



Randomized Double-Blind Phase II Study of Maintenance Pembrolizumab Versus Placebo After First-Line Chemotherapy in Patients With Metastatic Urothelial Cancer

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PURPOSE Platinum-based chemotherapy for first-line treatment of metastatic urothelial cancer is typically administered for a fixed duration followed by observation until progression. “Switch maintenance” therapy with PD-1 blockade at the time of chemotherapy cessation may be attractive for mechanistic and pragmatic reasons.

PATIENTS AND METHODS Patients with metastatic urothelial cancer achieving at least stable disease on first-line platinum-based chemotherapy were enrolled. Patients were randomly assigned double-blind 1:1 to switch maintenance pembrolizumab 200 mg intravenously once every 3 weeks versus placebo for up to 24 months. Patients with disease progression on placebo could cross over to pembrolizumab. The primary objective was to determine the progression-free survival. Secondary objectives included determining overall survival as well as treatment outcomes according to PD-L1 combined positive score (CPS).

RESULTS Between December 2015 and November 2018, 108 patients were randomly assigned to pembrolizumab (n = 55) or placebo (n = 53). The objective response rate was 23% with pembrolizumab and 10% with placebo. Treatment-emergent grade 3-4 adverse events occurred in 59% receiving pembrolizumab and 38% of patients receiving placebo. Progression-free survival was significantly longer with maintenance pembrolizumab versus placebo (5.4 months [95% CI, 3.1 to 7.3 months] v 3.0 months [95% CI, 2.7 to 5.5 months]; hazard ratio, 0.65; log-rank *P* = .04; maximum efficiency robust test *P* = .039). Median overall survival was 22 months (95% CI, 12.9 months to not reached) with pembrolizumab and 18.7 months (95% CI, 11.4 months to not reached) with placebo. There was no significant interaction between PD-L1 CPS \geq 10 and treatment arm for progression-free survival or overall survival.

CONCLUSION Switch maintenance pembrolizumab leads to additional objective responses in patients achieving at least stable disease with first-line platinum-based chemotherapy and prolongs progression-free survival in patients with metastatic urothelial cancer.

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INTRODUCTION

Platinum-based combination chemotherapy has been standard first-line treatment of metastatic urothelial cancer for decades.¹ Cisplatin-based regimens, or carboplatin-based regimens for patients deemed cisplatin ineligible,² are typically administered for approximately 6 cycles and then discontinued, given concerns for cumulative toxicities in the setting of diminishing benefit.³ However, the vast majority of patients experience disease progression soon after completing first-line chemotherapy, with a median progression-free survival of approximately 3 months.⁴

Immune checkpoint blockade with anti-PD-1 or PD-L1 antibodies has changed the treatment landscape

for metastatic urothelial cancer. Five PD-1/PD-L1 inhibitors have received regulatory agency approval for the treatment of metastatic urothelial cancer on the basis of trials demonstrating durable responses achieved in a subset of patients in the context of a relatively favorable tolerability profile.⁵⁻⁹ A randomized phase III trial in patients with metastatic urothelial cancer progressing despite prior platinum-based chemotherapy reported a significant improvement in overall survival (OS) with the PD-1 inhibitor pembrolizumab versus second-line chemotherapy.⁵

The initiation of immune checkpoint blockade immediately after cessation of first-line platinum-based chemotherapy, as “switch maintenance” therapy, may

ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objectives

To define the impact of switch maintenance pembrolizumab versus placebo chemotherapy in patients with metastatic urothelial cancer with at least stable disease after first-line chemotherapy.

Knowledge Generated

Switch maintenance pembrolizumab significantly improves progression-free survival in patients with metastatic urothelial cancer completing first-line chemotherapy.

Relevance

Sequential integration of chemotherapy and immune checkpoint blockade using a switch maintenance approach may improve outcomes in patients with metastatic urothelial cancer.

be an attractive strategy for both scientific and pragmatic reasons.¹⁰ Initial chemotherapy could potentially induce immunogenic cell death or depletion of suppressive immune cell populations such as myeloid-derived suppressor cells, thereby enhancing the effects of subsequent immune checkpoint blockade.¹¹ Alternatively, switch maintenance immune checkpoint blockade could potentially confer benefit largely for practical reasons. Chemotherapy and immune checkpoint blockade are non-cross resistant, and observational studies reveal that only approximately 30%-50% of patients with metastatic urothelial cancer initiating first-line chemotherapy are able to receive subsequent lines of systemic therapy.^{12,13} Therefore, earlier use of immune checkpoint blockade may simply increase the likelihood that individual patients are exposed to potentially active therapy.

