Phase I Results of a Phase I/II Study of Weekly *nab*-Paclitaxel in Pediatric Patients With Recurrent/Refractory Solid Tumors: a Collaboration With Innovative Therapies for Children With Cancer

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Abstract (249/250)

Background: *nab*-Paclitaxel has demonstrated efficacy in adults with solid tumors and preclinical activity in pediatric solid tumor models. Results from phase I of a phase I/II study in pediatric patients with recurrent/refractory solid tumors treated with *nab*-paclitaxel are reported.

Patients and methods: Patients with recurrent/refractory extracranial solid tumors received *nab*-paclitaxel on days 1, 8, and 15 every 4 weeks at 120, 150, 180, 210, 240, or 270 mg/m^2 (rolling-6 dose-escalation) to establish the maximum tolerated dose (MTD) and recommended phase II dose (RP2D).

Results: Sixty-four patients were treated. Dose-limiting toxicities were grade 3 dizziness at 120 mg/m^2 and grade 4 neutropenia >7 days at 270 mg/m^2. The most frequent grade 3/4 adverse events were hematologic, including neutropenia (36%), leukopenia (36%), and lymphopenia (25%). Although the MTD was not reached, 270 mg/m^2 was declared nontolerable due to grade 3/4 toxicities during cycles 1-2 (neutropenia, *n*=5/7; skin toxicity, *n*=2/7; peripheral neuropathy, *n*=1/7). Of 58 efficacy-evaluable patients, complete response occurred in 1 patient (2%; Ewing sarcoma) and partial responses in 4 patients (7%; rhabdomyosarcoma, Ewing sarcoma, renal tumor with pulmonary metastases [high-grade, malignant], and sarcoma not otherwise specified); all responses occurred at ≥210 mg/m^2. Thirteen patients (22%) had stable disease (5 lasting ≥16 weeks) per RECIST.

Conclusions: *nab*-Paclitaxel 240 mg/m^2 qw3/4 (nearly double the adult recommended monotherapy dose for this schedule in metastatic breast cancer) was selected as the

RP2D based on the tolerability profile, pharmacokinetics, and antitumor activity. Phase II is currently enrolling patients with recurrent/refractory neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma.

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Introduction

Cancer is a leading cause of childhood death in developed countries [1]. Despite a relatively high combined survival rate for childhood cancers, recurrent/refractory disease is common in pediatric patients with certain solid tumor types, such as metastatic sarcoma and high-risk neuroblastoma, and long-term outcomes are poor [2-6]. Therefore, effective treatment options are needed.

Solvent-based taxanes have demonstrated antitumor activity in children with refractory solid tumors. However, their use has been compromised by dose-limiting toxicities (DLTs) that, in some cases, may result from the solvent-based formulation of these agents [7-9]. In a phase I trial, paclitaxel treatment resulted in DLTs, including acute neurological toxicities such as coma and possibly severe allergic toxicity, as well as delayed peripheral neurotoxicity potentially attributable to both the ethanol and polyethoxylated castor oil or polysorbate 80 components of solvents [7]. In a phase I study, docetaxel treatment resulted in dose-limiting neutropenia in heavily and less-heavily pretreated children with refractory solid tumors [8]. Similarly, in 2 phase I trials of >60 pediatric patients with refractory solid tumors, docetaxel administration resulted in dose-limiting neutropenia and desquamative dermatitis [9].

nab-Paclitaxel, an albumin-bound form of paclitaxel, is ethanol free and may be a feasible treatment option for pediatric patients with refractory/relapsed solid tumors because it was designed to increase antitumor activity and reduce toxicities, including hypersensitivity reactions [10, 11]. Further, compared with conventional paclitaxel, *nab*-paclitaxel has demonstrated enhanced transport across endothelial cell monolayers, faster and deeper tissue penetration, and slower elimination of paclitaxel [11, 12].

