ORIGINAL ARTICLE

Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

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ABSTRACT

BACKGROUND

The role of adjuvant treatment in high-risk muscle-invasive urothelial carcinoma after radical surgery is not clear.

METHODS

In a phase 3, multicenter, double-blind, randomized, controlled trial, we assigned patients with muscle-invasive urothelial carcinoma who had undergone radical surgery to receive, in a 1:1 ratio, either nivolumab (240 mg intravenously) or placebo every 2 weeks for up to 1 year. Neoadjuvant cisplatin-based chemotherapy before trial entry was allowed. The primary end points were disease-free survival among all the patients (intention-to-treat population) and among patients with a tumor programmed death ligand 1 (PD-L1) expression level of 1% or more. Survival free from recurrence outside the urothelial tract was a secondary end point.

RESULTS

A total of 353 patients were assigned to receive nivolumab and 356 to receive placebo. The median disease-free survival in the intention-to-treat population was 20.8 months (95% confidence interval [CI], 16.5 to 27.6) with nivolumab and 10.8 months (95% CI, 8.3 to 13.9) with placebo. The percentage of patients who were alive and disease-free at 6 months was 74.9% with nivolumab and 60.3% with placebo (hazard ratio for disease recurrence or death, 0.70; 98.22% CI, 0.55 to 0.90; P<0.001). Among patients with a PD-L1 expression level of 1% or more, the percentage of patients was 74.5% and 55.7%, respectively (hazard ratio, 0.55; 98.72% CI, 0.35 to 0.85; P<0.001). The median survival free from recurrence outside the urothelial tract in the intention-to-treat population was 22.9 months (95% CI, 19.2 to 33.4) with nivolumab and 13.7 months (95% CI, 8.4 to 20.3) with placebo. The percentage of patients who were alive and free from recurrence outside the urothelial tract at 6 months was 77.0% with nivolumab and 62.7% with placebo (hazard ratio for recurrence outside the urothelial tract or death, 0.72; 95% CI, 0.59 to 0.89). Among patients with a PD-L1 expression level of 1% or more, the percentage of patients was 75.3% and 56.7%, respectively (hazard ratio, 0.55; 95% CI, 0.39 to 0.79). Treatment-related adverse events of grade 3 or higher occurred in 17.9% of the nivolumab group and 7.2% of the placebo group. Two treatment-related deaths due to pneumonitis and one treatment-related death due to bowel perforation were noted in the nivolumab group.

CONCLUSIONS

In this trial involving patients with high-risk muscle-invasive urothelial carcinoma who had undergone radical surgery, disease-free survival was longer with adjuvant nivolumab than with placebo in the intention-to-treat population and among patients with a PD-L1 expression level of 1% or more. (Funded by Bristol Myers Squibb and Ono Pharmaceutical; CheckMate 274 ClinicalTrials.gov number, NCT02632409.)

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Radical surgery involving cystectomy for tumors arising in the bladder or nephroureterectomy for tumors arising in the upper urinary tract is the standard of care for patients with muscle-invasive urothelial carcinoma.[1,2] Although radical surgery is performed with curative intent, more than 50% of patients with pathological evidence of cancer invading through the muscularis propria or involving the regional lymph nodes will have lethal metastatic recurrence.[1-4] Adjuvant chemotherapy may prolong disease-free survival among patients with locally advanced upper tract urothelial carcinoma,[5] but no consensus has emerged regarding routine adjuvant cisplatin-based chemotherapy, and some patients with urothelial carcinoma are ineligible for or decline neoadjuvant cisplatin-based chemotherapy.[1,2,6-9] Furthermore, despite a high risk of metastatic recurrence, no standard adjuvant systemic therapies have been shown to improve outcomes in patients with pathological evidence of residual disease after neoadjuvant cisplatin-based chemotherapy.[10-12]

Nivolumab is a fully human IgG4 monoclonal antibody directed against programmed death 1. At a dose of 3 mg per kilogram of body weight every 2 weeks, nivolumab has been shown to have antitumor activity in patients with metastatic urothelial carcinoma who had previously received platinum treatment[13-15]; it was approved in this population on the basis of the results of the CheckMate 275 trial.[14,16,17] However, to date, no immune-checkpoint inhibitor has shown efficacy as adjuvant therapy in patients with urothelial carcinoma at high risk for metastatic recurrence after radical surgery with curative intent.[18,19] Thus, the phase 3 CheckMate 274 trial was conducted to evaluate the efficacy and safety of adjuvant nivolumab, as compared with placebo, in patients with muscle-invasive urothelial carcinoma after radical surgery (with or without previous neoadjuvant cisplatin-based combination chemotherapy).

