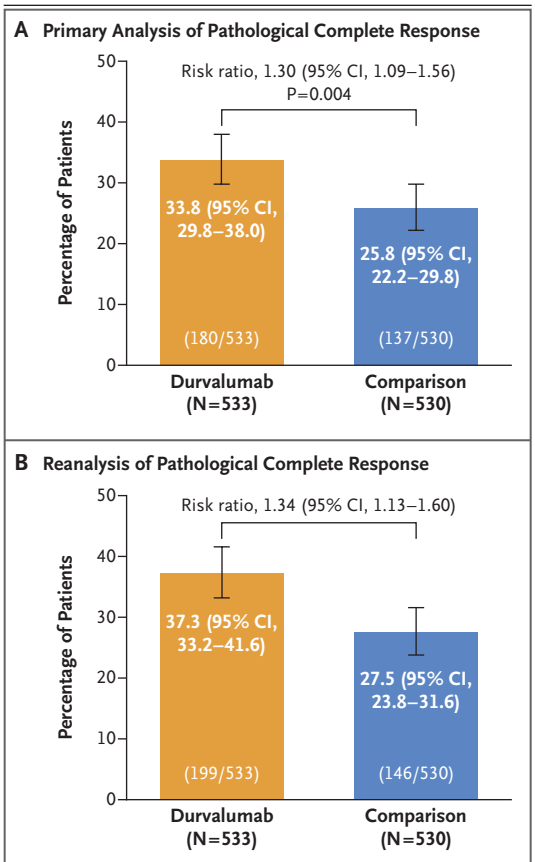


Figure 1. Pathological Complete Response in the Intention-to-Treat Population.

Shown in Panel A are the results of the primary analysis of pathological complete response (as assessed by blinded central pathology review) as of the data-cutoff date (January 14, 2022) in patients who were assigned to receive neoadjuvant chemotherapy plus durvalumab, followed by adjuvant durvalumab after cystectomy (durvalumab group), or neoadjuvant chemotherapy, followed by cystectomy alone (comparison group). The risk ratio for pathological complete response did not reach significance (P=0.004), which was defined as a two-sided P value of 0.001. Shown in Panel B are the results of a descriptive reanalysis of pathological complete response that included the results of 59 evaluable samples that were omitted from the primary analysis because the date of central assessment (which occurred after January 14, 2022), rather than the date of surgery (which occurred before January 14, 2022), was used as the data-cutoff date. The intention-to-treat population included all the patients who underwent randomization. A risk ratio of greater than 1 favors durvalumab.

Efron's method for handling ties was used to estimate hazard ratios and associated 95% confidence intervals. Event-free survival and overall survival at prespecified time points were estimated with the Kaplan–Meier method. Additional details about these end points are provided in the Supplementary Appendix.

Data reported for pathological complete response are from the primary (formal) analysis, which was conducted approximately 6 months after the last patient underwent randomization (data cutoff, January 14, 2022), and an unplanned, descriptive reanalysis that was performed at the time of the analysis of event-free survival (data cutoff, April 29, 2024) and included the results for 59 samples that were mistakenly omitted from the primary analysis. The reasons for this repeat analysis are provided in the Supplementary Appendix.

Data reported for event-free survival are from the second planned interim superiority analysis, which was to be performed when approximately 410 events of progression, recurrence, not undergoing radical cystectomy, or death from any cause had occurred (resulting in a critical value of approximately 0.81 for statistical significance with respect to event-free survival) in the trial groups or in April 2024, whichever occurred first. The prespecified data-maturity target was reached on April 29, 2024 (data-cutoff date). The first interim analysis of overall survival was prespecified to occur at the time of the second interim analysis of event-free survival and was to be formally tested only if there was a significant difference in event-free survival between the trial groups. The full statistical analysis plan is available with the trial protocol.

