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Phase II results from a phase I/II study to assess the safety and efficacy of weekly nab-paclitaxel in paediatric patients with recurrent or refractory solid tumours: A collaboration with the European Innovative Therapies for Children with Cancer Network

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KEYWORDS
Albumin-bound paclitaxel;
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Abstract ***Background:*** The phase I component of a phase I/II study defined the recommended phase II dose and established the tolerability of nab-paclitaxel monotherapy in paediatric patients with recurrent or refractory solid tumours. The activity and safety of nab-paclitaxel monotherapy was further investigated in this phase II study.
Patients and methods: Paediatric patients with recurrent or refractory Ewing sarcoma, neuroblastoma or rhabdomyosarcoma received 240 mg/m^2 of nab-paclitaxel on days 1, 8 and 15 of each 28-day cycle. The primary end-point was the overall response rate (ORR; complete response [CR] + partial response [PR]). Secondary end-points included duration of response, disease control rate (DCR; CR + PR + stable disease [SD]), progression-free survival, 1-year overall survival, safety and pharmacokinetics.
Results: Forty-two patients were enrolled, 14 each with Ewing sarcoma, neuroblastoma and rhabdomyosarcoma. The ORRs were 0%, 0% and 7.1% (1 confirmed PR), respectively. The DCRs were 30.8% (4 SD), 7.1% (1 SD) and 7.1% (1 confirmed PR and 0 SD) in the Ewing sarcoma, neuroblastoma and rhabdomyosarcoma groups, respectively. The median progression-free survival was 13.0, 7.4 and 5.1 weeks, respectively, and the 1-year overall survival rates were 48%, 25% and 15%, respectively. The most common grade III/4IVadverse events were haematologic (neutropenia [50%] and anaemia [48%]), and grade III/IV peripheral neuropathy occurred in 2 patients (14%) in the rhabdomyosarcoma group. Pharmacokinetics analyses revealed that paclitaxel tissue distribution was both rapid and extensive.
Conclusions: In this phase II study, limited activity was observed; however, the safety of nab-paclitaxel in paediatric patients was confirmed.
Trial registration: NCT01962103 and EudraCT 2013-000144-26.
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1. Introduction

Cancer remains the leading cause of childhood death due to disease in the United States and Europe [1,2] despite a relatively high 5-year survival rate (83%) in the 0- to 14-year-old population [1]. Recurrent or refractory disease is common with certain tumour types and is associated with poor long-term outcomes [3–7]. For example, the 5-year overall survival (OS) rates in paediatric patients with recurrent disease are 28% for rhabdomyosarcoma [7], 20% for neuroblastoma [4] and 23% for Ewing sarcoma [3], with little to no improvement in survival for recurrent and metastatic rhabdomyosarcoma and Ewing sarcoma for decades [8,9]. Based on these poor survival outcomes, there is a significant unmet need for more efficacious treatment options for paediatric patients with metastatic or relapsed disease.

Taxanes have modest antitumour activity in children, but toxicities may limit efficacious dose delivery [10–12]. The solvent-based formulation of conventional taxanes may contribute to their associated toxicities, as has been shown in a phase I trial in children treated with paclitaxel [12]. nab-Paclitaxel (nab-P), an albumin-bound form of paclitaxel that is free of ethanol and Kolliphor EL (previously known as Cremophor EL), has demonstrated safety and efficacy in adults with various solid tumour types, including metastatic breast cancer [13], advanced non-small-cell lung cancer [14] and metastatic pancreatic cancer [15]. nab-P also demonstrated dose-dependent cytotoxicity in several paediatric solid tumour cell lines [16]. Furthermore, antitumour activity was observed in mouse xenograft models of Ewing sarcoma, neuroblastoma and rhabdomyosarcoma [16–18]. Based on these preclinical results and the known efficacy in adult patients with solid tumours, a phase I/II clinical trial of nab-P monotherapy in paediatric patients with solid tumours was initiated.