Methods

Patients

Eligible patients must have had radical surgery (R0, with negative surgical margins) within 120 days before randomization, with or without neoadjuvant cisplatin-based chemotherapy. Patients must have had pathological evidence of urothelial carcinoma (originating in the bladder, ureter, or renal pelvis) with a high risk of recurrence (pathological stage of pT3, pT4a, or pN+ and patient not eligible for[20] or declined adjuvant cisplatin-based combination chemotherapy for patients who had not received neoadjuvant cisplatin-based chemotherapy and pathological stage of ypT2 to ypT4a or ypN+ for patients who received neoadjuvant cisplatin). Enrollment of patients with upper tract urothelial carcinomas was capped at approximately 20% to prevent substantial deviation from the natural prevalence of bladder disease as compared with upper tract disease. Eligible patients must have been disease-free as determined by means of a complete physical examination and imaging within 4 weeks before randomization, had adequate tumor tissue for biomarker analysis, and had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability). Further details are included in the Methods section of the Supplementary Appendix, available with the full text of this article at NEJM.org.

A Quick Take is available at NEJM.org

Trial Design and Treatments

This was a phase 3, multicenter, double-blind, randomized trial of adjuvant nivolumab as compared with placebo. Patients were assigned to the trial groups in a 1:1 ratio, with stratification according to tumor programmed death ligand 1 (PD-L1) expression level (≥1% vs. <1% or indeterminate), pathological nodal status (N+ vs. N0 or NX with <10 nodes removed vs. N0 with ≥10 nodes removed), and use of neoadjuvant cisplatin-based combination chemotherapy (yes vs. no). Further details are included in the Methods section of the Supplementary Appendix.

Nivolumab (240 mg) or placebo was administered every 2 weeks as a 30-minute intravenous infusion for up to 1 year or until disease recurrence or discontinuation from the trial. Dose delays or discontinuations were allowed to manage toxic effects.

End Points and Assessments

The two primary end points were disease-free survival among all the patients who underwent randomization (intention-to-treat population) and among those with a tumor PD-L1 expression level of 1% or more. Disease-free survival was defined as the time between the date of randomization and the date of first recurrence (local recurrence in the urothelial tract, local recurrence

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outside the urothelial tract, or distant recurrence) or death. Local recurrences outside the urothelial tract were defined as any recurrence in pelvic soft tissue or involving pelvic nodes below the aortic bifurcation. Disease-free survival was also evaluated in prespecified subgroups. Disease recurrence was investigator-reported, with biopsy encouraged by the protocol (available at NEJM.org) whenever feasible and at the clinical judgment of the treating physician.

Secondary end points included survival free from recurrence outside the urothelial tract (to exclude non–life-threatening second primary urothelial cancers common in this disease), overall survival, and disease-specific survival, all in both trial populations. Survival free from recurrence outside the urothelial tract (also known as non–urothelial tract recurrence–free survival) was defined as the time between the date of randomization and the date of first local recurrence outside the urothelial tract, distant recurrence, or death. Distant metastasis–free survival, safety, side-effect profile, and health-related quality of life were among the exploratory end points. PD-L1 status was defined by the percentage of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated with the use of the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako).

The safety analysis was performed both in the group of all randomly assigned patients who received at least one dose of nivolumab or placebo and in the group of all such patients with a PD-L1 expression level of 1% or more. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[21] Relatedness of adverse events to the trial regimen was determined by the investigators. Select adverse events (those with a potential inflammatory mechanism requiring more frequent monitoring or a specific intervention, such as immunosuppressants or endocrine-replacement therapy) were also reported.

Assessments of health-related quality of life were completed with the use of the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), a 30-item instrument comprising six functional scales,[22] and the EuroQol Group 5-Dimension 3-Level questionnaire (EQ-5D-3L).[23] Detailed definitions of end points and assessments are provided in the Methods section of the Supplementary Appendix.

TRIAL OVERSIGHT

This trial was approved by the institutional review boards at the participating institutions and conducted in accordance with Good Clinical Practice guidelines as defined by the International Council for Harmonisation. All the patients provided written informed consent adhering to Declaration of Helsinki principles. A data monitoring committee provided oversight of safety and efficacy considerations. The trial was designed by the authors in collaboration with Bristol Myers Squibb. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. The authors, with the assistance of a medical writer employed by Bristol Myers Squibb, drafted and provided final approval of the manuscript that was submitted.

STATISTICAL ANALYSIS

The sample size of approximately 700 patients was based on the between-group comparisons of the primary end points. We calculated that approximately 410 events of disease recurrence or death in the intention-to-treat population would provide approximately 87% power to detect an average hazard ratio of 0.72 with an overall type I error of 2.5% (two-sided). In patients with a PD-L1 expression level of 1% or more, approximately 162 events of disease recurrence or death would provide approximately 80% power to detect an average hazard ratio of 0.61 with an overall type I error of 2.5% (two-sided).

One interim analysis was planned to be performed when 85% of events of disease recurrence or death in each trial population had been observed (348 events in the intention-to-treat population and 137 in the group of patients with a PD-L1 expression level of ≥1%). The alpha level (0.01784 for the intention-to-treat population and 0.01282 for the group of patients with a PD-L1 expression level of ≥1%) for disease-free survival was adjusted for the planned interim analysis with the use of a Lan–DeMets alpha spending function with the O'Brien–Fleming type of boundary[24] in East software, version 6 (Cytel).

Disease-free survival was compared between the nivolumab and placebo groups with the use of a two-sided stratified log-rank test. Hazard

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ratios and corresponding confidence intervals for disease-free survival, survival free from recurrence outside the urothelial tract, and distant metastasis–free survival were estimated with the use of a stratified Cox proportional-hazards model. The secondary end point of overall survival was planned to be formally compared with the use of a hierarchical procedure in each population and will be assessed with longer follow-up, on the basis of the number of deaths specified in the trial protocol.

