ORIGINAL ARTICLE

Nivolumab plus Gemcitabine–Cisplatin in Advanced Urothelial Carcinoma

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ABSTRACT

BACKGROUND

No new agent has improved overall survival in patients with unresectable or metastatic urothelial carcinoma when added to first-line cisplatin-based chemotherapy.

METHODS

In this phase 3, multinational, open-label trial, we randomly assigned patients with previously untreated unresectable or metastatic urothelial carcinoma either to receive intravenous nivolumab (at a dose of 360 mg) plus gemcitabine–cisplatin (nivolumab combination) every 3 weeks for up to six cycles, followed by nivolumab (at a dose of 480 mg) every 4 weeks for a maximum of 2 years, or to receive gemcitabine–cisplatin alone every 3 weeks for up to six cycles. The primary outcomes were overall and progression-free survival. The objective response and safety were exploratory outcomes.

RESULTS

A total of 608 patients underwent randomization (304 to each group). At a median follow-up of 33.6 months, overall survival was longer with nivolumab-combination therapy than with gemcitabine–cisplatin alone (hazard ratio for death, 0.78; 95% confidence interval [CI], 0.63 to 0.96; P=0.02); the median survival was 21.7 months (95% CI, 18.6 to 26.4) as compared with 18.9 months (95% CI, 14.7 to 22.4), respectively. Progression-free survival was also longer with nivolumab-combination therapy than with gemcitabine–cisplatin alone (hazard ratio for progression or death, 0.72; 95% CI, 0.59 to 0.88; P=0.001). The median progression-free survival was 7.9 months and 7.6 months, respectively. At 12 months, progression-free survival was 34.2% and 21.8%, respectively. The overall objective response was 57.6% (complete response, 21.7%) with nivolumab-combination therapy and 43.1% (complete response, 11.8%) with gemcitabine–cisplatin alone. The median duration of complete response was 37.1 months with nivolumab-combination therapy and 13.2 months with gemcitabine–cisplatin alone. Grade 3 or higher adverse events occurred in 61.8% and 51.7% of the patients, respectively.

CONCLUSIONS

Combination therapy with nivolumab plus gemcitabine–cisplatin resulted in significantly better outcomes in patients with previously untreated advanced urothelial carcinoma than gemcitabine–cisplatin alone. (Funded by Bristol Myers Squibb and Ono Pharmaceutical; CheckMate 901 ClinicalTrials.gov number, NCT03036098.)

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*A complete list of the investigators in the CheckMate 901 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Platinum-based chemotherapy is the standard of care for previously untreated patients with unresectable or metastatic urothelial carcinoma, with cisplatin-based chemotherapy being the preferred treatment over carboplatin-based chemotherapy for eligible patients.[1-4] First-line cisplatin-based chemotherapy has shown a response in more than 40% of patients, with a median overall survival of approximately 15 months, but durable responses with this treatment are uncommon.[1,2,5]

To date, no novel agent has improved survival when added concurrently to platinum-based chemotherapy in the first-line treatment of metastatic urothelial carcinoma.[6,7] Avelumab switch maintenance treatment is a standard of care for the subgroup of patients who have not had disease progression during or immediately after first-line platinum-based chemotherapy.[5,8] An unmet need remains for more effective treatment.

Nivolumab is an antibody directed against programmed death 1 (PD-1) and is approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma after previous platinum-based chemotherapy as well as for adjuvant treatment of high-risk muscle-invasive urothelial carcinoma after radical resection.[9-13] Phase 2 trials that explored cisplatin-based chemotherapy in combination with PD-1 blockade suggested promise for the treatment of urothelial carcinoma.[14,15] Here, we report the results from the CheckMate 901 trial evaluating nivolumab plus gemcitabine–cisplatin as compared with gemcitabine–cisplatin alone in patients with previously untreated unresectable or metastatic urothelial carcinoma.

METHODS

PATIENTS

Eligible patients were at least 18 years of age with histologically confirmed unresectable or metastatic urothelial carcinoma involving the renal pelvis, ureter, bladder, or urethra. Patients had measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher numbers reflecting greater disability). All the patients had undergone tumor biopsy of the primary site or a metastatic site. Patients had to be eligible to receive cisplatin therapy, which included adequate renal function (glomerular filtration rate, ≥60 ml per minute). Previous systemic chemotherapy for unresectable or metastatic urothelial carcinoma was not permitted. Previous intravesical therapy was permitted if the treatment had been completed at least 4 weeks before the initiation of the trial treatment. Previous neoadjuvant therapy, radiation, or adjuvant platinum-based chemotherapy was permitted with recurrence 12 months or more after the completion of therapy.

