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Phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART) SWOG S1609: the desmoid tumors

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ABSTRACT

Background Dual inhibition using anti-programmed death-1 (PD-1) and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) checkpoint inhibitors has proven effective in many cancers. However, its efficacy in rare solid cancers remains unclear. Desmoid tumors are ultrarare soft-tissue tumors, traditionally treated with surgery. This study reviews the first results of using ipilimumab and nivolumab in the desmoid tumor cohort of the SWOG S1609 Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors (DART) trial.

Methods DART is a prospective/open-label/multicenter (1,016 US sites)/multicohort phase II trial of ipilimumab (1 mg/kg intravenously every 6 weeks) plus nivolumab (240 mg intravenously every 2 weeks) that opened at 1,016 US sites. The primary endpoint included overall response rate (ORR) defined as confirmed complete (CR) and partial responses (PR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1. Secondary endpoints include progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR; stable disease (SD) ≥6 months plus CR and PR) and toxicity.

Results Sixteen evaluable patients (median age: 37) with desmoid tumors and a median of 1.5 prior therapies (with no prior exposure to immunotherapy) were analyzed. The tumors varied in location (eight abdomen, three lower limb, two upper limb, two pelvis, and one neck). ORR was 18.8% (3/16; 3 confirmed PR): 40% regression (PFS 30+ months), 83% regression (PFS 16 months) and 71% regression (PFS 8.4 months). Seven additional patients (43.8%) had prolonged SD over 6 months (PFS: 16.5, 22.4+, 22.6, 30.1, 38.2+, 48.3+ and 60.7+ months). Overall CBR was 62.5% (10/16). Median PFS was 19.4 months, with 6-month PFS of 73% and 1-year PFS of 67%. All patients were alive at 1 year; median OS was not assessable, as 13 patients were alive at analysis. Common adverse events included fatigue, nausea and hypothyroidism, with 50% experiencing grade 3–4 events. There were no grade 5 events.

Conclusion Treatment with ipilimumab and nivolumab in desmoid tumors yielded an ORR of 18.8% and a CBR of 62.5% with durable responses seen. This is the first prospective study exploring the efficacy of this combination in this rare disease. Ongoing studies aim to identify markers for response and resistance. Expanded trials are necessary.

Trial registration number NCT02834013.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Dual inhibition using anti-programmed death-1 (PD-1) and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) checkpoint inhibitors has proven effective in many cancers.

WHAT THIS STUDY ADDS

⇒ The SWOG Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors S1609 study is the first to evaluate ipilimumab and nivolumab in rare tumors, including desmoid tumors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study demonstrated promising results in desmoid tumors (3 partial responses (8.4 to 30+ months) plus 7 durable stable diseases (16.5 to 60.7+ months)) with ongoing studies aimed to identify markers for response and resistance.

INTRODUCTION

Desmoid tumors are an ultrarare type of neoplasm that originates from monoclonal fibroblast proliferation; their incidence rate is 5–6 cases per 1 million individuals per annum, peaking between the ages of 30–40 years.[1 2] While most desmoid tumors arise sporadically, up to 15% of cases are associated with familial adenomatous polyposis (FAP).[3–5] Desmoid tumors are caused by somatic mutations in the CTNNB1 (β-catenin) gene in sporadic cases, but those with FAP have germline mutations in the APC gene, which encodes a protein-regulating

β-catenin levels and confers a 1000-fold increased risk of developing desmoid tumors.[6–9]

While desmoid tumors are not characterized by metastatic potential, their locally invasive behavior can manifest in a range of complications, including intense pain, edema, anatomical deformities, diminished joint mobility, gastrointestinal obstructions or perforations, impairment of vital organs and, in severe instances, mortality.[10] The highest mortality rates, reaching up to 11%, are observed among patients presenting with intra-abdominal tumors, particularly in cases associated with FAP.[11]

Over the past few decades, there has been a significant shift in the treatment approach for desmoid tumors, moving away from aggressive surgery towards a more conservative strategy. Current guidelines now advocate for active surveillance as the preferred course of action, which has shown a 3-year treatment-free survival rate of 65.9%.[6 12 13] In fact, studies indicate that 20%–30% of patients with sporadic desmoid tumors may experience spontaneous regression.[14–16] As a result, surgery is now reserved for carefully selected cases due to the high risk of recurrence and potential complications associated with it.

