Sorafenib for Advanced and Refractory Desmoid Tumors

Mrinal M. Gounder, M.D., Michelle R. Mahoney, M.S.,
Brian A. Van Tine, M.D., Ph.D., Vinod Ravi, M.D., Steven Attia, D.O.,
Hari A. Deshpande, M.D., Abha A. Gupta, M.D., Mohammed M. Milhem, M.D.,
Robert M. Conry, M.D., Sujana Movva, M.D., Michael J. Pishvaian, M.D., Ph.D.,
Richard F. Riedel, M.D., Tarek Sabagh, M.D., William D. Tap, M.D.,
Natally Horvat, M.D., Ethan Basch, M.D., Lawrence H. Schwartz, M.D.,
Robert G. Maki, M.D., Ph.D., Narasimhan P. Agaram, M.B., B.S.,
Robert A. Lefkowitz, M.D., Yousef Mazaheri, Ph.D.,
Rikiya Yamashita, M.D., Ph.D., John J. Wright, M.D., Ph.D.,
Amylou C. Dueck, Ph.D., and Gary K. Schwartz, M.D.

ABSTRACT

BACKGROUND

Desmoid tumors (also referred to as aggressive fibromatosis) are connective tissue neoplasms that can arise in any anatomical location and infiltrate the mesentery, neurovascular structures, and visceral organs. There is no standard of care.

METHODS

In this double-blind, phase 3 trial, we randomly assigned 87 patients with progressive, symptomatic, or recurrent desmoid tumors to receive either sorafenib (400-mg tablet once daily) or matching placebo. Crossover to the sorafenib group was permitted for patients in the placebo group who had disease progression. The primary end point was investigator-assessed progression-free survival; rates of objective response and adverse events were also evaluated.

RESULTS

With a median follow-up of 27.2 months, the 2-year progression-free survival rate was 81% (95% confidence interval [CI], 69 to 96) in the sorafenib group and 36% (95% CI, 22 to 57) in the placebo group (hazard ratio for progression or death, 0.13; 95% CI, 0.05 to 0.31; P<0.001). Before crossover, the objective response rate was 33% (95% CI, 20 to 48) in the sorafenib group and 20% (95% CI, 8 to 38) in the placebo group. The median time to an objective response among patients who had a response was 9.6 months (interquartile range, 6.6 to 16.7) in the sorafenib group and 13.3 months (interquartile range, 11.2 to 31.1) in the placebo group. The objective responses are ongoing. Among patients who received sorafenib, the most frequently reported adverse events were grade 1 or 2 events of rash (73%), fatigue (67%), hypertension (55%), and diarrhea (51%).

CONCLUSIONS

Among patients with progressive, refractory, or symptomatic desmoid tumors, sorafenib significantly prolonged progression-free survival and induced durable responses. (Funded by the National Cancer Institute and others; ClinicalTrials.gov number, NCT02066181.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Gounder at Memorial Sloan Kettering Cancer Center, 300 E. 66th St., New York, NY 10065, or at gounderm@mskcc.org.

DESMOID TUMORS (ALSO CALLED AGGRESsive fibromatosis) are rare, locally aggressive neoplasms that arise from connective tissues.[1] The annual incidence of the condition is estimated to be 1000 patients in the United States, and the prevalence may be higher. Desmoid tumors typically affect young adults in their 20s and 30s, but they can occur in children, adolescents, and older adults. Most desmoid tumors are sporadic (>90%) and harbor *CTNBB1* mutations; a minority of tumors are associated with germline *APC* mutations and Gardner's syndrome.[2-4] Common primary sites affected by these tumors include the abdominal wall, mesentery, and neurovascular bundle of the extremities. Desmoid tumors do not metastasize and pose a low risk of death (except in Gardner's syndrome), but they confer substantial complications. Patients may be asymptomatic or may present with severe pain, swelling, deformity, loss of range of motion, bowel obstruction or perforation, or compromise of vital organs.[5] Additional associated complications in young adults include long-term opioid use, social isolation, insomnia, anxiety, depression, and interruption of education and employment.[6]

Although a number of agents have activity against desmoid tumors, no accepted standard of care exists for systemic treatment of the tumors.[7] Beyond a few prospective trials, most relevant clinical data have been derived from case series and retrospective analyses. Interpretation of the data is challenging, given the unpredictable natural history of the condition. Desmoid tumors can show rapid growth followed by periods of stabilization, spontaneous regression, or subsequent growth phases.[2] Spontaneous regression is reported in up to 20% of patients.[8] An up-front watch-and-wait strategy is increasingly advocated for many patients.[9-11] Surgery has been the standard of care for primary treatment, but the risk of local recurrence remains unacceptably high (>40%). Local (radiation therapy) or systemic treatments are usually indicated in patients who have disease-related symptoms or progressive disease. Systemic treatment options include hormonal blockade, cytotoxic chemotherapy, and tyrosine kinase inhibitors; the response rates associated with these treatments vary (0 to 40%).[12-19] For example, in small prospective studies, imatinib has been found to have limited activity (6 to 11%), and no predictive biomarkers of benefit were found.[20]

In a retrospective analysis, sorafenib, an oral multitargeted receptor tyrosine kinase inhibitor, at a starting dose of 400 mg once daily was shown to have acceptable safety and was associated with a response rate of 25%, as evaluated with Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, as well as with improvements in quality of life.[21] The retrospective study also highlighted that RECIST may underestimate efficacy and that a better criterion may be magnetic resonance imaging (MRI) T_2-weighted signal intensity, an imaging biomarker that signifies a biologic transformation from a cellular tumor to a collagenous scar.[22] This hypothesis prompted us to conduct a randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the safety and efficacy of sorafenib in the treatment of desmoid tumors.