RESULTS

PATIENTS

From November 2018 through July 2021, a total of 1063 patients from 22 countries underwent randomization, of whom 533 were assigned to the durvalumab group and 530 to the comparison group (Fig. S1 in the Supplementary Appendix). Baseline characteristics were generally balanced between the trial groups (Table 1). The trial population was representative of the overall population of patients with muscle-invasive bladder cancer in Europe, Asia, North America, Australia, and South America; however, Black patients were underrepresented (Table S1).

A total of 417 of 530 patients (78.7%) in the durvalumab group and 389 of 526 patients (74.0%) in the comparison group completed neoadjuvant

treatment; adverse events were the primary reason for not completing neoadjuvant treatment (in 15.5% and 15.2% of the patients, respectively). Two patients (0.4%) in the durvalumab group and 4 patients (0.8%) in the comparison group discontinued neoadjuvant treatment because of disease progression.

Of the patients who underwent randomization (intention-to-treat population), 469 (88.0%) in the durvalumab group and 441 (83.2%) in the comparison group underwent radical cystectomy. Patient decision was the most common reason for not undergoing radical cystectomy in each group (6.0% of the patients in the durvalumab group and 6.8% of those in the comparison group). Of the patients who underwent radical or partial cystectomy, 424 of 470 (90.2%) in the durvalumab group and 399 of 446 (89.5%) in the comparison group underwent cystectomy within 56 days after the last dose of neoadjuvant therapy. The median time from the last dose of neoadjuvant therapy to cystectomy was 39.0 days (range, 8 to 118) in the durvalumab group and 38.0 days (range, 12 to 333) in the comparison group.

Of the 469 patients in the durvalumab group who underwent radical cystectomy, 383 (81.7%; 72.3% of the patients who received at least one dose of neoadjuvant treatment [as-treated population]) started adjuvant treatment. Of these 383 patients, 288 (75.2%; 54.3% of the patients in the as-treated population) completed adjuvant treatment. Adverse events and disease relapse were the primary reasons for not completing adjuvant treatment. The median number of cycles of adjuvant durvalumab was 8 (range, 1 to 8).

At the time of this analysis, 53 patients in the durvalumab group and 93 patients in the comparison group had received at least one subsequent anticancer therapy after treatment discontinuation. The current trial had largely been conducted before nivolumab was approved as adjuvant treatment for high-risk muscle-invasive bladder cancer, and only 4 patients in the trial received adjuvant nivolumab.

EFFICACY

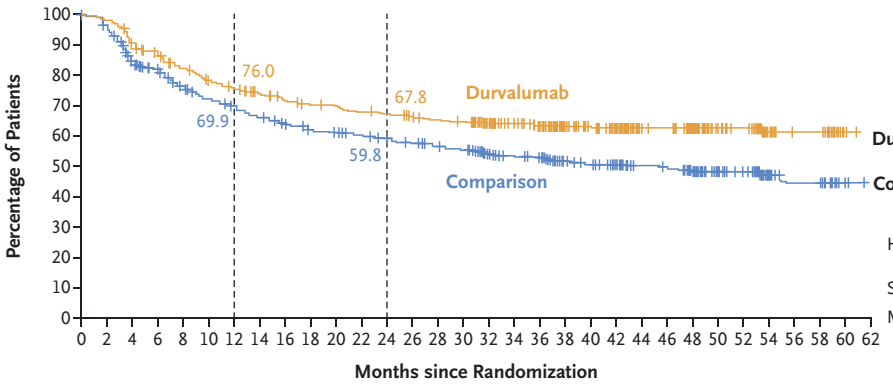
According to the primary analysis, a pathological complete response (as assessed by central pathology review) occurred in 33.8% (95% confidence interval [CI], 29.8 to 38.0) of the patients in the durvalumab group and in 25.8% (95% CI, 22.2 to 29.8) of those in the comparison group (risk ratio, 1.30; 95% CI, 1.09 to 1.56; P=0.004); the difference between the trial groups was not significant according to the type 1 error of 0.1% allocated to the comparison (Fig. 1). In the reanalysis including the results for the 59 samples omitted from the primary analysis, a pathological complete response (as assessed by central pathology review) occurred in 37.3% (95% CI, 33.2 to 41.6) of the patients in the durvalumab group and in 27.5% (95% CI, 23.8 to 31.6) of those in the comparison group (risk ratio, 1.34; 95% CI, 1.13 to 1.60) (Fig. 1). The results of both primary analysis and reanalysis of pathological complete response according to subgroup were consistent with the results in the overall population (Figs. S3 and S4). Among all the patients who underwent randomization, 265 (49.7%) in the durvalumab group and 215 (40.6%) in the comparison group had a pathological tumor stage of less than T2 as assessed by the investigator.

