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Original Research

Phase I results of a phase I/II study of weekly *nab*-paclitaxel in paediatric patients with recurrent/refractory solid tumours: A collaboration with innovative therapies for children with cancer

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KEYWORDS
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Ewing sarcoma;
Solid tumour

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

Patients and methods: Patients with recurrent/refractory extracranial solid tumours 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 haematologic, including neutropenia (36%), leukopenia (36%) and lymphopenia (25%). Although the MTD was not reached, 270 mg/m^2 was declared non-tolerable 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 one patient (2%; Ewing sarcoma) and partial responses in four patients (7%; rhabdomyosarcoma, Ewing sarcoma, renal tumour 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 antitumour activity. Phase II is currently enrolling patients with recurrent/refractory neuroblastoma, rhabdomyosarcoma and Ewing sarcoma.

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EudraCT: 2013-000144-26.

1. 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 paediatric patients with certain solid tumour 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 antitumour activity in children with refractory solid tumours. 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 tumours [8]. Similarly, in 2 phase I trials of >60 paediatric patients with refractory solid tumours, 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 paediatric patients with refractory/relapsed solid tumours because it was designed to increase antitumour 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 tumour types [10,11,13–16]. *nab*-Paclitaxel has been approved in the United States 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 paediatric solid-

tumour cell lines and antitumour activity in rhabdomyosarcoma, neuroblastoma and Ewing sarcoma mouse xenograft models, supporting its clinical exploration in paediatric solid tumour 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 paediatric patients with recurrent/refractory solid tumours. 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.

2. Patients and methods

2.1. Study population

Paediatric patients aged ≥6 months to <18 years with recurrent/refractory solid tumours 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 $\geq 1.0 \times 10^9$/L, platelets $\geq 80 \times 10^9$/L, haemoglobin ≥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 tumours, 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).

2.2. Study design

Phase I of this multicentre, open-label and 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 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 (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 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.

2.3. Study assessment

The phase I primary end-points were the incidences of DLTs and treatment-emergent adverse events (AEs). Secondary end-points included pharmacokinetics and overall response rate per Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 [22]. Exploratory end-points were response by ^{123}metaiodobenzylguanidine scintigraphy using Curie score [23] for patients with neuroblastoma and biomarker analyses in archival tumour 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 six 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 non-haematologic AE (excluding transient transaminitis), grade 3/4 nausea or vomiting lasting >5 days despite antiemetic treatment, grade 4 thrombocytopenia or anaemia 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 haematologic 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.

3. Results

3.1. Patients

Phase I enrolled 65 patients; 64 patients aged 2–17 years were treated, and one patient withdrew before treatment. Thirty-seven patients were enrolled in six 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 (i.e. during the periods in which placement in one of the six dose-determining cohorts was not available (Fig. 1)). Most patients (69%) had a Lansky/Karnofsky performance status of 90–100 (Table 1). Diagnoses included rhabdomyosarcoma (22%), Ewing sarcoma (20%), neuroblastoma (16%) and other less-frequent tumour types. All patients weighed >10 kg. The median number of prior treatment lines was three.

3.2. Treatment exposure and selection of the recommended phase II dose

In all treated patients, a median of two (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, 11 (17%) due to AEs, 11 (17%) due to clinical symptomatic deterioration, five (8%) due to withdrawal by patient or parent/guardian and one (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 seven patients in the dose-determining set for the 270 mg/m^2 dose, four patients continuing beyond cycle 1 required a dose reduction due to toxicity. Although DLT-based criteria to determine the non-tolerable dose were not met, the safety monitoring committee declared 270 mg/m^2 as the non-tolerable dose based on the totality of safety information, including grade 3/4 toxicities during the first two 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 six dose cohorts, *nab*-paclitaxel 240 mg/m^2 was identified as the RP2D.

3.3. Safety

Overall, 88% of the 64 patients experienced ≥1 treatment-emergent grade 3/4 AEs. At all tested dose levels, grade 3/4 AEs were mainly haematologic (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 two patients, both of whom received *nab*-paclitaxel 270 mg/

