Original Article

Results of a Multicenter, Phase 2 Study of Nivolumab and Ipilimumab for Patients With Advanced Rare Genitourinary Malignancies

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BACKGROUND: In this multicenter, single-arm, multicohort, phase 2 trial, the efficacy of nivolumab and ipilimumab was evaluated in patients with advanced rare genitourinary cancers, including bladder and upper tract carcinoma of variant histology (BUTCVH), adrenal tumors, platinum-refractory germ cell tumors, penile carcinoma, and prostate cancer of variant histology (NCT03333616). **METHODS:** Patients with rare genitourinary malignancies and no prior immune checkpoint inhibitor exposure were enrolled. Patients received nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg intravenously every 3 weeks for 4 doses, and this was followed by 480 mg of nivolumab intravenously every 4 weeks. The primary endpoint was the objective response rate (ORR) by the Response Evaluation Criteria in Solid Tumors (version 1.1). **RESULTS:** Fifty-five patients were enrolled at 6 institutions between April 2018 and July 2019 in 3 cohorts: BUTCVH (n = 19), adrenal tumors (n = 18), and other tumors (n = 18). The median follow-up was 9.9 months (range, 1 to 21 months). Twenty-eight patients (51%) received 4 doses of nivolumab and ipilimumab; 25 patients received nivolumab maintenance for a median of 4 cycles (range, 1-18 cycles). The ORR for the entire study was 16% (80% confidence interval, 10%-25%); the ORR in the BUTCVH cohort, including 2 complete responses, was 37%, and it was 6% in the other 2 cohorts. Twenty-two patients (40%) developed treatment-related grade 3 or higher toxicities; 24% (n = 13) required high-dose steroids (≥40 mg of prednisone or the equivalent). Grade 5 events occurred in 3 patients; 1 death was treatment related. **CONCLUSIONS:** Nivolumab and ipilimumab resulted in objective responses in a subset of patients with rare genitourinary malignancies, especially those with BUTCVH. An additional cohort exploring their activity in genitourinary tumors with neuroendocrine differentiation is ongoing. ***Cancer* 2021;127:840-849**. © *2020 American Cancer Society*.

LAY SUMMARY:

- Patients with rare cancers are often excluded from studies and have limited treatment options.
- Fifty-five patients with rare tumors of the genitourinary system were enrolled from multiple sites and were treated with nivolumab and ipilimumab, a regimen used for kidney cancer.
- The regimen showed activity in some patients, particularly those with bladder or upper tract cancers of unusual or variant histology; 37% of those patients responded to therapy.
- Additional studies are ongoing to better determine who benefits the most from this combination.

KEYWORDS: adrenal tumor, bladder or upper tract tumor of variant histology, genitourinary, immunotherapy, rare cancer.

INTRODUCTION

Rare cancers pose unique therapeutic challenges with limited data to guide treatment decisions. Although the International Rare Cancer Initiative defines a rare cancer as one with an incidence less than 6 cases per 100,000 per year, these diverse malignancies collectively account for more than 20% of all cancer diagnoses.[1] Rare genitourinary malignances based on this definition include penile carcinoma and adrenocortical carcinoma (ACC), both of which have few established therapeutic options.[2-6] Germ cell tumors, also a rare diagnosis, generally have an excellent prognosis, but once they are platinum refractory, treatment options are limited.[7] Among more common tumors, those with variant histology have a poor prognosis. In urothelial carcinoma, the incidence of divergent differentiation in cystectomy specimens is as high as 33%, and the World Health Organization has noted more than 10 histologic variants.[8,9] Although accounting for only 1% of prostate cancers, small cell carcinoma of the prostate is associated with

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a poor prognosis and limited therapeutic options.[10,11] Collectively, these rare genitourinary malignancies are often excluded from clinical trials, and this leaves these patients with a dearth of options beyond experimental therapies.

Immune checkpoint inhibitor–containing regimens are a cornerstone of the treatment of urothelial and renal cell carcinomas.[12-18] They also have a role in prostate cancer, where the tumor-agnostic approval of pembrolizumab, a monoclonal antibody inhibitor of programmed death 1 (PD-1), for patients with microsatellite instability has led to durable responses in a subset of the small number of patients (<5%) harboring this alteration.[19,20] Nivolumab (also a PD-1 inhibitor) in combination with ipilimumab, an anti–cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) antibody, is approved for the treatment of advanced renal cell carcinoma, and this combination is currently being explored in urothelial carcinoma as well.[17,21] Because of the challenges of treating rare genitourinary cancers (including those with predominant variant histology), we pursued a multicenter, single-arm, phase 2 study of nivolumab and ipilimumab in those patients with bladder and upper tract carcinoma of variant histology (BUTCVH), adrenal tumors, prostate cancer of variant histology (PCVH; including squamous or neuroendocrine differentiation), penile carcinoma, or platinum-refractory germ cell tumors (PRGCTs; NCT03333616).