The phase I dose-finding portion of the study demonstrated the feasibility of nab-P monotherapy in paediatric patients with recurrent or refractory solid tumours [19]. Dose-limiting toxicities occurred in 2 of 37 patients (5.4%), which included grade III dizziness (120 mg/m^2) and grade IV neutropenia lasting $>$ 7 days (270 mg/m^2). The most common grade III/IV treatment-emergent adverse events (TEAEs) were haematologic (neutropenia and leukopenia; 36% each). Peripheral neuropathy is a TEAE of interest with nab-P, but the rate of grade $\geq$III peripheral neuropathy in the paediatric population (3%) was lower than the rates observed in adults with lung or breast cancer treated with nab-P monotherapy (5%–38%) [19,20]. In the phase I portion of the study, the recommended phase II dose (RP2D) of nab-P was identified as 240 mg/m^2 on days 1, 8 and 15 of each 28-day cycle (qw3/4) [19].

The phase II portion of this study, conducted in collaboration with the Innovative Therapies for Children with Cancer European Consortium (http://www.itcc-consortium.org/), evaluated the safety and efficacy of nab-P using the RP2D in paediatric patients with 3 specific solid tumour types: Ewing sarcoma, neuroblastoma and rhabdomyosarcoma. Results

describing the response rates, survival outcomes, safety and pharmacokinetic (PK) profile are reported here.

2. Patients and methods

2.1. Study oversight

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation. Approval from an institutional review board or independent ethics committee was obtained from each institution before the start of the study. Informed consent/assent was obtained from all patients or legal representatives before enrolment. The study is registered with ClinicalTrials.gov (NCT01962103) and EudraCT (2013-000144-26).

2.2. Study population

Patients aged $\geq$ 6 months to $\leq$ 24 years were eligible. Other key inclusion criteria included radiologically documented, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, (or ^{123}I-metaiodobenzylguanidine [MIBG]/Curie score for neuroblastoma) diagnosed as Ewing sarcoma, neuroblastoma or rhabdomyosarcoma; treatment failure with $\leq$ 3 prior lines of therapy; Lansky/Karnofsky performance status $\geq$ 70% and adequate bone marrow function, assessed as absolute neutrophil count $\geq$ 1.0 $\times$ 10^9 cells/L, platelet count $\geq$ 80 $\times$ 10^9 cells/L (for patients with known bone marrow involvement, the threshold was $\geq$ 50 $\times$ 10^9 cells/L) and haemoglobin level $\geq$ 8 g/dL (transfusion was permitted to fulfil this criterion). Key exclusion criteria were primary brain tumour(s) or brain metastasis, grade $\geq$ II peripheral neuropathy at screening and therapeutic-dose chemotherapy or radiotherapy $\leq$ 21 days before the start of study treatment.

2.3. Study design and treatment

This phase I/II open-label, multicenter, single-arm study was conducted as described previously [19]. In addition, phase II used a Simon 2-stage minimax design to determine the number of patients to enrol. In stage 1, 14 patients were enrolled in each of 3 tumour types: Ewing sarcoma, neuroblastoma and rhabdomyosarcoma. If $\geq$ 2 of the 14 evaluable patients had a confirmed complete response (CR) or partial response (PR) in stage 1, the study would proceed to stage 2 and an additional 9 patients would be enrolled (up to 23 total in each tumour type). At the final analysis, the study treatment would be concluded with more than a 5% true response rate if $\geq$ 5 of 23 patients in a given tumour type had a response. Therefore, the phase II target response rate was 21.74%, with 80% power and a 10% significance level.

Patients received nab-P (240 mg/m^2 in patients weighing $>$ 10 kg (as established previously [19]) and 11.5 mg/kg in patients weighing $\leq$ 10 kg) administered intravenously over approximately 30 min on days 1, 8 and 15 of each 28-day cycle until disease progression, initiation of a new anticancer treatment, withdrawal of consent, parent/guardian/patient refusal, physician decision, unmanageable toxicity or study termination. In children weighing $\leq$ 10 kg and aged $\geq$ 6 months, the body surface area-based dose was converted to mg/kg by dividing the total dose at the median body surface area (0.41 m^2) with the median weight (8.7 kg). Patients weighing $\leq$ 10 kg received treatment at 1 dose level lower during the first cycle. Treatment with non-anticancer concomitant medications was allowed at the investigator's discretion; all concomitant treatments were recorded.

