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Pembrolizumab Combined With Either Docetaxel or Gemcitabine in Patients With Advanced or Metastatic Platinum-Refractory Urothelial Cancer: Results From a Phase I Study

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Abstract

Although immune checkpoint inhibitor therapy has led to modest response rates in patients with advanced urothelial cancer, the combination of chemotherapy with immune checkpoint inhibition has not been previously clinically studied. In this phase I study, we found that the combination of pembrolizumab with either docetaxel or gemcitabine in patients with platinum-refractory advanced urothelial cancer was feasible and active.

Introduction: Cytotoxic chemotherapy might prime urothelial cancer (UC) to checkpoint inhibition, prompting a trial of chemotherapy with the programmed death receptor-1 inhibitor pembrolizumab.

Patients and Methods: Patients with advanced, platinum-refractory UC received pembrolizumab and either docetaxel (arm A) or gemcitabine (arm B). Primary end points were assessments of maximum tolerated dose and dose-limiting toxicity (DLT). Secondary end points were overall response rate (ORR) and progression-free survival (PFS).

Results: Twelve patients were enrolled in the initial cohorts; 6 in each arm. One DLT was seen in each arm: Grade 3 hypophosphatemia (arm A), Grade 3 diarrhea (arm B). Adverse events of Grade >3 were observed in 7 (54%), the most common being anemia (6; 50%), fatigue (6; 50%), hyponatremia (4; 33%) and neutropenia (3; 25%), with no treatment-related deaths. There were 5 confirmed responses (1 complete, 4 partial), with an ORR of 42% and disease control rate (DCR) of 58%. Arm A had an ORR of 50% and DCR of 67%, whereas arm B had an ORR of 33% and DCR of 50%. Median PFS was 4.8, 5.7, and 3.7 months for the overall cohort, arm A, and arm B, respectively.

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Disclosure

The authors have stated that they have no conflicts of interest.

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Conclusion: Pembrolizumab with either docetaxel or gemcitabine is feasible for treatment of platinum-refractory advanced UC patients. Preliminary efficacy was observed. Further examination is warranted.

Keywords

Checkpoint inhibition; Chemotherapy; Immunotherapy; Platinum-refractory; Urothelial Carcinoma

Introduction

Bladder cancer accounts for approximately 5% of all new cancer cases in the United States, with an estimated 79,030 new cases diagnosed, and 16,870 deaths due to disease in 2016.[1] The prognosis for patients who develop distant disease (ie, advanced or metastatic urothelial carcinoma) remains poor, with 5-year survival estimated at 5.2%. Cisplatin-based combination chemotherapy regimens are established as initial therapy as of the past 3 decades. MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) and gemcitabine with cisplatin are the standard regimens in clinical use, on the basis of established phase III trials.[2–7] Unfortunately with either treatment regimen, median overall survival is only 9 to 15 months, and only 10% to 15% of patients enjoy long-term survival.

Until recently, there has been no commonly accepted treatment for metastatic urothelial carcinoma with progression after initial platinum-based therapy. Small studies supported the use of single-agent chemotherapy including paclitaxel, docetaxel, vinflunine, gemcitabine, and pemetrexed in the second-line setting, all yielding response rates ranging from 10% to 20%.[8] Gemcitabine was studied in a phase II study of 35 patients with advanced or metastatic urothelial carcinoma previously treated with platinum-based therapy in either the adjuvant or metastatic setting with an overall response rate (ORR) of 22%.[9] In another phase II study, 30 patients with cisplatin-refractory metastatic urothelial carcinoma were treated with gemcitabine with an ORR of 11%.[10] Docetaxel was studied in 30 patients with metastatic urothelial carcinoma refractory to cisplatin-based therapy.[11] In this phase II trial, the ORR was 13.3%.

The role for immunotherapy in early stage bladder cancer had been established for some time; intravesicular bacillus CalmetteeGuerin therapy has been used in the treatment of nonemuscle-invasive bladder cancer and it is thought to be in part because of immune-mediated antitumor effects.[12] Immunotherapy in the metastatic setting has been a fruitful area of recent clinical investigation. With the advent of immune checkpoint inhibitors, efficacy of antibodies targeting the programmed death ligand-1 (PD-L1) and programmed death receptor-1 (PD-1) has been clearly shown. Whereas PD-1 is expressed on activated T cells, PD-L1 and programmed death ligand-2 (PD-L2) are present on immune and tumor cells. The interaction between PD-1 and PD-L1 or PD-L2 normally allows evasion of the cellular immune response, whereas disruption of the signaling might restore antitumor activity.[13] At present, the immune checkpoint inhibitors atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab are all approved by the US Food and Drug

Administration (FDA) for the treatment of patients with advanced or metastatic urothelial carcinoma who have disease progression during or after platinum-based treatment.