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TRIAL DESIGN AND TREATMENTS

CheckMate 901 is a phase 3, international, open-label, randomized trial performed in two parts. In the first part (reported here), patients were assigned to receive either nivolumab plus gemcitabine–cisplatin (nivolumab combination) or gemcitabine–cisplatin alone; in the second part (ongoing), patients were assigned to receive either nivolumab plus ipilimumab or platinum-based chemotherapy. Each part of the trial had a separate determination of statistical power. Details regarding the trial design are provided in the protocol, available with the full text of this article at NEJM.org.

Briefly, cisplatin-eligible patients were randomly assigned in a 1:1:1:1 ratio across the two parts of the trial with stratification according to the tumor expression of programmed death ligand 1 (PD-L1) and the presence or absence of liver metastasis. In the current trial, patients were assigned to receive either intravenous nivolumab (at a dose of 360 mg) in combination with gemcitabine–cisplatin every 3 weeks for up to six cycles, followed by nivolumab (at a dose of 480 mg) every 4 weeks until disease progression, unacceptable toxic effects, withdrawal of consent, or up to a maximum of 2 years or to receive gemcitabine–cisplatin alone every 3 weeks for up to six cycles. Reductions in the prespecified doses of nivolumab were not permitted. Dose reductions of gemcitabine and cisplatin were permitted according to the trial protocol. Dose delays for both nivolumab and gemcitabine–cisplatin were permitted. Patients who discontinued cisplatin alone could be switched to gemcitabine–carboplatin for the remainder of the platinum-doublet cycles up to six cycles in total.

OUTCOMES AND ASSESSMENTS

The primary outcomes were overall survival and progression-free survival according to blinded independent central review (central review). Overall survival and progression-free survival were also evaluated in prespecified subgroups. Overall survival was defined as the time between randomization and death from any cause. For patients without documentation of death, data regarding overall survival were censored on the last date the patient was known to have been alive. If a patient had undergone randomization but had no follow-up, data regarding overall survival were censored on the date of randomization. Overall survival was followed continuously while patients were receiving any trial drug and every 3 months after they had discontinued the drug.

Progression-free survival was defined as the time between randomization and the first documented disease progression, according to central review on the basis of RECIST, or death from any cause (whichever occurred first). Data for patients who were alive without disease progression were censored at the time of the last evaluable tumor assessment. Data for patients who were alive but had received no tumor assessments during the trial were censored at the time of randomization. Data for patients who received subsequent anticancer therapy before disease progression were censored at the time of the last evaluable tumor assessment that was conducted on or before the date of initiation of the subsequent anticancer therapy. We performed a sensitivity analysis of progression-free survival that did not include censoring of data for patients who had received subsequent anticancer therapy before progression.

Secondary outcomes included overall survival and progression-free survival by central review in patients with tumor PD-L1 expression of 1% or more. PD-L1 status was defined according to the percentage of positive staining of tumor-cell membrane (minimum, 100 tumor cells) that could be evaluated with the use of an immunohistochemical assay for PD-L1 (IHC 28-8 pharmDx immunohistochemical assay [Dako]). The other secondary outcome was an assessment of the change from baseline in health-related quality of life according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) Global Health Status score.

Exploratory outcomes included an evaluation of the objective response to treatment (by central review) and safety. The objective response was defined as a confirmed complete or partial response, according RECIST assessment. The safety analysis included all the patients who had received at least one dose of a trial drug. Adverse events in each treatment group were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Also evaluated were data regarding immune-mediated adverse events, which were defined as adverse events that were consistent with an immune-mediated mechanism or component for which a noninflammatory cause (e.g., infection or tumor) had been ruled out and for which immune-modulating medication had been initiated.

OVERSIGHT

The trial was approved by the institutional review board at each trial center and was conducted in accordance with Good Clinical Practice guidelines of the International Council for Harmonisation. All the patients provided written informed consent in adherence to the Declaration of Helsinki principles.

A data monitoring committee provided oversight of safety and efficacy considerations. Bristol Myers Squibb (the sponsor), in collaboration with Ono Pharmaceutical, funded the trial, provided the trial drugs, and collaborated with the academic authors on the trial design and on the collection, analysis, and interpretation of the data. The authors had access to the trial data and participated in the development or review of the manuscript. Medical writing support, including the development of the first draft of the manuscript under the guidance of the authors, was funded by the sponsor. The authors and their institutions were required to maintain data confidentiality during the trial. All the authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol (available at NEJM.org).

STATISTICAL ANALYSIS

We estimated that the enrollment of approximately 600 patients would provide the trial with

85% power to detect an average hazard ratio of 0.70 for overall survival (the first primary outcome) among the patients who were assigned to receive nivolumab-combination therapy as compared with those who were assigned to receive gemcitabine–cisplatin alone on the basis of the occurrence of at least 356 deaths. The overall alpha level was 0.05, split between overall survival and progression-free survival. Overall survival was evaluated at an alpha level of 0.04, accounting for one formal interim analysis after 75% of estimated deaths had occurred and one final analysis. Progression-free survival according to central review was analyzed at an alpha level of 0.01, accounting for one final analysis.

