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► To cite this version:

Birgit Georger, Bruce Morland, Irene Jiménez, Didier Frappaz, Andrew D.J. Pearson, et al.. Phase 1 dose-escalation and pharmacokinetic study of regorafenib in paediatric patients with recurrent or refractory solid malignancies. *European Journal of Cancer*, 2021, 153, pp.142-152. 10.1016/j.ejca.2021.05.023 . hal-04493290

HAL Id: hal-04493290

<https://hal.science/hal-04493290>

Submitted on 22 Jul 2024

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

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Running title: A phase 1 study of regorafenib in pediatric patients.

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Data Availability 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 upon 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 (US) 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 January 01, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized 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 anonymized 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.

Highlights

- Regorafenib had acceptable tolerability in pediatric patients
- The recommended phase 2 dose (RP2D) in pediatric patients was 82 mg/m²
- Exposure at the RP2D was comparable with adult exposure at the standard 160 mg/day
- Preliminary anti-tumor activity supports further studies in pediatric patients
- Regorafenib treatment downregulated circulating target proteins c-KIT and VEGFR2

Abstract

Background: This phase 1 study evaluated safety, pharmacokinetics (PK), maximum tolerated dose (MTD), and antitumor activity of regorafenib in pediatric patients with solid tumors.

Patients and methods: Patients (6 months to <18 years) with recurrent/refractory solid tumors received oral regorafenib once daily for 3 weeks on/1 week off. The starting dose (60 mg/m²) 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 (NCI-CTCAE) 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/m²). Five of 23 evaluable patients experienced dose-limiting toxicities (DLTs; grade 4 thrombocytopenia, grade 3 maculopapular rash, pyrexia, hypertension, and exfoliative dermatitis [each n = 1]). The MTD was defined as 82 mg/m². The most common grade ≥3 drug-related TEAE was thrombocytopenia (10%). The incidence and severity of hypertension, diarrhea, fatigue, hypothyroidism, and hand–foot skin reaction, were lower than reported in adults. Regorafenib exposure increased with dose, with substantial overlap due to 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 pediatric patients with solid malignancies is 82 mg/m². Regorafenib demonstrated acceptable tolerability and preliminary antitumor activity, supporting further investigation in pediatric patients.

Clinical Trial Number: NCT02085148.

Keywords: regorafenib, solid tumor, pediatric, phase 1, pharmacokinetics

Introduction

Angiogenesis plays a critical role in the growth and metastatic spread of pediatric 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 pediatric gliomas [9-12] and in the development of resistance [13].

The oral multikinase inhibitor regorafenib blocks the activity of protein kinases involved in tumor angiogenesis, proliferation, immunity, metastasis, and the microenvironment [14, 15] and has shown potent, broad-spectrum antitumor 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 pediatric solid malignancies, due to its antiangiogenic effects and kinase inhibition profile [14, 15], which is supported by the antitumor activity demonstrated by regorafenib alone and in combination with standard anticancer treatments in preclinical models of pediatric tumors [25].

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

Methods

Patients

Eligible pediatric patients (6 months to <18 years of age) had malignant solid or central nervous system (CNS) tumors 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 $\geq 70\%$; 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.

Study design

This was an open-label, non-randomized, phase 1, dose-escalation study of regorafenib conducted across five sites of the European Innovative Therapies for Children with Cancer (ITCC) 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 prior to study entry.

Escalating ('rolling 6 design') regorafenib doses of 60, 72, 82, and 93 mg/m²/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). In order 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.

Study objectives

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

Treatment

Regorafenib doses were calculated according to body surface area (BSA); patients received a starting daily dose of 60 mg/m² (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.

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. Tumor response was assessed every two cycles until tumor progression or until the patient discontinued, and was based on RECIST version 1.1 [28] and International Neuroblastoma Response Criteria in patients with neuroblastoma [29].

Pharmacokinetics

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

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

Biomarkers and acceptability of formulations

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

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.

Results

Patients

Of 54 patients assessed for eligibility between April 2014 and October 2015, 42 were included and 41 received treatment. Median age was 13 years (**Table 1**). Patients were treated with regorafenib at four dose levels from 60 mg/m² to 93 mg/m² (**Table 1**), for a median of two treatment cycles (range: 1–17); median treatment duration was 49 days (range: 2–463). Treatment duration for each patient is shown in **Supplementary Fig. S1**.

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.

Safety and tolerability

Of 23/41 evaluable patients 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**). Following two DLTs at the highest dose level tested (93 mg/m²), the MTD was defined as 82 mg/m².

