# Systemic Chemotherapies Retain Antitumor Activity in Desmoid Tumors Independent of Specific Mutations in *CTNNB1* or *APC*: A Multi-institutional Retrospective Study

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## ABSTRACT

**Purpose:** Determine whether specific *CTNNB1* or *APC* mutations in patients with desmoid tumor were associated with differences in clinical responses to systemic treatments.

**Experimental Design:** We established a multi-institutional dataset of previously treated patients with desmoid tumor across four U.S. sarcoma centers, including demographic and clinicopathologic characteristics, treatment regimens, and clinical and radiographic responses. *CTNNB1* or *APC* mutation status was determined from prior pathology records, or archival tissue was requested and analyzed by Sanger sequencing and/or next-generation sequencing. Evaluable patients with mutation results were analyzed to determine clinical progression-free survival (cPFS), RECIST 1.1 PFS (rPFS), time to next treatment (TTNT), and overall survival (OS). Kaplan–Meier analysis and Cox proportional hazards regression were performed to identify differences in cPFS, rPFS, TTNT, and OS by mutation subtype, desmoid tumor location, and treatment regimen.

**Results:** A total of 259 evaluable patients were analyzed for at least one of the survival outcomes, with 177 patients having mutation data. First- and second-line cPFS, rPFS, and TTNT were not significantly affected by mutation subtype; however, *APC*-mutant desmoid tumors demonstrated nonstatistically significant inferior outcomes. Extremity/trunk desmoid tumor location and treatment with doxorubicin-based, methotrexate/vinca alkaloids and sorafenib regimens were associated with better clinical outcomes compared with surgery or "other" therapies, including estrogen-receptor blockade and imatinib. OS was significantly worse with *APC* or *CTNNB1* negative/other mutations.

**Conclusions:** Mutation subtype did not affect responses to specific systemic therapies. *APC* mutations and nonextremity desmoid tumor locations remain prognostic for worse outcomes, and earlier initiation of systemic therapy for these higher-risk desmoid tumors should be prospectively evaluated.

*See related commentary by Greene and Van Tine, p. 3911*

## Introduction

Desmoid tumors, also known as desmoid fibromatosis, are rare soft-tissue neoplasms driven by aberrant β-catenin signaling, either through activating mutations of the gene encoding β-catenin (*CTNNB1*) or loss of the pathway suppressor *APC* (1). Despite a low incidence of approximately two to four cases per million per year (2–4), desmoid tumors can be locally extensive and invasive, and prone to

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## Translational Relevance

Desmoid tumors are clonal soft-tissue neoplasms driven by constitutive β-catenin/WNT signaling, either through specific, well-characterized activating mutations in *CTNNB1*, or loss of suppression of the pathway by *APC* deletions as occurs in familial adenomatous polyposis. Surgery has been the historical mainstay of desmoid treatment; however, postoperative recurrence is frequent. Systemic therapy is effective but can be associated with significant toxicity. *APC* deletions and *CTNNB1* S45F mutations have been associated with inferior prognosis and more aggressive clinical behavior in some studies, but it is unknown whether individual mutation types are associated with resistance to systemic therapies. We retrospectively examined a desmoid tumor patient cohort and determined that various chemotherapy regimens retain antitumor efficacy independently of the mutation subtype. Thus, our data support the idea that initiation and choice of chemotherapy regimen should be based on symptoms and individual patient risk, rather than the presence of a specific genetic alteration.

multiple local recurrences, leading to substantial morbidity. Desmoid tumors do not metastasize but can be locally aggressive. When they occur in proximity to major organs and structures, desmoid tumors can lead to significant morbidity and even to death (5). Importantly, clinical behavior of desmoid tumors is highly variable, with up to a 20% spontaneous regression rate, and other patients exhibit stable, asymptomatic disease for years without requiring treatment (6). Conversely, other patients exhibit more rapid growth and symptoms that can severely affect quality of life and threaten life or limb. Surgery is highly effective in treatment of progressive desmoid tumors; however, there remains a high postoperative recurrence rate of up to 39% in some series, even with negative margins (5). Systemic therapy is also active in desmoid tumors, but some regimens impart significant toxicity, which is undesirable for a nonmalignant neoplasm occurring in younger and otherwise healthy individuals. Identifying prognostic and predictive factors to determine which desmoid tumors are likely to behave in an indolent fashion and determining which tumors should be treated more aggressively with specific systemic chemotherapy regimens would greatly impact clinical care for patients with desmoid tumor.

The genetic drivers of desmoid tumors have been well established, and some evidence suggests that specific mutations may be prognostic. A total of 80% to 90% of desmoid tumors carry mutations in *CTNNB1*, defined as sporadic desmoid tumors, with the most common mutations occurring in exon 3 in codon 41 (T41A), or codon 45 (S45F or S45P; refs. 7, 8), leading to intranuclear accumulation of β-catenin and activation of downstream β-catenin/Wnt signaling (9). Some studies have shown that *CTNNB1* codon 45 mutations may have worse progression-free survival (PFS) and higher risk of recurrence (10–12), although other studies suggested a lack of prognostic significance (13, 14). About 10%–20% of desmoid tumors are thought to arise from deletions in *APC*, with the majority being germline mutations and associated with familial adenomatous polyposis (FAP) syndromes (7). *APC* negatively regulates β-catenin (15), and loss of *APC* leads to an increased risk of developing colon polyps, colon cancer, thyroid cancer, as well as desmoid tumors (16). Patients with FAP carry a risk of developing desmoid tumors of about 10% to 30% (17–19). Importantly, FAP patients tend to develop multifocal desmoid tumors, with a predisposition for mesenteric tumors (17). On

the basis of the biology of this disease, FAP-associated desmoid tumors have clearly been associated with worse prognosis and risk of death.

While the consensus approach for desmoid tumors has evolved to avoid initial surgical resection, with a "watch and wait" philosophy based on the unpredictable behavior, a variety of systemic therapies have been used to treat progressive or symptomatic desmoid tumors (20, 21). These treatments have included estrogen-receptor (ER) suppressive therapies such as tamoxifen, particularly for desmoid tumors associated with pregnancy or other hormonal exposure (22), and anti-inflammatories such as meloxicam/sulindac. Traditional cytotoxic chemotherapies include doxorubicin/dacarbazine (ADIC), pegylated liposomal doxorubicin, and methotrexate (MTX) with vinca alkaloids, most commonly vinblastine. Newer therapies include tyrosine kinase inhibitors (TKI) such as imatinib, sorafenib, and pazopanib, and multiple novel treatments including gamma-secretase inhibitors, Wnt/β-catenin inhibitors, and even immune checkpoint inhibitors are being studied in clinical trials (23). A few studies have examined the susceptibility of *CTNNB1* mutation subtypes to various chemotherapies, with S45F mutations having worse outcomes with meloxicam, and no difference observed in different mutations in patients treated with MTX/vinblastine and imatinib (24–26). However, no data exist for doxorubicin-based treatments and sorafenib. To further address the question of whether mutation data can inform selection of systemic therapy or its optimal timing, we performed a multi-institutional retrospective analysis of patients with desmoid tumor who received systemic chemotherapies, to evaluate the impact of specific mutation subtypes on clinical and radiographic responses.

## Materials and Methods

### Data collection

We established a deidentified REDCAP database to capture data from patients with desmoid tumor treated at four institutions: The University of Texas MD Anderson Cancer Center (MDACC, Houston, TX), the University of Miami (UM, Miami, FL), the Mount Sinai Medical Center (MSMC, New York, NY), and the Dana-Farber Cancer Institute (DFCI, Boston, MA). Under individual institutionally approved Institutional Review Board protocols providing waiver of informed consent in accordance with the U.S. Common Rule, patients with desmoid tumor were retrospectively identified from each institution by the investigators. Clinical data, including demographics, clinicopathologic features, mutation testing results, treatment regimens, and clinical and radiographic outcomes were abstracted. Surgery, surgery with adjuvant radiation or chemotherapy, radiation/ ablation, and the few formally documented observation periods were considered as unique treatment episodes alongside various systemic regimens. Patients were required to have a diagnosis of desmoid tumor previously confirmed by pathologists at the respective institutions. For patients from UM and DFCI with available archival tissue and no prior mutation testing, we performed Sanger sequencing to determine specific *CTNNB1* mutations, with next-generation sequencing for *APC* or *CTNNB1* mutations in specimens negative by Sanger sequencing.