Regimens containing *nab*-paclitaxel have demonstrated safety and efficacy in adults with various solid tumor types [10, 11, 13-16]. *nab*-Paclitaxel has been approved in the US and Europe for the treatment of metastatic breast cancer after failure of prior treatment, for the treatment of advanced non-small cell lung cancer in combination with carboplatin, and for the treatment of metastatic pancreatic cancer in combination with gemcitabine [10, 17]. *nab*-Paclitaxel received its first indication as a single agent in metastatic breast cancer at a dose of 260 mg/m^2 every 3 weeks [10]. In adults with early-stage breast cancer, *nab*-paclitaxel monotherapy has also demonstrated efficacy at 125 mg/m^2 weekly (3 of 4 weeks; qw3/4) [18]. Single-agent *nab*-paclitaxel has displayed dose-dependent cytotoxicity in several pediatric solid-tumor cell lines and antitumor activity in rhabdomyosarcoma, neuroblastoma, and Ewing sarcoma mouse xenograft models, supporting its clinical exploration in pediatric solid tumor malignancies [19, 20].

This phase I/II dose-finding study, conducted in collaboration with the Innovative Therapies for Children with Cancer European Consortium, is evaluating the safety, tolerability, and efficacy of weekly *nab*-paclitaxel in pediatric patients with recurrent/refractory solid tumors. Phase I results describing the *nab*-paclitaxel maximum tolerated dose (MTD), recommended phase II dose (RP2D), safety, pharmacokinetic profile, and preliminary clinical activity are reported here.

Patients and Methods

Study Population

Pediatric patients ≥6 months to <18 years of age with recurrent/refractory solid tumors were enrolled. The study included patients whose disease progressed on standard therapy or for whom no standard therapy exists. Key eligibility criteria included a Lansky/Karnofsky performance status of ≥70, adequate bone marrow function (absolute neutrophil count [ANC] ≥1.0 × 10^9/L, platelets ≥80 × 10^9/L, hemoglobin ≥8 g/dL), and adequate organ function (ie, aspartate aminotransferase, alanine aminotransferase ≤2.5 × upper limit of normal range [ULN], total bilirubin ≤1.5 × ULN, creatinine ≤1.5 × ULN). Patients with primary brain tumors, active/untreated brain metastasis, or baseline peripheral neuropathy grade ≥2 were excluded.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation. Informed consent/assent was obtained from all patients or legal representatives (parents/guardians) prior to study entry. The trial is registered with ClinicalTrials.gov (NCT01962103) and EudraCT (2013-000144-26).

Study Design

Phase I of this multicenter, open-label, dose-finding study, which was conducted at 16 sites across Europe, the United States, and Canada, used a rolling-6 dose-escalation design to establish the MTD and RP2D of *nab*-paclitaxel [21]. The first patient was enrolled in December of 2013, and follow-up remains ongoing. Patients received *nab*-paclitaxel on days 1, 8, and 15 of a 28-day cycle (qw3/4) at 120 mg/m^2 (starting dose equivalent to 80% of the adult MTD corrected for body surface area), 150, 180, 210, 240, or 270 mg/m^2 doses. In any given dose-level cohort, if ≥2 patients experienced a DLT, the MTD was considered exceeded and the previous lower dose

declared the MTD. Patients enrolled while awaiting cohort DLT evaluation were treated at the previously declared safe dose level in order to avoid suspending recruitment. Patients enrolled under these circumstances were not considered for identification of the MTD/RP2D, but were included in safety, pharmacokinetic, and efficacy analyses.

Decisions on dose escalation, MTD/RP2D, and study continuation were determined by the Safety Monitoring Committee, which included an academic lead, site investigators, the Celgene clinical research physician and research scientists, and the product-safety physician.

Study Assessment

The phase I primary endpoints were the incidences of DLTs and treatment-emergent adverse events (AEs). Secondary endpoints included pharmacokinetics and overall response rate (ORR) per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 [22]. Exploratory endpoints were response by ^{123}metaiodobenzylguanidine (MIBG) scintigraphy using Curie score [23] for patients with neuroblastoma and biomarker analyses in archival tumor tissue. A post hoc analysis using recently updated International Neuroblastoma Response Criteria (INRC) was also conducted [24]. See Supplemental Methods for details on the efficacy-evaluable population and response assessments.