METHODS

PATIENTS

We enrolled patients 18 years of age or older with a histologically documented desmoid tumor (aggressive fibromatosis) if they had measurable disease and radiographic progression (of ≥10%) in maximum unidimensional measurement within the previous 6 months, recurrent or primary disease that was deemed inoperable or as requiring extensive surgery, or symptomatic disease. An additional entry criterion was an absence of previous sorafenib exposure; no minimum or maximum number of previous systemic treatments was stipulated. The complete entry and crossover eligibility criteria, including baseline laboratory values, are provided in the protocol, available with the full text of this article at NEJM.org.

TRIAL OVERSIGHT

The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and federal and local policy on bioethics and human biologic specimens. Each participating institution obtained approval from a local or central institutional review board. All the patients signed informed consent forms in

accordance with federal and institutional guidelines. The trial was designed by the first author and monitored by the Alliance Data and Safety Monitoring Board for the evaluation of safety and the primary end point.

This trial was funded by the National Cancer Institute and was conducted by the Alliance Clinical Trials in Oncology Group and the National Clinical Trials Network (Table S1 in the Supplementary Appendix, available at NEJM.org). Sorafenib was provided by the National Cancer Institute through a research collaboration with Bayer Pharmaceuticals.

All the data were collected, subjected to quality-assurance measures, and analyzed by the Alliance Statistics and Data Center. Archival tumor tissue for central pathological review, biopsy specimens (optional), and MRI scans were de-identified with regard to patient health information and, after completion of quality-assurance measures, were sent for central pathological review and correlative studies. The authors attest to the accuracy and completeness of the data and for the adherence of the trial to the protocol. The first draft of the manuscript was written by the principal investigators (the first and second authors); all the authors reviewed the manuscript. No one who is not an author contributed to the writing of the manuscript.

TRIAL DESIGN AND TREATMENT

In this investigator-initiated, double-blind, placebo-controlled, phase 3 trial, patients were randomly assigned (in a 2:1 ratio) to receive either sorafenib (at a starting dose of 400 mg once daily) or placebo. Desmoid tumors were imaged by means of computed tomography (CT) or MRI at baseline and every 8 weeks. Efficacy was assessed at local institutions with the use of RECIST, version 1.1.[23] Administration of sorafenib or placebo continued until disease progression, unacceptable side effects, or withdrawal of consent. At disease progression, the patients were told whether they had been receiving sorafenib or placebo, and those who had been receiving placebo were eligible to cross over to the sorafenib group if they still met the trial entry criteria. Dose interruptions (of up to 28 days) and one dose reduction (to 200 mg once daily) were permitted and described in the trial protocol.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, as determined by the treating physicians in accordance with RECIST, version 1.1. This end point was defined as the time from randomization to progressive disease (radiographic, clinical, or both) or death, and data were censored at the most recent disease assessment. A modification of the traditional intention-to-treat principle was used for the analysis of the primary end point, in which patients with an incorrect histologic diagnosis were excluded. The secondary end points were toxic effects, the rate of radiographic response, and overall survival. Ineligible patients who received a trial agent were included in the assessment of toxic effects, in which the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, were used.

At enrollment, patients were given the option of consenting to undergo tumor biopsies and surveys with patient-reported outcome questionnaires at baseline and while taking the trial regimen. Exploratory end points included assessment of pain with the use of the Brief Pain Inventory and assessment of 11 side effects with the patient-reported outcomes version of the CTCAE (PRO-CTCAE, version 1.0) before crossover. Exploratory imaging end points included a comparison of RECIST measurements with total tumor volume and MRI T_2-weighted signal intensity in patients.

STATISTICAL ANALYSIS

We calculated that a sample of 75 patients, each with 12 months of follow-up, would provide 90% power at a one-sided significance level of 0.025 (with the use of a stratified log-rank test) to detect a median progression-free survival that was 9 months longer with sorafenib than with placebo (with an expected median progression-free survival of 6 months among patients receiving placebo) and a hazard ratio of 0.4 for progression or death in the sorefenib group relative to the placebo group. Enrollment was estimated at 4 patients per month, for an anticipated duration of 21 months to complete enrollment. The final analysis was to occur at the time that 52 patients had had disease progression or had died. Sorafenib was to be declared as superior with regard to progression-free survival if the one-sided P value associated with the stratified

log-rank test statistic was less than 0.025. A preplanned, nonbinding futility analysis was performed when 24 (45%) of the 52 required events had been observed.

