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Original Research

Phase 1 dose-escalation and pharmacokinetic study of regorafenib in paediatric patients with recurrent or refractory solid malignancies

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Abstract ***Background:*** This phase 1 study evaluated safety, pharmacokinetics (PK), maximum tolerated dose (MTD), and antitumour activity of regorafenib in paediatric patients with solid tumours.

Patients and methods: Patients (aged 6 months to <18 years) with recurrent/refractory solid tumours received oral regorafenib once daily for 3 weeks on/1 week off. The starting dose (60 mg/m^2) was derived from an adult physiology-based PK model and scaled to children; dose escalation was followed by safety expansion of the MTD cohort. Treatment-emergent adverse events (TEAEs) were evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Regorafenib PK was evaluated using a population PK model.

Results: Forty-one patients (median age 13 years) received regorafenib (four cohorts: 60–93 mg/m^2). Five of 23 evaluable patients experienced dose-limiting toxicities (Grade 4 thrombocytopenia, Grade 3 maculopapular rash, pyrexia, hypertension, and exfoliative dermatitis [each n = 1]). The MTD was defined as 82 mg/m^2. The most common Grade ≥3 drug-related TEAE was thrombocytopenia (10%). The incidence and severity of hypertension, diarrhoea, fatigue, hypothyroidism, and hand–foot skin reaction were lower than reported in adults. Regorafenib exposure increased with dose, with substantial overlap because of moderate-to-high interpatient variability. One patient with rhabdomyosarcoma experienced an unconfirmed partial response; 15 patients had stable disease, five for >16 weeks.

Conclusions: The recommended phase 2 dose of single-agent regorafenib in paediatric patients with solid malignancies is 82 mg/m^2. Regorafenib demonstrated acceptable tolerability and preliminary antitumour activity, supporting further investigation in paediatric patients.

Clinical trial number: NCT02085148.

1. Introduction

Angiogenesis plays a critical role in the growth and metastatic spread of paediatric malignancies [1–6]. It is multifactorial and driven by vascular endothelial growth factor (VEGF) and other potentially oncogenic proteins, including platelet-derived growth factor receptor (PDGFR) and/or fibroblast growth factor receptor (FGFR) [7,8]. In addition, *PDGFRA* aberrations have been implicated as oncogenic drivers in paediatric gliomas [9–12] and in the development of resistance [13].

The oral multikinase inhibitor regorafenib blocks the activity of protein kinases involved in tumour angiogenesis, proliferation, immunity, metastasis, and the microenvironment [14,15] and has shown potent, broad-spectrum antitumour activity in preclinical models [14,15] and in clinical trials in various solid malignancies in adults [16–24]. There is a strong rationale for evaluating regorafenib in selected paediatric solid malignancies because of its antiangiogenic effects and kinase inhibition profile [14,15], which is supported by the antitumour activity demonstrated by regorafenib alone and in combination with standard anticancer treatments in preclinical models of paediatric tumours [25].

We initiated a phase 1 dose-finding study to establish the safety and pharmacokinetics (PK) of regorafenib in paediatric patients with recurrent/refractory solid malignancies. Here, we present the results of the single-agent recommended phase 2 dose (RP2D) part of the study.

2. Methods

2.1. Patients

Eligible paediatric patients (aged 6 months to <18 years) had malignant solid or central nervous system (CNS) tumours recurrent or refractory to standard therapy, with no known effective treatment. Additional inclusion criteria included life expectancy ≥12 weeks; ≥1 measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; Karnofsky (>12 years of age) or Lansky (≤12 years of age) performance status ≥70%; and adequate organ function. Key exclusion criteria included prior exposure to regorafenib and known hypersensitivity to the study agent or formulation excipients. Other anticancer treatments or radiotherapy were not permitted ≤4 weeks before the start of the study.

2.2. Study design

This was an open-label, non-randomised, phase 1, dose-escalation study of regorafenib conducted across five sites of the European Innovative Therapies for Children with Cancer Consortium (NCT02085148). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and approval was obtained from the appropriate ethics committees or institutional review boards. All patients or their parents or legal

guardians provided written informed consent or age-appropriate assent before study entry.

Escalating ('rolling 6 design') regorafenib doses of 60, 72, 82, and 93 mg/m^2/day were administered to cohorts of up to six evaluable patients [26]. The starting dose was derived from a physiology-based PK (PBPK) model developed for adults and scaled to children to provide approximately 80% of the total adult regorafenib exposure [27]. Doses were escalated to the maximum tolerated dose (MTD), defined as the dose level at which, in Cycle 1, none or one of six participants experienced a dose-limiting toxicity (DLT); at least two of three to six participants had to experience a DLT at the next highest dose. DLT is based on the incidence of selected adverse events (AEs). To establish an RP2D, the MTD cohort was expanded to include at least 12 additional patients. Treatment with regorafenib could be continued at the discretion of the investigator until disease progression, unacceptable toxicity, withdrawal of consent, or death.