Mixed-effects linear regression for repeated-measures analyses was performed with the use of the EORTC QLQ-C30 and EQ-5D-3L instruments to estimate treatment effects on each of the scores over time. The model included the covariates trial group, time, stratification factors, baseline score, interaction between baseline score and time, and interaction between trial group and time, all as fixed effects, and random intercept and random slope for the time variable. Further information regarding statistical analyses is included in the Methods section of the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENTS

Between April 2016 and January 2020, a total of 709 patients underwent randomization at 156 sites in 29 countries in North and South America, Europe, Asia, and Australia. In the intention-to-treat population, 353 patients were randomly assigned to receive nivolumab and 356 to receive placebo. The population with a PD-L1 expression level of 1% or more comprised 140 patients in the nivolumab group and 142 patients in the placebo group, as recorded at randomization by means of the interactive voice-response system (282 patients). In the intention-to-treat population, 53.3% of the patients in the nivolumab group and 56.3% of those in the placebo group discontinued the trial regimen. The most common reason for discontinuation was disease recurrence (25.6% in the nivolumab group and 42.2% in the placebo group) (Fig. S1 in the Supplementary Appendix). In the intention-to-treat population, 47.3% of the patients who received nivolumab and 47.2% of those who received placebo had resected lymph nodes with urothelial carcinoma invasion. Previous neoadjuvant cisplatin-based combination chemotherapy was administered in 43.3% of the patients in the nivolumab group and in 43.5% of those in the placebo group. The characteristics of the patients at baseline were balanced between the two groups in the intention-to-treat population (Table 1) and in the group of patients with a PD-L1 expression level of 1% or more (Table S1).

EFFICACY

The median follow-up was 20.9 months (range, 0.1 to 48.3) among patients who received nivolumab and 19.5 months (range, 0 to 50.0) among those who received placebo (minimum follow-up, 5.9 months). The median disease-free survival was 20.8 months (95% confidence interval [CI], 16.5 to 27.6) in the nivolumab group and 10.8 months (95% CI, 8.3 to 13.9) in the placebo group in the intention-to-treat population. The percentage of patients who were alive and disease-free at 6 months was 74.9% with nivolumab and 60.3% with placebo in the intention-to-treat population (hazard ratio for disease recurrence or death, 0.70; 98.22% CI, 0.55 to 0.90; $P<0.001$) (Fig. 1A). Among patients with a PD-L1 expression level of 1% or more, the percentage who were alive and disease-free at 6 months was 74.5% with nivolumab and 55.7% with placebo (hazard ratio, 0.55; 98.72% CI, 0.35 to 0.85; $P<0.001$) (Fig. 1B).

The subgroup analysis is shown in Figure 2. A higher probability of disease-free survival with nivolumab than with placebo was observed regardless of nodal status, PD-L1 status, or use or nonuse of previous neoadjuvant cisplatin-based chemotherapy. A total of 83.6% of the patients with censored data in the entire trial population were still receiving nivolumab or placebo or were in follow-up at the time of the database lock (August 27, 2020) (Table S2).

In the intention-to-treat population, the median survival free from recurrence outside the urothelial tract was 22.9 months (95% CI, 19.2 to 33.4) among patients who received nivolumab and 13.7 months (95% CI, 8.4 to 20.3) among those who received placebo. The percentage of patients who were alive and free from recurrence outside the urothelial tract at 6 months was 77.0% with nivolumab and 62.7% with placebo (hazard ratio for recurrence outside the urothelial tract or death, 0.72; 95% CI, 0.59 to 0.89)

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

Characteristic	Nivolumab (N=353)	Placebo (N=356)
Age		
Mean (range) — yr	65.3 (30–92)	65.9 (42–88)
<65 yr — no. (%)	155 (43.9)	136 (38.2)
≥65 yr — no. (%)	198 (56.1)	220 (61.8)
Sex — no. (%)		
Male	265 (75.1)	275 (77.2)
Female	88 (24.9)	81 (22.8)
Race or ethnic group — no. (%)†		
White	264 (74.8)	272 (76.4)
Asian	80 (22.7)	75 (21.1)
Black	2 (0.6)	3 (0.8)
American Indian or Alaska Native	1 (0.3)	0
Other	6 (1.7)	5 (1.4)
Not reported	0	1 (0.3)
ECOG performance-status score — no. (%)‡		
0	224 (63.5)	221 (62.1)
1	122 (34.6)	125 (35.1)
2	7 (2.0)	9 (2.5)
Not reported	0	1 (0.3)
Tumor origin at initial diagnosis — no. (%)		
Urinary bladder	279 (79.0)	281 (78.9)
Renal pelvis	44 (12.5)	52 (14.6)
Ureter	30 (8.5)	23 (6.5)
Time from initial diagnosis to randomization — no. (%)		
<1 yr	325 (92.1)	324 (91.0)
≥1 yr	28 (7.9)	32 (9.0)
PD-L1 expression level of ≥1% by IVRS — no. (%)	140 (39.7)	142 (39.9)
Previous neoadjuvant cisplatin therapy — no. (%)	153 (43.3)	155 (43.5)
Pathological tumor stage and nodal status at resection — no. (%)§		
pT2N–	25 (7.1)	29 (8.1)
pT3,4N–	158 (44.8)	159 (44.7)
pT0–4N1	71 (20.1)	72 (20.2)
pT0–4N2,3	96 (27.2)	96 (27.0)
pTisN–	1 (0.3)	0
Not reported	2 (0.6)	0
Pathological tumor stage at resection — no. (%)¶		
pTX	5 (1.4)	0
pT0	5 (1.4)	7 (2.0)
pTis	4 (1.1)	3 (0.8)
pT1	13 (3.7)	14 (3.9)
pT2	62 (17.6)	65 (18.3)
pT3	206 (58.4)	204 (57.3)
pT4a	57 (16.1)	62 (17.4)
Not reported	1 (0.3)	1 (0.3)
Nodal status at resection — no. (%)		
N0 or NX with <10 nodes removed	94 (26.6)	99 (27.8)