Systemic therapy is indicated in cases of unresectable tumors, locoregional recurrences, symptomatic tumors with high surgical risk, and initial non-surgical treatment of growing tumors in patients with FAP.[17 18] The response rates to treatments, such as non-steroidal anti-inflammatory drugs, hormonal therapy, tyrosine kinase inhibitors, and chemotherapy, vary significantly.[19] Sorafenib and nirogacestat are approved for adult patients with progressing disease, though questions remain about its tolerability, long-term resistance and inconsistent efficacy.[6 20–22]

As dual inhibition with anti-programmed death-1 (PD-1) and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitors (ICIs) has been found to be efficacious in many malignancies, this study evaluated its role in desmoid tumors.[23] We present the first results of ipilimumab and nivolumab used in the desmoid tumor cohort of the SWOG S1609 Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors (DART) trial.

PATIENTS AND METHODS

This trial was carried out at 1,016 locations across the USA with the supervision of the Early Therapeutics and Rare Cancer Committee of the SWOG Cancer Research Network/National Cancer Institute (NCI). Nivolumab and ipilimumab agents were provided through the Cancer Therapy Evaluation Program of the NCI, under the NCI Cooperative Research and Development Agreement (CRADA) with Bristol Myers Squibb. Each participant in the study willingly provided written informed consent on a document which had been approved by the CIRB and human subject protection committee of each participating institution.

Rationale for included study population

This trial aimed to include patients with rare and ultrarare tumors that had no ongoing clinical trials investigating the use of dual ICIs. Rare cancers were defined as malignancies with an incidence of less than 6 in 100,000 per year.[24] The assessment of tumor pathology and grade was carried out by pathologists from the participating institutions or local pathologists, with the study principal investigators reviewing the pathology reports. Tumor types were classified based on criteria outlined in the WHO Classification of Soft Tissue and Bone Tumors, 5th Edition.[25] However, there was no central pathology review conducted. The results presented in this paper are from the desmoid tumor cohort 27 of the DART trial.

Inclusion criteria and patient selection

For this trial, patients were eligible for inclusion if they had a histologically confirmed desmoid tumor and either had no other treatment options known to improve overall survival (OS), declined available treatments, or had contraindications to them. Since the NCCN recommends that participation in a clinical trial is the best approach for managing any cancer patient, this trial is consistent with their guidelines. Patients who cannot receive other standard therapy that has been shown to prolong survival due to medical issues (or if no standard treatment exists that has been shown to prolong survival) will be eligible, if other eligibility criteria are met. Initially, patients were categorized by the site primary investigator. However, at the time of study closure, the study authors reviewed and, in some cases, recategorized patients based on pathology reports and clinical history. To be enrolled, patients needed to be at least 18 years old, have a Zubrod performance status ranging from 0 to 2, and exhibit adequate hematological, hepatic, thyroid, adrenal axis, and renal function (absolute neutrophil count ≥1,000/µL, platelets ≥75,000/µL, hemoglobin ≥8 g/dL, creatinine clearance ≥50 mL/min, total bilirubin ≤2.0× institutional upper limit of normal (IULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0× IULN, thyroid-stimulating hormone or free T4 serum ≤IULN, and normal adrenocorticotropic hormone). Adequate contraception was required during the study, and participants of childbearing potential had to provide a negative serum pregnancy test on enrollment.