PATIENTS AND METHODS

Study Design and Treatment

Hoosier Cancer Research Network GU14-182 is an investigator-initiated multicenter double-blind randomized phase II trial. Patients with metastatic urothelial cancer achieving at least stable disease on first-line cisplatin- or carboplatin-based combination chemotherapy regimens were eligible for enrollment. Patients were randomly assigned to receive pembrolizumab 200 mg intravenously every 3 weeks versus placebo, in the absence of prohibitive toxicities or disease progression, for up to 24 months. Random assignment was stratified based on the presence of visceral metastatic disease (lung, liver, or bone or other solid organs) at the time of initiation of first-line chemotherapy and response to first-line chemotherapy (complete and partial response *v* stable disease). At the time of disease progression, patients randomly assigned to placebo could cross over to receive open-label pembrolizumab.

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by local ethics committees at each participating site, and informed consent was provided by all patients before enrollment. The trial was registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: [NCT02500121](https://clinicaltrials.gov/ct2/show/study/NCT02500121)).

Patients

Eligible patients were ≥ 18 years of age, with metastatic urothelial cancer. Patients were required to have received up to 8 cycles of first-line platinum-based combination chemotherapy for metastatic urothelial cancer, to have achieved at least stable disease, and to commence study treatment within 2-6 weeks after receiving their last dose of first-line chemotherapy. Urothelial cancer with variant histology was permitted provided that the predominant component was urothelial cancer. Measurable disease was not required, because patients could have achieved a complete response with first-line chemotherapy. Patients were required to have adequate organ function and an Eastern Cooperative Oncology Group performance status of ≤ 1 . Exclusion criteria included: active brain metastases, chronic use of immunosuppressive drugs, and prior treatment with immune checkpoint blockade.

Disease Assessments

Tumor assessments were conducted using cross-sectional imaging of the chest, abdomen, and pelvis after every 4 cycles until evidence of disease progression. Response and progression-free survival (PFS) were investigator assessed and were determined both by RECIST 1.1 and by immune-related RECIST (irRECIST).¹⁴ The RECIST 1.1 and irRECIST classification of response and progression differ only in that confirmation of progression is required per irRECIST. That is, for patients continuing in study treatment post progression according to RECIST 1.1, repeat imaging 4-6 weeks later was required to confirm progression. The initial date of progression, if confirmed on the subsequent imaging study, was considered the date of progression. Patients were eligible to continue study treatment post RECIST 1.1-defined progression provided the absence of (1) signs and symptoms of progression, (2) decline in performance status, (3) rapid disease progression on imaging, or (4) site of progression that might result in the near-term need for urgent intervention.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse

Events (v4.0). Adverse events suspected related to pembrolizumab were managed according to algorithms on the basis of the specific toxicity as defined in the protocol.

Unblinding of Study Treatment and Crossover

Patients were unblinded from study treatment if there was evidence of disease progression, treatment discontinuation due to unacceptable toxicity, or a medical event in which knowledge of the treatment was deemed critical to the subject's clinical management. At the time of unblinding for disease progression, patients found to be on placebo could cross over to receive open-label pembrolizumab 200 mg intravenously every 3 weeks, in the absence of prohibitive toxicities or disease progression, for up to 24 months.

PD-L1 Testing

Immunohistochemistry for PD-L1 was performed in a central laboratory (QualTek Molecular Laboratories, Newtown, PA) using the antibody clone 22C3 as previously described.¹⁵ PD-L1 expression was quantified by a single genitourinary pathologist (G.K.H.) using the combined positive score (CPS), defined as the percentage of PD-L1-expressing tumor and infiltrating immune cells relative to the total number of tumor cells.¹⁶ A cut point of $CPS \geq 10$ was used to define "high" PD-L1 expression as per prior studies in urothelial cancer.¹⁶

