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Population Pharmacokinetic and Exposure–Response Analyses for Ponatinib in the Phase 3 PhALLCON Study

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ABSTRACT

In March 2024, ponatinib received accelerated FDA approval for the treatment of newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) in combination with chemotherapy based on the Phase 3 PhALLCON study (NCT03589326), which demonstrated a 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%; $p = 0.002$). Patients received ponatinib (30 mg QD with reduction to 15 mg QD upon achievement of MRD-negative CR at EOI) or imatinib (600 mg QD) combined with 20 cycles of reduced-intensity chemotherapy (induction: 3 cycles; consolidation: 6 cycles; and maintenance: 11 cycles). Ponatinib pharmacokinetics (PK) were similar in patients in PhALLCON and patients in a previous population PK analysis. Bayesian re-estimation of the previously developed population PK model adequately described PhALLCON PK data. Exposure–efficacy analyses did not identify a significant relationship between ponatinib exposure and the probability of MRD-negative CR at EOI ($p = 0.619$), suggesting a consistent efficacy benefit across exposures. Ponatinib exposure was not a significant predictor of arterial occlusive events, venous thromboembolic events, thrombocytopenia, or lipase increase ($p > 0.05$). However, higher exposures were associated with a higher probability of hypertension ($p = 0.0340$) and alanine aminotransferase (ALT) increase ($p = 0.0034$). Dose reduction from 30 to 15 mg was predicted to decrease the odds of experiencing hypertension by 37.7% and ALT increase by 44.2%. Collectively, exposure–response analyses support a favorable benefit–risk profile of the approved ponatinib dosage (30 mg QD reduced to 15 mg QD upon achievement of MRD-negative CR at EOI), combined with chemotherapy, for frontline treatment of Ph + ALL.

1 | Introduction

Ponatinib is a next-generation BCR::ABL1 tyrosine kinase inhibitor (TKI) that potently inhibits BCR::ABL1, including variant forms of the protein with T315I and other single-point mutations that confer resistance to first- and second-generation BCR::ABL1 TKIs [1, 2]. Several clinical studies have demonstrated a favorable benefit–risk profile for ponatinib as a single agent in patients with refractory chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) [2–7]. In 2012, ponatinib received its initial approval as a single agent at a dosage of 45 mg once daily (QD) for the treatment of CML and Ph + ALL based on the results of the pivotal PACE trial (NCT01207440) [3, 6]. Subsequently, the randomized Phase 2 OPTIC trial (NCT02467270) was conducted to evaluate the efficacy and safety of three ponatinib starting doses (45, 30, or 15 mg) in patients with chronic-phase CML (CP-CML) resistant to ≥ 2 TKIs or with a T315I mutation [7]. Patients randomized

Summary

- What is the current knowledge on the topic?
  - Ponatinib, a tyrosine kinase inhibitor, received accelerated approval in March 2024 for newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) in combination with chemotherapy based on the results of the Phase 3 PhALLCON study.
- What question did this study address?
  - Do exposure–response relationships for efficacy and safety endpoints in PhALLCON support the recommended ponatinib dosage (30 mg QD with reduction to 15 mg QD upon achievement of minimal residual disease [MRD]-negative complete remission [CR] at end of induction [EOI]) combined with chemotherapy for newly diagnosed Ph+ ALL?
- What does this study add to our knowledge?
  - No significant relationship was identified between ponatinib exposure and efficacy (MRD-negative CR at EOI), suggesting a consistent benefit across the exposure range. Statistically significant exposure–safety relationships were observed for hypertension and alanine aminotransferase increase, with higher exposures associated with a higher probability of experiencing these adverse events.
- How might this change clinical pharmacology or translational science?
  - The exposure–response analysis results support a favorable benefit–risk profile of the approved response-based dosage for ponatinib in combination with chemotherapy.

to the 45- or 30-mg starting dose cohorts in OPTIC underwent a dose reduction to 15 mg QD upon achievement of ≤ 1% *BCR::ABL1*^{IS}. All three ponatinib starting doses showed clinical benefit in patients with CP-CML. However, the 45 mg QD starting dose with a dose reduction to 15 mg QD upon achievement of response was associated with optimal benefit–risk outcomes [7], resulting in this dosing regimen being approved in 2020 for the treatment of patients with CP-CML resistant or intolerant to ≥ 2 prior TKIs [8]. Importantly, the prospective dosage adjustment for ponatinib upon response demonstrated a lower rate of arterial occlusive events (AOEs) in OPTIC compared with the 45 mg QD continuous regimen evaluated in PACE [3, 6–8].

More recently, in March 2024, ponatinib received accelerated approval in the United States for the treatment of adults with newly diagnosed Ph + ALL in combination with chemotherapy [8]. This accelerated approval was based on the results of the global, Phase 3, open-label, randomized PhALLCON (NCT03589326) study comparing ponatinib versus imatinib, administered in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph + ALL [9]. The primary endpoint of PhALLCON was met, with the rate of minimal residual disease (MRD)–negative complete remission (CR) at the end of induction being significantly higher in the ponatinib arm (34.4%) than in the imatinib arm (16.7%; $p = 0.002$) [9]. The safety profile of ponatinib was manageable and comparable to imatinib when combined with reduced-intensity chemotherapy [9]. AOEs were infrequent in PhALLCON, with similar incidences in the ponatinib and imatinib arms (2.5% and 1.2%, respectively).

The PhALLCON study included a secondary objective to collect sparse pharmacokinetic (PK) samples for population PK and exposure–response analyses for ponatinib. As described herein, the results of these analyses support a favorable benefit–risk profile of the approved ponatinib dosage (starting dosage of 30 mg QD with a reduction to 15 mg QD upon achievement of MRD-negative CR at the end of induction), combined with chemotherapy, for the treatment of patients with newly diagnosed Ph + ALL.