Pembrolizumab, a humanized, monoclonal immunoglobulin G4 antibody against PD-1, was studied in a randomized, phase III study (Keynote-045), which compared pembrolizumab versus investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) in patients whose disease had progressed after platinum-based chemotherapy.[14] The study showed a statistically significant benefit in overall survival to pembrolizumab compared with the chemotherapy group by almost 3 months (hazard ratio for death, 0.73; 95% confidence interval, 0.59–0.91; $P = .002$). In the pembrolizumab group, an ORR of 21% was observed, compared with 11% in the chemotherapy group.

With the benefit seen with PD-1 and PD-L1 inhibition, a combination approach with chemotherapy has the potential for enhanced benefit. Cytotoxic therapies can lead to immunogenic modulation of tumor cells such that cytotoxic T-lymphocytes have enhanced activity.[15] Preclinical data have shown potential immunostimulatory effects resulting from treatment with gemcitabine and docetaxel.[16–19] We sought to combine pembrolizumab with either gemcitabine or docetaxel for treatment of patients with metastatic urothelial carcinoma previously treated with a platinum agent, to determine feasibility of combination therapy and to assess a preliminary estimate of efficacy.

Patients and Methods

Clinical Trial

Patients aged 18 years or older were eligible if they had histologically or cytologically confirmed urothelial carcinoma, and had received previous platinum-based therapy for recurrent or advanced disease. Patients could have received up to 2 previous lines of therapy, excluding therapy they might have received in the neoadjuvant or adjuvant setting. In addition, chemotherapy-naive patients who declined to receive first-line chemotherapy were considered eligible. Patients were required to have measurable disease according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST), and to have archival or newly obtained core or excisional biopsy of a tumor lesion. Other key inclusion criteria included anticipated life expectancy >6 months, a performance status of 0 to 2 according to Eastern Cooperative Oncology Group (ECOG) criteria, and adequate hematological and end-organ function according to lab results obtained within 10 days before starting treatment (absolute neutrophil count >1500 cells/μL; platelet count >100,000 cells/μL; hemoglobin >9 g/dL; serum creatinine <1.5 times the upper limit of normal [ULN], or for those with creatinine >1.5 times the ULN, measured or calculated creatinine clearance >60 mL/min; aspartate transaminase [AST] and alanine transaminase [ALT] <2.5 times the ULN, except for those with documented liver metastases [AST and/or ALT <5 times the ULN]; serum total bilirubin <1.5 times the ULN or direct bilirubin less than the ULN in subjects with total bilirubin levels >1.5 times the ULN). Patients could not have any active autoimmune disease that required systemic treatment up to 2 years before enrollment; replacement therapy such as thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency was not considered a form of systemic treatment. However, if patients had a history of pneumonitis that required steroids, they were not eligible for enrollment.

Patients could not have received previous therapy with any antie−PD-1, antie−PD-L1, or antie−PD-L2 therapy.

Study Design

For the phase I portion of the study reported herein, patients who met eligibility requirements were assigned to 1 of t2wo arms, arm A or arm B (Figure 1). Patients who had previously received gemcitabine-containing regimens could not be assigned to arm B. The trial initially involved a 3 + 3 design in which patients would undergo dose escalation of pembrolizumab, but in October 2016, the study was amended on the basis of the revised FDA recommended flat dosing for pembrolizumab. Thus, patients in arm A and B received a fixed dose of 200 mg intravenous pembrolizumab on day 1 of each 21-day cycle. Dose interruptions for pembrolizumab were allowed for toxicity, but dose reductions were not permitted. Patients in arm A were treated with pembrolizumab with 75 mg/m^2 intravenous docetaxel on day 1 of each 21-day cycle, whereas patients in arm B were treated with pembrolizumab in combination with 1000 mg/m^2 intravenous gemcitabine on days 1 and 8 of each 21-day cycle. In each arm, if 1 or fewer patients experienced a dose-limiting toxicity (DLT), an additional 3 patients would be enrolled in each arm, with 1 or more additional DLTs leading to termination of that study arm. If fewer than 2 patients had a DLT subsequently, enrollment of the phase II expansion phase was planned to ensue, with planned enrollment of 10 patients per arm. Patients who discontinued treatment because of a DLT were evaluated every 3 weeks until the adverse event (AE) was stable or resolved. If patients developed unacceptable toxicity from chemotherapy, pembrolizumab could be continued as a single agent in either arm of the trial.