The clinical outcomes under investigation included clinical PFS (cPFS), RECIST 1.1 PFS (rPFS), time to next treatment (TTNT), and overall survival (OS). cPFS was defined as the time from the date of a baseline scan prior to beginning a treatment regimen, or if no baseline scan was performed, from the start date of the treatment regimen, until the date of clinical progression as documented in the treating physician's notes. Determination of clinical progression was abstracted from

the physician's notes, and could be based on worsening of symptoms, or general radiographic progression (not necessarily based on RECIST). Patients who did not have documented clinical progression but treatment was stopped or changed for other reasons, including toxicity, investigator or patient preferences, or unknown reasons were censored at the date of last contact or next treatment regimen start date. To determine rPFS, standard calculations were made based on the longest tumor diameter in any plane based on available CT or MRI reports documented in the clinical database. For a subset of patients with scans available, these were rereviewed by fellowship trained radiologists blinded to clinical treatment outcome to determine greatest tumor diameter and response according to RECIST 1.1. TTNT was calculated for each treatment episode as the time elapsed from completion of one treatment episode, until the start date of the next treatment episode for the patient. Patients who did not have a subsequent treatment episode were censored at the date of last follow-up. OS was calculated as the time from desmoid tumor diagnosis by pathology report to death from any cause. In addition to these outcomes, we also evaluated response rates for patients with available radiographic data, with a decrease in maximum tumor diameter of ≥30% considered partial response (PR), −30% to +20% considered stable disease (SD), and increase of ≥20% considered progressive disease (PD).

### Statistical analysis

We conducted analysis on two levels, by individual patients, and by treatment episodes. Demographic and clinical data, treatment regimens, and mutation status for evaluable patients within the entire study population were summarized using frequency tables. Continuous variables were reported as median and interquartile range (IQR), and categorical variables were reported as frequencies and percentages of the patient population, and then evaluated by mutation subgroup. Comparisons made across mutation subtype groups were descriptive in nature, with continuous variables tested using Kruskal–Wallis nonparametric test, and categorical variables compared using Fisher exact test.

OS analyses were conducted for the entire patient population incorporating first-line treatments. For cPFS, rPFS, and TTNT, analysis was limited to treatment regimens received in the first-line and second-line setting based on evaluable patient numbers. Survival probabilities for these outcomes were calculated by the Kaplan–Meier (KM) method, and the survival curves and median survival time reported with the corresponding two-sided 95% Brookmeyer–Crowley confidence interval (CI) if feasible. We used the log-rank test to compare survival endpoints by mutation subtype, desmoid tumor anatomic location, and first- and second-line treatment regimens. We then used the Cox proportional hazards model to compare survival endpoints by specific mutation, desmoid tumor anatomic location, and first- and second-line treatment modalities while adjusting for additional covariates as feasible for model convergence, which included age at diagnosis, sex, race/ethnicity, total number of treatments, and history of FAP (for location and treatment analyses only). For second-line survival analyses, the time to second-line therapy was also included as a covariate to correct for biologic variation among patients with desmoid tumor. The adjusted HR with 95% CI was calculated and reported.

We then conducted a separate analysis to evaluate the impact of mutation subtype, desmoid tumor location, and treatment regimens on cPFS, rPFS, and TTNT of all individual treatment episodes across the evaluable patients without taking into account the line of therapy. Survival probabilities were calculated by the KM method, and the

survival curve and the median survival time were reported with the corresponding two-sided 95% Brookmeyer–Crowley CI if feasible. The log-rank test was used to compare the survival endpoints by mutation subtype, desmoid tumor location, and treatment regimen. The log-rank test results were understood to be less robust because multiple treatment episodes associated with the same patient were not independent. Thus, multivariable Cox proportional hazards models incorporating random patient effect (frailty covariate) and the previously mentioned covariates were used to compare survival outcomes by specific mutation, desmoid tumor location, and treatment regimen. The adjusted HRs with 95% CIs were calculated and reported. We also conducted a subgroup analysis to evaluate the effects of mutation subtype on cPFS, rPFS, and TTNT for four key treatment episode types, ADIC, single-agent doxorubicin, MTX/vinca alkaloids, and sorafenib. Survival outcomes in this analysis were compared by KM analysis and Cox proportional hazards models as described above. For episodes with radiographic tumor size data available for the four primary systemic treatments, as well as "other" which primarily included tamoxifen and imatinib, waterfall plots depicting best change in tumor dimensions with these regimens and a summary table of response rates [defined as proportion achieving complete response (CR) or PR], and disease control rates (proportion achieving CR or PR, or SD) were reported.

All statistical analyses were performed by an independent statistician to ensure unbiased data review and conducted on R version 4.1.0. *P* values less than 0.05 were considered statistically significant. Because of the exploratory and hypothesis-generating nature of this study, no multiple comparison adjustment was implemented.

### Data availability

The data collected and genetic sequencing generated in this study are available upon request from the corresponding author.

## Results

### Patient and treatment characteristics

A total of 309 patients with desmoid tumor were retrospectively identified, with 106 from MDACC, 108 from DFCI, 68 from UM, and 7 from MSMC who were diagnosed and treated between 1985 and 2018 (**Fig. 1A**). A total of 50 patients were excluded for inadequate data. A total of 259 patients were included in the patient-level analysis for at least one of the survival outcomes. Of the 259 patients in the total evaluable population, 177 (68%) had mutation testing, including *CTNNB1* T41A (n = 68, 26%), *CTNNB1* S45F (n = 47, 18%), *APC* (n = 11, 4%), negative or other mutations (n = 51, 20%) which included S45P (n = 4, 8.3%), *CTNNB1* p.P16S (n = 1, 2%), or *MYH* G382D and Y165C (n = 1, 2%), and 32% had no available mutation data, due to either unavailable archival tissue or failure of sequencing (**Table 1**). Of note, a significant number of patients had been sequenced prior to the development of next-generation sequencing techniques and were recorded as "negative" for *CTNNB1* mutations without further information available.

Patients were predominantly female (67%) with a median age of 35 years (IQR, 25–46), and predominantly Caucasian (57%), (**Table 1**). The majority of desmoid tumors were located in the extremity/trunk (51%), with abdominal/pelvic locations in 37%, and other locations (including head/neck, paraspinal, and multifocal desmoid tumors) making up the remaining 13%. 20% of all patients had a known history of FAP, including 10 of the 11 patients in the *APC* mutation subgroup, but importantly also 33 patients (65%) in the negative/other mutation subset and 8 (10%) in the
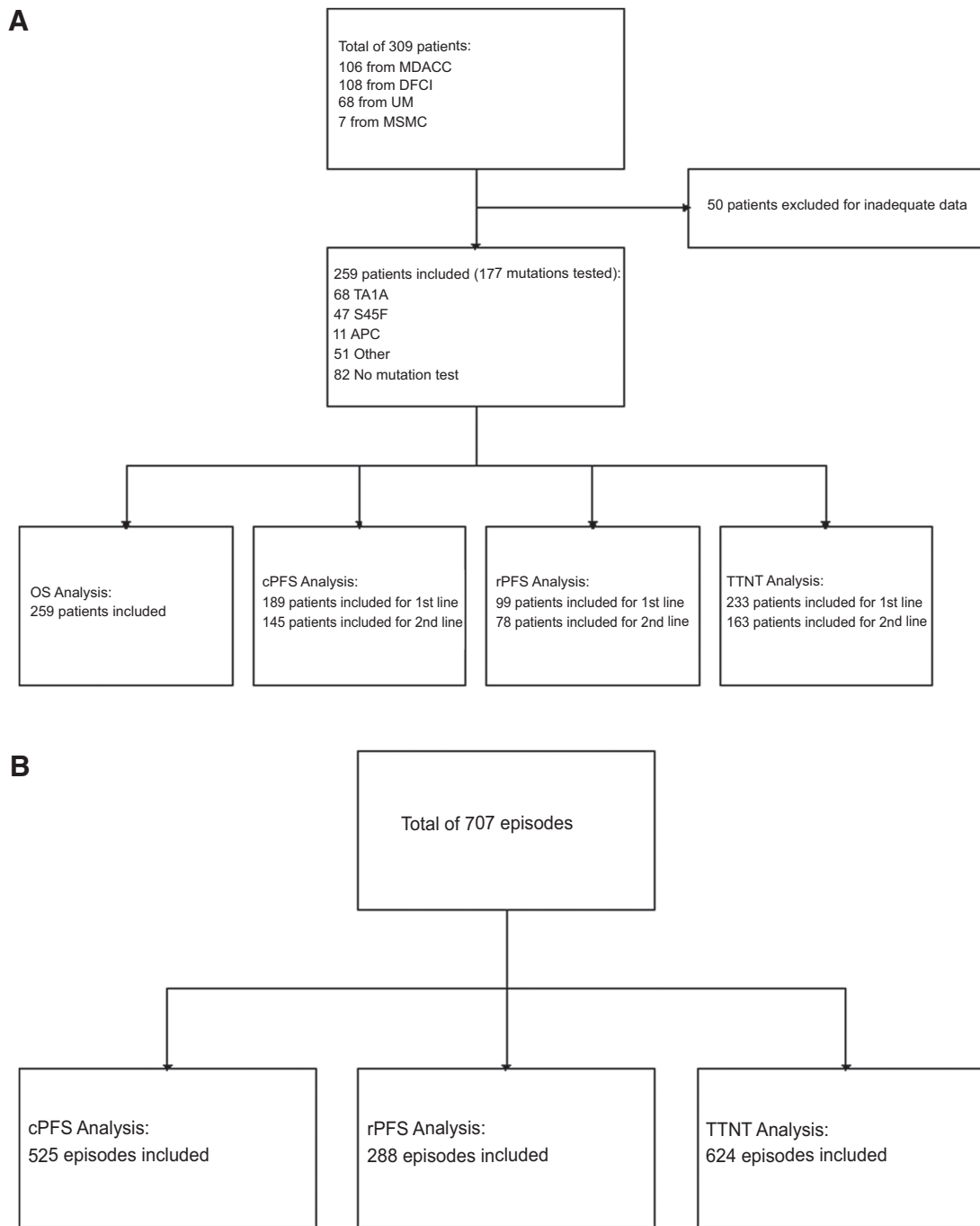
**A**

