Population pharmacokinetic and exposure-response analyses for the phase 3 PhALLCON study of ponatinib in Philadelphia chromosome–positive acute lymphoblastic leukemia

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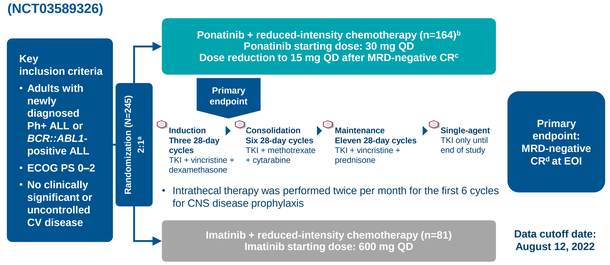
Background

- Ponatinib is a third-generation BCR::ABL1 tyrosine kinase inhibitor (TKI) that was initially approved in 2012 at a dosage of 45 mg once daily (QD) for the treatment of refractory chronic myeloid leukemia (CML) and Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) based on results of the pivotal PACE trial (NCT01207440)[1,2]
- Subsequently, the efficacy and safety of 3 ponatinib starting doses (45, 30, or 15 mg) were evaluated in patients with chronic-phase CML (CP-CML) resistant to ≥2 TKIs or with a T315I mutation in the randomized phase 2 OPTIC trial (NCT02467270)[3]
  - Patients randomized to the 45-mg or 30-mg starting dose cohorts had a dose reduction to 15 mg QD upon achievement of ≤1% *BCR::ABL1*[IS]
- The 45-mg QD starting dose with dose reduction to 15 mg QD upon achievement of response was associated with optimal benefit-risk outcomes,[3] resulting in the 2020 approval of this response-based dosing regimen for the treatment of CP-CML resistant or intolerant to ≥2 prior TKIs[4]
- Importantly, this response-based dosage for ponatinib demonstrated a lower rate of arterial occlusive events (AOEs) in OPTIC compared with the 45-mg QD continuous regimen evaluated in PACE[1,3]
- In March 2024, ponatinib received accelerated approval in the US for the treatment of adults with newly diagnosed Ph+ ALL in combination with chemotherapy based on results of the global phase 3 PhALLCON study[4,5]
  - The primary endpoint of PhALLCON was met, with a significantly higher rate of minimal residual disease (MRD)–negative complete remission (CR) at the end of induction (EOI) with ponatinib (34.4%) versus imatinib (16.7%; *P*=0.002)[5]
  - The safety profile of ponatinib was manageable and comparable to imatinib when combined with reduced-intensity chemotherapy[5]
  - AOEs were infrequent, with similar incidences in the ponatinib (2.5%) and imatinib (1.2%) arms[5]
- PhALLCON included a secondary objective to collect sparse pharmacokinetic (PK) samples for population PK and exposure-response analyses for ponatinib; the results of these analyses are reported herein

Methods

Study design

Figure 1: PhALLCON: Global, phase 3, randomized, open-label, multicenter trial (NCT03589326)



[a]Randomization was stratified by age group (18 to <45 y; 45 to <60 y; ≥60 y).
[b]An additional 8 patients were enrolled at sites in Japan and assigned to the ponatinib arm only as part of a country-specific protocol amendment; these patients were not included in the analysis of the primary efficacy endpoint but were included in the population PK and exposure-safety analyses.
[c]Dose reduction to 15 mg QD was implemented in patients who achieved MRD-negative CR after completion of the induction phase.
[d]MRD-negative CR was defined as hematologic CR (≤4 weeks) in combination with MRD negativity (*BCR::ABL1/ABL1*[IS] ≤0.01%)
CNS, central nervous system; CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; PS, performance status

PK assessments and population PK analyses

- Sparse blood samples were collected during Cycles 1 through 12 to measure plasma concentrations of ponatinib using a validated liquid chromatography/tandem mass spectrometry assay[6,7]
  - Predose samples were collected prior to dosing on Day 1 of Cycles 1, 2, 3, 4, 6, 9, and 12; on Day 1 of Cycle 2, samples were also collected at 1, 4, and 6 hours postdose
  - Additional postdose samples were collected on Day 14 of Cycles 1 and 2 before and after the vincristine infusion, and an unscheduled trough sample was to be collected at the first scheduled visit after a dose reduction of ≥7 days
- A Bayesian re-estimation approach was used to estimate individual PK parameters of ponatinib using a previously developed population PK model as a prior[8]
- The population PK analysis was performed using NONMEM version 7.4.3 for nonlinear mixed-effects models

Question

Is ponatinib exposure associated with occurrence of clinically relevant AEs?

