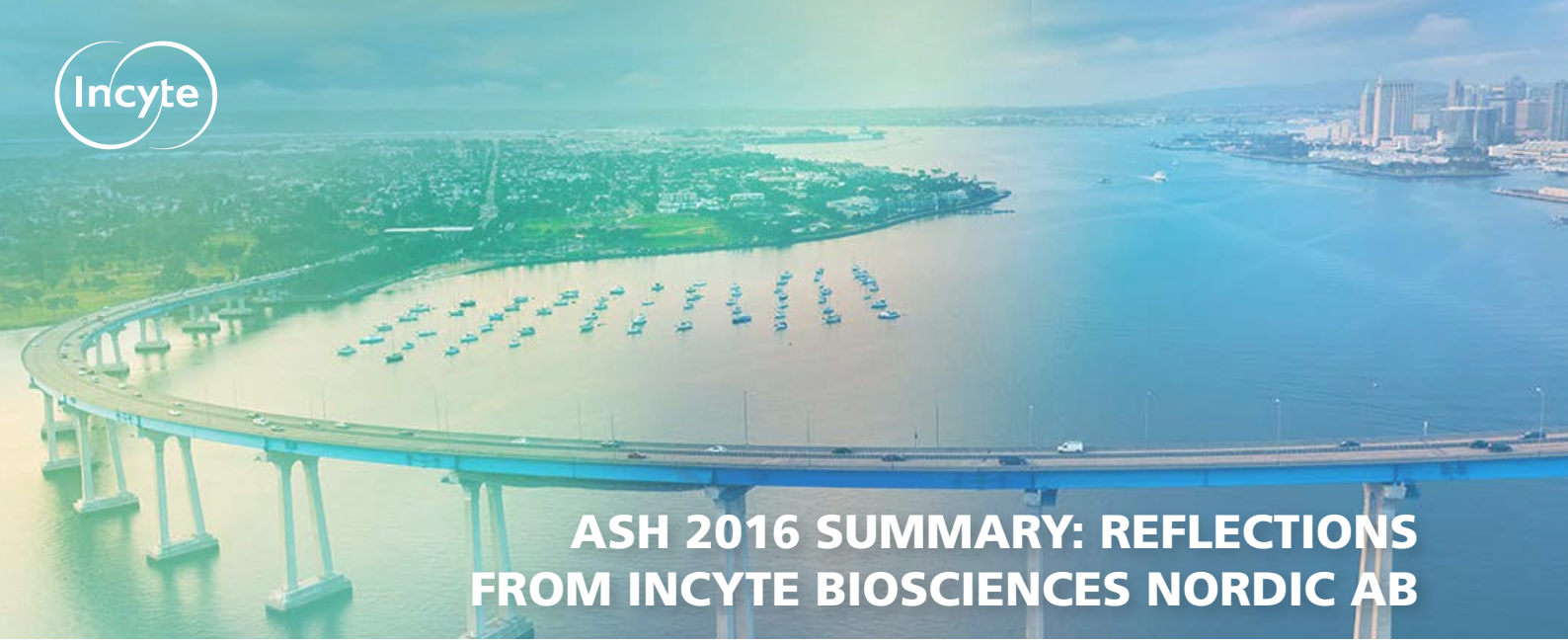

ASH 2016 SUMMARY: REFLECTIONS FROM INCYTE BIOSCIENCES NORDIC AB

Ponatinib in Chronic-Phase Chronic Myeloid Leukemia Patients: Final Report from a Phase 1 Trial

Final results from the ponatinib phase 1, dose-escalation trial in patients with relapsed/refractory dematologic malignancies

