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Phase II basket trial of Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors (DART) SWOG S1609: adrenocortical carcinoma cohort

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ABSTRACT

Objectives Multiple common cancers benefit from immunotherapy; however, less is known about efficacy in rare tumors. We report the results of the adrenocortical carcinoma cohort of NCI/SWOG S1609 Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors.

Design/setting A prospective, phase 2 clinical trial of ipilimumab plus nivolumab was conducted by the SWOG Early Therapeutics and Rare Cancers Committee for multiple rare tumor cohorts across >1,000 National Clinical Trial Network sites.

Participants 21 eligible patients were registered. Median age was 53 years (range 26–69); 16 (76%) were women.

Interventions Ipilimumab 1 mg/kg intravenously every 6 weeks with nivolumab 240 mg intravenously every 2 weeks was administered until disease progression, symptomatic deterioration, treatment delay for any reason >56 days, unacceptable or immune-related toxicity with inability to decrease prednisone to <10 mg daily, or per patient request.

Main outcome measures The primary endpoint was the overall response rate (ORR) (RECIST V.1.1). Secondary endpoints include clinical benefit rate (CBR) (includes stable disease (SD)>6 months), progression-free survival (PFS), overall survival (OS), and toxicity. Immune-related outcomes included immune ORR (iORR), immune CBR (iCBR), and immune PFS (iPFS). A two-stage design was used assuming: null=5% alternative=30%, n=6 in the first stage, 16 max, one-sided alpha=13%.

Results The median number of prior therapy lines was 2 (range: 1–9). 3 of 21 patients attained confirmed partial response (PR) (ORR=14%). In addition, one patient had an unconfirmed PR; one, stable disease (SD)>6 months; one, immune-related RECIST (iRECIST) PR (iPR); and one patient attained iSD>6 months: clinical benefit rate (response or SD>6 months)=5/21 (24%), iORR=4/21 (19%), iCBR=7/21 (33%). The 6-month PFS was 24%; 6-month iPFS, 33%. The PFS for patients (N=7) with iRECIST clinical benefit were 57, 52, 18, 15, 13, 7, and 7 months. The 6-month OS was 76%; the median OS, was 15.8 months. The most common toxicities were fatigue (62%) and rash (38%), and the most common grade 3/4 immune-related adverse events were hepatic dysfunction (9.5%) and adrenal insufficiency (9.5%). Treatment-related adverse events

leading to discontinuation of therapy in four patients (21%). There were no grade 5 adverse events.

Conclusions Ipilimumab plus nivolumab is active in refractory metastatic adrenocortical cancer meeting the primary endpoint of the study, with a 19% iORR and 33% iCBR (includes SD/iSD>6 months) and with the longest PFS/iPFS of 52 and 57 months.

Trial registration number NCT02834013 (registered 15 July, 2016; <https://clinicaltrials.gov/ct2/show/NCT02834013>).

INTRODUCTION

Cancer immunotherapy has dramatically improved outcomes for patients with cancer with rare tumors including but not limited to Merkel cell carcinoma, anal cancer, and Hodgkin's lymphoma.^{1–3} To address the lack of data in other rare tumor types, SWOG 1609 DART (Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors) was launched, the first federally funded basket immunotherapy study investigating multiple rare tumors using lower-dose ipilimumab with nivolumab. The trial investigated combinatorial immune checkpoint blockade across 53 rare tumor types across the USA at over 1,000 sites at its peak, with 798 accruals over an approximately 4-year period—demonstrating the feasibility of clinical trials in rare tumors.

Advanced/metastatic adrenocortical cancers are lethal malignancies, with few patients achieving 5-year survival. Median survival is only about 1 year, and treatment guidelines generally include mitotane and platinum-based regimens.⁴

We have previously reported our results with ipilimumab and nivolumab across several rare tumor types.^{5–9} We describe here the clinical activity of ipilimumab and nivolumab in a

dedicated cohort of advanced/metastatic adrenocortical carcinoma within the S1609 DART trial.