2.3. Study objectives

The primary objectives of the study were to define the safety, MTD, and RP2D and characterise the PK of regorafenib in paediatric patients. Secondary objectives included preliminary antitumour activity and the acceptability and palatability of the formulations.

2.4. Treatment

Regorafenib doses were calculated according to body surface area (BSA); patients received a starting daily dose of 60 mg/m^2 (as 20 mg tablets or granulates) orally in the morning after a low-fat breakfast. Three weeks on therapy were followed by 1 week off, in a 4-week cycle.

2.5. Assessments

Safety assessments were performed throughout. AEs were graded for severity using NCI-CTCAE version 4.0 and coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Tumour response was assessed every two cycles until tumour progression or until the patient discontinued and was based on RECIST version 1.1 [28] and the International Neuroblastoma Response Criteria in patients with neuroblastoma [29].

2.6. Pharmacokinetics

Depending on the age of the patient, two to five blood samples were collected during Cycle 1 or 2, 2–4 h post-dose on Day 1; pre-dose on Day 15; and pre-dose, 2–4 h post-dose, and 5–8 h post-dose on Day 21.

Regorafenib was measured using a validated bioanalytical method [30]. PK data were analysed using a previously developed population PK model for adults [31]. Supplementary Appendix provides further methodology.

2.7. Biomarkers and acceptability of formulations

Biomarker analysis and method of determining the acceptability and palatability of formulations are described in the Supplementary Appendix.

2.8. Statistical analysis

Data are presented descriptively. The chosen sample size of at least 12 additional patients was considered to be sufficient to establish the RP2D for this study. PK data are reported as geometric means with geometric coefficient of variation (CV). For biomarker analysis, a paired *t*-test was used to calculate the significance of changes observed after treatment. *P* values were adjusted for multiple testing using the Benjamini–Hochberg method, and significance results ($P < 0.05$) reported. Data cut-off was November 2015.

3. Results

3.1. Patients

Of 54 patients assessed for eligibility between April 2014 and October 2015, 42 were included and 41 received treatment. The median age was 13 years (Table 1). Patients were treated with regorafenib at four dose levels from 60 mg/m^2 to 93 mg/m^2 (Table 1) for a median of two treatment cycles (range: 1–17); the median treatment duration was 49 days (range: 2–463). Treatment duration for each patient is shown in Supplementary Fig. S1.

The reasons for treatment discontinuation were progressive disease (PD; n = 33), treatment-emergent adverse events (TEAEs) associated with clinical progression (n = 3), TEAEs likely associated with regorafenib (n = 3; one of which was a drug-related serious TEAE [Grade 3 wound dehiscence]), and withdrawal of consent (n = 1). At the time of data cut-off, one patient with ependymoma remained on treatment; the patient received 17 cycles of treatment with a treatment duration of 463 days, and follow-up after study cut-off date was for efficacy only.

3.2. Safety and tolerability

Of 41 evaluable patients, 23 treated in the dose-escalation phase, five experienced DLTs during Cycle 1 (Table 2). Regorafenib exposure in those five patients appeared to be comparable to patients without DLTs (Fig. 1). After two DLTs at the highest dose level tested (93 mg/m^2), the MTD was defined as 82 mg/m^2.

The MTD cohort was subsequently expanded to determine the RP2D (Table 2). The occurrence of two drug-related Grade 4 haematologic events (thrombocytopenia

Table 1
Baseline demographic and disease characteristics.

