Impact of dose intensity of ponatinib on selected adverse events: Multivariate analyses from a pooled population of clinical trial patients

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A B S T R A C T

Ponatinib is approved for adults with refractory chronic myeloid leukemia or Philadelphia chromosome–positive acute lymphoblastic leukemia, including those with the T315I BCR-ABL1 mutation. We pooled data from 3 clinical trials (N = 671) to determine the impact of ponatinib dose intensity on the following adverse events: arterial occlusive events (cardiovascular, cerebrovascular, and peripheral vascular events), venous thromboembolic events, cardiac failure, thrombocytopenia, neutropenia, hypertension, pancreatitis, increased lipase, increased alanine aminotransferase, increased aspartate aminotransferase, rash, arthralgia, and hypertriglyceridemia. Multivariate analyses allowed adjustment for covariates potentially related to changes in dosing or an event. Logistic regression analysis identified significant associations between dose intensity and most events after adjusting for covariates. Pancreatitis, rash, and cardiac failure had the strongest associations with dose intensity (odds ratios > 2). Time-to-event analyses showed significant associations between dose intensity and risk of arterial occlusive events and each subcategory. Further, these analyses suggested that a lag exists between a change in dose and the resulting change in event risk. No significant association between dose intensity and risk of venous thromboembolic events was evident. Collectively, these findings suggest a potential causal relationship between ponatinib dose and certain adverse events and support prospective investigations of approaches to lower average ponatinib dose intensity.

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1. Introduction

BCR-ABL1 tyrosine kinase inhibitors (TKIs) are effective for improving outcomes in the treatment of chronic myeloid leukemia (CML) and Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL); however, in many cases, resistance develops through BCR-ABL1 mutations or other mechanisms [1]. The T315I mutation occurs in 5% to 20% of imatinib-resistant patients with BCR-ABL1 mutations and confers resistance to imatinib, dasatinib, nilotinib, and bosutinib [2–6]. Other mutations that may confer resistance to 1 or more of these drugs include Y253F/H, E255K/V, F359V/I/C, F317L/V/I/C, and V299L [1]. The BCR-ABL1 TKI ponatinib is unique in its broad-spectrum efficacy against both unmutated and mutant forms of BCR-ABL1, including the T315I mutant [7–9]. Data from the single-arm, open-label phase 2 Ponatinib Ph+ ALL and CML Evaluation (PACE) trial (ClinicalTrials.gov identifier: NCT01207440), which was conducted in patients in

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whom dasatinib or nilotinib had failed or who had the T315I mutation, demonstrated the efficacy and safety of ponatinib in patients with or without T315I [10] and provided the basis for the regulatory approval of ponatinib in 2012. Thus, ponatinib represents an effective treatment for patients with limited options.

Data obtained in October 2013 from the ongoing PACE trial showed that after a median of 24 months of follow-up, ponatinib was associated with an increased frequency of serious arterial occlusive events, compared with the frequency reported after 11 months of follow-up. Recommendations for dose reduction were implemented in October 2013 to mitigate the risk of additional serious adverse events.

In previous retrospective analyses of data from the phase 2 PACE trial, it was suggested that ponatinib dose intensity had a significant association with efficacy and adverse events [11], suggesting a potential causal relationship. Ponatinib has also been studied in a single-arm, open-label, phase 1 dose-finding trial of heavily pretreated patients with CML or other hematologic malignancies (ClinicalTrials.gov identifier: NCT00660920) [12] and in the randomized, open-label phase 3 Evaluation of Ponatinib vs. Imatinib in CML (EPIC) trial in patients with newly diagnosed chronic-phase CML (ClinicalTrials.gov identifier: NCT01650805) [13]. To further explore the association of ponatinib dose intensity with arterial occlusive disease as well as other adverse events, we conducted a post hoc pooled analysis of the data from these 3 trials, using an expanded set of safety measures. The objectives of the pooled analysis were: 1) to evaluate the impact of the dose intensity of ponatinib on selected adverse events that are frequent or clinically relevant, 2) to perform multivariate analyses to allow adjustment for covariates that may be related to the event or to decisions regarding dose reductions or interruptions, 3) to provide information on covariates that are predictive of the occurrence of each adverse event, and 4) to evaluate the timing of dose changes relative to the occurrence of arterial occlusive events.