PATIENTS AND METHODS

The trial was conducted by the SWOG Early Therapeutics and Rare Cancers Committee, and the investigational agents were provided by the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) under an NCI CRADA (Cooperative Research and Development Agreements) agreement with Bristol-Myers Squibb. The protocol and all amendments were approved by SWOG, the NCI, the NCI Central Institutional Review Board, and by the regulatory committees at the participating institutions. All study subjects provided their voluntary, written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Rationale for population

Rare cancers for S1609 cohort design were identified based on an incidence of less than 6 in 100,000 per year.¹⁰ A local pathology review was used and a pathology report was reviewed by the SWOG study team. No separate central pathology confirmatory review was performed.

Patient selection

Patients were required to be 18 years of age or older, have an ECOG (Eastern Cooperative Oncology Group) performance status of 0–2, with absolute neutrophil count $\geq 1,000/\text{mL}$, platelets $\geq 75 \times 10^9/\text{L}$, hemoglobin $\geq 80\text{ g/L}$, creatinine clearance $\geq 50\text{ mL/min}$, total bilirubin $\leq 2.0 \times$ institutional upper limit of normal (IULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3.0 \times$ IULN, TSH (thyroid stimulating hormone) or free T4 serum \leq IULN, and adrenocorticotropic hormone (ACTH) \leq IULN. All patients had at least one line of prior therapy. Women of childbearing potential were required to have a negative serum pregnancy test, and subjects were required to practice adequate birth control during protocol participation.

Treatment and monitoring

Treatment consisted of ipilimumab 1 mg/kg intravenously every 6 weeks with nivolumab 240 mg intravenously every 2 weeks until disease progression, symptomatic deterioration, treatment delay for any reason >56 days, unacceptable or immune-related toxicity with inability to decrease prednisone to <10 mg daily, or per patient request.

Patients were evaluated with a history and physical, and toxicity assessment at least every 6 weeks at the beginning of each cycle. Laboratory evaluation included complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, free thyroxine, ACTH, cortisol, lipase. Imaging studies by CT for disease assessment were performed pre-study, week 8, week 16, week 24, and then every 12 weeks until progression.

Statistical methods and outcomes

The primary objective was to evaluate the overall response rate (ORR, confirmed complete and partial

responses (CR and PR)) by RECIST (Response Evaluation Criteria in Solid Tumors) V.1.1 based on local assessment. A two-stage design was used to distinguish between a true $\text{ORR} \leq 5\%$ (null hypothesis, as patients had failed all known active therapies) versus $\geq 30\%$ (alternative hypothesis, deemed a potentially clinically meaningful difference in tumor response in refractory solid tumors). The first stage sample size was 6 patients, if 1 or more had a response (confirmed CR or PR), an additional 10 patients were to be accrued. The design specified 2 or more responses out of 16 patients would reject the null hypothesis (one-sided $\alpha=13\%$, power=87%). Accrual targets were inflated by 10% of patients to account for ineligible patients. The secondary objectives were to estimate progression-free survival (PFS), overall survival (OS), immune ORR (iORR) by immune-related RECIST (iRECIST), PFS by iRECIST, and toxicity assessment by CTCAE (Common Terminology Criteria for Adverse Events) V.4.0. Data are as of July 12, 2023. Clinical benefit rate (CBR) (stable disease (SD) >6 months/PR/CR) was also assessed. Toxicity was defined as treatment-related adverse event PFS was measured from the start of protocol therapy to the first date of progression by RECIST V.1.1 or death by any cause, with patients last known to be alive without progression censored at the date of last contact. OS was measured from the date of study registration to the date of death by any cause, with patients last known to be alive censored at the date of last contact. PFS and OS estimates were calculated using the Kaplan-Meier method. CIs for medians were constructed using the method of Brookmeyer and Crowley, and CIs for point estimates (eg, 6-month PFS) were calculated using the log–log transformation.¹¹ All analyses were performed using R V.4.3.0.