Statistical Analysis

The primary end point was PFS, defined as the time from random assignment to death or progression (whichever occurred first), according to irRECIST, with pembrolizumab versus placebo. When the study was initially designed in 2014, we sought to enroll 200 patients to detect an improvement in PFS with a hazard ratio (HR) of 0.6. However, the study was amended in 2017, after enrollment of 70 patients, on the basis of two considerations: (1) the study was accruing at slower than the projected rate, and (2) concerns regarding whether the HR is an optimal approach to measure the potential benefits conferred by immune checkpoint blockade. Specifically, the results of several randomized studies exploring immune checkpoint blockade in various solid tumors had emerged at the time, demonstrating survival curves that routinely violated the proportional hazards assumption and suggesting the benefits of immune checkpoint blockade were most apparent during later phases of the survival curve.^{5,17} Therefore, we amended the study on the basis of assumptions related to three theoretical phases of treatment effect. We assumed that during months 0-2 there would be no treatment effect, during months 2-3 there would be a minor treatment effect, and that after month 3 the full effect would be achieved (ie, HR of 1 before month 2 and a target HR value $\gamma < 1$ after month 3). We set the target value γ of the full treatment effect as $HR = 0.462$, extrapolating from Kaplan-Meier curves from emerging studies.⁵ The sample size was determined by inverting the test statistic proposed by Zucker and Lakatos.¹⁸ With a type

I error as 0.05 and power as 80%, this amended analysis plan required a sample size of at least 104 patients. No interim analyses had taken place when the study was amended, and the study remained blinded.

To compare the two treatment arms, we used both the standard log-rank test and the test proposed by Zucker and Lakatos,¹⁸ labeled as the maximum efficiency robust test (MERT). Hazard ratios for PFS and OS were estimated from the Cox model. However, because of the violation of the proportional hazards assumption, we also used the restricted mean survival time (RMST) as an alternative to the hazard ratio.^{19,20} Differences in RMST for both PFS and OS at 24 months were compared between the treatment arms.

The relationship between CPS for PD-L1 and treatment arm on PFS and OS was explored using interaction tests from the Cox model.

RESULTS

Patients

Between 2015 and 2018, 117 patients were screened and 108 patients were randomly assigned to placebo ($n = 53$) versus pembrolizumab ($n = 55$); one patient randomly assigned to placebo was excluded from the analysis because of inadvertent receipt of pembrolizumab rather than placebo intermittently during the initial several cycles of study treatment (Fig 1). The baseline characteristics are shown in Table 1. The distribution of baseline characteristics was similar in patients randomly assigned to pembrolizumab compared with placebo (Table 1).

Treatment

Patients assigned to pembrolizumab received a median of 8 cycles (interquartile range, 4-15 cycles), and patients assigned to placebo received a median of 6 cycles (interquartile range, 4-9 cycles). The most common reasons for treatment discontinuation included progression of disease (70%) and adverse events (17%).

Safety

Treatment-emergent grade 3-4 adverse events occurred in 59% of patients receiving pembrolizumab and 38% of patients receiving placebo (Table 2). Immune-related adverse events requiring systemic steroid treatment occurred in 20% of patients randomly assigned to initial pembrolizumab. There was one fatal treatment-related adverse event (hepatitis) in the pembrolizumab arm.

Objective Response Rate

Patients with a complete radiographic response to first-line chemotherapy on study entry were not considered assessable for objective response with pembrolizumab or placebo (Table 3). After excluding such patients, the objective response rate in patients randomly assigned to placebo was 10%, and in patients randomly assigned to pembrolizumab it was 23%. There were no complete