2.4. Study end-points and assessments

The primary end-point for phase II was investigator-assessed overall response rate (ORR, defined as the percentage of patients who achieved a CR or PR confirmed no less than 4 weeks after criteria for response were first met). Secondary end-points were duration of response (DOR, defined as the time from the date of first observed response, either a CR or PR, until the date progressive disease [PD] was first observed), disease control rate (DCR, defined as the percentage of patients who achieved either stable disease [SD] maintained for $\geq$ 16 weeks or confirmed CR or PR [confirmed no less than 4 weeks after criteria for response were first met]), progression-free survival (PFS, defined as the time from the date of first nab-P dose until the date PD was first observed or date of death [any cause], whichever occurred first), 1-year OS (OS was defined as the time from the first dose to death from any cause), safety and PK profile.

Response assessments were performed at screening (up to 28 days before the start of study treatment) and every 8 weeks ($\pm$5 days) from cycle 1, day 1, until disease progression, start of a new anticancer therapy or withdrawal of consent from the entire study. Response was determined per RECIST, version 1.1, guidelines [21]. Patients with neuroblastoma were also assessed using MIBG evaluation and the Curie score at screening and every 8 weeks. Response was determined per previously established criteria [22–24].

Disease progression occurred if the patient had disease progression per response assessment or treatment/study discontinuation due to disease progression or symptomatic deterioration. Patients without disease progression who had not died were censored at the last known time that the patient was free of progression. Median PFS and OS were calculated using the

Table 1
Demographics and baseline characteristics.

Characteristic	Ewing sarcoma n = 14	Neuroblastoma n = 14	Rhabdomyosarcoma n = 14	Total N = 42
Age				
Median (range), years[a]	8.5 (4–18)	7.0 (1–15)	14.0 (3–24)	8.0 (1–24)
< 2 years, n (%)	0	1 (7)	0	1 (2)
≥ 2 to < 12 years, n (%)	10 (71)	11 (79)	5 (36)	26 (62)
≥ 12 to < 18 years, n (%)	3 (21)	2 (14)	7 (50)	12 (29)
≥ 18 to ≤ 24 years, n (%)	1 (7)	0	2 (14)	3 [7]
Sex, n (%)				
Male	8 (57)	9 (64)	5 (36)	22 (52)
Female	6 (43)	5 (36)	9 (64)	20 (48)
Lansky/Karnofsky performance status, n (%)[b]				
100%	6 (43)	10 (71)	7 (50)	23 (55)
90%	6 (43)	1 (7)	5 (36)	12 (29)
80%	2 (14)	2 (14)	1 (7)	5 (12)
70%	0	1 (7)	1 (7)	2 (5)
Prior systemic anticancer regimens, median (range), n	2.5 (2.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Prior cancer treatment or supportive care, n (%)	14 (100)	14 (100)	14 (100)	42 (100)
Radiation therapy	12 (86)	10 (71)	10 (71)	32 (76)
Cancer surgery	10 (71)	11 (79)	6 (43)	27 (64)
Systemic anticancer therapy	14 (100)	14 (100)	14 (100)	42 (100)
Autologous stem cell transplant	3 (21)	10 (71)	0	13 (31)
Other anticancer therapy	1 (7)	6 (43)	0	7 (17)

[a] Age was calculated as integer ≤ ([date of informed consent − date of birth + 1]/365.25).
[b] Reported as a combination of Karnofsky performance status (patients ≥ 12 years old) and Lansky performance status (patients < 12 years old).

Kaplan–Meier method, while 95% confidence interval (CIs) were determined using the Greenwood method.

Safety was assessed through clinical evaluations, vital sign measurements, laboratory tests and adverse event (AE) monitoring. AEs were analysed in terms of TEAEs (any AE that began or worsened on or after the start of nab-P through 28 days after the last dose) and documented per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. AEs were categorised per Medical Dictionary for Regulatory Activities, version 20.0, and summarised by system organ class and preferred term.