Measurable lesions were assessed and documented before treatment was started. Patients underwent tumor assessments with radiographic imaging every 6 weeks after start of treatment until there was evidence of disease progression according to RECIST criteria. Patients were treated until disease progression according to RECIST criteria, unacceptable toxicity, withdrawal of consent, or by investigator decision, for up to 12 months. Subjects who discontinued trial treatment for a reason other than disease progression were continued to be assessed using imaging every 6 weeks to monitor disease status until disease progression or 6 months, whichever was longer. Response rate was assessed in all patients who had received at least 1 dose of the combination of pembrolizumab and either docetaxel or gemcitabine.

Safety

The study was approved by the institutional review board (IRB) at the University of California Davis (UCD), and was done in full conformance of the provisions of the Declaration of Helsinki and Good Clinical Practice Guidelines. Approval from the IRB and the UCD Comprehensive Cancer Center’s Scientific Review Committee was obtained before the start of the study, and was documented. A data safety monitoring committee met when the last subject in each cohort completed a DLT assessment. An independent data and safety monitoring committee reviewed any new serious AEs (SAEs) related to the drugs every month. All AEs and SAEs occurring within 30 days of the last dose were reported according

to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE).

Immunohistochemical Studies

Patient tumor samples, provided as 10 unstained slides or 1 block of formalin-fixed paraffin embedded samples, were obtained for analysis from a biopsy of a tumor lesion not previously irradiated, and had to be obtained after the diagnosis of metastatic disease. PD-L1 membrane expression was obtained using the commercially available Dako 22C3 antibody (Agilent Technologies, California). The PD-L1 modified proportion score (MPS) was used: this score is used to evaluate mononuclear inflammatory cells (MICs) and tumor cells reactive for PD-L1 in relation to tumor cells. MICs in stroma and adjacent tissue were not included in the MPS.

Outcomes

Incidence, nature, and severity of AEs were graded according to the NCI CTCAE. The secondary end points involved an evaluation of efficacy, and included a preliminary assessment of ORR according to RECIST, and progression-free survival (PFS), defined as time from enrollment to the first occurrence of disease progression determined by the investigator using RECIST, or death from any cause.

Statistical Analysis

The primary objective of the phase I portion of the study was to determine the maximum tolerated dose and assess DLTs. The lead-in phase reported herein was planned to establish a recommended dose of pembrolizumab in combination with either docetaxel or gemcitabine. After the aforementioned amendment in October 2016, if fewer than 2 DLTs were observed in an arm, the study was designed to assess preliminary evidence of efficacy in the expansion phase II cohort. That portion of the trial continues to accrue and results will be reported separately.

Results

Patient Characteristics

Between September 1, 2015 and December 31, 2016, 12 patients were enrolled in the clinical trial; 6 in arm A and 6 in arm B. All 12 patients received at least 1 dose of pembrolizumab. Baseline patient characteristics are presented in Table 1. Most patients were male (67%). The median age of patients enrolled was 66 (range, 45–84) years. Most patients were white race (83%). The median number of previous lines of systemic chemotherapy was 1. Of the 12 patients enrolled, 2 had received chemotherapy in the neoadjuvant setting. ECOG performance status ranged from 0 to 2, but median performance status was 1.

Safety

Overall, treatment was well tolerated. One DLT was observed in each arm of the study. In arm A, 1 patient had Grade 3 hypophosphatemia, which qualified as a DLT. In arm A, 1 patient discontinued docetaxel after 7 cycles because of Grade 3 fatigue, whereas another

discontinued docetaxel after 8 cycles because of Grade 2 clinically intolerable peripheral neuropathy. Both of these patients subsequently continued pembrolizumab treatment. In arm B, 1 patient had Grade 3 diarrhea; this DLT was considered attributable to pembrolizumab, and did require permanent discontinuation of pembrolizumab and oral steroids, with resolution of symptoms. As of the data cutoff, 2 patients were continuing active treatment. Treatment was discontinued for 7 patients because of progression of disease. Treatment was discontinued in 1 patient because of physician discretion, and in 1 patient because of patient preference.

There were no treatment-related deaths. Five patients died from disease progression. In total, 1 or more Grade >3 AEs were observed in 54% of patients (Table 2). The most common AEs Grade >3 were anemia (6; 50%), fatigue (6; 50%), hyponatremia (4; 33%), and neutropenia (3; 25%). Hyponatremia was not attributable to adrenal insufficiency and did not require pharmacologic intervention or therapy discontinuation. One patient had an SAE (cerebrovascular accident) that led to discontinuation from trial.