	Regorafenib 60 mg/m^2 (n = 6)	Regorafenib 72 mg/m^2 (n = 14)	Regorafenib 82 mg/m^2 (n = 14)	Regorafenib 93 mg/m^2 (n = 7)	Total (N = 41)
Median age, years (range)	12.5 (9–15)	14.0 (6–17)	9.5 (3–17)	11.0 (5–17)	13.0 (3–17)
Female, n (%)	2 (33)	7 (50)	7 (50)	5 (71)	21 (51)
Median BSA, m^2 (range)	1.36 (1.09–1.56)	1.49 (0.93–2.01)	1.02 (0.62–2.10)	0.98 (0.68–1.60)	1.33 (0.62–2.10)
Lansky/Karnofsky PS, n (%)					
100%	3 (50)	5 (36)	7 (50)	3 (43)	18 (44)
90%	2 (33)	6 (43)	5 (36)	2 (29)	15 (37)
70–80%	1 (17)	3 (21)	2 (14)	2 (29)	8 (20)
Histology at diagnosis: CNS tumours, n (%)	5 (83)	7 (50)	5 (36)	3 (43)	20 (49)
Glioblastoma	0	3 (21)	1 (7)	0	4 (10)
Other malignant gliomas (oligodendroglioma, astrocytoma, malignant glioma)	2 (33)	2 (14)	1 (7)	1 (14)	6 (15)
Cerebral PNET	1 (17)	1 (7)	0	2 (29)	4 (10)
Ependymoma	1 (17)	1 (7)	1 (7)	0	3 (7)
Medulloblastoma	1 (17)	0	2 (14)	0	3 (7)
Histology at diagnosis: extracranial tumours, n (%)	1 (17)	7 (50)	9 (64)	4 (57)	21 (51)
Ewing sarcoma family of tumours	0	2 (14)	3 (21)	0	5 (12)
Carcinoma (colon adenocarcinoma, adrenal, NOS, epithelial–myoepithelial)	1 (17)	1 (7)	1 (7)	1 (14)	4 (10)
Osteosarcoma	0	1 (7)	1 (7)	1 (14)	3 (7)
Rhabdomyosarcoma	0	0	3 (21)	0	3 (7)
Nephroblastoma	0	1 (7)	1 (7)	0	2 (5)
Other sarcomas (undifferentiated, desmoplastic small round cell)	0	2 (14)	0	0	2 (5)
Neuroblastoma	0	0	0	1 (14)	1 (2)
Epithelioid hemangioendothelioma	0	0	0	1 (14)	1 (2)
Disease status at study entry, n (%)					
Relapsing	3 (50)	6 (43)	4 (29)	3 (43)	16 (39)
Relapsing/refractory	1 (17)	5 (36)	7 (50)	1 (14)	14 (34)
Refractory	2 (33)	3 (21)	3 (21)	2 (29)	10 (24)
Missing	0	0	0	1 (14)	1 (2)
Tumour extent at study entry, n (%)					
Localised disease	1 (17)	6 (43)	2 (14)	0	9 (22)
Locally advanced	1 (17)	1 (7)	2 (14)	0	4 (10)
Metastatic disease	4 (67)	7 (50)	10 (71)	7 (100)	28 (68)
Median time since initial diagnosis, weeks (range)	114 (57–314)	83 (44–337)	145 (41–316)	136 (54–166)	120 (41–337)
Median time since most recent progression, weeks (range)	5 (<1–20)	4 (<1–20)	5 (1–25)	3 (<1–11)	4 (<1–25)
Prior systemic anticancer therapy[a]	6 (100)	13 (93)	14 (100)	7 (100)	40 (98)
Prior radiotherapy[b]	6 (100)	14 (100)	14 (100)	7 (100)	41 (100)

BSA, body surface area; CNS, central nervous system; NOS, not otherwise specified; PNET, primitive neuroectodermal tumour; PS, performance status.
As the recruitment of patients unable to swallow tablets was only possible approximately 10 months after the first patient visit, when the granulate formulation became available, children aged younger than 6 years were only enrolled at the higher dose levels (82 mg/m^2 and 93 mg/m^2); therefore, the median age and BSA were lower in the higher dose levels than the lower levels. The granulate formulation was received by four of 14 patients at the 82 mg/m^2 dose level and by three of seven patients at the 93 mg/m^2 dose level.
[a] Eight patients had received high-dose chemotherapy/autologous transplant.
[b] One patient with ependymoma had only undergone radiotherapy and six had received craniospinal irradiation. One patient had previously received a tyrosine kinase inhibitor (erlotinib).

and neutropenia) during the first cycle of 82 mg/m^2 led to a second expansion at 72 mg/m^2 to examine further the safety profile of regorafenib in paediatric patients. Further analysis of PK data, combined with a comprehensive safety review, suggested that haematologic toxicities were not dose dependent, so 82 mg/m^2 was selected as the RP2D.

All 41 patients experienced at least one TEAE, considered related to regorafenib in 40 (98%); most were Grade 1/2. No drug-related Grade 5 TEAEs were observed. Drug-related Grade ≥3 TEAEs were experienced by 15 patients (37%), most commonly thrombocytopenia (10%; Table 3). Seven patients (17%) experienced at least one serious TEAE considered to be possibly drug related; these were pyrexia (n = 4), haemolysis, systemic inflammatory response syndrome, lung infection, wound dehiscence, hypertension, and maculopapular rash (all n = 1). Notably, of eight patients

Table 2
DLTs during Cycle 1 and additional relevant regorafenib-related TEAEs in later cycles or expansion cohorts.