The median duration of follow-up for event-free survival in patients with censored data was 42.3 months (range, 0.03 to 61.3). An event occurred in 187 patients (35.1%) in the durvalumab group and in 246 patients (46.4%) in the comparison group (Table S3). The estimated event-free survival at 24 months was 67.8% (95% CI, 63.6 to 71.7) in the durvalumab group and 59.8% (95% CI, 55.4 to 64.0) in the comparison group (hazard ratio for progression, recurrence, not undergoing radical cystectomy, or death from any cause, 0.68; 95% CI, 0.56 to 0.82; P<0.001 by stratified log-rank test) (Fig. 2A).

The results of a subgroup analysis of event-free survival in the intention-to-treat population are shown in Figure 2B. The results of sensitivity analyses of event-free survival that accounted for attrition, evaluation-time bias, and not undergoing radical cystectomy were consistent with the results in the intention-to-treat population (Table S2 and Fig. S2). Because assessment of the TC/IC25% algorithm showed inconsistencies among the central laboratories in the reported prevalence of PD-L1 expression on immune cells, we analyzed event-free survival according to PD-L1 expression levels of 1% and 25% of tumor cells, and the results were consistent with those in the intention-to-treat population (see the Supplementary Appendix).

In the intention-to-treat population, death occurred in 136 patients (25.5%) in the durvalumab group and 169 patients (31.9%) in the comparison group (Table S4). The estimated overall

A Event-free Survival



	No. of Patients with Event/Total No. (%)	Median Event-free Survival (95% CI)
		mo
Durvalumab	187/533 (35.1)	NR (NR–NR)
Comparison	246/530 (46.4)	46.1 (32.2–NR)

Hazard ratio for event, 0.68 (95% CI, 0.56–0.82)
Stratified P<0.001 by log-rank test
Median follow-up among patients with censored data, 42.3 mo (range, 0.03–61.3)

No. at Risk

Durvalumab	533	475	424	386	356	344	330	315	282	255	202	141	115	86	81	32	20	20	1	0
Comparison	530	437	381	343	313	296	281	264	228	214	172	132	94	69	62	24	18	16	2	0

B Subgroup Analysis for Event-free Survival

Subgroup	No. of Patients	Durvalumab	Comparison	Hazard Ratio for Event (95% CI)
		no. of patients with event/total no.		
All patients	1063	187/533	246/530	0.68 (0.56–0.82)
Age at randomization				
<65 yr	499	86/258	105/241	0.71 (0.53–0.94)
≥65 yr	564	101/275	141/289	0.67 (0.52–0.86)
Sex				
Male	870	157/437	199/433	0.71 (0.58–0.88)
Female	193	30/96	47/97	0.56 (0.35–0.88)
Race				
White	712	130/354	169/358	0.71 (0.56–0.89)
Non-White	315	54/165	67/150	0.65 (0.45–0.92)
Geographic region				
Asia	294	50/151	63/143	0.68 (0.46–0.98)
Europe	552	102/265	134/287	0.76 (0.58–0.98)
North America and Australia	128	17/66	27/62	0.50 (0.27–0.92)
South America	89	18/51	22/38	0.55 (0.29–1.03)
Histologic type at baseline				
Urothelial carcinoma	898	163/457	197/441	0.72 (0.58–0.89)
Urothelial carcinoma with divergent differentiation or histologic subtypes	165	24/76	49/89	0.52 (0.32–0.84)
Previous BCG therapy				
Yes	57	11/31	12/26	0.66 (0.29–1.51)
No	1006	176/502	234/504	0.68 (0.56–0.83)
Regional lymph-node stage at baseline				
N0	1005	176/505	232/500	0.68 (0.56–0.82)
N1	58	11/28	14/30	0.75 (0.33–1.64)
Tumor stage at baseline				
T2N0	428	78/215	88/213	0.81 (0.60–1.10)
Higher than T2N0	635	109/318	158/317	0.61 (0.48–0.78)
Creatinine clearance at baseline				
≥60 ml/min/1.73 m^2	862	141/432	189/430	0.68 (0.54–0.84)
40 to <60 ml/min/1.73 m^2	201	46/101	57/100	0.69 (0.46–1.01)
PD-L1 expression level at baseline				
High	777	129/389	168/388	0.70 (0.56–0.88)
Low or none	286	58/144	78/142	0.62 (0.44–0.87)