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Table 1. (Continued.)

Characteristic	Nivolumab (N=353)	Placebo (N=356)
N0 with ≥10 nodes removed	91 (25.8)	88 (24.7)
N1	71 (20.1)	72 (20.2)
N2	84 (23.8)	76 (21.3)
N3	12 (3.4)	20 (5.6)
Not reported	1 (0.3)	1 (0.3)

* Percentages may not total 100 because of rounding. IVRS denotes interactive voice-response system, and PD-L1 programmed death ligand 1.
† Race or ethnic group was reported by the patient.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
§ This was not a prespecified subgroup. Patients with pT2N– disease were eligible only if they received neoadjuvant cisplatin-based chemotherapy. N– includes N0 and NX, and T0 includes pTX, pT0, and pTis.
¶ The pathological tumor staging included patients with any nodal status.

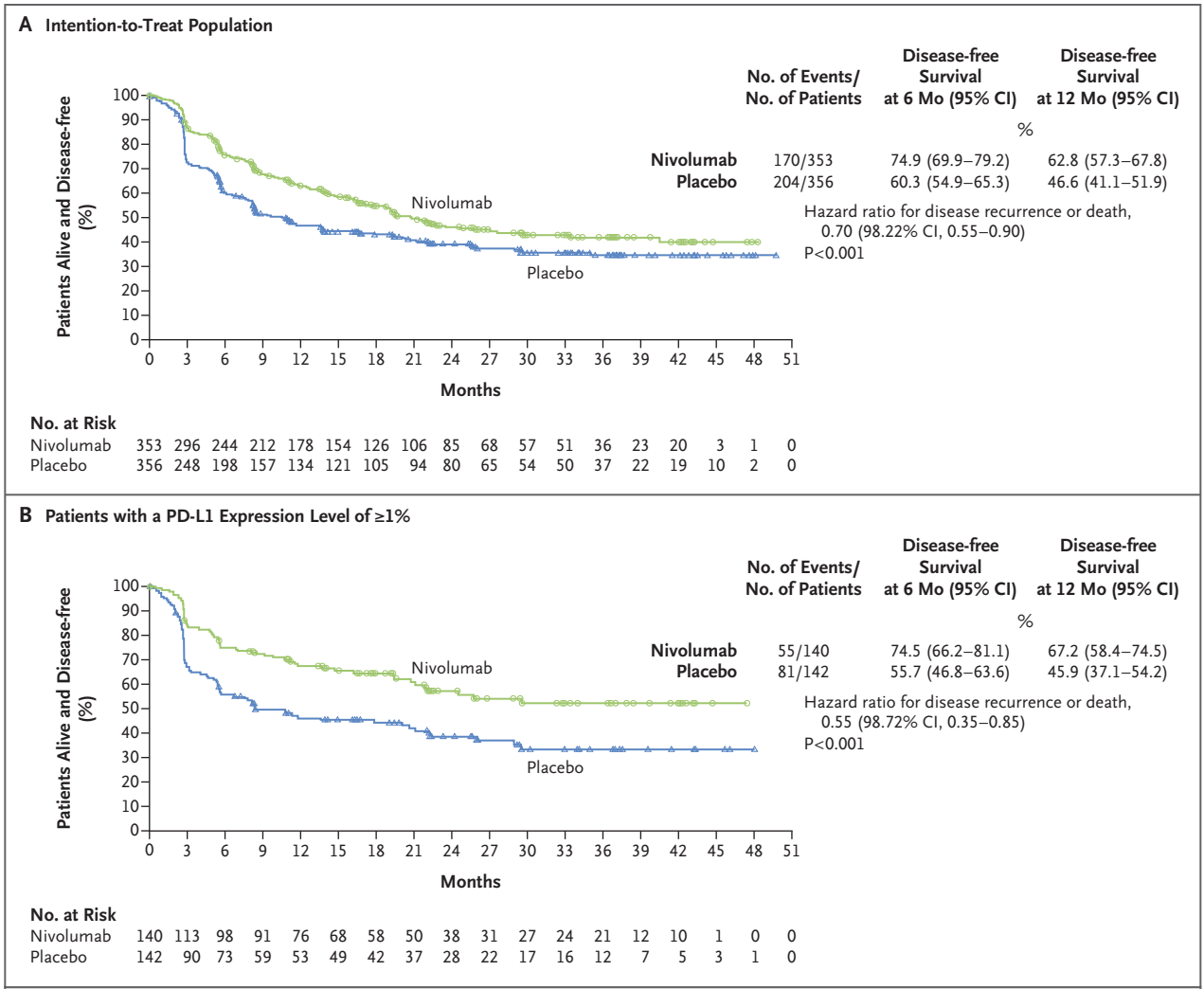

Figure 1. Disease-free Survival.