Cohort	Regorafenib (mg/m^2)	Patients treated, n	Patients evaluable for DLT, n	Number of DLTs	DLTs	Additional relevant regorafenib-related TEAEs[a]
Cohort 1	60	6	6	1	G4 thrombocytopenia C1D18	–
Cohort 2	72	7	6	1	G3 rash (maculopapular) C1D16	G4 neutropenia (C2) G2 wound infection and G3 wound dehiscence (C2)
Cohort 3	82	6	6	1	G3 pyrexia C1D17	–
Cohort 4	93	7	5	2	G3 hypertension C1D8 G3 exfoliative dermatitis C1D15	–
Expansion #1	82	8	NA	–	–	G3 bilirubin increase C1D8 G4 thrombocytopenia C1D21 G4 neutropenia C1D28 G3 HFSR C4
Expansion #2	72	7	NA	–	–	G3 rash C1D15 (n = 2)

C, Cycle; D, Day; DLT, dose-limiting toxicity; G, grade; HFSR, hand–foot skin reaction (palmar–plantar erythrodysesthesia syndrome); NA, not applicable; TEAE, treatment-emergent adverse event.
A DLT was defined as any of the following regorafenib-related events occurring during Cycle 1: haematologic toxicity (absolute neutrophil count [ANC] $<500/mm^3$ for $\geq$7 days; febrile neutropenia with ANC $<500/mm^3$; platelets $<25{,}000/mm^3$; or Grade $\geq$3 thrombocytopenic bleeding); or Grade 3/4 non-haematologic toxicity (except for the following toxicities if manageable by dose interruption, and adequate treatment for diarrhoea and HFSR, within 3 days: Grade 3 diarrhoea; Grade 3 HFSR; or Grade 3 aspartate aminotransferase [AST] or alanine aminotransferase [ALT] $\leq 8 \times$ upper limit of normal [ULN] without bilirubin increase). AST and/or ALT $>3 \times$ ULN associated with bilirubin increase $>2 \times$ ULN was considered a DLT.
[a] Not classed as DLTs; occurring in one patient each unless otherwise stated.

with drug-related Grade 3/4 haematologic toxicities, five (63%) had received previous myeloablative treatment, including high-dose chemotherapy with stem cell rescue and/or craniospinal irradiation.

Overall, patients received a median of 94% of the planned dose of regorafenib (range: 63–114%); 27 patients (66%) had at least one dose modification. Most (90%) dose interruptions/delays were because of TEAEs and lasted for a median of 4 days (range: 1–17). Pyrexia, thrombocytopenia, and maculopapular rash were the most common TEAEs that led to dose interruption. Drug-related TEAEs led to a dose reduction in 14 patients (34%) across dose cohorts.

Laboratory parameters remained unchanged from baseline (by CTCAE grade) in more than 80% of patients. The most frequent laboratory-related TEAEs (by MedDRA preferred term; all grades and Grade 3/4) are listed in Table 3.