RESULTS

Patient characteristics

23 patients from 12 National Clinical Trial Network institutions were registered between June 2017 and July 2019. 2 patients were not eligible (1 with ACTH and cortisol outside the normal limit and 1 with platelets outside range); a total of 21 patients met eligibility criteria and received protocol therapy. The median age was 53 years (range, 26–69). Overall, 24% of patients in this cohort were men. Performance status was 0–1 for 100% of patients. 71% of patients self-reported as white and 19% as black; 14% of patients self-reported as Hispanic, and the remaining (86%) as non-Hispanic. The median number of prior lines of therapy was 2 (range, 1–9) (table 1). 4 of 21 patients had microsatellite status information available, and 3 out of those 4 were microsatellite stable (MSS). The one patient with microsatellite instability-high (MSI-H) mutation had PMS2 loss.

Outcomes

Among the 21 patients evaluated, 3 patients had a confirmed PR (PFS, 7, 13, and 15 months), 1 patient had SD for 6+ months (PFS of 57 months), 1 patient had an

Table 1 Patient characteristics and outcome (N=21 patients)

Characteristic	Summary	
Age (years) (median (range))	53 (26–69)	
Gender		
Female	16 (76%)	
Male	5 (24%)	
Performance status		
0	8 (38%)	
1	13 (62%)	
Ethnicity		
Hispanic	3 (14%)	
Not Hispanic	18 (86%)	
Race		
White	15 (71%)	
Black	4 (19%)	
Unknown	2 (10%)	
RECIST/iRECIST response summary*		
Outcome	Best RECIST response (N (%))	PFS/ immune PFS (iPFS)
Confirmed PR	3 (14)*	7, 13 and 15 months
Unconfirmed PR	1 (5)	7 months
Clinical benefit (stable disease for 6+ months)	1 (5)	57 months
Clinical benefit (immune stable disease for 6+ months)	1 (5)	18 months
Immune PR (iPR)	1 (5)	52 months
Not assessed	1 (5)	
Progression*	13 (62)	

Progression includes patients whose disease progressed as their best response by RECIST or iRECIST.
 *In total, three patients had a confirmed PR (with PFS of 7 months, 13 months, and 15 months), one patient had stable disease for 6+ months (PFS of 57 months), one patient had an iPR (with iPFS of 52 months), one patient had an unconfirmed PR (with PFS of 7 months), and one patient had an immune stable disease for >6 months (iPFS of 18 months).
 iPFS, immune PFS; iRECIST, immune-related RECIST ; PFS, progression-free survival ; PR, partial responses.

immune PR (iPR) (immune PFS (iPFS), 52 months), 1 patient had an unconfirmed PR (PFS, 7 months), and 1 patient had an immune SD for >6 months (iPFS, 18 months). Therefore 5 of 21 (24%) had a response or prolonged SD either by RECIST and 7 of 21 patients (33%) had a response or prolonged SD either by RECIST or iRECIST criteria. The PFS for patients (N=7) with iRECIST clinical benefit were 57, 52, 18, 15, 13, 7, and 7 months (table 1).

The waterfall plot is reported in figure 1 (1A for RECIST and 1B for iRECIST). Eight of the patients did not have tumor measurements available due to either progression with a new lesion at the first assessment (n=5), symptomatic deterioration before the first assessment (n=1), receipt of palliative radiation therapy before the first assessment (n=1), or death before the first assessment (n=1). The 6-month OS rate was 76% (95% CI 60% to 97%), the 12-month OS rate was 52% (95% CI 35% to 79%), and the median OS was 15.8 months (95% CI 6.6 to 28.9). The 6-month PFS rate was 24% (95% CI 11% to 51%), the 12-month PFS rate was 14% (95% CI 5% to

41%), and the median PFS was 1.8 months (95% CI 1.7 to 7.1) (figure 2A,B).

Duration of response is shown in figure 3 for the five patients with clinical benefit, with PFS duration of 57, 15, 13, 7, and 7 months. We also assessed patients with iRECIST, with one patient having an immune PR and one patient having an immune SD (figures 1B and 3B). The 6-month iPFS rate was 33% (95% CI 18% to 61%), and the median iPFS was 1.8 months (95% CI 1.7 to 13.3) (Figure S1). The patient with immune PR had an iPFS of 52 months, and the patient with immune SD had an iPFS of 18 months (figure 3B).