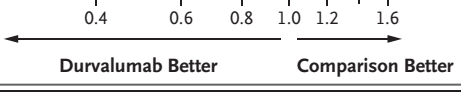


Figure 2 (facing page). Event-free Survival in the Intention-to-Treat Population.

Shown in Panel A are Kaplan–Meier estimates of event-free survival (as assessed by blinded independent central review) as of the data-cutoff date (April 29, 2024). Tick marks indicate patients with censored data. Dashed lines indicate event-free survival at 12 months and 24 months. Panel B shows a forest plot of event-free survival in prespecified baseline subgroups. The gray shading indicates the 95% confidence interval for the hazard ratio for an event in the intention-to-treat population. Prespecified subgroup analyses were performed with the use of an unstratified Cox proportional-hazards model with treatment as the only covariate and the use of Efron's approach for handling ties. Race was reported by the patients. Disease stage was defined according to the eighth edition of the American Joint Committee on Cancer *AJCC Cancer Staging Manual*.[16] Histologic type, tumor stage, and regional lymph-node stage were assessed by the investigator on the basis of a pathological tumor assessment of a sample obtained during transurethral resection of the bladder tumor, an examination of the patient under anesthesia after the transurethral resection of the bladder tumor, and findings on computed tomography or magnetic resonance imaging. The baseline programmed death ligand 1 (PD-L1) expression level was assessed with the use of immunohistochemical staining (Ventana PD-L1 [SP263] assay; Ventana Medical Systems), in which a high expression level was defined as PD-L1 expression on at least 25% of tumor cells, at least 25% of immune cells if immune cells were present in more than 1% of the tumor area, or 100% of immune cells if immune cells were present in 1% of the tumor area. BCG denotes bacille Calmette–Guérin, and NR not reached.

survival at 24 months was 82.2% (95% CI, 78.7 to 85.2) in the durvalumab group and 75.2% (95% CI, 71.3 to 78.8) in the comparison group (hazard ratio for death, 0.75; 95% CI, 0.59 to 0.93; P=0.01 by stratified log-rank test) (Fig. 3A). Overall survival according to subgroup is shown in Figure 3B.

SAFETY

Of the patients who received at least one dose of neoadjuvant treatment, adverse events of any cause occurred in 99.4% of those in the durvalumab group and in 99.8% of those in the comparison group, with adverse events of grade 3 or 4 occurring in 69.4% and 67.5% of the patients, respectively (Table 2). In both trial groups, the most common adverse events of any cause were nausea, anemia, and constipation (Table S5). Treatment-related adverse events of any grade occurred in 94.7% of the patients in the durvalumab group and in 92.6% of those in the comparison group, with treatment-related adverse events of grade 3 or 4 occurring in 40.6% and 40.9% of the patients, respectively (Table 2).

Treatment-related adverse events leading to death occurred in 3 patients (0.6%) in each group. All three deaths in the durvalumab group occurred during neoadjuvant therapy (one death was due to cardiorespiratory arrest related to durvalumab and chemotherapy, and one death each was due to pulmonary embolism and myocardial infarction related to chemotherapy only). In the comparison group, two deaths occurred during neoadjuvant treatment, and one death occurred after surgery. Surgery-related adverse events leading to death within the first 90 days after radical cystectomy occurred in 10 patients (2.1%) in the durvalumab group and in 8 patients (1.8%) in the comparison group.