A population PK model was developed based on both the dense PK data from phase I and the sparse PK data from phase II. Blood samples were collected at cycle 1, day 1, from all patients in both phase I and II portions of the study. In phase I, samples were collected over 24 h for patients < 6 years old (1–2 min before the end of infusion, 15 min, 3 h, 5 h and 24 h after the end of infusion) and over 72 h for patients ≥ 6 years old (1–2 min before the end of infusion, 15 min, 1, 3, 5, 8, 24, 48 and 72 h after the end of infusion). In phase II, samples were collected over 24 h (15 min, 3 h and 24 h after the end of infusion). The population PK analysis was performed using non-linear mixed-effect modelling (NONMEM, version 7.3) with the first order conditional estimation and the INTERACTION option. Evaluation of the PK model and the results were further analysed using R® (version 3.4.2). Concentration data obtained from both the dense and sparse PK sampling were combined to develop the population PK model. Effects of age and body size on nab-P PK were assessed.

For this study, a previously described three-compartment model with saturable distribution and elimination [25] was reevaluated to fit concentrations collected. Non-linear mixed-effects models were fitted to the concentration–time data of paclitaxel described by the three-compartment structural PK model. The quality of fit of structural population PK models was assessed using a variety of model discrimination tools. The performance of the final population PK model of paclitaxel was evaluated with non-parametric bootstrap resampling and visual predictive check. The final population PK model was then used to predict paclitaxel exposure measures area under the blood concentration-time curve (AUC and Cmax) after administration of nab-P.

3. Results

3.1. Patient demographics and disposition

A total of 42 patients were enrolled in phase II: 14 each with Ewing sarcoma, neuroblastoma and rhabdomyosarcoma. The median age was 8.5, 7.0 and 14.0 years in the Ewing sarcoma, neuroblastoma and rhabdomyosarcoma groups, respectively (Table 1). All patients discontinued treatment. A total of 34 patients discontinued due to PD (11 with Ewing sarcoma, 12 with neuroblastoma and 11 with rhabdomyosarcoma), 4 patients discontinued due to symptomatic deterioration not fulfilling RECIST criteria for PD (2 each with Ewing sarcoma and neuroblastoma) and 4 patients discontinued due to AEs (1 with Ewing sarcoma

[peripheral sensorimotor neuropathy] and 3 with rhabdomyosarcoma [peripheral sensory neuropathy, 2 patients, and neuralgia]).

3.2. Response

The efficacy-evaluable population included 13 patients in the Ewing sarcoma group (1 patient failed to meet the eligibility criteria relevant to efficacy) and 14 patients each in the neuroblastoma and rhabdomyosarcoma groups. One patient with rhabdomyosarcoma had a confirmed PR (ORR, 7.1%). No confirmed CR or PR was observed in patients with Ewing sarcoma or neuroblastoma (Table 2). Confirmed SD was achieved in 4 patients with Ewing sarcoma (30.8%) and 1 patient with neuroblastoma (7.1%). In the rhabdomyosarcoma group, the patient who achieved a confirmed PR experienced a DOR of 6.1 weeks. Based on the ORRs, the study did not progress to stage 2 of the Simon 2-stage minimax design in any of the 3 groups. A total of 5 patients achieved an unconfirmed PR: 2 (15.4%) in the Ewing sarcoma group and 3 (21.4%) in the rhabdomyosarcoma group. DCRs were 30.8%, 7.1% and 7.1% in the Ewing sarcoma, neuroblastoma and rhabdomyosarcoma groups, respectively.

3.3. Survival

Survival was assessed for patients in the efficacy-evaluable population (Table 3). The median PFS in the Ewing sarcoma, neuroblastoma and rhabdomyosarcoma groups was 13.0, 7.4 and 5.1 weeks, respectively (Table 3 and Fig. 1). The 1-year OS rates were 48%, 25% and 15%, while the median OS was 32.1, 26.7 and 19.6 weeks in the Ewing sarcoma, neuroblastoma and rhabdomyosarcoma groups, respectively (Table 3 and Fig. 2).