Total of 309 patients:
106 from MDACC
108 from DFCI
68 from UM
7 from MSMC

50 patients excluded for inadequate data

259 patients included (177 mutations tested):
68 TA1A
47 S45F
11 APC
51 Other
82 No mutation test

OS Analysis:
259 patients included

cPFS Analysis:
189 patients included for 1st line
145 patients included for 2nd line

rPFS Analysis:
99 patients included for 1st line
78 patients included for 2nd line

TTNT Analysis:
233 patients included for 1st line
163 patients included for 2nd line

**B**

Total of 707 episodes

cPFS Analysis:
525 episodes included

rPFS Analysis:
288 episodes included

TTNT Analysis:
624 episodes included

**Figure 1.**
CONSORT diagrams showing numbers of patients (**A**) and numbers of episodes (**B**) included in each analysis. cPFS, clinical progression-free survival; DFCI, Dana-Farber Cancer Institute; MDACC, The MD Anderson Cancer Center; MSMC, Mount Sinai Medical Center; OS, overall survival; rPFS, RECIST 1.1 progression-free survival; TTNT, time to next treatment; UM, University of Miami.

untested subset (**Table 2**). A total of 48% of patients received surgery with or without adjuvant therapy as primary management of the desmoid tumor, whereas 52% received systemic therapies and/or radiotherapy as primary management. The median number of treatment regimens per patient, which included surgical and radiation regimens, was 2 (range, 1–10), with 43% of patients having received three or more treatment regimens. Significant differences seen across mutation subgroups included age, desmoid tumor location, history of FAP, vital status at last follow-up, and median follow-up time (**Table 2**). Patients with *APC* or negative/other mutations were younger. Abdominal/pelvis desmoid tumors were seen in 61% of negative/other mutations, compared

**Table 1.** Clinical, demographic, and treatment characteristics for the entire study population.

| Characteristics | Levels | All *N* (%) |
|---|---|---|
| Sex | Female | 174 (67) |
| | Male | 85 (33) |
| Race | Caucasian | 148 (57) |
| | Hispanic | 35 (14) |
| | African American | 21 (8) |
| | Asian | 10 (4) |
| | Other | 10 (4) |
| | (Missing) | 35 (14) |
| Age at diagnosis | Median (IQR) | 35 (25–46) |
| Mutation type | T41A | 68 (26) |
| | S45F | 47 (18) |
| | APC | 11 (4) |
| | Negative/other[a] | 51 (20) |
| | (Missing) | 82 (32) |
| Desmoid location | Abdominal/pelvis | 95 (37) |
| | Extremity/trunk | 131 (51) |
| | Other[b] | 33 (13) |
| History of FAP | No | 190 (73) |
| | Yes | 51 (20) |
| | (Missing) | 18 (7) |
| Number of treatments | 1 | 72 (28) |
| | 2 | 77 (30) |
| | 3+ | 110 (43) |
| First-line treatment | Surgery[c] | 124 (48) |
| | ADIC | 18 (7) |
| | Doxorubicin single agent[d] | 36 (14) |
| | Sorafenib | 11 (4) |
| | MTX/vinca alkaloids | 24 (9) |
| | Other[e] | 46 (18) |
| Status at last follow-up | Censored | 245 (95) |
| | Died | 14 (5) |
| Follow-up time in months | Median (IQR) | 64.4 (28–110) |

Abbreviations: IQR, interquartile range; ADIC, doxorubicin/dacarbazine; FAP, familial adenomatous polyposis; MTX, methotrexate.
[a]Negative/other mutations include *CTTNB1* negative, S45P, other *CTNNB1*, non-*CTNNB1*/non-*APC* (**Table 2**).
[b]Other location includes head and neck, paraspinal, other location, or multifocal.
[c]Includes surgery alone, or surgery with adjuvant radiation or systemic therapies (Supplementary Fig. S1).
[d]Includes liposomal and traditional doxorubicin (Supplementary Fig. S1).
[e]Primarily estrogen-suppressing therapies, imatinib, and others (Supplementary Fig. S1).

with 23%–40% in other subgroups, and extremity/flank tumors occurred in only 18% of *APC* and 24% of negative/other mutant desmoid tumors, compared with 52%–62% in other subgroups. Other/multifocal locations were also most common in *APC* mutant tumors (45%), compared with 8.8%–16% in other subsets. Patients with *APC* mutations and negative/other mutations were also more likely to have received three or more treatment lines compared with other subsets (*APC* 55%, negative/other 61%, compared with 38%–43% in other subsets).

Across all patients, there were 707 discrete treatment episodes identified, with 624 episodes having adequate data for analysis for at least one of the survival outcomes (**Fig. 1B**). A total of 374 of these episodes had associated mutation testing data available. Of the total number of treatment episodes administered in the first line, surgery alone was most frequent (41%), followed by single-agent doxorubicin [14%, primarily pegylated liposomal doxorubicin (89%) rather than traditional doxorubicin], ER blockade with or without anti-inflammatories

(12%), MTX/vinca alkaloids (9%), and then ADIC (7%; Supplementary Fig. S1). In the second-line setting, ER blockade with/without anti-inflammatories was most common (22%), with surgery alone the next most frequent approach (19%). In third or greater lines, surgery was still commonly utilized (23%); however, more similar distributions were seen between single-agent doxorubicin (14%), ER blockade with/without anti-inflammatory medication (13%), MTX/vinca alkaloids (13%), sorafenib (11%), ADIC (8.8%), and other TKIs (6.9%).

### First- and second-line cPFS, rPFS, and TTNT are not affected by mutation subtype, but are impacted by desmoid tumor location and treatment regimen

KM analysis and Cox proportional hazards analysis for cPFS, rPFS, and TTNT were only performed for patients receiving first and second lines of treatment, due to limited numbers of patients treated with three or more lines of treatment. Of patients with mutation testing completed, 122 patients were evaluable for first-line cPFS, and 109 patients were evaluable for second-line cPFS. KM analysis showed no significant differences in first- or second-line cPFS by mutation status (**Fig. 2A**, $P = 0.49$; **Fig. 2B**, $P = 0.25$). Nonstatistically significant worse outcomes with *APC* mutations were observed, with first-line median cPFS of 17 months, and second-line median cPFS of 13 months. In addition, S45F mutations had nonstatistically significant inferior cPFS (median PFS of 13 months). However, in Cox proportional hazards analysis, no significant impact was seen from mutation subtype on either first- or second-line cPFS (**Tables 3A** and **3B**). Similar findings were observed for first- and second-line rPFS and TTNT, with no significant differences by KM or Cox multivariable analysis, but nonstatistically significant inferior outcomes for *APC* mutant tumors (Supplementary Figs. S2 and S3; Supplementary Tables S1–S4).