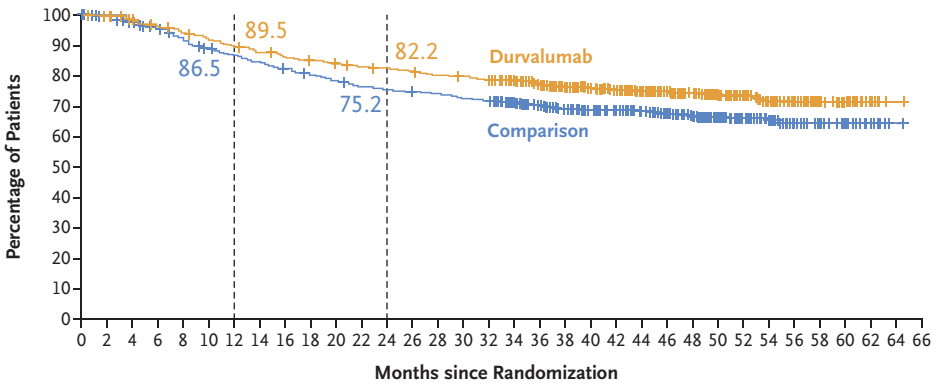
Adverse events leading to the discontinuation of neoadjuvant treatment occurred in 14.9% of the patients in the durvalumab group and in 15.2% of those in the comparison group (Table S6). The percentage of patients with adverse events precluding or delaying surgery was similar in the trial groups (Table 2). Of the 383 patients who started adjuvant durvalumab therapy, adverse events led to treatment discontinuation in 30 (7.8%) (Table S7).

Overall, immune-mediated adverse events occurred in 111 patients (20.9%) in the durvalumab group and in 16 patients (3.0%) in the comparison group. Immune-mediated adverse events that occurred in at least 1% of the patients in the durvalumab group included hypothyroid events (in 10.4% of the patients), hyperthyroid events (in 2.5%), dermatitis or rash (in 2.3%), renal events (in 1.7%), diarrhea or colitis (in 1.5%), and pneumonitis (in 1.3%). No immune-mediated adverse events led to death in the durvalumab group; immune-mediated pneumonitis led to death in 1 patient in the comparison group.

DISCUSSION

In cisplatin-eligible patients with muscle-invasive bladder cancer, perioperative durvalumab plus neoadjuvant chemotherapy with radical cystectomy significantly improved event-free survival and overall survival as compared with neoadjuvant chemotherapy with radical cystectomy alone.

A Overall Survival



	No. of Deaths/Total No. (%)
Durvalumab	136/553 (25.5)
Comparison	169/530 (31.9)

Hazard ratio for death, 0.75 (95% CI, 0.59–0.93)
Stratified P=0.01 by log-rank test
Median follow-up among patients with censored data, 46.3 mo (range, 0.03–64.7)

No. at Risk

Durvalumab	533	517	492	468	446	434	423	410	400	349	295	238	182	125	96	68	34	21	7	1	0
Comparison	530	507	467	438	413	392	378	368	358	311	259	215	174	113	90	60	38	21	10	2	0