2. Methods

2.1. Patients

Data were pooled from patients with CML, Ph+ ALL, or other hematologic malignancies who received ponatinib in the phase 1 trial (n = 81), the phase 2 PACE trial (n = 449), or the phase 3 EPIC trial (n = 153); starting doses of ponatinib were 2–60 mg once daily, 45 mg once daily, and 45 mg once daily, respectively. Each of these 3 trials required patients to provide written informed consent, and were conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation, Good Clinical Practice, and the US Food and Drug Administration regulations for the protection of the rights and welfare of human patients participating in biomedical research.

2.2. Endpoints

The primary analysis method was logistic regression, with the outcome defined as the presence or absence of a selected treatment-emergent adverse event of interest prior to the last day of dosing. The primary predictor variable was average dose intensity measured up to the day of the event for patients with an event, and through the date of the last reported dose for patients without an event. Treatment-emergent adverse events analyzed were: arterial occlusive events (including cardiovascular, cerebrovascular, and peripheral vascular events), venous thromboembolic events, cardiac failure, thrombocytopenia, neutropenia, hypertension, pancreatitis, increased lipase, increased alanine aminotransferase, increased aspartate aminotransferase, rash, arthralgia, and hypertriglyceridemia. Cardiovascular, cerebrovascular, and peripheral vascular events were the subsets of arterial occlusive events specifically related to the coronary arteries, the arteries in and around the brain, and the peripheral arterial system, respectively. Arterial occlusive events and venous thromboembolic events were queried through a broad collection of more than 400 Medical Dictionary for Regulatory Activities preferred terms related to vascular ischemia or thrombosis. The baseline covariates that were present in most patients (671 out of 683) in the pooled analysis and that were potentially related to the events or to the decision to reduce the dose were: medical history of diabetes at study entry (yes/no), medical history of ischemic disease at study entry (yes/no), age at study entry, log baseline platelet count, log baseline neutrophil count, number of prior TKIs, and time from diagnosis to first dose.

2.3. Safety

In all 3 trials, investigators were directed to temporarily interrupt and/or reduce the dose of ponatinib to manage adverse events according to protocol-defined criteria. In addition, in October 2013, after updated PACE trial data regarding the increased frequency of serious arterial occlusive events were obtained, the following prospective dose reductions were implemented across all ponatinib clinical trials: 1) for patients with chronic-phase CML who achieved major cytogenetic response in the phase 1 and phase 2 trials or who achieved major molecular response in the phase 3 trial, a dose reduction to 15 mg/d was requested, with an escalation to 30 mg/d allowed upon loss of response; and 2) for all other patients, a dose reduction to 30 mg/d was requested. Investigators were allowed to consider patients’ CML characteristics, BCR-ABL1 mutation status, and cardiovascular risk in determining whether other ponatinib doses were justified. The EPIC trial was terminated shortly after these recommendations were implemented [13].

The safety population included all patients who received ponatinib. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version used for each trial (version 3.0 for the phase 1 trial, and version 4.0 for the PACE and EPIC trials).

2.4. Statistical methods

2.4.1. Logistic regression analysis

For each outcome and dose intensity measure, 3 sets of logistic regression analyses were performed: 1) univariate, for dose intensity and each baseline covariate; 2) full multivariate, which adjusted simultaneously for dose intensity and all covariates; 3) reduced multivariate, in which less impactful covariates were removed from the full model by stepwise regression with backward selection until all covariates were significant at a level of 0.2. Dose intensity was calculated as the average daily dose intensity up to the day of the first occurrence of the event of interest in patients experiencing an event, and as the average daily dose intensity through the last reported dose in patients not experiencing the event of interest. Dose intensity was not part of the backward selection and was retained in each model. For each of the 3 logistic regression models, the results reported included odds ratios for the covariates and the associated P values for testing the odds ratio = 1.