3.4. Treatment exposure

Patients in the Ewing sarcoma, neuroblastoma and rhabdomyosarcoma groups received a median of 4.0, 2.0 and 2.0 treatment cycles, with a median treatment duration of 14.0, 7.0 and 5.0 weeks, respectively (Table 4). Patients received a median cumulative dose of 2389.11, 1281.59 and 941.35 mg/m^2, respectively. Dose reductions ($\geq$ 1) occurred in 14 patients, while dose interruptions ($\geq$ 1) occurred in 5 patients. All dose reductions and most interruptions (4 of 5 interruptions; 80%) were due to AEs.

3.5. Safety

All 14 patients in each of the 3 tumour types were included in the safety population. TEAEs of any grade occurred in 100% of patients in all groups. Grade III/IV TEAEs occurred in 86%, 93% and 86% of patients in the Ewing sarcoma, neuroblastoma and rhabdomyosarcoma groups, respectively (Table 5). Grade III/IV haematologic TEAEs were the most common, with grade III/IV neutropenia occurring in 21 patients (50%) and grade III/IV anaemia occurring in 20 patients (48%). Peripheral neuropathy of any grade occurred in 8 patients (19%), with grade III/IV peripheral neuropathy

Table 2
Response rates per RECIST version 1.1 and/or MIBG response (neuroblastoma group only; efficacy-evaluable population).

Response	Ewing sarcoma n = 13	Neuroblastoma[a] n = 14	Rhabdomyosarcoma n = 14	Total N = 41
Confirmed response, n (%)				
Complete response	0	0	0	0
Partial response	0	0	1 (7.1)	1 (2.4)
Stable disease	4 (30.8)	1 (7.1)	0	5 (12.2)
ORR, n (%)	0	0	1 (7.1)	1 (2.4)
DCR, n (%)	4 (30.8)	1 (7.1)	1 (7.1)	6 (14.6)
Best overall response, n (%)[b]				
Complete response	0	0	0	0
Partial response	2 (15.4)	0	3 (21.4)	5 (12.2)
Stable disease	5 (38.5)	1 (7.1)	0	6 (14.6)
$\geq$ 16 weeks	3 (23.1)	1 (7.1)	0	4 (9.8)
< 16 weeks	2 (15.4)	0	0	2 (4.9)
Progressive disease	5 (38.5)	10 (71.4)	11 (78.6)	26 (63.4)
Symptomatic deterioration[c]	1 (7.7)	2 (14.3)	0	3 (7.3)
Not evaluable	0	1 (7.1)[d]	0	1 (2.4)

DCR, disease control rate; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors; MIBG, ^{123}I-metaiodobenzylguanidine.

[a] For patients with neuroblastoma who had both RECIST, version 1.1, and Curie score tumour evaluations, both tumour response results were considered and an overall response was derived.

[b] Best overall response was based on unconfirmed responses.

[c] Patients discontinuing treatment due to symptomatic deterioration before a tumour assessment was conducted.

[d] Patient was started on another therapy but still had a tumour assessment performed.

Table 3
PFS and OS (efficacy-evaluable population).

Survival outcome[a]	Ewing sarcoma n = 13	Neuroblastoma n = 14	Rhabdomyosarcoma n = 14	Total N = 41
Follow-up time, median (range), weeks	24.9 (7.6–66.7)	19.4 (3.4–59.6)	18.3 (1.4–66.3)	21.4 (1.4–66.7)
PFS				
Median (95% CI), weeks	13.0 (7.4–16.1)	7.4 (4.6–8.1)	5.1 (2.1–7.9)	7.6 (7.2–8.1)
2-month rate (95% CI), %	54 (25–76)	16 (3–40)	21 (5–45)	30 (17–45)
6-month rate (95% CI), %	15 (2–39)	NE	NE	6 (1–18)
OS				
Median (95% CI), weeks	32.1 (16.7-NE)	26.7 (12.0-NE)	19.6 (4.0–25.7)	25.7 (19.6–33.0)
2-month rate (95% CI), %	92 (57–99)	86 (54–96)	70 (38–87)	83 (67–91)
6-month rate (95% CI), %	65 (31–85)	59 (27–81)	23 (6–48)	48 (31–63)
12-month rate (95% CI), %	48 (14–76)	25 (4–54)	15 (2–39)	29 (14–46)

CI, confidence interval; NE, not evaluable; OS, overall survival; PFS, progression-free survival.
[a] Median PFS and OS times were estimated using the Kaplan–Meier method; 95% CI for median time to PFS and OS events using the Greenwood method.

occurring only in 2 patients (14%) in the rhabdomyosarcoma group. No treatment-related TEAEs leading to death were reported.

