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ORIGINAL ARTICLE

A phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART) SWOG S1609: durable responses and delayed pseudoprogression in small cell carcinoma of the ovary, hypercalcemic type cohort

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Abstract

Background: The combined use of anti-programmed cell death protein 1 (*PD-1*)/anti-cytotoxic T-lymphocyte associated protein 4 (*CTLA-4*) checkpoint inhibitors has been effective in various cancer types. The Southwest Oncology Group (SWOG) Dual Anti-*CTLA-4* and Anti-*PD-1* Blockade in Rare

List of abbreviations:: CBR, clinical benefit rate by RECIST criteria; CI, confidence interval; CR, complete response by RECIST criteria; iCBR, clinical benefit rate by oRECIST criteria; iCR, complete response by iRECIST criteria; iORR, overall response rate by iRECIST criteria; iPFS, progression-free survival by iRECIST criteria; irAE, immune-related adverse events; IULN, institutional upper limit of normal; ORR, overall response rate by RECIST criteria; OS, overall survival; PFS, progression-free survival by RECIST criteria; PR, partial response by RECIST criteria; SCCOHT, small cell ovarian carcinoma, hypercalcemic type.

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Tumors (DART) S1609 study investigated ipilimumab and nivolumab in ultra-rare cancers, including small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). The purpose of the study was to evaluate the potential clinical benefit of ipilimumab and nivolumab in patients with SCCOHT.

Methods: DART was a prospective, open-labeled, multicenter (>1,000 US sites), multi-cohort phase II clinical trial of intravenous administration of ipilimumab (1 mg/kg, every 6 weeks) plus nivolumab (240 mg, every 2 weeks). The primary endpoint was overall response rate [ORR, confirmed complete response (CR) and partial response (PR)] per RECIST. Secondary endpoints included progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR; overall response plus stable disease ≥6 months), and toxicity. Immune responses were also evaluated.

Results: Six patients (median age, 30.5 years; median, 2 prior therapies; no prior immunotherapy exposure) with advanced/metastatic SCCOHT were evaluable. ORR and CBR were both 16.7% (1/6) with one patient having a confirmed CR lasting 46.2+ months. However, another patient had a confirmed immune CR (iCR) with immune PFS (iPFS) of 53+ months [ORR/iORR, 33.3% (2/6)]. Notably, the latter patient had a progressing lesion at 24 weeks after initial response, but with renewed regression with ongoing therapy, suggesting delayed pseudo-progression. At 12-months, 3 patients remained alive. Median PFS was 1.4 months (range, 0.9 months-not reached); median OS was 14.2 months (2 months-not reached). No adverse events caused treatment discontinuation.

Conclusion: Two of 6 patients (33.3%) with SCCOHT achieved durable CR/iCR and long-term survival with ipilimumab plus nivolumab. Correlative studies to determine response and resistance markers are ongoing.

Clinicaltrials.Gov Registry: NCT02834013

KEYWORDS
DART, ipilimumab, nivolumab, rare tumors, S1609, small cell carcinoma of the ovary hypercalcemic type

1 | BACKGROUND

Small cell ovarian carcinoma of hypercalcemic type (SCCOHT) is an extremely rare and highly aggressive malignancy, comprising less than 0.01% of all ovarian neoplasms [1, 2]. It affects young women, with a mean age of 24, and there have been fewer than 500 reported cases to date. The majority of SCCOHT tumors (over 95%) are driven by inactivating germline and somatic mutations of the switch/sucrase non-fermentable-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4 (*SMARCA4*) gene [3–6]. This gene encodes the Brama-regulate gene 1 (*BRG1)* protein, a core ATPase subunit of the switch/sucrose non-fermentable (*SWI/SNF*) chromatin remodeling complex that is crucial in DNA damage repair pathways.

Given the rarity of the disease and the lack of prospective studies, there is currently no agreed-upon standard of care, resulting in varied management strategies. Nonetheless, prior treatment recommendations based on small case series have suggested that primary cytoreductive surgery, similar to that used for epithelial ovarian cancer, and a multimodal approach involving multi-agent chemotherapy and/or radiotherapy may be appropriate for patients with SCCOHT [7–10]. SCCOHT has a poor prognosis under the current standard of care, with the mean overall survival (OS) declining from 35 months for stage I disease to 3.3 months for stage IV disease [1, 9, 11–13]. Despite an initial positive response to chemotherapy, recurrence is frequently observed in up to 75% of cases [11, 12]. Moreover, subsequent chemotherapy typically has limited effectiveness, with an average period of 15.7 months

elapsing between recurrence and tumor-associated death[12].