B Subgroup Analysis for Overall Survival

Subgroup	No. of Patients	Durvalumab (no. of deaths/total no.)	Comparison (no. of deaths/total no.)	Hazard Ratio for Death (95% CI)
All patients	1063	136/533	169/530	0.75 (0.59–0.93)
Age at randomization				
<65 yr	499	58/258	73/241	0.70 (0.49–0.98)
≥65 yr	564	78/275	96/289	0.80 (0.59–1.07)
Sex				
Male	870	114/437	133/433	0.80 (0.62–1.02)
Female	193	22/96	36/97	0.56 (0.32–0.94)
Race				
White	712	97/354	130/358	0.70 (0.53–0.90)
Non-White	315	37/165	34/150	0.94 (0.59–1.51)
Geographic region				
Asia	294	34/151	32/143	0.98 (0.60–1.60)
Europe	552	76/265	96/287	0.79 (0.58–1.07)
North America and Australia	128	11/66	20/62	0.51 (0.23–1.04)
South America	89	15/51	21/38	0.43 (0.22–0.84)
Histologic type at baseline				
Urothelial carcinoma	898	117/457	130/441	0.81 (0.63–1.04)
Urothelial carcinoma with divergent differentiation or histologic subtypes	165	19/76	39/89	0.53 (0.30–0.90)
Previous BCG therapy				
Yes	57	7/31	8/26	NC (NC–NC)
No	1006	129/502	161/504	0.75 (0.60–0.95)
Regional lymph-node stage at baseline				
N0	1005	130/505	160/500	0.75 (0.59–0.94)
N1	58	6/28	9/30	NC (NC–NC)
Tumor stage at baseline				
T2N0	428	56/215	60/213	0.89 (0.61–1.28)
Higher than T2N0	635	80/318	109/317	0.67 (0.50–0.89)
Creatinine clearance at baseline				
≥60 ml/min/1.73 m^2	862	99/432	131/430	0.70 (0.54–0.91)
40 to <60 ml/min/1.73 m^2	201	37/101	38/100	0.89 (0.56–1.40)
PD-L1 expression level at baseline				
High	777	99/389	112/388	0.83 (0.63–1.09)
Low or none	286	37/144	57/142	0.58 (0.38–0.88)

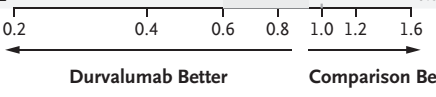


Figure 3 (facing page). Overall Survival in the Intention-to-Treat Population.

Panel A shows Kaplan–Meier estimates of overall survival (as assessed by blinded independent central review) as of the data-cutoff date (April 29, 2024). Tick marks indicate patients with censored data. Dashed lines indicate survival at 12 months and 24 months. Panel B shows a forest plot of overall survival in prespecified baseline subgroups. The gray shading indicates the 95% confidence interval for the hazard ratio for death in the intention-to-treat population. Prespecified subgroup analyses were performed with the use of an unstratified Cox proportional-hazards model with treatment as the only covariate and the use of Efron's approach for handling ties. NC denotes not calculated.

The event-free survival benefit was broadly consistent across prespecified subgroups. Furthermore, the percentage of patients who underwent surgery was similar in the two trial groups, which means that the addition of neoadjuvant durvalumab to chemotherapy did not lead to a reduction in the percentage of patients who underwent radical cystectomy.

In patients with muscle-invasive bladder cancer, pathological complete response has not yet been established as a surrogate for survival end points in clinical trials.[19,20] In the current trial, although the percentage of patients with a pathological complete response was not significantly different in the trial groups, the numerical between-group difference in this percentage and the early separation of the Kaplan–Meier curves for event-free survival suggest that the addition of durvalumab to chemotherapy improves efficacy in the neoadjuvant treatment phase. Recent clinical and preclinical research in metastatic urothelial carcinoma supports the benefit of combining cisplatin-based chemotherapy with immune-checkpoint inhibitors.[21,22] Our trial was designed to assess the perioperative treatment in its totality in a population of patients with muscle-invasive bladder cancer, but it was not designed to assess the treatment effect of durvalumab in the neoadjuvant phase as compared with the adjuvant phase in either the intention-to-treat population or in patients with a pathological complete response. Exploratory work from this and other ongoing trials[23-27] may include such assessments.

Biomarkers other than tumor PD-L1 expression, such as circulating tumor DNA (ctDNA), may play a role in assisting treatment decisions in the future. Negative ctDNA status after neoadjuvant atezolizumab treatment appears to be associated with a reduced risk of relapse in patients with muscle-invasive bladder cancer.[28] Also, ctDNA positivity after cystectomy may be correlated with a response to adjuvant immune-checkpoint inhibitor monotherapy.[29] Exploratory analyses of ctDNA in trials such as ours may also provide further insight.