3.6. nab-P PK profile

In the phase I part of the study, whole blood paclitaxel volume of distribution, clearance (CL) and half-life remained constant over the 120–240 mg/m^2 dose range but increased at the 270 mg/m^2 dose level. At the RP2D of 240 mg/m^2, the mean CL of paclitaxel and the mean terminal half-life were 19.1 L/h and 13.5 h, respectively.

None of the tested covariates (using NONMEM) were retained in the final population PK model of nab-P. Final population PK parameters of nab-P were as follows (based on all patients for each tumour type). The maximum elimination rate from the central compartment (VMEL) was 31,983 μg/h, and the concentration in the central compartment at 50% of VMEL was 951 μg/L. The volume of distribution of the central compartment (V1) was 11.8 L. The intercompartmental clearance between the central compartment and first peripheral compartment (Q2) was 22.4 L/h. The volume of distribution of the first peripheral compartment (V2) was 545 L. Intercompartmental clearance between the central compartment and second peripheral compartment (Q3) was 34.8 L/h. The volume of distribution of the second peripheral compartment (V3) was 45.3 L. The estimated allometric function for VMEL, Q2 and Q3 was 1.12, while that for V1, V2 and V3 was 0.888.

4. Discussion

The primary outcome of the phase II study revealed ORRs of 0%, 0% and 7.1% (1 confirmed PR) in patients with Ewing sarcoma, neuroblastoma and rhabdomyosarcoma, respectively; therefore, stage 2 of the trial was not initiated in any of the disease groups. The current phase I/II study revealed a manageable safety profile of weekly nab-P monotherapy in paediatric patients. The phase II results confirmed the safety findings from phase I—the most common TEAEs were haematologic, and the incidence of grade III/IV peripheral neuropathy was low. No new safety signals were identified in paediatric

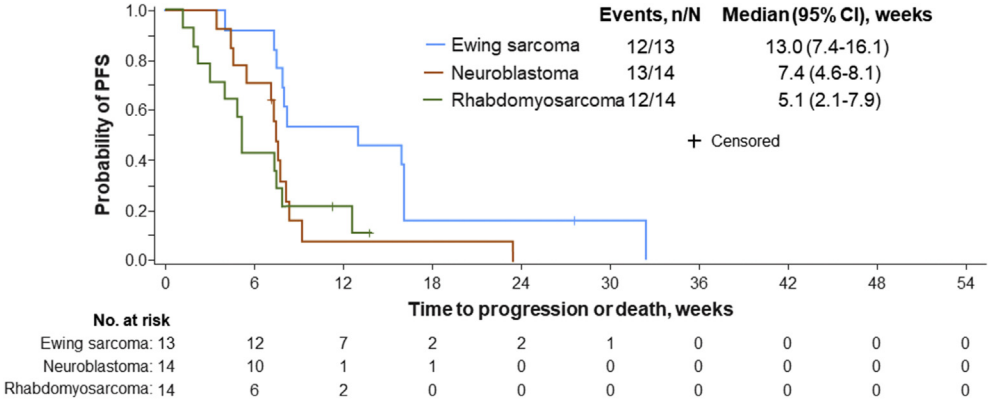

Fig. 1. PFS in patients with Ewing sarcoma, neuroblastoma and rhabdomyosarcoma (efficacy-evaluable population). PFS, progression-free survival.