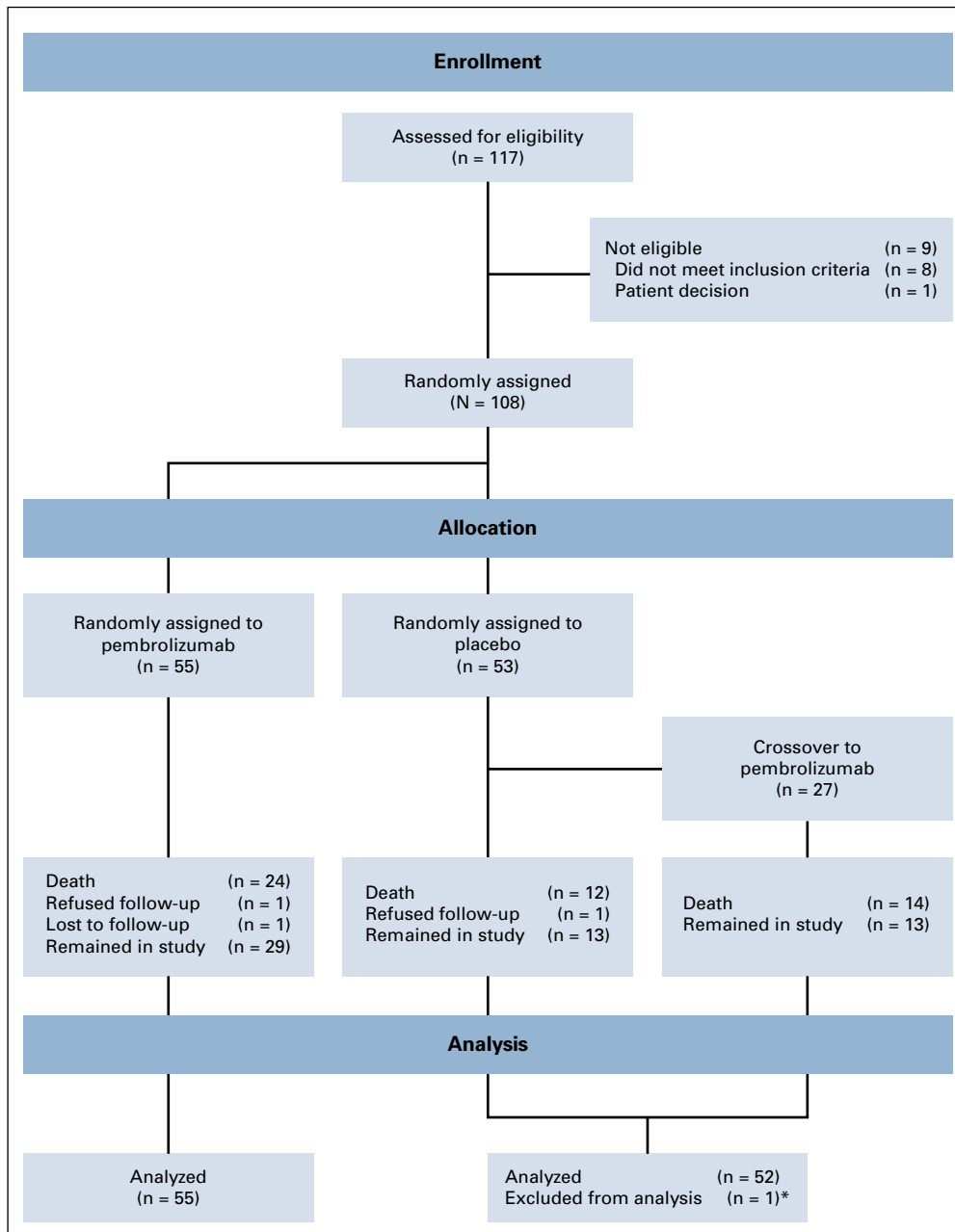


FIG 1. CONSORT diagram. (*) One patient randomly assigned to placebo was excluded from the analysis because of inconsistent receipt of pembrolizumab rather than placebo during the initial several cycles of study treatment.

responses achieved in the placebo arm, whereas the complete response rate with pembrolizumab was 9%.

PFS and OS

After a median follow-up of 12.9 months (range, 0.9-34.5 months), 50/107 patients have died. Given that no patients received treatment beyond initial RECIST 1.1–defined progression, the PFS on the basis of irRECIST and RECIST was identical. The PFS was significantly longer in patients randomly assigned to pembrolizumab versus placebo (MERT $P = .039$; Fig 2A). The difference in 24-month restricted mean progression-free survival time (RMPFST) with pembrolizumab versus placebo adjusted for the two stratification factors (response to first-line chemotherapy

and presence of visceral metastases) was 3.4 months (95% CI, 0.7 to 6.2 months; $P = .015$). The PFS curves stratified by response to first-line chemotherapy, presence or absence of visceral metastases, and first-line cisplatin-versus carboplatin-based chemotherapy are shown in the Data Supplement. As a secondary end point, the HR was calculated given general familiarity with this measure. The median PFS was 5.4 months with pembrolizumab (95% CI, 3.1 to 7.3 months) and 3.0 months with placebo (95% CI, 2.7 to 5.5 months), with an HR of 0.65 (log-rank P value = .04).

