86PD Biomarker prevalence study and phase I trial of afatinib in children with malignant tumours

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Background: Dysregulation of the ErbB pathway may play a role in the development of paediatric neuroectodermal and mesenchymal tumours, suggesting that afatinib, an oral, irreversible ErbB family blocker, could be an effective treatment. A biomarker prevalence study assessed the frequency of ErbB-deregulations; in parallel, a Phase I trial (NCT02372006) was conducted.

Methods: Archived tissue samples from 277 neuroectodermal tumours and rhabdomyosarcomas were tested for protein expression of HER1–HER4, gene amplification of HER1/HER2 and mRNA expression of ErbB receptors and ligands. A Phase I afatinib trial in children aged 2 to $<$ 18 years used a rolling 6 dose escalation design to determine the MTD/RP2D, starting at 18 mg/m^2/d (80% of the BSA-equivalent adult MTD dose), increasing to 23, 29, and 35 mg/m^2. PK was analysed after 1st dose and at steady state. Anti-tumour activity was assessed as per disease standards.

Results: In the biomarker prevalence study, ErbB deregulation markers were defined as: (A) HER1 gene amplification: HER1/Cen7 $\geq$2.0; $\geq$10% of cells with $\geq$15 copies; $\geq$40% of cells with $\geq$4 copies; or gene cluster in $\geq$ 10% of cells; (B) HER2 gene amplification: HER2/CEP17 $\geq$2.0; Protein expression (membrane); (C) EGFR H-score $>$150; and (D) HER2 H-score $>$0. Patients (pts) with tumours positive for $\geq$2 markers (A–D) will be selected to enrich the trial expansion cohorts. In the Phase I trial, 23 pts were screened, 17 treated and 12 evaluable for MTD. 1/7 pts experienced DLTs at 18 mg/m^2 and 2/5 at 23 mg/m^2. DLT events were decreased appetite, diarrhoea, dehydration, hypernatraemia, hypokalaemia, cheilitis, rash. Diarrhoea (12 pts) and dry skin (6 pts) were the most frequently reported drug-related AEs. Exploratory PK analysis suggested that exposure at 18 mg/m^2 in children was in a similar range as in adults treated with 40 mg/d. 1 pt with ependymoma had stable disease for 8 treatment cycles.

Conclusions: Afatinib was tolerable in children, with a safety profile similar to adults. The MTD was established at 18 mg/m^2/d and resulted in drug exposure considered effective in adults. The biomarker prevalence study identified exploratory screening markers being used to enrich patient selection in the ongoing expansion cohort.

Clinical trial identification: NCT02372006

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Disclosure: D. Frappaz: Advisory board: BMS. P. Varlet: Advisory board: Roche (Herby trial), Novartis (dabrafinib trial), Boehringer (afatinib trial), Nanostring Technologies. D. Hargrave: Payments for being part of an advisory board in relation to the development of afatinib in childhood cancer. S. Gallego: Advisory board: Loxo Oncology. M. Kieran: Advisory board for Afatinib but do not receive any funds or payments. M. Casanova: Advisory board: Boehringer Ingelheim Pharma GmbH & Co. KG, Roche, Lilly, Bayer, Loxo Oncology. A. Lahogue, S. Wind, B. Stolze, D. Roy, M. Uttenreuther-Fischer: Employee of Boehringer Ingelheim. B. Geoerger: Advisory board: Boehringer Ingelheim. All other authors have declared no conflict of interest.