MATERIALS AND METHODS

Patient Population

This study enrolled patients with histologically confirmed advanced rare genitourinary malignancies in 3 cohorts. Cohort 1 enrolled patients with BUTCVH. Cohort 2 enrolled patients with adrenal tumors, including ACCs and pheochromocytomas/paragangliomas. Cohort 3 enrolled patients with other tumors, including PCVH (squamous and small cell), PRGCTs, Leydig cell tumors, and penile carcinoma. Patients with variant histology were deemed eligible if >90% of the pathologic specimen (surgical specimen or biopsy) represented the variant histology. A pathology review at each institutional site, conducted by a genitourinary pathologist, was required to confirm the histology. Advanced disease was defined as unresectable, locally recurrent, or metastatic according to the seventh edition of the American Joint Committee on Cancer staging system. Patients could have received any number of prior therapies provided that they had not had any PD-1/PD-L1 or CTLA-4 inhibitors; patients enrolled with PRGCTs must have progressed on platinum therapy in both the initial and salvage settings. Other inclusion criteria included the presence of measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), an Eastern Cooperative Oncology Group performance status $\leq$ 2, adequate organ function at the baseline, and an absence of active brain metastases. Patients with a history of autoimmune disease requiring $\geq$10 mg of prednisone per day or the equivalent were excluded. The study was approved by the institutional review board at each participating institution. All patients provided written informed consent.

Study Design

This was a multicenter, investigator-initiated, single-arm, phase 2 study. Before the initiation of therapy, patients underwent a baseline tumor biopsy unless this was not medically feasible. Eligible patients received treatment with nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg intravenously every 3 weeks for 4 doses; this was followed by 480 mg of nivolumab every 4 weeks until intolerable toxicity or withdrawal of consent. Dose modifications were not permitted, although dose delays were allowed. Clinical and laboratory assessments were performed with each infusion. Imaging assessments occurred at the baseline, at 12 weeks, and every 8 weeks thereafter. The response was assessed by RECIST (version 1.1). In patients who experienced a response, subsequent imaging assessments were used for response confirmation every 6 weeks. Patients experiencing progression but continuing to derive a clinical benefit (as determined by the treating investigator) could continue on therapy beyond progression. After treatment discontinuation, an optional tumor biopsy was performed in patients with an objective response to therapy and subsequent disease progression. Toxicity was assessed with the Common Terminology Criteria for Adverse Events (version 4.0).

Statistical Analysis

The primary endpoint was the objective response rate (ORR) with a complete response or partial response as the best overall response according to RECIST (version 1.1) by investigator assessment. The 1-stage design was used to enroll 19 eligible patients per cohort; this provided 94% power to distinguish a true ORR of 35% versus 10% under a 1-sample binomial test with a 1-sided α value of .11. At least 4 responses among 19 patients were required to consider the treatment promising. Evaluable patients who received at least 1 dose of either study treatment were included in the analysis.

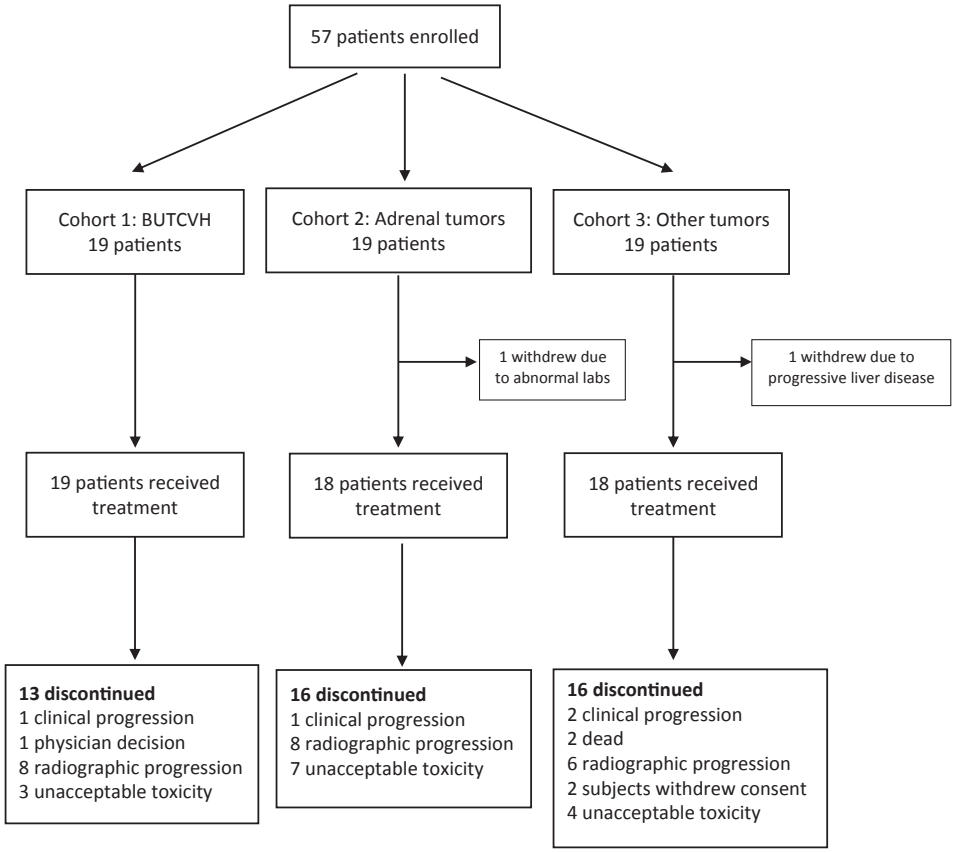

Figure 1. Enrollment and treatment exposure across 3 cohorts. BUTCVH indicates bladder and upper tract carcinoma of variant histology.