The median OS was 22 months (95% CI, 12.9 months to not reached) in patients randomly assigned to pembrolizumab and 18.7 months (95% CI, 11.4 months to not

TABLE 1. Baseline Characteristics

Characteristic	Placebo (n = 52)	Pembrolizumab (n = 55)	P
Age, years, median (range)	65 (44-87)	68 (41-83)	.2
Male, No. (%)	42 (81)	39 (71)	.3
Race, No. (%)			.6
White	46 (88)	50 (91)	
Black	3 (6)	4 (7)	
Other	3 (6)	1 (2)	
Visceral metastases, %	62	71	.3
ECOG PS, No. (%)			.7
0	23 (44)	22 (40)	
1	29 (56)	33 (60)	
First-line chemotherapy			
No. of cycles, median (IQR)	6 (4-6)	6 (4-6)	.3
Complete/partial response, %	69	73	.8
Cisplatin based, %	77	65	.5

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

reached) in patients randomly assigned to placebo (HR, 0.91; 95% CI, 0.52 to 1.59; Fig 2B). The difference in 24-month RMST with pembrolizumab versus placebo adjusted for the two stratification factors (response to first-line chemotherapy and presence of visceral metastases) was 0.4 months (95% CI, -2.8 to 3.6 months; $P = .8$). The OS curves stratified by clinical characteristics are shown in the Data Supplement. The OS of patients randomly assigned to maintenance pembrolizumab versus placebo with patients on placebo censored at crossover is shown in the Data Supplement. To further explore the potential effect of pembrolizumab maintenance in the context of crossover, we included treatment as a time-dependent covariate in the Cox model for OS (HR, 1.2; 95% CI, 0.62 to 2.38; $P = .6$).

Outcomes on the Basis of PD-L1 Expression

Among the 107 evaluable patients, archival tumor tissue was available for PD-L1 testing from 94 patients. The anatomic sites from which the tumor tissue was derived are listed in the Data Supplement. The CPS was ≥ 10 in 14/47 (30%) of specimens from patients randomly assigned to pembrolizumab and 14/47 (30%) of specimens from patients randomly assigned to placebo. There was no significant interaction between PD-L1 CPS ≥ 10 and treatment arm on PFS or OS ($P = .8$ and $.9$, respectively); additional cut points of CPS ≥ 1 , 5, and 15 were also explored (Data Supplement).

Crossover From Placebo to Pembrolizumab

Among 52 patients initially randomly assigned to placebo who experienced disease progression by the time of the data lock, 27 crossed over to receive pembrolizumab and 12 did not cross over (7 patients died before receiving any further systemic therapy, and 5 patients opted for further treatment off study). The objective response

rate with pembrolizumab among these 27 patients was 22%. The median PFS from crossover was 2.7 months (95% CI, 2.5 to 9.3 months) and median OS from crossover was 15.8 months (95% CI, 8 months to not reached).

DISCUSSION

Metastatic urothelial cancer is a relatively chemotherapy-sensitive solid tumor. However, the vast majority of patients experience disease progression despite first-line platinum-based chemotherapy while on treatment, or within months of completing treatment, highlighting the need for better therapeutic strategies. PD-1/PD-L1 blockade has changed the landscape of treatment of patients experiencing progression despite platinum-based chemotherapy, with durable responses achieved in a subset of patients.⁵⁻⁹ Here, we show that earlier use of PD-1 blockade with pembrolizumab, at the time of cessation of first-line chemotherapy, leads to additional objective responses and significantly prolongs PFS compared with placebo. Importantly, in this placebo-controlled double-blind trial, the adverse event profile of pembrolizumab was similar to that reported in prior studies.²¹

For both pragmatic and scientific reasons, we modified our original sample size and analysis plan during enrollment, adapting to emerging data from clinical trials exploring immune checkpoint blockade in urothelial cancer and other solid tumors.⁵ Specifically, we were concerned that the HR would not represent a meaningful summary measure, given multiple prior studies with immune checkpoint blockade where the proportional hazards assumption has been invalid, with crossing of the survival curves.^{5,17} We assumed no difference in PFS during the