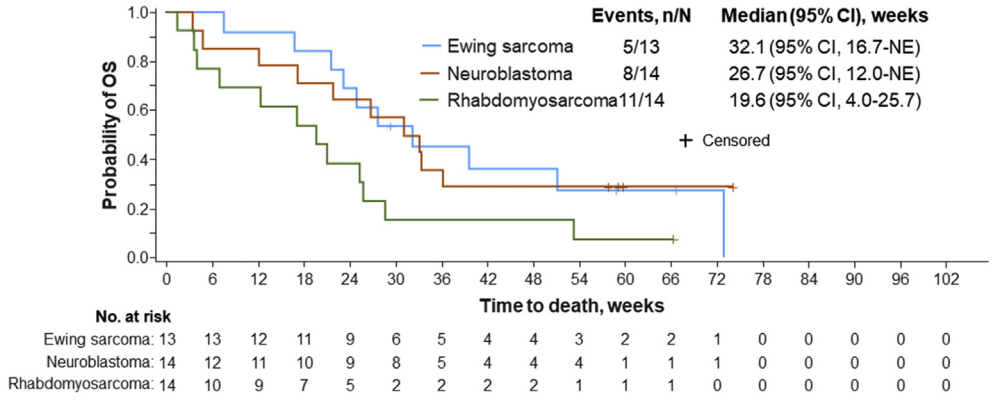

Fig. 2. OS in patients with Ewing sarcoma, neuroblastoma and rhabdomyosarcoma (efficacy-evaluable population). NE, not evaluable; OS, overall survival.

Table 4
Treatment exposure and dose modifications (safety population).

Parameter	Ewing sarcoma n = 14	Neuroblastoma n = 14	Rhabdomyosarcoma n = 14	Total N = 42
Treatment exposure				
Treatment cycles, median (range), n	4.0 (1–6)	2.0 (1–6)	2.0 (1–4)	2.0 (1–6)
Treatment duration, median (range), weeks[a]	14.0 (3–31)	7.0 (3–23)	5.0 (1–13)	7.0 (1–31)
Relative dose intensity, median (range), %[b]	97.58 (81.3–102.2)	97.94 (77.3–102.8)	99.44 (64.3–101.0)	98.63 (64.3–102.8)
Cumulative dose, median (range), mg/m^2	2389.11 (720.0 –4125.0)	1281.59 (700.9 –3345.6)	941.35 (236.4–2115.7)	1419.59 (236.4 –4125.0)
Dose modifications				
≥1 dose reduction, n (%)	4 (29)	6 (43)	4 (29)	14 (33)
Time to first dose reduction, median (range), weeks	8 (5–20)	4 (2–8)	5 (2–9)	5 (2–20)
≥1 dose interruption, n (%)	2 (14)	2 (14)	1 (7)	5 (12)
Time to first dose interruption, median (range), weeks	8 (6–10)	4 (2–6)	3 (3–3)	6 (2–10)

[a] Treatment duration was calculated as ([date of last study drug administration] − [date of first study drug administration] + 7)/7.
[b] Relative dose intensity was defined as 100 × average dose intensity divided by planned dose intensity.

patients compared with those observed in other studies of adults with various solid tumours.

In phase I of this study, which included patients with Ewing sarcoma, neuroblastoma, rhabdomyosarcoma and osteosarcoma, the ORR and DCR for all patients were 8.6% and 17.2%, respectively, which included 2 responses (1 CR and 1 PR) among patients with Ewing sarcoma and 1 PR among patients with rhabdomyosarcoma [19]. The phase II results revealed lower ORRs (0%, 0% and 7.1%) and varied DCRs (30.8%, 7.1%, and 7.1%) in the Ewing sarcoma, neuroblastoma and rhabdomyosarcoma groups, respectively. Differences in response rates between study phases may be attributed to the different inclusion criteria: phase I did not restrict the type of solid tumour required for patient enrolment, while only patients with Ewing sarcoma, neuroblastoma or rhabdomyosarcoma were enrolled in phase II. Although ORRs were low in phase II, SD rates and early indications of response (initially determined to be PR but unconfirmed until ≥ 4 weeks after the criteria for response were first met) were encouraging: 5 patients (38.5%) achieved SD and 2 (15.4%) achieved an unconfirmed PR in the Ewing sarcoma group, 1 patient (7.1%) achieved SD in the neuroblastoma group and 3 patients (21.4%) achieved an unconfirmed PR, 1 of whom had a confirmed PR, in the rhabdomyosarcoma group.