Kaplan–Meier methods and Cox proportional-hazards modeling were used to estimate the distributions of time-to-event variables and hazard ratios (including confidence intervals), respectively, accounting for stratification factors.[24,25] Summary statistics, frequency tables, and parametric and nonparametric statistical tests were used, as applicable. The maximum PRO-CTCAE score for each item during the intervention with accounting for baseline PRO-CTCAE score was tabulated for each trial group, and the difference between the groups in the proportion of patients with a score of at least 1 and, separately, with a score of at least 3 was computed with exact 95% confidence intervals.[26] All P values and confidence intervals are two-sided and unadjusted for multiplicity. All the observed data were included in the analysis without imputation for missing data. All the analyses were performed with the use of SAS software, version 9.4 (SAS Institute). The data-lock date was January 31, 2018.
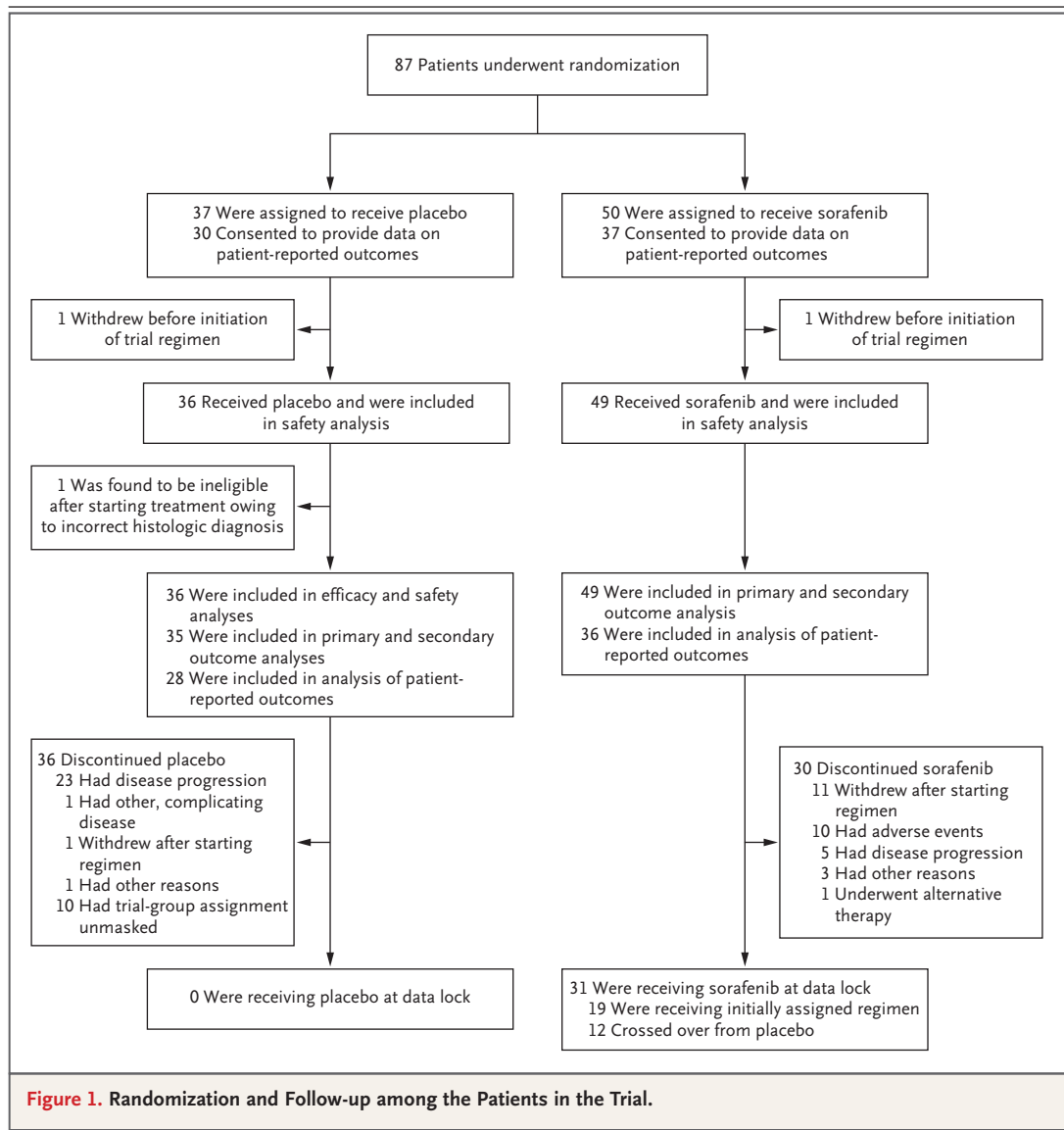

Figure 1. Randomization and Follow-up among the Patients in the Trial.

RESULTS

PATIENTS, ENROLLMENT, AND TREATMENT

From March 21, 2014, to January 6, 2016, a total of 87 patients were enrolled across 24 sites; 50 patients were randomly assigned to the sorafenib group and 37 to the placebo group (Fig. 1). A systems computer algorithm error was detected after 70 patients (38 in the sorafenib group and 32 in the placebo group) had been enrolled. The randomization ratio was approximately 1.6 to 1.7:1 (sorafenib:placebo) instead of the prespecified 2:1 ratio. This error was shared with the data and safety monitoring board, institutional review boards, treating physicians, and patients (in October 2015), with correction for the remainder of enrollment.

