Abstract #10542

# Phase I dose-escalation and pharmacokinetic (PK) study of regorafenib in pediatric subjects with recurrent or refractory solid malignancies


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## BACKGROUND

- Regorafenib is an oral multikinase inhibitor that blocks the activity of multiple protein kinases involved in oncogenesis, angiogenesis, and the tumor microenvironment such as c-RAF, wild-type and mutant (V600E) b-RAF, VEGFR1–3, PDGFR, FGFR1–2, TIE-2, RET, and c-KIT[1]
- Regorafenib is approved for the treatment of adults with metastatic colorectal cancer (CRC) and advanced gastrointestinal stromal tumors (GIST) at the dose of 160 mg taken orally once daily (qd) in a 3 weeks on/1 week off schedule in repeating cycles of 28 days[2,3]
- The most common grade ≥3 regorafenib-related treatment-emergent adverse events (TEAEs) in the phase 3 CORRECT study, which evaluated regorafenib in adult patients with metastatic CRC, were hand–foot skin reaction (HFSR), fatigue, diarrhea, hypertension, and rash/desquamation[4]
- The most serious adverse drug reactions in subjects receiving regorafenib are severe liver injury, hemorrhage, and gastrointestinal perforation[2]
- Regorafenib has demonstrated antitumor activity alone and in combination with standard anticancer treatments in preclinical models of various pediatric solid malignancies[5]
- We present the completed phase I part of a study assessing the safety, tolerability, and PK of regorafenib in pediatric patients
  - The cut-off date for this analysis was 19 November, 2015, therefore, information in this poster differs from that in the abstract due to a later data cut-off date and additional PK analysis

## OBJECTIVES

- Primary objectives: to define the safety profile, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of regorafenib in pediatric subjects and to characterize the PK of regorafenib in this population
- Secondary objectives: to evaluate the preliminary antitumor activity and pharmacodynamic parameters of regorafenib, and the acceptability and palatability of the formulations

## METHODS

- This was a multicenter, open-label, non-randomized, phase I dose-escalation study of regorafenib in pediatric subjects aged 6 months to <18 years with solid malignant tumors recurrent or refractory to standard therapy (NCT02085148)
- Doses were calculated per BSA and administered as 20 mg tablets or granulates (5 mg and 20 mg sachets available) qd in a 3 weeks on/1 week off schedule in repeating cycles of 28 days
- The starting dose of 60 mg/m$^2$ was derived from a physiology-based PK (PBPK) model developed for regorafenib in adults and scaled to children aged 2–18 years. The starting dose was predicted to result in 80% of steady-state exposure of total regorafenib (regorafenib and its pharmacologically active metabolites, M-2 and M-5) in adults. Steady-state exposure is defined as area under the concentration–time curve ($AUC_{(0-24)}$) after 21 days of 160 mg regorafenib qd
- Doses of 60, 72, 82, and 93 mg/m$^2$/day were assessed by a rolling-6 design
- MTD was defined as the dose level at which none or 1 of 6 participants experienced a dose-limiting toxicity (DLT) and when at least 2 of 3–6 participants experienced a DLT at the next highest dose
- In order to establish a RP2D, the MTD cohort was expanded to have at least 12 evaluable subjects. For the assessment of the MTD, the incidence of DLTs per cohort, defined as selected AEs occurring in Cycle 1, was considered. The AEs of subjects who entered the safety expansion were not counted as DLTs. However, the overall safety information across treatment cycles, and including all subjects that received at least one dose of study drug, was taken into consideration for the establishment of RP2D
- Subjects were permitted to continue treatment with regorafenib at the discretion of the investigator until tumor progression, unacceptable toxicity, withdrawal of consent, or death
- Serial PK samples were collected, and the PK of regorafenib, and its two active metabolites M-2 and M-5 were documented using a previously established adult population PK (popPK) model that was subsequently scaled to pediatric subjects. Exposure on Day 21 was estimated using nominal dosing (assuming no dose adjustment) and actual dosing in which the dose interruptions and adjustments, if any, were taken into account

## RESULTS

- A total of 41 subjects (Table 1) were included and treated as follows: 6 in dose level 1 (60 mg/m$^2$); 14 in dose level 2 (72 mg/m$^2$); 14 in dose level 3 (82 mg/m$^2$); and 7 in dose level 4 (93 mg/m$^2$)
- Subjects received a median of 2 cycles (range: 1–17)
- Median duration of treatment (including time off drug/interruptions) was 49 days (range: 2–463)