Preclinical studies have proposed innovative therapeutic approaches that focus on kinases and take advantage of synthetic lethal interactions that arise due to SMARCA4 loss [6, 14–21]. However, these strategies are yet to be translated into human treatments. Several studies suggest that SMARCA4 and other chromatin remodeling gene alterations in SCCOHTs may enhance their sensitivity to immune checkpoint blockade [22, 23]. Furthermore, an immune-active environment has been reported in SCCOHT as having anecdotal responses to anti-PD1 therapy [24].

Dual checkpoint inhibition with anti-programmed death-1 (PD-1) and anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitors has demonstrated efficacy in many malignancies [25] and has shown anecdotal evidence in SCCOHT. Our prospective Southwest Oncology Group (SWOG) S1609 Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors (DART) trial was conducted to evaluate whether ipilimumab-nivolumab combination therapy could induce responses in this ultra-rare cancer cohort.

2 | PATIENTS AND METHODS

2.1 | Trial oversight

This trial was carried out across 1,084 sites throughout the United States under the guidance of the Early Therapeutics and Rare Cancer Committee of the SWOG Cancer Research Network/National Cancer Institute (NCI, Bethesda, MD, USA). The original protocol and any modifications underwent scrutiny and received approval from SWOG, the NCI Central Institutional Review Board, and the regulatory committees of participating institutions. Nivolumab (MA5-41974) and ipilimumab (MA5-41799) agents used in the trial were provided through the Cancer Therapy Evaluation Program of the NCI under the NCI Collaborative agreement with Bristol Myers Squibb (Princeton, NJ, USA). Each participant in the study willingly provided a written informed consent document, which was duly approved by the human subject protection committee of each participating institution.

2.2 | Rationale for included study population

This basket trial incorporated patients with rare and ultra-rare tumors for which no active clinical trial evaluating dual immune checkpoint inhibitors is in progress. Rare cancers were specified as those with an occurrence of fewer than 6 in every 100,000 individuals per annum [26]. The participating institution's pathologists or local pathologists, with the pathology reports examined by the principal investigators of the study, reviewed tumor pathology and grade. Tumor types were classified based on the World Health Organization (WHO) Classification of Female Genital Tumours, 5th Edition's criteria [27]. There was no execution of a centralized pathology review. This paper encapsulates the results obtained from the SCCOHT, which was designated cohort 49 of the basket trial.

2.3 | Inclusion criteria and patient selection

The trial included eligible patients who had a pathologically confirmed SCCOHT diagnosis through histological tests and had experienced disease progression following at least one round of standard systemic therapy or had no other available treatment options associated with prolonged OS. Initial categorization of patients was at the site primary investigator's discretion. They were later reassessed and sometimes recategorized upon study closure by the study authors, based on pathology reports and clinical history. At enrollment, patients were required to be at least 18 years of age, possess a Zubrod performance status of 0-2, and exhibit adequate hematologic, hepatic, thyroid, adrenal axis, and renal function [specifically an absolute neutrophil count of $\geq$ 1,000/μL, platelets of $\geq$ 75,000/μL, hemoglobin of $\geq$ 8 g/dL, creatinine clearance of $\geq$ 50 mL/min, total bilirubin of $\leq$ 2.0 × institutional upper limit of normal (IULN), AST and ALT of $\leq$ 3.0 × IULN, thyroid stimulating hormone (TSH) or free T4 serum $\leq$ IULN, and normal adrenocorticotropic hormone (ACTH)]. Enrollees were mandated to utilize adequate birth control throughout the protocol, and a negative serum pregnancy test was required for all women of childbearing potential at enrollment.

2.4 | Treatment and monitoring

Patients underwent intravenous administration of nivolumab (240 mg) every two weeks and ipilimumab (1 mg/kg) every six weeks on a consistent schedule [28]. Dose modifications and brief therapy interruptions for treatment-related toxicities were carried out in accordance with the guidelines outlined in Sections 8.0 and 18.4 of the protocol (Supplementary file of protocol). Removal from protocol treatment was due to reasons such as disease progression, symptomatic deterioration, any cause of treatment delay for >56 days, intolerable or immune-related toxicity with the inability to reduce prednisone to <10 mg daily, or at the patient's request.