The MTD cohort was subsequently expanded to determine the RP2D (**Table 2**). The occurrence of two drug-related grade 4 hematologic events (thrombocytopenia and neutropenia) during the first cycle of 82 mg/m² led to a second expansion at 72 mg/m² to examine further the safety profile of regorafenib in pediatric patients. Further analysis of PK data, combined with a comprehensive safety

review, suggested that hematologic toxicities were not dose dependent, so 82 mg/m² 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), hemolysis, systemic inflammatory response syndrome, lung infection, wound dehiscence, hypertension, and maculopapular rash (all n = 1). Notably, of eight patients with drug-related grade 3/4 hematologic 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 due to 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**.

Grade 1/2 hypothyroidism was reported as regorafenib related in five of 41 (12%) patients (two patients at 72 mg/m² and three patients at 82 mg/m²). 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/m² dose level [regorafenib related] and grade 2 in one patient at the 93 mg/m² dose level [not regorafenib related]); in the third patient, a concurrent urinary infection was a confounding factor.

Pharmacokinetics

The regorafenib PK parameter estimates for all 41 subjects based on a population PK analysis are summarized in **Table 4**. The estimated median area under the concentration–time curve after multiple dosing from time zero to 24 hours ($AUC_{(0-24)md}$) increased with dose level from 60 to 82 mg/m². Inter-individual 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 (normalized to BSA) and age, although samples from children aged <6 years were limited (**Fig. 1B**). The BSA normalized clearance (geometric mean [CV%]) was 0.84 L/h*m² (54.9; n = 8) for patients aged ≥2–<6 years, 0.93 L/h*m² (36.2; n = 22) for those aged ≥6–<12 years, and 0.83 L/h*m² (39.2; n = 31) for those aged ≥12–<18 years.

Tumor 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/m² regorafenib had an unconfirmed 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 tumors (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 tumor size from baseline to PD ranged from –35.0% to 65.2%. The highest tumor shrinkage (–35.0%) was observed in the patient with alveolar rhabdomyosarcoma who experienced an unconfirmed PR.

Biomarkers

Baseline demographic and disease characteristics for protein and genetic biomarker cohorts are shown in **Supplementary Table S1**. Somatic aberrations were found in eight 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 analyzed (mast/stem cell growth factor receptor [SCFR], vascular endothelial growth factor receptor 2 [VEGFR-2], angiotensin-converting enzyme [ACE], sex hormone binding globulin [SHBG], osteocalcin, von Willebrand factor [vWF]) altered significantly between baseline and the end of regorafenib treatment (adjusted $p < 0.05$; **Supplementary Table S2**).

Discussion

This is the first study of regorafenib in pediatric patients with malignant solid and CNS tumors that are recurrent or refractory to standard therapy. In the dose-escalation phase, the MTD of single-agent regorafenib in pediatric patients was determined to be 82 mg/m²; dose escalation was stopped at 93 mg/m² after two DLTs (hypertension and exfoliative dermatitis). Following the expansion of the 72 and 82 mg/m² dose cohorts, the safety profile was similar in both, with no dose dependency for hematologic toxicity. These results, together with further analysis of the PK data, led to the selection of 82 mg/m² as the RP2D of single-agent regorafenib in pediatric 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 the majority of TEAEs were manageable with dose modifications and reversible after treatment discontinuation. The incidence and severity of known regorafenib-related TEAEs such as hypertension, diarrhea, fatigue, hypothyroidism, and hand-foot skin reaction were lower in this pediatric trial compared with their reported incidences in adults. In contrast, myelosuppressive effects, particularly thrombocytopenia and neutropenia,

seemed more pronounced. Based on the observed results, we hypothesize that there is a relationship between an increased incidence of drug-related grade 3/4 hematologic 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 tumors, and hepatocellular carcinoma). However, even in this group of heavily pretreated patients, hematologic toxicity appeared to be dose independent.

High inter-individual 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/m² 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/m² 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/m² would have resulted in 80% of the adult exposure in pediatric patients, consistent with normalizing the adult dose by BSA, a PBPK approach to guide dosing in pediatric 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 pediatric 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 antitumor 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 pediatric 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 pediatric 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 in this disease.

Key oncogenic mutations were not found in the tumors of the patients included in this study; however, analysis of circulating proteins identified six that were influenced by regorafenib treatment. Among the five down-regulated proteins, SCFR (c-KIT) and VEGFR2 are known regorafenib targets [15]. vWF was upregulated: it has been reported to control angiogenesis by inhibiting VEGFR2 signaling, 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 down-regulated 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/m²

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 pediatric patients with recurrent sarcomas.