If the difference in overall survival was significant at either the interim or the final analysis, it was specified that the significance level of 0.04 would be passed on to the primary comparison of progression-free survival and that progression-free survival would be tested at a significance level of 0.05. Similarly, if the difference in progression-free survival was significant at the final analysis, the significance level of 0.01 would be passed on to the overall survival final analysis and the overall survival would be tested at a significance level of 0.05 in the final analysis. If the difference in overall survival was significant at the interim analysis, formal testing of progression-free survival would be performed with the use of a hierarchical testing procedure to allow for early stopping for superiority.

For the comparison of progression-free survival, we determined that 460 events of disease progression or death would provide the trial with 70% power to detect an average hazard ratio of 0.70 with an overall type I error of 0.01. The two-sided significance level was 0.0311 for overall survival and 0.01 for progression-free survival. Additional details regarding the statistical analysis plan are provided in the Supplementary Appendix, available at NEJM.org. There was no prespecified approach for multiplicity correction except for the dual comparisons of primary outcomes. Therefore, other reported confidence intervals were not adjusted for multiplicity and thus should be interpreted with caution.

We performed mixed-effects linear regression for repeated-measures analysis of the EORTC QLQ-C30 data to assess the effect of the trial treatments on the patients' quality of life from baseline through week 16. Covariates that were included in the model as fixed effects were treatment group, time, stratification factors, baseline score, interaction between baseline score and time, and interaction between treatment group and time; intercept and time were included as random effects. A 10-point difference in the overall score at specific time points was deemed to be clinically meaningful.[16]

RESULTS

PATIENTS

From January 30, 2018, to September 28, 2022, a total of 608 patients underwent randomization at 135 sites in 30 countries. In the intention-to-treat population, 304 patients were assigned to receive nivolumab plus gemcitabine–cisplatin and 304 patients to receive gemcitabine–cisplatin alone. Treatment was completed by 74.0% of the patients who received nivolumab-combination therapy and by 54.5% of those who received gemcitabine–cisplatin alone.

At least one dose of carboplatin was received instead of cisplatin in 49 of 304 treated patients (16.1%) in the nivolumab-combination group and in 43 of 288 treated patients (14.9%) in the gemcitabine-cisplatin group. Disease progression was the most common reason for discontinuation in each group (55.3% of patients in the nivolumab-combination group [6.6% during the chemotherapy portion of the treatment] and 17.4% of those in the gemcitabine–cisplatin group) (Fig. S1 in the Supplementary Appendix).

The clinical and demographic characteristics of the patients were well balanced in the two groups at baseline (Table 1). The trial patients were representative of the overall population of patients with unresectable or metastatic urothelial carcinoma (Table S1).

EFFICACY

At the final analysis, the median follow-up was 33.6 months (range, 7.4 to 62.4). Overall survival was significantly longer with nivolumab-combination therapy, with a hazard ratio for death of 0.78 (95% confidence interval [CI], 0.63 to 0.96; P=0.02). The median overall survival was 21.7 months (95% CI, 18.6 to 26.4) in the nivolumab-

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

Characteristic	Nivolumab plus Gemcitabine–Cisplatin (N = 304)	Gemcitabine–Cisplatin Alone (N = 304)
Age		
Median (range) — yr	65 (32–86)	65 (35–85)
Distribution — no. (%)		
<65 yr	150 (49.3)	148 (48.7)
≥65 yr	154 (50.7)	156 (51.3)
Sex — no. (%)		
Male	236 (77.6)	234 (77.0)
Female	68 (22.4)	70 (23.0)
Race or ethnic group — no. (%)†		
White	211 (69.4)	225 (74.0)
Asian	75 (24.7)	63 (20.7)
American Indian or Alaska native	1 (0.3)	1 (0.3)
Black	0	2 (0.7)
Other	17 (5.6)	13 (4.3)
Geographic region — no. (%)		
United States	19 (6.2)	21 (6.9)
Europe	134 (44.1)	142 (46.7)
Asia	72 (23.7)	61 (20.1)
Other region	79 (26.0)	80 (26.3)
ECOG performance-status score — no. (%)		
0	162 (53.3)	162 (53.3)
1	140 (46.1)	142 (46.7)
>1	2 (0.7)	0
Tumor type at initial diagnosis — no. (%)		
Urinary bladder	235 (77.3)	219 (72.0)
Renal pelvis	33 (10.9)	44 (14.5)
Other	36 (11.8)	41 (13.5)
Time from initial diagnosis		
Median (range) — yr	0.51 (0–27.8)	0.36 (0–23.9)
Distribution — no. (%)		
<1 yr	179 (58.9)	199 (65.5)
≥1 yr	125 (41.1)	105 (34.5)
Histologic variant — no. (%)		
None	150 (49.3)	142 (46.7)
Adenocarcinoma	53 (17.4)	50 (16.4)
Squamous-cell carcinoma	20 (6.6)	23 (7.6)
Micropapillary	17 (5.6)	16 (5.3)
Other	62 (20.4)	71 (23.4)
Not reported	2 (0.7)	2 (0.7)

Table 1. (Continued.)