At the start of each cycle (or at least every six weeks), patients underwent an evaluation with a history and physical, laboratory analyses (complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, free thyroxine, ACTH, cortisol, lipase), and toxicity assessment. Dose modifications for the management of immune-related adverse events (irAEs) were done based on specific guidance criteria in the protocol. Tumor size was measured with computed tomography or magnetic resonance imaging scan (whole body scan required for non-target lesions) before the study, week 8, week 16, week 24, and then every 12 weeks until progression.

2.5 | Statistical methods and outcomes

This phase II trial was conducted with the primary endpoint of assessing the objective response rate [ORR, confirmed complete and partial responses (CR and PR, respectively)] per investigator by RECIST v1.1 criteria, powered to distinguish a genuine ORR of 5% (null hypothesis) versus 30% (alternative hypothesis). A two-stage design was used wherein the first six eligible patients to undergo protocol therapy were examined in the first stage. If one or more of the first six patients had a confirmed CR or PR, an additional 10 patients were to be added. Two or more patients with a confirmed CR or PR out of 16 patients was considered evidence of activity (87% power, one-sided alpha = 13%).

Secondary objectives included progression-free survival (PFS) per RECISTv1.1, OS, clinical benefit rate [CBR; stable disease (SD) ≥ 6 months plus ORR], ORR per immune-related RECIST (iRECIST), PFS per iRECIST (iPFS), and toxicity assessment. PFS was measured from the first day of treatment initiation to the time of progression or death due to any cause, with patients last known to be alive without progression censored at the date of last contact. OS was calculated from the date when the participant registered to the trial 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 were estimated using the Kaplan-Meier method, medians were calculated using the Brookmeyer and Crowley method [29]. Point estimate confidence intervals (CIs) (for example, 6-month PFS) were computed using the log-log transformation. All analyses were executed using R version 4.3.3 (https://cran.r-project.org).

3 | RESULTS

3.1 | Patient characteristics

Patients were enrolled into the S1609 study from January 2017 to March 2023, and the maximum length of time a single patient was followed up on was 5 years. Six patients were enrolled in the advanced/metastatic SCCOHT cohort from 4 of 1,084 participating National Clinical Trial Network institutions (Supplementary Figure S1). All patients met the eligibility criteria, received treatment as per the study protocol, and were included in the analysis (Table 1, Supplementary Table S1). The median age of the patients was 30.5 years, with an age range of 25 to 39 years. The number of prior therapies ranged from 0 to 3. No patients had received prior immunotherapy or radiotherapy.

TABLE 1 Demographics and RECIST best response summary of six evaluable patients with small cell carcinoma of the ovary, hypercalcemic type treated on the DART immunotherapy protocol (nivolumab plus ipilimumab).

Variable	SCCOHT cohort
Performance status [cases (%)]	
0	4 (66.7)
1	1 (16.7)
2	1 (16.7)
Ethnicity [cases (%)]	
Hispanic	2 (33.3)
Not Hispanic	4 (66.7)
Race [cases (%)]	
White	3 (50.0)
Black	1 (16.7)
Asian	1 (16.7)
Unknown	1 (16.7)
Response [cases (%)]	
Confirmed CR	1 (16.7)
Unconfirmed PR	1 (16.7)
Number of prior lines of systemic therapy	2 (0-3)
Prior surgery [cases (%)]	6 (100)
FIGO stage [cases (%)]	
I	3 (50.0)
III	3 (50.0)

Abbreviations: CR, complete response; FIGO: International Federation of Gynecology and Obstetrics; PR, partial response.

3.2 | Outcomes

Of the 6 patients assessed, the ORR and CBR were both 16.7% (1/6). However, the ORR and iORR combined was 33.3% (2/6). The best response observed was a confirmed CR with a PFS of more than 46.2+ months (Table 1, Figures 1–2). Another patient initially showed an unconfirmed PR with an 80.6% regression, followed by a brief increase in lesion size at week 24; immunotherapy was continued and the lesion size decreased subsequently, resulting in a confirmed immune complete response (iCR)