Acknowledgements

The authors would like to thank the patients, their families, and the participating study centers. We would also like to thank Ellen Bolotin, Zuzana Jirakova Trnkova, Mark Rutstein, and Henrik Seidel for their input into this study. We thank Teun Post and Stefan Zeiser from LAP&P Consultants BV, Leiden, the Netherlands, for performing the population PK analysis. This study was sponsored by Bayer. Editorial assistance in the preparation of this manuscript was provided by Alex Coulthard, Matthew Naylor, and Katrin Gudmundsdottir of OPEN Health Medical Communications (London, UK), with financial support from Bayer.

Funding

This study was sponsored by Bayer. 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.

Disclosures

BG has received advisory board fees from Bayer. BM has received honoraria from Takeda and consulting or advisory board fees from Bayer and Clinigen Group. IJ has received travel, accommodation, and expenses from Chugai Pharma. DF has received advisory board fees from Bristol-Myers Squibb. ADJP has received advisory board fees from Boehringer Ingelheim, Celgene, Genentech, Lilly, Merck, Novartis, and Takeda. GV 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. PM is an employee of Bayer. JK is an employee of Bayer. UM is an employee of ClinStat and has received

consulting or advisory board fees from Bayer. SS is an employee of Bayer. MT was an employee of Bayer until January 2020 and owns stock in Bayer and is currently an employee of Boehringer Ingelheim. BAP is an employee of Bayer and owns stock in Bayer. AC is an employee of Bayer and owns stock in Bayer and AstraZeneca. ACA is an employee of Novartis Pharmaceuticals and was an employee of Bayer until May 2018. LVM 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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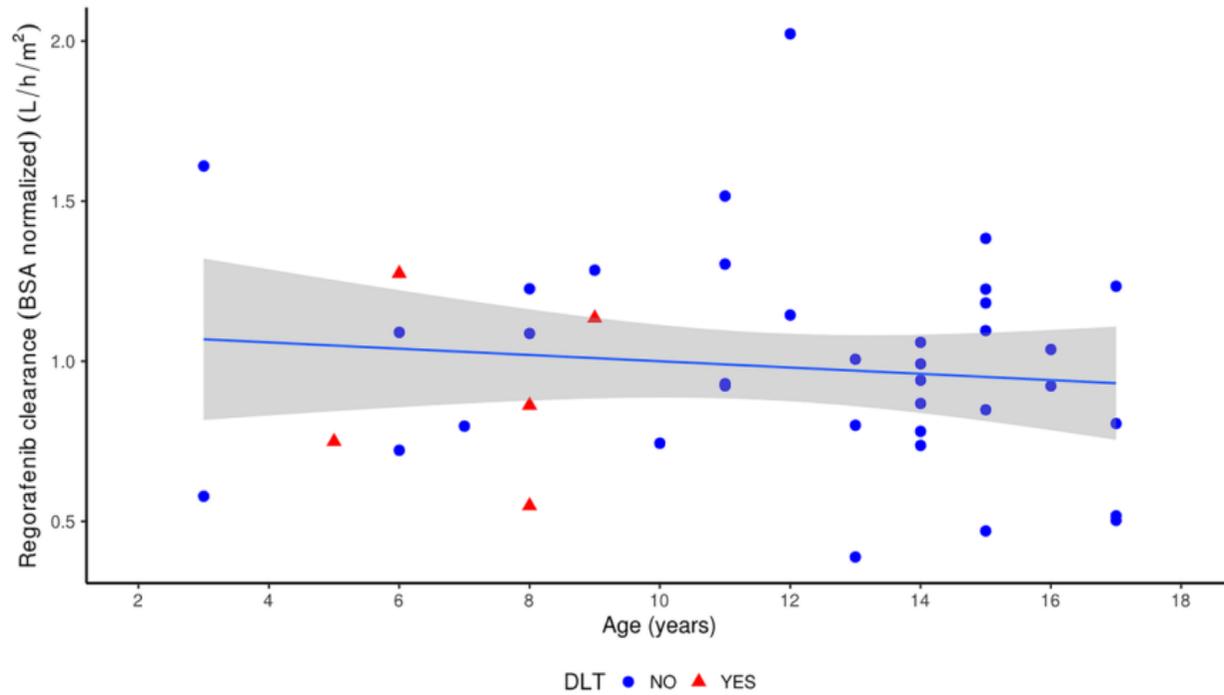
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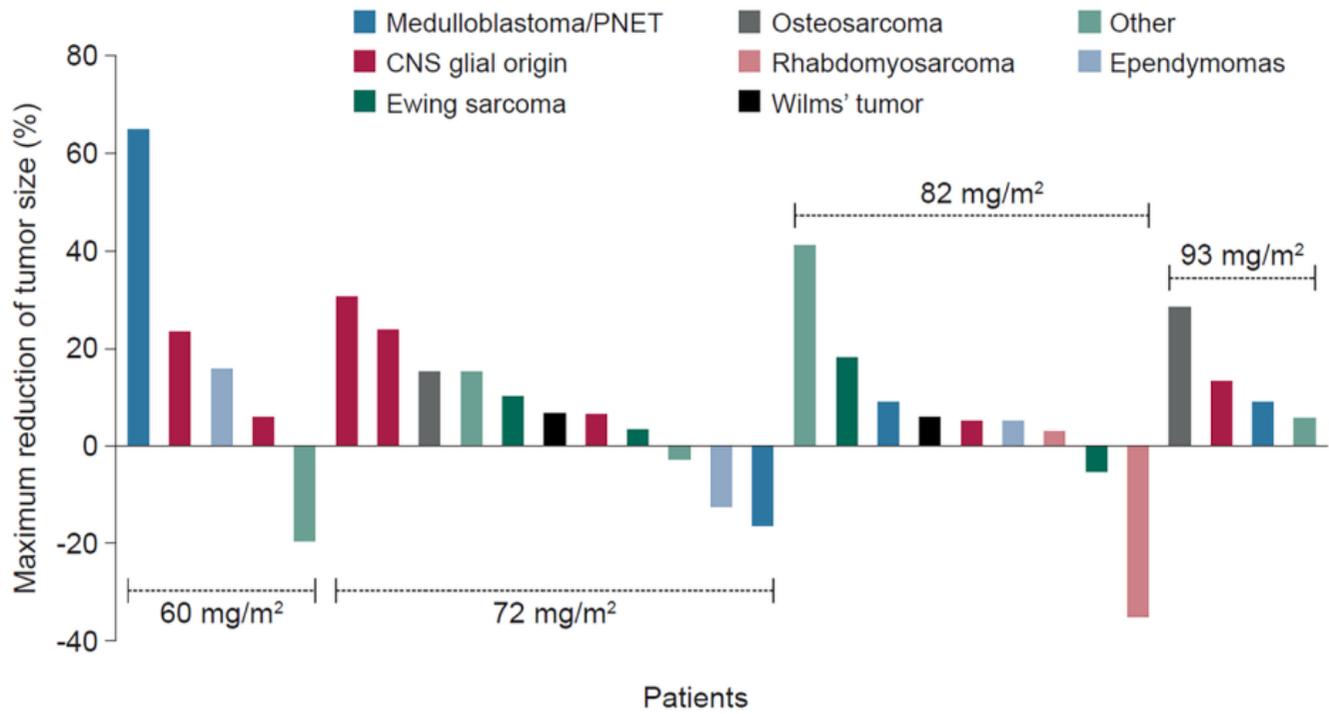