Characteristic	Nivolumab plus Gemcitabine–Cisplatin (N=304)	Gemcitabine–Cisplatin Alone (N=304)
Disease stage — no. (%)		
Metastatic	261 (85.9)	269 (88.5)
Locally unresectable or nonmetastatic	41 (13.5)	33 (10.9)
Not reported	2 (0.7)	2 (0.7)
Tumor PD-L1 expression — no. (%)		
≥1%	111 (36.5)	110 (36.2)
<1%	193 (63.5)	194 (63.8)
Liver metastasis — no. (%)		
Yes	64 (21.1)	64 (21.1)
No	240 (78.9)	240 (78.9)

* ECOG denotes Eastern Cooperative Oncology Group, and PD-L1 programmed death ligand 1.
† Race or ethnic group was reported either by the patients or by the investigators, depending on the trial site.

combination group and 18.9 months (95% CI, 14.7 to 22.4) in the gemcitabine–cisplatin group (Fig. 1A). Overall survival was 70.2% and 62.7%, respectively, at 12 months and 46.9% and 40.7%, respectively, at 24 months.

Progression-free survival according to central review was also significantly longer in the nivolumab-combination group, with a hazard ratio for progression or death of 0.72 (95% CI, 0.59 to 0.88; P=0.001). Median progression-free survival according to central review was 7.9 months (95% CI, 7.6 to 9.5) in the nivolumab-combination group and 7.6 months (95% CI, 6.1 to 7.8) in the gemcitabine–cisplatin group (Fig. 1B). Progression-free survival was 34.2% and 21.8%, respectively, at 12 months and 23.5% and 9.6%, respectively, at 24 months. Progression-free survival according to investigator assessment was also better with nivolumab-combination therapy than with gemcitabine–cisplatin alone (hazard ratio, 0.70; 95% CI, 0.57 to 0.85) (Fig. S2).

Censoring of data for progression-free survival because of subsequent anticancer therapy before disease progression occurred in 24 patients (7.9%) with nivolumab combination and in 74 (24.3%) with gemcitabine–cisplatin. Avelumab or pembrolizumab was subsequently administered before disease progression in 2.0% of the patients in the nivolumab-combination group and in 14.5% of those in the gemcitabine–cisplatin group. The results of a sensitivity analysis of progression-free survival that did not include censoring of data for patients who had received subsequent anticancer therapy before disease progression were consistent with the primary analysis of progression-free survival (hazard ratio, 0.74; 95% CI, 0.62 to 0.89) (Fig. S3).

In subgroup analyses of overall survival (Fig. 2) and progression-free survival according to central review (Fig. S4), hazard ratios favored nivolumab combination over gemcitabine–cisplatin alone across most subgroups that were analyzed. In the population of patients with tumor PD-L1 expression of 1% or more, hazard ratios favored nivolumab combination over gemcitabine–cisplatin alone for both overall survival (hazard ratio, 0.75; 95% CI, 0.53 to 1.06) and progression-free survival according to central review (hazard ratio, 0.60; 95% CI, 0.41 to 0.81).

The objective response according to central review was 57.6% with nivolumab combination and 43.1% with gemcitabine–cisplatin alone (Table 2); a complete response was reported in 21.7% and 11.8%, respectively. The median time until either an objective response or a complete response was 2.1 months in each treatment group. Data regarding the objective response and complete response according to investigator assessment were consistent with the results on central review (Table S2). The median duration

