Characteristics of children enrolled in treatment trials for NF1-related plexiform neurofibromas

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ABSTRACT

Objective: To describe the characteristics of children enrolled in treatment trials for neurofibromatosis type 1 (NF1)–related plexiform neurofibroma (PN), PN tumor burden, PN-related complications, and treatment outcomes and to highlight the differences between characteristics of children with NF1 vs children with cancers entered on early phase drug trials.

Methods: Pre-enrollment characteristics and complications of PN were retrospectively analyzed in a cohort of 59 children with NF1-related PN treated on 1 of 7 clinical trials at the NIH between 1996 and 2007. Outcome was analyzed in a subset of 19 patients enrolled in phase I trials. Comparisons to children with cancer were made from a similar analysis performed recently.

Results: The median age at enrollment was 8 years. The median PN volume was 555 mL. Most patients had no prior chemotherapy or radiation, but nearly half had previous surgery for PN. PN-associated complications and NF1 manifestations were common, including pain (53%), other tumors (18%), and hypertension (8%). Investigational drug therapy was well tolerated. A median of 10 treatment cycles was administered. Patients with NF1-related PN were younger, had better performance score, had less prior therapy, and remained on study longer than cancer patients.

Conclusions: Children with NF1-related plexiform neurofibroma (PN) enrolled in clinical trials had large tumors with substantial morbidity. Clinical trials in these children provide information about drug tolerance, cumulative toxicity, and pharmacokinetics in a younger population than early phase pediatric cancer trials. This report may aid in the evaluation of the applicability of traditional pediatric cancer trial designs and endpoints for NF1-related PN. ***Neurology*® 2009;73:1273–1279**

GLOSSARY

DLT = dose-limiting toxicities; **ECOG** = Eastern Cooperative Oncology Group; **MTD** = maximum tolerated dose; **NF1** = neurofibromatosis type 1; **PK** = pharmacokinetic; **PN** = plexiform neurofibroma.

Plexiform neurofibromas (PN) are a common and debilitating complication of neurofibromatosis type 1 (NF1). These benign nerve sheath tumors cause significant morbidity through disfigurement and compression of vital structures.[1,2] PN are thought to be congenital, have complex shapes, and appear to grow faster in children <8 years old.[3] Surgery is currently the only standard treatment option for PN, but complete resection is often difficult due to their large size, location, local invasiveness, or involvement of critical peripheral nerves.[1,4]

Research focused on the biology of NF1 and pathogenesis of PN[4-7] has identified numerous potential targets, many of which are shared with cancers for which new drugs are being developed, such as RAS, angiogenesis, growth factors, and the mammalian target of rapamycin. Clinical trials of these new drugs are under way in children with refractory cancers and NF1-related PN. Most NF1 trials use designs and endpoints that are similar to oncology trials, but some aspects of NF1 and PN differ from refractory cancers and require new approaches toward drug development. For example, standard methods used to measure tumor size and assess response in cancer trials (RECIST[8] and WHO[9] criteria) were inadequate to quantify clinically

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meaningful changes in PN[5] and recently volumetric methods[10-12] were developed for response evaluation.[3,7]

The objectives of this report were to characterize the population of pediatric patients who enroll in treatment trials for NF1-related PN, to examine PN disease burden and associated complications, and to evaluate the primary outcomes for patients who have participated in phase I trials. We also compared baseline characteristics and outcomes of children with NF1 to children with refractory cancers enrolled in phase I trials from a similar analysis we recently performed.[13] Understanding these disease and outcome characteristics in children with NF1-related PN treated on investigational drug trials may aid in subject selection, trial design, and informed consent discussions for physicians and patients with NF1 considering enrollment in a clinical trial.

METHODS Potential study participants were patients enrolled, treated, and followed in 1 of 7 investigational drug trials for NF1-related PN (table 1)[5,7,14-16] at the NIH Clinical Center between August 1996 and July 2007. The patients at the NIH are drawn from a national referral base. During this time period, 88 patients were screened at the NIH for a treatment trial, and the 59 patients who were found eligible and enrolled in a trial were all included in this retrospective cohort analysis. For 19 patients who subsequently participated in a second or third treatment trial, only their participation in the first trial at the NIH was included. Protocol registries, hospital charts, and research charts were the source of data.