2 | Methods

The population PK and exposure–response analyses considered data obtained from patients treated with ponatinib in PhALLCON as of the final analysis for the primary endpoint of MRD-negative CR at the end of induction (data cutoff date of August 12, 2022). Full details and results of the PhALLCON study have been previously published [9]. In brief, 245 patients with newly diagnosed Ph + ALL were randomized 2:1 to ponatinib ($n = 164$) or imatinib ($n = 81$) in combination with twenty 28-day cycles of reduced-intensity chemotherapy (including 3 cycles of induction therapy [vincristine and dexamethasone], 6 cycles of consolidation therapy [alternating cytarabine and methotrexate], and 11 cycles of maintenance therapy [vincristine and prednisone]). The primary endpoint of the study was evaluated in the intent-to-treat population with a baseline *BCR::ABL1* dominant p190 or p210 variant identified by central laboratory assessments ($N = 232$; 154 patients in the ponatinib arm and 78 patients in the imatinib arm). An additional eight patients were enrolled at sites in Japan and assigned to the ponatinib arm only as part of a country-specific protocol amendment; therefore, these patients did not contribute to the evaluation of the primary efficacy endpoint and were excluded from the exposure–efficacy analysis. However, patients enrolled in Japan were included in the population PK and exposure–safety analyses. Ponatinib was administered at a starting dosage of 30 mg QD, and patients had their dose reduced to 15 mg QD if MRD-negative CR was achieved at the end of induction. Re-escalation to ponatinib 30 mg QD was possible if MRD negativity was lost after the dose reduction, and stepwise dose reductions down to 10 mg QD were allowed to manage AEs. The selection of the 30-mg QD ponatinib starting dose for this study versus the higher 45-mg ponatinib dose was based on the expectation of a better benefit–risk profile at 30 mg in combination with chemotherapy due to the potential for overlapping toxicities.

The PhALLCON study protocol was approved by the institutional review boards or ethics committees of participating sites. The study was conducted in compliance with applicable regulatory requirements and the International Council for Harmonisation Guideline for Good Clinical Practice. All patients provided written informed consent.

2.1 | Ponatinib PK Assessments and Population PK Analyses

Sparse blood samples were collected during Cycles 1 through 12 of the study to measure plasma concentrations of ponatinib.

Specifically, a predose sample was 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 h postdose. Additional postdose PK samples were obtained on Day 14 of Cycles 1 and 2, with one sample collected before initiating the vincristine infusion and one sample collected after the vincristine infusion before the patient left the clinic. An unscheduled trough sample collection was also to be performed at the first scheduled visit following a dose reduction of at least 7-day duration prior to the visit. The PK sampling times were selected based on the known PK profile of ponatinib and feasibility for collection as part of the Phase 3 study. Plasma concentrations of ponatinib were measured using a previously reported validated liquid chromatography/tandem mass spectrometry assay [10, 11].

A previous population PK analysis provided a robust and comprehensive characterization of ponatinib PK and sources of variability using data from both healthy participants and patients with cancer [12]. As a result, a Bayesian re-estimation approach was used to derive individual PK parameters of ponatinib for patients in PhALLCON using the previously developed population PK model as a prior [12]. The population PK analysis was performed using NONMEM Version 7.4.3 for nonlinear mixed-effects models.

In addition, the individual predicted exposure following 30 mg ponatinib was calculated based on the individual estimated apparent oral clearance values (CL/F; i.e., area under the plasma concentration–time curve [AUC] = 30 mg/[CL/F]). To evaluate potential trends between covariates and individual predicted exposure, ponatinib AUC was then subsequently correlated with individual covariates based on linear regression models.

2.2 | Exposure–Response Analyses

The individual PK parameters estimated from the population PK analysis were used to derive ponatinib systemic exposure metrics for the examination of exposure–response relationships for selected efficacy and safety outcomes from the PhALLCON study. Patients were considered for the exposure–response analyses if they had both PK (i.e., exposure) and response (i.e., efficacy or safety) information available. 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 a given time after the first dose and was calculated using the following equation:

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

In this equation, $C(\tau)$ represented the individual predicted concentration of ponatinib exposure at time τ, and $t_{day\ i}$ was the time indicating a particular study day. In the analysis of ponatinib efficacy, $t_{day\ i}$ represented the time of the last nonzero ponatinib dose before the response assessment at the end of induction was evaluated. For the time to first AE-related dose reduction or interruption analyses, $t_{day\ i}$ represented the time of the last nonzero ponatinib dose before the first AE-related dose reduction or interruption. For the analyses of ponatinib safety, $t_{day\ i}$ represented the time of the event for an AE occurring in the period of dosing and the time of the last nonzero ponatinib dose if the AE occurred later. For patients not experiencing an event, NCE was based on their entire period of dosing. As such, NCE was equivalent to the average ponatinib concentration from time 0 to $t_{day\ i}$. This exposure metric was selected because it accounted for any dose reductions or interruptions from the start of treatment to the time of the event, including the protocol-specified dose reduction to 15 mg for patients achieving MRD-negative CR at the end of induction.

Covariate analysis based on an iterative forward addition process followed by backward elimination was performed as part of the exposure–response analyses if ponatinib exposure was identified as a statistically significant predictor ($p < 0.05$). The likelihood ratio test was used to evaluate the significance of incorporating or removing covariate effects in the model. For forward addition and backward elimination, significance levels of 0.01 and 0.001 were used, respectively. In the first forward addition step, the improvement relative to the base model was assessed when each of the covariates was added alone (i.e., univariate analysis). The most statistically significant model was used in the subsequent forward addition step. Only covariates that resulted in a statistically significant improvement in the model fit in a given forward addition step were considered in the next step. During the backward elimination process, covariates were removed from the model one at a time if their deletion led to nonsignificant increases in the log-likelihood of the model. The least significant covariate was removed first, and the procedure was repeated until no more nonsignificant covariates were left in the model. The covariates examined in the exposure–response analyses are presented in Table S1. The derivation of exposure metrics and the exposure–response analyses were performed using R version 4.0.2.

As described subsequently, the exposure–response models estimated the effect of a 1 ng/mL increase in ponatinib NCE on the log odds ratio of response/AE. The impact of reducing the ponatinib dose from 30 to 15 mg was calculated as the inverse logit of the difference in typical exposure predicted by the population PK model for 30 and 15 mg, multiplied by the exposure–response model effect estimate.

2.3 | Exposure–Efficacy Analyses

The efficacy endpoint evaluated was the primary endpoint of the study, MRD-negative CR at the end of induction. The probability of achieving MRD-negative CR at the end of induction was related to ponatinib exposure (NCE) using a logistic regression model taking the following general form:

$$\log\left(\frac{P_i}{1-P_i}\right) = \beta_0 + \beta_1 \bullet NCE + \beta_2 \bullet X_2 + \ \ldots\ \beta_p \bullet X_p$$

In this equation, P_i was the probability of MRD-negative CR at the end of induction for patient i, β_0 was an intercept that defined the logit of the probability of response in the absence of ponatinib exposure (and other potential covariates), and β_1 was the slope for the effect of exposure such that the odds of response increased multiplicatively by e^{β_1} for every unit increase in ponatinib exposure, considering all other effects (if any) in the model

fixed. The parameters β_2 to β_p were included to capture the effect of other potential covariates X_2 to X_p.