Treatment and monitoring

Patients received treatment consisting of nivolumab (240 mg intravenously) every 2 weeks and ipilimumab (1 mg/kg intravenously) every 6 weeks on an ongoing schedule.[26] The protocol allowed for dose adjustments and temporary treatment breaks to manage treatment-related toxicities. Patients were removed from protocol treatment if they experienced disease progression, symptomatic deterioration, treatment delays exceeding 56 days for any reason, inability to reduce prednisone dosage to less than 10 mg daily due to unacceptable or immune-related toxicity, or on patient request. Throughout

the study, patients underwent regular evaluations (at the beginning of each cycle or at least every 6 weeks) including history and physical examinations, laboratory analyses, and toxicity assessments. Dose modifications for management of immune-related adverse events were made according to specific guidance criteria provided. Imaging studies were conducted at specific intervals (prestudy, week 8, week 16, week 24, and then every 12 weeks until progression) to assess disease burden.

Statistical methods and outcomes

The primary endpoint was overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 criteria per investigator. The study was powered to distinguish a null hypothesis of a 5% ORR against an alternative hypothesis of a 30% ORR. A two-stage design was used. If one or more of the first 6 eligible patients had a confirmed CR or PR, an additional 10 patients were to be enrolled. Two or more patients with a confirmed CR or PR of 16 were considered evidence of activity (87% power, one-sided alpha=13%).

Secondary objectives included measuring progression-free survival (PFS) per RECIST v.1.1, OS, clinical benefit rate (CBR), ORR per immune-related RECIST (iRECIST), PFS per iRECIST (iPFS), and toxicity assessment. PFS (measured from the first day of protocol therapy to the time of progression or death by any cause, with patients last known to be alive without progression censored at the date of last contact) and OS (measured from the date of protocol registration to the date of death by any cause, with patients last known to be alive censored at the date of last contact) were estimated using the Kaplan-Meier method, with medians determined using the Brookmeyer and Crowley method.[27] Confidence intervals (CI) for estimates, such as 6-month PFS, were computed using the log–log transformation. Statistical analyses were performed using R v.4.3.3.

RESULTS

Patient characteristics

From January 2017 to March 2023, the S1609 study enrolled patients, with the longest duration of monitoring a single patient being 5 years. Cohort 27 enrolled 16 patients with desmoid tumors from 11 of the 1,016 participating National Clinical Trial Network institutions. The primary tumor sites were as follows: soft tissue (n=8, 50%), small intestine (n=2, 12%), mesentery (n=2, 12%), rectum (n=1, 6%), skeleton (n=1, 6%), thyroid (n=1, 6%), and left medial masticator, pharyngeal mucosal, and submandibular spaces (n=1, 6%). All 16 patients met the eligibility criteria, received treatment according to the protocol, and were included in the analyses (table 1, online supplemental table 1). The median age was 37 years (range, 20–82 years), and 25% of the patients were male (table 1). The median number of prior therapies was 1.5 (range, 0–5), with no prior exposure to PD-1 inhibitor monotherapy.

Table 1 Demographics and RECIST best response summary of 16 evaluable patients with desmoid tumors treated on the DART immunotherapy protocol (nivolumab plus ipilimumab)

Desmoid tumor (n=16)	N (%)
Age (years) (median (range))	37 (20, 82)
Sex	
Female	12 (75.0)
Male	4 (25.0)
Performance status	
0	9 (56.3)
1	7 (43.8)
Primary site	
Left medial masticator, pharyngeal mucosal and submandibular spaces	1 (6.3)
Mesentery	2 (12.5)
Rectum	1 (6.3)
Skeleton	1 (6.3)
Small intestine	2 (12.5)
Soft tissue	8 (50.0)
Thyroid	1 (6.3)
Ethnicity	
Hispanic	3 (18.8)
Not Hispanic	13 (81.3)
Race	
White	12 (75.0)
Black	2 (12.5)
Unknown race	2 (12.5)
Response	
Confirmed PR	3 (18.8)
SD ≥6 months	7 (43.8)
Clinical benefit*	10 (62.5)
SD <6 months	3 (18.8)
Not assessable†	3 (18.8)

*Clinical benefit=SD ≥ 6 months plus confirmed objective responses.
†One patient was not assessed (withdrew consent before the first scan), and the other two patients did not receive adequate scans.
DART, Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors; PR, partial response; SD, stable disease.