Symbols represent patients with censored data. The percentage of patients who were alive and disease-free at 12 months may be unstable owing to censoring of data. PD-L1 denotes programmed death ligand 1.

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Subgroup	No. of Patients	Nivolumab	Placebo	Hazard Ratio for Disease Recurrence or Death (95% CI)
		no. of events/no. of patients		
All patients	709	170/353	204/356	0.70 (0.57–0.86)
Age				
<65 yr	291	74/155	70/136	0.77 (0.55–1.07)
≥65 yr and <75 yr	295	64/131	100/164	0.68 (0.49–0.94)
≥75 yr	123	32/67	34/56	0.63 (0.38–1.06)
Sex				
Male	540	125/265	156/275	0.68 (0.54–0.87)
Female	169	45/88	48/81	0.76 (0.50–1.16)
Race or ethnic group				
White	536	126/264	162/272	0.65 (0.52–0.83)
Black	5	1/2	3/3	NA
Asian	155	37/80	35/75	0.83 (0.51–1.35)
American Indian or Alaska Native	1	1/1	0	NA
Native Hawaiian or other Pacific Islander	0	0	0	NA
Other	11	5/6	3/5	NA
Not reported	1	0	1/1	NA
Geographic region				
United States	102	24/49	36/53	0.45 (0.26–0.80)
Europe	341	87/170	96/171	0.84 (0.63–1.13)
Asia	154	37/80	34/74	0.85 (0.52–1.39)
Rest of the world	112	22/54	38/58	0.39 (0.21–0.72)
ECOG performance-status score at baseline				
0	445	105/224	126/221	0.69 (0.53–0.90)
1	247	64/122	71/125	0.77 (0.54–1.09)
2	16	1/7	7/9	NA
Not reported	1	0	0/1	NA
Hemoglobin level at baseline				
<10 g/dl	46	8/19	17/27	0.30 (0.08–1.06)
≥10 g/dl	653	162/332	185/321	0.72 (0.58–0.88)
Not reported	10	0/2	2/8	NA
Creatinine clearance at baseline				
<60 ml/min	309	83/151	91/158	0.87 (0.64–1.18)
≥60 ml/min	388	86/199	111/189	0.58 (0.44–0.78)
Not reported	12	1/3	2/9	NA
Initial tumor origin				
Urinary bladder	560	129/279	166/281	0.62 (0.49–0.78)
Renal pelvis	96	24/44	25/52	1.23 (0.67–2.23)
Ureter	53	17/30	13/23	1.56 (0.70–3.48)
Minor histologic variants				
Yes	286	70/145	76/141	0.73 (0.53–1.02)
No	423	100/208	128/215	0.69 (0.53–0.90)
Nodal status				
N+	335	95/167	116/168	0.64 (0.48–0.85)
N0 or NX with <10 nodes removed	193	46/94	50/99	0.85 (0.57–1.28)
N0 with ≥10 nodes removed	179	29/91	37/88	0.67 (0.41–1.10)
Not reported	2	0/1	1/1	NA
Pathological tumor stage				
pT0–2	166	35/80	40/86	0.88 (0.54–1.43)
pT3	410	97/206	120/204	0.63 (0.48–0.82)
pT4a	119	36/57	40/62	0.77 (0.47–1.25)
Other	12	1/9	3/3	NA
Not reported	2	1/1	1/1	NA
Pathological tumor stage and nodal status				
pT2N–	54	6/25	10/29	0.54 (0.16–1.86)
pT3,4N–	317	68/158	78/159	0.75 (0.54–1.05)
pT0–4N1	143	39/71	45/72	0.74 (0.47–1.15)
pT0–4N2,3	192	56/96	71/96	0.57 (0.40–0.83)
pTisN–	1	0/1	0	NA
Not reported	2	1/2	0	NA
Previous neoadjuvant cisplatin therapy				
Yes	308	70/153	100/155	0.52 (0.38–0.71)
No	401	100/200	104/201	0.92 (0.69–1.21)
Any previous neoadjuvant systemic therapy				
Yes	319	75/160	104/159	0.53 (0.39–0.72)
No	390	95/193	100/197	0.91 (0.69–1.21)
Days from surgery to randomization				
0–30	5	0/2	2/3	NA
>30–60	149	43/79	40/70	0.66 (0.40–1.06)
>60–90	342	78/165	93/177	0.76 (0.55–1.03)
>90–120	198	47/103	62/95	0.67 (0.44–1.00)
>120	15	2/4	7/11	NA
Smoking status				
Current or former smoker	484	116/237	141/247	0.70 (0.55–0.90)
Never smoked	215	53/111	61/104	0.67 (0.45–0.98)
Unknown	10	1/5	2/5	NA
PD-L1 expression level at baseline				
≥1%	280	55/139	79/141	0.56 (0.40–0.80)
<1%	419	114/210	120/209	0.82 (0.63–1.06)
Indeterminate or not able to be evaluated	8	1/3	4/5	NA
Not reported	2	0/1	1/1	NA

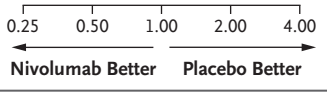

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Figure 2 (facing page). Disease-free Survival According to Subgroups in the Intention-to-Treat Population.

