Aim: Retrospective analyses of clinical studies of pazopanib showed an increased median PFS in patients with plasma trough levels (TLs) ≥20.6 mg/L compared to patients with lower TLs (49.4 wks vs. 20.3 wks). This is in line with preclinical data showing optimal efficacy at concentrations above 17.5 mg/L. Due to inter-individual variability in plasma exposure, target TLs are not reached in ~30% of patients with the current dosing schedule of 800 mg daily. Therefore, a Phase I study was performed to determine the safety and feasibility of pharmacokinetically (PK)-guided dosing of pazopanib.

Methods: 30 patients with solid tumors with a potential benefit from pazopanib treatment were included. Weekly TLs were measured by LC-MS/MS. At week 3, 5 and 7 the dose could be increased when the measured TL was <20 mg/L. If the TL was <15 mg/L or between 15 and 20 mg/L and the patient did not show any non-tolerable toxicity (≥ grade 3 toxicity (CTCAE 4.02)), the daily pazopanib dose was increased by 400mg or 200 mg, respectively. If the patient experienced ≥grade 3 toxicity, the pazopanib dose was interrupted and lowered by steps of 200 mg.

Results: At data cut-off (April 2014) the planned total of 30 patients was included of which 26 patients had completed the PK evaluation period of 8 weeks or had stopped treatment due to toxicity (n = 4). 14 out of 26 patients had at least one TL below the target during this period. Of these, 8 patients had successful dose increases of 25% to 125% (1,000 to 1,800 mg), without non-tolerable toxicity. The mean TL (CV%, range) increased from 12.3(41.9, 7.80 – 22.5) to 22.4 (44.0, 8.77 – 43.1) mg/L. In the remaining 6 patients dose escalation was not possible due to toxicity. 12 out of 26 patients had all TLs above target. Of these 12 patients, 8 patients needed a dose reduction due to grade 3 and 4 toxicity and, therefore, the mean TL in this group decreased from 49.1 (39.9, 30.2 – 79.5) to 26.3 (27.5, 17.8 – 36.0) mg/L.

Conclusions: Individualized pharmacokinetically guided dosing of pazopanib is feasible and safe and leads to a higher proportion of patient reaching the desired target exposure. Additional (randomized) clinical trials on outcome parameters such as response rate and progression free survival are needed.

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