23% (5/21) of the patients with adrenocortical carcinoma (ACC) in this cohort had microsatellite status information available, and 4/5 were (MSS). The one patient with MSI-H mutation had PMS2 loss. The response rate in MSS patients was 50% (2/4) confirmed PR, with 2/4 having progression of disease among patients with known MSS status. The patient with MSI-H mutation had a PR that lasted 7 months. Out of the remaining 16 patients with unknown microsatellite

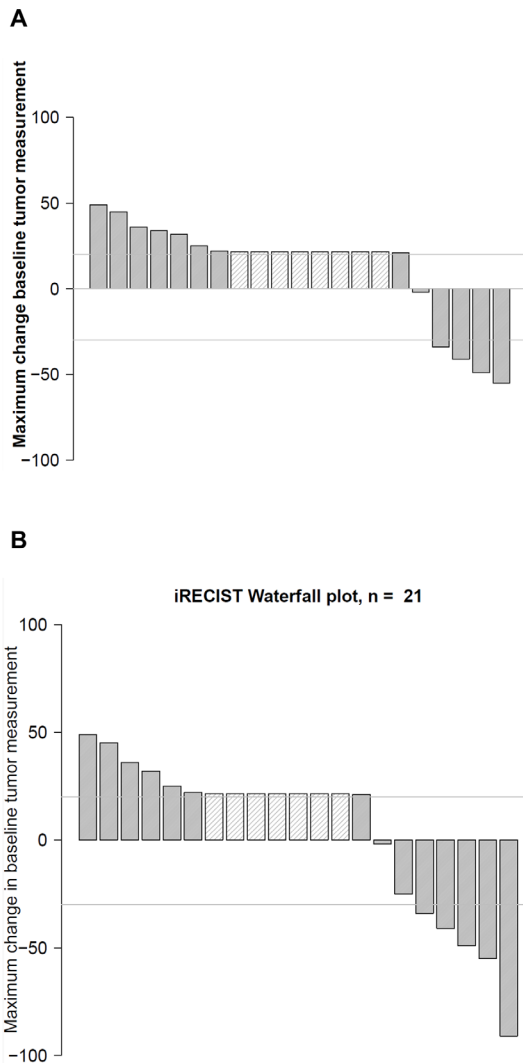


Figure 1 (A) RECIST waterfall plot. Waterfall plot of 21 patients demonstrating 4 patients with partial response (1 of whom had an unconfirmed partial response), and 1 patient with stable disease by RECIST. Eight patients did not have tumor measurements available due to either progression with new lesions at first assessment ($n=5$), symptomatic deterioration before first assessment ($n=1$), receipt of palliative radiation therapy before first assessment ($n=1$), and death before first assessment ($n=1$), which are denoted as columns with hashmarks. (B) iRECIST waterfall plot of 21 patients demonstrating 5 patients with partial response, 1 patient with unconfirmed partial response, 2 patients with stable disease, 13 patients with progression. Seven patients did not have tumor measurements available due to either progression with new lesions at first assessment ($n=4$), symptomatic deterioration before first assessment ($n=1$), receipt of palliative radiation therapy before first assessment ($n=1$), and death before first assessment ($n=1$), which are denoted as columns with hashmarks. In total, three patients had a confirmed PR (with PFS of 7 months, 13 months, and 15 months), one patient had stable disease for 6+ months (PFS of 57 months), one patient had an iPR (with iPFS of 52 months), one patient had an unconfirmed PR (with PFS of 7 months), and one patient had an immune stable disease for >6 months (iPFS of 18 months). iPFS, immune PFS; iPR, immune PR; iRECIST, immune-related RECIST; PFS, progression-free survival; PR, partial responses.