We then evaluated the impact of desmoid tumor location on first- and second-line cPFS, hypothesizing that cPFS may be driven by high-risk sites such as the mesentery. The median first-line cPFS of abdominal/pelvic desmoid tumors was only 18 months, less than extremity/trunk (33 months) and other locations (20 months), and second-line cPFS also showed nonstatistically significant inferior outcomes with "other" locations (13 months), compared with extremity/trunk location (25 months; Supplementary Tables S5 and S6). Cox multivariable analysis confirmed superior cPFS in extremity/trunk desmoid tumor location relative to abdominal/pelvis location in the first line [HR, 0.59 (95% CI, 0.35–0.99), $P = 0.047$], but was not significant in the second line. Similar findings were observed in the first- and second-line rPFS analysis, with superior outcomes with extremity/trunk location, but we found no significant differences in TTNT by desmoid tumor location (data not shown).

Next, we analyzed the effects of specific first- or second-line treatments on cPFS. Treatment choice did significantly impact first-line cPFS, with notably worse outcomes with surgery (median PFS 13 months) and "other" treatments [primarily ER blockade/anti-inflammatories (Supplementary Fig. S1), median PFS 23 months], compared with treatment with ADIC, single-agent doxorubicin, sorafenib, and MTX/vinca alkaloids (Supplementary Table S7, $P = <0.001$). Cox multivariable analysis confirmed significant improvement in first-line cPFS with ADIC chemotherapy [HR, 0.30 (95% CI, 0.11–0.77), $P = 0.013$], with nonstatistically significant improvement with single-agent doxorubicin [HR, 0.50 (95% CI, 0.24–1.1), $P = 0.075$] and MTX/vinca alkaloids [HR, 0.50 (95% CI, 0.21–1.2, $P = 0.13$] (Supplementary Table S7C). Analysis of second-line cPFS by

**Table 2.** Clinical, demographic, and treatment characteristics stratified by mutation types.

| Characteristics | Levels | T41A | S45F | APC | Negative/Other[a] | (Missing) | P |
|---|---|---|---|---|---|---|---|
| Sex | Female | 51 (75) | 34 (72) | 5 (46) | 29 (57) | 55 (67) | 0.064 |
| N (%) | Male | 17 (25) | 13 (28) | 6 (55) | 22 (43) | 27 (33) | |
| Race | Caucasian | 47 (69) | 23 (49) | 8 (73) | 36 (71) | 34 (42) | 0.753 |
| N (%) | Hispanic | 7 (10) | 8 (17) | 2 (18) | 5 (10) | 13 (16) | |
| | African American | 6 (9) | 5 (11) | 1 (9) | 2 (4) | 7 (9) | |
| | Asian | 5 (7) | 1 (2) | 0 (0) | 1 (2) | 3 (4) | |
| | Other | 1 (2) | 1 (2) | 0 (0) | 1 (2) | 7 (9) | |
| | (Missing) | 2 (3) | 9 (19) | 0 (0) | 6 (12) | 18 (22) | |
| Age at diagnosis | Median (IQR) | 37 (25–47) | 38 (27–46) | 32 (29–38) | 28 (23–36) | 40 (27–50) | 0.017 |
| Desmoid location | Abdominal/pelvis | 27 (40) | 11 (23) | 4 (36) | 31 (61) | 22 (27) | <0.001 |
| N (%) | Extremity/trunk | 35 (52) | 29 (62) | 2 (18) | 12 (24) | 53 (65) | |
| | Other[b] | 6 (9) | 7 (15) | 5 (46) | 8 (16) | 7 (9) | |
| History of FAP | No | 63 (93) | 45 (96) | 0 (0) | 18 (35) | 64 (78) | <0.001 |
| N (%) | Yes | 0 (0) | 0 (0) | 10 (91) | 33 (65) | 8 (10) | |
| | (Missing) | 5 (7) | 2 (4) | 1 (9) | 0 (0) | 10 (12) | |
| Number of treatments | 1 | 12 (18) | 15 (32) | 2 (18) | 9 (18) | 34 (42) | 0.141 |
| N (%) | 2 | 27 (40) | 14 (30) | 3 (27) | 11 (22) | 22 (27) | |
| | 3+ | 29 (43) | 18 (38) | 6 (55) | 31 (61) | 26 (32) | |
| First-line treatment | Surgery[c] | 37 (54) | 19 (40) | 4 (36) | 30 (59) | 34 (42) | 0.390 |
| N (%) | ADIC | 7 (10) | 5 (11) | 3 (27) | 1 (2) | 2 (2) | |
| | Doxorubicin single agent[d] | 7 (10) | 8 (17) | 1 (9) | 8 (16) | 12 (15) | |
| | Sorafenib | 3 (4) | 1 (2) | 1 (9) | 1 (2) | 5 (6) | |
| | MTX/vinca alkaloids | 2 (3) | 4 (9) | 0 (0) | 4 (8) | 14 (17) | |
| | Other[e] | 12 (18) | 10 (21) | 2 (18) | 7 (14) | 15 (18) | |
| Status at last follow-up | Censored | 68 (100) | 46 (98) | 9 (82) | 43 (84) | 79 (96) | 0.001 |
| N (%) | Died | 0 (0) | 1 (2) | 2 (18) | 8 (16) | 3 (4) | |
| Follow-up time in months | Median (IQR) | 75 (36–107) | 35 (20–92) | 44 (25–90) | 87 (48–157) | 61 (28–108) | 0.006 |

Note: Continuous variables were reported by median and IQR, and compared using Kruskal–Wallis nonparametric test. For categorical variables, the frequencies and percentages were calculated, and compared by Fisher exact test. Patients without mutation information were excluded from testing.
Abbreviations: ADIC, doxorubicin/dacarbazine; FAP, familial adenomatous polyposis; IQR, interquartile range; MTX, methotrexate.
[a]Negative/other mutations: *CTNNB1* negative (n = 42, 88%), S45P (n = 4, 8%), other *CTNNB1* (n = 1, 2%), non-*CTNNB1*/non-APC (n = 1, 2%).
[b]Other location includes head and neck, paraspinal, other location, or multifocal.
[c]Includes surgery alone, or surgery with adjuvant radiation or systemic therapies (Supplementary Fig. S1).
[d]Includes liposomal and traditional doxorubicin (see Supplementary Fig. S1).
[e]Primarily estrogen-suppressing therapies, imatinib, and others (see Supplementary Fig. S1).

treatment type also did not reach statistical significance (Supplementary Table S8). Analysis of first- and second-line rPFS and TTNT showed similarly superior outcomes with doxorubicin-based regimens and sorafenib, compared with surgery and "other" treatments (data not shown).

In summary, cPFS, rPFS, and TTNT were not significantly impacted by mutation subtype; however, trends were observed toward worse outcomes with *APC* mutant tumors. Extremity/trunk desmoid tumor location and treatment with doxorubicin-based, MTX/vinca alkaloids and sorafenib chemotherapy regimens were associated with better clinical outcomes compared with other treatment alternatives.

## OS is significantly affected by *APC* or negative/other mutation subtype and abdominal/pelvis desmoid tumor location

Out of 259 patients included, 14 patients died and 245 were censored. Six patients died from desmoid tumor complications, 6 died from colorectal cancer, and 2 had an unknown cause of death. Of the patients who died from desmoid tumors, 5 had known FAP and mesenteric desmoid tumor location, and 1 had a retroperitoneal desmoid tumor with an S45F mutation. The median OS time was not reached with a median follow-up time of 64 months. Among the 177 patients with mutation testing, negative impact of mutation on OS was seen in patients with *APC* mutations and negative/other mutations (**Fig. 2C**, P = 0.015). OS was also significantly worse in patients with

abdominal/pelvis desmoid tumor, with 5-year OS rate of 91% compared with 99% in extremity/trunk, and 95% in other sites. There were no effects on OS by type of first-line treatment.