ORR was summarized with the exact binomial 80% confidence intervals (CIs) for each cohort separately. A pooled analysis of all tumor types was also conducted as a secondary analysis. Medians and 95% CIs of times to event endpoints such as progression-free survival (PFS; time from treatment initiation to progression by RECIST criteria or death from any cause, censored at the date of the last disease assessment) and overall survival (OS; time from treatment initiation to death, censored at the date of the last follow-up for those who had not died) were summarized with Kaplan-Meier estimates. Statistical analysis was performed with SAS 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Baseline Characteristics

Between April 2018 and July 2019, 57 patients were enrolled from 6 centers in the United States (Dana-Farber Cancer Institute, Boston, Massachusetts; Beth Israel Deaconess Medical Center, Boston, Massachusetts; Moores Cancer Center of the University of California San Diego, La Jolla, California; The University of Texas MD Anderson Cancer Center, Houston, Texas; Winship Cancer Institute of Emory University, Atlanta, Georgia; and The Ohio State Cancer Center, Columbus, Ohio), as outlined in Figure 1. Two patients never initiated therapy and were excluded from the primary analysis cohort (n = 55). The final analysis included 19 patients with BUTCVH in cohort 1 (squamous cell [n = 6], adenocarcinoma [n = 4], urachal carcinoma [n = 4], small cell carcinoma [n = 3], plasmacytoid carcinoma [n = 1], and spindle cell carcinoma [n = 1]), 18 patients with adrenal tumors in cohort 2 (ACC [n = 16] and paraganglioma [n = 2]), and 18 patients with other tumors in cohort 3 (PCVH [n = 5], penile carcinoma [n = 6], PRGCT [n = 5], Sertoli cell tumor [n = 1], and squamous carcinoma of the prostatic urethra [n = 1]). Patient demographics are noted in Table 1; the median age was 59 years with an excellent performance status (Eastern Cooperative Oncology Group

TABLE 1. Patient Demographics and Disease Characteristics

Characteristic	Cohort 1: BUTCVH	Cohort 2: Adrenal Tumors	Cohort 3: Other	Total Cohort
Patients, No.	19	18	18	55
Age, median, y	61	45	60	59
Sex, No. (%)				
Female	5	13	2	20 (36.4)
Male	14	5	16	35 (63.6)
Race, No. (%)				
White	14	12	14	40 (72.7)
African American	2	3	1	6 (10.9)
Other	3	3	3	9 (16.4)
M stage at initial diagnosis, No. (%)				
M0	9	5	6	20 (36.4)
M1	6	6	4	16 (29.1)
Unknown	4	7	8	19 (34.5)
Prior systemic therapies, No. (%)				
No	6	4	2	12 (21.8)
Yes	13	14	16	43 (78.2)
No. of prior systemic therapies, No. (%)				
0	6	4	2	12 (21.8)
1	9	4	4	17 (30.9)
2	3	9	6	18 (32.7)
≥3	1	1	6	8 (14.6)
ECOG performance status, No. (%)				
0	13	11	8	32 (58.2)
1	6	7	9	22 (40.0)
2	—	—	1	1 (1.8)

Abbreviations: BUTCVH, bladder and upper tract carcinoma of variant histology; ECOG, Eastern Cooperative Oncology Group.

performance status of 0 or 1, 98%). Among those with BUTCVH, 68% of the patients (n = 13) had received prior systemic chemotherapy, with 21% (n = 4) having received 2 or more lines of therapy. Among those with ACC, 17% (n = 3) received concurrent mitotane.

Treatment Exposure

Of the 55 patients who received at least 1 treatment, 51% (n = 28) received all 4 doses of nivolumab and ipilimumab, whereas 35% (n = 19) received 2 or fewer cycles. Maintenance nivolumab was provided to 45% of the patients (n = 25); 23 of these patients completed all 4 doses of ipilimumab with nivolumab, and 2 received only 3 doses of ipilimumab with nivolumab. Treatment delays occurred in 15% of the patients (n = 8) during induction, and 7% (n = 4) required a delay during maintenance. The median number of cycles of maintenance nivolumab was 4 (range, 1-18). At the time of the data cutoff, 82% (n = 45) had discontinued therapy: 51% (n = 28) because of disease progression or death, 25% (n = 14) because of toxicity, and 5% (n = 3) because of other reasons.

Efficacy

As of the data cutoff (February 10, 2020), the overall median follow-up was 9.9 months (range, <1-21 months) from protocol treatment initiation. Because of differences in accrual rates, this varied among cohorts: 16.6 months (range, 1.2-21 months) for patients with BUTCVH, 8.9 months (range, 2.6-17.1 months) for patients with adrenal tumors, and 6.5 months (range, 1-12.8 months) for patients with other tumors. Overall, the ORR was 16% (80% CI, 10%-25%). The ORR was 37% (80% CI, 22%-54%) in the BUTCVH cohort and 6% (80% CI, 1%-20%) in both cohorts 2 and 3. The breakdown by histology and prior therapy within each cohort is detailed in Table 2. Overall, 38% (n = 21), including 47% (n = 9) in the BUTCVH cohort, experienced some degree of tumor shrinkage (Fig. 2). The median duration of response was not reached for those with a response. Sixty-seven percent (6 of 9) maintained a response for more than 9 months, with 78% (n = 7) still on therapy at the time of analysis. The median PFS was 2.8 months (95% CI, 2.7-5.2 months), and the 12-month OS rate was 56% (95% CI, 38%-70%), with variability among the cohorts (Fig. 3).