For comparison purposes, the data collection for this study was modeled on the analysis of baseline and outcome characteristics of children with refractory cancers who enrolled in early phase drug trials at the NIH (n = 262).[13]

The clinical trials (table 1) had similar eligibility criteria, which required a diagnosis of NF1 based on NIH consensus criteria,[17] Eastern Cooperative Oncology Group (ECOG) performance status (or equivalent Lansky/Karnofsky score) of 0–2, serum hepatic transaminases ≤2 times the upper limit of normal, bilirubin ≤1.5 times the upper limit of normal, absolute neutrophil count ≥1,500/μL, and platelet count ≥100,000/μL. Three phase I trials (phenylbutyrate, phenylacetate, and tipifarnib) enrolled patients with refractory cancers and NF1-related PN simultaneously and defined a maximum tolerated dose (MTD) for the combined patient groups. All trials required that PN were inoperable, and 4 trials required that patients had progressive disease (phenylacetate, phenylbutyrate, tipifarnib phase II, pirfenidone phase II), although progression was objectively defined only in the phase II trials. Three trials (pirfenidone phase I and II, tipifarnib phase II) required PN with the potential to cause significant morbidity, such as head and neck PN

Table 1 Pediatric oncology branch NF1-related plexiform neurofibroma clinical trials included in analysis

Study no.	Drug	Mechanism of action	Phase	Schedule	Endpoint	Response evaluation	Patient no.*	Result	Reference
1	Phenylbutyrate†	Differentiating agent	I	IV 24 h × 28 d	Toxicity PK	WHO	1	MTD: 12.5 g/m^2; DLT: somnolence	14
2	Phenylacetate†	Differentiating agent	I	IV 24 h × 28 d	Toxicity PK	WHO	2	MTD: 9 g/m^2; DLT: somnolence	15
3	Tipifarnib†	Farnesyl-transferase inhibitor	I	PO BID × 21 d q 28 d PO BID × 28 d	Toxicity PK	WHO	7	MTD: 200 mg/m^2/dose; DLT: myelosuppression, rash, vomiting, diarrhea	5
4	Tipifarnib	Farnesyl-transferase inhibitor	II‡	PO 200 mg/m^2 BID × 21 d q 28 d	TTP	Volumetric	33	Ongoing (masked)	—
5	Peginterferon alfa-2b	Immune modulation, angiogenesis	I	SC q wk	Toxicity	WHO then volumetric	3	MTD: 1 μg/kg SC weekly	16
6	Pirfenidone	Antifibrotic	I	PO TID × 28 d	Toxicity PK	Volumetric	6	Optimal dose: 500 mg/m^2/dose; DLT: diarrhea, nausea	7
7	Pirfenidone	Antifibrotic	II	PO 500 mg/m^2 BID × 21 d q 28 d	TPP	Volumetric	7	Ongoing	—

*Number of patients enrolled in the trial at the National Cancer Institute.
†Protocol enrolled patients who had refractory solid tumors as well.
‡Randomized double-blind placebo-controlled crossover trial design.
PK = pharmacokinetics; MTD = maximum tolerated dose; DLT = dose-limiting toxicity; SC = subcutaneous; TTP = time to progression.

Table 2 Baseline patient characteristics

Characteristic	No. of patients (n = 59)	Frequency (%)
Male/female	40/19	38/32
Family history for NF1: maternal/paternal/spontaneous	12/8/39	20/14/66
Caucasian/African American/Hispanic	5 /7/1	86/12/2
Median (range) age at diagnosis of NF1, y	2 (<1 to 19)	
Median (range) age at enrollment in trial, y	8 (2 to 21)	
Median (range) height percentiles	31 (1 to 99)	
Median (range) weight percentiles	39 (1 to 99)	
Performance status		
ECOG 0/1/2	33/23/2	56/39/3
Unavailable	1	2
Systolic blood pressure percentile		
0–95	44	75
>95	13	22
Unavailable	3	5
Diastolic blood pressure percentile		
0–95	51	86
>95	5	8
Unavailable	3	5
Baseline labs, mean ± SD		
Absolute neutrophil count (10^3/mm^3)	3.3 ± 1.4	
Hemoglobin (g/dL)	13.6 ± 1.3	
Platelets (10^3/mm^3)	323 ± 78	
Total bilirubin (mg/dL)	0.6 ± 0.4	
History of other tumors		
None	46	78
Glioma	4	7
Optic glioma	5	8
MPNST	2	3
Unavailable	2	3
Bony complications		
Scoliosis	23	39
Pseudoarthrosis	1	2
Limb length discrepancy	9	15
Pectus	4	7
Cognitive deficits (i.e., learning deficit)	30	51
Prior myelosuppressive chemotherapy	3	5
Prior radiation	2	3
Pain		
No	18	31
Yes	31	53
Unavailable	10	16
Daily narcotic use		
No	52	88
Yes	3	5
As needed	4	7
Median (range) concomitant medications	1 (0 to 10)	

ECOG = Eastern Cooperative Oncology Group; MPNST = malignant peripheral nerve sheath tumor.