TABLE 2. Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of Patients

Adverse Event	Placebo (n = 52)								Pembrolizumab (n = 55) ^a							
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Any adverse event	14	27	14	27	20	38	0	—	9	16	9	16	24	44	8	15
Abdominal pain	5	10	3	6	1	2	0	—	3	5	1	2	0	—	0	—
Alanine aminotransferase increased	0	—	1	2	0	—	0	—	4	7	3	5	2	4	1	2
Alkaline phosphatase increased	4	8	3	6	1	2	0	—	6	11	5	9	1	2	0	—
Anemia	11	21	3	6	5	10	0	—	7	13	5	9	5	9	0	—
Anorexia	2	4	5	10	0	—	0	—	6	11	3	5	1	2	0	—
Arthralgia	8	15	1	2	0	—	0	—	2	4	0	—	0	—	0	—
AST increased	3	6	1	2	0	—	0	—	8	15	1	2	3	5	0	—
Back pain	2	4	0	—	1	2	0	—	7	13	1	2	1	2	0	—
Blood bilirubin increased	2	4	0	—	1	2	0	—	3	5	0	—	0	—	0	—
Blurred vision	2	4	0	—	0	—	0	—	6	11	0	—	0	—	0	—
Chills	2	4	0	—	0	—	0	—	5	9	0	—	0	—	0	—
Constipation	10	19	1	2	1	2	0	—	10	18	2	4	1	2	0	—
Cough	7	13	1	2	0	—	0	—	14	25	1	2	0	—	0	—
Creatinine increased	6	12	6	12	0	—	0	—	7	13	9	16	1	2	0	—
Dehydration	1	2	0	—	2	4	0	—	0	—	3	5	0	—	0	—
Diarrhea	7	13	3	6	0	—	0	—	17	31	3	5	0	—	0	—
Dizziness	9	17	0	—	0	—	0	—	7	13	0	—	0	—	0	—
Dry mouth	0	—	0	—	0	—	0	—	5	9	1	2	0	—	0	—
Dyspnea	6	12	1	2	0	—	0	—	12	22	0	—	3	5	0	—
Edema limbs	4	8	1	2	0	—	0	—	7	13	1	2	1	2	0	—
Fatigue	17	33	3	6	0	—	0	—	12	22	5	9	4	7	0	—
Fever	6	12	0	—	0	—	0	—	4	7	1	2	1	2	0	—
Flank pain	2	4	1	2	0	—	0	—	2	4	2	4	1	2	0	—
Gastroesophageal reflux disease	2	4	0	—	0	—	0	—	3	5	1	2	0	—	0	—
GI disorders, other	3	6	1	2	1	2	0	—	1	2	1	2	0	—	0	—
Generalized muscle weakness	3	6	0	—	0	—	0	—	1	2	3	5	1	2	0	—
Headache	5	10	0	—	0	—	0	—	6	11	0	—	0	—	0	—
Hematuria	8	15	0	—	1	2	0	—	5	9	2	4	2	4	0	—
Hypercalcemia	2	4	0	—	0	—	0	—	4	7	0	—	0	—	0	—
Hyperglycemia	3	6	4	8	1	2	0	—	4	7	1	2	3	5	3	—
Hyperkalemia	3	6	2	4	0	—	0	—	5	9	0	—	0	—	0	—
Hypertension	2	4	4	8	5	10	0	—	1	2	3	5	5	9	0	—
Hypoalbuminemia	5	10	1	2	0	—	0	—	1	2	5	9	0	—	0	—
Hypomagnesemia	1	2	0	—	0	—	0	—	4	7	1	2	0	—	0	—
Hyponatremia	5	10	1	2	0	—	0	—	5	9	5	9	0	—	0	—
Hypothyroidism	2	4	0	—	0	—	0	—	3	5	2	4	0	—	0	—
Insomnia	1	2	2	4	0	—	0	—	9	16	2	4	0	—	0	—
Lymphocyte count decreased	1	2	3	6	4	8	0	—	9	16	6	11	2	4	0	—
Musculoskeletal and connective tissue disorder, other	2	4	0	—	0	—	0	—	3	5	1	2	0	—	0	—
Myalgia	1	2	0	—	0	—	0	—	5	9	0	—	0	—	0	—

(continued on following page)

TABLE 2. Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of Patients (continued)

Adverse Event	Placebo (n = 52)								Pembrolizumab (n = 55) ^a							
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Nasal congestion	1	2	1	2	0	—	0	—	3	5	1	2	0	—	0	—
Nausea	8	15	3	6	0	—	0	—	8	15	1	2	0	—	0	—
Pain	4	8	1	2	1	2	0	—	4	7	3	5	0	—	0	—
Pain in extremity	4	8	1	2	0	—	0	—	5	9	4	7	0	—	0	—
Paresthesia	1	2	1	2	0	—	0	—	4	7	0	—	0	—	0	—
Pelvic pain	2	4	1	2	0	—	0	—	3	5	0	—	2	4	0	—
Peripheral sensory neuropathy	3	6	2	4	0	—	0	—	8	15	1	2	0	—	0	—
Platelet count decreased	6	12	1	2	0	—	0	—	7	13	0	—	0	—	0	—
Pruritus	7	13	0	—	0	—	0	—	12	22	0	—	1	2	0	—
Rash, maculopapular	4	8	0	—	0	—	0	—	8	15	4	7	0	—	0	—
Renal and urinary disorders, other	3	6	0	—	0	—	0	—	2	4	1	2	0	—	0	—
Skin and subcutaneous tissue disorders, other	0	—	3	6	0	—	0	—	5	9	1	2	0	—	0	—
Upper respiratory infection	0	—	4	8	0	—	0	—	1	2	1	2	0	—	0	—
Urinary frequency	3	6	0	—	0	—	0	—	2	4	1	2	0	—	0	—
Urinary tract infection	0	—	5	10	0	—	0	—	2	4	4	7	4	7	0	—
Vomiting	1	2	1	2	1	2	0	—	7	13	2	4	0	—	0	—
WBC decreased	2	4	0	—	0	—	0	—	2	4	3	5	0	—	0	—