Toxicity

Adverse events were assessed in all 55 patients who received at least 1 dose of therapy. The most common treatment-related adverse events of any grade occurring in >10% of the patients included elevated liver enzymes (38%), fatigue (36%), rashes (35%), diarrhea (24%), thyroid disorders (22%), pruritus (18%), elevated lipase (16%), pulmonary symptoms (15%), hypnatremia (11%) and arthralgias

TABLE 2. Response Rates

Patient Cohort	Response, No. CR/PR	SD	PD	ORR, % (80% CI)
Overall	9	16	29	16 (10-25)
Cohort 1: BUTCVH (n = 19)	7	4	8	37 (22-54)
Adenocarcinoma	1	—	3	
Plasmacytoid	1[a]	—	—	
Small cell carcinoma	2[a]	—	1	
Spindle cell	—	—	1	
Squamous cell carcinoma	2	2	2	
Urachal	1	2	1	
Received prior chemotherapy				
No	2	—	4	
Yes	5	4	4	
Cohort 2: adrenal tumors (n = 18)	1	8	9	6 (1-20)
Adrenocortical carcinoma	1	7	8	
Paraganglioma	—	1	1	
Received prior chemotherapy				
No	—	2	2	
Yes	1	6	7	
Cohort 3: other (n = 17[b])	1	4	12	6 (1-20)
PRGCT	—	1	4	
Penile carcinoma	—	2	3	
PCVH	1	—	4	
Other	—	1	1	
Received prior chemotherapy				
No	—	1	1	
Yes	1	3	11	

Abbreviations: BUTCVH, bladder and upper tract carcinoma of variant histology; CI, confidence interval; CR, complete response; ORR, objective response rate; PCVH, prostate cancer of variant histology; PD, progressive disease; PR, partial response; PRGCT, platinum-refractory germ cell tumor; SD, stable disease.
[a]Including one CR
[b]One patient who withdrew in cycle 2 without a response evaluation is not listed in this table but was included in the calculation of the response rate.

(11%; Table 3). A treatment related grade 3 or higher toxicity was experienced by 22 patients (40%). There were 3 deaths during the study: 2 were related to disease progression, and 1 was attributed to treatment-related encephalopathy. Thirteen patients (24%) experienced immune-related adverse events requiring high-dose corticosteroids (≥40 mg of prednisone per day or the equivalent).

DISCUSSION

Our findings suggest that the combination of nivolumab and ipilimumab has efficacy in a subset of rare genitourinary malignancies. We observed differential responses between the cohorts of rare genitourinary malignancies, with the most robust objective responses seen in the BUTCVH cohort; this provides a rationale for exploring the combination further in this subpopulation. The safety profile of the combination of nivolumab and ipilimumab in this study is consistent with that previously reported in larger trials, and it is favorable in comparison with regimens with higher doses of ipilimumab.[22]

In a trial devoted exclusively to patients with rare genitourinary malignancies, we enrolled 55 patients from 6 medical centers in less than 18 months. Although basket trials are being explored across tumors on the basis of genetic alterations and umbrella trials are exploring drugs in the same cancers with different mutations, our tumor-agnostic approach tests immunotherapy (an established regimen in renal cell carcinoma) across genitourinary malignancies that would otherwise be ineligible for clinical trials. The rapidity of this trial's accrual exemplifies the unmet need for rare genitourinary malignancies. This study is complementary to the Dual Anti–CTLA-4 and Anti–PD-1 Blockade in Rare Tumors (DART) trial (NCT02834013), a large cooperative group trial exploring the combination of ipilimumab at a dose of 1 mg/kg every 6 weeks with nivolumab at 240 mg every 2 weeks in patients with rare malignancies, including BUTCVH, squamous cell carcinoma variants of the genitourinary system, adrenal tumors, penile carcinoma, and PRGCTs. However, this trial is not limited to those with genitourinary malignancies, and there are no data published aside from data for high-grade nonpancreatic neuroendocrine tumors.[23] Given our limited patient population, we were able to enroll and present results that could have an immediate impact on patient care.

The robust response in the BUTCVH cohort is noteworthy. Although these tumors account for less than 5% of all urinary tract tumors, treatment options are limited. The largest set of prospective data available is from a trial of 20 patients treated with ifosfamide, paclitaxel, and cisplatin (histology, adenocarcinoma [n = 11], squamous cell [n = 8], or small cell [n = 1]). The ORR was 35% with a median survival of 25 months (although survival was less than 9 months for patients with squamous cell carcinoma, even though these patients were all treatment naive).[24] Our report is not the first for immunotherapy in this setting: 47 patients with BUTCVH treated with the PD-L1 inhibitor atezolizumab showed an ORR of 9%,[25] whereas combination therapy with the PD-L1 inhibitor durvalumab and the CTLA-4 inhibitor tremelimumab did not show any activity in 13 patients with BUTCVH.[26] The ORR of 37% in our BUTCVH cohort, with responses seen