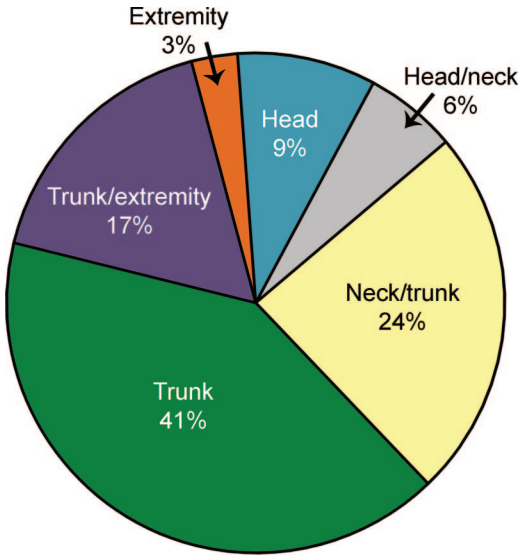
that could compromise the airway or great vessels, brachial or lumbar plexus PN that could cause nerve compression and loss of function, PN that could result in major deformity (e.g., orbital lesions) or significant cosmetic problems, PN of the extremity that cause limb hypertrophy or loss of function, and painful PN. Patients were treated and followed per the individual treatment protocol.

Pre-enrollment characteristics. Pre-enrollment characteristics collected included age at enrollment, age at diagnosis of NF1, sex, family history, race, performance status, height, weight, blood pressure, complete blood count, hepatic enzymes and bilirubin, tumor volume, tumor location, prior surgery, other malignancies, prior treatment regimens and radiation (for PN or other tumors such as optic glioma), presence of pain, daily narcotic use, and concomitant medications, which included regularly scheduled medications that patients were taking prior to starting the treatment trial and excluded medications that were administered on an as-needed basis, vitamin supplements, and topical medications. Associated conditions with NF1 were also tabulated, such as skeletal complications (scoliosis, pseudoarthrosis, limb length discrepancy, pectus excavatum) and cognitive deficits (caregiver reported). In addition, the PN location, size, and associated actual or potential complications were categorized as follows: major physical deformity—cosmetically significant facial, trunk, extremity masses, or spine (scoliosis related to PN); limb hypertrophy; airway compression—present (clinical compromise such as tracheostomy, airway stent, or continuous positive airway pressure) or potential (PN in close proximity to upper and lower airway); spinal cord compression—present (deformity of spinal cord by neurofibroma, disruption of CSF surrounding spinal cord) or potential (spinal neurofibroma protruding into the spinal canal, but not deforming spinal cord); blood vessel compression—present (clinical vascular compromise) or potential (PN encasing large blood vessels of the heart such as aorta, or others such as femoral artery); major bodily dysfunction—present (motor weakness, decreased vision, or urinary or bowel incontinence as a result of PN) or potential (PN involving spinal or peripheral nerves, or surrounding bladder and rectum).

Outcome characteristics. Outcome characteristics were collected in 19 patients enrolled in phase I trials. Patients on phase II trials (pirfenidone and tipifarnib) were excluded from this analysis because the trials were ongoing or included a masked placebo control arm. Outcome data collected included total cycle number received, participation in pharmacokinetic (PK) studies, grade >2 toxicities experienced by the patient and judged to be at least possibly related to the investigational agent, dose-limiting toxicities (DLT) as defined by each protocol, hospitalizations, blood product transfusions, off study reason, and time to progression. Subjects were considered evaluable for toxicity if they completed at least one treatment cycle or if they experienced a DLT during the first treatment cycle. Progression was defined as ≥20% increase in PN volume for the pegintron and pirfenidone phase I and a 25% increase in bidimensional measurements by WHO criteria for the tipifarnib, phenylbutyrate, and phenylacetate phase I trials.