Treatment was given until disease progression, death, withdrawal of consent, or unacceptable toxicity. Safety was assessed in all treated patients. AEs were classified by the Medical Dictionary for Regulatory Activities v18.1, and severity was assessed per the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0.

Dose reductions, delays, discontinuations, and clinical laboratory data were also evaluated.

The MTD/RP2D determination was performed on the dose-determining set, which included patients treated in the 6 dose levels who had adequate safety assessments during the DLT assessment period and either experienced a DLT or received all 3 weekly *nab*-paclitaxel doses in the first cycle. A DLT was defined as a treatment-related AE occurring within the first cycle of treatment that led to treatment discontinuation or met 1 of the following criteria: grade 3/4 nonhematologic AE (excluding transient transaminitis), grade 3/4 nausea or vomiting lasting >5 days despite antiemetic treatment, grade 4 thrombocytopenia or anemia that persists >7 days or requires transfusion >7 days, grade 3 thrombocytopenia with bleeding, grade 4 uncomplicated neutropenia lasting >7 days, febrile neutropenia with confirmed bacterial infection, or grade 3 hematologic toxicity delaying treatment >21 days. Granulocyte colony-stimulating factors were not permitted during the DLT assessment period but were subsequently allowed per institutional guidelines for the treatment of neutropenia.

Results

Patients

Phase I enrolled 65 patients; 64 patients aged 2 to 17 years were treated, and 1 patient withdrew before treatment. Thirty-seven patients were enrolled in 6 dose levels and formed the dose-determining set (6 patients in each dose level except for 270 mg/m^2, which included 7 patients), and 27 patients were enrolled outside of the

specifications required for the dose-determining set (ie, during the periods in which placement in 1 of the 6 dose-determining cohorts was not available (Figure 1). Most patients (69%) had a Lansky/Karnofsky performance status of 90 to 100 (Table 1). Diagnoses included rhabdomyosarcoma (22%), Ewing sarcoma (20%), neuroblastoma (16%), and other less-frequent tumor types. All patients weighed >10 kg. The median number of prior treatment lines was 3.

Treatment Exposure and Selection of the Recommended Phase II Dose

In all treated patients, a median of 2 (range, 1-12) cycles were administered. Overall, the median treatment duration was 7.0 weeks. All 64 patients discontinued treatment; of these, 35 (55%) discontinued due to progressive disease (PD), 11 (17%) due to AEs, 11 (17%) due to clinical symptomatic deterioration, 5 (8%) due to withdrawal by patient or parent/guardian, and 1 (2%) due to physician decision.

Protocol-defined DLTs were grade 3 dizziness (1 patient at the 120 mg/m^2 dose level) and grade 4 neutropenia lasting >7 days (1 patient at the 270 mg/m^2 dose level). Out of the 7 patients in the dose-determining set for the 270 mg/m^2 dose, 4 patients continuing beyond cycle 1 required a dose reduction due to toxicity. Although DLT-based criteria to determine the nontolerable dose were not met, the safety monitoring committee declared 270 mg/m^2 as the nontolerable dose based on the totality of safety information, including grade 3/4 toxicities during the first 2 cycles (neutropenia, 5 of 7 patients; skin toxicity, 2 of 7 patients; and peripheral neuropathy, 1 of 7 patients).

Based on the combined safety, pharmacokinetic, and preliminary efficacy profiles of the 6 dose cohorts, *nab*-paclitaxel 240 mg/m^2 was identified as the RP2D.