The characteristics of the patients at baseline were well balanced between the two trial groups (Table 1).[27] A larger percentage of female than male patients were enrolled (69%), and the median age of the patients was 37 years (interquartile range, 28 to 50), findings consistent with the natural history of desmoid tumors; 80% of the patients reported their race as white. The median dose of sorafenib that was administered across the entire trial was 400 mg daily. Dose interruptions occurred in 65% of the patients in the sorafenib group (32 of 49) and 34% of the patients in the placebo group (12 of 35), and dose reductions due to toxic effects occurred in 31% (15 of 49) and 11% (4 of 35), respectively. At data cutoff, 19 patients (39%) who had initially been assigned to the sorafenib group continued to take the drug. At the time of the interim analysis, the data and safety monitoring board also requested an efficacy analysis, and subsequently the trial was halted and unblinded.

EFFICACY

Of the 87 patients who underwent randomization, 84 (97%) were included in the analysis of primary and secondary end points, with a median follow-up of 27.2 months (interquartile range, 22.0 to 31.7) among the 83 surviving patients. Although the median progression-free survival has not yet been reached, the estimates of the progression-free survival rates at 1 year were 89% (95% confidence interval [CI], 80 to 99) in the sorafenib group and 46% (95% CI, 32 to 67) in the placebo group, and the estimates

at 2 years were 81% (95% CI, 69 to 96) and 36% (95% CI, 22 to 57), respectively. The results for progression-free survival favored sorafenib, with an 87% lower risk of progression or death in the sorafenib group than in the placebo group (hazard ratio for disease progression or death, 0.13; 95% CI, 0.05 to 0.31; P<0.001) (Fig. 2). Overall, 33% of the patients in the trial (28 of 84) had disease progression: 12% of the patients (6 of 49) in the sorafenib group and 63% of the patients (22 of 35) in the placebo group. Clinical deterioration in the absence of radiographic evidence was the sole indicator of progression in 11 of the 28 patients with progression (39%; 9 patients in the placebo group and 2 in the sorafenib group).

The overall rate of objective response was 33% (95% CI, 20 to 48) in the sorafenib group (16 patients [1 with a complete response and 15 with partial responses] of 49) and 20% (95% CI, 8 to 37) in the placebo group (7 patients [all of whom had a partial response] of 35) (Fig. 3A, and Fig. S1 in the Supplementary Appendix). The mean best percentage change in the sum of the target lesions (RECIST) was −26% (range, −100 to 7) in the sorafenib group and −12% (range, −85 to 32) in the placebo group. The median time to a RECIST-defined response among patients who had a response was 9.6 months (interquartile range, 6.6 to 16.7) in the sorafenib group and 13.3 months (interquartile range, 11.2 to 31.1) in the placebo group (Fig. 3B). The earliest RECIST-defined partial response occurred at 2.2 months in sorafenib group and at 8.8 months in the placebo group.

In the exploratory imaging analysis, 498 MRI scans were obtained from 55 patients. We selected a training set of 11 patients who were treated at a single institution (Memorial Sloan Kettering Cancer Center), and we analyzed 167 MRI scans for changes in tumor dimension (according to RECIST) and compared this value with the changes in total tumor volume and T_2-weighted signal intensity. As shown in Figure S2 in the Supplementary Appendix, changes in T_2-weighted signal intensity and volumetric measurements may be better measures of treatment effect than RECIST. This is particularly evident when the best response according to RECIST is stable disease.

Table 1. Demographic and Clinical Characteristics of the Patients at Randomization.*

Characteristic	Placebo (N = 37)	Sorafenib (N = 50)
Median age (range) — yr	37 (21–67)	37 (18–72)
Female sex — no. (%)	26 (70)	34 (68)
ECOG performance-status score — no. (%)†		
0	22 (59)	35 (70)
1	15 (41)	15 (30)
Median sum of target lesions at randomization (range) — cm	7.6 (2.6–26.5)	8.4 (1.2–19.3)
BPI worst pain score at randomization — no. (%)‡§		
0–2	14 (38)	17 (34)
3–6	14 (38)	21 (42)
7–10	9 (24)	12 (24)
Intraabdominal disease — no. (%)‡	16 (43)	16 (32)
Primary tumor site — no. (%)		
Abdominal	16 (43)	14 (28)
Extraabdominal	18 (49)	32 (64)
Both abdominal and extraabdominal	3 (8)	4 (8)
Previous radiation therapy — no. (%)	3 (8)	6 (12)
Previous systemic therapy — no. (%)	15 (41)	18 (36)
Previous surgical resection — no. (%)	18 (49)	23 (46)
Disease status — no./total no. (%)		
Newly diagnosed	19/37 (51)	26/48 (54)
Recurrent	18/37 (49)	22/48 (46)
Trial inclusion criteria — no. (%)¶		
Disease determined to be unresectable or to require surgery with unacceptably high associated morbidity	28 (76)	44 (88)
Progression detected by radiographic imaging within 6 months before randomization	16 (43)	19 (38)
Symptomatic disease with BPI worst pain score ≥3 and consideration of pain narcotic introduction or escalation‖	11 (30)	16 (32)