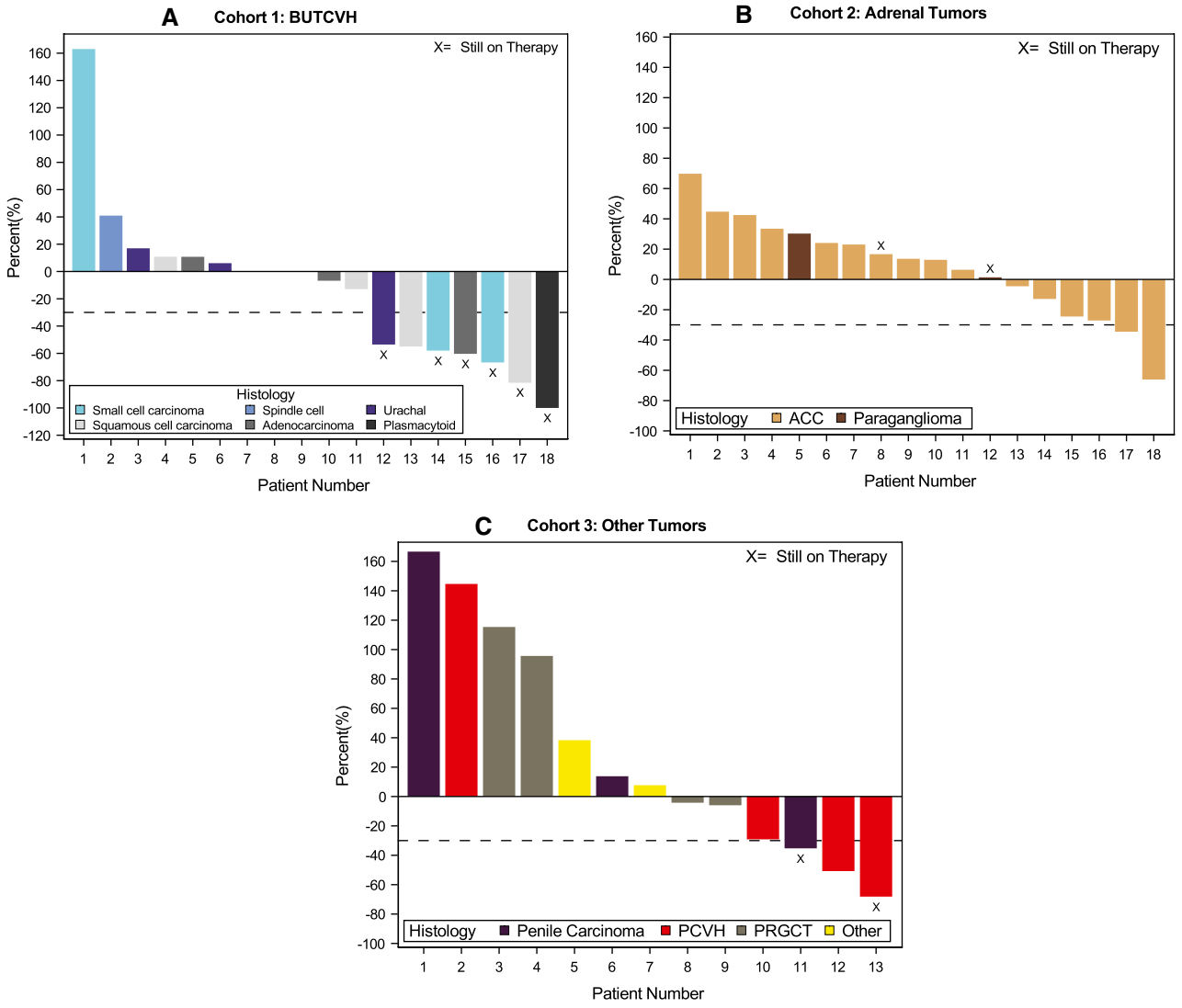

Figure 2. Maximum Tumor shrinkage with nivolumab and ipilimumab across the 3 cohorts for 55 evaluable patients: (A) patients with BUTCVH, (B) patients with ACC and adrenal tumors, and (C) patients with penile carcinoma, PCVH, PRGCTs, and other rare genitourinary tumors. The dotted lines represent a partial response by RECIST criteria. ACC indicates adrenocortical carcinoma; BUTCVH, bladder and upper tract carcinoma of variant histology; PCVH, prostate cancer of variant histology; PRGCT, platinum-refractory germ cell tumor; RECIST, Response Evaluation Criteria in Solid Tumors.

across all histologies in both treatment-naive and experienced settings, is very compelling and higher than that seen with single-agent PD-1 inhibition after treatment with platinum-containing chemotherapy.[25] A multicohort study in bladder carcinoma using ipilimumab at 1 mg/kg and nivolumab at 3 mg/kg showed an ORR of 26.9%. However, the ORR rose to 38.0% when an alternative dosing schedule of ipilimumab at 3 mg/kg and nivolumab at 1 mg/kg was administered, albeit with an absolute 10% increase in the rates of grade 3 or higher toxicities.[21] Because of its superior efficacy, this is the regimen being explored as a first-line treatment of metastatic urothelial carcinoma (NCT03036098), although our data showed a comparable ORR with a lower, less toxic dose of ipilimumab (1 mg/kg) in conjunction with nivolumab (3 mg/kg). The addition of cabozantinib to immune checkpoint inhibition is also intriguing: in expansion cohorts of an initial phase 1 trial, patients were treated with 40 mg of cabozantinib daily in addition to nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg (penile carcinoma, n = 3; Sertoli cell tumor, n = 1; and bladder small cell carcinoma, n = 1) or nivolumab at 3 mg/kg (BUTCVH, n = 11; PRGCT, n = 5; and penile, n = 1). Between the 2 cohorts, the