Safety

Overall, 88% of the 64 patients experienced ≥1 treatment-emergent grade 3/4 AE. At all tested dose levels, grade 3/4 AEs were mainly hematologic (Table 2). Two patients reported grade 3/4 peripheral neuropathy, one each receiving *nab*-paclitaxel 240 and 270 mg/m^2. Grade 3/4 hand-foot syndrome occurred in 2 patients, both of whom received *nab*-paclitaxel 270 mg/m^2. Grade ≥2 peripheral neuropathy occurred in 11% of patients, with a median time to onset of 62 days.

Overall, 17% and 36% of patients had ≥1 *nab*-paclitaxel dose reduction or dose interruption, respectively. The *nab*-paclitaxel relative dose intensity was 99.6% in all cohorts combined (Table 3).

Early nab*-Paclitaxel Pharmacokinetic Profile*

Based on an interim analysis, increased *nab*-paclitaxel blood exposure was approximately proportional to dose from 120 to 270 mg/m^2, with mean area under the curve $[AUC]_{24}$ ranging from 6392 to 11982 h•ng/mL, and mean maximum concentration (C_{max}) ranging from 3488 to 8078 ng/mL. Between 240 and 270 mg/m^2, no difference was observed in mean AUC_{24} (11982 vs 9768 h•ng/mL) or mean C_{max} (7910 vs 8078 ng/mL), which could be accounted for by the small (12.5%) dose increment and interpatient variability. A full pharmacokinetic analysis will be conducted once data from phase II become available.

Antitumor Activity Per RECIST

The efficacy population included 58 patients. Complete and partial responses occurred in 1/58 (2%) and 4/58 (7%) of patients, respectively (Table 4). The complete

response was observed in a patient with Ewing sarcoma, and partial responses were observed in patients with rhabdomyosarcoma, Ewing sarcoma, renal tumor with pulmonary metastases (high-grade malignant tumor not otherwise specified [NOS]), and sarcoma NOS. All responding patients were treated at doses ≥210 mg/m^2. Stable disease was achieved in 13 patients (22%), 5 (9%) of whom had stable disease lasting for ≥16 weeks (1 patient with neuroblastoma and 2 each with Ewing sarcoma and sarcoma NOS). One patient with immature ovarian teratoma received 12 cycles, experienced prolonged stable disease as best response, and ultimately discontinued treatment due to clinical symptomatic deterioration.

Antitumor Activity in Patients With Neuroblastoma

Seven patients with neuroblastoma were evaluable for efficacy. The current study was initiated prior to the publication of the revised INRC guidelines [24]; however, post hoc analyses demonstrated that, using revised INRC criteria, 2 patients with neuroblastoma had minor response due to robust decreases in Curie score of 60% and 63%, but only stable disease by RECIST. One patient had stable disease, and 4 patients had progressive disease.

Discussion

The phase I portion of this study met its primary objective by determining the MTD/RP2D of weekly *nab*-paclitaxel in pediatric patients with recurrent/refractory solid tumors. Weekly *nab*-paclitaxel at the recommended dose of 240 mg/m^2 resulted in a manageable safety profile. As in adults, the most common AEs were hematologic in

nature. Peripheral neuropathy and hand-foot syndrome were rare, and no central neurotoxicity occurred. Per RECIST, responses were observed in 5 of 58 patients (9%); all responses occurred at ≥210 mg/m^2 (the response rate for these doses combined was 21%). Stable disease was achieved in 13 patients (22%) in the total cohort. Two of 7 patients (28%) with neuroblastoma had an INRC-defined minor response with significant decreases in Curie score.

The *nab*-paclitaxel RP2D was defined as 240 mg/m^2 based on the totality of safety data, despite not meeting protocol-defined DLT criteria at the highest *nab*-paclitaxel dose level tested (270 mg/m^2). This RP2D is higher than that of adult doses, possibly related to the lower incidence of peripheral neuropathy compared with the adult population, which is often dose-limiting. *nab*-Paclitaxel is not formulated in a chemical solvent, that is at least a partial contributor to neurotoxicity; this allows for achievement of higher dosages. Hematologic toxicity was manageable but led to frequent dose reductions and delays. Although cross-trial comparisons should be made with caution due to differences in study populations and designs, the overall incidence of grade 3/4 treatment-emergent peripheral neuropathy reported in the current study (3%) was lower than the rate of grade 3 treatment-related sensory neuropathy reported in a phase III trial of women with breast cancer receiving *nab*-paclitaxel 260 mg/m^2 monotherapy every 3 weeks [14]. Skin toxicity in this study was not dose limiting and occurred only at the highest dose level examined.