Study design

Adults with newly diagnosed Ph+ ALL

Ponatinib + chemotherapy
- Ponatinib starting dose: 30 mg QD
- Response-based dose reduction to 15 mg QD upon MRD-negative CR after EOI

Sparse PK sampling (Cycles 1–12)

- Population PK analyses
- Exposure-response analyses

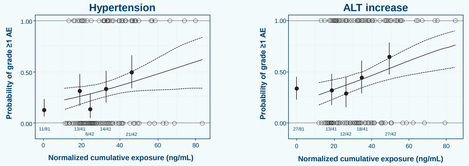
Results: Exposure-safety analyses

- Exposure-safety analysis dataset included 166 patients treated with ponatinib and with adequate safety and PK data
- Ponatinib exposure was not a significant predictor of AOEs, VTEs, thrombocytopenia, or lipase increase
- Higher ponatinib exposure was associated with higher probability of experiencing hypertension or ALT increase; no additional covariates were identified as statistically significant in subsequent covariate analyses
- Based on the final exposure-safety models, a dose reduction from 30 mg to 15 mg was predicted to decrease the odds of hypertension by 37.7% (odds ratio [OR]: 0.623 [95% CI: 0.403–0.963]) and ALT increase by 44.2% (OR: 0.558 [95% CI: 0.376–0.828])

AE	OR (95% CI)[a]	*P* value
AOE	0.933 (0.824–1.06)	0.202
VTE	0.992 (0.954–1.03)	0.689
Thrombocytopenia	0.997 (0.974–1.02)	0.788
Lipase increase	1.00 (0.979–1.03)	0.766
Hypertension	1.02 (1.00–1.05)	0.0340
ALT increase	1.03 (1.01–1.05)	0.0034

[a]Estimated OR corresponding to a 1 ng/mL increase in ponatinib NCE.

Observed and model-predicted proportion of patients with grade ≥1 hypertension or ALT increase



Key Takeaway

These results support both the prospective dose reduction to 15 mg QD upon achievement of response and the dose reduction recommendations for patients experiencing treatment-emergent toxicities

Exposure-response analyses

- The ponatinib exposure metric used in the exposure-response analyses was the normalized cumulative exposure (NCE) from the beginning of treatment (i.e., time 0) to the time of an efficacy or safety event:

$$NCE_{day\,i} = \int_0^{t_{day\,i}} C(\tau)\,d\tau \Big/ t_{day\,i}$$

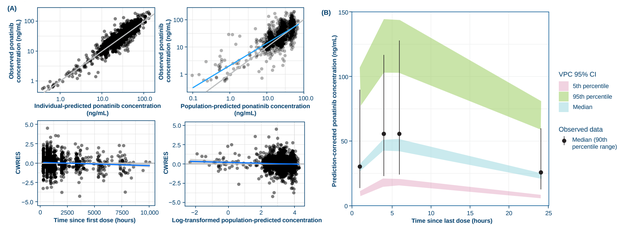
- In this equation, C(τ) represents the individual predicted concentration of ponatinib exposure at time τ, and $t_{day\,i}$ was the study day of the last non-zero ponatinib dose before the relevant efficacy or safety event. For patients not experiencing an event, NCE was based on their entire period of dosing
- In the exposure-efficacy analyses, the probability of achieving MRD-negative CR at EOI was related to ponatinib exposure (NCE) using a logistic regression model
- In the exposure-safety analyses, relationships between ponatinib exposure (NCE) and the probabilities of experiencing clinically relevant AEs (AOEs, venous thromboembolic events [VTEs], lipase increase, hypertension, alanine aminotransferase [ALT] increase, and thrombocytopenia) were evaluated by proportional odds logistic regression models
- Relationships between exposure and time to first AE-related dose reduction or interruption were assessed in 2 Cox proportional hazards time-to-event (TTE) models: 1) Dose modifications from Day 1 of Cycle 1 to EOI; 2) Dose modifications after EOI in efficacy responders
- The derivation of exposure metrics and the exposure-response analyses were performed using R version 4.0.2

Results

Population PK analyses

- Ponatinib PK data from 166 patients in PhALLCON contributed to the Bayesian re-estimation
- Goodness-of-fit plots of the final Bayesian re-estimation model demonstrated that the final model adequately described the observed PK data **(Figure 2A)**
- Visual predictive check (VPC) results demonstrated that the model generally described the observed data well, thereby indicating that the PK of ponatinib in PhALLCON could be adequately described using the previously developed population PK model **(Figure 2B)**