* The intention-to-treat population included all patients who underwent randomization with the exception of those who were identified after randomization as not having a desmoid tumor and those who did not initiate the trial regimen and did not undergo further follow-up. Randomization was based on a dynamic allocation algorithm developed and implemented by the Alliance Statistics and Data Center. An error in the assignment of the trial regimen was detected and rectified after 70 patients (38 in the sorafenib group and 32 in the placebo group) had been enrolled. The program deriving the assignments of trial regimens incorrectly recognized a patient's crossover regimen as the initial assigned regimen when balancing for new enrollments. Randomization was stratified according to anatomical location and level of pain at the time of randomization, assessed with the use of the worst pain item of the Brief Pain Inventory (BPI) completed by the patient within 28 days before randomization. There were no significant differences (P<0.05) between the groups in any of the characteristics at the time of randomization. Percentages may not total 100 because of rounding.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability; a score of 5 indicates death.
‡ The characteristic was a stratification factor at randomization.
§ The BPI worst pain question was "Please rate your pain by circling the one number that best describes your pain at its WORST in the last 24 hours: 0 (no pain)–10 (pain as bad as you can imagine)."
¶ Patients had to meet at least one of these three criteria to be eligible for participation in the trial.
‖ Consideration of pain narcotic introduction or escalation was defined as an inability to control pain with nonsteroidal antiinflammatory drugs and consideration of the addition of narcotics or a more than 30% increase in the current use of narcotics or the addition of a new opioid narcotic.
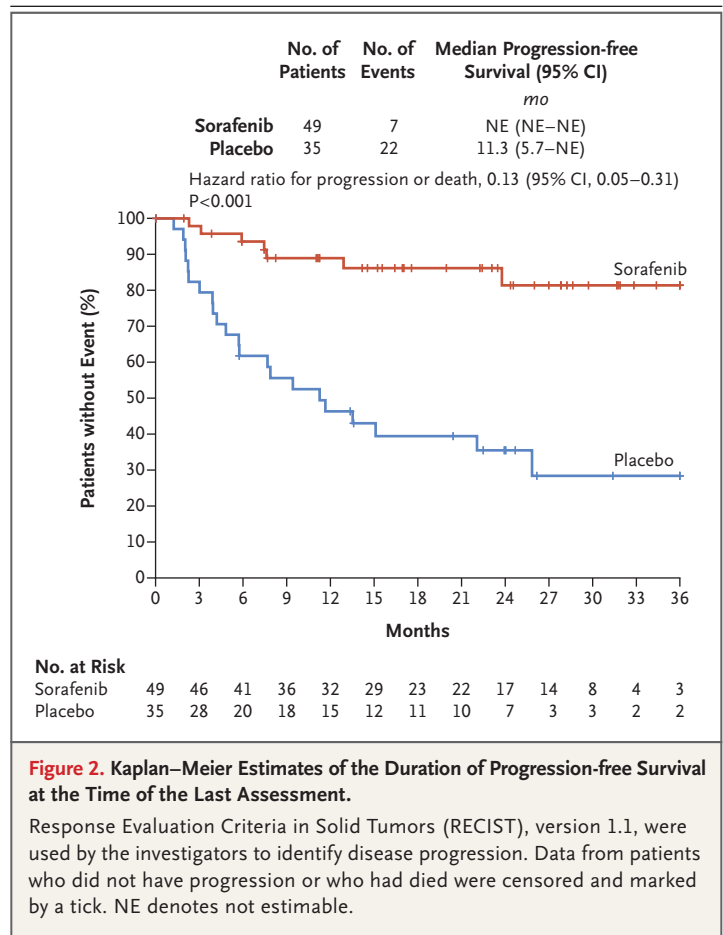
SAFETY

A total of 85 patients (49 in the sorafenib group and 36 in the placebo group) were included in the assessment of safety with the use of CTCAE, version 4.0. A summary of the most common adverse events is provided in Table 2. Adverse events led to a significantly higher rate of discontinuation of the trial regimen in the sorafenib group than in the placebo group (20% vs. no patients). The most common reason for dose reduction in the sorafenib group was skin disorders. Grade 3 adverse events that were attributed to the trial regimen by the investigators occurred in 29% of patients in the sorafenib group and 14% of patients in the placebo group. Grade 4 events that were associated with sorafenib included thrombocytopenia (2%) and anemia (2%). One patient in the sorafenib group died from disease-related bowel perforation. A list of the side effects reported by the patients with the use of PRO-CTCAE is provided in Table S4 and Figure S3 in the Supplementary Appendix. The proportions of patients with nausea, diarrhea, rash, and hand–foot syndrome were higher in the sorafenib group than in the placebo group.

CROSSOVER

In the placebo group, 27 patients met the eligibility criteria for open-label sorafenib treatment (20 at disease progression and 7 when the data and safety monitoring board released results), and 12 patients continue to take sorafenib; however, the data remain immature. The toxic effects among the patients receiving open-label sorafenib were similar to those among the patients who were initially randomly assigned to receive sorafenib and are listed in Table S7 in the Supplementary Appendix.