Pharmacokinetic analyses showed that the increase in blood exposure to *nab*-paclitaxel was approximately dose proportional in pediatric patients with solid tumors. Of note, the RP2D of *nab*-paclitaxel 240 mg/m^2 qw3/4 determined from this study in an

advanced and heavily pretreated pediatric cancer population is nearly double that of the dose tested (125 mg/m^2) on the same schedule in a recent phase III trial in adult women with early breast cancer [18]. However, the dose-adjusted blood exposure (AUC and C_{max}) to *nab*-paclitaxel in the current study was similar to that observed in adult patients with advanced solid tumors [25].

In conclusion, *nab*-paclitaxel 240 mg/m^2 qw3/4 had a manageable toxicity profile and demonstrated preliminary clinical activity in pediatric patients with solid tumors, and results from the phase I portion of this study warrant further investigation of *nab*-paclitaxel in the pediatric population. The phase II portion of this study evaluating *nab*-paclitaxel monotherapy at the established RP2D in patients with neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma is currently enrolling.

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Disclosures

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All remaining authors declare no conflict of interest.

Table 1. Patient Characteristics: Safety Population[a]

Characteristic	*nab*-Paclitaxel Dose						
	120 mg/m^2 *n* = 16	**150 mg/m^2 *n* = 8**	**180 mg/m^2 *n* = 14**	**210 mg/m^2 *n* = 11**	**240 mg/m^2 *n* = 8**	**270 mg/m^2 *n* = 7**	**Total *N* = 64**
Dose-determining set, n	6	6	6	6	6	7	37
Age, median, years	12.5	14.0	11.0	9.0	12.0	13.0	12.0
2-11 years, n (%)	6 (38)	2 (25)	7 (50)	6 (55)	3 (38)	3 (43)	27 (42)
12-17 years, n (%)	10 (63)	6 (75)	7 (50)	5 (45)	5 (63)	4 (57)	37 (58)
Male, n (%)	7 (44)	4 (50)	5 (36)	4 (36)	7 (88)	4 (57)	31 (48)
Lansky/Karnofsky PS, n (%)							
90-100	12 (75)	5 (63)	9 (64)	9 (82)	5 (63)	4 (57)	44 (69)
70-80	4 (25)	3 (38)	5 (36)	2 (18)	3 (38)	3 (43)	20 (31)
Solid tumor type, n (%)							
Neuroblastoma	2 (13)	0	2 (14)	4 (36)	2 (25)	0	10 (16)
Rhabdomyosarcoma	3 (19)	1 (13)	7 (50)	2 (18)	1 (13)	0	14 (22)
Ewing sarcoma	3 (19)	2 (25)	2 (14)	1 (9)	1 (13)	4 (57)	13 (20)
Osteosarcoma	4 (25)	1 (13)	0	1 (9)	1 (13)	1 (14)	8 (13)
Other[b]	4 (25)	4 (50)	3 (21)	3 (27)	3 (38)	2 (29)	19 (30)
Prior treatment lines, median (range), n	3 (1-8)	3 (1-7)	3 (1-7)	3 (1-10)	3 (1-5)	3 (2-4)	3 (1-10)

NOS, not otherwise specified; PC, performance status.

[a] Includes all patients who received ≥1 dose of *nab*-paclitaxel. [b] Includes patients with adrenocortical carcinoma, clear cell sarcoma of the kidney, desmoplastic small round cell tumor, hepatoblastoma, hepatocarcinoma, immature ovarian teratoma, left adrenocortical carcinoma, left renal tumor with pulmonary metastases, nasopharyngeal carcinoma, sarcoma NOS, Wilms tumor, and yolk sac tumor.

