

Original Investigation

Association Between BCR-ABL Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia and Cardiovascular Events, Major Molecular Response, and Overall Survival

A Systematic Review and Meta-analysis

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IMPORTANCE A phase 3 trial with ponatinib in patients with chronic myeloid leukemia (CML) was interrupted due to an important increase of vascular occlusive events. A similar risk was also suspected with nilotinib, another BCR-ABL tyrosine kinase inhibitor (TKI) used in patients with CML.

OBJECTIVE To assess the risk of vascular occlusive events in patients with CML treated by new generations of TKIs and provide an overall assessment of the clinical benefit.

DATA SOURCES Two independent reviewers selected studies from PubMed, Scopus, and the Cochrane library database from their inception to October 21, 2014. Abstracts published during the past 3 years at international congresses and a trial register were also searched.

STUDY SELECTION Two independent reviewers screened abstracts and titles against inclusion and exclusion criteria published previously in the PROSPERO 2014 protocol: CRD42014014147. Among the 249 abstracts identified, 10 studies fulfilled the established criteria.

DATA EXTRACTION AND SYNTHESIS Two investigators independently extracted data using a standard form.

MAIN OUTCOMES AND MEASURES Information extracted included study and patients characteristics, type of intervention and data on vascular occlusive events, overall survival, and major molecular response (MMR). The meta-analysis was performed using a fixed-effects model. Odds ratios (ORs) with 95% CIs were computed using the Peto method.

RESULTS Ten randomized clinical trials (3043 patients) were analyzed. Risk of vascular occlusive events was increased with dasatinib (OR, 3.86; 95% CI, 1.33-11.18), nilotinib (OR, 3.42; 95% CI, 2.07-5.63), and ponatinib (OR, 3.47; 95% CI, 1.23-9.78) compared with imatinib in patients with CML. No significant difference was found with bosutinib (OR, 2.77; 95% CI, 0.39-19.77). New-generation TKIs increased the rate of MMR at 1 year compared with imatinib (overall OR, 2.22; 95% CI, 1.87 to 2.63). No statistical difference in overall survival at 1 year was found (overall OR, 1.20; 95% CI, 0.63-2.29). Inaccessibility to individual data and time-to-event data and differences in evaluation criteria between studies could have introduced bias.

CONCLUSIONS AND RELEVANCE Dasatinib, nilotinib, and ponatinib increase vascular occlusive events. New-generation TKIs improve MMR but not the overall survival at 1 year in patients with CML.

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Ponatinib is a BCR-ABL tyrosine kinase inhibitor (TKI) indicated in adult patients with chronic myeloid leukemia (CML) or “Philadelphia chromosome-positive” (Ph+) acute lymphoblastic leukemia (ALL). A high incidence of arterial events, including peripheral artery occlusive disease (PAOD), has been observed with ponatinib during the clinical development.¹ This prompted the Food and Drug Administration (FDA) to include a boxed warning in the prescribing information for arterial thrombosis.² This warning indicated that 8% of patients treated by ponatinib experienced serious arterial thrombosis.²

Serious cases of PAOD were also reported in patients with CML treated with nilotinib in clinical trials and in post-marketing experience.^{3,4} Although the exact relationship between nilotinib and vascular events remains speculative,⁵ several retrospective studies have demonstrated a higher incidence of cardiovascular events with nilotinib than with imatinib.⁴⁻⁷ However, these reports were not conclusive owing to the small number of patients and the retrospective designs.⁷ To our knowledge, no signal of increased risk of vascular thrombosis and embolism has been found in clinical trials with imatinib and dasatinib. However, some postmarketing cases have been reported.^{8,9} To our knowledge, no meta-analysis has been performed to assess the risk of vascular occlusive events associated with the different BCR-ABL TKIs.

The aim of this meta-analysis is to compare the risk of vascular occlusive events associated with new-generation BCR-ABL TKIs (ie, bosutinib, dasatinib, nilotinib, and ponatinib) vs imatinib in patients with CML. Stratifications by BCR-ABL TKI are performed to provide product-specific risk assessment. Data on the overall survival and the major molecular response (MMR) were also extracted to provide global benefit-risk evaluation.