2.4 | Exposure–Safety Analyses

Exposure–safety analyses were performed to examine the relationship between ponatinib exposure and the following clinically relevant AEs: AOEs, venous thromboembolic events (VTEs), lipase increase, hypertension, alanine aminotransferase (ALT) increase, and thrombocytopenia. In the PhALLCON study, AOEs and VTEs were adjudicated by an independent cardiovascular endpoint adjudication committee [9]. Adverse events (AEs) were considered for the exposure–safety analyses if they occurred from the first day of ponatinib dosing until 30 days after the last ponatinib dose. For an AE occurring more than once for a patient, the time to the first occurrence of the worst grade of the AE was used in the analysis.

The relationship between ponatinib exposure (NCE) and the probability of experiencing each AE was estimated by proportional odds logistic regression models taking the following general form:

$$logit\left(P_{ik,AE}\right) = log\left(\frac{P_{ik,AE}}{1-P_{ik,AE}}\right) = \beta_{0k} + \beta_1 \bullet NCE + \beta_2 \bullet X_2 + \ \ldots \ \beta_p \bullet X_p,$$

$$\beta_{01} > \beta_{02} > \beta_{03} > \beta_{04}$$

In this equation, β_{0k} represents the baseline logit for AE of grade k or lower, and β_1 was the slope for the ponatinib exposure effect. The parameters β_2 to β_p relate to the effect of other potential covariates, X_2 to X_p, in the same manner described above for the exposure–efficacy model.

2.5 | Exposure–Dose Adjustment Analyses

The relationship between ponatinib exposure and the time to first AE-related ponatinib dose reduction or interruption was assessed in two separate time-to-event (TTE) models reflecting the protocol-specified dose reduction to 15 mg for patients who achieved MRD-negative CR at the end of the induction phase of the study (i.e., Day 1 of Cycle 4). The first TTE analysis evaluated the time to first AE-related dose reduction or interruption from Day 1 of Cycle 1 to the end of induction. The second TTE analysis considered the time to first AE-related dose reduction or interruption after induction (i.e., after Day 1 of Cycle 4). Only efficacy responders who achieved MRD-negative CR at the end of induction and who did not undergo AE-related dose reductions or interruptions during induction were included in this second TTE analysis of the time to first AE-related dose reduction or interruption after Day 1 of Cycle 4.

Cox proportional hazards TTE models were developed to describe the time to first AE-related dose reduction or interruption. The basic form of the Cox proportional hazards model was the following equation that related the probability of being event-free (i.e., no dose reduction or interruption) up to time t, $S(t)$, to the hazard function $h(t)$:

$$S(t) = e^{-\int_0^t h(\tau)d\tau}$$

The hazard function was modeled according to the following equation:

$$h(t) = h_0(t) \times f\left(\text{NCE}, \beta_X\right) \times \exp\left\{\beta_2 \bullet X_2 + \ \ldots \ \beta_p \bullet X_p\right\}$$

where $h_0(t)$ represented a nonparametric baseline hazard, the general function, f, was the effect of ponatinib exposure (NCE) as a predictor of dose reductions or interruptions, and parameters β_2 to β_p described the effect of other potential covariates, X_2 to X_p, in the same manner described above.

3 | Results

3.1 | 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 S1). A prediction-corrected visual predictive check was also performed to evaluate if the previously developed population PK model [12] with parameter values (fixed effects and random effects variances) fixed to the final estimates would be able to adequately predict ponatinib plasma concentration–time data from PhALLCON. Overall, the previously developed population PK model adequately described the PK of ponatinib in PhALLCON (Figure 1).

Compared with the overall variability in exposure, the relative changes in individual-predicted ponatinib exposures at the 5th and 95th percentiles for continuous covariates or between groups for categorical covariates were not clinically meaningful (Figure 2). These post hoc analysis results are consistent with the findings from the previously reported covariate evaluation in the original population PK analysis that demonstrated no clinically relevant effects of these covariates on ponatinib PK [12].

3.2 | Exposure–Efficacy Analyses

The exposure–efficacy analysis dataset included 150 patients randomized to the ponatinib arm of the study who had *BCR::ABL1* dominant variants of p190 or p210 confirmed by central laboratory assessments and adequate PK information available. No statistically significant relationship was identified between ponatinib exposure and the probability of achieving MRD-negative CR at the end of induction (odds ratio [OR]: 1.01 [95% confidence interval (CI): 0.982–1.03]; $p = 0.619$). Therefore, no additional covariate analysis was performed. Figure 3 shows the observed and model-predicted probability of achieving MRD-negative CR at the end of induction versus ponatinib exposure.

3.3 | Exposure–Safety Analyses

The analysis dataset for the exposure–safety analyses included 166 patients treated with ponatinib with adequate safety and PK data available. No statistically significant relationship was identified between ponatinib exposure and the probability of experiencing an AOE, VTE, thrombocytopenia, or lipase increase (Table 1). Accordingly, no additional covariate analysis was conducted. The observed and model-predicted proportion