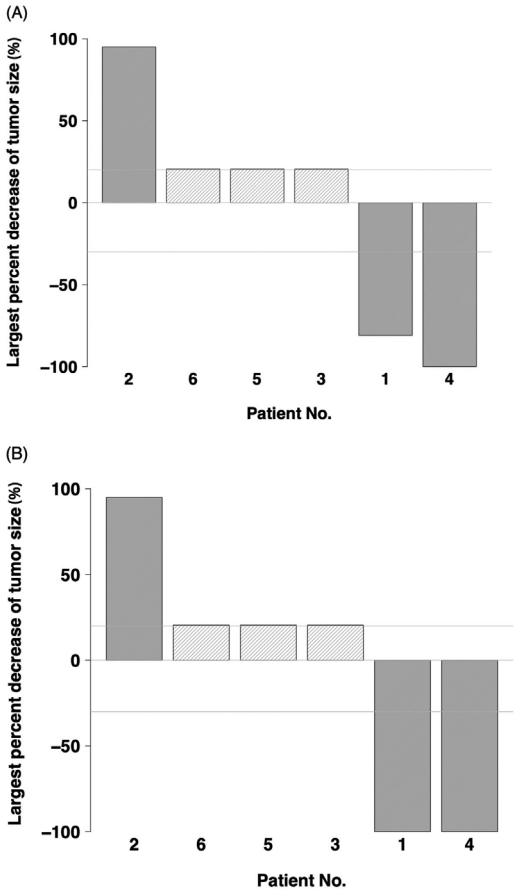

FIGURE 1 Waterfall plots indicating largest percent decrease in baseline tumor size of SCCOHT following protocol therapy (ipilimumab plus nivolumab) according to RECIST v1.1 (A) and iRECIST (B). Bars below the line indicate regressing disease; above the line, enlarging disease. Crosshatch indicates participants did not have tumor measurements available due to new lesions at first scan ($n = 1$), symptomatic deterioration ($n = 1$), and no data submitted to date ($n = 1$). (B) The patient with iCR had <100% regression because of lymph node <1.0 cm. Change in tumor size was calculated as (1 - tumor size after immunotherapy / tumor size before immunotherapy) × 100%. Abbreviations: iCR, immune complete response; iRECIST, immune response evaluation criteria in solid tumors; RECIST, response evaluation criteria in solid tumors; SCCOHT, small cell carcinoma of the ovary, hypercalcemic type.

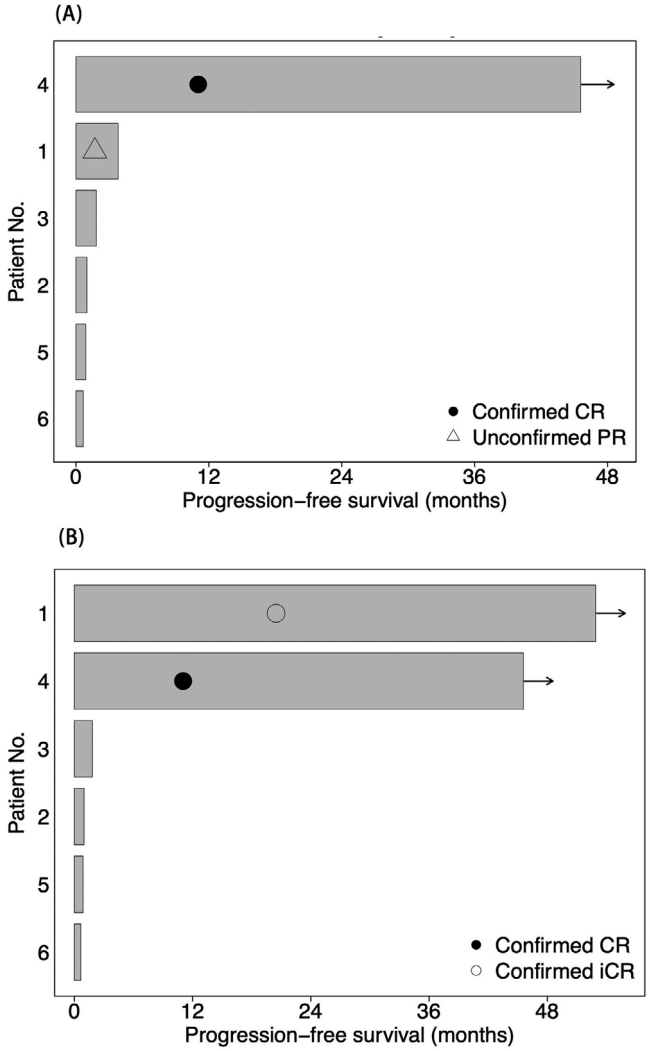

FIGURE 2 Swimmer's plots of progression-free survival of patients with SCCOHT following protocol therapy (ipilimumab plus nivolumab) according to RECIST v1.1 (A) and iRECIST (B). Bars indicate PFS per individual patient. Abbreviations: CR, complete response; iCR, immune-related complete response; iPFS, immune-related progression-free survival; iPR, immune-related partial response; iRECIST, immune response evaluation criteria in solid tumors; PFS, progression-free survival; PR, partial response; RECIST, response evaluation criteria in solid tumors; SCCOHT, small cell carcinoma of the ovary, hypercalcemic type.