DISCUSSION

This randomized trial provides data on the efficacy of sorafenib in patients with progressive or symptomatic desmoid tumors. Other agents that are used to treat these tumors include anthracyclines (e.g., pegylated liposomal doxorubicin), vinca alkaloids, and pazopanib. On the basis of the predictable toxic-effects profile and substantial progression-free survival advantage conferred by sorafenib, the drug has antitumor activity as

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Sorafenib	49	7	NE (NE–NE)
Placebo	35	22	11.3 (5.7–NE)

Hazard ratio for progression or death, 0.13 (95% CI, 0.05–0.31) P<0.001

No. at Risk
Sorafenib	49	46	41	36	32	29	23	22	17	14	8	4	3
Placebo	35	28	20	18	15	12	11	10	7	3	3	2	2

Figure 2. Kaplan–Meier Estimates of the Duration of Progression-free Survival at the Time of the Last Assessment.

Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, were used by the investigators to identify disease progression. Data from patients who did not have progression or who had died were censored and marked by a tick. NE denotes not estimable.

first-line therapy or as subsequent therapy for desmoid tumors.

For a locally infiltrative tumor, the prevention of further worsening or compromise of vital structures is a clinically meaningful end point. In that context, among patients with progressive, symptomatic, or recurrent desmoid tumors, the rate of progression-free survival with sorafenib at 1 year was 89%. Patients treated with sorafenib had an 87% lower risk of disease progression or death than those who received placebo. To balance the efficacy of the drug against the long-term drug-related toxic effects, we chose a starting dose of sorafenib (one 400-mg tablet daily) that was lower than the dose used in other types of cancer and permitted dose interruptions and reductions.[5] The modest toxicity of sorafenib was confirmed in both clinician-reported and patient-reported assessments of adverse events. Consistent with previous literature,
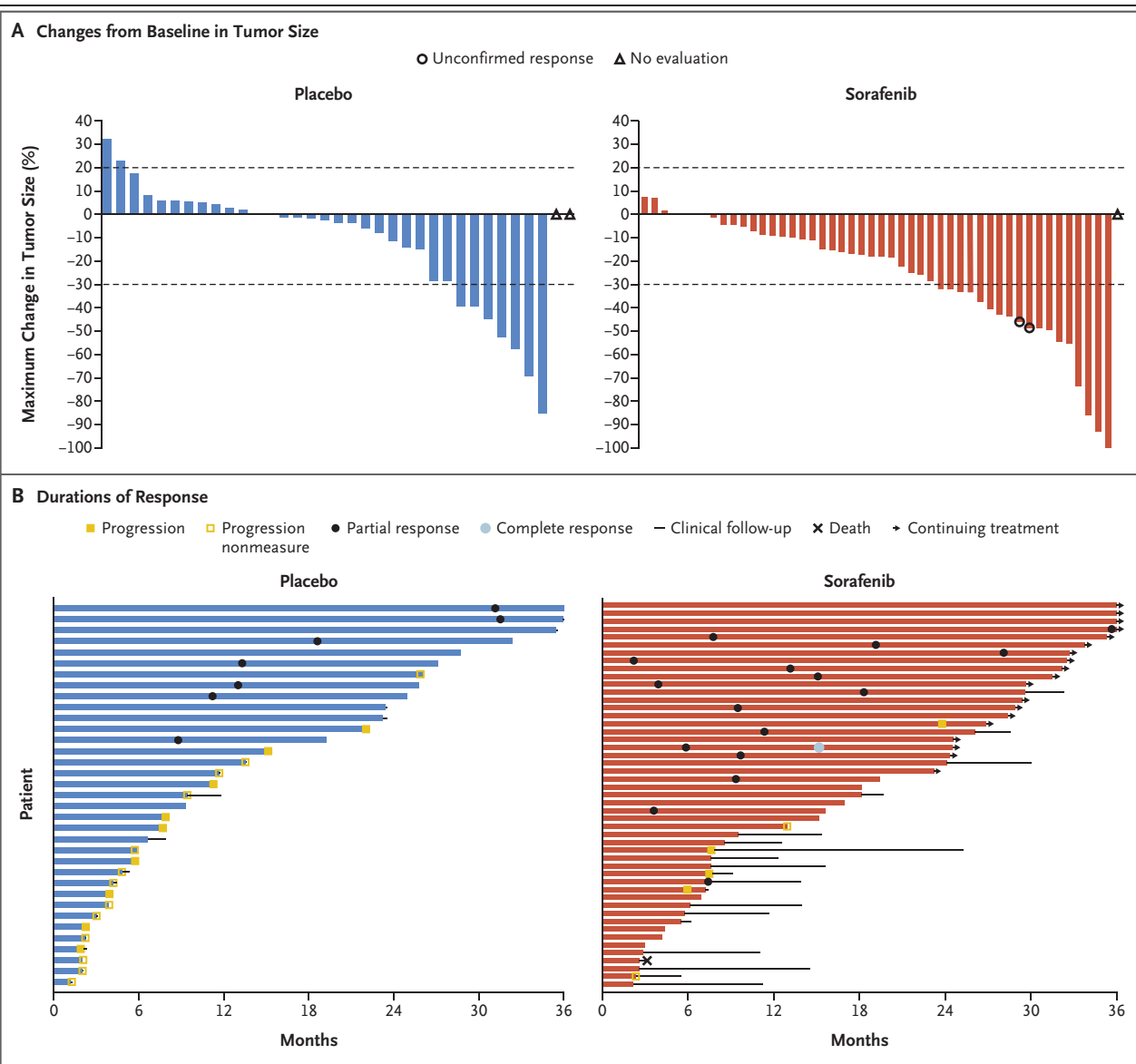
A Changes from Baseline in Tumor Size

○ Unconfirmed response △ No evaluation

B Durations of Response

■ Progression ▢ Progression nonmeasure ● Partial response ● Complete response — Clinical follow-up ✕ Death → Continuing treatment

Figure 3. Tumor Responses and Clinical Outcomes.