Summary statistics were generated for pre-enrollment and outcome characteristics. Time to progression was calculated using Kaplan-Meier analysis from time of enrollment to progressive disease. All patients were enrolled in an investigational drug trial. Missing data values for patients per category were listed as unavailable. For the 19 patients for whom outcome data were evaluated, none were lost to follow-up. Statis-

Figure Plexiform neurofibroma (PN) anatomic location



A total of 87 PN were evaluated in 59 patients. A total of 23 patients had ≥2 PN. PN location: head (n = 6), head/neck (n = 8), neck/trunk (n = 5), trunk (n = 35), trunk/extremities (n = 21), extremity only (n = 3).

tical analyses were performed using STATA version 9.0 (College Station, TX).

Standard protocol approvals, registrations, and patient consents. All protocols were approved by the NCI Institutional Review Board, and all patients or their legal guardians signed a document of informed consent indicating their understanding of the investigational nature and the risks of the study.

RESULTS Of the 59 patients included in this analysis, 19 patients were enrolled in phase I trials and 40 patients were enrolled in phase II trials. Most clinical trials evaluated noncytotoxic agents, but myelosuppression was a DLT on the tipifarnib phase I trial.[5] Sixteen patients (27%) participated sequentially in 2 separate trials, and 3 patients (5%) participated in 3 trials.

Baseline characteristics prior to enrollment are described in table 2. Most patients were young and had not received substantial prior chemotherapy or radiation treatment. They had a number of manifestations of NF1, including hypertension and history of other tumors. Other common nontumor manifestations included cognitive deficits (51%), such as learning disabilities or developmental delay, skeletal complications, such as scoliosis (39%), and pain (53%).

The majority of PN were located in the head, neck, and trunk (figure) and were large with a median PN volume of 555 mL (range 20–5,630 mL). Approximately half of the patients had debulking surgery for their PN and 40% of these patients underwent ≥2 operations on the same PN prior to enrollment. The PN in this population resulted in substantial complications including compression of the airway and spinal cord (table 3). More than 90% of patients had PN with the potential to cause ≥1 of the complications shown in table 3.

Table 4 describes the outcome characteristics for 19 patients enrolled in phase I trials. All patients happened to be enrolled on dose levels at or above the MTD. Participation in optional PK studies was 100% for studies in which PKs were an objective. DLT during the first cycle was observed in 5 (26%) patients (diarrhea n = 2, rash n = 1, somnolence n = 1). Three of those patients were enrolled on dose levels above the MTD. Patients received treatment for long durations, although a significant portion of patients had their doses transiently held (n = 12) mostly due to toxicity, but all patients resumed treatment after recovery. Eight patients underwent dose reductions, the majority of which occurred during the first cycle (75%). Patient hospitalizations on study (32%) were for elective surgeries (n = 4) or nonneutropenic infections (n = 2). No patients required blood product transfusions. The median time to progression on study was 14 months.

Several clinically relevant differences between the characteristics and outcomes of children with NF1 and children with refractory solid tumors treated on phase I trials[13] were observed. Patients with NF1, in comparison to patients with cancer, were younger at trial enrollment (median of 8 vs 14 years); had a better performance status (56% having an ECOG of 0 vs 29%); had infrequently received prior myelosuppressive chemotherapy (5% vs 94%); had infrequently received prior radiation therapy (3% compared to 73%); remained on experimental therapy longer (median [range] of 10 cycles [1–24] vs median of 1 cycle [0–31]); were removed from the study for disease progression less frequently (42% compared to 85%); and had longer survival (all but one NF1 patient remained alive compared to a median survival of 5 months).

DISCUSSION The advent of molecularly targeted anticancer drugs, which block signaling pathways responsible for the malignant phenotype in cancers, and advances in knowledge of the signaling pathways involved in NF1-related tumors has recently led to the development of clinical trials of investigational targeted agents in patients with NF1-related PN. These clinical trials have generally used designs and endpoints similar to those traditionally used for cancer clinical trials. In fact, 3 of the phase I trials included in our analysis simultaneously enrolled children with refractory cancers or NF1-related PN and defined the single MTD for children with NF1

Table 3 Plexiform neurofibroma characteristics and associated complications at enrollment