## Episode-level analysis demonstrates no significant impact on clinical PFS, RECIST PFS, or TTNT by mutation status or desmoid tumor location, but is affected by treatment regimen

Because of the number of patients in our cohort and the heterogeneity of treatment patterns, we were unable to evaluate activity of systemic treatments used in later lines of therapy. Thus, we performed a second analysis of treatment episodes, to capture activity of multiple treatments utilized across the same patients. Recognizing that different treatments applied to the same patient would not be independent observations, and that patients with higher numbers of treatment lines were likely to have more biologically aggressive disease, we included additional covariates including the number of prior treatments as well as a frailty covariate. Analysis at the episode level showed no significant differences in cPFS, rPFS, or TTNT by mutation subtype or desmoid tumor location. Non-statistically significant inferior outcomes were associated with *APC* and negative/other mutations, as well as abdominal/pelvic location. However, cPFS was significantly affected by type of treatment, with favorable outcomes of ADIC chemotherapy [HR, 0.50 (95% CI, 0.30–0.82), P = 0.006], single-agent doxorubicin [HR, 0.38 (0.24–0.59), P < 0.001], and sorafenib [HR, 0.33 (95% CI,
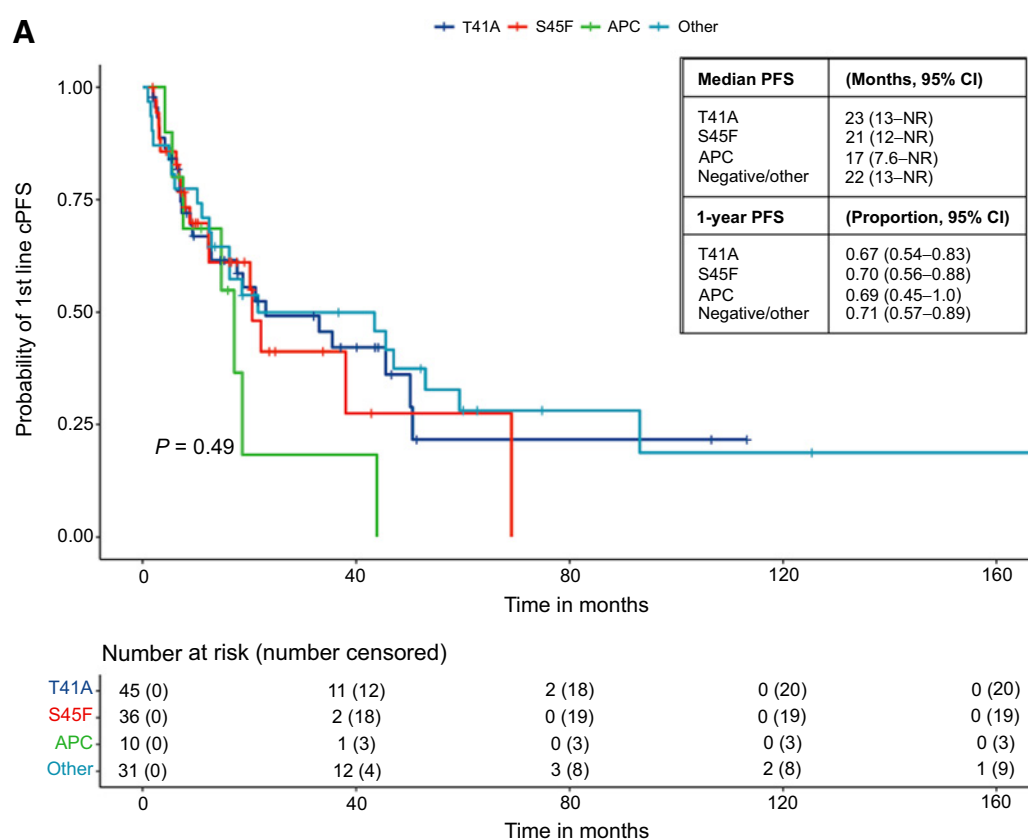
**A**



Legend: + T41A  + S45F  + APC  + Other

| Median PFS | (Months, 95% CI) |
|---|---|
| T41A | 23 (13–NR) |
| S45F | 21 (12–NR) |
| APC | 17 (7.6–NR) |
| Negative/other | 22 (13–NR) |

| 1-year PFS | (Proportion, 95% CI) |
|---|---|
| T41A | 0.67 (0.54–0.83) |
| S45F | 0.70 (0.56–0.88) |
| APC | 0.69 (0.45–1.0) |
| Negative/other | 0.71 (0.57–0.89) |

P = 0.49

Number at risk (number censored)

| | 0 | 40 | 80 | 120 | 160 |
|---|---|---|---|---|---|
| T41A | 45 (0) | 11 (12) | 2 (18) | 0 (20) | 0 (20) |
| S45F | 36 (0) | 2 (18) | 0 (19) | 0 (19) | 0 (19) |
| APC | 10 (0) | 1 (3) | 0 (3) | 0 (3) | 0 (3) |
| Other | 31 (0) | 12 (4) | 3 (8) | 2 (8) | 1 (9) |

Time in months

**Figure 2.**
KM analysis of first-line clinical PFS (**A**), (*Continued on the following page.*)

0.17–0.61), $P = 0.001$], relative to surgery (Supplementary Table S9). Similar findings were observed with inferior rPFS with "other" treatments [HR, 3.41 (95% CI, 1.2–9.9), $P = 0.024$], (Supplementary Table S10), and significantly improved TTNT with single-agent doxorubicin [HR, 0.56 (95% CI, 0.38–0.80), $P = 0.0002$] and sorafenib [HR, 0.49 (95% CI, 0.29–1.2), $P = 0.010$] relative to surgery, and statistically insignificant benefit with ADIC chemotherapy [HR, 0.69 (95% CI, 0.46–1.0), $P = 0.075$] relative to surgery (Supplementary Table S11).

Given our findings that the use of chemotherapy was the strongest factor impacting our clinical outcomes, we again reviewed the impact of mutation status on cPFS for ADIC, single-agent doxorubicin, MTX/vinca alkaloids, and sorafenib treatment episodes. No significant differences were observed by KM analysis among these four therapies by mutation status (**Fig. 3**). In Cox multivariable analysis, *APC* and other/negative mutations tended to do worse regardless of specific therapy. We did note that no clinical progression occurred in patients treated with sorafenib who had S45F mutations (**Fig. 3D**). For episodes with radiographic tumor measurements, we created waterfall plots by mutation for treatment episodes from the four main therapies as well as the "other" therapy group to look at activity from ER blockade/anti-inflammatories and imatinib. Overall, ADIC, single-agent doxorubicin, MTX/vinca alkaloids, and sorafenib all had consistent anti-tumor activity for desmoid tumors, with no obvious differences across mutation subtypes (Supplementary Fig. S4; Supplementary Table S12). Response rates ranged from 24% to 34% across the different treatments, with the "other" treatment cohort showing a lower response rate at 11%. Disease control rates were overall high with the "other"

therapy cohort achieving 72%, doxorubicin-based regimens at greater than 90%, and MTX/vinca alkaloids and sorafenib at 87% and 89%, respectively. Overall, we did not see convincing evidence of resistance to chemotherapies across the various mutations.

## Discussion

The treatment paradigm for desmoid tumors has evolved considerably in recent years, with adoption of a "watch and wait" approach based on variable biology in individual desmoid tumors and patients (20, 27). However, the recommendation to monitor a large desmoid tumor with uncertain potential for future problems can be difficult for both patients and clinicians to accept. Prognostic factors for desmoid tumors have largely been based on postoperative recurrences, including clinical factors such as large size (greater than 5 cm), extraabdominal tumor location, superficial and deep fascial locations, and controversially, margin status at surgery (14, 28, 29). In addition, a recent study reported on 64 cases of desmoid tumors and showed that a three gene risk score including *IFI6*, *LGMN*, and *CKLF* was a strong prognostic indicator for recurrence-free survival (30). The specific mutation leading to desmoid tumor formation has been suggested in some, but not all series to be a marker for recurrence risk, with *CTNNB1* S45F and *APC* mutations previously being ascribed with more aggressive behavior (10–12, 17). A prognostic system for FAP-related desmoid tumors has been derived by investigators at the Cleveland Clinic to predict 5-year mortality rates encompassing desmoid tumor–related death, secondary neoplasms, and surgical and supportive
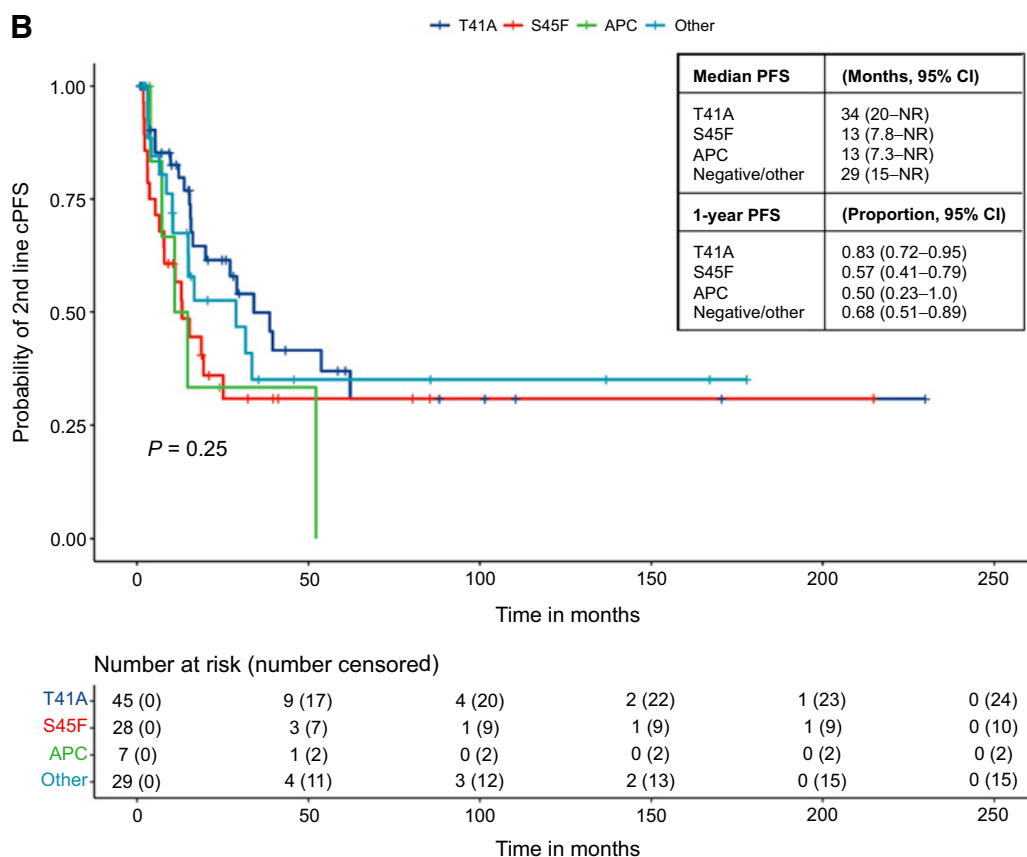
**B**