The hazard ratio was not computed for categories with fewer than 10 patients per trial group (denoted by NA [not applicable]). Confidence intervals are not adjusted for multiplicity. Arrows indicate that the limits of the confidence interval are not shown. Race or ethnic group was reported by the patient. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Combined pathological tumor stage and nodal status was not a prespecified subgroup. Patients with pT2N– disease were eligible only if they received neoadjuvant cisplatin-based chemotherapy. For the combination of tumor stage and nodal status, N– includes N0 and NX, and T0 includes pTX, pT0, and pTis. Previous chemotherapy regimens that were received by patients in the trial included carboplatin, cisplatin, cisplatin–doxorubicin–methotrexate–vinblastine, cisplatin–gemcitabine, doxorubicin, epirubicin, fluorouracil, gemcitabine, investigational agent, methotrexate, paclitaxel, tuberculin, vinblastine, and vincristine.

(Fig. 3A). Among patients with a PD-L1 expression level of 1% or more, the percentage who were alive and free from recurrence outside the urothelial tract at 6 months was 75.3% with nivolumab and 56.7% with placebo (hazard ratio, 0.55; 95% CI, 0.39 to 0.79) (Fig. 3B).

Distant metastasis–free survival was also longer with nivolumab than with placebo in both trial populations. In the intention-to-treat population, the median distant metastasis–free survival was 40.5 months (95% CI, 22.4 to could not be estimated) among patients who received nivolumab and 29.5 months (95% CI, 16.7 to could not be estimated) among those who received placebo. The percentage of patients who were alive and free from distant metastasis at 6 months was 82.5% with nivolumab and 69.8% with placebo (hazard ratio for distant metastasis or death, 0.75; 95% CI, 0.59 to 0.94) (Fig. S2A). Among patients with a PD-L1 expression level of 1% or more, the percentage who were alive and free from distant metastasis at 6 months was 78.7% with nivolumab and 65.7% with placebo (hazard ratio, 0.61; 95% CI, 0.42 to 0.90) (Fig. S2B).

EXPOSURE AND SAFETY

A total of 351 patients in the nivolumab group and 348 in the placebo group received at least one dose of the trial regimen. The median duration of exposure was 8.8 months (range, 0 to 12.5) in the nivolumab group and 8.2 months (range, 0 to 12.6) in the placebo group.

Adverse events of any cause occurred in 98.9% of the patients in the nivolumab group and 95.4% of those in the placebo group; events of grade 3 or higher occurred in 42.7% and 36.8% of the patients in the respective groups. Treatment-related adverse events of any grade occurred in 77.5% of the patients in the nivolumab group and 55.5% of those in the placebo group; events of grade 3 or higher occurred in 17.9% and 7.2% of the patients in the respective groups (Table 2). The most common treatment-related adverse events of any grade in the nivolumab group were pruritus (23.1%), fatigue (17.4%), and diarrhea (16.8%). The most common treatment-related adverse events of grade 3 or higher in the nivolumab group were elevations in the serum levels of lipase (5.1%) and amylase (3.7%) as well as diarrhea (0.9%), colitis (0.9%), and pneumonitis (0.9%). Treatment-related select adverse events (i.e., those events with a potential inflammatory mechanism requiring more frequent monitoring or a specific intervention, such as immunosuppressants or endocrine-replacement therapy) are summarized in Table S3. The safety profile of nivolumab was similar in patients with a PD-L1 expression level of 1% or more (data not shown).

Treatment-related deaths due to pneumonitis occurred in two patients in the nivolumab group. Both patients began glucocorticoid treatment at the onset of pneumonitis; one patient began 3 days after the last dose of trial therapy, and the other began 16 days after the last dose of trial therapy. There was one treatment-related death due to bowel perforation in the nivolumab group. This patient began glucocorticoid treatment 5 days after the last dose of trial therapy.

Treatment-related adverse events of any grade that led to discontinuation of the trial regimen occurred in 12.8% of the patients in the nivolumab group and 2.0% of those in the placebo group. The most frequent treatment-related adverse events leading to discontinuation of nivolumab were pneumonitis (1.7%), rash (1.1%), colitis (0.9%), and an increased alanine aminotransferase level (0.9%).