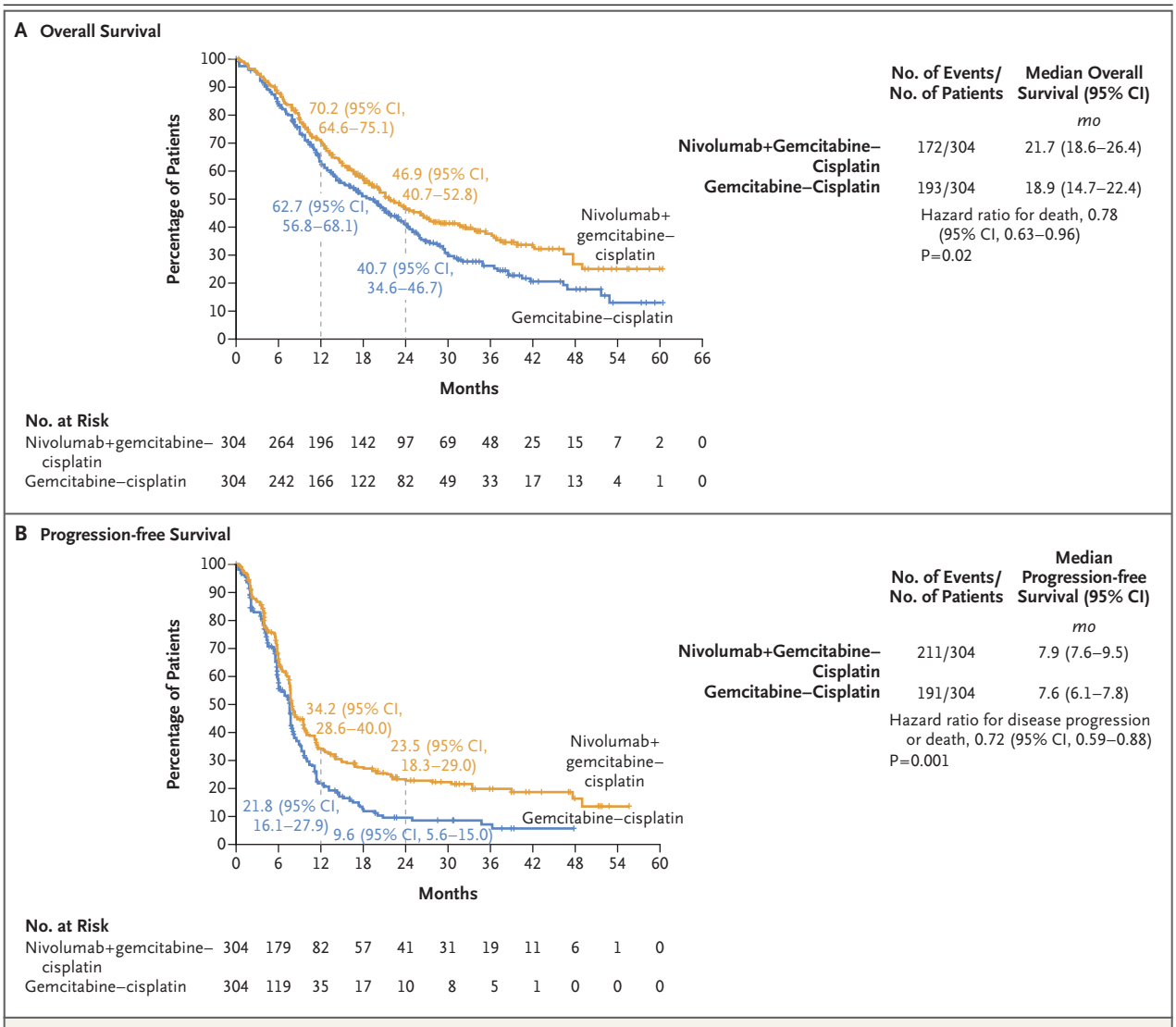

Figure 1. Overall Survival and Progression-free Survival.

Shown are the probabilities of overall survival (Panel A) and progression-free survival (Panel B) — the two primary outcomes — in the intention-to-treat population of patients with previously untreated unresectable or metastatic urothelial carcinoma who were assigned to receive intravenous nivolumab plus gemcitabine–cisplatin (nivolumab combination) or gemcitabine–cisplatin alone, according to blinded independent central review. In the analysis of progression-free survival, data for patients who received subsequent anticancer therapy before disease progression were censored.

of response according to central review was longer with nivolumab combination (9.5 months; 95% CI, 7.6 to 15.1) than with gemcitabine–cisplatin alone (7.3 months; 95% CI, 5.7 to 8.9) (Table 2 and Fig. S5); the median duration of complete response was 37.1 months (95% CI, 18.1 to not estimable) and 13.2 months (95% CI, 7.3 to 18.4), respectively. The best tumor change from baseline in target lesions on central review is illustrated in Figure S6. Subsequent systemic therapy was administered to 35.5% of the patients in the nivolumab-combination group and to 51.3% of those in the gemcitabine–cisplatin group (Table S3).

SAFETY

A total of 304 patients in the nivolumab-combination group and 288 patients in the gemcitabine–cisplatin group were included in the safety analysis. The median duration of therapy was 7.4

Subgroup	No. of Patients	Nivolumab+ Gemcitabine–Cisplatin	Gemcitabine–Cisplatin	Unstratified Hazard Ratio for Death (95% CI)
		no. of events/no. of patients		
All patients	608	172/304	193/304	0.78 (0.63–0.95)
Age				
<65 yr	298	85/150	100/148	0.69 (0.51–0.92)
65 to <75 yr	236	65/120	66/116	0.89 (0.63–1.26)
≥75 yr	74	22/34	27/40	0.86 (0.49–1.52)
Sex				
Male	470	133/236	147/234	0.76 (0.60–0.97)
Female	138	39/68	46/70	0.82 (0.54–1.26)
Race				
White	436	123/211	145/225	0.80 (0.63–1.02)
Asian	138	38/75	36/63	0.71 (0.45–1.12)
Other	32	11/18	10/14	0.84 (0.35–1.97)
Geographic region				
United States	40	18/19	15/21	1.92 (0.95–3.88)
Asia	133	36/72	34/61	0.73 (0.46–1.17)
Europe	276	72/134	90/142	0.73 (0.53–0.99)
Rest of the world	159	46/79	54/80	0.73 (0.49–1.08)
ECOG performance-status score				
0	324	74/162	87/162	0.70 (0.51–0.95)
1	282	96/140	106/142	0.85 (0.64–1.11)
PD-L1 expression				
≥1%	221	64/111	67/110	0.75 (0.53–1.06)
<1% or indeterminate	387	108/193	126/194	0.80 (0.62–1.04)
Liver metastases				
Yes	128	45/64	48/64	0.77 (0.51–1.16)
No	480	127/240	145/240	0.77 (0.61–0.98)
Previous systemic cancer therapy				
Yes	156	44/88	41/68	0.90 (0.59–1.38)
No	452	128/216	152/236	0.76 (0.60–0.96)