by iRECIST around 24 months after start of therapy, with an ongoing iPFS of 52.9+ months (Figures 2–3). At the 12-month mark, 3 patients were still alive, and 1 had not experienced disease progression. The overall median PFS was 1.4 months (95% CI 0.9 month-not reached), with the 6-month PFS rate being the same as the 12-month PFS at 16.7% (95% CI 2.8%-99.7%) (Figure 4A). iPFS showed the same trend (Figure 4B). The median OS was 14.2 months (95% CI 2.0 months-not reached), with the 6-month OS rate being the same as the 12-month OS at 50.0% (95% CI 22.5%-100.0%) (Figure 4C).

3.3 | Adverse events (AEs)

Overall, 4 (66.7%) of the 6 patients experienced AEs of any grade that may be attributed to the treatment (Table 2); 2 (33.3%) had a grade 3-4 AE. The most frequent AEs included fatigue, nausea, pruritus, dry mouth, maculopapular rash, and elevation of aspartate aminotransferase (33.3%, 2/6 each). There were two instances (33.3%, 2/6) of grade 3-4 AEs at least possibly treatment-related. No AEs

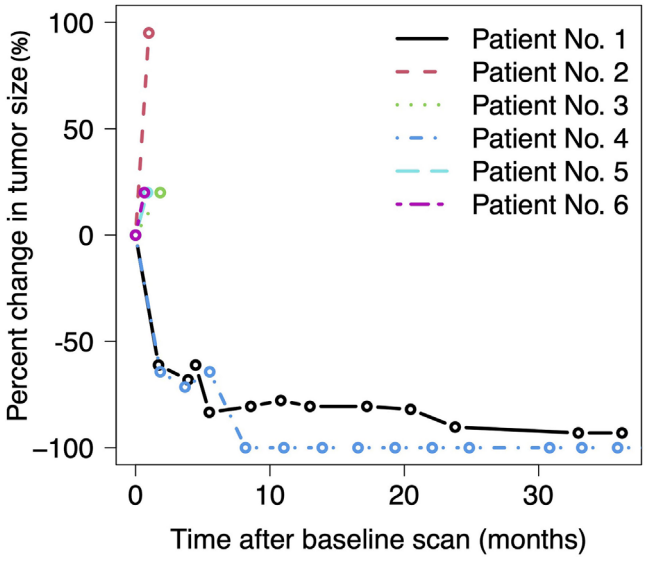

FIGURE 3 Spider plot of tumor response in patients with SCCOHT following protocol therapy (ipilimumab plus nivolumab). Two durable responses among six patients with small cell carcinoma of the ovary, hypercalcemic type. Red indicates delayed pseudoprogression (*) characterized by lesion enlargement at 24 weeks following the initial response, which is then followed by complete regression under continuous therapy (plot demonstrates <100% regression because of lymph node <1.0 cm). Abbreviations: SCCOHT, small cell carcinoma of the ovary, hypercalcemic type.

caused treatment discontinuation or death. No serious or grade 5 AEs occurred.

Three patients had immune-related AEs. The most common immune-related AEs were pruritus, maculo-papular rash, and aspartate aminotransferase elevation (33.3%, 2/6 each). One (16.7%) patient was reported to have a grade 3-4 immune-related AE.

4 | DISCUSSION

Our phase II study utilized an open-label, multicenter, multi-cohort design to evaluate the efficacy of a combination immunotherapy approach, comprising ipilimumab and nivolumab, in the treatment of SCCOHT. Among the 6 patients assessed, both the ORR and CBR were 16.7% (1 out of 6). One patient achieved a durable confirmed CR lasting over 3 years, and another patient, initially with an unconfirmed PR, eventually had a confirmed iCR. Therefore, the CR and iCR rate combined was 33.3% (2/6), and both of these responses are ongoing with an PFS/iPFS of 46.2+ and 53+ months from therapy initiation. The combination therapy showed a manageable AE profile that was similar to other studies with nivolumab and ipilimumab [30–34].