Table 1. Baseline demographic and disease characteristics.

	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 tumors, 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 tumors, n (%)	1 (17)	7 (50)	9 (64)	4 (57)	21 (51)
Ewing sarcoma family of tumors	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)
Tumor extent at study entry, n (%)					
Localized 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*	6 (100)	13 (93)	14 (100)	7 (100)	40 (98)
Prior radiotherapy [†]	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 tumor; 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 younger than 6 were only enrolled at the higher dose levels (82 mg/m² and 93 mg/m²); 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/m² dose level and by three of seven patients at the 93 mg/m² dose level.

* Eight patients had received high-dose chemotherapy/autologous transplant. [†] One patient with ependymoma had only undergone radiotherapy and six had received craniospinal irradiation. One patient had previously received a tyrosine kinase inhibitor (erlotinib).

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*
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: hematologic toxicity (absolute neutrophil count [ANC] <500/mm³ for ≥7 days; febrile neutropenia with ANC <500/mm³; platelets <25,000/mm³; or grade ≥3 thrombocytopenic bleeding); or grade 3/4 non-hematologic toxicity (except for the following toxicities if manageable by dose interruption, and adequate treatment for diarrhea and HFSR, within 3 days: grade 3 diarrhea; grade 3 HFSR; or grade 3 aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≤8 × upper limit of normal [ULN] without bilirubin increase). AST and/or ALT >3 × ULN associated with bilirubin increase >2 × ULN was considered a DLT.

* Not classed as DLTs; occurring in one patient each unless otherwise stated.

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 analyzed using the MedDRA version 18.1 terminology and graded according to NCI-CTCAE version 4.0.

The following terms were combined: ^arash and maculopapular rash; ^bhyperbilirubinemia, blood bilirubin increased, and blood bilirubin unconjugated increased; ^cpalmar–plantar erythrodysesthesia syndrome and palmar erythema; ^dthrombocytopenia and platelet count decreased; ^elymphopenia 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.

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	Median	Geometric mean	Median
		(CV%)	(range)	(CV%)	(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 hours 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.