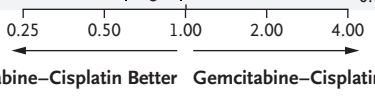

Figure 2. Overall Survival According to Subgroup.

Shown in the risk of death from any cause in the two treatment groups according to subgroup. With the exception of the subgroups of age, race, region, and sex, hazard ratios were not computed for categories with fewer than 10 patients per treatment group. Categories without a meaningful estimate of the hazard ratio are not shown. Tumor PD-L1 expression levels and liver metastases were evaluated with the use of interactive response technology. There was no prespecified approach for multiplicity correction except for the dual comparisons of the primary outcomes, so other reported confidence intervals should not be used for hypothesis testing. Previous systemic cancer therapy refers to neoadjuvant or adjuvant therapies for patients undergoing radical resection or as part of a bladder-sparing approach in muscle-invasive bladder cancer. ECOG denotes Eastern Cooperative Oncology Group.

months (range, 0 to 47.9) in the nivolumab-combination group and 3.7 months (range, 0 to 14.3) in the gemcitabine–cisplatin group. Adverse events of any cause occurred in 99.7% of the patients in the nivolumab-combination group and in 98.6% of those in the gemcitabine–cisplatin group; adverse events of grade 3 or higher occurred in 76.6% and 67.7% of the patients, respectively.

Adverse events of any grade that were deemed by the investigator to be related to a trial treatment occurred in 97.4% of the patients in the nivolumab-combination group and in 92.7% of those in the gemcitabine–cisplatin group; the corresponding percentages of patients with adverse events of grade 3 or higher were 61.8% and 51.7% (Table 3). A grade 5 treatment-related adverse event (sepsis) occurred in 1 patient in the nivolumab-combination group and in 1 patient (acute kidney injury) in the gemcitabine–cisplatin group.

Treatment-related adverse events of any grade

Table 2. Objective and Best Overall Responses and Time to Response.*

Variable	Nivolumab plus Gemcitabine–Cisplatin (N=304)	Gemcitabine–Cisplatin Alone (N=304)
Objective response — % (95% CI)	57.6 (51.8–63.2)	43.1 (37.5–48.9)
Confirmed best overall response — no. (%)		
Complete response	66 (21.7)	36 (11.8)
Partial response	109 (35.9)	95 (31.2)
Stable disease	77 (25.3)	86 (28.3)
Progressive disease	29 (9.5)	39 (12.8)
Unevaluable	23 (7.6)	48 (15.8)
Median time until objective response (IQR) — mo		
Any objective response	2.1 (2.0–2.3)	2.1 (2.0–2.2)
Complete response	2.1 (1.9–2.2)	2.1 (1.9–2.2)
Median duration of objective response (95% CI) — mo		
Any objective response	9.5 (7.6–15.1)	7.3 (5.7–8.9)
Complete response	37.1 (18.1–NE)	13.2 (7.3–18.4)

* All responses were assessed by blinded independent central review. The objective response was defined as a confirmed complete or partial response, according Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The most common reasons for an unevaluable best overall response included death before the first tumor assessment during the trial, withdrawal of consent, discontinuation of treatment because of toxic events, lack of treatment, and receipt of subsequent anticancer therapy before the first tumor assessment. IQR denotes interquartile range, and NE not estimable.

leading to discontinuation occurred in 21.1% of the patients in the nivolumab-combination group and in 17.4% of those in the gemcitabine–cisplatin group; the corresponding percentages for adverse events of grade 3 or higher leading to discontinuation were 11.2% and 7.6%. Immune-mediated adverse events are summarized in Table S4.

HEALTH-RELATED QUALITY OF LIFE

More than 90% of the patients in the two groups completed the EORTC QLQ-C30 survey at baseline. In the two groups, completion ranged from 78 to 86% through week 10, after which completion decreased to 40% in the nivolumab-combination group and to 66% in the gemcitabine–cisplatin group. The EORTC QLQ-C30 global health status was stable in the two groups with no change of more than 10 points in either direction through week 16 (Fig. S7).