Figure 2: Goodness-of-fit plots (A) and prediction-corrected visual predictive check results (B) for the Bayesian re-estimation model



Exposure-efficacy and exposure-safety analyses

- The exposure-efficacy analysis dataset included 150 patients randomized to ponatinib who had *BCR::ABL1* dominant variants of p190 or p210 confirmed by a central laboratory and adequate PK information available
- No statistically significant relationship was identified between ponatinib exposure and the probability of achieving MRD-negative CR at EOI (OR: 1.01 [95% CI: 0.982–1.03]; *P*=0.619) **(Figure 3)**
- No statistically significant relationships were identified between ponatinib exposure and AOEs, VTEs, thrombocytopenia, or lipase increase **(Figure 4)**

Figure 3: Observed and model-predicted probability of achieving MRD-negative CR at EOI versus ponatinib exposure

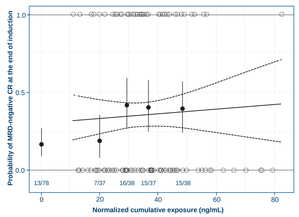
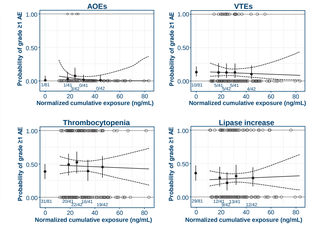


Figure 4: Observed and model-predicted proportion of patients with grade ≥1 AOEs, VTEs, thrombocytopenia, and lipase increase



Exposure-dose adjustment analyses

- Ponatinib exposure was not identified as a statistically significant predictor of the time to the first AE-related dose reduction or interruption from Day 1 of Cycle 1 up to EOI **(Table 1)**
- In contrast, a statistically significant relationship was identified between ponatinib exposure and the time to the first AE-related ponatinib dose reduction or interruption after Day 1 of Cycle 4, with higher exposures associated with an increase in the hazard **(Table 1)**

Table 1: Estimated HRs for ponatinib exposure in the final TTE models describing first AE-related ponatinib dose reduction or interruption

Endpoint	No. of patients in the analysis dataset	HR (95% CI)[a]	*P* value
Dose reduction or interruption from Day 1 of Cycle 1 to EOI	164	0.992 (0.975–1.01)	0.321
Dose reduction or interruption after Day 1 of Cycle 4	51	1.06 (1.00–1.12)	0.0454

[a]Estimated hazard ratio (HR) corresponding to a 1 ng/mL increase in ponatinib NCE

Conclusions

- In the exposure-efficacy analysis, no statistically significant relationship was identified between ponatinib exposure and the probability of achieving MRD-negative CR at EOI, indicating that the efficacy benefit of ponatinib was consistent across the range of exposures achieved with the response-based dosing regimen
- No statistically significant relationships were identified between ponatinib exposure and probability of AOEs, VTEs, thrombocytopenia, or lipase increase
- In contrast, higher ponatinib exposure was associated with a higher probability of experiencing hypertension and ALT increase. A dose reduction from 30 mg to 15 mg QD was predicted to decrease the odds of experiencing hypertension by 37.7% and ALT increase by 44.2%
  - These findings support both the prospective dose reduction to 15 mg QD upon achievement of response, as well as the dose reduction recommendations for safety-related AEs occurring during treatment
- Collectively, these results support a favorable benefit-risk profile for the approved ponatinib response-based dosing regimen of a 30-mg QD starting dose with a reduction to 15 mg QD upon achievement of MRD-negative CR at EOI, in combination with reduced-intensity chemotherapy, for patients with newly diagnosed Ph+ ALL

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Acknowledgments

The authors thank all the patients and their families and the investigators and staff at all clinical sites for their participation in the study. This study is sponsored by Takeda Development Center Americas, Inc. Medical writing support for the development of this poster, under the direction of the authors, was provided by Lela Creutz, PhD of Peloton Advantage, LLC, an OPEN Health company, and funded by Takeda Development Center Americas, Inc., Cambridge, MA, and complied with the Good Publication Practice (GPP) guidelines (DeTora LM, et al. Ann Intern Med 2022;175:1298-1304).

Disclosures

MJH, TRL, JS, BW, AV, and **NG** report employment with Takeda. **PD, KH,** and **AL** report employment with Certara and consulting roles with Takeda.

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