Table 2. Treatment-Emergent Adverse Events: Safety Population[a]

AEs, n (%)	*nab*-Paclitaxel Dose						
	120 mg/m^2 *n* = 16	150 mg/m^2 *n* = 8	180 mg/m^2 *n* = 14	210 mg/m^2 *n* = 11	240 mg/m^2 *n* = 8	270 mg/m^2 *n* = 7	All Treated Patients *N* = 64
Grade 3/4 AEs reported in ≥20% of patients in ≥1 dosing cohort							
Hematologic[b]							
Neutropenia	4 (25)	1 (13)	3 (21)	6 (55)	4 (50)	5 (71)	23 (36)
Leukopenia	3 (19)	1 (13)	6 (43)	5 (45)	4 (50)	4 (57)	23 (36)
Lymphopenia	3 (19)	1 (13)	2 (14)	3 (27)	3 (38)	4 (57)	16 (25)
Nonhematologic							
Skin pain	0	0	0	0	0	2 (29)	2 (3)
Hand-foot syndrome	0	0	0	0	0	2 (29)	2 (3)
Hyponatremia	1 (6)	3 (38)	0	0	0	0	4 (6)
Hypotension	0	2 (25)	1 (7)	0	0	0	3 (5)
TEAEs of special interest							
Peripheral neuropathy	0	0	0	0	1 (13)	1 (14)	2 (3)
Arthralgia	0	1 (13)	0	2 (18)	0	0	3 (5)
Nausea	0	1 (13)	0	0	0	1 (14)	2 (3)

AE, adverse event; TEAE, treatment-emergent adverse event.
[a] Safety population includes all patients who received ≥1 dose of *nab*-paclitaxel. [b] Hematologic events reported from laboratory values collected on dosing days.

Table 3. Treatment Exposure: Safety Population[a]

Parameter	*nab*-Paclitaxel Dose						
	120 mg/m^2 *n* = 16	**150 mg/m^2 *n* = 8**	**180 mg/m^2 *n* = 14**	**210 mg/m^2 *n* = 11**	**240 mg/m^2 *n* = 8**	**270 mg/m^2 *n* = 7**	**Total *N* = 64**
Total number of treatment cycles, median (range)	2 (1-5)	2 (1-12)	2 (1-8)	2 (1-5)	3 (1-5)	2 (1-10)	2 (1-12)
Relative dose intensity, median (range), %[b]	100.0 (97-111)	99.6 (80-116)	99.5 (73-107)	99.9 (89-107)	95.8 (77-101)	94.8 (64-101)	99.6 (64-116)
Cumulative dose, median, mg/kg	715.6	816.3	1074.5	1248.4	1806.0	1536.5	1004.6
Patients with ≥1 treatment-emergent AE leading to dose reduction, n (%)[c]	0	1 (13)	2 (14)	1 (9)	3 (38)	3 (43)	10 (16)
Patients with ≥1 treatment-emergent AE leading to discontinuation, n (%)[c]	4 (25)	0	2 (14)	1 (9)	2 (25)	2 (29)	11 (17)

AE, adverse event.
[a] Includes all patients who received ≥1 dose of *nab*-paclitaxel. [b] Defined as 100 × the average dose intensity/the planned dose intensity. [c] Over all cycles.