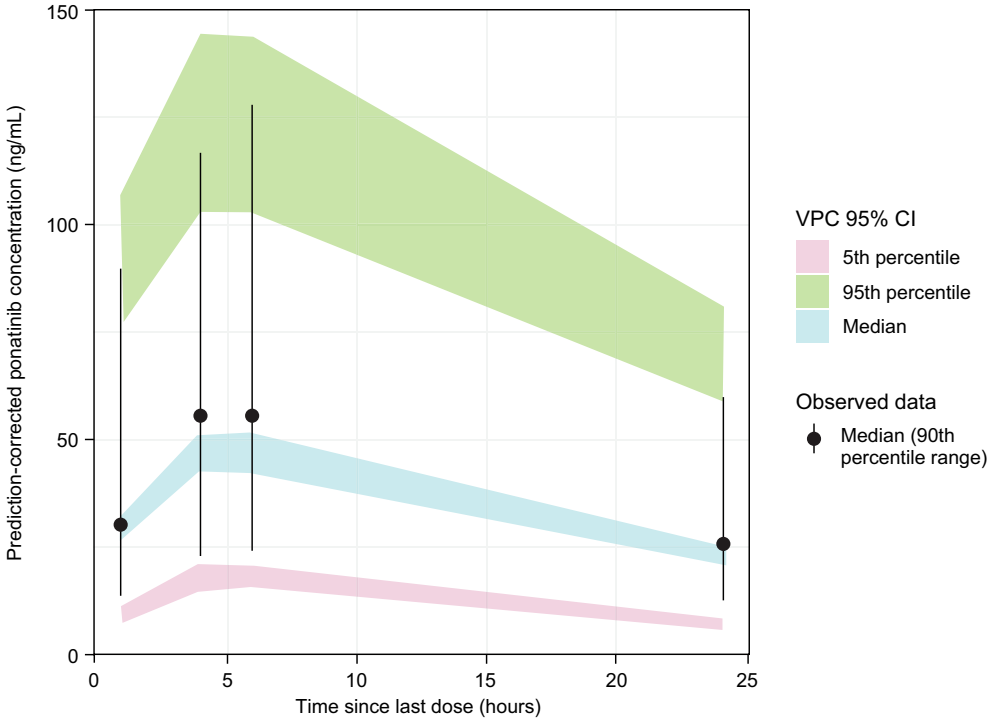

FIGURE 1 | Prediction-corrected visual predictive check of the final Bayesian re-estimation PK model for the PhALLCON study. The black circles (lines) represent the median (90th percentile range) of observed ponatinib plasma concentrations. The colored shaded regions represent the 95% CIs of predicted 5th (pink), 50th (blue), and 95th (green) percentiles of ponatinib plasma concentrations. CI, confidence interval; PK, pharmacokinetic; VPC, visual predictive check.

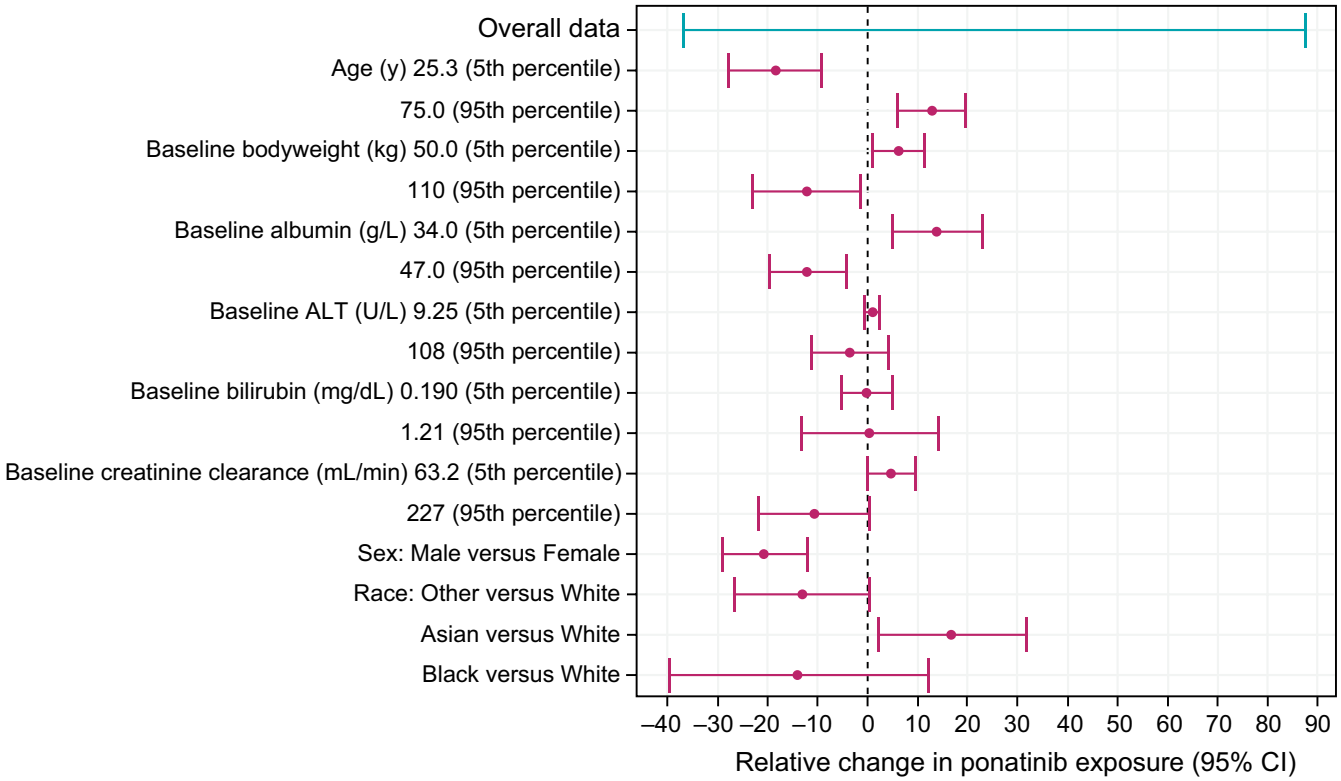

FIGURE 2 | Comparison of individual-predicted exposures at the 5th and 95th percentiles for continuous covariates or between groups for categorical covariates with the overall PhALLCON study population. The dashed black line represents a relative change in ponatinib exposure of 0. The blue bar shows the 90th percentile range (i.e., 5th to 95th percentile) of ponatinib exposures relative to the median of individual predicted exposures. The pink circles and error bars show exposures and 95% CI at the given covariate values compared with exposure at the median (for continuous covariates) or most common (for categorical covariates) covariate value. ALT, alanine aminotransferase; CI, confidence interval.