DISCUSSION

In this population of patients with previously untreated unresectable or metastatic urothelial carcinoma, the two primary outcomes — overall survival and progression-free survival — were significantly longer with nivolumab combination than with gemcitabine–cisplatin alone. Hazard ratios for overall survival and progression-free survival favored the nivolumab-combination group over the gemcitabine–cisplatin group regardless of the patients' tumor PD-L1 expression level. The significance for overall survival was particularly notable given that the median overall survival of 18.9 months that was observed in the gemcitabine–cisplatin group was longer than what had been reported previously.[1,2] Furthermore, the complete response in the nivolumab-combination group was nearly double that in the gemcitabine–cisplatin group (21.7% vs. 11.8%). The nivolumab-combination group had early antitumor activity, with a median time to response of about 2 months, which was similar to that with gemcitabine–cisplatin alone. The median duration of complete response was almost three times as long in the nivolumab-combination group as in the gemcitabine–cisplatin group (37.1 vs. 13.2 months), despite a maximum of 2 years of nivolumab treatment in the combination group. Therefore, nivolumab plus gemcitabine-cisplatin improved

Table 3. Treatment-Related Adverse Events.*

Adverse Event	Nivolumab plus Gemcitabine–Cisplatin (N=304)		Gemcitabine–Cisplatin Alone (N=288)	
	Any Grade	Grade ≥3†	Any Grade	Grade ≥3†
	number of patients (percent)			
Any adverse event	296 (97.4)	188 (61.8)	267 (92.7)	149 (51.7)
Anemia	174 (57.2)	67 (22.0)	137 (47.6)	51 (17.7)
Nausea	142 (46.7)	1 (0.3)	138 (47.9)	3 (1.0)
Neutropenia	93 (30.6)	57 (18.8)	86 (29.9)	44 (15.3)
Decreased neutrophil count	75 (24.7)	44 (14.5)	60 (20.8)	32 (11.1)
Fatigue	74 (24.3)	6 (2.0)	69 (24.0)	4 (1.4)
Decreased appetite	68 (22.4)	4 (1.3)	45 (15.6)	1 (0.3)
Decreased platelet count	66 (21.7)	23 (7.6)	43 (14.9)	14 (4.9)
Decreased white-cell count	64 (21.1)	30 (9.9)	40 (13.9)	11 (3.8)
Vomiting	55 (18.1)	4 (1.3)	48 (16.7)	6 (2.1)
Asthenia	47 (15.5)	3 (1.0)	46 (16.0)	5 (1.7)
Thrombocytopenia	45 (14.8)	20 (6.6)	35 (12.2)	13 (4.5)
Pruritus	44 (14.5)	2 (0.7)	8 (2.8)	0
Constipation	44 (14.5)	0	40 (13.9)	1 (0.3)
Rash	41 (13.5)	2 (0.7)	10 (3.5)	1 (0.3)
Diarrhea	40 (13.2)	4 (1.3)	25 (8.7)	0
Hypothyroidism	40 (13.2)	0	0	0
Increased blood creatinine	39 (12.8)	1 (0.3)	35 (12.2)	0
Leukopenia	38 (12.5)	7 (2.3)	33 (11.5)	5 (1.7)

* Shown are adverse events that were reported in at least 10% of the patients in either group between the first dose of a trial medication and 30 days after the end of the treatment period. The determination that the adverse event was related to a trial treatment was made by the investigator.

† One grade 5 event occurred in each group (sepsis in the nivolumab plus gemcitabine–cisplatin group and acute kidney injury in the gemcitabine–cisplatin group).

survival over gemcitabine–cisplatin alone in patients with metastatic urothelial cancer and resulted in deep, durable responses in more than one fifth of the patients.

The safety profile of nivolumab plus gemcitabine–cisplatin was consistent with the established safety profiles of these agents in previous trials involving patients with urothelial carcinoma, and treatment-related deaths were rare.[1,11,13] Furthermore, the assessment of health-related quality-of-life outcomes revealed stable and maintained EORTC QLQ-C30 global health status in the two treatment groups.

Concurrent immunotherapy plus chemotherapy combinations have resulted in more benefits in terms of overall survival and progression-free survival than has chemotherapy alone in several tumor types.[17-19] However, phase 3 trials that examined new agents including immune checkpoint inhibitors for first-line treatment of metastatic urothelial carcinoma have not shown improvement in both overall survival and progression-free survival when they were combined with platinum-based chemotherapy.[6,7] In the KEYNOTE-361 trial of pembrolizumab in combination with either gemcitabine–cisplatin or gemcitabine–carboplatin, the addition of pembrolizumab did not significantly improve either overall survival or progression-free survival.[6] Similarly, atezolizumab in combination with chemotherapy did not result in longer overall survival than placebo plus chemotherapy in the

overall population in the IMvigor130 trial despite improvement in progression-free survival.[7] Exploratory analyses of both KEYNOTE-361 and IMvigor130 showed longer progression-free survival (and overall survival in IMvigor130) in patients receiving blockade of PD-1 and PD-L1 added to cisplatin-based therapy but not to carboplatin-based therapy.[6,20]