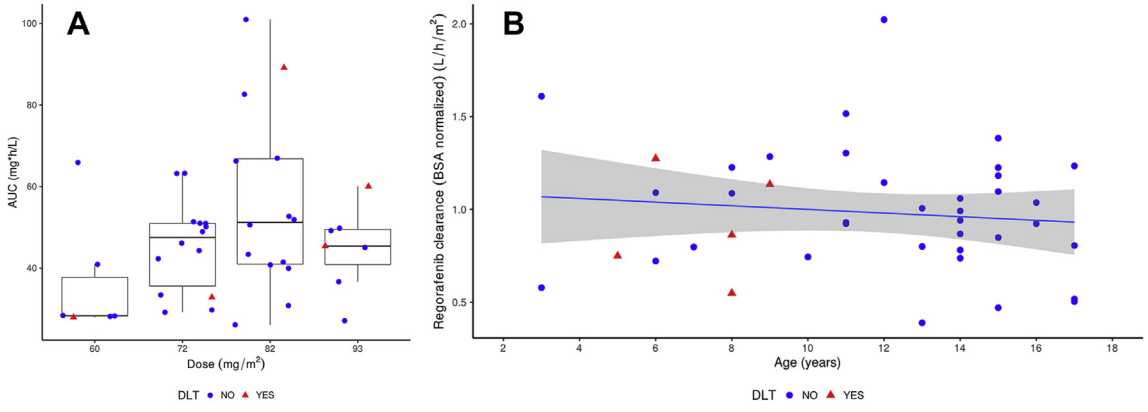

Fig. 1. **Estimated individual exposure ($AUC_{(0–24)md}$) at Day 21 of Cycle 1 by regorafenib dose level (N = 41)**. (A) and body surface area (BSA) normalised clearance by age (N = 41) (B). Individual data are depicted with blue dots and red triangles for patients without and with dose-limiting toxicity (DLT), respectively. In Panel A, the boxes show the interquartile range, and the median is presented with a black line. In Panel B, linear regression is depicted with a black line with the shaded area showing 95% confidence interval ($R^2 = 0.01$, $P = 0.46$). AUC, area under the concentration–time curve; $AUC_{(0–24)md}$, area under the concentration–time curve after multiple dosing from time 0 to 24 h.

Table 3
Most frequent (occurring in >20% of patients at any grade) regorafenib-related TEAEs (N = 41 patients).

Regorafenib-related TEAE (MedDRA preferred term)	Regorafenib 60 mg/m^2 (n = 6)		Regorafenib 72 mg/m^2 (n = 14)		Regorafenib 82 mg/m^2(n = 14)		Regorafenib 93 mg/m^2(n = 7)		Total (N = 41)	
	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)
Rash/maculopapular rash[a]	1 (17)	0	7 (50)	3 (21)	4 (29)	0	5 (71)	0	17 (41)	3 (7)
Hyperbilirubinemia[b]	2 (33)	0	5 (36)	0	8 (57)	2 (14)	0	0	15 (37)	2 (5)
HFSR[c]	1 (17)	0	6 (43)	0	4 (29)	1 (7)	3 (43)	0	14 (34)	1 (2)
AST increased	0	0	4 (29)	0	7 (50)	0	3 (43)	0	14 (34)	0
ALT increased	0	0	4 (29)	0	5 (36)	0	4 (57)	0	13 (32)	0
Fatigue	4 (67)	0	4 (29)	0	2 (14)	0	3 (43)	0	13 (32)	0
Nausea	2 (33)	0	4 (29)	0	3 (21)	0	4 (57)	0	13 (32)	0
Thrombocytopenia[d]	2 (33)	1 (17)	4 (29)	1 (7)	5 (36)	1 (7)	2 (29)	1 (14)	13 (32)	4 (10)
Pyrexia	0	0	5 (36)	0	5 (36)	1 (7)	2 (29)	0	12 (29)	1 (2)
Decreased appetite	1 (17)	0	6 (43)	0	1 (7)	0	3 (43)	0	11 (27)	0
Neutropenia	1 (17)	0	6 (43)	1 (7)	3 (21)	1 (7)	0	0	10 (24)	2 (5)
Lymphopenia[e]	1 (17)	0	2 (14)	0	5 (36)	1 (7)	1 (14)	1 (14)	9 (22)	2 (5)

Adverse events were analysed using the MedDRA version 18.1 terminology and graded according to NCI-CTCAE version 4.0.
The following terms were combined: [a]rash and maculopapular rash; [b]hyperbilirubinemia, blood bilirubin increased, and blood bilirubin unconjugated increased; [c]palmar–plantar erythrodysesthesia syndrome and palmar erythema; [d]thrombocytopenia and platelet count decreased; [e]lymphopenia and lymphocyte count decreased.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HFSR, hand–foot skin reaction; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Grade 1/2 hypothyroidism was reported as regorafenib related in 5 of 41 (12%) patients (two patients at 72 mg/m^2 and three patients at 82 mg/m^2). In three patients, the presence of protein in urinalysis was detected to be abnormal and reported as a TEAE in two of 41 (5%) patients (Grade 1 in one patient at the 72 mg/m^2 dose level [regorafenib related] and Grade 2 in one patient at the 93 mg/m^2 dose level [not regorafenib related]); in the third patient, a concurrent urinary infection was a confounding factor.

3.3. Pharmacokinetics

The regorafenib PK parameter estimates for all 41 subjects based on a population PK analysis are summarised in Table 4. The estimated median area under the concentration–time curve after multiple dosing from time 0 to 24 h ($AUC_{(0-24)md}$) increased with dose level from 60 to 82 mg/m^2. Interindividual variability in regorafenib clearance in this study was found to be high (44%), as has also been reported in adult patients [31]. This resulted in substantial overlap in exposure between dose levels (Fig. 1A). There was no distinct correlation between regorafenib clearance (normalised to BSA) and age, although samples from children aged <6 years were limited (Fig. 1B). The BSA normalised clearance (geometric mean [CV%]) was 0.84 L/h*m^2 (54.9; n = 8) for patients aged ≥2 to <6 years, 0.93 L/h∗m^2 (36.2; n = 22) for those aged ≥6 to <12 years, and 0.83 L/h∗m^2 (39.2; n = 31) for those aged ≥12 to <18 years.