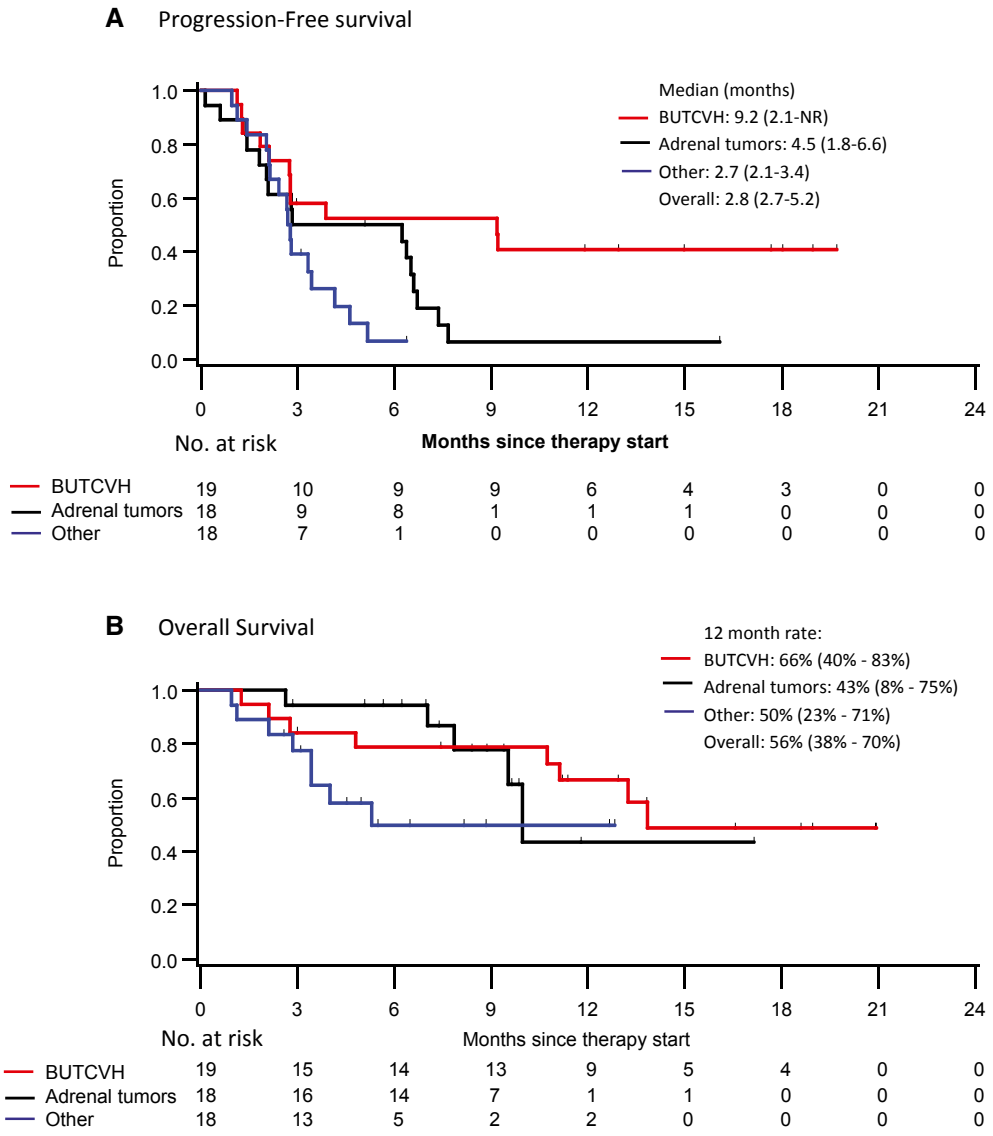

Figure 3. Kaplan-Meier curves for (A) progression-free survival and (B) overall survival by cohort. The cohorts included patients with BUTCVH, patients with adrenal tumors, and patients with other rare genitourinary tumors (penile carcinoma, platinum-refractory germ cell tumors, prostate cancer of variant histology, and others). BUTCVH indicates bladder and upper tract carcinoma of variant histology; NR, not reached.

ORR was 36% and notably included 4 complete responses and 2 partial responses for penile carcinoma, although 71% of the patients experienced a grade 3 or higher adverse event.[27] Although more patients may benefit from combining targeted therapy with checkpoint inhibitors, the ORR of 37% for BUTCVH in our study is intriguing and supports further study of this regimen with an expansion of this cohort planned.

ACC is another unmet need with a bimodal age distribution with pediatric, adolescent, and adult populations.[28] Mitotane, an oral adrenolytic, is the only approved therapy for metastatic ACC. It is often combined with cisplatin, doxorubicin, and etoposide on the basis of phase 3 data demonstrating superiority to its combination with streptozocin; however, the ORR is 23% with a PFS of only 5 months.[29] Options at the time of disease progression are lacking. Single-agent pembrolizumab has shown some activity, with responses seen in 2 of 14 patients (14.3%) and in 9 of 39 patients (23%) in a second study.[30,31] In the largest study to date of immune checkpoint blockade in ACC (n = 55), the PD-L1 inhibitor avelumab showed an ORR of 6%, with 50% of

TABLE 3. Treatment-Related Adverse Events in the Overall Cohort (n = 55)