Panel A shows waterfall plots of percentage changes from baseline in tumor size as assessed by investigators according to RECIST, version 1.1. Each bar represents one patient. Horizontal dashed lines indicate the changes in tumor size that would represent a partial response (30% decrease) or progressive disease (20% increase). One patient in the sorafenib group had a complete response, defined as total disappearance of tumor. Panel B shows swimmer plots of the duration of response and clinical outcomes among patients during the trial. "Progression nonmeasure" denotes clinical progression without radiographic progression (20% growth). One patient in the sorafenib group died from disease-related intestinal perforation. Duration of response was calculated as the time between the first objective response and disease progression; data from patients with ongoing responses were censored at the most recent disease assessment. Time to response during the time of the blinded trial intervention was calculated from the start of the intervention to the date of the first objective response or to the most recent disease assessment (for patients without a response). Time to progression was the time to disease progression or to the most recent assessment if the patient did not have disease progression.

the rates of adverse events that were based on clinician reporting were substantially lower than those that were based on patient reporting.[28]

Many of these differences were due to the ability to detect more lower-grade mild-to-moderate side effects with the use of the patient-reported

Table 2. Incidence of Adverse Events of Any Cause According to Initially Assigned Trial Regimen.*

Event	Sorafenib (N = 49)		Placebo (N = 36)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
	number of patients (percent)			
Any adverse event	26 (53)	23 (47)	25 (69)	9 (25)
Events during receipt of trial regimen with incidence ≥10%†				
Palmar–plantar erythrodysesthesia syndrome	34 (69)	1 (2)	8 (22)	0
Rash				
Any rash or skin disorder	36 (73)	7 (14)	15 (42)	0
Papulopustular	24 (49)	6 (12)	6 (17)	0
Acneiform	6 (12)	0	0	0
Maculopapular	7 (14)	0	1 (3)	0
Skin or subcutaneous tissue disorders — other‡	7 (14)	1 (2)	5 (14)	0
Pruritus	7 (14)	0	0	0
Fatigue	33 (67)	3 (6)	22 (61)	1 (3)
Hypertension	27 (55)	4 (8)	14 (39)	0
Diarrhea	25 (51)	0	12 (33)	0
Nausea	24 (49)	0	14 (39)	1 (3)
Myalgia	18 (37)	1 (2)	12 (33)	0
Alopecia	18 (37)	0	3 (8)	0
Arthralgia	17 (35)	1 (2)	9 (25)	0
Abdominal pain	15 (31)	1 (2)	9 (25)	4 (11)
Anorexia	15 (31)	0	9 (25)	0
Constipation	11 (22)	0	4 (11)	0
Oral mucositis	11 (22)	0	6 (17)	0
Vomiting	10 (20)	1 (2)	6 (17)	2 (6)
Anemia	8 (16)	1 (2)	2 (6)	1 (3)
Increase in alanine aminotransferase level	7 (14)	0	4 (11)	0
Decrease in platelet count	6 (12)	2 (4)	1 (3)	0
Hyperglycemia	6 (12)	1 (2)	3 (8)	0
Peripheral sensory neuropathy	6 (12)	0	1 (3)	0
Increase in aspartate aminotransferase level	5 (10)	1 (2)	3 (8)	0
Increase in blood bilirubin level	5 (10)	0	3 (8)	1 (3)
Decrease in neutrophil count	5 (10)	0	2 (6)	0
Dry skin	5 (10)	0	1 (3)	0
Headache	4 (8)	0	6 (17)	0
Decrease in white-cell count	3 (6)	0	6 (17)	0
Musculoskeletal connective-tissue disorders — other§	3 (6)	0	4 (11)	0

* Events that occurred while the patient was taking the initially assigned trial regimen (before crossover) are shown. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. The events reported reflect the maximum severity in each category for a given patient during the treatment period; multiple occurrences of the same event in a single patient were counted once, at the highest grade at which it occurred. All 85 patients were included in the assessment of safety.

† Events that had an incidence of 10% or higher in either trial group are shown. One patient in the sorafenib group died from disease-related bowel perforation (not shown in this table) that was judged by the investigators not to have been related to the drug; no other grade 5 events occurred.

‡ Events in this category included callus, swelling, plantar wart, hidradenitis supportiva, and pain.

§ Events in this category included pain and cramping.

PRO-CTCAE. Accordingly, we surmised that the high rate of withdrawal from the trial due to adverse events (20%) suggests that even greater dose flexibility may be necessary to balance toxicity and benefit.