2.4.2. Time-to-event modeling

To address potential limitations of the logistic regression analyses, time-to-event analyses were performed on arterial occlusive events (including the subcategories of cardiovascular, cerebrovascular, and peripheral vascular events) and venous thromboembolic events. These analyses accounted for the timing of the event and the different durations of patient follow-up, and adjusted for the
same covariates as the logistic regression model. Analyses used daily dosing to help identify the timing of dosing most predictive of arterial occlusive events and venous thromboembolic events. For each event type, a series of different models was created using average dose as a time-varying covariate for a series of combinations of lag and window based on the time of the event. Lag was defined as the time between dosing and event onset, and window was defined as the number of days of dosing to use when averaging the dose intensity (Fig. 1). A Cox regression model was used to model the time to the first event with dose intensity and covariates from the reduced multivariate model. Modeling was performed with all combinations of lags from 0 to 270 days and windows from 1 to 180 days. For each category or subcategory of event considered, a heat map of the percent change in relative risk (per 15-mg/d change in average dose intensity) for all combinations of lag and window over this range was created. This heat map was used to identify the lag/window combinations most predictive of increased risk of the event with a 15-mg/d increase in dose intensity.

3. Results

3.1. Patients

As of January 6, 2014, 683 patients across the phase 1, the phase 2 PACE, and the phase 3 EPIC trials had received ponatinib. Median duration of treatment was 7.4 months, with a median dose intensity of 37.2 mg/d. The pooled analysis contained 671 ponatinib–treated patients, as 12 patients had 1 or more missing covariates and were therefore excluded. Although most patients initially received ponatinib 45 mg once daily, individual dose intensities varied with dose reductions and interruptions, and the median dose intensity was higher in advanced-phase patients than in chronic-phase CML patients. The duration of follow-up differed across the 3 studies and was longer in the chronic-phase CML patients. Primary results of the phase 1 trial [12], the PACE trial [10], and the EPIC trial [13] have been reported. In this pooled analysis, patients received 45 mg/d on about half of all dosing days, and received lower doses or no treatment (as part of a dose interruption) on the remaining days (Table 1).

3.2. Distribution of covariates

Notable differences were observed in the distribution of covariates for arterial occlusive events and venous thromboembolic events by dose-intensity quartile, as summarized in Table 2. History of diabetes mellitus, history of ischemic disease, older age, and longer time from diagnosis to first dose were more frequent in the lower 2 dose-intensity quartiles, while the lowest baseline platelet and neutrophil counts were found in the highest dose-intensity quartile. Thus, multivariate analyses were needed to remove the influence of these factors on outcomes when evaluating the impact of ponatinib dose intensity on adverse events.
Table 3
Adverse events associated with ponatinib dose intensity: reduced multivariate logistic regression analyses (N=671).

<table>
<thead>
<tr>
<th>Event (number of patients with event prior to last dose)</th>
<th>Odds ratio for 15-mg/d increase in dose intensity</th>
<th>P value</th>
<th>Other significant covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis (n=45)</td>
<td>2.7</td>
<td>&lt;0.001*</td>
<td>History of diabetes</td>
</tr>
<tr>
<td>Rash (n=266)</td>
<td>2.4</td>
<td>&lt;0.001*</td>
<td>Baseline platelet count</td>
</tr>
<tr>
<td>Cardiac failure (n=38)</td>
<td>2.3</td>
<td>0.001**</td>
<td>Time from diagnosis to first dose</td>
</tr>
<tr>
<td>Cardiovascular event (n=58)</td>
<td>2.0</td>
<td>&lt;0.001*</td>
<td>History of ischemia Age at study entry</td>
</tr>
<tr>
<td>Thrombocytopenia (n=237)</td>
<td>1.9</td>
<td>&lt;0.001*</td>
<td>Baseline neutrophil count</td>
</tr>
<tr>
<td>Increased lipase (n=142)</td>
<td>1.9</td>
<td>&lt;0.001*</td>
<td>Time from diagnosis to first dose</td>
</tr>
<tr>
<td>Arterial occlusive event (n=102)</td>
<td>1.7</td>
<td>&lt;0.001*</td>
<td>History of ischemia Age at study entry</td>
</tr>
<tr>
<td>Arthralgia (n=181)</td>
<td>1.6</td>
<td>&lt;0.001*</td>
<td>History of diabetes Baseline platelet count</td>
</tr>
<tr>
<td>Increased AST (n=88)</td>
<td>1.6</td>
<td>0.002</td>
<td>-</td>
</tr>
<tr>
<td>Increased ALT (n=101)</td>
<td>1.6</td>
<td>0.002</td>
<td>-</td>
</tr>
<tr>
<td>Cerebrovascular event (n=30)</td>
<td>1.4</td>
<td>0.13</td>
<td>Time from diagnosis to first dose</td>
</tr>
<tr>
<td>Venous thromboembolic event (n=20)</td>
<td>1.4</td>
<td>0.23</td>
<td>Baseline neutrophil count</td>
</tr>
<tr>
<td>Hypertiglyceridemia (n=35)</td>
<td>1.4</td>
<td>0.16</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension (n=158)</td>
<td>1.3</td>
<td>0.02</td>
<td>-</td>
</tr>
<tr>
<td>Peripheral vascular event (n=35)</td>
<td>1.2</td>
<td>0.41</td>
<td>History of diabetes Age at study entry</td>
</tr>
<tr>
<td>Neutropenia (n=122)</td>
<td>1.2</td>
<td>0.21</td>
<td>Baseline neutrophil count</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TKI, tyrosine kinase inhibitor.