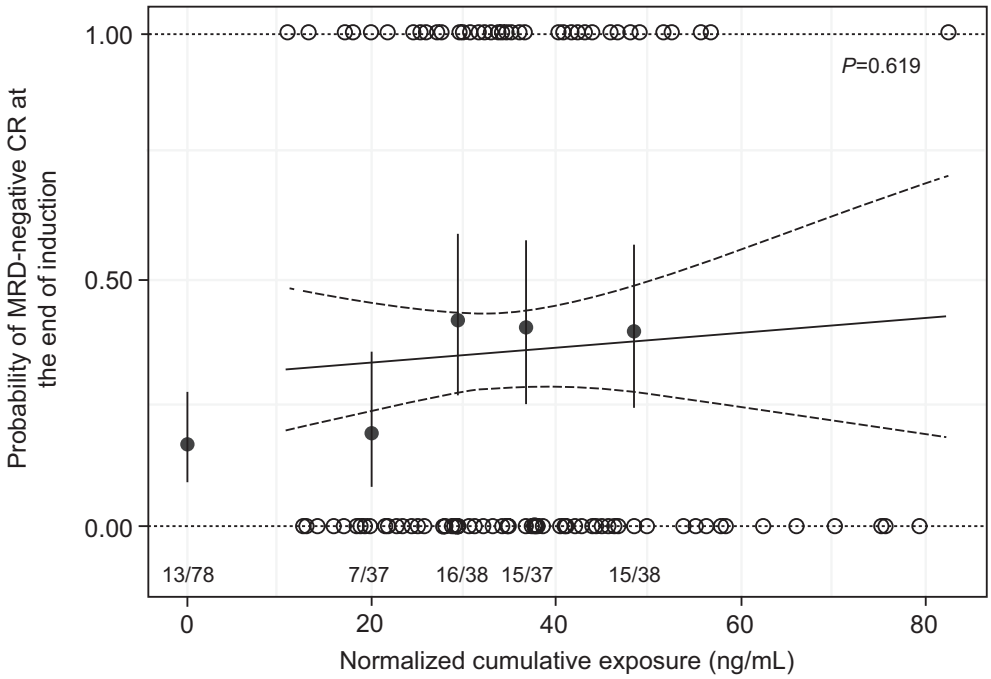

FIGURE 3 | Observed and model-predicted probability of achieving MRD-negative CR at the end of induction versus ponatinib exposure. The solid (dashed) black lines represent the model-predicted probability of being a responder (95% CI). The filled black circles (error bars) represent the observed proportion of responders (95% CI) for each ponatinib exposure quartile and the imatinib arm (filled circle at 0 exposure). The gray open circles indicate data from individual patients. n/N is the number of patients with an event/total number of patients in each ponatinib exposure quartile or the imatinib arm. CI, confidence interval; CR, complete remission; MRD, minimal residual disease.

TABLE 1 | Estimated odds ratios for ponatinib exposure in the final exposure–safety models.

Adverse event	Odds ratio (95% CI)[a]	*p*
AOE	0.933 (0.824–1.06)	0.202
VTE	0.992 (0.954–1.03)	0.689
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
Thrombocytopenia	0.997 (0.974–1.02)	0.788

Abbreviations: ALT, alanine aminotransferase; AOE, arterial occlusive event; CI, confidence interval; VTE, venous thromboembolic event.
[a]Estimated odds ratio corresponding to a 1 ng/mL increase in ponatinib normalized cumulative exposure.

of patients with grade ≥1 AOEs, VTEs, thrombocytopenia, or lipase increase is shown in Figure 4a–d.

A statistically significant relationship was identified between ponatinib exposure and the probability of experiencing hypertension or ALT increase, with higher exposures associated with a higher probability of experiencing these AEs (Table 1). No additional covariates were identified as statistically significant in the subsequent covariate analyses. Based on the final exposure–safety models, a ponatinib dose reduction from 30 to 15 mg was predicted to decrease the odds of hypertension by 37.7% (OR: 0.623 [95% CI: 0.403–0.963]) and ALT increase by 44.2% (OR: 0.558 [95% CI: 0.376–0.828]). This finding supports the prospective dose reduction to 15 mg for ponatinib upon response, as well as the current dose reduction recommendations for patients experiencing treatment-emergent toxicities. Figure 5a,b presents the observed and model-predicted proportion of patients with grade ≥1 hypertension or ALT increase.

3.4 | Exposure–Dose Adjustment Analyses

The analysis dataset for the time to first AE-related dose reduction or interruption from Day 1 of Cycle 1 to the end of induction included 164 patients treated with ponatinib, with both PK and dosing information available, and the analysis dataset for the time to first AE-related dose reduction or interruption after Day 1 of Cycle 4 included 51 patients treated with ponatinib.

In the analysis of time to first AE-related dose reduction or interruption from Day 1 of Cycle 1 to the end of induction, ponatinib exposure was not identified as a statistically significant predictor (Table 2). As a result, no additional covariate analysis was performed. In contrast, a statistically significant relationship was identified between ponatinib exposure and the time to 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 2). A subsequent covariate analysis was performed, and no additional covariates were identified as statistically significant.

4 | Discussion

In the pivotal Phase 3 PhALLCON study, ponatinib demonstrated a statistically significant and clinically meaningful