3.4. Tumour response

Overall, 39 patients were evaluable for efficacy analysis. Among those for whom best response assessments were available (n = 34), one patient with alveolar rhabdomyosarcoma treated with 82 mg/m^2 regorafenib had an unconfirmed partial response (PR). Fifteen patients had stable disease (SD; best percentage change from baseline −19.0% to 15.9%). SD for >16 weeks was reported for five patients – two with anaplastic ependymoma (one for 64 weeks and one for 31.6 weeks), one pancreatic carcinoma (24.1 weeks), one embryonal rhabdomyosarcoma (16.2 weeks), and one Ewing sarcoma family of tumours (16.1 weeks). Eighteen patients experienced radiologic PD as best response. The best overall response for the 29 patients with target lesion data at baseline is shown in Fig. 2. Among these patients, the maximum percentage change in tumour size from baseline to PD ranged from −35.0% to 65.2%. The highest tumour shrinkage (−35.0%) was observed in the patient with alveolar rhabdomyosarcoma, who experienced an unconfirmed PR.

Table 4
PK parameters of regorafenib in plasma following multiple-dose (Cycle 1, Day 21) administration of regorafenib by dose level (N = 41).

Assigned dose (mg/m^2)	n	$AUC_{(0-24)md}$ (mg*h/L)		$t_{1/2eff,md}$ (hours)	
		Geometric mean (CV%)	Median (range)	Geometric mean (CV%)	Median (range)
60	6	34.6 (36.0)	28.3 (28.0–65.9)	33.2 (35.6)	30.1 (23.4–61.5)
72	14	44.2 (25.9)	47.5 (29.2–63.3)	36.1 (32.7)	35.5 (22.2–77.7)
82	14	52.1 (41.1)	51.2 (26.1–101.0)	32.9 (30.0)	33.2 (19.4–55.5)
93	7	43.6 (26.1)	45.4 (27.1–60.1)	26.1 (26.3)	27.0 (16.5–36.1)

$AUC_{(0-24)md}$, area under the concentration–time curve from time zero to 24 h after multiple dosing based on actual dose records over the first 21 days of dosing; CV, coefficient of variation; PK, pharmacokinetic; $t_{1/2eff,md}$, effective half-life after multiple dosing.

3.5. Biomarkers

Baseline demographic and disease characteristics for protein and genetic biomarker cohorts are shown in Supplementary Table S1. Somatic aberrations were found in 8 of 10 samples, none of which were in known targets of regorafenib (including *FGFR*, *PDGFR*, or *KIT*). No alteration was found in the remaining two samples. The expression levels of six of the 294 circulating proteins analysed (mast/stem cell growth factor receptor [SCFR], VEGF receptor 2 [VEGFR-2], angiotensin-converting enzyme, sex hormone–binding globulin, osteocalcin, and von Willebrand factor[vWF]) altered significantly between baseline and the end of regorafenib treatment (adjusted $P < 0.05$; Supplementary Table S2).

4. Discussion

This is the first study of regorafenib in paediatric patients with malignant solid and CNS tumours that are recurrent or refractory to standard therapy. In the dose-escalation phase, the MTD of single-agent regorafenib in paediatric patients was determined to be 82 mg/m^2; dose escalation was stopped at 93 mg/m^2 after two DLTs (hypertension and exfoliative dermatitis). After the expansion of the 72 and 82 mg/m^2 dose cohorts, the safety profile was similar in both, with no dose dependency for haematologic toxicity. These results, together with further analysis of the PK data, led to the selection of 82 mg/m^2 as the RP2D of single-agent regorafenib in paediatric patients. This dose provided similar exposure to the approved dose of 160 mg daily in adults, although because tolerable doses of molecularly targeted agents are often equivalent to BSA-corrected adult doses, in retrospect, a starting dose could have been selected to provide 100% of the total regorafenib exposure in adults [32].