Efficacy

All 12 patients enrolled in the trial received at least 1 dose of pembrolizumab. The median number of cycles of therapy received was 4.5 (range, 2–14); the median in arm A was 5 (range, 2–14) and in arm B was 3 (range, 2–9). In total, 1 patient achieved a complete response (CR), 4 patients had a partial response (PR), and 2 maintained stable disease (SD). Of note, the patient with a CR maintained response despite discontinuation of therapy after 4 treatments of pembrolizumab. Similarly, 1 patient with a PR discontinued from trial for personal preference after 1 dose of pembrolizumab, with maintenance of PR at the time of primary analysis. The ORR in the lead-in phase of the study was 42%. Disease control rate (DCR) was 58%. ORR in arm A was 50% (1 CR, 2 PRs, 1 SD), with a DCR of 67%. In arm B, ORR was 33% (2 PRs, 1 SD) with a DCR of 50%.

Median PFS in arm A was 5.7 months; median PFS in arm B was 3.7 months (KaplaneMeier plots of PFS are shown in Supplemental Figures 1 and 2 in the online version). Overall, median PFS was 4.8 months. Figure 2 is a swimmer plot that summarizes individual responses and duration of responses. Similarly, the best responses to treatment while in the study further delineated according to arm are shown in Figure 3. Of the 12 patients in the cohort, 7 had PD-L1 MPS <1, whereas 5 were found to have MPS >1. PD-L1 expression did not appear to correlate to response to treatment in this cohort, as shown in Figure 4.

Discussion

Until recently, patients with metastatic urothelial carcinoma were left with modest options after treatment in the first-line setting with platinum-based combination chemotherapy. For the past 3 decades, several cytotoxic agents have been evaluated, none with enough demonstrated efficacy for there to be an established regimen as an option for treatment in the second-line setting according to National Comprehensive Cancer Network guidelines. However, in the past 3 years, immune checkpoint inhibitors, including atezolizumab, avelumab, nivolumab, durvalumab, and pembrolizumab, have established activity after

disease progression during platinum-based chemotherapy and are now considered second-line therapy.[14,20–23]

In the lead-in phase of the study reported herein, 200 mg pembrolizumab intravenously every 3 weeks combined with either gemcitabine or docetaxel was found to be a feasible regimen for treatment of patients with metastatic urothelial carcinoma whose disease had progressed or recurred after platinum-based combination chemotherapy. Although there was a DLT observed in each arm of the trial, there were no treatment-related discontinuations, and in general, toxicities were manageable.

The ORR observed in the overall lead-in phase was 42%, with an ORR of 50% in the arm involving combination therapy with docetaxel, and 33% in the arm involving combination treatment with gemcitabine. These response rates exceed those seen in the aforementioned trials of single-agent checkpoint inhibitors. Two of the patients in this trial were still receiving therapy at the time of data cutoff, indicating that, as in some of the other immune checkpoint inhibition studies, there are durable responses seen in some patients. Similarly, some patients received limited cycles of therapy while maintaining response. Thus far, our results do not indicate a relationship between PD-L1 status and response, although the study is certainly not powered to draw conclusions from this finding. There is a subtle difference in PD-L1 evaluation in this study compared with subsequent studies with pembrolizumab, in that the combined positive score (CPS) has replaced the MPS for PD-L1 expression analysis. Whereas MPS counts tumor cells and tumor-associated immune cells reactive to PD-L1, immune cells in the adjacent tissue or stroma reactive to PD-L1 are excluded. In contrast, CPS includes any PD-L1 reactive cells. The denominators for both tests are the same: total tumor cells.

This lead-in phase is appropriate in size for determining feasibility for further expansion to evaluate combining chemotherapy with pembrolizumab in this patient population. However, the sample size limits evaluation of efficacy. Although the ORR results seen in the lead-in phase of the trial are encouraging, the expansion phase will provide further data regarding efficacy. It is also not possible to attribute the observed ORR as secondary to combining these therapies rather than one of the treatments alone because of the lack of a control arm. Nevertheless, enough encouraging antitumor activity is seen in this trial to warrant continuation to the expansion cohorts with combination therapy of an acceptable toxicity profile.