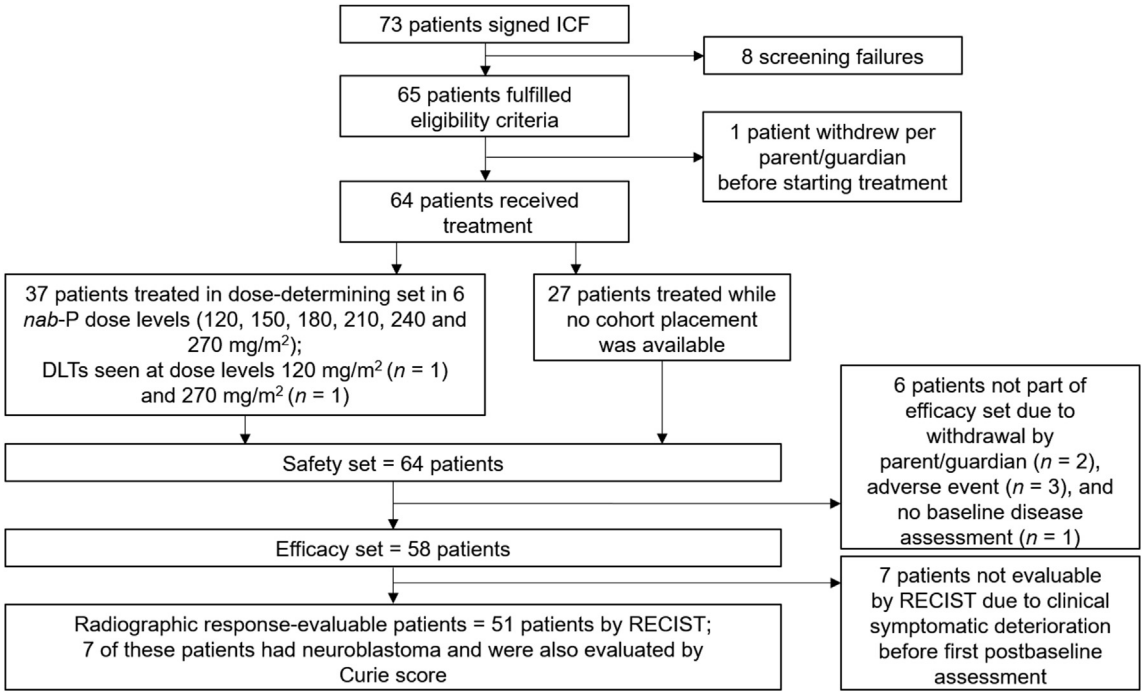

Fig. 1. Patient enrolment and evaluable populations. DLT, dose-limiting toxicity; ICF, informed consent form; *nab*-P, *nab*-paclitaxel; RECIST, Response Evaluation Criteria In Solid Tumours.

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, n (%)	6 (38)	2 (25)	7 (50)	6 (55)	3 (38)	3 (43)	27 (42)
12–17, 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 tumour 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; PS, 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 tumour, hepatoblastoma, hepatocarcinoma, immature ovarian teratoma, left adrenocortical carcinoma, left renal tumour with pulmonary metastases, nasopharyngeal carcinoma, sarcoma NOS, Wilms tumour, and yolk sac tumour.

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							
Haematologic[b]							
Neutropenia	4 (25)	1 (13)	3 (21)	6 (55)	4 (50)	5 (71)	23 (36)
Leucopenia	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)
Non-haematologic							
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] Haematologic events reported from laboratory values collected on dosing days.

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).

3.4. 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 11,982 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 versus 9768 h ng/mL) or mean C_{max} (7910 versus 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.

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] Overall cycles.

Table 4
Best response per RECIST in efficacy-evaluable population.[a]

Parameter	Response, n (%)					
	CR	PR	SD		PD	Clinical symptomatic deterioration
			All	≥16 wks		
Tumour 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 tumour (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 Tumours; 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 tumour, hepatoblastoma, hepatocarcinoma, immature ovarian teratoma, left adrenocortical carcinoma, left renal tumour with pulmonary metastases, nasopharyngeal carcinoma, sarcoma NOS, Wilms tumour, and yolk sac tumour.

3.5. Antitumour 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 tumour with pulmonary metastases (high-grade malignant tumour 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%), five (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.

3.6. Antitumour activity in patients with neuroblastoma

Seven patients with neuroblastoma were evaluable for efficacy. The current study was initiated before the publication of the revised INRC guidelines [24]; however, *post hoc* analyses demonstrated that, using revised INRC criteria, two patients with neuroblastoma had minor response due to robust decreases in Curie score of 60% and 63%, but only had stable disease as per

RECIST. One patient had stable disease, and four patients had progressive disease.

4. Discussion

The phase I portion of this study met its primary objective by determining the MTD/RP2D of weekly *nab*-paclitaxel in paediatric patients with recurrent/refractory solid tumours. 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 haematologic in nature. Peripheral neuropathy and hand-foot syndrome were rare, and no central neurotoxicity occurred. Per RECIST, responses were observed in five of 58 patients (9%); all responses occurred at $\geq$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 seven patients (28%) with neuroblastoma had an INRC-defined minor response with significant decreases in Curie score.

The trial included 64 patients. This sizeable sample size is explained by two reasons: first, in the absence of DLTs, more dose levels than initially planned were needed to find the paediatric RP2D, as discussed below. Second, patients could be enrolled at a lower dose level at times when enrolment for the dose cohorts was paused. Patient waitlists in early clinical trials are frustrating for patients, parents and clinicians, and this cohort contributed to the trial by providing additional safety, pharmacokinetic and antitumour activity data.

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. Haematologic 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 paediatric patients with solid tumours. Of note, the paediatric RP2D of *nab*-paclitaxel 240 mg/m^2 qw3/4 determined from this study in an advanced and heavily pretreated childhood 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 tumours [25].

In conclusion, *nab*-paclitaxel 240 mg/m^2 qw3/4 had a manageable toxicity profile and demonstrated preliminary clinical activity in paediatric patients with solid tumours, and results from the phase I portion of this study warrant further investigation of *nab*-paclitaxel in the paediatric 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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Conflict of interest statement

L. M. has participated in advisory boards for Novartis, AstraZeneca, Roche/Genentech, Mundipharma, Bayer and Amgen and has received honoraria from Celgene for an educational event and travel grants from Celgene and Amgen.

M. C. served as a consultant/advisor for Roche, Loxo Oncology and Boehringer Ingelheim.

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S. B. has stock ownership in MetronomX, Inc., has received honoraria from Celgene, is a consultant/advisor to Celgene and has received research funding from Servier.

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All remaining authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2018.05.002.

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