* P<0.05; indicates statistically significant association with dose intensity.

Table 4
Prognostic factors for arterial occlusive events: univariate and multivariate logistic regression analyses (N=671).

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate</th>
<th>Multivariate (full)</th>
<th>Multivariate (reduced)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>P value</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Dose intensity</td>
<td>1.12</td>
<td>0.39</td>
<td>1.71</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>2.06</td>
<td>0.06**</td>
<td>1.60</td>
</tr>
<tr>
<td>History of ischemic disease</td>
<td>3.33</td>
<td>&lt;0.001*</td>
<td>2.64</td>
</tr>
<tr>
<td>Age at study entry</td>
<td>1.70</td>
<td>&lt;0.001*</td>
<td>1.63</td>
</tr>
<tr>
<td>Log baseline platelet count</td>
<td>1.20</td>
<td>0.41</td>
<td>1.36</td>
</tr>
<tr>
<td>Log baseline neutrophil count</td>
<td>1.06</td>
<td>0.67</td>
<td>1.04</td>
</tr>
<tr>
<td>Number of prior TKIs</td>
<td>1.37</td>
<td>&lt;0.001*</td>
<td>1.20</td>
</tr>
<tr>
<td>Time from diagnosis to first dose</td>
<td>2.09</td>
<td>&lt;0.001*</td>
<td>1.58</td>
</tr>
</tbody>
</table>

TKI, tyrosine kinase inhibitor.

Odds ratios are based on 15-mg/d increments for dose intensity, yes/no for history of diabetes and history of ischemic disease, 10-year increments for age at study entry and time from diagnosis to first dose, 1-log increments for log baseline platelet count and log baseline neutrophil count (10-fold increments for baseline laboratory values), and increments of 1 TKI for number of prior TKIs.

A cutoff of P<0.05 was used in the reduced model.

P<0.05; indicates statistically significant association. Time from diagnosis to first dose had P values of 0.0478 and 0.0463 in the multivariate (full) and multivariate (reduced) models, respectively.

3.3. Dose intensity and safety

After adjusting for covariates, we observed significant associations between dose intensity and most adverse events by reduced multivariate logistic regression analysis, with the strongest associations (odds ratios >2) seen for pancreatitis, rash, and cardiac failure (Table 3). Other strong associations with dose intensity (odds ratios >1.5) were observed for cardiovascular events, thrombocytopenia, increased lipase, arterial occlusive events, arthralgia, increased aspartate aminotransferase, and increased alanine aminotransferase; hypertension was also significantly correlated with dose intensity, though more weakly (odds ratio = 1.3). The associations between dose intensity and cerebrovascular events, venous thromboembolic events, hypertiglyceridemia, and peripheral vascular events were not significant; however, these events were relatively infrequent, thus reducing the power to detect an association. Neutropenia was the only event that occurred in more than 10% of patients and did not have a statistically significant association with dose intensity. Lack of an association with dose intensity may be attributed to these events occurring early, generally, and often during a dose reduction following thrombocytopenia.