Outcomes

Among the 16 evaluable patients in cohort 27, the ORR was 18.8% (3/16), and the overall CBR was 62.5% (10/16). Three patients had a PR: one with a 40% regression and an ongoing duration of response of over 30+ months, one with an 83% regression and PFS of 16.1 months, and one with a 71% regression and PFS of 8.4 months (table 1, figures 1 and 2). Additionally, seven patients (43.8%) had evidence of tumor shrinkage and durable SD ranging in duration from

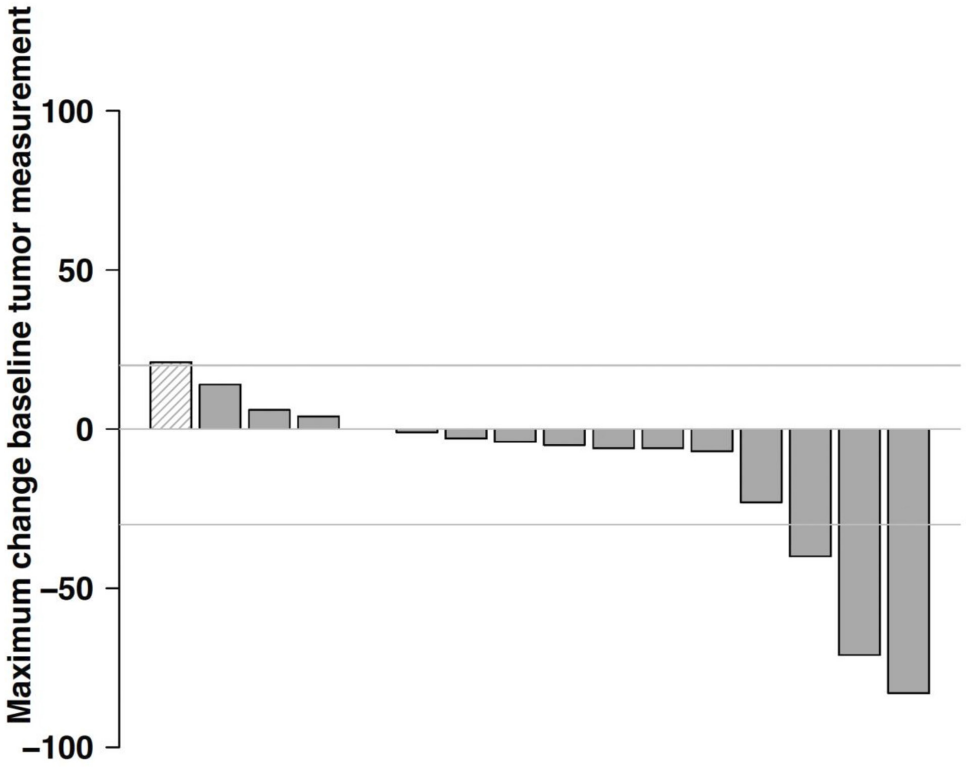

Figure 1 RECIST V.1.1 Waterfall plot indicating maximum change in baseline tumor measurement following protocol therapy. Bars below the line indicate regressing disease; above the line, enlarging disease. Crosshatch indicates participants did not have tumor measurements available due to withdrawal of consent for further follow-up before the first scan. RECIST, response evaluation criteria in solid tumors.