| Median PFS | (Months, 95% CI) |
|---|---|
| T41A | 34 (20–NR) |
| S45F | 13 (7.8–NR) |
| APC | 13 (7.3–NR) |
| Negative/other | 29 (15–NR) |

| 1-year PFS | (Proportion, 95% CI) |
|---|---|
| T41A | 0.83 (0.72–0.95) |
| S45F | 0.57 (0.41–0.79) |
| APC | 0.50 (0.23–1.0) |
| Negative/other | 0.68 (0.51–0.89) |

$P = 0.25$

Number at risk (number censored)

| | 0 | 50 | 100 | 150 | 200 | 250 |
|---|---|---|---|---|---|---|
| T41A | 45 (0) | 9 (17) | 4 (20) | 2 (22) | 1 (23) | 0 (24) |
| S45F | 28 (0) | 3 (7) | 1 (9) | 1 (9) | 1 (9) | 0 (10) |
| APC | 7 (0) | 1 (2) | 0 (2) | 0 (2) | 0 (2) | 0 (2) |
| Other | 29 (0) | 4 (11) | 3 (12) | 2 (13) | 0 (15) | 0 (15) |

**Figure 2.**
(*Continued.*) second-line clinical PFS (**B**), (*Continued on the following page.*)

care complications (31). Unfortunately, there have not yet been data to link these prognostic factors to desmoid tumor treatment outcomes, to guide timing for initiation or to predict response to particular therapies. An ongoing clinical trial of patients with desmoid tumor includes mutation testing during the "watch and wait" period and will hopefully offer some prospective guidance on these issues (NCT02547831).

To address this deficiency, we conducted a large, retrospective analysis to evaluate potential links between desmoid tumor mutation subtypes and clinical responses to surgery and chemotherapy regimens chosen in standard clinical practice at four large U.S. sarcoma centers. The patients included in this analysis were managed prior to the development of modern consensus recommendations that suggest the following: (i) active surveillance is most appropriate for primary/recurrent desmoid tumors given variable biologic behavior, (ii) surgical resection should be reserved for sporadic desmoid tumors of the abdominal wall that progress on observation, and (iii) medical therapies should be utilized instead of surgery for nonabdominal wall desmoid tumors that progress on observation (20). Importantly, our data did not permit reliable assessment of clinical outcomes from the "watch and wait" observation approach and our analysis was focused on patients who actually received systemic treatments.

Overall, we could not conclusively identify worse clinical outcomes with *CTNNB1* S45F mutations compared with T41A mutations in the first-line treatment setting, which is in accord with more recent

prognostic studies (13, 14). We did note trends suggesting that *APC* and other/negative mutations (which were largely patients with clinical history of FAP) had worse outcomes with treatment, but few of these analyses were statistically significant. Despite these findings, we feel that mutation testing still has important roles in the management of patients with desmoid tumor. The numbers of patients in this study are small, and prospective evaluation of mutation subtype, clinical course, and response to treatment is warranted to confirm our findings and to settle the conflicting reports on prognostic impact of S45F *CTNNB1* mutations. In addition, performing mutation testing helps to confirm the desmoid tumor diagnosis when histologic analysis can be misleading, and identification of an *APC* deletion in a desmoid tumor prompts germline testing for FAP which has important connotations for risk of other cancers.

Importantly, the strongest impact on clinical outcomes was observed from systemic therapies, especially doxorubicin-containing regimens, which were associated with longer cPFS, rPFS, and TTNT compared with surgery or "other" systemic therapies, primarily ER blockade and imatinib. This finding supports future testing of the hypothesis that desmoid tumors who progress on "watch and wait" periods will have better outcomes with doxorubicin-based, MTX/vinca alkaloid, or sorafenib chemotherapy compared with surgery or ER blockade/imatinib therapy. While patients with *APC* and negative/other mutations tended to have worse outcomes with these therapies compared with T41A and S45F mutations, our subgroup analysis did

**C**



| Median OS | (Months, 95% CI) |
|---|---|
| T41A | NR (NR–NR) |
| S45F | NR (NR–NR) |
| APC | NR (110–NR) |
| Negative/other | NR (210–NR) |
| **5-year OS** | **(Proportion, 95% CI)** |
| T41A | 1.0 (1.0–1.0) |
| S45F | 1.0 (1.0–1.0) |
| APC | 0.83 (0.58–1.0) |
| Negative/other | 0.90 (0.82–1.0) |

Number at risk (number censored)

| | 0 | 100 | 200 | 300 | 400 |
|---|---|---|---|---|---|
| T41A | 68 (0) | 21 (47) | 4 (64) | 0 (68) | 0 (68) |
| S45F | 47 (0) | 8 (38) | 1 (45) | 0 (46) | 0 (46) |
| APC | 11 (0) | 3 (7) | 1 (8) | 0 (9) | 0 (9) |
| Other | 51 (0) | 22 (24) | 6 (38) | 1 (42) | 0 (43) |

Time in months
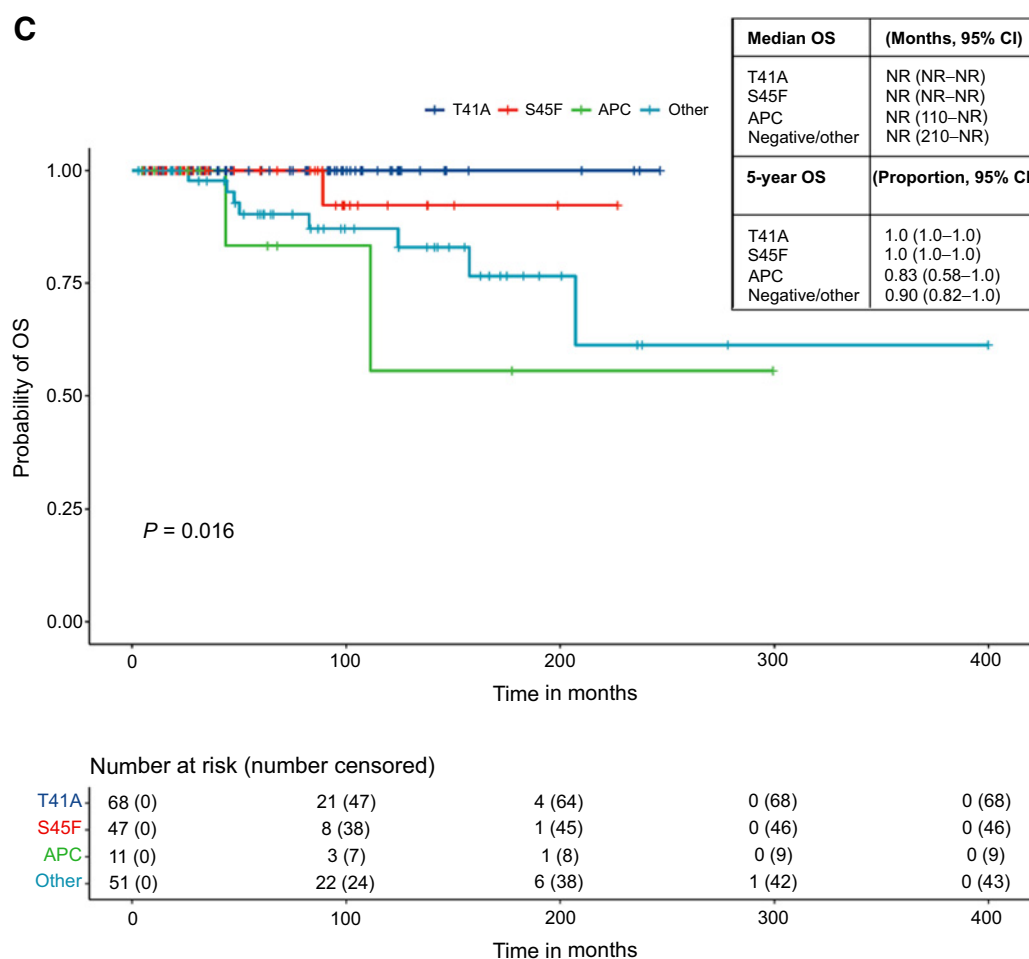
**Figure 2.**
(*Continued.*) and OS (**C**) by mutation subtype. Survival was calculated for patients with available data and analyzed using the KM method, with the survival curve, median survival time, and proportion free from progression at 1 year (clinical PFS) or 5 years (OS) along with corresponding two-sided 95% Brookmeyer–Crowley CIs. Curves corresponding to specific mutation subtypes were compared using log-rank test, with P < 0.05 considered statistically significant.