There are numerous combination trials currently ongoing that are evaluating the efficacy of immune checkpoint inhibition combined with chemotherapy in bladder cancer. Similar to this trial, early phase studies combining checkpoint inhibitors with docetaxel, paclitaxel, nab-paclitaxel, and eribulin are ongoing. In addition, large studies are evaluating the combination of immune checkpoint inhibition with platinum-based chemotherapy in treatment-naive patients (NCT02853305, NCT03036098). Results will further our understanding of the role of immunotherapy and its interaction with cytotoxic chemotherapy, as well as optimal sequencing of these therapies.

Conclusion

The combination of pembrolizumab and either docetaxel or gemcitabine exhibited an acceptable safety profile. Encouraging efficacy was observed, with further clinical evaluation warranted. A phase II cohort will provide further data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

- In patients with advanced or metastatic urothelial carcinoma with disease progression after treatment with platinum-based chemotherapy, chemotherapy modalities such as single-agent docetaxel or gemcitabine historically showed limited efficacy.
- More recently, immune checkpoint inhibitors such as pembrolizumab have exhibited modest efficacy in the same patient population.
- The novel combination of pembrolizumab with chemotherapy (either docetaxel or gemcitabine) was studied in this trial, and the phase I results established an acceptable safety profile. The ORR was 42%.
- The phase II expansion cohort from this trial, as well as other ongoing trials evaluating chemotherapy with immune checkpoint inhibition, might establish a role for combination therapy in bladder cancer.

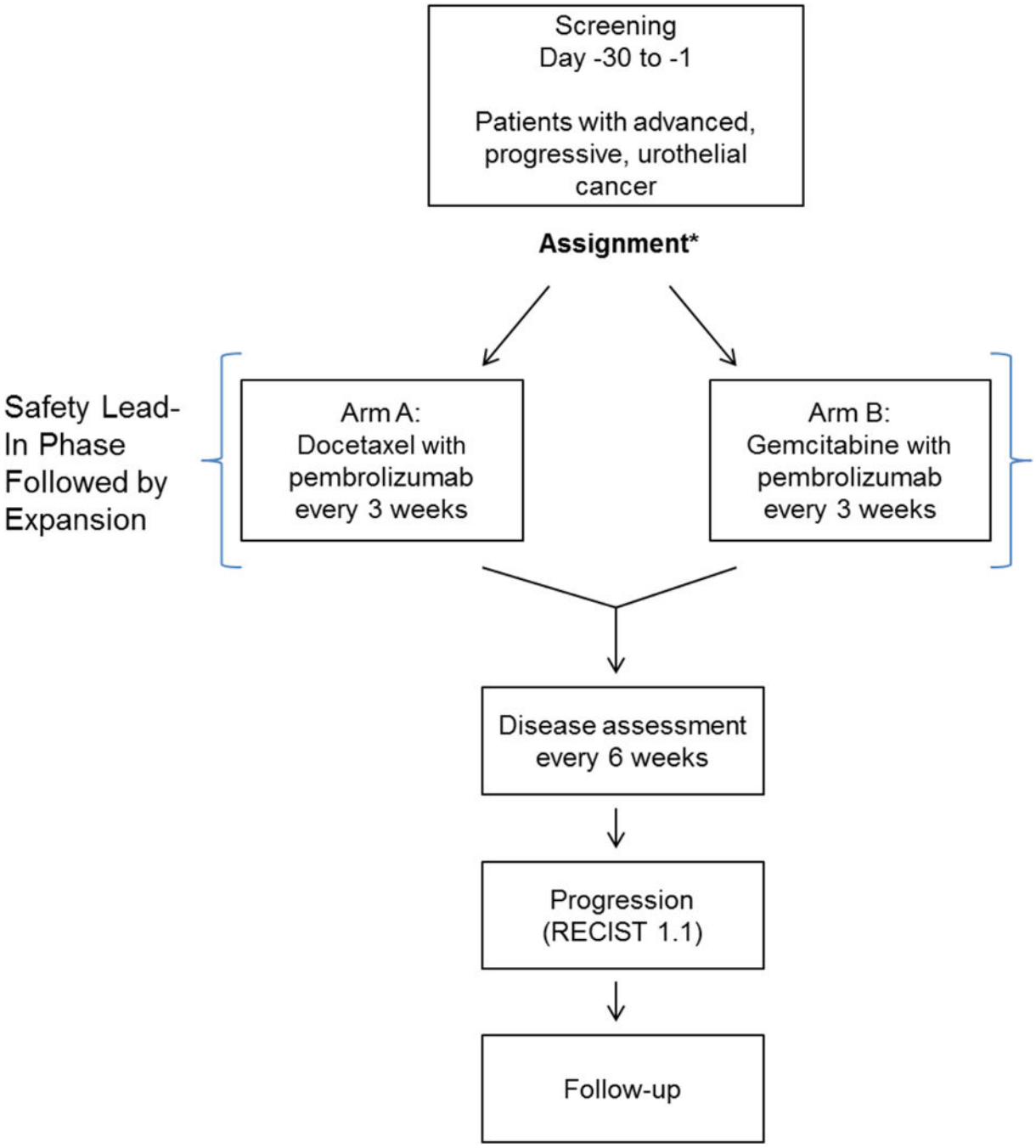

Figure 1.