16.5 to 60.7+ months (online supplemental table 1). Three patients (18.8%) were missing data for RECIST response (table 1). At the time of analysis, six patients (37.5%) showed ongoing responses (figure 2). Overall, the 6-month PFS was 73% (95% CI 54% to 100%), the 12-month PFS was 67% (95% CI 47% to 95%), and the median PFS was 19.4 months (95% CI 8.3 months-not reached) (figure 3). The assessment under iRECIST criteria revealed unchanged responses and PFS in patients. The survival rates at 6 months and

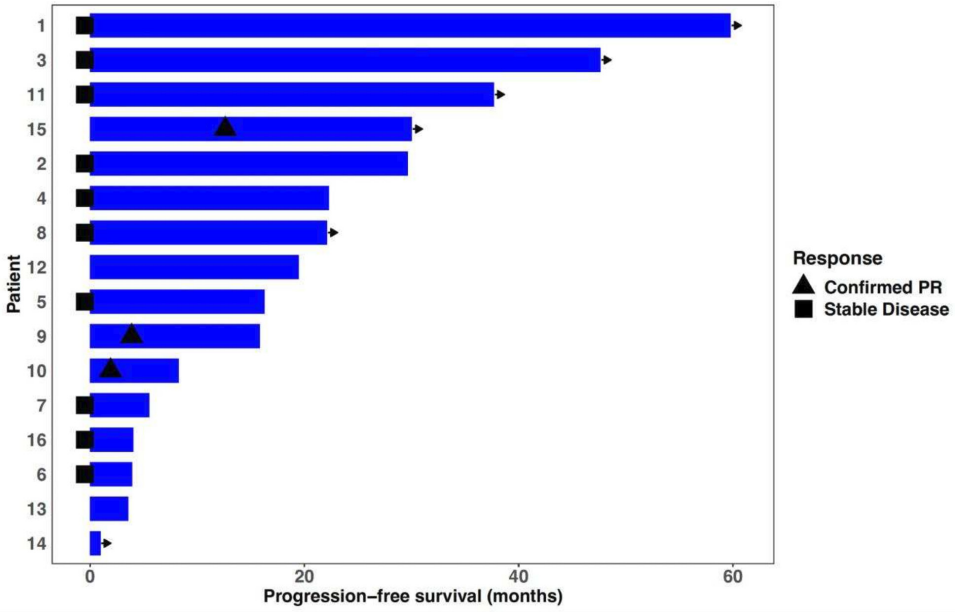

Figure 2 RECIST V.1.1 Swimmer's plot of progression-free survival (PFS) following protocol therapy. Bars indicate PFS per individual patient. Response patterns are specified with symbols as described. PR, partial response; RECIST, response evaluation criteria in solid tumors.