Overall, regorafenib toxicity across all dose levels was consistent with the known safety profile in adults, with no new major safety findings [18,33,34]. Furthermore, and in line with findings in adult patients, there was no evidence for cumulative toxicity, and most TEAEs were

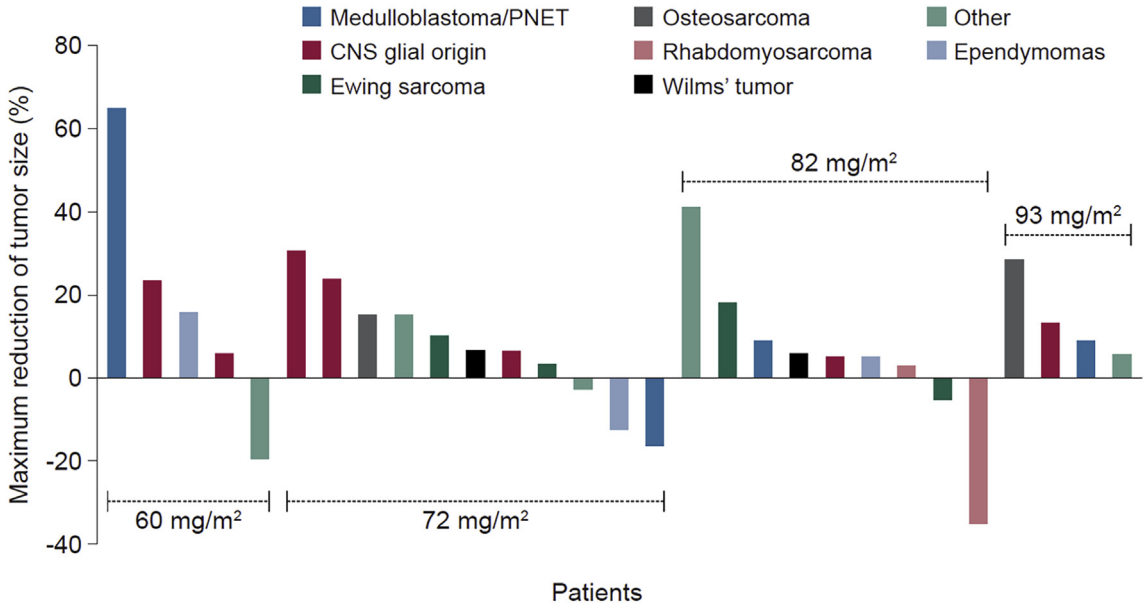

Fig. 2. **Waterfall diagram: best overall response by dose level in patients with RECIST v1.1 tumour assessment (N = 29)**. CNS, central nervous system; PNET, primitive neuroectodermal tumour; RECIST, Response Evaluation Criteria in Solid Tumors.

manageable with dose modifications and reversible after treatment discontinuation. The incidence and severity of known regorafenib-related TEAEs, such as hypertension, diarrhoea, fatigue, hypothyroidism, and hand–foot skin reaction, were lower in this paediatric trial compared with their reported incidences in adults. By contrast, myelosuppressive effects, particularly thrombocytopenia and neutropenia, seemed more pronounced. Based on the observed results, we hypothesise that there is a relationship between an increased incidence of drug-related Grade 3/4 haematologic toxicity and prior myelotoxic anticancer treatments, such as high-dose chemotherapy followed by autologous stem cell rescue and/or craniospinal irradiation, which were not received as prior therapies in the regorafenib-treated adult patient clinical trial population (in colorectal cancer, gastrointestinal stromal tumours, and hepatocellular carcinoma). However, even in this group of heavily pretreated patients, haematologic toxicity appeared to be dose independent.

High interindividual variability in exposure to regorafenib was observed, and exposure at all doses was in a similar range to that observed in adults [35,36]. The estimated nominal exposure $AUC_{(0-24)md}$ increased with dose, and the estimated geometric mean/median exposure after nominal and actual dosing for the 82 mg/m^2 dose level was similar to that observed in adults at the recommended dose of 160 mg daily [35,36]. The starting dose for this first trial in children was determined using a PBPK model that was developed for regorafenib in adults and scaled to children aged 2–18 years [27]. The initial dose of 60 mg/m^2 was predicted to result in 80% of the total regorafenib exposure in adults at the recommended phase 2 dose; however, the PBPK predictions of regorafenib exposure were higher than those observed in this study [27]. Therefore, a difference in regorafenib PK between children and adults irrespective of all known age-related differences cannot be excluded. Although a higher starting dose of 72 mg/m^2 would have resulted in 80% of the adult exposure in paediatric patients, consistent with normalising the adult dose by BSA, a PBPK approach to guide dosing in paediatric patients was a more conservative approach and would still be preferred. This is especially the case for compounds such as regorafenib, which are cleared by metabolic elimination pathways that differ in children and adults or are subject to complex PK processes such as enterohepatic recirculation.