Study Schema. *Arm A Assigned to Any Patients Who Had Previously Received Gemcitabine With Cisplatin (GC) or Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (MVAC). Arm B Assigned Only to Patients Who Did Not Previously Receive Gemcitabine

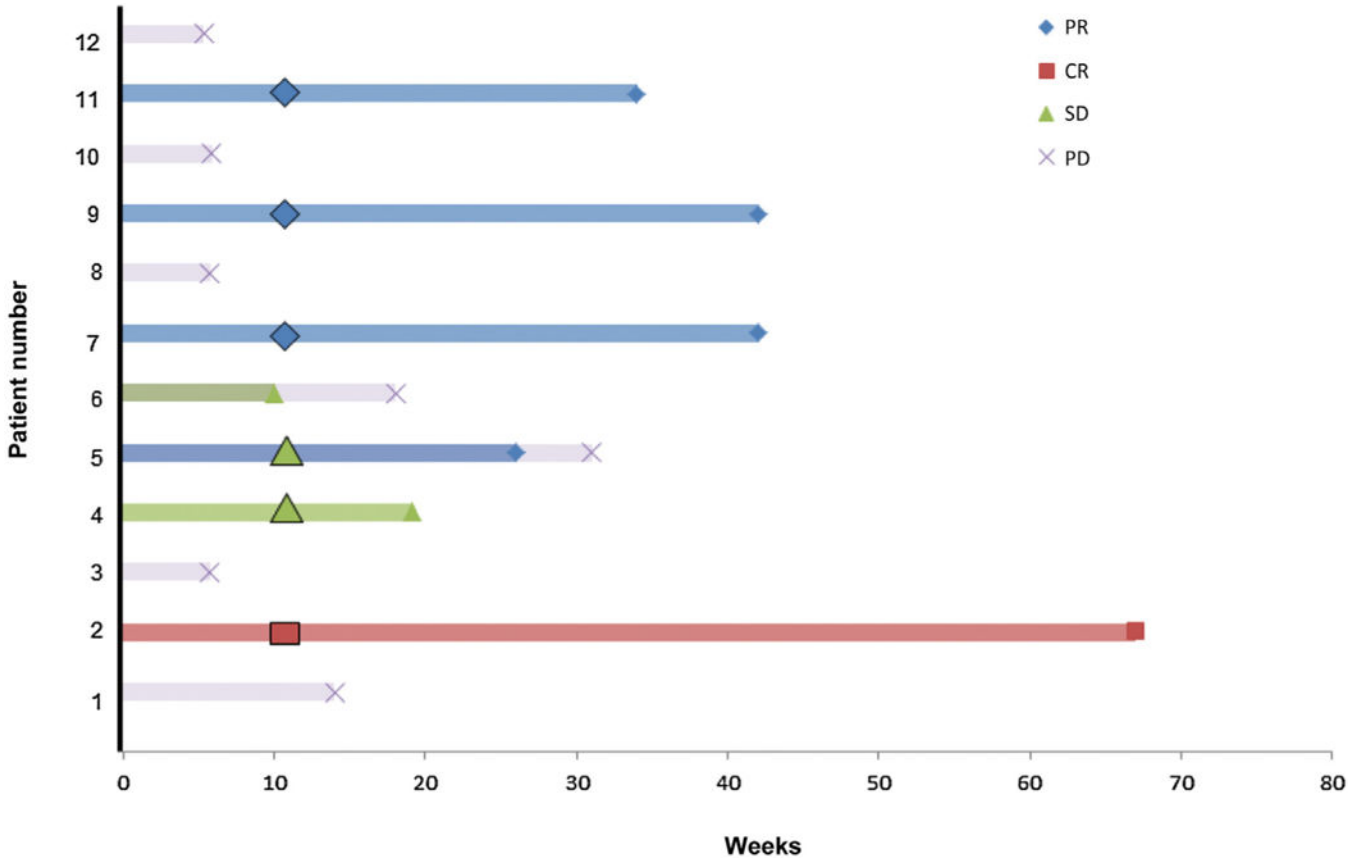

Figure 2.