Of interest, the patient who achieved an iCR (53+ months iPFS) displayed delayed pseudoprogression, with initial 81% regression followed by lesion size increasing at 24 weeks post-response, then substantially regressing upon continued therapy (ipilimumab was discontinued due to weight loss, but nivolumab was continued).

This mirrors the experience of a 78-year-old patient with metastatic lung adenocarcinoma treated with nivolumab, detailed in a case report, where apparent tumor growth after 15 cycles was later identified as pseudoprogression through biopsy findings of necrotic and inflammatory tissue without malignancy [35]. These cases highlight the critical role of biopsy in distinguishing true progression from pseudoprogression in immunotherapy, even in the delayed setting, emphasizing the potential for continued treatment in cases of suspected pseudoprogression.

Large-scale prospective cohort studies have not yet established the clinical benefits of immunotherapy in SCCOHT, and the available evidence is limited to

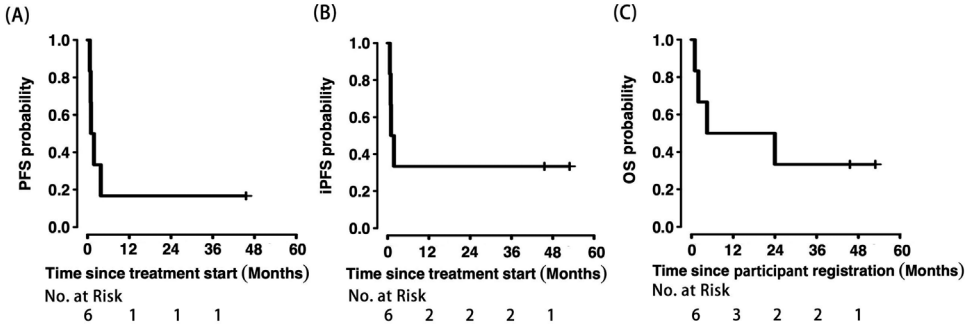

FIGURE 4 PFS and OS of patients with SCCOHT following protocol therapy (ipilimumab plus nivolumab). (A) RECIST v1.1-based PFS. (B) iRECIST-based iPFS. (C) OS. Abbreviations: iPFS, immune progression-free survival; iRECIST, immune response evaluation criteria in solid tumors; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors; SCCOHT, small cell carcinoma of the ovary, hypercalcemic type.

TABLE 2 Potential treatment-related adverse events of 6 evaluable patients with small cell carcinoma of the ovary, hypercalcemic type treated on the DART immunotherapy protocol (nivolumab plus ipilimumab)[a].