NOTE. Maximum grade per event per patient shown (N = 107).

^aOne patient died as a result of immune-related hepatitis.

early follow-up period, and more robust differences with later follow-up, and used a weighted log-rank test placing more emphasis on the later follow-up period. Nonetheless, we did observe a significant improvement in PFS with pembrolizumab versus placebo both using this weighted approach as specified in our primary analysis or by using a more traditional log-rank test. We also observed an

improvement in outcomes with pembrolizumab using the restricted mean PFS time. This latter approach, which is a measure of the difference in the area under the PFS curve until a defined time-point with pembrolizumab versus placebo, has recently received increased attention as a potentially more intuitive and clinically relevant approach to survival analyses in immunotherapy trials.^{20,22,23}

TABLE 3. Objective Response Rate (RECIST 1.1)

Response	Placebo (n = 42)	Pembrolizumab (n = 43)
Overall response	10	23
Partial response	10	14
Complete response	0	9
Stable disease	29	35
Progressive disease	54	33
Not evaluable	5	10

NOTE. Data are presented as %. Patients enrolling in the study with a complete response to first-line chemotherapy were not considered assessable for an objective response to maintenance treatment, given the lack of measurable disease at baseline. There were 10 patients enrolled in the placebo arm and 12 patients enrolled in the pembrolizumab arm with a baseline complete response.

At the time that we initially conceived the current trial, there were no immune checkpoint inhibitors approved by regulatory authorities for the treatment of urothelial cancer. However, we anticipated this was highly likely to occur during the course of the trial, and given the primary end point of PFS, for practical reasons related to accrual, and to ensure detailed capture of post-progression therapies, crossover from placebo to pembrolizumab at the time of progression was integrated into the design. Remarkably, despite follow-up every 3 weeks of this clinical trial cohort, at the time of the data lock 13% of patients randomly assigned to placebo (including patients who had achieved stable disease and partial responses, but not complete responses, with first-line chemotherapy) had died before receiving any second-line systemic therapy, a potential concern that has been highlighted in prior observational studies.^{12,13} These findings underscore at least one of the potential rationales underlying a switch maintenance approach with an active non-cross-resistant therapeutic class.