not suggest a superior choice of therapy for mutation subtypes. Our data suggest that at least in the first- and second-line settings, a clinically meaningful likelihood of desmoid tumor regression or prolonged stability can be achieved regardless of mutation type with the use of doxorubicin-based, MTX/vinca alkaloid, or sorafenib therapy.

Despite the superior results of doxorubicin-containing therapies, ADIC is associated with potential long-term toxicities, including loss of fertility, cardiomyopathy, and development of secondary cancers. Pegylated liposomal doxorubicin is better tolerated, but the duration of dosing is often limited by significant skin toxicity, at least when given at the approved dose and schedule. We were unable to perform a direct comparison to determine whether the addition of dacarbazine in ADIC significantly improved outcomes over single-agent doxorubicin to warrant the additional toxicity. With the emergence of better tolerated treatments with very promising activity, such as sorafenib (32), pazopanib (33), and nirogacestat (34), or novel interventional strategies such as cryoablation and high-intensity frequency ultrasound procedures (35), the future of doxorubicin-containing regimens and MTX/vinca alkaloids for desmoid tumors is uncertain, and likely

will continue to be reserved for desmoid tumors where a rapid decrease in tumor bulk or severe symptoms is needed for life or limb threats. Importantly, our study also contained relatively few patients treated with radiation, which has historically had excellent results for management of desmoid tumors, albeit with significant long-term toxicity (36).

Promising signals of activity were seen in our study with sorafenib across all mutation subtypes, with none of the S45F patients progressing on sorafenib, though the small numbers of patients treated in this series limits statistical significance. We found this finding interesting, given that previous preclinical data suggested a mechanism for resistance to sorafenib in S45F-mutant desmoid tumor cell lines (37). However, the positive results from a pivotal phase III trial of sorafenib versus placebo for desmoid tumors support the hypothesis that sorafenib maintains activity across all mutation subgroups. The results from this trial showed 2-year PFS of 81% in the sorafenib group (95% CI, 69–96) versus 36% in the placebo group (95% CI, 22–57), with an objective response rate of 33% (95% CI, 20–48) in the sorafenib group compared with 20% in the placebo group (95% CI, 8–38; ref. 32). Correlative biopsies from patients treated on this study would be an

**Table 3A.** Cox proportional hazards model analysis for first-line clinical PFS by mutation status.

| Variable | | All | HR (univariable) (95% CI, P) | HR (multivariable) (95% CI, P) |
|---|---|---|---|---|
| Sex | Female | 125 (100) | — | — |
| | Male | 64 (100) | 0.75 (0.49–1.2, P = 0.19) | 0.83 (0.45–1.5, P = 0.54) |
| Race | Caucasian | 115 (100) | — | — |
| | Hispanic/Latino | 23 (100) | 0.91 (0.48–1.7, P = 0.78) | 1.6 (0.72–3.6, P = 0.25) |
| | African American | 15 (100.0) | 1.08 (0.54–2.2, P = 0.83) | 0.99 (0.45–2.2, P = 0.99) |
| | Asian | 8 (100.0) | 0.77 (0.24–2.5, P = 0.66) | 0.77 (0.17–3.4, P = 0.74) |
| | Other/unknown | 7 (100.0) | 0.94 (0.34–2.6, P = 0.91) | 0.78 (0.09–7.0, P = 0.83) |
| Age | Mean (SD) | 36.9 (14.9) | 0.99 (0.97–1.0, P = 0.096) | 0.99 (0.97–1.0, P = 0.42) |
| No. of treatment lines | 1 | 73 (100.0) | — | — |
| | 2 | 45 (100.0) | 6.7 (3.4–13, P < 0.001) | 7.9 (2.2–28, P = 0.001) |
| | 3+ | 71 (100.0) | 8.6 (4.5–16.4, P < 0.001) | 11 (3.2–35, P < 0.001) |
| Mutation subtype | T41A | 45 (100.0) | — | — |
| | S45F | 36 (100.0) | 1.1 (0.61–2.1, P = 0.68) | 1.0 (0.50–2.0, P = 0.99) |
| | APC | 10 (100.0) | 1.8 (0.75–4.1, P = 0.20) | 1.2 (0.49–2.9, P = 0.69) |
| | Other | 31 (100.0) | 0.89 (0.49–1.6, P = 0.70) | 0.68 (0.32–1.4, P = 0.30) |

**Table 3B.** Cox proportional hazards model analysis for second-line clinical PFS by mutation status.

| Variable | | All | HR (univariable) (95% CI, P) | HR (multivariable) (95% CI, P) |
|---|---|---|---|---|
| Sex | Female | 99 (100) | — | — |
| | Male | 46 (100) | 0.90 (0.54–1.5, P = 0.69) | 1.1 (0.59–2.2, P = 0.71) |
| Age | Mean (SD) | 35.3 (14) | 0.98 (0.97–1.0, P = 0.07) | 0.99 (0.97–1.0, P = 0.38) |
| Time to second-line treatment | Mean (SD) | 16.3 (21) | 1.0 (0.98–1.01, P = 0.57) | 1.0 (0.98–1.01, P = 0.77) |
| No. of treatment lines | 2 | 68 (100) | — | — |
| | 3+ | 77 (100) | 5.4 (3.0–9.7, P < 0.001) | 6.0 (2.5–14.4, P < 0.001) |
| Mutation subtype | T41A | 45 (100) | — | — |
| | S45F | 28 (100) | 1.7 (0.92–3.3, P = 0.09) | 1.8 (0.89–3.8, P = 0.10) |
| | APC | 7 (100) | 2.0 (0.78–5.6, P = 0.14) | 1.59 (0.57–4.5, P = 0.38) |
| | Other | 29 (100) | 1.2 (0.62–2.4, P = 0.57) | 1.1 (0.50–2.3, P = 0.85) |

ideal platform to further confirm any impact of mutation status in sorafenib-treated patients.

We noted that at times, the differences in outcomes between rPFS and cPFS or TTNT were striking; the overall first-line median rPFS for all patients was 168 months, compared with median cPFS of 31 months and median TTNT of 18 months. While we ensured that RECIST measurements were performed by musculoskeletal radiologists, scans were not available for all patients, and were not done at consistent times across the patient cohort. Despite this, the observed differences demonstrate how RECIST could be misleading for clinical outcomes for patients with desmoid tumor. Slow growing, large desmoid tumors are well known to display unusual growth patterns that may not lend themselves to longest tumor diameter measurements. In addition, when becoming dormant, desmoid tumors may not change size but become more collagenized. Even if active, large desmoid tumors may not reach the RECIST PD threshold (20% growth failure cutoff in longest tumor diameter from nadir) for a very long time, and the RECIST PR criterion (30% decrease in longest tumor diameter from baseline) may also underestimate benefit of potentially effective therapies. The inefficiency of RECIST is further evidenced in our review of the waterfall plots for various treatment regimens, that show very high disease control rates that incorporate SD, but relatively modest response rates, usually less than 30%. Our findings support continued exploration of alternative response criteria for desmoid tumors,

including three-dimensional volumetrics and MRI radiomics to better assess changes in response to therapies (38–41), which are being incorporated in ongoing clinical trials (NCT03785964).