Adverse event	Any grade	Grade 3-4
Any	**4 (66.7%)**	**2 (33.3%)**
Occurred in >10% of patients		
Symptom/condition		
Dry mouth	2 (33.3%)	0 (0.0%)
Fatigue	2 (33.3%)	1 (16.7%)
Nausea	2 (33.3%)	0 (0.0%)
Pruritus	2 (33.3%)	0 (0.0%)
Maculo-papular rash	2 (33.3%)	0 (0.0%)
Weight loss	1 (16.7%)	1 (16.7%)
Abdominal pain	1 (16.7%)	0 (0.0%)
Adrenal insufficiency	1 (16.7%)	0 (0.0%)
Alopecia	1 (16.7%)	0 (0.0%)
Anemia	1 (16.7%)	0 (0.0%)
Anorexia	1 (16.7%)	0 (0.0%)
Arthralgia	1 (16.7%)	0 (0.0%)
Back pain	1 (16.7%)	0 (0.0%)
Chills	1 (16.7%)	0 (0.0%)
Cognitive disturbance	1 (16.7%)	0 (0.0%)
Dehydration	1 (16.7%)	0 (0.0%)
Diarrhea	1 (16.7%)	0 (0.0%)
Dizziness	1 (16.7%)	0 (0.0%)
Erythema hands and feet	1 (16.7%)	0 (0.0%)
Erythema multiforme	1 (16.7%)	0 (0.0%)
Fever	1 (16.7%)	0 (0.0%)
Headache	1 (16.7%)	0 (0.0%)
Hypothyroidism	1 (16.7%)	0 (0.0%)
Left neck cyst	1 (16.7%)	0 (0.0%)
Mucositis oral	1 (16.7%)	0 (0.0%)
Myalgia	1 (16.7%)	0 (0.0%)
Neck pain	1 (16.7%)	0 (0.0%)
Oral candidiasis	1 (16.7%)	0 (0.0%)
Peripheral motor neuropathy	1 (16.7%)	0 (0.0%)
Peripheral sensory neuropathy	1 (16.7%)	0 (0.0%)
Skin hypopigmentation	1 (16.7%)	0 (0.0%)
Vomiting	1 (16.7%)	0 (0.0%)
Laboratory abnormality		
Aspartate aminotransferase increased	2 (33.3%)	1 (16.7%)
Alanine aminotransferase increased	1 (16.7%)	0 (0.0%)
Auto monocyte percent high	1 (16.7%)	0 (0.0%)
Basophil percent high	1 (16.7%)	0 (0.0%)
BUN/creatinine ratio high	1 (16.7%)	0 (0.0%)
Chloride high	1 (16.7%)	0 (0.0%)
Chloride low	1 (16.7%)	0 (0.0%)
CO2/carbon dioxide low	1 (16.7%)	0 (0.0%)
Eosinophil count increased	1 (16.7%)	0 (0.0%)
Globulin level high	1 (16.7%)	0 (0.0%)
Globulin level low	1 (16.7%)	0 (0.0%)
Hypokalemia	1 (16.7%)	0 (0.0%)
Hypomagnesemia	1 (16.7%)	0 (0.0%)
Lymphocyte count decreased	1 (16.7%)	0 (0.0%)
Monocyte count increased	1 (16.7%)	0 (0.0%)
Neutrophil count decreased	1 (16.7%)	0 (0.0%)
Neutrophil percent low	1 (16.7%)	0 (0.0%)
Osmolality low	1 (16.7%)	0 (0.0%)
Platelet count decreased	1 (16.7%)	0 (0.0%)
Total bilirubin decreased	1 (16.7%)	0 (0.0%)
Total protein decreased	1 (16.7%)	0 (0.0%)
Total protein increased	1 (16.7%)	0 (0.0%)
Vitamin D, 25 hydroxy low	1 (16.7%)	0 (0.0%)
White blood cell decreased	1 (16.7%)	0 (0.0%)
Immune-mediated	**3 (50.0%)**	**1 (16.7%)**
Maculo-papular rash	2 (33.3%)	0 (0.0%)
Pruritus	2 (33.3%)	0 (0.0%)
Adrenal insufficiency	1 (16.7%)	0 (0.0%)
Arthralgia	1 (16.7%)	0 (0.0%)
Diarrhea	1 (16.7%)	0 (0.0%)
Hyperthyroidism	1 (16.7%)	0 (0.0%)
Hypothyroidism	1 (16.7%)	0 (0.0%)
Aspartate aminotransferase increased	2 (33.3%)	1 (16.7%)
Alanine aminotransferase increased	1 (16.7%)	0 (0.0%)

[a]Some patients experienced more than one adverse event.

anecdotal case reports. A study aiming to associate program death-ligand 1 (*PD-L1*) expression levels with response to immunotherapy described one patient with a combined positive score of 15 primarily in tumor cells achieving CR after four cycles of ipilimumab-nivolumab, while two patients with minimal PD-L1 expression had disease progression on pembrolizumab [36]. In two other cases, combining immunotherapy with targeted therapy resulted in positive responses. In a case report, a patient with SMARCA4-deficient SCCOHT achieved a two-month CR with ipilimumab-nivolumab, but experienced recurrence during nivolumab maintenance and eventual progression after rechallenge with the same therapy; however, the patient showed a response to combination therapy with nivolumab and a cyclin-dependent kinases 4 and 6 inhibitor, abemaciclib, and continued response after four months [37]. In another case, the combination of a vascular endothelial growth factor receptor 2 inhibitor, apatinib, and a *PD-1* inhibitor, camrelizumab, achieved a

durable PR for 28 months [38]. Nonetheless, the specific contributions of each agent to the efficacy of the combined immunotherapy-targeted therapy regimen remain uncertain.

As monotherapy, PD-1 immune checkpoint therapy showed favorable responses in treating SCCOHT. For instance, one patient with refractory SCCOHT achieved durable CR for over three years with nivolumab [39]. In a separate group of four patients, one patient had a sustained PR for six months after pembrolizumab, and three patients remained disease-free for at least 1.5 years after receiving nivolumab; all three patients had previously undergone radiation therapy, which may have enhanced their antitumor immune response [24, 40–42]. On the other hand, a pembrolizumab phase II basket trial reported disease progression in all four patients with advanced or recurrent SCCOHT who received pembrolizumab [43]. Ongoing trials are evaluating pembrolizumab monotherapy as consolidation therapy (NCT05368207) or in combination with etoposide-cisplatin-based chemotherapy as first-line therapy (NCT04602377) for SCCOHT.