Micheael J Mauro, et al. Abstract 3063

The original phase 1, dose-escalation study that evaluated the safety, tolerability and pharmacokinetics of ponatinib enrolled 81 patients with relapsed/refractory hematologic malignancies, of whom 43 had chronic-phase chronic myeloid leukemia (CP-CML). In the initial report the median follow up was 12.9 months and ponatinib demonstrated robust clinical activity in heavily pre-treated patients with Philadelphia positive leukemias. In the final report presented this year at ASH 2016, treatment of CP-CML with ponatinib, with a median follow-up of 4.6 years, demonstrated deep, long-lasting responses in patients who had limited treatment options at the time of entry to the trial. This is the longest clinical evaluation of ponatinib reported to date. Of the 43 patients with CP-CML, 20 were discontinued due to administrative decision (including study termination), 11 patients due to adverse events, 6 patients due to progressive disease, 4 patients due to consent withdrawn, 1 patient was lost to follow-up and 1 patient died. The cumulative rates of major cytogenetic response (MCyR), complete cytogenetic response (CCyR) and major molecular response (MMR) were 72%, 65% and 56% respectively. Using Kaplan–Meier estimates, the probability of sustaining a MCyR, CCyR and MMR at 4 years was 72%, 70% and 46%, respectively. The median duration of MMR was 27.1 months. Among the patients with CP-CML treated with ponatinib in this phase 1 study, the exposure-adjusted incidences of arterial occlusive events (AOEs) and venous thromboembolic events were 10.5 and 1.7 events per 100 patient–years, respectively. Overall, the most common treatment-emergent adverse events were consistent with the adverse event profile of ponatinib across the clinical development program. The authors conclude that the observed rates of AOEs should be considered in the context of the potential benefit of ponatinib, including the rate, depth and duration of response, regardless of mutational status, in a heavily pre-treated patient population.

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Predictors of Ponatinib Therapy Duration Among Real-world Chronic-Phase Chronic Myeloid Leukemia (CP-CML) Patients in the US

Demographic, clinical and prescribing physician characteristics from real-world US pharmacy data for ponatinib as potential predictors of duration of response

Micheael J Mauro, et al. Abstract 3081

This study was a retrospective analysis of 475 patients with CP-CML starting ponatinib treatment over a 2.5 year period between January 1, 2014 and June 30, 2016 using pharmacy data. For the majority (85%) of patients included in the analysis, ponatinib was their third-, fourth or fifth-line therapy. The median duration on ponatinib therapy was 20.7 months (Kaplan–Meier estimate). Potential predictors of ponatinib therapy duration were assessed using a multivariate proportional hazard regression to identify primary drivers of therapy duration. Unadjusted Kaplan–Meier analysis showed that gender was the only significant predictor of time on therapy – women had significantly shorted duration of treatment than men. There was a trend, however, for patients with the T315I mutation to have a longer duration of treatment than patients without the T315I mutation. When the analyses were adjusted for other covariates, significantly shorter durations of ponatinib treatment were observed for non-T315I patients and patients whose most recent tyrosine kinase inhibitor (TKI) was not imatinib. Third- and fourth-line treatment had longer duration than second-line treatment with ponatinib. This could be due to the availability of more treatment alternatives in earlier treatment lines. No significant differences in therapy duration were observed in the analyses by age (<65 years vs ≥65 years), starting dose (45 vs 30 and 15 mg/day), and physician experience with ponatinib (as measured by the number of ponatinib patients per physician). These differences between adjusted and unadjusted results suggest a complex interaction between the presence of the T315I mutation, line of therapy, and most recent TKI prior to receiving ponatinib.

Download the full poster **here**.