Overall, our study represents one of the largest retrospective series and one of the few studies to examine the effect of desmoid tumor mutation status on response to systemic therapies in desmoid tumors. However, this study has several critical limitations. All retrospective studies are subject to reporting and follow-up biases and given that patients were studied from tertiary referral centers, these patients likely represent more refractory cases that were more heavily treated than would be in lower volume centers and certainly in the community (referral bias). In addition, we relied heavily on clinical impression and decision-making for outcomes, which can be biased by subjective rather than objective assessments, as evidenced by the differences observed between cPFS and rPFS. Over the timeframe in this study, there was significant variation in practice patterns, without standardization of the number of cycles or doses used for systemic chemotherapy, or timing of imaging, which can affect assessment of PFS. Despite the large numbers of patients, we were still limited in statistical power by the numbers of patients with mutation data within various treatment subsets, due to lack of next-generation sequencing at the time of original testing, inability to obtain archival samples, or failure of DNA extraction from very old or poorly preserved materials. After subdividing our patient population by treatments, lines of therapy, and
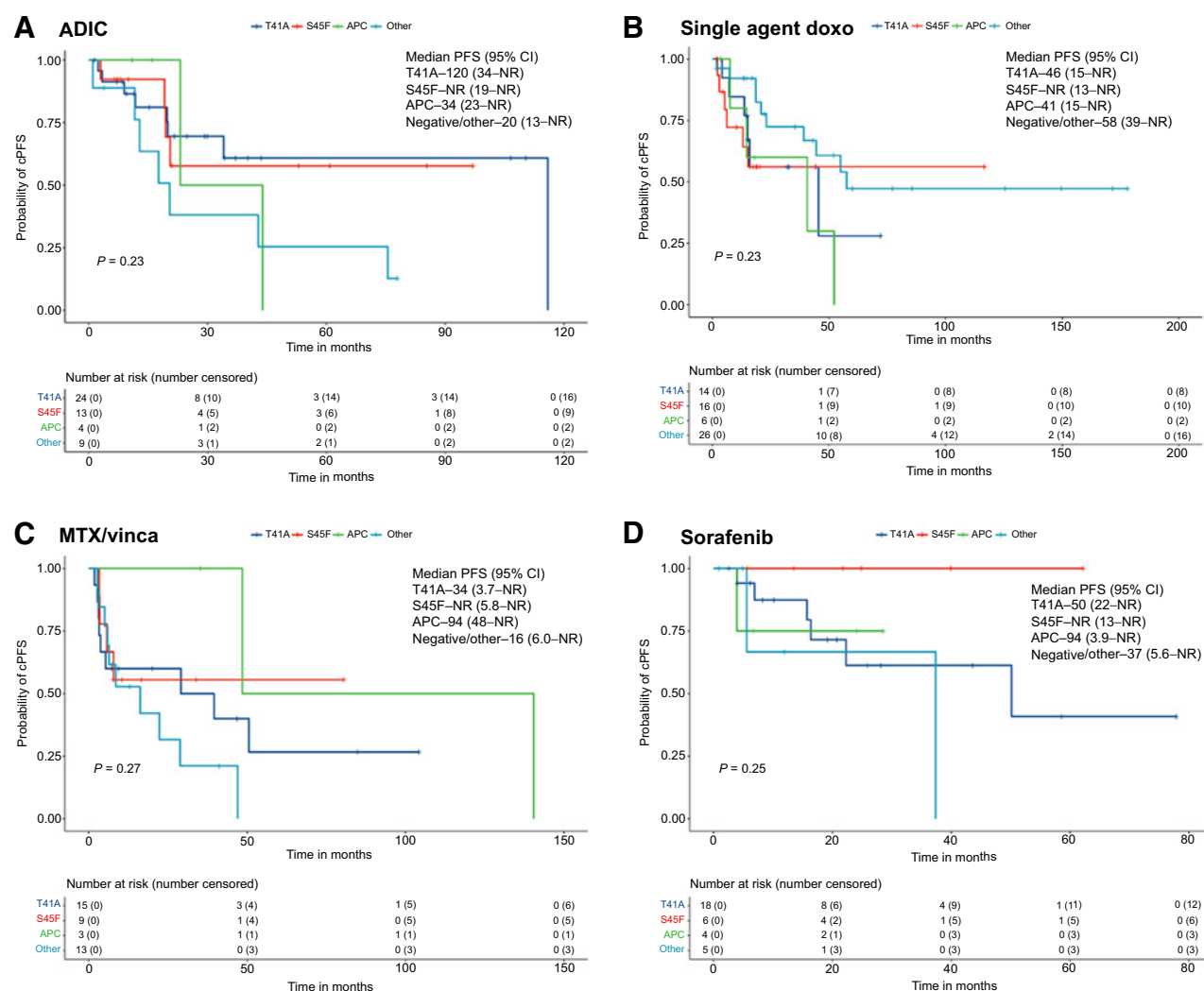
**Figure 3.**
KM analysis of clinical PFS for treatment episodes by mutation status. Survival curves and median clinical PFS shown for ADIC (**A**), single-agent doxorubicin (primarily liposomal doxorubicin (**B**), MTX/vinca alkaloids (**C**), and sorafenib (**D**). Survival was calculated for patients with available data and analyzed using the KM method, with the survival curve, median survival time, and proportion free from progression at 1 year (clinical PFS) or 5 years (OS) along with corresponding two-sided 95% Brookmeyer-Crowley CIs. Curves corresponding to specific mutation subtypes were compared using log-rank test, with $P < 0.05$ considered statistically significant.

mutation subtypes, patients were lumped into categories that may dilute a signal of activity. Finally, there were patients with clinically documented FAP, but where an *APC* mutation could not be confirmed, and thus, included in the negative/other mutation category.

The results from our study are descriptive and hypothesis-generating and highlight important questions for the next generation of prospective clinical trials. First, we look forward to the results of ongoing prospective observational studies to analyze mutation subtype and desmoid tumors location for patients on active observation, who are then initiated on traditional and novel systemic therapies. We also noted improved clinical outcomes with treatment for extremity/trunk desmoid tumor locations, which contrasts with the higher risk of recurrence that has been reported in extremity desmoid tumors even over intraabdominal tumors postoperatively (14). Our data suggest that extremity tumors may have a higher response rate overall when treatment is needed and argues for future prospective studies to evaluate whether earlier initiation of systemic treatments should be adopted for

extremity desmoid tumors. On the basis of our observations and outcomes from recently reported clinical trials of desmoid tumor treatment, prospective evaluation of sorafenib or pazopanib compared with pegylated liposomal doxorubicin would formally compare the activity, toxicity, and quality-of-life measures of these commonly used regimens in modern practice. In addition, FAP-associated desmoid tumors continue to be a significant challenge with worse outcomes regardless of systemic therapy, in need of further clinical trials. With the emergence of novel treatments including gamma secretase inhibitors and Wnt/β-catenin inhibitors, and increasing use of targeted approaches such as high frequency ultrasound and cryoablation, it is likely that the treatment landscape will continue to evolve over the next years for this rare and challenging group of neoplasms.

## Authors' Disclosures

## Authors' Contributions

**M.J. Nathenson:** Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **J. Hu:** Formal analysis, methodology, writing–original draft, writing–review and editing. **R. Ratan:** Data curation. **N. Somaiah:** Data curation. **R. Hsu:** Data curation, writing–review and editing. **P.J. DeMaria:** Data curation, writing–review and editing. **H.W. Catoe:** Data curation. **A. Pang:** Data curation. **T.K. Subhawong:** Resources, data curation, supervision, visualization, methodology, writing–review and editing. **B. Amini:** Resources, data curation, visualization, writing–review and editing.

**K. Sweet:** Data curation, visualization, writing–review and editing. **K. Feister:** Data curation, visualization. **K. Malik:** Data curation, visualization, methodology. **J. Jagannathan:** Data curation, visualization, methodology. **M. Braschi-Amirfarzan:** Data curation, visualization. **J. Sheren:** Resources, data curation, formal analysis, methodology. **Y. Caldas:** Data curation. **C. Moreno Tellez:** Data curation. **A.E. Rosenberg:** Resources, data curation, writing–review and editing. **A.J. Lazar:** Resources, data curation, writing–review and editing. **R.G. Maki:** Conceptualization, resources, data curation, supervision, writing–review and editing. **P. Benedetto:** Data curation. **J. Cohen:** Data curation. **J.C. Trent:** Data curation. **V. Ravi:** Conceptualization, resources, software, methodology. **S. Patel:** Resources, data curation. **B.A. Wilky:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, investigation, methodology, writing–original draft, writing–review and editing.

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## Note

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