QUALITY OF LIFE

The percentage of patients who completed the EORTC QLQ-C30 was 85% or greater during the treatment period and 75% or greater in the follow-up period. Changes from baseline in the EORTC QLQ-C30 global health status score and

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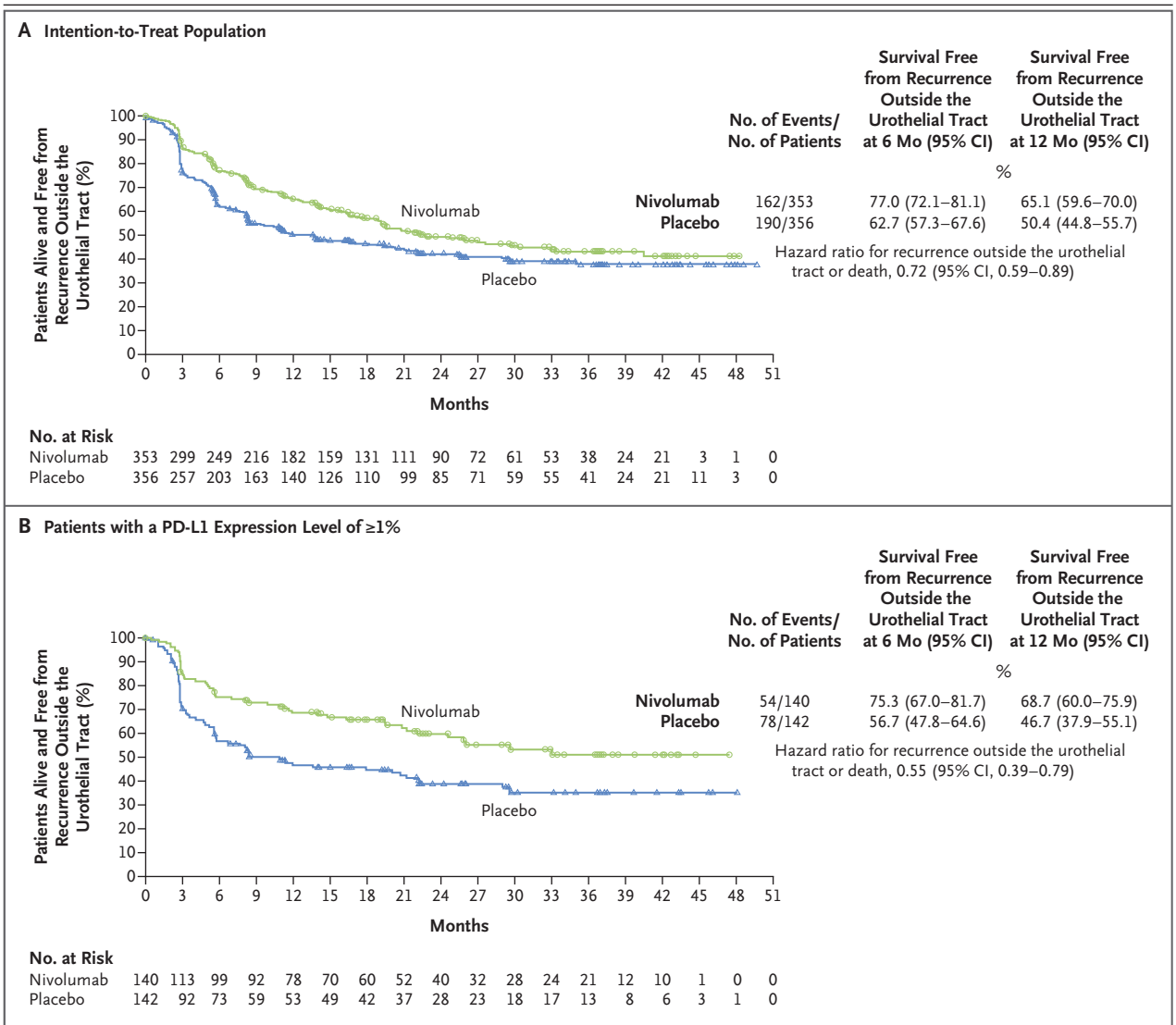

Figure 3. Survival Free from Recurrence Outside the Urothelial Tract.

Symbols represent patients with censored data. The percentage of patients who were alive and free from recurrence outside the urothelial tract at 12 months may be unstable owing to censoring of data.

the EQ-5D-3L visual analogue scale score over time indicated that there was no meaningful difference in deterioration in quality of life between patients who received nivolumab and those who received placebo, both in the intention-to-treat population and in patients with a PD-L1 expression level of 1% or more (Figs. S3 and S4).

DISCUSSION

Among patients with high-risk muscle-invasive urothelial carcinoma who had undergone radical surgery, disease-free survival was significantly longer with adjuvant nivolumab than with placebo, both in the intention-to-treat population and among patients with a tumor PD-L1 expression level of 1% or more. In the intention-to-treat population, the median disease-free survival with nivolumab was nearly double that with placebo (20.8 months vs. 10.8 months). Survival free from recurrence outside the urothelial tract and distant metastasis–free survival were also longer with nivolumab than with placebo in both trial populations.