Plexiform neurofibroma characteristics	No. of patients (n = 59)	Frequency (%)
Median (range) tumor volume on MRI (mL)*	555 (20–5,630)	
Prior debulking surgery		
None	31	53
1 prior surgery for PN	17	29
2 prior surgeries for same PN	9	15
3 prior surgeries for same PN	2	3
Major physical deformity/disfigurement†		
Spine (scoliosis) related to PN	10	17
Face/neck	17	29
Trunk/extremities	15	25
Other	1	2
Total	43	73
Limb hypertrophy	8	14
Airway compression (present/potential)‡	4/17	7/29
Spinal cord compression (present/potential)		
Cervical spine	4/5	7/9
Thoracic spine	0/1	0/2
Lumbar spine	0/10	0/17
Multiple levels	10/12	17/20
Total	14/28	24/47
Blood vessel compression (present/potential)		
None	0/21	0/36
Great vessels of the heart	0/18	0/31
Other major vessels	0/20	0/34
Loss of function (present/potential)§		
Motor	18/ 24	31/41
Bladder/rectal	5/1	9/2
Vision	3/2	5/3
Hearing	1/1	2/2
Organ (kidney/liver)	0/3	0/5
Total	27/31	46/53

*51 total patients had volumetric MRI done.
†For 13 patients with 2 deformities/disfigurements, the worst is listed.
‡Present and potential complications are defined based on clinical and MRI findings. See text for detailed definition.
§For 9 patients with more than one present or potential complication, the worst is listed.

or cancer.[5,14,15] However, differences between individuals with refractory cancers and NF1-related PN may require more disease-specific approaches to drug development.

Our primary objectives for this analysis were to describe the characteristics of pediatric patients enrolled in treatment trials for NF1-related PN, to understand the disease burden and associated complications of their PN, to describe key outcomes on completed trials, and to compare children with NF1-related PN to children with refractory cancers entering early phase clinical trials. Our study represents a single institution experience, which allowed for the analysis of detailed subject information that would be difficult to obtain from a review of published trials. It is important to recognize that our study inherently represents a skewed population, as all patients were treated in a single institution on clinical trials, which required PN to be progressive or to have potential for morbidity. The characteristics described here therefore cannot be generalized to all children with NF1-related PN.

Although PN are benign tumors, they can cause substantial morbidity, and may even be life-threatening.[1] This was confirmed in the patients enrolled in our clinical trials whose PN were large, centrally located, and unresectable. A significant portion of patients presented with pain and had PN associated with the presence or the potential for life-threatening complications such as airway or spinal cord compression, physical deformity, or bodily dysfunction. Although the natural history of PN is not fully understood, the eligibility criteria for the trials included in this analysis selected a patient population with substantial actual or potential morbidity that could benefit from novel treatments to slow or reverse the manifestations of their disease, therefore justifying the potential risks of participation in investigational treatment trials.

Phase I trials proved to be safe for children with NF1-related PN. Toxicities were manageable and reversible. The DLT rate of 26% was similar to that observed in children with refractory cancers on investigational drug trials.[13,18] No life-threatening toxicities were observed in children with NF1, and only 2 patients came off of study due to toxicity.

Compared to children with refractory cancers, the NF1 population was younger, had better performance status, had received less prior therapy, was on study drug for longer durations, had different reasons for discontinuing therapy, and survived the disease, which is in contrast to the median survival of 5 months for children with refractory cancer who enroll in phase I trials.[13] All but one patient with NF1 in this study remain alive, consistent with the observation that while the life expectancy in NF1 is decreased compared to the general population, with a median lifespan of 59 years, most patients will reach adulthood.[19] In addition, in contrast to children with refractory cancers, children with NF1 typically had other NF1-related morbidity. These clinically significant differences highlight the need to evaluate the applicability of trial design and endpoints for traditional pediatric cancer trials when developing trials for children with NF1-related tumors. Children with NF1-related PN should be evaluated for longer dura-

Table 4 Outcome characteristics for patients with NF1 enrolled in phase I trials

Outcomes	No. of patients (n = 19)	Frequency (%)
Pharmacokinetic participation (n = 16)*	16	100
Dose-limiting toxicity on cycle 1†	5	26
Dose-limiting toxicity on subsequent cycles†	3	16
CTC grade 2 toxicity‡ during any cycle	16	84
CTC grade 3 toxicity‡ during any cycle	9	47
CTC grade 4 toxicity‡ during any cycle	0	0
Median (range) cycles received	10 (1–24)	
Doses held		
Yes	12	63
No	7	37
Dose reduced	8	42
Hospitalizations	6	32
PRBC or platelet transfusions	0	0
Off-protocol reason (n = 18)§		
Progressive disease	8	44
Insufficient response	1	6
Withdrew consent	3	17
Completed study	4	22
Toxicity	2	11
Time to progression, mo	14	

*Pharmacokinetics were not performed on the phase I peg interferon study (n = 3).
†Based on the version of the NIH common toxicity criteria (CTC) used on the study.
‡Toxicity at least possibly related to investigational agent.
§One patient was still on study (18 months) at the time of data collection.
CTC = common toxicity criteria; PRBC = packed red blood cells.

tions of therapy to determine tolerability, may require more conservative definitions of DLT, starting doses, and dose escalation schedules, and require different outcome measures to assess drug activity.