Toxicity	Toxicity Grade (CTCAE, Version 4.0), No.			Total, No. (%)
	Grade 1 or 2	Grade 3	Grade ≥ 4	
Liver abnormalities	14	7	—	21 (38)
Fatigue	20	—	—	20 (36)
All rashes	19	—	—	19 (35)
Diarrhea	8	5	—	13 (24)
Thyroid disorders	11	1	—	12 (22)
Pruritus	10	—	—	10 (18)
Lipase increased	6	3	—	9 (16)
Pulmonary	8	—	—	8 (15)
Arthralgia	4	2	—	6 (11)
Hyponatremia	4	1	1	6 (11)
Anemia	2	1	—	3 (5)
Autoimmune disorder	—	—	2	2 (4)
Encephalopathy	—	—	1[a]	1 (2)
Seizure	—	—	1	1 (2)
Pneumonitis	—	1	—	1 (2)
CPK increased	—	—	1	1 (2)
Sinus tachycardia	—	1	—	1 (2)
Hypokalemia	—	1	—	1 (2)
Generalized muscle weakness	—	1	—	1 (2)

Abbreviations: CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events.
Listed adverse events occurred at a frequency >10% or were grade 3 or higher according to the Common Terminology Criteria for Adverse Events.
[a]Grade 5 toxicity.

the patients continuing on mitotane.[32] Similarly to the series with pembrolizumab, the combination of avelumab and mitotane could be administered safely. Although the ORR in our ACC cohort was only 6%, the clinical benefit rate approached 50%. In the 2 patients with metastatic paraganglioma, there were no observed responses, although these numbers are too small to make inferences about efficacy. In a phase 2 study of pembrolizumab that included 9 patients with paraganglioma, there were no confirmed responses, but the disease control rate at 27 weeks was 33%.[33] Further analysis of the nature and duration of disease control needs to be performed to define the role of this combination in adrenal tumors.

The final cohort is limited by the heterogeneity of its tumor histologies, but the ORR observed is not encouraging for penile carcinoma or PRGCTs. There is a strong rationale for the use of immunotherapy in penile carcinoma extrapolated from other human papillomavirus–related malignancies.[34] However, in our limited study, patients with penile carcinoma (n = 5) did not respond; this was akin to another small study with single-agent pembrolizumab, in which only 1 of 3 patients showed a response.[33] Dedicated trials such as NCT03774901, which is exploring the role of maintenance avelumab therapy, will be critical to understanding whether immune checkpoint inhibitors have a role in penile carcinoma, and so will further studies of cabozantinib for determining its efficacy in light of phase 1 data.[27] Our data add to the growing literature showing that immunotherapy does not play a role in PRGCTs.[35,36] It should be noted that none of the patients in our study had choriocarcinoma, for which preclinical work exploring the role of PD-1 in immune tolerance and the activity of immune checkpoint blockade in gestational trophoblastic disease suggests that immunotherapy may have efficacy.[1,37]

The data for patients with small cell histology is noteworthy. The majority of treatments for small cell carcinoma of the genitourinary tract are extrapolated from small cell carcinoma of the lung, for which a platinum doublet with etoposide is a standard of care.[38,39] Recently, atezolizumab administered concurrently with platinum chemotherapy has been granted regulatory approval because of a 2-month improvement in OS in comparison with platinum therapy alone.[40] However, in the context of lung cancer, a strategy not incorporating chemotherapy, such as immunotherapy escalation with the combination of nivolumab and ipilimumab, has been disappointing. In a phase 3 study of patients with chemorefractory small cell lung cancer, patients were randomized 3:2 to nivolumab at 3 mg/kg every 2 weeks or nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks for 4 cycles followed by maintenance nivolumab. Although the ORR increased with nivolumab plus ipilimumab (21.9% vs 11.6%), OS was not improved, whereas a 3-fold increase in grade 3 or 4 treatment-related adverse events was seen with the combination.[41] In contrast, our data showed an ORR of 66% (2 of 3) in those with small cell carcinoma of

the bladder and an ORR of 20% (1 of 5) in those with small cell carcinoma of the prostate along with less toxicity from this combination of lower dose ipilimumab with higher dose nivolumab. In conjunction with data from the DART trial showing a 44% ORR to nivolumab with ipilimumab at 1 mg/kg every 6 weeks in patients with high-grade nonpancreatic neuroendocrine tumors (n = 18), there is a role for combined checkpoint inhibition in this setting.[23] To that end, our trial continues to enroll a fourth cohort of patients with small cell or high-grade neuroendocrine tumors from any site within the genitourinary tract.

In summary, our results provide important insights into the treatment of rare genitourinary malignancies with the combination of nivolumab and ipilimumab. The rapidity with which this trial accrued patients with these rare malignancies highlights the unmet need for these patients. Aside from exhibiting efficacy in some genitourinary tumors with a manageable toxicity profile, our data exemplify collaboration between academia and industry. Focusing trials on rare tumors within a certain field enables adaptive trial designs with rapid enrollment and analysis of the data to allow for expansion for those tumor types that show a response, as has already been done with small cell carcinoma of the genitourinary tract with an expansion of the BUTCVH cohort planned. Ongoing correlative work exploring (but not limited to) the PD-L1 status and the tumor mutational burden will be critical to further delineating which patients derive the most benefit from this combination.