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Table 2. Adverse Events.*

Adverse Event	Nivolumab (N=351)		Placebo (N=348)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Adverse event of any cause	347 (98.9)	150 (42.7)	332 (95.4)	128 (36.8)
Adverse event related to nivolumab or placebo†	272 (77.5)	63 (17.9)	193 (55.5)	25 (7.2)
Pruritus	81 (23.1)	0	40 (11.5)	0
Fatigue	61 (17.4)	1 (0.3)	42 (12.1)	0
Diarrhea	59 (16.8)	3 (0.9)	38 (10.9)	1 (0.3)
Rash	53 (15.1)	2 (0.6)	19 (5.5)	0
Increased lipase level	34 (9.7)	18 (5.1)	20 (5.7)	9 (2.6)
Hypothyroidism	34 (9.7)	0	5 (1.4)	0
Increased amylase level	33 (9.4)	13 (3.7)	20 (5.7)	5 (1.4)
Hyperthyroidism	33 (9.4)	0	3 (0.9)	0
Asthenia	24 (6.8)	2 (0.6)	17 (4.9)	0
Nausea	24 (6.8)	0	13 (3.7)	0
Decreased appetite	20 (5.7)	2 (0.6)	11 (3.2)	0
Increased blood creatinine level	20 (5.7)	1 (0.3)	11 (3.2)	0
Maculopapular rash	19 (5.4)	2 (0.6)	4 (1.1)	0

* Shown are events that were reported between the first dose and 30 days after the last dose of nivolumab or placebo.
† Shown are events that occurred in at least 5% of the patients in either trial group. There were two treatment-related deaths due to pneumonitis and one treatment-related death due to bowel perforation in the nivolumab group.

The safety profile of nivolumab monotherapy was consistent with that in previous trials involving patients with metastatic urothelial carcinoma and other cancers.[13,14,25] Both treatment-related adverse events of grade 3 or higher and treatment-related adverse events leading to discontinuation of the trial regimen occurred in less than 18% of the patients who received nivolumab and in less than 8% of those who received placebo. The favorable efficacy and safety results are supported by EORTC QLQ-C30 and EQ-5D-3L results that showed no deterioration in health-related quality of life over time in patients who received nivolumab as compared with those who received placebo. Two treatment-related deaths due to pneumonitis and one treatment-related death due to bowel perforation occurred in the nivolumab group.

On the basis of CheckMate 274 results, nivolumab improved clinical outcomes when administered as adjuvant therapy to patients with urothelial carcinoma at high risk for local and metastatic recurrence after surgery. In contrast, a previously reported phase 3 trial (IMvigor010) that compared adjuvant atezolizumab, an anti–PD-L1 antibody, with observation in a similar population of patients with high-risk muscle-invasive urothelial carcinoma who had undergone surgery did not show a significant difference in disease-free survival.[19] Explanations for the outcome differences between the IMvigor010 and CheckMate 274 trials would be speculative.

Patients with completely resected, high-risk urothelial cancer (defined as residual cancer ≥pT2 or pN+ after neoadjuvant cisplatin-based chemotherapy or ≥pT3 or pN+ without previous chemotherapy) frequently have recurrence and have a 5-year survival of 60% or less.[4,26,27] Although adjuvant cisplatin-based chemotherapy may improve outcomes after definitive surgery in patients eligible for cisplatin who have not received neoadjuvant chemotherapy, no previous adjuvant systemic therapies have been shown to improve outcomes in patients not eligible for cisplatin or in those with pathological evidence of residual disease despite neoadjuvant cisplatin-

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based chemotherapy.[2] These initial results from CheckMate 274 show that adjuvant nivolumab extends disease-free survival for these patients and thus may affect clinical decision making in this context.

A subgroup analysis of disease-free survival was completed. This analysis reveals the possibility of a larger effect size in patients with bladder urothelial carcinoma than in those with renal pelvic and ureteral tumors as well as a larger effect size in patients previously treated with neoadjuvant chemotherapy than in those who had not received neoadjuvant chemotherapy; however, the trial was designed to assess the efficacy of nivolumab as compared with placebo in the entire trial population. These observations should be considered hypothesis-generating; subsequent translational analyses are planned to further interrogate these and other patient subgroups.

This interim analysis is limited by the short duration of follow-up; however, at a median follow-up of approximately 20 months, 48.2% of the patients in the nivolumab group and 57.3% of those in the placebo group had already had disease recurrence or had died. Data for certain secondary and exploratory end points, including overall survival, are to follow in accordance with the statistical analysis plan and may provide greater insight into the efficacy of nivolumab in this context. Previous studies have indicated that disease-free survival at 2 or 3 years is highly correlated with overall survival among patients with muscle-invasive urothelial carcinoma.[28-32] In addition, the trial is limited by the relatively small number of enrolled patients from underrepresented minorities.

Disease-free survival was significantly longer with adjuvant nivolumab than with placebo among patients with high-risk muscle-invasive urothelial carcinoma after radical surgery with curative intent. Further follow-up is planned to assess overall survival. Nivolumab monotherapy was associated with the expected level of toxicity, and no deterioration in quality of life was observed relative to placebo. The CheckMate 274 trial showed a significant and clinically meaningful benefit of adjuvant systemic immunotherapy as compared with placebo, both in the intention-to-treat population and in patients with a PD-L1 expression level of 1% or more.

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APPENDIX

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