The primary objectives of pediatric phase I trials are to define the dose, PK, tolerance, and toxicity profiles of investigational agents in children. Trials performed in children with refractory cancers often accrue a predominantly adolescent population, as evidenced by the median age at enrollment.[13] The NF1 trials provide data for these objectives in a younger population, and these data from NF1 trials may also be applicable to younger patients with cancer.

Many of the molecularly targeted drugs under evaluation for cancer and NF1-related PN alter signaling pathways that play a role in normal growth and development, so studying these agents in younger children during phase I testing is essential to determine whether toxicities unique to growing children may occur. For example, inhibition of angiogenesis in growing but not aged animals resulted in growth retardation and expanded epiphyseal growth plates.[20,21] This toxicity cannot be readily monitored in children with refractory cancers on phase I trials because they tend to be older, are more likely to have closed growth plates, and typically remain on trial for short periods.[13,22] Evaluation of these agents in separate phase I trials for children with NF1, who tend to remain on study for multiple treatment cycles, therefore becomes necessary to carefully assess the drug for effects on normal growth and development prior to implementing larger phase II or III trials.

The ability to assess cumulative toxicity in children enrolled in trials for NF1-related PN is an advantage for including this population on phase I trials when there is a strong scientific rationale for studying the drug in NF1. This is particularly important for the development of molecularly targeted drugs, which typically require oral administration on a chronic dosing schedule and may require multiple treatment cycles to exhibit toxic or therapeutic effects. The tipifarnib phase I trial, for example, confirmed the absence of cumulative toxicity in patients with NF1-related PN, and this supported the rationale for the development of a phase II trial for this population.[5] Information about cumulative and late toxicity and PK in children from NF1 trials of investigational agents that are also undergoing development for cancer will benefit drug development for all children as some of these agents may require chronic administration for upfront treatment of childhood cancers.

PN are slow-growing benign tumors,[3] and the molecularly targeted drugs being tested are more likely to prevent PN growth than reduce the size of these lesions. Therefore, children with NF1-related PN may have to take active drugs for prolonged periods of time, and less severe toxicities (Common Terminology Criteria grade 1 and 2), which would be considered tolerable in the cancer population, may become intolerable if present for prolonged intervals. This is important to consider when defining DLT for phase I trials in children with NF1-related PN.

Hypertension has been reported to be more prevalent in patients with NF1,[23] and 8% of patients in our cohort of 59 enrolled in clinical trials had a diastolic blood pressure above the 95th percentile for age. NF1 has also been associated with increased prevalence of vascular and cerebrovascular lesions.[23,24] Hypertension is one of the most common side effects of antiangiogenic drugs,[25] such as the VEGF receptor inhibitors that are currently in clinical development for children with NF1-related PN. Eligibility criteria for trials with antiangiogenic agents should exclude patients with preexisting NF1-related hypertension or cerebrovascular abnormalities in order to limit potential serious toxicities.

The eligibility criteria of current clinical trials for NF1-related PN select for a patient population with

substantial actual and potential morbidity from their PN. Investigational agents were safely administered to children with NF1 on early clinical trials. Differences between children with NF1-related PN and with refractory cancers require careful consideration for the design of future NF1 clinical trials.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by AeRang Kim, MD (NCI).

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DISCLOSURE

Dr. Kim, A. Gillespie, Dr. Dombi, A. Goodwin, and W. Goodspeed report no disclosures. Dr. Fox serves as an Associate Editor of the *Journal of the National Cancer Institute*. Dr. Balis serves as Senior Editor and CME Editor for *The Oncologist* and on the editorial boards of *Clinical Cancer Research* and *Cancer Chemotherapy & Pharmacology*; and receives royalty payments on US Patent 5,525,711, Pteridine nucleotide analogs as fluorescent DNA probes (issued 6/11/96), US Patent 5,612,468, Pteridine nucleotide analogs as fluorescent DNA probes (issued 3/18/97), and US Patent 6,716,971 B1, Pteridine nucleotide analogs (adenosine analogs) (issued 4/6/04). Dr. Widemann serves on the editorial board of *The Oncologist.*

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