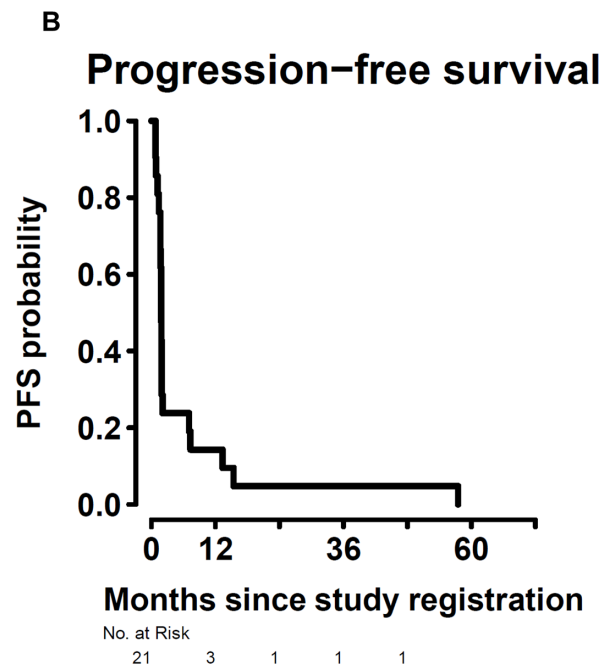
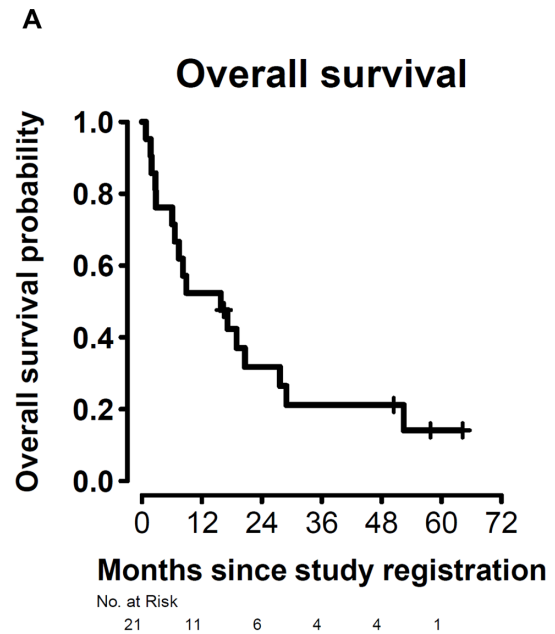


Figure 2 (A) Overall survival Kaplan-Meier curve of 21 patients with adrenocortical carcinoma with a 6-month OS rate of 76% (95% CI 60% to 97%), 12-month OS rate 52% (95% CI 35% to 79%), and median OS 15.8 months (95% CI 6.6 to 28.9). (B) Progression-free survival Kaplan-Meier curve of 21 patients with adrenocortical carcinoma, with 6-month PFS rate of 24% (95% CI 11% to 51%), 12-month PFS rate of 14% (95% CI 5% to 41%), and median PFS of 1.8 months (95% CI 1.7 to 7.1). PFS, progression-free survival; OS, overall survival.