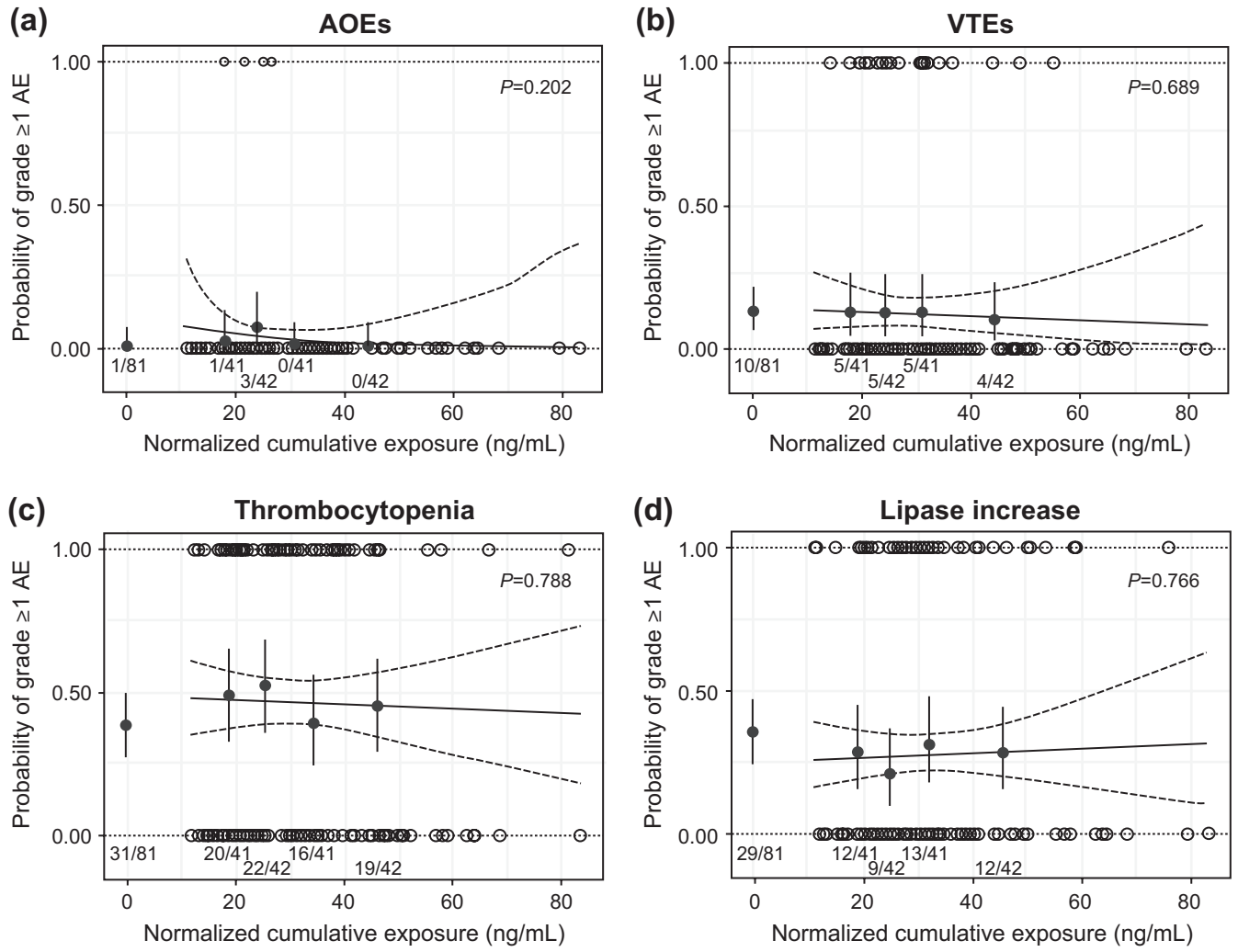

FIGURE 4 | Observed and model-predicted proportion of patients with grade ≥1 (a) AOEs, (b) VTEs, (c) thrombocytopenia, or (d) lipase increase. The solid (dashed) black lines represent the model-predicted probability of the AE (95% CI). The filled black circles (error bars) represent the observed proportion of patients with the AE (95% CI) for each ponatinib exposure quartile and the imatinib arm (filled circle at 0 exposure). The gray open circles indicate data from individual patients. n/N is the number of patients with an event/total number of patients in each ponatinib exposure quartile or the imatinib arm. AE, adverse event; AOEs, arterial occlusive events; CI, confidence interval; VTEs, venous thromboembolic events.

higher rate of MRD-negative CR at the end of induction compared with imatinib when combined with a reduced-intensity chemotherapy backbone for patients with newly diagnosed Ph + ALL [9]. Based on the results from this Phase 3 study, ponatinib received accelerated approval in the United States in March 2024 for newly diagnosed Ph + ALL in combination with chemotherapy [8]. Sparse PK samples were collected in the PhALLCON study to contribute to population PK and exposure–response analyses for ponatinib.

Ponatinib was administered in PhALLCON using a dosing regimen consisting of a 30 mg QD starting dosage with a reduction to 15 mg QD upon achievement of MRD-negative CR at the end of induction. This posology was supported by previous population PK analyses that showed that ponatinib dosages of 15 to 45 mg QD are associated with steady-state average concentrations in the pharmacologically active range for inhibition of BCR::ABL1 and that approximate or exceed concentrations shown to suppress T315I mutants in preclinical studies [12]. In addition, previous dose intensity analyses indicated that higher ponatinib dose intensities were associated with higher response rates in patients with CP-CML in the PACE study [13], as well as with an increased risk for certain AEs (including AOEs) based on a pooled analysis of data from three clinical studies [14]. Thus, a 30 mg QD ponatinib starting dosage was expected to provide systemic exposures in the efficacious range while still maintaining an acceptable safety profile when ponatinib was administered in combination with reduced-intensity chemotherapy. Furthermore, the prospective dose reduction to 15 mg QD upon achievement of MRD-negative CR at the end of induction was anticipated to further reduce the risk for AEs during longer-term treatment with ponatinib.

The Bayesian re-estimation of ponatinib PK using data from the PhALLCON study showed that the PK profile of ponatinib was similar when administered in combination with chemotherapy in patients with newly diagnosed Ph + ALL compared with single-agent ponatinib in patients included in a previous population PK analysis [12]. Additionally, an evaluation of the relationships between individual-predicted ponatinib exposures