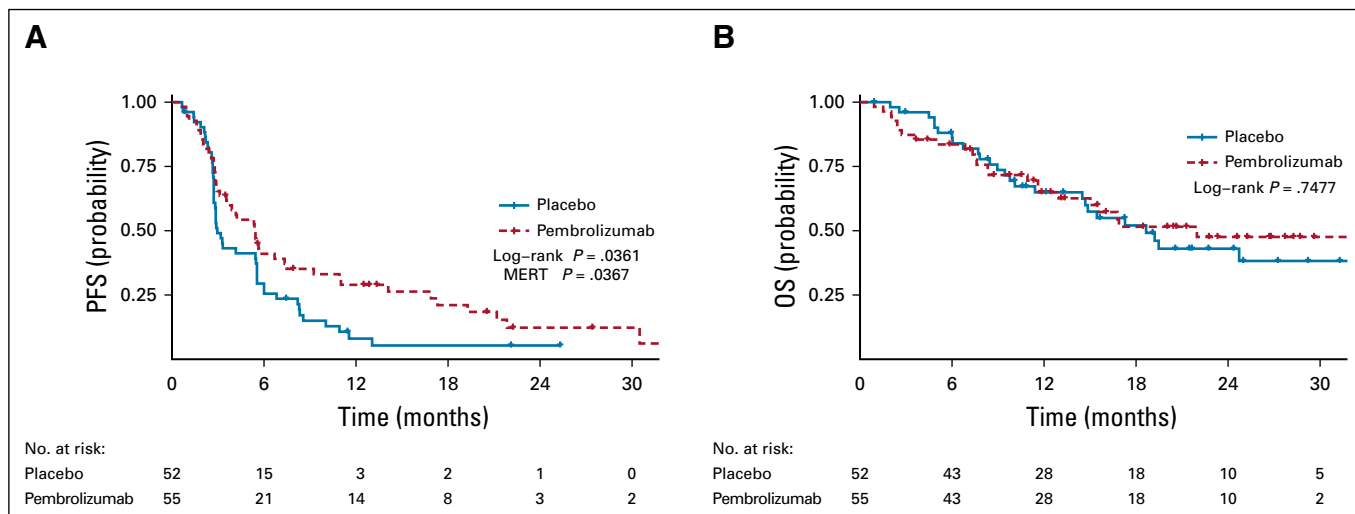


FIG 2. Kaplan-Meier curves for (A) progression-free survival (PFS), and (B) overall survival (OS) in patients treated with pembrolizumab versus placebo (N = 107). MERT, maximum efficiency robust test.

Only three prospective randomized trials, to our knowledge, have previously explored a switch maintenance strategy in patients with metastatic urothelial cancer (Data Supplement). In a small randomized phase II trial, Grivas et al⁴ reported no difference in PFS in patients randomly assigned to sunitinib versus placebo. A randomized phase II trial of switch maintenance vinflunine did report a significant improvement in PFS.²⁴ Notably, enrollment in that trial was limited to patients who had received 6 cycles of first-line gemcitabine plus cisplatin, and randomization was versus supportive care without placebo control. In the only phase III trial of switch maintenance therapy in patients with metastatic urothelial cancer reported to date, Powles et al²⁵ compared lapatinib with placebo in a cohort of patients selected for enrollment on the basis of tumor overexpression of HER-1 or HER-2 by immunohistochemistry; there was no significant difference in PFS or OS between the treatment arms.

PD-L1 testing did not clearly enrich for patients for whom switch maintenance pembrolizumab was beneficial. Though limited by the small sample size of the subsets in the current study, the PD-L1 biomarker findings are consistent with other studies of PD-1/PD-L1 blockade in the post-platinum setting in urothelial cancer.²¹ Whether related to tumor evolution and/or chemotherapy-related tumor/host modulation, PD-L1 testing may play a more important role in the chemotherapy-naïve setting in metastatic urothelial cancer. Furthermore, the study was not designed or powered to determine whether patient subsets on the basis of clinical characteristics (eg, response to first-line chemotherapy) derive differential benefit from maintenance therapy.

The ultimate measures of benefit from a new treatment approach relate to improvements in how patients feel, function, or survive. Furthermore, the risk of financial toxicity must be carefully considered in the context of a disease state in which observation is the standard approach. OS in the current study was not significantly different in patients randomly assigned to maintenance pembrolizumab versus placebo. However, OS was a secondary end point, the study was not adequately powered to detect a survival improvement, and the survival outcomes of patients in both arms were favorable relative to data from the pre-PD-1/PD-L1 blockade era (Data Supplement). Importantly, switch maintenance PD-L1 blockade was recently reported in a press release to improve OS in a phase III study (ClinicalTrials.gov identifier: [NCT02603432](https://clinicaltrials.gov/ct2/show/study/NCT02603432)).²⁶ Additional ongoing randomized phase III trials, including the recently reported IMvigor130 study (ClinicalTrials.gov identifier: [NCT02807636](https://clinicaltrials.gov/ct2/show/study/NCT02807636)),²⁷ are exploring even earlier use of PD-1/PD-L1 blockade in metastatic urothelial cancer, administered concurrently with first-line chemotherapy and continuing as maintenance. Theoretical advantages to a sequential (ie, switch maintenance), compared with concurrent, combination approach include the lack of concomitant administration of immune suppressive chemotherapy and corticosteroid antiemetic prophylaxis, although a sustained negative impact of concurrent chemotherapy on lymphocyte subsets, at least as measured in peripheral blood, has not been well established.²⁸ Ultimately, the outcomes of the several pending randomized trials will together shape the near-term landscape of first-line treatment of metastatic urothelial cancer, a disease state characterized by a paucity of advances in decades.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Double-Blind Phase II Study of Maintenance Pembrolizumab Versus Placebo After First-Line Chemotherapy in Patients With Metastatic Urothelial Cancer

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