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CONFLICT OF INTEREST DISCLOSURES

Bradley Alexander McGregor discloses payment for consulting from Bayer, Astellas, AstraZeneca, Seattle Genetics, Exelixis, Nektar, Pfizer, Janssen, Genentech, Eisai, and EMD Serono and personal fees from Dendreon and Bristol-Myers Squibb and has received research support for the Dana-Farber Cancer Institute from Bristol-Myers Squibb, Calithera, Exelixis, and Seattle Genetics. Matthew T. Campbell discloses payment for consulting/advisory boards from Apricity Health, Astellas, Exelixis, AstraZeneca, Eisai, EMD Serono, Genentech, Seattle Genetics, and Pfizer; reports sponsored education programs by Bristol-Myers Squibb, Roche, and AstraZeneca; has performed education programs (not continuing medical education) for Roche and Pfizer/EMD Serono; and has received support for research from Exelixis, Janssen, AstraZeneca, Pfizer/EMD Serono, and Apricity Health. Mehmet A. Bilen has acted as a paid consultant for and/or as a member of advisory boards for Exelixis, Bayer, Bristol-Myers Squibb, Eisai, Pfizer, AstraZeneca, Janssen, Genomic Health, Nektar, and Sanofi and has received grants for his institution from Xencor, Bayer, Bristol-Myers Squibb, Genentech/Roche, Seattle Genetics, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Peleton Therapeutics, and Pfizer for work performed outside the submitted work. Andrew L. Schmidt has received educational travel assistance from Astellas and Pfizer. Guru P. Sonpavde discloses payment for consulting from Dava Oncology, Pfizer, Bristol-Myers Squibb, Genentech, EMD Serono, Novartis, Merck, Sanofi, Seattle Genetics/Astellas, AstraZeneca, Exelixis, Janssen, Amgen, Eisai, and Bicycle Therapeutics; personal fees from UpToDate, Physicians Education Resource, OncLive, Research to Practice, Medscape, and Elsevier Practice Update; grants from Janssen; research support for his institution from Boehringer-Ingelheim, Bayer, Pfizer, Merck, Sanofi, and AstraZeneca; and travel fees from Bristol-Myers Squibb and AstraZeneca. He is also on steering committees for trials for Bristol-Myers Squibb, Bavarian Nordic, Seattle Genetics, and QED (all unpaid) and AstraZeneca and Debiopharm (both paid). Atish D. Choudhury discloses honoraria from Clovis, Dendreon, and Bayer and research funding for his institution from Bayer and Pfizer. Amir Mortazavi serves on advisory boards for Seattle Genetics and Pfizer and on a scientific advisory board for Debiopharm Group; he has received research funding for his institution from Acerta Pharma, Genentech, Roche, Merck, Novartis, Seattle Genetics, Astellas Pharma, Mirati Therapeutics, Bristol-Myers Squibb, and Debiopharm Group. Amishi Y. Shah discloses payment for consulting from Eisai, Oncology Information Group/Roche, Pfizer, and Exelixis; personal fees from Bristol-Myers Squibb; and research support from Bristol-Myers Squibb, Eisai, and EMD Serono. Aradhana M. Venkatesan reports consulting for Pfizer; research support from the National Institutes of Health/National Cancer Institute (award P30 CA016672); awards from the Institutional Research Grant Program and the Radiation Oncology and Cancer Imaging Program of The University of Texas MD Anderson Cancer Center; and grants from Toshiba America Medical Systems and the Radiological Society for North America. Arlene O. Siefker-Radtke has served on advisory boards for AstraZeneca, Bavarian Nordic, Genentech, Janssen, Merck, Mirati, Nektar Therapeutics, and Seattle Genetics; has received research funding through her institution from Basilea Pharmaceutica, Bristol-Myers Squibb, Janssen, Merck, Millennium, Mirati, and Nektar Therapeutics; and is a speaker for Janssen. Rana R. McKay has received research funding from Bayer, Pfizer, and Tempus; serves on advisory boards for Bayer, Bristol-Myers Squib, Exelixis, Janssen, Novartis, Pfizer, Sanofi, Tempus, and Merck; and is a consultant for Dendreon and Vividion. Toni K. Choueiri reports grants and personal fees from AstraZeneca, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Merck, Exelixis, Genentech, and Corvus; personal fees from Bayer, Cerulean, Foundation Medicine, Roche, Prometheus Labs, and Ipsen; and grants from Pfizer, Novartis, Peloton, EMD Serono, Lilly, Risai, Tracon, and Astellas outside the submitted work. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Bradley Alexander McGregor: Literature search, study design, data collection, data interpretation, analysis, and writing. **Matthew T. Campbell:** Data collection, data interpretation, and writing. **Wanling Xie:** Study design, data interpretation, analysis, and writing. **Subrina Farah:** Study design, data interpretation, analysis, and writing. **Mehmet A. Bilen:** Data collection, data interpretation, and writing. **Andrew L. Schmidt:** Data collection, data interpretation, and writing. **Guru P. Sonpavde:** Data collection, data interpretation, and writing. **Kerry L. Kilbridge:** Data collection, data interpretation, and writing. **Atish D. Choudhury:** Data collection, data interpretation, and writing. **Amir Mortazavi:** Data collection, data interpretation, and writing. **Amishi Y. Shah:** Data collection, data interpretation, and writing. **Aradhana M. Venkatesan:** Data collection, data interpretation, and writing. **Glenn J. Bubley:** Data collection, data interpretation, and writing. **Arlene O. Siefker-Radtke:** Data collection, data interpretation, and writing. **Rana R. McKay:** Literature search, study design, data collection, data interpretation, analysis, and writing. **Toni K. Choueiri:** Literature search, study design, data collection, data interpretation, analysis, and writing.

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