Dose intensity, history of ischemic disease, and age were the strongest independent predictors of increased risk of an arterial occlusive event (Table 4). The odds ratio for dose intensity in this model was 1.71, which results in a prediction of an approximately 33% reduction in the risk of an arterial occlusive event for each 15-mg/d decrease in average ponatinib dose intensity (Fig. 2).
Fig. 3. Time to first arterial occlusive event (any arterial occlusive event [A] or a cardiovascular [C], cerebrovascular [E], or peripheral vascular [G] event) and relation of events to ponatinib dose lag and window. Orange lines in time-to-event plots (A, C, E, and G) represent 95% confidence intervals. Heat maps (B, D, F, and H) show percent change in relative risk per 15-mg/d change in average ponatinib dose intensity according to different combinations of ponatinib dose lag and window.
The phenomena occurring later, such as cerebrovascular and peripheral vascular events, showed a stronger association and a greater magnitude of risk based on dose intensity when compared with the logistic models.

4. Discussion

In this exploratory post hoc analysis, we pooled data from the phase 1 dose-finding trial, the phase 2 PACE trial, and the phase 3 EPIC trial of ponatinib in patients with CML, Ph+ ALL, or other hematologic malignancies to determine the impact of dose intensity on select adverse events. Dose modifications leading to lower dose intensity were more common in older patients and in patients with medical histories of diabetes and ischemic disease. Patients with lower baseline platelet and neutrophil counts were generally able to tolerate a higher dose of ponatinib. After adjusting for these factors, analyses demonstrated that higher ponatinib doses were associated with higher rates of most adverse events. The greatest magnitude of association with ponatinib dose was observed with pancreatitis, rash, and cardiac failure (not venous thromboembolic events). Notably, ponatinib dose was also highly significantly associated with the occurrence of arterial occlusive events as well as the cardiovascular subset. In addition to dose, older age and prior history of ischemic disease were independent factors strongly associated with the development of arterial occlusive events, suggesting that careful attention to dose is warranted in patients with these risk factors.

These findings support a potential causal relationship between ponatinib dose intensity and the identified dose-related adverse events, and expand on the findings of prior phase 2 PACE retrospective analyses suggesting a causal relationship [11]. Other prior analyses of PACE data have shown that efficacy was retained at lower doses [14]. Therefore, effective management of patients receiving ponatinib might possibly be achieved with dose modification, such that efficacy and safety are balanced. While it is possible that dose reduction alone might not completely prevent dose-related adverse events, the extent to which lower doses mitigate these events can be investigated prospectively. Randomized clinical trials examining approaches to achieve a lower average dose intensity of ponatinib in patients with CML or Ph+ ALL are needed to confirm the observations in the current analysis. Where feasible, a more detailed investigation of cardiovascular risk factors and all key cardiovascular and metabolic parameters (including general vascular health as determined by ultrasound; the ankle-brachial index; and cholesterol, glucose, and hemoglobin A1C levels) should be performed before and during therapy, regardless of dose.

This analysis informs the usual approach to dose reduction as a method for adverse event management. The data suggest that dose-related adverse events might possibly be best managed with dose reduction. However, time-to-event modeling indicated that the lag between reductions in dose and the maximum model-predicted percent change in relative risk (per 15-mg/d change in
average dose intensity) varied by event type. In general, measures that lower dose intensity (starting treatment at doses <45 mg/d and/or reducing dose after response) are predicted to lower event rates. However, the results of the time-to-event analyses suggest that there may be up to a 6-month delay following dose alteration before a change in risk manifests for some arterial occlusive events. For patients in whom reduced doses of ponatinib may not be desirable (such as those with advanced disease), alternate strategies, including combination therapy [15], may be required.

These analyses included as many patients as possible from the pooled study population to enable a robust assessment of the relationship of dose intensity and other covariates to the selected adverse events. However, the study is not without limitation. The included phase 3 trial was conducted in previously untreated patients, in contrast to the heavily pretreated populations of the phase 1 and 2 trials, and had a shorter follow-up period. Further, patients who had dose adjustments tended to have other adverse clinical characteristics. We attempted to account for these covariates; nevertheless, additional salient clinical factors may have gone unmeasured. For example, none of the 3 studies included in the pooled analysis involved comprehensive vascular pre-screening assessments; therefore, patient-specific risk factors may have contributed to the occurrence of arterial occlusive events. Previous work has suggested that currently prescribed BCR-ABL TKIs, including dasatinib, nilotinib, and ponatinib, are associated with cardiovascular adverse events [16–22]. Relevant clinical factors, such as the presence of atherosclerosis, should thus be assessed in any patient treated with BCR-ABL TKIs, including ponatinib, before and during treatment.