***Table 1. Baseline subject and disease characteristics***

| | Total N=41 |
|---|---|
| Median age, years (range) | 13.0 (3–17) |
| Gender, n (%) | |
| Female | 21 (51.2) |
| Male | 20 (48.8) |
| BSA, m$^2$ (range) | 0.62–2.10 |
| Lansky or Karnofsky performance status, n (%) | |
| 100% | 18 (43.9) |
| 90% | 15 (36.6) |
| 70–80% | 8 (19.5) |
| Tumor types, n (%) | |
| CNS of glial origin (including DIPG) | 10 (24.4) |
| Medulloblastoma/PNET | 6 (14.6) |
| Ewing sarcoma/PNET | 5 (12.2) |
| Rhabdomyosarcoma | 3 (7.3) |
| Osteosarcoma | 3 (7.3) |
| Anaplastic ependymoma | 3 (7.3) |
| Wilms' tumor | 2 (4.9) |
| Neuroblastoma | 1 (2.4) |
| Other* | 8 (19.5) |
| Disease status at study entry, n (%) | |
| Relapsing | 16 (39.0) |
| Relapsing/refractory | 14 (34.1) |
| Refractory | 10 (24.4) |

*Other includes: adrenocortical carcinoma, CNS cancer NOS, cancer of unknown primary, colon cancer, pancreatic cancer, peritoneal desmoplastic round cell tumor, renal cell carcinoma, soft tissue sarcoma.
BSA, body surface area; CNS, central nervous system; DIPG, diffuse intrinsic pontine glioma; NOS, not otherwise specified; PNET, primitive neuroectodermal tumor.

## Safety

- All 41 treated subjects were evaluable for safety; 23 subjects were considered for the assessment of DLT
- DLTs were thrombocytopenia, rash, pyrexia, hypertension, and exfoliative dermatitis (Table 2)

***Table 2. Dose-limiting toxicities (DLTs) and selected relevant regorafenib-related adverse events***

| Cohort | Regorafenib (mg/m$^2$) | Number of subjects treated | Evaluable for DLT | Number of DLTs | DLTs | Selected relevant regorafenib-related AEs |
|---|---|---|---|---|---|---|
| Cohort 1 | 60 | 6 | 6 | 1 | G4 thrombocytopenia C1D18 | |
| Cohort 2 | 72 | 7 | 6 | 1 | G3 rash (maculo-papular) 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; G3 rash C1D15 |

- MTD was defined as 82 mg/m$^2$ and the MTD cohort was expanded to confirm the RP2D. The occurrence of 2 drug-related grade 4 hematologic events at this safety expansion led to a second expansion at 72 mg/m$^2$ to support the decision on the RP2D
- All subjects had at least 1 TEAE and 40/41 (98%) had at least 1 AE considered possibly drug related, the majority of which were grades 1 or 2; the most frequent AEs (>20% incidence) are depicted in Table 3
- Seven subjects (17.1%) had at least 1 serious TEAE considered possibly drug related: hemolysis (1 event in 1 subject), pyrexia (5 events in 4 subjects), systemic inflammatory response syndrome (1 event in 1 subject), lung infection (1 event in 1 subject), wound dehiscence (1 event in 1 subject), hypertension (2 events in 1 subject), and rash maculo-papular (1 event in 1 subject)
- Twenty-seven subjects (65.9%) experienced TEAEs leading to any dose modification of study drug (Table 4), with a median of 81% of the planned dose received (range: 5–102)
- Treatment discontinuation was due to progressive disease (33 subjects), AEs associated with clinical progression (3 subjects), AEs not associated with clinical progression (3 subjects, 1 subject due to a drug-related AE [grade 3 wound dehiscence]), and withdrawal (1 subject); 1 patient remains on treatment
- Grade 3–4 myelosuppressive effects, in particular with respect to thrombocytopenia, seem to be more pronounced in this trial than in adults; there seems to be an effect of regorafenib on thrombocytes, lymphocytes, and neutrophils, although no clear-cut dose dependency was seen as it occurred throughout different cohorts