One unconfirmed partial response was seen in a patient with rhabdomyosarcoma, and 15 patients had SD (duration of >16 weeks in five patients), suggesting that single-agent regorafenib is potentially active in paediatric patients, consistent with the results observed in adults [18]. Multikinase inhibitors, such as regorafenib, have been selected for anticancer treatment based on two principal mechanisms of action. The inhibition of key oncogenic drivers, such as mutated *KIT* and *PDGFRA*, results in substantial antitumour activity, and this has translated into clinical efficacy for a number of multikinase inhibitors [24,37–39]. The second mechanism relates to their potential to target additional factors involved in angiogenesis compared with selective anti-VEGF inhibitors and thus overcome upregulation of proangiogenic signals and resistance, as exemplified by the role of multiple agents, including regorafenib, in targeting angiogenesis in colorectal cancer [40,41]. Several early-phase paediatric clinical trials have evaluated the safety and preliminary activity of pan-VEGFR and multitargeted tyrosine kinase inhibitors, and overall, suggested limited single-agent activity of these agents in paediatric malignancies [42–46]. Pazopanib is the first tyrosine kinase inhibitor to be approved for soft tissue sarcoma in adults [47]. Moreover, recent clinical trials evaluating cabozantinib [48] and regorafenib [17] demonstrated significant benefit in patients with bone sarcoma, supporting further evaluation of this disease.

Key oncogenic mutations were not found in the tumours of the patients included in this study; however, analysis of circulating proteins identified six that were influenced by regorafenib treatment. Among the five downregulated proteins, SCFR (c-KIT) and VEGFR2 are known regorafenib targets [15]. vWF was upregulated: it has been reported to control angiogenesis by inhibiting VEGFR2 signalling, so increased vWF levels may therefore overcome the antiangiogenic effects of regorafenib [49]. In an exploratory analysis of the Phase 3 CORRECT trial in adult patients with metastatic colorectal cancer, plasma concentrations of baseline vWF were associated with regorafenib activity in terms of progression-free survival but not overall survival [50]. An association of the downregulated proteins angiotensin-cleaving enzyme, sex hormone–binding globulin, and osteocalcin with regorafenib has not been previously described. Thus, our data provide additional insights into potential resistance mechanisms, including those associated with multikinase inhibitors.

Based on the overall safety profile and drug exposure across dose levels, the RP2D of oral single-agent regorafenib in children and adolescents with solid malignancies was established as 82 mg/m^2 daily in a 4-week cycle of 3 weeks on/1 week off. Further clinical investigation of regorafenib in combination with cytotoxic chemotherapy is currently ongoing in paediatric patients with recurrent sarcomas.

Data statement

Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA 'Principles for responsible clinical trial data sharing'. This pertains to scope, time point, and process of data access. As such, Bayer commits to sharing on request from qualified scientific and medical

researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after 1st January 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal. Data access will be granted to anonymised patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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The study sponsor was involved in the design or conception of the study, the analysis and interpretation of the data and drafting and critically reviewing the publication.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: B.G. has received advisory board fees from Bayer. B.M. has received honoraria from Takeda and consulting or advisory board fees from Bayer and Clinigen Group. I.J. has received travel, accommodation, and expenses from Chugai Pharma. D.F. has received advisory board fees from Bristol-Myers Squibb. A.D.J.P. has received advisory board fees from Boehringer Ingelheim, Celgene, Genentech, Lilly, Merck, Novartis, and Takeda. G.V. has provided advice to Bayer, Bristol-Myers Squibb, Incyte, Roche-Genentech, Celgene, Lilly, and Ipsen, without personal remuneration and received travel and accommodation from Bayer, Bristol-Myers Squibb, and Roche-Genentech. P.M. is an employee of Bayer. J.K. is an employee of Bayer. U.M. is an employee of ClinStat and has received consulting or advisory board fees from Bayer. S.S. is an employee of Bayer. M.T. was an employee of Bayer until January 2020 and owns stock in Bayer and is currently an employee of Boehringer Ingelheim. B.A.P. is an employee of Bayer and owns stock in Bayer. A.C. is an employee of Bayer and owns stock in Bayer and AstraZeneca. A.C.A. is an employee of Novartis Pharmaceuticals and was an employee of Bayer until May 2018. L.V.M. has received honoraria and consulting or advisory board fees from Bayer (outside of the agent/study covered in the manuscript) and consulting or advisory board fees from Bristol-Myers Squibb, Eisai, and Tesaro.

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Appendix A. Supplementary data

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