Other potential limitations include aspects of the logistic regression analysis. Specifically, the logistic regression analysis did not account for time on study, which varied among the trials. Because dose usually decreases over time, this can create a bias in which the dose intensity approximation could overestimate the true dose intensity for events that happen early and may underestimate the true effect in events that occur later. Moreover, the logistic model employed in these analyses treats the dose intensity in a patient who drops out early the same as that in a patient who has a much longer exposure without an event. It should also be noted that the failure to identify a significant association in this analysis may be due to insufficient statistical power to detect such a relationship between dose intensity and certain rare events.

As previously noted, cardiovascular, cerebrovascular, and peripheral vascular events have been reported in patients treated with other BCR-ABL TKIs. In a trial of nilotinib in newly diagnosed CML patients, the cardiovascular event rate, including arterial vascular occlusive events, was 9.3% and 15.2% with nilotinib 300 mg twice daily and 400 mg twice daily, respectively, after a median of 5 years on therapy [23]. In a trial of dasatinib in newly diagnosed CML patients, cardiovascular adverse events included cardiac ischemic events (3.9%), cardiac-related fluid retention (8.5%), conduction system abnormalities (7.0%), and transient ischemic attacks (0.8%), with 5 years of follow-up [24]. Dasatinib is also associated with pulmonary hypertension and may increase risk of pulmonary arterial hypertension [24,25]. It is noteworthy that the most potent BCR-ABL TKIs have similar vascular adverse event profiles. The results presented here suggest that this association is a dose-related phenomenon, and prospective, randomized data for nilotinib at 300 mg and 400 mg twice daily corroborate this finding [23]. Ponatinib is currently the only BCR-ABL TKI that is active against the T315I mutant and approved for refractory CML and Ph+ ALL [7–9,23,24,26–29]. Given that the T315I mutation is associated with disease progression and compromised survival [3,30–33], the appropriate use of ponatinib is critical to the achievement of positive long-term outcomes in these patients. Among patients without the T315I mutation, daily dose could also likely be optimized to achieve and maintain efficacy, as previously reported [10,12], while minimizing serious adverse events.

5. Conclusion

The results of these exploratory analyses support the prospective investigation of approaches to lowering the average dose intensity of ponatinib, such as starting at lower doses and/or reducing dose after response, to optimize patient outcomes. Two such studies, both randomized clinical trials, are currently enrolling patients: OPTIC, a phase 2 dose-ranging trial (NCT02467270) in patients with refractory CML to prospectively evaluate the efficacy and safety of 3 starting doses (15 mg/d, 30 mg/d, and 45 mg/d, with reductions to 15 mg/d upon achievement of major cytogenetic response), and OPTIC-2L, a phase 3 comparative trial (NCT02627677) of the efficacy and safety of 2 starting doses of ponatinib (30 mg/d and 15 mg/d) vs. nilotinib (400 mg twice daily) in patients with imatinib-resistant CP-CML.

Role of the funding source

ARIAD Pharmaceuticals, Inc., designed the study and collected, analyzed, and interpreted the data in collaboration with the authors. DJD, RKK, and FGH are employees of ARIAD. All authors contributed to the writing and critical revision of all drafts and agreed to submit the paper for publication.

Conflicts of interest statement

This study was sponsored by ARIAD Pharmaceuticals, Inc. DJD, RKK, and FGH are employees of ARIAD and hold stock or other ownership interests. MB has received honoraria from BMS, Novartis, and Pfizer; served as a consultant or advisor for ARIAD, Novartis, and Pfizer; and participated in a speakers bureau for ARIAD, BMS, Novartis, and Pfizer. JEC has served as a consultant or advisor for ARIAD, BMS, Novartis, and Pfizer, and has received research funding from ARIAD, BMS, Novartis, Pfizer, and Teva. AH has received research funding from ARIAD. MT has served as a consultant or advisor for ARIAD, Novartis, and Pfizer, and has received research funding from ARIAD, Incyte, Novartis, Pfizer, and Sanofi.

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