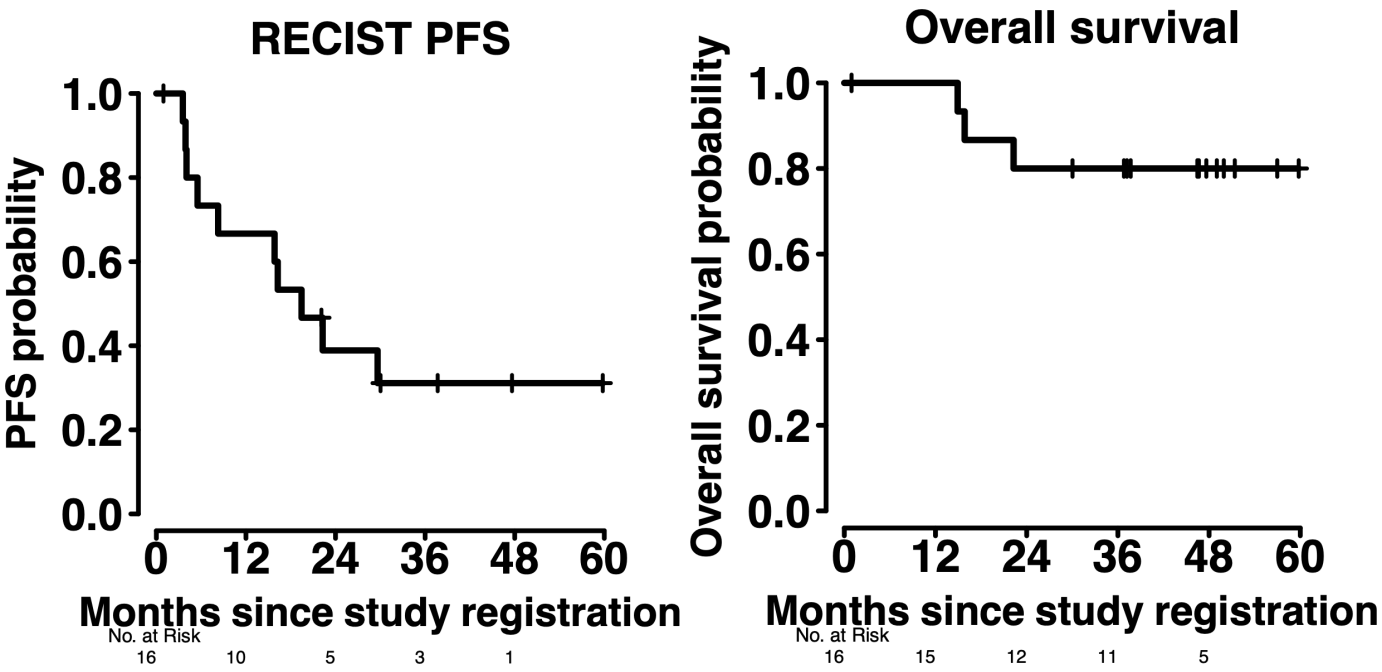

Figure 3 RECIST V.1.1 (A) progression-free and (B) overall survival following protocol therapy. RECIST, response evaluation criteria in solid tumors.

12 months were both 100% (95% CI 100% to 100%), and the median OS was not accessible as 13 patients were still alive at the time of analysis (figure 3, online supplemental file 3).

Toxicities

Every patient in cohort 27 (n=16) encountered adverse events of varying grades potentially linked to the treatment, with half of them (n=8) experiencing adverse events of grade 3 or higher (see table 2). Grade 3 or higher toxicities, possibly related to the treatment, were observed in cycles 1, 1, 3, 4, 4, 14, 15, and 19, each cycle spanning 6 weeks. The most common adverse events included fatigue (43.8%, n=7), nausea (37.5%, n=6), hypothyroidism (31.3%, n=5), diarrhea (25%, n=4), hyperthyroidism (25%, n=4), headache (25%, n=4), and adrenal insufficiency (25%, n=4) among others. Seven treatment-related adverse events led to treatment discontinuation, but no deaths were reported as a result of these adverse events (online supplemental file 2). Overall, 87.5% (n=14) of adverse events were considered immune mediated, with the most common being hypothyroidism (31.3%, n=5), adrenal insufficiency (25%, n=4), and diarrhea (25%, n=4). Five immune-mediated adverse events (31.3%) were of grades 3–5. Prolonged therapy may have been partly associated with the development of toxicity, as five of the eight patients experienced their first appearance of these toxicities more than 24 weeks after starting the drug.[28] Modified dosing could be considered in future studies, particularly for patients undergoing therapy for extended periods of time.

DISCUSSION

Currently, there is limited prior experience with immunotherapy in the treatment of desmoid tumors. To our knowledge, this is the first study to prospectively evaluate the response of desmoid tumor to isolated ICI therapy. Ipilimumab combined with nivolumab showed a trial response rate of 18.8% (3/16) and CBR of 62.5% (10/16). Among the responders, 1 individual having PR was a woman in her 60s, while 6 patients demonstrating SD with evident tumor reduction were women ranging in age from 33 to 43 years. Although the cause of the tumor regression is uncertain and could be due to spontaneous regression linked to menopausal transition or postpartum status, the fact that the two other cases of PR are male provides evidence supporting the hypothesis that the response to ICI is the underlying cause.[16 29] Dual anti-CTLA-4 and anti-PD-1 blockade with nivolumab and ipilimumab may represent another treatment option with modest survival benefit.

