Phase I dose-escalation and pharmaco kinetic study of regorafenib in pediatric subjects with recurr ent or refractory solid malignancies

**Background**

Regorafenib was selected for this study because it has shown clinical activity in refractory pediatric solid tumors. The cut-off date for this analysis was 19 November, 2015, therefore, 60 patients were evaluable for safety. 13 (31.7) weeks of treatment were received. A total of 38 of 41 subjects were evaluable for PK (PBPK) model developed for regorafenib in adults and scaled to pediatric subjects with pediatric solid malignancies. Regorafenib has demonstrated antitumor activity alone and in combination with other targeted agents in the adult population. The most serious adverse drug reactions in subjects receiving regorafenib were rash; skin disorders (50.0%); diarrhea, nausea, vomiting, and other gastrointestinal disorders (48.9%); and dermatitis (26.7%).

**Methods**

A multicenter, open-label, non-randomized, phase I study of regorafenib in pediatric subjects aged 6 months to 18 years with solid tumors known or suspected to be refractory to conventional therapies. Subjects were permitted to continue treatment with regorafenib at the individual physician discretion, although no clearcut dosedependency was seen as it continued. The toxicity of regorafenib in pediatric subjects was tolerable across all dose levels. The individual observed data are depicted with the green dots. The boxes show the interquartile range and actual dosing for the 60 mg/m2 treatment. The most serious adverse drug reactions in subjects receiving regorafenib were rash; skin disorders (50.0%); diarrhea, nausea, vomiting, and other gastrointestinal disorders (48.9%); and dermatitis (26.7%).

**Results**

A total of 60 subjects (13 were included and treated as follows: 6 dose level 3 (91.6 mg/m2), and 1 dose level 2 (82 mg/m2), 1 in dose level 1 (60 mg/m2). Subjects were treated with a median of 81% of the planned dose level; hence the MTD cohort was expanded to 100% of the planned dose level. The most common grade 3/4 adverse drug reactions in subjects receiving regorafenib were rash; skin disorders (50.0%); diarrhea, nausea, vomiting, and other gastrointestinal disorders (48.9%); and dermatitis (26.7%).

**Safety**

No deaths occurred in this study on d1. The MTD cohort was expanded to 100% of the planned dose level. The occurrence of 2 drug-related grade 4 hematologic events of the safety laboratory test at a maximum exposure to 82 mg/m2 in 3 subjects was documented using a previously developed logistic regression model provided by Bayer. A total of 38 of 41 subjects were evaluable for PK (PBPK) model developed for regorafenib in adults and scaled to pediatric subjects with pediatric solid malignancies. Regorafenib has demonstrated antitumor activity alone and in combination with other targeted agents in the adult population. The most serious adverse drug reactions in subjects receiving regorafenib were rash; skin disorders (50.0%); diarrhea, nausea, vomiting, and other gastrointestinal disorders (48.9%); and dermatitis (26.7%).

**Conclusions**

The most serious adverse drug reactions in subjects receiving regorafenib were rash; skin disorders (50.0%); diarrhea, nausea, vomiting, and other gastrointestinal disorders (48.9%); and dermatitis (26.7%). The toxicity of regorafenib in pediatric subjects was tolerable across all dose levels. The individual observed data are depicted with the green dots. The boxes show the interquartile range and actual dosing for the 60 mg/m2 treatment. The most serious adverse drug reactions in subjects receiving regorafenib were rash; skin disorders (50.0%); diarrhea, nausea, vomiting, and other gastrointestinal disorders (48.9%); and dermatitis (26.7%).

**References**


3. Waterfall diagram: Best overall response by dose level (N=28)