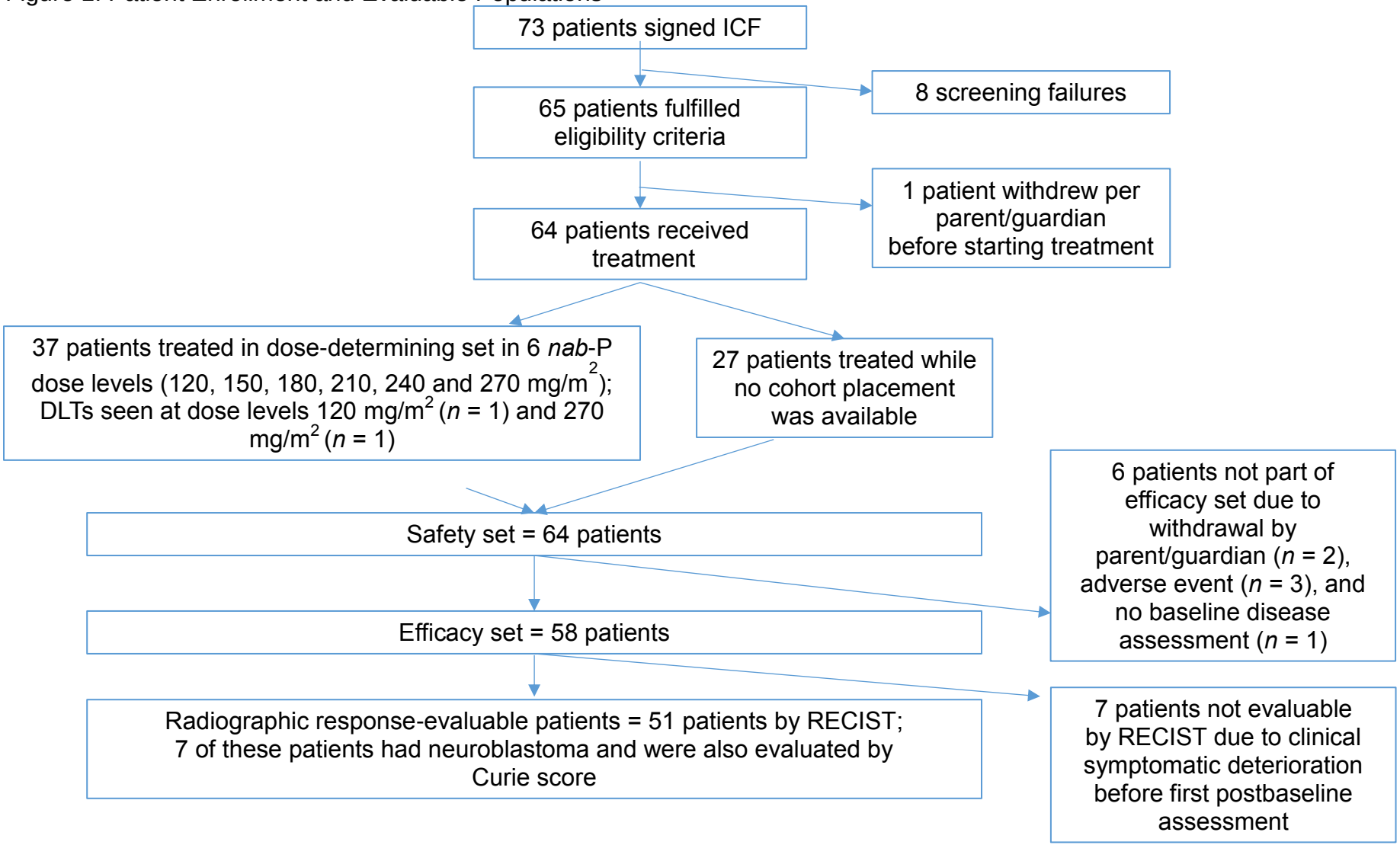
Table 4. Best Response Per RECIST in Efficacy-Evaluable Population[a]

