Abstract #404

High-Resolution Analysis of the Relationship Between Ponatinib Dose and Molecular Response in CP-CML Patients in the PACE Trial

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Objectives: Understanding the relationship between dose and efficacy is a critical step in optimizing the benefit-risk ratio of therapeutic agents. Ponatinib, a potent pan-BCR-ABL TKI, induced major cytogenetic and molecular responses in heavily pretreated CP-CML patients in the PACE trial. Investigation of the dose-response relationship (45mg starting dose) revealed that induction of MCyR was dose-dependent and that responses were maintained upon dose reduction (to 15 or 30mg). To further explore the dose-efficacy relationship of ponatinib, we developed a novel approach to associate drug exposure with changes in BCR-ABL transcript levels. The method, BCR-ABL Response-Dose association (BARD), enables a higher-resolution view of the dose-response relationship in CML than endpoint analyses because of the high sensitivity, broad dynamic range, and frequency of molecular response assessments.

Methods: BCR-ABL levels were measured every 3 months from CP-CML patients (N=267). The change in BCR-ABL levels, average daily dose, and proportion of dose holds were calculated for every measurement interval (window) in which at least one BCR-ABL value was between 0.01 and 10% (N=1818). Smoothing-adjusted values for individual windows were replotted relative to average daily dose within an individual window, and a model fit to the smoothed data.

Results: BARD analysis of the first 6 months of dosing suggested a relatively linear dose-response relationship, with maximal decreases in BCR-ABL levels achieved at 45mg. However, examination of windows beyond 6 months revealed a flatter dose-response, with similar decreases in BCR-ABL levels across a 15- to 45-mg dose range. Overall, average daily doses as low as 10mg ponatinib (including dose holds) were associated with decreases in BCR-ABL levels. Broader analysis of the impact of dose holds revealed that windows in which dose was withheld >50% of the time were associated with a trend toward increased BCR-ABL levels, irrespective of the dose otherwise administered.

Conclusions: BARD enables a detailed evaluation of dose-response relationships in CML. Analysis of PACE CP-CML patients indicates that 45mg ponatinib induced maximal decreases in BCR-ABL levels within the first 6 months. After 6 months, decreases in BCR-ABL levels were similar at doses ranging from 15-45mg. A dose-ranging trial of ponatinib in refractory CML is being planned.