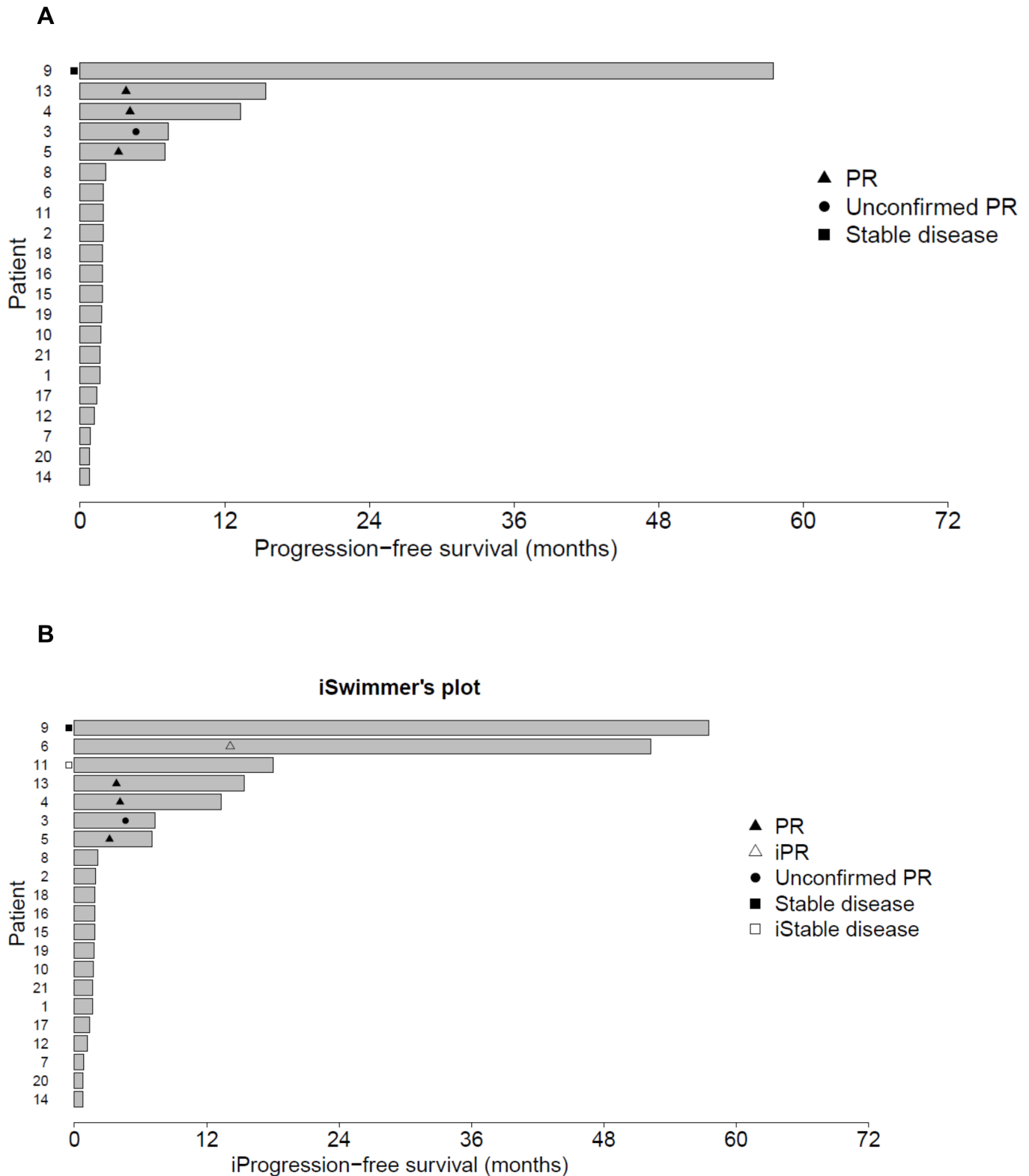


Table 2 Treatment-related adverse events

Treatment related adverse events for cohort(s) 31 (n=21)			
	Any Grade	Grade 3–4	Grade 5
Any	20 (95.2%)	11 (52.4%)	0 (0.0%)
Serious	10 (47.6%)	7 (33.3%)	0 (0.0%)
Led to discontinuation	4 (19.0%)	3 (14.3%)	0 (0.0%)
Lead to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
>10% of patients			
Fatigue	13 (61.9%)	3 (14.3%)	0 (0.0%)
Rash maculo-papular	8 (38.1%)	0 (0%)	0 (0.0%)
Alanine aminotransferase increased	6 (28.6%)	2 (9.5%)	0 (0.0%)
Aspartate aminotransferase increased	6 (28.6%)	2 (9.5%)	0 (0.0%)
Pruritus	5 (23.8%)	1 (4.8%)	0 (0.0%)
Nausea	5 (23.8%)	0 (0%)	0 (0.0%)
Diarrhea	4 (19.0%)	1 (4.8%)	0 (0.0%)
Arthralgia	4 (19.0%)	0 (0%)	0 (0.0%)
Hyperglycemia	3 (14.3%)	1 (4.8%)	0 (0.0%)
Platelet count decreased	3 (14.3%)	1 (4.8%)	0 (0.0%)
Alkaline phosphatase increased	3 (14.3%)	0 (0%)	0 (0.0%)
Anorexia	3 (14.3%)	0 (0%)	0 (0.0%)
Hypothyroidism	3 (14.3%)	0 (0%)	0 (0.0%)
Rash acneiform	3 (14.3%)	0 (0%)	0 (0.0%)
Vomiting	3 (14.3%)	0 (0%)	0 (0.0%)
Immune-mediated	16 (76.2%)	6 (28.6%)	0 (0.0%)
Rash maculo-papular	8 (38.1%)	0 (0%)	0 (0.0%)
Alanine aminotransferase increased	6 (28.6%)	2 (9.5%)	0 (0.0%)
Aspartate aminotransferase increased	6 (28.6%)	2 (9.5%)	0 (0.0%)
Pruritus	5 (23.8%)	1 (4.8%)	0 (0.0%)
Diarrhea	4 (19.0%)	1 (4.8%)	0 (0.0%)
Arthralgia	4 (19.0%)	0 (0%)	0 (0.0%)
Hypothyroidism	3 (14.3%)	0 (0%)	0 (0.0%)
Adrenal insufficiency	2 (9.5%)	2 (9.5%)	0 (0.0%)
Lipase increased	2 (9.5%)	1 (4.8%)	0 (0.0%)
Colitis	2 (9.5%)	0 (0%)	0 (0.0%)
Serum amylase increased	2 (9.5%)	0 (0%)	0 (0.0%)
Blood bilirubin increased	1 (4.8%)	1 (4.8%)	0 (0.0%)
Pneumonitis	1 (4.8%)	1 (4.8%)	0 (0.0%)
Hyperthyroidism	1 (4.8%)	0 (0%)	0 (0.0%)