	Response, n (%)					
	CR	PR	SD		PD	Clinical Symptomatic Deterioration
			All	≥16 wks		
Tumor type						
Neuroblastoma (*n* = 7)	0	0	2 (28.6)	1 (14.3)	2 (28.6)	3 (42.9)
Rhabdomyosarcoma (*n* = 12)	0	1 (8.3)	1 (8.3)	0	9 (75.0)	1 (8.3)
Ewing sarcoma (*n* = 12)	1 (8.3)	1 (8.3)	3 (25.0)	2 (16.7)	6 (50.0)	1 (8.3)
Osteosarcoma (*n* = 8)	0	0	1 (2.5)	0	6 (75.0)	1 (12.5)
Wilms tumor (*n* = 4)	0	0	0	0	4 (100.0)	0
Other[b] (*n* = 15)	0	2 (13.3)	6 (40.0)	2 (13.3)	6 (40.0)	1 (6.7)
***nab*-Paclitaxel dose, mg/m^2**						
120 (*n* = 14)	0	0	2 (14.3)	0	10 (71.4)	2 (14.3)
150 (*n* = 8)	0	0	2 (25.0)	2 (25.0)	5 (62.5)	1 (12.5)
180 (*n* = 12)	0	0	4 (33.3)	1 (8.3)	7 (58.3)	1 (8.3)
210 (*n* = 10)	1 (10.0)	0	2 (20.0)	1 (10.0)	5 (50.0)	2 (20.0)
240 (*n* = 7)	0	3 (42.9)	1 (14.3)	0	2 (28.6)	1 (14.3)
270 (*n* = 7)	0	1 (14.3)	2 (28.6)	1 (14.3)	4 (57.1)	0
All efficacy-evaluable patients (*n* = 58)	1 (1.7)	4 (6.9)	13 (22.4)	5 (8.6)	33 (56.9)	7 (12.1)

CR, complete response; NOS, not otherwise specified; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; wk, week.

[a] Included all treated patients who met study eligibility criteria, received ≥1 dose of *nab*-paclitaxel, and had a baseline efficacy assessment and either ≥1 postbaseline assessment or symptomatic deterioration. [b] Includes patients with adrenocortical carcinoma, clear cell sarcoma of the kidney, desmoplastic small round cell tumor, hepatoblastoma, hepatocarcinoma, immature ovarian teratoma, left adrenocortical carcinoma, left renal tumor with pulmonary metastases, nasopharyngeal carcinoma, sarcoma NOS, Wilms tumor, and yolk sac tumor.

Figure 1. Patient Enrollment and Evaluable Populations



DLT, dose-limiting toxicity; ICF, informed consent form; *nab*-P, *nab*-paclitaxel; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors.

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Supplemental Methods

Efficacy was evaluated in all treated patients who met study eligibility criteria, received ≥1 dose of *nab*-paclitaxel, and had a baseline efficacy assessment and either ≥1 postbaseline assessment or symptomatic deterioration. Patients with neuroblastoma were also assessed with ^{123}metaiodobenzylguanidine (MIBG) scintigraphy using the Curie score [23]. For Curie score assessment in patients with neuroblastoma, an absolute score was calculated based on the sum of lesions detected throughout the body, and a relative score was calculated by dividing the absolute score at each assessment time point by the corresponding pretreatment overall score. As defined in the protocol, response was classified as complete if the postscreening absolute score = 0 (all areas of uptake on MIBG scan completely resolved), partial if the relative score was ≥ 0.1 to ≤ 0.5 (lesions strongly reduced), stable disease if the relative score was > 0.5 (lesions weakly but significantly reduced), and progressive disease if new lesions were detected on MIBG scan, regardless of relative score. Overall response rate was defined as the number of patients achieving either a complete or partial response while receiving study therapy (confirmed ≥ 4 weeks after response criteria were first met) divided by the number of patients available for the analysis.

Response was assessed by investigator using computed tomography or magnetic resonance imaging at screening and every 8 weeks per Response Evaluation Criteria In Solid Tumors (RECIST) to < 1 (lesions not reduced) and progressive disease if new lesions were identified on MIBG scan, regardless of relative score. The study protocol was completed before recent revisions to INRC criteria [24]. After publication of the new

INRG response criteria, a post hoc assessment of patients with neuroblastoma was conducted using these revised criteria instead of the protocol-defined criteria.