In the CheckMate 901 trial, we specifically addressed the benefit of adding PD-1 blockade to cisplatin-based chemotherapy. The discrepancies in the phase 3 trials that have been reported to date may be partially explained by potential differences in the immunomodulatory effects of cisplatin and carboplatin.[20-22] In an analysis of the IMvigor130 trial, pretreatment tumors harboring increased PD-L1 expression were associated with more favorable outcomes in patients treated with gemcitabine plus cisplatin but not with gemcitabine plus carboplatin.[20] Single-cell RNA sequencing of circulating immune cells revealed on-treatment up-regulation of immune-related transcriptional programs, including those involved in antigen presentation, with gemcitabine plus cisplatin but not with gemcitabine plus carboplatin.[20] Together, these data reinforce the potential immunogenic effects of cisplatin and support the hypothesis that chemotherapy based on cisplatin rather than carboplatin may combine particularly favorably with immune checkpoint blockade in the treatment of metastatic urothelial carcinoma.

On the basis of the results of the JAVELIN Bladder 100 trial (which were reported while our trial was ongoing), maintenance avelumab became a standard of care for patients receiving first-line treatment for metastatic urothelial carcinoma that had not progressed during or after platinum-based chemotherapy. In our trial, a subgroup of patients in the gemcitabine–cisplatin group received maintenance checkpoint inhibitors. However, cross-trial comparisons with the JAVELIN Bladder 100 trial cannot be made, given the differences in trial populations. Although a component of the activity that was seen in our trial could have been associated with the maintenance phase of therapy, such factors as timing, frequency, and duration of complete response in our trial suggest a favorable interaction between gemcitabine–cisplatin and nivolumab, which supports concurrent rather than sequential therapy in this cisplatin-eligible subgroup of patients.

Nivolumab plus gemcitabine–cisplatin showed a significant and clinically meaningful benefit, including deep and durable responses, in patients with previously untreated unresectable or metastatic urothelial carcinoma. Our findings provide evidence of the benefit of concurrent administration of an immune checkpoint inhibitor and chemotherapy in improving survival in this population.

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APPENDIX

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REFERENCES

1. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000;18:3068-77.
2. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602-8.
3. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30:191-9.
4. Teply BA, Kim JJ. Systemic therapy for bladder cancer — a medical oncologist's perspective. J Solid Tumors 2014;4:25-35.
5. Yu E-M, Mudireddy M, Biswas R, Aragon-Ching JB. The role of switch maintenance therapy in urothelial cancers. Ther Adv Urol 2023;15:17562872221147760.
6. Powles T, Csőszi T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:931-45.
7. Galsky MD, Arija JÁA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1547-57.
8. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med 2020;383:1218-30.
9. Opdivo (nivolumab). Princeton, NJ: Bristol Myers Squibb, 2023 (package insert).
10. European Medicines Agency. Opdivo. Summary of product characteristics (https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf).
11. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2017;18:312-22.
12. Sharma P, Callahan MK, Bono P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol 2016;17:1590-8.
13. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med 2021;384:2102-14.
14. Gupta S, Sonpavde G, Weight CJ, et al. Results from BLASST-1 (Bladder Cancer Signal Seeking Trial) of nivolumab, gemcitabine, and cisplatin in muscle invasive bladder cancer (MIBC) undergoing cystectomy. J Clin Oncol 2020;38:Suppl:439. abstract (https://ascopubs.org/doi/10.1200/JCO.2020.38.6_suppl.439).
15. Galsky MD, Daneshmand S, Izadmehr S, et al. Gemcitabine and cisplatin plus nivolumab as organ-sparing treatment for muscle-invasive bladder cancer: a phase 2 trial. Nat Med 2023 October 2 (Epub ahead of print).
16. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139-44.
17. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398:27-40.
18. Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. N Engl J Med 2022;386:449-62.
19. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med 2018;378:2078-92.
20. Galsky MD, Guan X, Banchereau R, et al. 658MO Cisplatin (cis)-related immunomodulation and efficacy with atezolizumab (atezo) + cis- vs carboplatin (carbo)-based chemotherapy (chemo) in metastatic urothelial cancer (mUC). Ann Oncol 2021;32:Suppl 5:S682-S683. abstract (https://www.annalsofoncology.org/article/S0923-7534(21)02268-7/fulltext).
21. Anker J, Pal SK, Kim-Schulze S, et al. Antitumor immunity as the basis for durable disease-free treatment-free survival in patients with metastatic urothelial cancer. J Immunother Cancer 2023;11(8):e007613.
22. Hato SV, Khong A, de Vries IJM, Lesterhuis WJ. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. Clin Cancer Res 2014;20:2831-7.