Individual Responses to Therapy Over Time; Swimmer Plot of Individual Responses to Treatment Are Shown Above. Responses Are Noted (PD, SD, PR, CR) Over the Course of Treatment. Of Note, Patient 5 Was Noted to Have SD After 4 Cycles With Subsequent PR at 12 Weeks Before Ultimately Progressing. Durable Responses (>6 Months) Were Observed in Patients 2, 7, 9, and 11

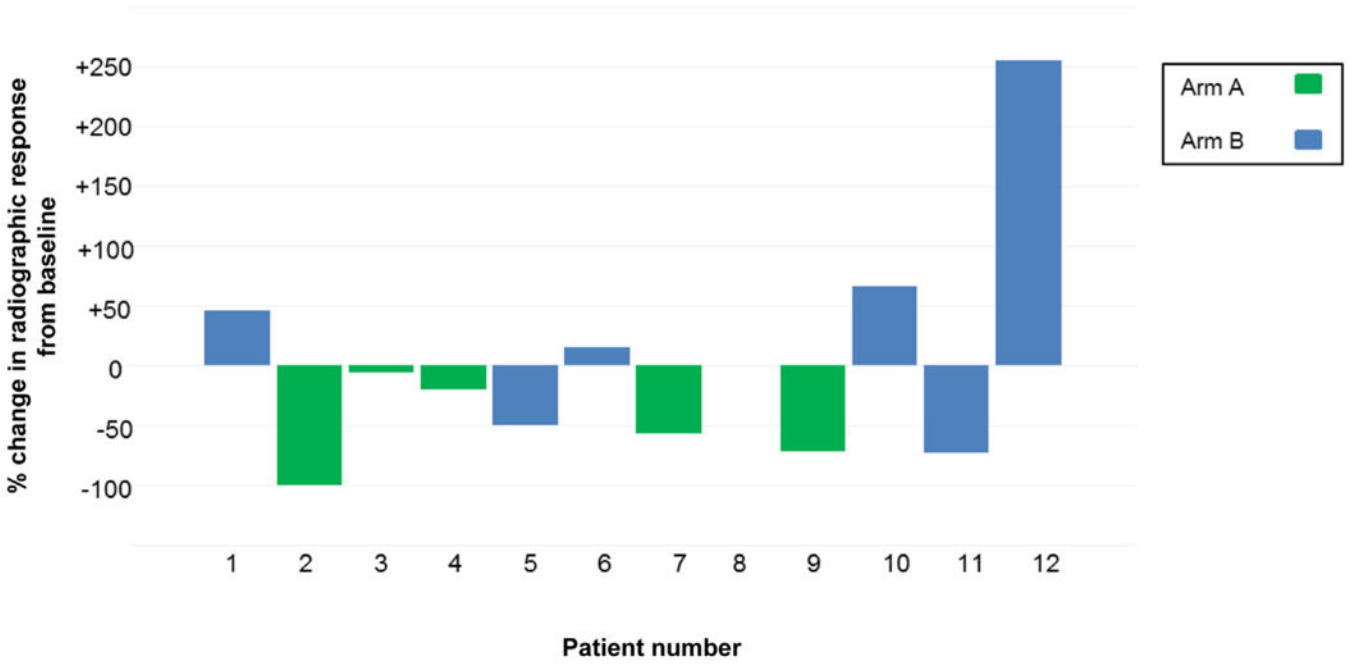

Figure 3.

Best Tumor Response From Baseline According to Therapy Received; Waterfall Plot of Best Tumor Responses From Baseline Are Shown; Target Lesions Were Used to Assess Radiographic Changes From Baseline. Of Note, Patient 8, in Arm A, Had No Change From Baseline, and Was Not Evaluated Radiographically Because of Discontinuation From the Trial. Responses to Pembrolizumab With Docetaxel (Arm A) Are Shown in Green, and Responses to Pembrolizumab With Gemcitabine (Arm B) Are Shown in Blue