The three-compartment model with saturable elimination adequately described the observed whole-blood concentrations of nab-P in this patient population. The results are consistent with the saturable elimination at higher doses, as well as the deep distribution of nab-P that was previously observed in adult patients with advanced or metastatic solid tumours [25]. In addition, the mean paclitaxel CL and terminal half-life data collected at the RP2D of 240 mg/m^2 from the phase I part of the study were consistent with those reported previously in adult patients [26].

Based on the primary outcome, stage 2 of the trial was not initiated in any of the disease groups due to the lack of activity in stage 1. However, this study confirmed the tolerability of nab-P in the paediatric population that was established in the phase I portion [19]. Disease control was achieved in 31% of patients with Ewing

Table 5
Grade III/IV TEAEs in ≥2 patients in any phase II group (by system organ class and preferred term; safety population).

Event, n (%)[a]	Ewing sarcoma n = 14	Neuroblastoma n = 14	Rhabdomyosarcoma n = 14	Total N = 42
Patients with ≥1 TEAE	12 (86)	13 (93)	12 (86)	37 (88)
Blood and lymphatic system disorders	10 (71)	12 (86)	11 (79)	33 (79)
Neutropenia	6 (43)	8 (57)	7 (50)	21 (50)
Anaemia	5 (36)	8 (57)	7 (50)	20 (48)
Leukopenia	5 (36)	6 (43)	5 (36)	16 (38)
Thrombocytopenia	0	5 (36)	2 (14)	7 (17)
Febrile neutropenia	1 (7)	0	3 (21)	4 (10)
Lymphopenia	2 (14)	0	0	2 (5)
General disorders and administration site conditions	1 (7)	2 (14)	2 (14)	5 (12)
General physical health deterioration	0	2 (14)	1 (7)	3 (7)
Nervous system disorders	0	1 (7)	4 (29)	5 (12)
Headache	0	1 (7)	2 (14)	3 (7)
Metabolism and nutrition disorders	3 (21)	0	1 (7)	4 (10)
Hypokalemia	2 (14)	0	0	2 (5)
Peripheral neuropathy[b]	0	0	2 (14)	2 (5)

AE, adverse event; TEAE, treatment-emergent adverse event.
[a] Patients with multiple AEs were counted once for each system organ class and/or preferred term using worst reported grade.
[b] Peripheral neuropathy includes the preferred terms peripheral sensory neuropathy, neuralgia, paraesthesia, peripheral motor neuropathy, dysaesthesia, muscular weakness, neuropathy peripheral and peripheral sensorimotor neuropathy.

sarcoma, with a median PFS of 13 weeks. Notably, this study investigated nab-P as monotherapy for safety purposes. The overall findings from this study do not support further development of nab-P in paediatric patients.

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Conflict of interest statement

G.B. reports serving in a consulting or advisory role for Clinigen Group and receiving travel expenses from Jazz Pharmaceuticals. J.C.C. reports serving in a consulting or advisory role for Bayer and Roche. F.D. reports serving in a consulting or advisory role for Bristol-Myers Squibb and Celgene (a Bristol-Myers Squibb Company), from which his institution has received funds, and receiving travel expenses from Bristol-Myers Squibb. L.M. reports serving in a consulting or advisory role for Novartis, AstraZeneca, Roche Genentech, Bayer, Amgen and MundiPharma; receiving honoraria for educational events from Celgene (a Bristol-Myers Squibb Company) and Novartis and receiving travel expenses from MundiPharma, Celgene (a Bristol-Myers Squibb Company) and Amgen. S.G.M. reports being in a paid advisory role for Loxo Oncology and Clinigen Group for work performed outside of the current study. R.S. reports serving as an employee of and holding stock/ownership in Bristol-Myers Squibb. N.C. reports serving as an employee of and holding stock/ownership in Bristol-Myers Squibb. Y.l.-B. reports serving as an employee of Celgene (a Bristol-Myers Squibb Company) International A Bristol-Myers Squibb Company and holding stock/ownership in Bristol-Myers Squibb. M.S. reports serving as an employee of Celgene (a Bristol-Myers Squibb Company) International A Bristol-Myers Squibb Company and holding stock/ownership in Bristol-Myers Squibb. G.V. reports receiving travel expenses from Bristol-Myers Squibb. All other authors declare no conflict of interest

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