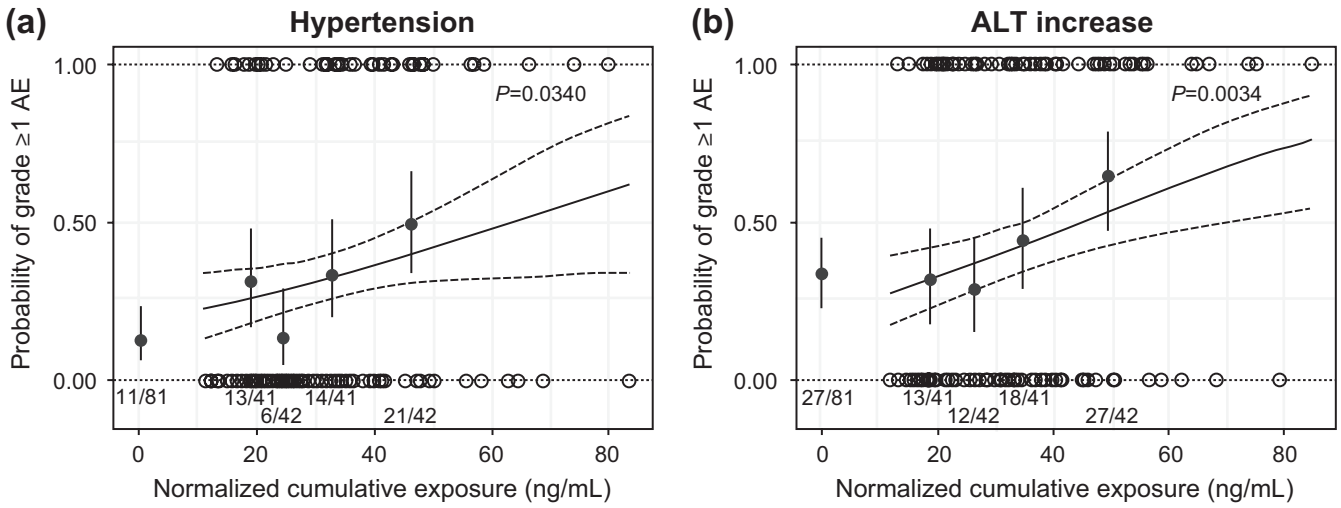

FIGURE 5 | Observed and model-predicted proportion of patients with grade ≥1 (a) hypertension or (b) ALT increase. The solid (dashed) black lines represent the model-predicted probability of the AE (95% CI). The filled black circles (error bars) represent the observed proportion of patients with the AE (95% CI) for each ponatinib exposure quartile and the imatinib arm (filled circle at 0 exposure). The gray open circles indicate data from individual patients. n/N is the number of patients with an event/total number of patients in each ponatinib exposure quartile or the imatinib arm. AE, adverse event; ALT, alanine aminotransferase; CI, confidence interval.

TABLE 2 | Estimated hazard ratios for ponatinib exposure in the final time-to-event models describing first AE-related ponatinib dose reduction or interruption.

Endpoint	Hazard ratio (95% CI)[a]	*p*
Dose reduction or interruption from Day 1 of Cycle 1 to the end of induction	0.992 (0.975–1.01)	0.321
Dose reduction or interruption after Day 1 of Cycle 4	1.06 (1.00–1.12)	0.0454

Abbreviations: AE, adverse event; CI, confidence interval.
[a]Estimated hazard ratio corresponding to a 1 ng/mL increase in ponatinib normalized cumulative exposure.

and covariates for patients in PhALLCON did not identify any clinically meaningful relationships when considering the overall variability in exposures. These findings are consistent with the results of the previous population PK analysis, where none of the covariates evaluated were found to have clinically meaningful effects on ponatinib CL/F [12].

In the exposure–efficacy analysis, no statistically significant relationship was identified between ponatinib exposure and the probability of achieving MRD-negative CR at the end of induction. This suggests that the efficacy benefit of ponatinib was consistent across the range of exposures achieved in the study with the dosing regimen (30 mg QD starting dosage with a reduction to 15 mg QD upon achievement of MRD-negative CR at the end of induction) [8]. In the exposure–safety analyses evaluating the relationships between ponatinib exposure and the incidence of AEs, no statistically significant relationship was identified for AOEs, VTEs, thrombocytopenia, or lipase increase. In contrast, statistically significant relationships were identified between ponatinib exposure and the AEs of hypertension and ALT increase, with higher exposures associated with a higher probability of experiencing these AEs. A ponatinib dose reduction from 30 to 15 mg QD was predicted to decrease the odds of experiencing hypertension by 37.7% and ALT increase by 44.2%. These exposure–safety results 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. Of note, ALT was selected for the exposure–safety analyses instead of aspartate aminotransferase (AST) because increased ALT was reported in a higher percentage of patients in the ponatinib arm of the study than increased AST.

Several factors may have contributed to the inability to discern statistically significant relationships for efficacy and some safety events in the present exposure–response analyses. A limited number of patients experienced certain AEs (e.g., only four patients [2.4%] with AOEs), and there was a potential for confounding for toxicities that overlapped with the agents in the reduced-intensity chemotherapy backbone (e.g., thrombocytopenia). Moreover, several VTEs were assessed as being related to the use of peripherally inserted central catheter lines or central venous catheters for the administration of the reduced-intensity chemotherapy backbone [9]. Finally, only one starting dose was evaluated in PhALLCON, which may have limited the available exposure range for the exposure–response analyses. Previous exposure–response analyses of the single-agent, randomized, Phase 2, dose-ranging OPTIC study that evaluated three ponatinib starting doses demonstrated that ponatinib exposure was a significant predictor of molecular response, AOEs, and grade ≥3 thrombocytopenia [15]. In that analysis, higher ponatinib exposures were associated with deeper molecular responses and an increased risk of experiencing AOEs and grade ≥3 thrombocytopenia [15].

In the exposure–dose adjustment TTE analyses, ponatinib exposure was not a statistically significant predictor of the time to first

AE-related dose reduction or interruption from Day 1 of Cycle 1 to the end of induction. In the post-induction phase (i.e., after Day 1 of Cycle 4) TTE analysis that considered only patients who achieved MRD-negative CR at the end of induction, ponatinib exposure was a statistically significant predictor of the time to first AE-related ponatinib dose reduction or interruption, with higher exposures associated with an increased risk. However, the percentage of patients in the analysis dataset experiencing an AE-related dose reduction or interruption after Day 1 of Cycle 4 was low and similar between the ponatinib arm (7.8%) and the imatinib arm (9.1%), thereby supporting the tolerability of ponatinib during extended dosing in the PhALLCON study.

It has been recognized that a poorly characterized dose and schedule during clinical development may result in the selection of a dosing regimen that increases toxicity without enhancing efficacy, potentially leading to severe toxicities that require a high rate of dose reductions or treatment discontinuations and a lost opportunity for continued clinical benefit from the drug [16]. A patient-focused approach using model-based analyses to inform dosing regimens, sometimes involving nonstatic posology, and patient-response or outcome-based dose adaptations can allow for individualized dosing that maximizes benefit versus risk [16, 17]. However, the inclusion of response-based dosing strategies in product labeling has been relatively limited to date [18]. For ponatinib, the value of a prospective dose reduction upon response to optimize benefit–risk was initially established for patients with CP-CML in the OPTIC study and its associated exposure–response analyses [7, 15]. The observed data and exposure–response analyses from the PhALLCON study further support the benefit of response-based dosing for ponatinib, specifically when administered in combination with reduced-intensity chemotherapy for patients with newly diagnosed Ph + ALL [8, 9]. This dosing approach for ponatinib provides patients with the opportunity for maximum clinical benefit while reducing the risk for AEs.

5 | Conclusions

Collectively, the results of the exposure–efficacy and exposure–safety analyses for ponatinib in the Phase 3 PhALLCON study support a favorable benefit–risk profile for the approved ponatinib dosing regimen of a 30 mg QD starting dosage with a reduction to 15 mg QD upon achievement of MRD-negative CR at the end of induction, in combination with reduced-intensity chemotherapy, for patients with newly diagnosed Ph + ALL.