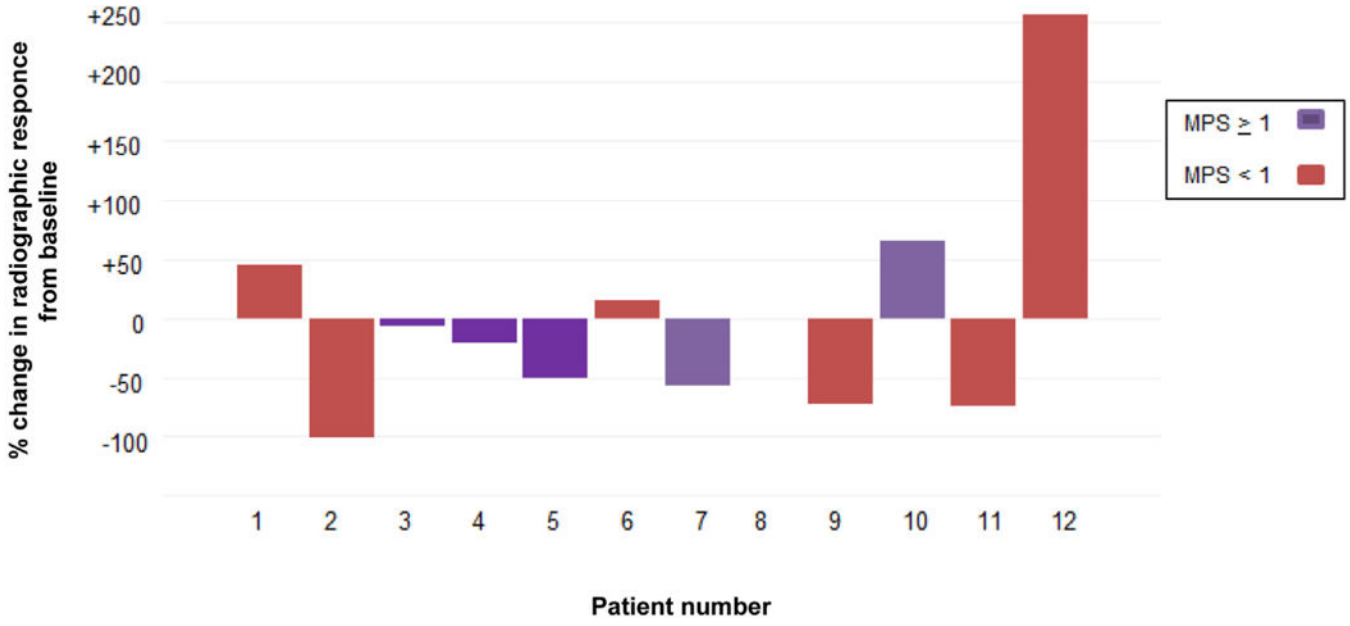

Figure 4.

Best Tumor Response From Baseline on the Basis of Programmed Death Ligand 1 (PD-L1) Expression; Waterfall Plot of Best Tumor Responses From Baseline Are Shown; Target Lesions Were Used to Assess Radiographic Changes From Baseline. Responses in Patients With PD-L1 Modified Proportion Score (MPS) >1 Are Shown in Purple, Responses in Patients With PD-L1 MPS <1 Are Shown in Red

Table 1

Baseline Demographic and Patient Characteristics

Characteristic	Overall (n = 12)	Arm A: Docetaxel With Pembrolizumab (n = 6)	Arm B: Gemcitabine With Pembrolizumab (n = 6)
Median Age (Range), Years	66 (45−84)	70 (66−84)	64 (45−73)
Male Sex, n (%)	8 (67)	3 (50)	5 (83)
Female Sex, n (%)	4 (33)	3 (50)	1 (17)
White Race, n (%)	10 (83)	6 (100)	4 (67)
Hispanic ethnicity, n (%)	2 (17)	2 (33)	0
Asian/Pacific-Islander, n (%)	2 (17)	0	2 (33)
Median Previous Lines of Systemic Chemotherapy, n (Range)	1 (1−2)	1.5 (1−2)	1.5 (1−2)
Received Neoadjuvant Therapy, n	2	0	2
Median ECOG (Range)	1 (0−2)	1 (0−2)	0.5 (0–1)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

Table 2

Summary of Grade >3 Adverse Events

	Arm A (n = 6)		Arm B (n = 6)	
Adverse Event	**n**	**%**	**n**	**%**
Anemia	3	50	3	50
Diarrhea	0	0	1	17
Injection Site Reaction	0	0	1	17
Fatigue	6	100	0	0
Edema Limbs	0	0	2	33
Sepsis	2	33	0	0
Lymphocyte Count Decreased	0	0	1	17
Lymphocyte Count Increased	0	0	2	33
Neutrophil Count Decreased	2	33	1	17
White Blood Cell Count Decreased	2	33	0	0
Platelet Count Decreased	0	0	1	17
Hyponatremia	2	33	2	33
Hypophosphatemia	2	33	0	0
Hypoalbuminemia	0	0	2	33
Rash, Maculopapular	1	17	0	0