***Table 3. Most frequent treatment-emergent adverse events (>20%) considered possibly related to regorafenib by the investigators (N=41)***

| Treatment-emergent adverse event (MedDRA Preferred Term) | All grades, n (%) | Grades 3–4, n (%) |
|---|---|---|
| Rash / rash maculo-papular | 17 (41.5) | 3 (7.3) |
| Hyperbilirubinemia* | 15 (36.6) | 1 (2.4) |
| Palmar-plantar erythrodysesthesia syndrome** | 14 (34.1) | 1 (2.4) |
| Aspartate aminotransferase (AST) increased | 14 (34.1) | – |
| Alanine aminotransferase (ALT) increased | 13 (31.7) | – |
| Fatigue | 13 (31.7) | – |
| Nausea | 13 (31.7) | – |
| Thrombocytopenia*** | 13 (31.7) | 4 (9.8) |
| Pyrexia | 12 (29.3) | 1 (2.4) |
| Decreased appetite | 11 (26.8) | – |
| Neutropenia | 10 (24.4) | 2 (4.9) |
| Lymphopenia | 9 (22.0) | 2 (4.9) |

The following terms were combined: *Hyperbilirubinemia + blood bilirubin increased; **Palmar-plantar erythrodysesthesia syndrome + palmar erythema; ***Thrombocytopenia + platelet count decreased.

***Table 4. Dose modifications per dose level (N=41)***

| | 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 |
|---|---|---|---|---|---|
| Subjects with any dose modifications, n (%) | 3 (50.0) | 11 (78.6) | 7 (50.0) | 6 (85.7) | 27 (65.9) |
| Subjects with AEs leading to dose reduction, n (%) | 0 | 5 (35.7) | 4 (28.6) | 5 (71.4) | 14 (34.1) |
| Subjects with AEs leading to dose interruption, n (%) | 3 (50.0) | 10 (71.4) | 7 (50.0) | 6 (85.7) | 26 (63.4) |
| Median total duration of interruption, days (range) | 3 (1–7) | 2 (1–17) | 7 (1–13) | 4.5 (1–11) | 4 (1–17) |

- Out of 8 subjects with grade 3-4 regorafenib-related hematologic toxicity events, 3 had previous high-dose chemotherapy with stem cell rescue and 2 craniospinal irradiation

## Pharmacokinetics

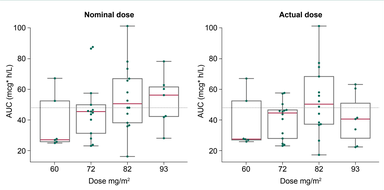
- A total of 38 of 41 subjects were evaluable for PK
- Nominal dosing is the estimated exposure based on the assigned dose level on Day 1, dosed continuously for 21 days; actual dosing is the estimated exposure based on the individual dosing history and with dose interruptions and adjustments taken into consideration
- Following repeated dosing of 160 mg regorafenib qd, the estimated nominal exposure $AUC_{(0-24)nmd}$ and exposure based on actual dosing increased with dose level from 60 to 82 mg/m$^2$ (Table 5)
- Based on nominal dosing and actual dosing total exposure across the different dose levels, the geometric mean exposure for the age groups did not exceed the exposure observed across multiple studies in adults (Table 5)
  - The estimated exposure in the 82 mg/m$^2$ cohort was 50.1 and 47.8 (mcg*h/L) for nominal and actual dosing, respectively, which is in the same range to that observed in adults at the dose level of 160 mg qd (48, 53, and 66 mcg*h/L)

***Table 5. Pharmacokinetic parameters of regorafenib in plasma following multiple-dose (Cycle 1, Day 21) administration of regorafenib in subjects by dose level***