SCCOHT is characterized by a low mutation load (<6 mutations per megabase of genome), genomic stability with few somatic copy number alterations (7/8 tumors analyzed), and significant inter- and intra-tumor homogeneity [5, 44–46]. However, one study showed a promising tumor immune landscape in SCCOHT ($n = 4$), with *PD-L1* expression in both tumor cells and stromal cells and infiltration of T cells and CD68+ macrophages; *PD-L1* expression was significantly associated with T-cell infiltration, and *PD-L1*-high tumors had increased expression of genes related to *Th1* and cytotoxic cell function [24]. These findings suggest that SCCOHT may resemble other immunogenic tumors. The sensitivity to immunotherapy in this cancer type may also be affected by the loss of *SWI/SNF* components, as evidenced by studies in patients with *SWI/SNF*-mutant clear cell renal carcinoma ($P = 0.01$) and NSCLC ($P = 0.01$) [22, 23, 47–49].

The DART study has so far found activity in a range of rare and ultra-rare tumor forms, including angiosarcoma ($n = 16$, ORR 25%, 6-month PFS 38% (20-71%), median OS not reached), nonpancreatic neuroendocrine tumors [$n = 32$, ORR 25% (44% in high-grade disease), 6-month PFS 31%, median OS 11 months], high-grade neuroendocrine tumors ($n = 19$, ORR 26%, 6-month PFS 32%, median OS 8.7 months), metaplastic breast cancer ($n = 17$, ORR 18%, 6-month PFS 18%, median OS 12 months), gestational trophoblastic neoplasia ($n = 4$, ORR 75%, 6-month PFS 75%, median OS not reached), and gallbladder cancer ($n = 19$, ORR 16%, 6-month PFS 26%, median OS 7.0 months) [30–34, 50]. Our study was able to overcome the challenges of studying rare cancers by leveraging a network of more than 1000 academic and community sites, with support from organizations such as the NCI, SWOG, and patient advocacy groups. This allowed us to enroll patients with a diverse range of tumor types, resulting in a comprehensive and impactful study. However, the study has limitations, including small sample size, lack of comparison with usual care through a randomized design, reliance on local site assessments, lack of *SMARCA4* gene mutation data, lack of *PD-1/PD*-L1 expression data, lack of scan images before and after treatment for the participants who achieved CR and CRi, and lack of patients' biomarker data for subgroup analysis. The NCI mandated the study close to accrual in March 2023 regardless of whether accrual to cohorts was complete. As this cancer is extremely rare, accrual was slow enough that even though the cohort met criteria to continue to up to 16 patients at the time the trial was closed to accrual, the cohort had only accrued 6 patients.

5 | CONCLUSIONS

SMARCA4-altered cancers such as SCCOHT can show durable responses lasting for years after dual immunotherapy. In addition to pseudoprogression early on in the course of immunotherapy, delayed psseudoprogression can occur; patients with delayed pseudoprogression can have renewed responses durable for years, with continued therapy. Translational biomarkers of response, resistance, and pseudoprogression are needed to better understand response and resistance after single-agent versus dual immunotherapy in SCCOHT.

AUTHOR CONTRIBUTIONS

YKC, SPP, and RK contributed to Conceptualization, Methodology, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing, Supervision, Funding acquisition. MO contributed to Conceptualization, Methodology, Software, Formal analysis, Resources, Data Curation, Visualization, Writing - Original Draft, Writing - Review & Editing. RA, KW, TP, ST, and WR contributed to Investigation, Writing - Review & Editing. HK and LC contributed to Data Curation, Writing - Original Draft, Writing - Review & Editing. CM, HC, ES, HS, CR, CB contributed to Resources, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The deidentified participant data generated in this study are available upon request from the following instructions according to SWOG policy: https://www.swog.org/sites/default/files/docs/2019-12/Policy43_0.pdf

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The original protocol and any modifications underwent thorough review and approval by SWOG, the NCI Central Institutional Review Board (No. 0925-0753), as well as the regulatory committees of participating institutions. Each participant in the study provided their informed consent in writing, voluntarily, and the consent document was approved by the human subject protection committee of each participating institution.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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