This trial highlights the importance of randomization in the conduct of clinical trials. Spontaneous regression was once considered to be anecdotal and rare (occurring in <5% of patients), but more recent retrospective, nonrandomized studies have shown higher rates of spontaneous remission.[8,9] Our prospective trial, in which desmoid tumors in patients who were taking placebo were evaluated, provides evidence in support of an initial period of observation in patients with newly diagnosed desmoid tumors, given that 20% of the patients in the placebo group had disease regression. In this trial, late responses were observed in the sorafenib group, and response rates may increase with further data maturation.

A final important clinical issue to note regards the feasibility and challenges of conducting clinical trials in very rare cancers. Rare cancers are defined as those with an incidence of less than 15 cases per 100,000 persons per year. Although individually uncommon, rare cancers account for 25% of all cancers and are associated with poor survival.[29,30] The main challenges in the design and execution of this phase 3 trial were the incidence of the cancer (0.3 cases per 100,000 persons per year), the lack of consensus on the standard of care, the lack of predictive biomarkers for the selection of patients, and the lack of validated, desmoid-specific patient-reported outcome measures. The unreliability of historical data on treatment and natural history (e.g., the rate of spontaneous regression) was an additional design challenge. All potential trial designs (e.g., frequentist or Bayesian) should be considered on the basis of not only their statistical properties but also their feasibility with regard to late events or logistic support for real-time data entry. The trial conducted was an international collaboration among U.S. and Canadian National Cancer Institutes, cooperative research groups, patient advocacy groups, and physician outreach groups, an endeavor that facilitated the enrollment of 87 patients in 17 months.[29,31]

A limitation of this trial is that it was not designed to directly compare the primary or secondary end points with meaningful improvements in pain palliation, functionality, or quality of life. The use of pain-palliation questionnaires was optional, and limited results were available. In our exploratory analysis, we were unable to use the Brief Pain Inventory to discern any difference between the groups (data not shown), contrary to previous reports. Symptoms that affect patients with desmoid tumors are wide-ranging, and since this trial was conducted, a prospective, desmoid tumor–specific, patient-reported outcome tool has been developed for future trials.[6] Beyond the traditional end points that are used in clinical trials, incorporating an evaluation of the patient experience is critical.[32]

The ability to use RECIST-defined responses to correlate with treatment effect and survival among patients with solid tumors is debated. Data from our exploratory analysis suggested that there is anatomical and mathematical discordance among assessments that are based on unidimensional measurement (RECIST), tumor volume, and T_2-weighted signal intensity; therefore, RECIST — the current regulatory metric — may underestimate treatment effects. This phenomenon is observed in other sarcomas, such as tenosynovial giant-cell tumors and gastrointestinal stromal tumors, in which tumor volume and density are better predictors of treatment effect than RECIST measurements.[33,34] Similarly, data have suggested that tumor volume or MRI T_2-weighted signal intensity — namely, a shift from a cellular mass to a collagenous scar — may be additional imaging biomarkers that can potentially be used to assess treatment effects on desmoid tumors.[22,35] The appropriate duration of sorafenib treatment and its cost and benefit relative to those of existing therapies remain unknown. Finally, the mechanism of action of sorafenib in desmoid tumors[36] is not known. Investigations into changes in gene expression and protein phosphorylation of receptor tyrosine kinases (e.g., platelet-derived growth factor receptor, fibroblast growth factor receptor, and transforming growth factor beta receptor) and the Wnt signaling pathway are ongoing in the 25 sets of paired biopsy specimens we obtained.

In conclusion, in this trial, therapy with sorafenib appeared to be effective in slowing disease progression in patients with desmoid tumors.

APPENDIX

The authors' affiliations are as follows: Memorial Sloan Kettering Cancer Center and Weill Cornell Medical Center (M.M.G., W.D.T., N.H., N.P.A., R.A.L., Y.M., R.Y.) and Columbia University Vagelos College of Physicians and Surgeons and New York Presbyterian Hospital (L.H.S., G.K.S.), New York, and Northwell Cancer Institute and Cold Spring Harbor Laboratory, Lake Success (R.G.M.) — all in New York; Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN (M.R.M.); Washington University School of Medicine, St. Louis (B.A.V.T.); M.D. Anderson Cancer Center, University of Texas, Houston (V.R.); Mayo Clinic in Florida, Jacksonville (S.A.); Yale University, New Haven, CT (H.A.D.); University Health Network Princess Margaret Cancer Centre, Toronto (A.A.G.); University of Iowa–Holden Comprehensive Cancer Center, Iowa City (M.M.M.); University of Alabama at Birmingham Cancer Center, Birmingham (R.M.C.); Fox Chase Cancer Center, Philadelphia (S.M.); Georgetown University, Lombardi Comprehensive Cancer Center, Washington, DC (M.J.P.); Duke Cancer Institute, Duke University Medical Center, Durham (R.F.R.), and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill (E.B.) — both in North Carolina; Dayton National Cancer Institute Community Oncology Research Program, Dayton, OH (T.S.); National Cancer Institute, Bethesda, MD (J.J.W.); and the Alliance Statistics and Data Center, Mayo Clinic, Scottsdale, AZ (A.C.D.).

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