These results need to be understood in the context of recent approvals in the treatment of desmoid tumors, which are heterogenous tumors that are usually slow growing. Since the initiation of this study, sorafenib and nirogacestat received recent Food and Drug Administration (FDA) approval for treatment of desmoid tumors. Nirogacestat showed PFS benefit over placebo with a 2-year event-free survival rate of 76% with nirogacestat and 44% with placebo (HR for disease progression or death, 0.29; p<0.001), and objective response was 41% with nirogacestat compared with 8% with placebo (p<0.001).[20] Sorafenib showed a 2-year PFS rate of 81% compared with 36% in the placebo group (HR for progression or death, 0.13; p<0.001), and an objective response rate

Table 2 Potential drug-related adverse events among 16 evaluable patients with desmoid tumors treated on the DART immunotherapy protocol (nivolumab plus ipilimumab)

Desmoid tumor (n=16)	Any grade	Grades 3–4	Grade 5
Any	16 (100.0%)	8 (50.0%)	0 (0.0%)
Serious	7 (43.8%)	7 (43.8%)	0 (0.0%)
Led to discontinuation	7 (43.8%)	6 (37.5%)	0 (0.0%)
Led to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
>10% of patients			
Symptoms/conditions			
Fatigue	7 (43.8%)	0 (0.0%)	0 (0.0%)
Nausea	6 (37.5%)	1 (6.3%)	0 (0.0%)
Hypothyroidism	5 (31.3%)	0 (0.0%)	0 (0.0%)
Adrenal insufficiency	4 (25.0%)	1 (6.3%)	0 (0.0%)
Diarrhea	4 (25.0%)	1 (6.3%)	0 (0.0%)
Hyperthyroidism	4 (25.0%)	1 (6.3%)	0 (0.0%)
Headache	4 (25.0%)	0 (0.0%)	0 (0.0%)
Abdominal pain	3 (18.8%)	0 (0.0%)	0 (0.0%)
Cough	3 (18.8%)	0 (0.0%)	0 (0.0%)
Rash maculo-papular	3 (18.8%)	0 (0.0%)	0 (0.0%)
Anemia	2 (12.5%)	0 (0.0%)	0 (0.0%)
Arthralgia	2 (12.5%)	0 (0.0%)	0 (0.0%)
Chills	2 (12.5%)	0 (0.0%)	0 (0.0%)
Constipation	2 (12.5%)	0 (0.0%)	0 (0.0%)
Hypophysitis	2 (12.5%)	0 (0.0%)	0 (0.0%)
Myalgia	2 (12.5%)	0 (0.0%)	0 (0.0%)
Neck pain	2 (12.5%)	0 (0.0%)	0 (0.0%)
Pruritus	2 (12.5%)	0 (0.0%)	0 (0.0%)
Vomiting	2 (12.5%)	0 (0.0%)	0 (0.0%)
Laboratory abnormalities			
Lymphocyte count decreased	3 (18.8%)	0 (0.0%)	0 (0.0%)
White blood cell decreased	2 (12.5%)	0 (0.0%)	0 (0.0%)
Immune mediated	14 (87.5%)	5 (31.3%)	0 (0.0%)
Hypothyroidism	5 (31.3%)	0 (0.0%)	0 (0.0%)
Adrenal insufficiency	4 (25.0%)	1 (6.3%)	0 (0.0%)
Diarrhea	4 (25.0%)	1 (6.3%)	0 (0.0%)
Hyperthyroidism	4 (25.0%)	1 (6.3%)	0 (0.0%)
Rash maculo-papular	3 (18.8%)	0 (0.0%)	0 (0.0%)
Arthralgia	2 (12.5%)	0 (0.0%)	0 (0.0%)
Pruritus	2 (12.5%)	0 (0.0%)	0 (0.0%)
Lipase increased	1 (6.3%)	1 (6.3%)	0 (0.0%)
Pneumonitis	1 (6.3%)	1 (6.3%)	0 (0.0%)
Alanine aminotransferase increased	1 (6.3%)	0 (0.0%)	0 (0.0%)
Aspartate aminotransferase increased	1 (6.3%)	0 (0.0%)	0 (0.0%)
Serum amylase increased	1 (6.3%)	0 (0.0%)	0 (0.0%)

DART, Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors.

of 33% in the sorafenib group and 20% in the placebo group before crossover.[21] The OS outcomes from these studies are yet to be reported.