Methods

Search Strategy and Study Selection

We conducted the literature search by screening the PubMed, Scopus, and Cochrane library databases, following a literature search strategy using specific keywords and Boolean operators (eMethods 1 in the [Supplement](#)). Systematic trial research was performed from inception of each database until October 21, 2014. Only English publications were considered. One publicly available trial register was searched (<https://www.clinicaltrials.gov>) to identify all clinical trials completed until November 21, 2014. The research of randomized clinical trials was performed for bosutinib, dasatinib, nilotinib, and ponatinib. Abstracts published from December 2011 through October 2014 at international congresses (American Society of Hematology, American Society of Clinical Oncology, and European Society of Medical Oncology) were also searched. Only randomized clinical trials that compared a new generation of BCR-ABL TKI vs standard of care (ie, imatinib) were included. The primary outcome of interest was vascular occlusive events. Data on the overall survival and the MMR were also extracted. We restricted our research to the subgroup analysis of clinical trials that involved patients with CML, as described in point 15 of the review questions in the protocol of

Key Points

Question: Do new-generation tyrosine kinase inhibitors induce a higher risk of vascular occlusive events than imatinib in patients with chronic myeloid leukemia (CML)?

Findings: In this meta-analysis, the risk of vascular occlusive events was increased dasatinib, nilotinib, and ponatinib compared with imatinib in patients with CML. No significant difference was found with bosutinib.

Meaning: Cardiovascular function of patients treated with dasatinib, nilotinib, and ponatinib should be monitored on a regular basis.

PROSPERO 2014: CRD42014014147.¹⁰ There was no restriction regarding the sex and the age of the patients.

Study selection was performed in 2 stages. Initially, 2 of us (J.D. and H.H.) screened abstracts and titles against inclusion and exclusion criteria.¹⁰ Then both reviewers assessed potentially relevant articles in their entirety and decided on inclusion. All reviewed and excluded articles were recorded on an Excel spreadsheet with annotations for reasons of exclusions. Any disagreements were discussed and, if necessary, resolved through discussion with a third reviewer (J.-M.D.).

Data Extraction and Assessment of the Quality of the Included Studies

Two of us (J.D. and H.H.) independently extracted data using a standard form. Disagreements were resolved through discussion with a third reviewer (J.-M.D.). Information extracted included study characteristics (study design, year of publication, population, and end points), patient characteristics (numbers of patients, age, and sex), type of intervention (dosage, frequency, and control), and data on the vascular occlusive events, overall survival, and MMR. A list of terms considered as vascular occlusive events is provided in eMethods 2 in the [Supplement](#). In case of missing or inconsistent data, authors were contacted, with a reminder after 15 days if they had not responded. If authors did not reply at all, data from published articles (or data at <https://www.clinicaltrials.gov> when published articles were not available) were used. To ascertain the validity of the eligible randomized trials, study quality was assessed by Jadad score calculation for each study.¹¹

Statistical Analysis

All calculations were performed using Comprehensive Meta-Analysis software, version 2.2.064 (Biostat Inc). The meta-analysis was performed using a fixed effects model (FEM) based on the assumption of a similar effect measure between studies. The statistical analysis using a random effects model is also presented for consistency. The odds ratios (ORs) and 95% CIs were calculated using the Peto method.¹² When applicable, 1-way sensitivity analyses were performed by removing a single study at a time to determine how robust the findings are. Stratifications per treatment were also performed.

Statistical heterogeneity across the various trials was tested using the Cochran Q statistic and quantified by the I^2 value.¹² Publication bias was assessed using funnel plot asymmetry.¹²

Table. Vascular Occlusive Events, Overall Survival, and Major Molecular Response to Evaluated BCR-ABL TKIs