Author Contributions

M.J.H., T.R.L., P.M.D., A.L., K.H., J.S., B.W., A.V., and N.G. wrote the manuscript; M.J.H., T.R.L., P.M.D., J.S., and N.G. designed the research; M.J.H., T.R.L., P.M.D., A.L., K.H., J.S., and N.G. performed research; and M.J.H., T.R.L., P.M.D., A.L., K.H., J.S., and N.G. analyzed the data.

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Conflicts of Interest

Michael J. Hanley: Employment (Takeda); Thomas R. Larson: Employment (Takeda); Paul M. Diderichsen: Employment (Certara), consulting (Takeda); Anna Largajolli: Employment (Certara), consulting (Takeda); Katrina Hui: Employment (Certara), consulting (Takeda); Jaydeep Srimani: Employment (Takeda); Bingxia Wang: Employment (Takeda); Alexander Vorog: Employment (Takeda); Neeraj Gupta: Employment (Takeda).

Data Availability Statement

The datasets, including the redacted study protocol, redacted analysis plan, and individual participant data of the completed study supporting the results reported in this article, will be made available within 3 months from the initial request to researchers who provide a methodologically sound proposal. The data will be provided after deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Prior Presentation

Some of these data were presented at the 2024 American College of Clinical Pharmacology (ACCP) Annual Meeting; Sep 8–10, 2024; in Rockville, MD, USA.

References

1. T. O'Hare, W. C. Shakespeare, X. Zhu, et al., "AP24534, a Pan-BCR-ABL Inhibitor for Chronic Myeloid Leukemia, Potently Inhibits the T315I Mutant and Overcomes Mutation-Based Resistance," *Cancer Cell* 16 (2009): 401–412.

2. J. E. Cortes, H. Kantarjian, N. P. Shah, et al., "Ponatinib in Refractory Philadelphia Chromosome-Positive Leukemias," *New England Journal of Medicine* 367 (2012): 2075–2088.

3. J. E. Cortes, D. W. Kim, J. Pinilla-Ibarz, et al., "A Phase 2 Trial of Ponatinib in Philadelphia Chromosome-Positive Leukemias," *New England Journal of Medicine* 369 (2013): 1783–1796.

4. P. Jain, H. Kantarjian, E. Jabbour, et al., "Ponatinib as First-Line Treatment for Patients With Chronic Myeloid Leukaemia in Chronic Phase: A Phase 2 Study," *Lancet Haematology* 2 (2015): e376-e383.

5. A. Tojo, T. Kyo, K. Yamamoto, et al., "Ponatinib in Japanese Patients With Philadelphia Chromosome-Positive Leukemia, a Phase 1/2 Study," *International Journal of Hematology* 106 (2017): 385–397.

6. J. E. Cortes, D. W. Kim, J. Pinilla-Ibarz, et al., "Ponatinib Efficacy and Safety in Philadelphia Chromosome Positive Leukemia: Final 5-Year Results of the Phase 2 PACE Trial," *Blood* 132 (2018): 393–404.

7. J. Cortes, J. Apperley, E. Lomaia, et al., "Ponatinib Dose-Ranging Study in Chronic-Phase Chronic Myeloid Leukemia: A Randomized, Open-Label Phase 2 Clinical Trial," *Blood* 138 (2021): 2042–2050.

8. Iclusig [package insert], "Takeda Pharmaceuticals America, Inc." 2024 Lexington, MA.

9. E. Jabbour, H. M. Kantarjian, I. Aldoss, et al., "Ponatinib vs Imatinib in Frontline Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial," *Journal of the American Medical Association* 331 (2024): 1814–1823.

10. N. I. Narasimhan, D. J. Dorer, K. Niland, F. Haluska, and D. Sonnichsen, "Effects of Ketoconazole on the Pharmacokinetics of Ponatinib in Healthy Subjects," *Journal of Clinical Pharmacology* 53 (2013): 974–981.

11. N. I. Narasimhan, D. J. Dorer, J. Davis, C. D. Turner, and D. Sonnichsen, "Evaluation of the Effect of Multiple Doses of Rifampin on the

Pharmacokinetics and Safety of Ponatinib in Healthy Subjects," *Clinical Pharmacology in Drug Development* 4 (2015): 354–360.

12. M. J. Hanley, P. M. Diderichsen, N. Narasimhan, S. Srivastava, N. Gupta, and K. Venkatakrishnan, "Population Pharmacokinetics of Ponatinib in Healthy Adult Volunteers and Patients With Hematologic Malignancies and Model-Informed Dose Selection for Pediatric Development," *Journal of Clinical Pharmacology* 62 (2022): 555–567.

13. A. Hochhaus, J. Pinilla-Ibarz, D-W. Kim, et al., "Clinical Impact of Dose Modification and Dose Intensity on Response to Ponatinib (PON) in Patients (Pts) With Philadelphia Chromosome-Positive (Ph+) Leukemias," *Journal of Clinical Oncology* 32 (2014): 7084.

14. D. J. Dorer, R. K. Knickerbocker, M. Baccarani, et al., "Impact of Dose Intensity of Ponatinib on Selected Adverse Events: Multivariate Analyses From a Pooled Population of Clinical Trial Patients," *Leukemia Research* 48 (2016): 84–91.

15. M. J. Hanley, P. Diderichsen, B. Rich, et al., "Response-Based Dosing for Ponatinib: Model-Based Analyses of the Dose-Ranging OPTIC Study," *Clinical Pharmacology and Therapeutics* 114 (2023): 413–422.

16. K. Venkatakrishnan, P. Jayachandran, S. K. Seo, P. H. van der Graaf, J. A. Wagner, and N. Gupta, "Moving the Needle for Oncology Dose Optimization: A Call for Action," *CPT: Pharmacometrics & Systems Pharmacology* 13 (2024): 909–918.

17. D. Samineni, K. Venkatakrishnan, A. A. Othman, et al., "Dose Optimization in Oncology Drug Development: An International Consortium for Innovation and Quality in Pharmaceutical Development White Paper," *Clinical Pharmacology and Therapeutics* 116 (2024): 531–545.

18. R. N. Schuck, M. Pacanowski, S. Kim, R. Madabushi, and I. Zineh, "Use of Titration as a Therapeutic Individualization Strategy: An Analysis of Food and Drug Administration-Approved Drugs," *Clinical and Translational Science* 12 (2019): 236–239.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.