Long-term Follow-up of the Efficacy and Safety of Ponatinib in Philadelphia Chromosome-Positive Leukemia Patients with the T315I Mutation

A pooled-analysis of the efficacy and safety of ponatinib in patients with the T315I mutation detected at baseline enrolled in the phase I and phase 2 PACE trial

Elias Jabbour, et al. Abstract 3067

Mutations in the BCR-ABL kinase domain of the fusion gene found on the Philadelphia chromosome that impair inhibitor binding are the primary cause of primary resistance to tyrosine kinase inhibitors (TKIs) in patients with chronic myeloid leukemia (CML). In particular the T315I mutation is associated with poor prognosis, high rates of disease progression and low survival rate. In one epidemiologic study reported in 2009 prior to the availability of ponatinib the median overall survival was 22.4 months for T315I positive CP-CML patients, with 3/82 patients alive at 4 years after detection of the mutation. In the ponatinib phase I and PACE trials, of the patients with chronic phase (CP)-CML who were T315I positive at baseline (phase 1, n=12; PACE, n=64), 92% and 70% achieve a major cytogenetic response (MCyR) by 12 months, respectively. In the pooled analysis presented at ASH 2016, these 76 T315I positive patients had a median follow-up of 40.3 months (range 1.5–91.4 months), with 26 (34%) remaining in the study. Overall in the PACE trial, patients with CP-CML and the T315I mutation at baseline were younger with fewer previous therapies and had a shorter time since diagnosis compared with the non-T315I patients with CP-CML. In the pooled analysis a total of 75% and 72% of T315I positive CP-CML patients achieved a MCyR or a complete cytogenetic response (CCyR). Using Kaplan-Meier estimates, the probabilities of MCyR and complete cytogenetic response (CCyR) being maintained at 4 years were 83% and 81% of the T315I positive CP-CML patients and the probability of survival 4 years was an estimated 72%. In T315I positive patients with CP-CML the safety profile of ponatinib was comparable with that observed among all CP-CML patients in the phase 1 and PACE trials.

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Analysis of the Sub-Clonal Origins of Compound Mutations in Patients with Refractory Ph+ Malignancies Treated with Ponatinib

Using multiple-level sensitivity sequencing strategies and mathematical modeling to profile mutational mechanisms that may account for survival outcomes observed in BP-CML and Ph+ ALL patients treated with ponatinib in the PACE trial

Justin R Pritchard, et al. Oral presentation 1061

Ponatinib is a tyrosine kinase inhibitor with high inhibitory activity against BCR-ABL and all single point resistant mutations. In the Phase 2 PACE study, ponatinib induced high rates of major hematologic response (MaHR) and major cytogenetic response (MCyR) in Philadelphia positive acute lymphoblastic leukemia (Ph+ ALL; 41% and 47%) patients, even though 91% had received at least 2 prior TKIs. However, the median progression free survival was only 3 months for Ph+ ALL. In the presentation by Justin Pritchard at ASH 2016, he explained that by using Sanger sequencing, next generation sequencing (NSG) and single molecule duplex sequencing, which is orders of magnitude more sensitive than NGS, his team were able to profile mutational mechanisms that may account for the survival outcomes of patients with Ph+ALL in the PACE trial. In the PACE trial, Ph+ ALL patients were more likely to relapse on ponatinib with acquired mutations in BCR-ABL1 than CP-CML patients. A larger proportion of Ph+ ALL patients (12/20) gained compound mutations in BCR-ABL1 by the end of treatment compared with 4/130 CP-CML patients ($p<0.001$; odds ratio 18.9; 95% confidence interval 5.1–88.8). Since the presence of pre-existing mutations from earlier TKI therapy is associated with further gain of mutations on ponatinib treatment, ultra sensitive duplex sequencing was used to successfully detect the resistant clone in samples collected at baseline in a small minority of cells from some of the patients with compound mutations. By using a combination of duplex sequencing and mathematical modeling, it was determined that many of the documented resistance mutations were pre-existing in refractory Ph+ ALL patients treated with ponatinib in the PACE trial. Compound mutations following prior TKI treatment failure suggest that a potent pan-TKI, such as ponatinib should be used early to reduce mutational risk. These findings emphasize the risk of large population expansions that occur following prior TKI treatment failure and may explain the relatively high 3-year event free survival rate of 80% observed in previously untreated Ph+ ALL patients who were treated with ponatinib + chemotherapy.

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