The safety profile of perioperative durvalumab with neoadjuvant chemotherapy was consistent with individual safety profiles for durvalumab and gemcitabine–cisplatin. The percentage of patients with adverse events leading to treatment discontinuation during the neoadjuvant period was approximately the same in both treatment groups, and adverse events leading to the discontinuation of adjuvant durvalumab therapy were infrequent. Preliminary results presented here suggest that the safety of surgery was similar in the treatment groups. Assessments of health-related quality of life and other secondary end points are ongoing.

The trial was limited by the open-label design, which was somewhat mitigated by the blinded independent central review of tumor assessments and the blinding of the sponsor to the trial-group assignments and patient-level efficacy data. Our trial was performed before the widespread availability of adjuvant nivolumab[13] for high-risk muscle-invasive bladder cancer or enfortumab vedotin with pembrolizumab[30] for advanced disease, and the potential effect of these treatment options on the observed survival benefit is unclear. Blinding of the sponsor during the trial limited the analysis of subsequent therapies in this interim analysis; unblinding and additional follow-up will allow greater understanding of subsequent therapies received by the patients in both groups. Finally, the trial was not designed to isolate the relative contributions of each treatment phase to the efficacy outcomes.

Perioperative durvalumab with neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy provided a significant event-free survival benefit and overall survival benefit to patients with muscle-invasive bladder cancer. The results of this trial support the use of perioperative durvalumab with neoadjuvant chemotherapy as a potential new treatment option for

Table 2. Adverse Events in the As-Treated Population.*

Adverse Event	Durvalumab (N=530)	Comparison (N=526)
	number of patients (percent)	
Adverse events of any cause		
Event of any grade	527 (99.4)	525 (99.8)
Event of grade 3 or 4†	368 (69.4)	355 (67.5)
Serious adverse event	326 (61.5)	287 (54.6)
Event leading to death	27 (5.1)	29 (5.5)
Event leading to discontinuation of trial treatment‡	112 (21.1)	80 (15.2)
Event leading to discontinuation of durvalumab	86 (16.2)	—
Event leading to discontinuation of chemotherapy	72 (13.6)	80 (15.2)
Event leading to cancellation of surgery	6 (1.1)	7 (1.3)
Event leading to a delay in surgery§	9 (1.7)	6 (1.1)
Treatment-related adverse events¶		
Event of any grade	502 (94.7)	487 (92.6)
Event of grade 3 or 4†	215 (40.6)	215 (40.9)
Serious adverse event	86 (16.2)	63 (12.0)
Event leading to death‖	3 (0.6)	3 (0.6)
Durvalumab-related event leading to discontinuation	42 (7.9)	—
Chemotherapy-related event leading to discontinuation	55 (10.4)	64 (12.2)

* The as-treated population included patients who received at least one dose of neoadjuvant treatment. Safety data are shown for the overall trial period, which included the time from the first dose of trial treatment and the earliest of 90 days after the last dose of trial treatment or surgery (in the durvalumab group); 90 days after the last neoadjuvant treatment, surgery, or last visit during the adjuvant phase (in the comparison group); the date of the first dose of subsequent anticancer therapy (in both groups); or the date of data cutoff (in both groups). Patients with multiple events in the same category are counted only once in that category.

† The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events, version 5.0. For patients with multiple episodes of the same adverse event, only the episode with the highest grade is included.

‡ Trial treatment is defined as durvalumab and gemcitabine–cisplatin and does not include surgery.

§ Delayed surgery was defined as surgery that occurred more than 56 days after the last dose of trial treatment during the neoadjuvant period.

¶ Data are for adverse events considered by the investigator to be related to the trial treatment. Adverse events with missing data were considered to be related to the trial treatment.

‖ Treatment-related adverse events leading to death were cardiorespiratory arrest, myocardial infarction, and pulmonary embolism in one patient each in the durvalumab group and cardiorespiratory arrest and pneumonitis in one patient each in the comparison group. The cause of death was unknown in one patient in the comparison group.

cisplatin-eligible patients with muscle-invasive bladder cancer.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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