status, 1/16 had an unconfirmed PR and 1/16 had SD (18 months).

Toxicities

Adverse events (AEs) are summarized in [table 2](#), with 95% of patients experiencing an AE in the study, 52% developing a grade 3–4 AE, and 0% developing a grade 5 AE. The most common toxicities of any grade were fatigue (62%) and rash (38%). The most common grade 3–4 toxicities were rash (14%), ALT and AST elevation (both 9.5%), followed by pruritus, diarrhea, hyperglycemia,

and thrombocytopenia (4.8% each). The most common immune-mediated toxicity was rash (38%), followed by ALT and AST elevation (both 29%). The most common grade 3/4 immune-related adverse events were ALT/AST abnormalities, and adrenal insufficiency (9.5% each), followed by pruritus, diarrhea, lipase elevation, hyperbilirubinemia, and pneumonitis (4.8% each). 4 out of 21 (19%) patient required permanent therapeutic discontinuation as management of their toxicity.

DISCUSSION

ACC is an aggressive neoplasm with a poor prognosis. Treatment consists of surgical resection whenever possible, followed by adjuvant mitotane with or without cisplatin-based chemotherapy and/or radiation based on the risk of recurrence.^{12,13} The unresectable disease is treated with mitotane in combination with etoposide, doxorubicin and cisplatin-based on the only phase 3 trial in metastatic ACC, which showed PFS superiority for mitotane, etoposide, doxorubicin, and cisplatin compared with mitotane and streptozocin (5 vs 2 months). There was, however, no median OS benefit (14.8 vs 12 m; $p=0.07$).¹⁴ Owing to its rarity, there are few prospective, randomized clinical trials for adjuvant or upfront systemic treatment in ACC, and treatment paradigms are thus derived largely from retrospective studies. Progress in the identification of new therapeutic agents in this entity has also been limited for the same reason.

Across S1609 DART, the combination of low-dose ipilimumab and nivolumab was chosen to maximize the likelihood of immunotherapeutic response relative to monotherapy, and the dose of ipilimumab of 1 mg/kg intravenously every 6 weeks was chosen on the balance of toxicity and efficacy, and based on the results of CheckMate 227.¹⁵

In this cohort of S1609 DART, 21 evaluable patients with ACC were treated with a combination of ipilimumab and nivolumab, the first study of combination immune checkpoint blockade in this rare, aggressive neoplasm. 3 of 21 patients had confirmed PRs for an ORR of 14%, and 1/21 patients had iPR, for an iORR of 19%. 1 of 21 patients had unconfirmed PR, 1/21 patients had SD>6-month, for a CBR of 24%. 1 of 21 patients had iSD (immune stable disease) for over 6 months, for an immune CBR of 33%. 6-month OS rate was 76% (95% CI 60% to 97%), 12-month OS was 52% (95% CI 35% to 79%), and median OS was 15.8 months (95% CI 6.6 to 28.9). Six-month PFS rate was 24% (95% CI 11% to 51%), 12-month PFS rate was 14% (95% CI 5% to 41%), and median PFS was 1.8 months (95% CI 1.7 to 7. Six-month iPFS rate of 33% (95% CI 18% to 61%), and median iPFS was 1.8 months (95% CI 1.7 to 13.3). Individual PFS duration were 57, 52, 18, 15, 13, 7, and 7 months (includes all patients with PR, iPR and/or SD>6 months or iSD>6 months). Durable remissions in this subset of patients (>12 months and in particular >50 months) is a characteristic feature of immunotherapeutic response