| Parameter | Unit | Assigned dose (mg/m$^2$) | n | Geometric mean | CV (%) | Min | Median | Max |
|---|---|---|---|---|---|---|---|---|
| $AUC_{(0-24)nmd}$ nominal dosing | (mcg*h/L) | 60 | 6 | 34.4 | 45.0 | 24.9 | 27.1 | 66.9 |
| | | 72 | 14 | 43.1 | 42.2 | 23.0 | 45.1 | 87.2 |
| | | 82 | 14 | 50.1 | 47.1 | 16.1 | 50.3 | 101 |
| | | 93 | 7 | 50.3 | 35.1 | 27.9 | 56.0 | 77.9 |
| $T_{1/2md}$ | (Hours) | 60 | 6 | 39.2 | 67.0 | 16.2 | 38.4 | 83.4 |
| | | 72 | 14 | 36.8 | 43.9 | 21.2 | 33.8 | 101 |
| | | 82 | 14 | 37.9 | 44.0 | 14.2 | 39.6 | 68.8 |
| | | 93 | 7 | 26.7 | 29.7 | 17 | 27.2 | 38.4 |
| $AUC_{(0-24)md}$ actual dosing | (mcg*h/L) | 60 | 6 | 34.9 | 43.4 | 25.7 | 27.4 | 66.7 |
| | | 72 | 14 | 38.3 | 33.3 | 23.0 | 44.5 | 57.3 |
| | | 82 | 14 | 47.8 | 48.9 | 17.0 | 50.3 | 101 |
| | | 93 | 7 | 37.6 | 44.1 | 22.0 | 40.3 | 62.9 |

- Similar to the adult population, high inter-subject variability was observed (Figure 1)

***Figure 1. Estimated individual exposure ($AUC_{(0-24)}$) after 21 days of treatment; nominal and actual dose (N=38)***




The individual observed data are depicted with the green dots. The boxes show the interquartile range and the median is presented with a red line, with the whiskers extending to data points within 1.5 times of the interquartile range. The grey dashed line is the observed mean exposure in adults after 160 mg qd for 21 days with no dose adjustment on the basis of multiple phase 1, 2, and 3 studies.

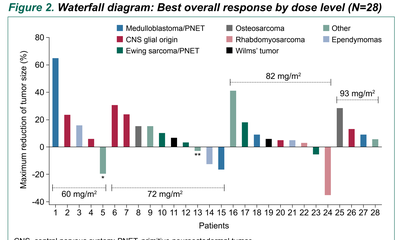
## Tumor response

- A total of 39 subjects were evaluable for efficacy
- One subject with alveolar rhabdomyosarcoma experienced a partial response (PR), 15 subjects had stable disease (SD), 18 subjects had progressive disease (PD), and 1 subject had non-complete response/non-PD; 4 subjects were not evaluable
- Out of the 15 subjects with SD, 5 had disease stabilization for ≥16 weeks; one patient with anaplastic ependymoma is still ongoing at the study cut-off at 16+ months (Table 6)
- Best response for each subject with target lesion at baseline is shown in Figure 2

***Table 6. Subjects with time to disease progression of 16 weeks or more***

| Tumor type | Best response | Time to disease progression |
|---|---|---|
| Anaplastic ependymoma | Stable disease | 64.3+ weeks (patient still ongoing in SD) |
| Anaplastic ependymoma | Stable disease | 31.5 weeks |
| Pancreatic carcinoma | Stable disease | 24 weeks |
| Rhabdomyosarcoma embryonal | Stable disease | 16.4 weeks |
| Ewing sarcoma | Stable disease | 16 weeks |

***Figure 2. Waterfall diagram: Best overall response by dose level (N=28)***




CNS, central nervous system; PNET, primitive neuroectodermal tumor.
*Pancreatic cancer. **Colorectal cancer.

## CONCLUSIONS

- The toxicity of regorafenib in pediatric subjects was tolerable across dose levels and, overall, the safety was consistent with the known safety profile. However, increased incidence of Grade 3/4 hematologic toxicity was observed in heavily pretreated subjects independent of dose levels. No new safety signals were identified for regorafenib
- DLTs were thrombocytopenia at 60 mg/m$^2$, rash at 72 mg/m$^2$, pyrexia at 82 mg/m$^2$, hypertension and exfoliative dermatitis at 93 mg/m$^2$. The MTD of single-agent regorafenib in pediatric subjects with solid malignant tumors is 82 mg/m$^2$
- The majority of treatment-related TEAEs was manageable with dose modifications
- Regorafenib showed high between-subject variability in exposure, and exposure at all doses was in a similar range to that observed in adults. The estimated geometric mean/median exposure both 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 qd
- Based on the overall safety profile and drug exposure across dose levels, the RP2D of regorafenib as a single agent in children and adolescents with solid tumors is 82 mg/m$^2$ taken orally qd in a 3 weeks on/1 week off schedule
- The prolonged disease stabilizations in 2 out of the 3 subjects with anaplastic ependymoma enrolled in the trial, as well as the PR in alveolar rhabdomyosarcoma warrants further investigation

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