An ongoing phase II study (NCT03886311) is studying the combination of nivolumab with talimogene laherparepvec, an oncolytic herpes virus, and trabectedin, a chemotherapy medication, in an advanced sarcoma cohort that includes desmoid tumors. Preliminary results show that this combination therapy may yield comparable results to the standard care (ORR 8.6% or 3/35; 3 PR, 27 SD, 5 PD; median PFS 2.0 months; 6-month PFS 62.1%); however, the exact number of patients with desmoid tumors enrolled in this trial has not been reported.[30 31] Moreover, whether the addition of talimogene laherparepvec and trabectedin to immunotherapy improves outcome remains unanswered.

Oncolytic peptides and other forms of immunotherapy, such as interferon-alpha therapy, have been explored as possible alternative treatments for desmoid tumors. In one patient with a desmoid tumor of the thoracic wall, intratumoral injection of LTX-315, an oncolytic peptide, for 18 weeks induced SD that lasted more than 2.5 years after the completion of treatment.[32] Various forms of interferon, including α-2b, γ, and pegylated, have demonstrated efficacy in inducing regression, as reported in multiple case studies, but the precise mechanism of its action in this tumor remains uncertain.[33–40] A retrospective analysis involving 13 patients with desmoid tumors revealed that local disease control was achieved in 85% (11/13) of cases, with 4 patients receiving interferon-α alone and 7 patients receiving combination therapy with tretinoin, and disease-free interval up to 68 months.[41] Nevertheless, the practical application of oncolytic peptides and interferon is limited by factors such as the scarcity of case studies and potential adverse reactions.

Studies suggest that desmoid tumors may be 'cold' tumors due to a depleted T-cell phenotype. The CTNNB1 gene mutations in desmoid tumors lead to activation of the β-catenin pathway, which may be responsible for T-cell exhaustion and resistance to anti-PD-1 therapy.[42 43] An analysis of 33 desmoid tumor samples revealed a strong immune infiltrate at the periphery but not within the tumor, with no PD-L1 driven immune suppression.[44] Therefore, β-catenin could serve as a potential negative predictor biomarker candidate, and stratification of the desmoid tumor cohort based on mutational signatures may be necessary to investigate the association between β-catenin and immunotherapy response. Future studies may include more desmoid biomarkers like β-catenin.

The DART platform study has several advantages, including support from the NCI and SWOG and the involvement of patients with rare/ultrarare cancers from 1,016 academic and community centers, proving that it was possible to quickly recruit patients, even the most uncommon tumors. Most importantly, this study filled the gap in available immunotherapy trials for multiple groups of patients with rare tumors. Up until now, the DART study has shown activity in several rare and ultrarare tumor types, including angiosarcoma, neuroendocrine tumor, metaplastic breast cancer, gestational trophoblastic neoplasia, and gallbladder cancer.[45–50]

The study has several limitations that should be considered when interpreting the results. First, there was no randomized comparison to the current standard of care, which is active surveillance. The sample size was also comparatively small, which could restrict the applicability of the results. Moreover, there was no centralized review of pathology and radiology, which could have led to inconsistencies in tumor evaluations. Finally, biomarker correlates are needed in future studies.

In conclusion, the combination of ipilimumab and nivolumab was used to treat desmoid tumor, which resulted in an ORR of 18.8% and CBR of 62.5% with durable responses. This is the first study that explored the efficacy of dual ICI for this rare disease. Further research is underway to identify markers of response and resistance. More extensive studies are necessary to understand the full potential of this treatment for desmoid tumors.

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

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