and an area being explored in future translational work. Among four patients with known MSS status, the ORR was 50% highlighting potential unique responses in MSS ACC due to dual immune checkpoint blockade. There is a need for more complete molecular testing, which can be done on tissue by methods such as immunohistochemistry or next-generation sequencing or on cell-free DNA derived from blood, for pan-cancer biomarkers such as MSI-H for which there is Food and Drug Administration approval of pembrolizumab,¹⁶ as well as for other potential biomarkers of response.

Other clinical trials of immune checkpoint blockade in ACC have also been reported. In a phase 2 study of pembrolizumab in advanced rare cancers, Naing *et al* reported that 2 of 13 patients achieved a PR for a 15% ORR, and 6/13 achieved SD of at least 6 months for a CBR of 54%. Microsatellite status was not available in that study.¹⁷ Carneiro *et al* report 1/10 patients with an unconfirmed PR (10%) (MSS). The median PFS was 1.8 months, and the median OS was 21.2 months.¹⁸ Lastly, in a phase 1b study of avelumab in metastatic ACC, Le Tourneau *et al* report 3/50 patients with PR for an ORR of 6%. Median PFS was 2.6 months, and the median OS was 10.6 months. Microsatellite status was not reported in this study.¹⁹ Overall, our experience is comparable to other studies of checkpoint blockade in ACC demonstrating durable benefit in a subset of patients even in patients with MSS disease. Clinically, given the multiple data sets, immune checkpoint blockade is a reasonable consideration in patients with refractory ACC.

Limited molecular profiling was available on this cohort with 5/21 patients having microsatellite status information available (4/5 patients having MSS disease, and 1/5 having MSI-H with PMS2 loss). Two of four MSS patients had confirmed PR, with the other 2/4 having progression of disease. The patient with MSI-H disease experienced a PR. These results reinforce the need for translational biomarker analyses as part of clinical trials in an effort to identify markers of response to include transcriptome profiling, programmed death-ligand 1 (PD-L1) protein expression by immunohistochemistry, next-generation sequencing, as part of a broad effort to interrogate cancer immunotherapeutic biomarkers across rare cancers.^{20–22}

The toxicities experienced in this cohort are consistent with prior studies of immune checkpoint blockade using lower dose ipilimumab (1 mg/kg every 6 weeks) with nivolumab, with the most common toxicities being fatigue (62%) and rash (38%). The most common grade 3–4 toxicities were rash (14%), and ALT and AST elevation (9.5% both). Rates of high-grade colitis (4.8%) and pneumonitis (4.8%) were as expected, the former likely due to the use of lower-dose ipilimumab. There were no grade 5 AEs. Broadly, this regimen was generally tolerable with immune dermatitis as the most common symptomatic AE.

In summary, we describe here the dedicated ACC neoplasm cohort of SWOG 1609 assessing low-dose ipilimumab plus nivolumab. Limitations of our study include its single-arm design, lack of power to assess OS, and lack of mandatory upfront MSI-H testing. Additionally, local radiographic assessments were used for the primary endpoint of ORR. Altogether, 7 of 21 patients (33%) had a response or prolonged SD either by RECIST or by iRECIST criteria, including 2 patients with PFS/iPFS of 52 and 57 months. Future studies should evaluate the role of single anti-programmed cell death protein-1 (PD-1) agents versus dual inhibition with anti-PD-1 and anti-cytotoxic T-lymphocyte associated protein 4. Clinical-grade biomarker testing and assessment of MSI status should be the routine standard of care across rare gastrointestinal, gynecologic, and other solid tumor types.²³ Additionally, fundamental research is needed to uncover predictive markers of response to immune checkpoint blockade as well as new therapies, in particular in MSS ACC.

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