TKI	Peto Method ¹² Odds Ratio (95% CI)		Heterogeneity ^a	
	Fixed Effects Model ^a	Random Effects Model	I ² Statistic	P Value ^b
Vascular Occlusive Events				
Overall	3.45 (2.30-5.18)	3.45 (2.30-5.18)	0.000	.85
Bosutinib	2.77 (0.39-19.77)	2.77 (0.39-19.77)	NA	NA
Dasatinib	3.86 (1.33-11.18)	3.86 (1.33-11.18)	0.000	.42
Nilotinib	3.42 (2.07-5.63)	3.42 (2.07-5.63)	0.000	.72
Ponatinib	3.47 (1.23-9.78)	3.47 (1.23-9.78)	NA	NA
Overall Survival				
Overall	1.20 (0.63-2.29)	1.14 (0.46-2.81)	34.328	.17
Bosutinib	2.38 (0.82-6.89)	2.38 (0.82-6.89)	NA	NA
Dasatinib	0.42 (0.14-1.31)	0.46 (0.11-2.01)	13.506	.32
Nilotinib	1.51 (0.38-5.99)	1.01 (0.09-10.96)	39.176	.20
Ponatinib	2.00 (0.21-19.33)	2.00 (0.21-19.33)	NA	NA
Major Molecular Response				
Overall	2.22 (1.87-2.63)	2.22 (1.87-2.63)	0.000	.63
Bosutinib	1.86 (1.29-2.70)	1.86 (1.29-2.70)	NA	NA
Dasatinib	2.17 (1.66-2.83)	2.17 (1.66-2.83)	0.000	.61
Nilotinib	2.45 (1.85-3.24)	2.45 (1.84-3.26)	0.578	.37
Ponatinib	4.95 (0.97-25.19)	4.95 (0.97-25.19)	NA	NA

Abbreviations: NA, not applicable; TKI, tyrosine kinase inhibitor.

^a Description of the heterogeneity is provided for fixed effects model.

^b All P values derived from the Q test.

Results

Selected Studies

After removing duplicates, 249 abstracts were identified from the different sources (eFigure 1 in the [Supplement](#)).¹³ After the first screening, 19 articles and 30 abstracts fulfilled the established criteria and were read in their entirety. A total of 6 articles and 3 abstracts contained relevant data and were included for statistical analysis.¹⁴⁻²² The clinicaltrials.gov database (<https://www.clinicaltrials.gov>) was screened to identify clinical trials that had not been published. Nineteen clinical trials were found to be eligible. Five clinical trials had been recently terminated, and results had not yet been published (neither in the literature nor at clinicaltrials.gov). Three others were terminated prematurely due to lack of recruitment. In these studies, the analysis of efficacy was not performed, and no data could be extracted. Another trial was excluded for inappropriate design, leaving 10 studies (3043 patients) identified through clinicaltrials.gov, of which 9 studies were also identified in the literature.¹⁴⁻²² Trial [NCT00320190](#) was not yet published in the literature. Regarding vascular occlusive events, except for the EPIC trial ([NCT01650805](#)), we used the data found at clinicaltrials.gov because it was more complete than any otherwise published version. Among the 10 studies (3043 patients) included, 3 studies did not report overall survival, and 9 studies reported vascular occlusive events and the efficacy outcome of MMR.

Study Characteristics

The general characteristics and the Jadad score of the studies selected for the meta-analysis are reported in eTable 1 in the [Supplement](#). All trials included were performed with a population of patients with CML. Most of the trials were not blinded

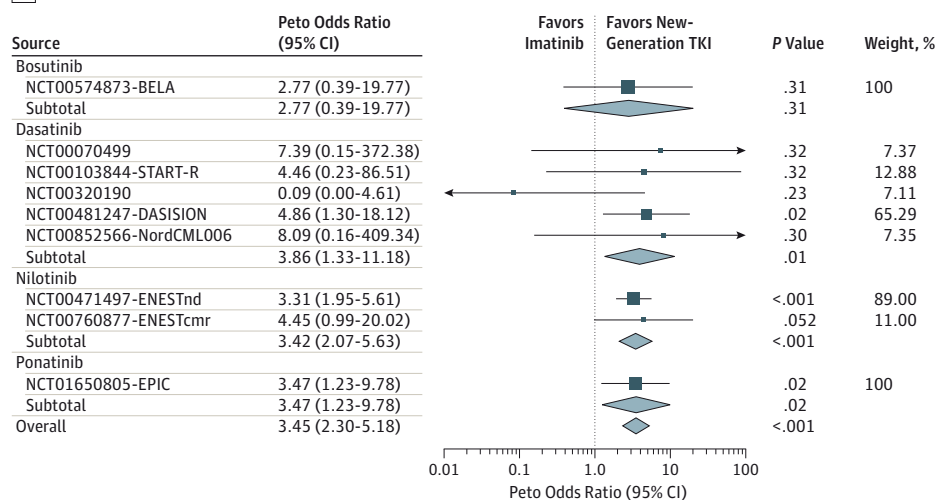
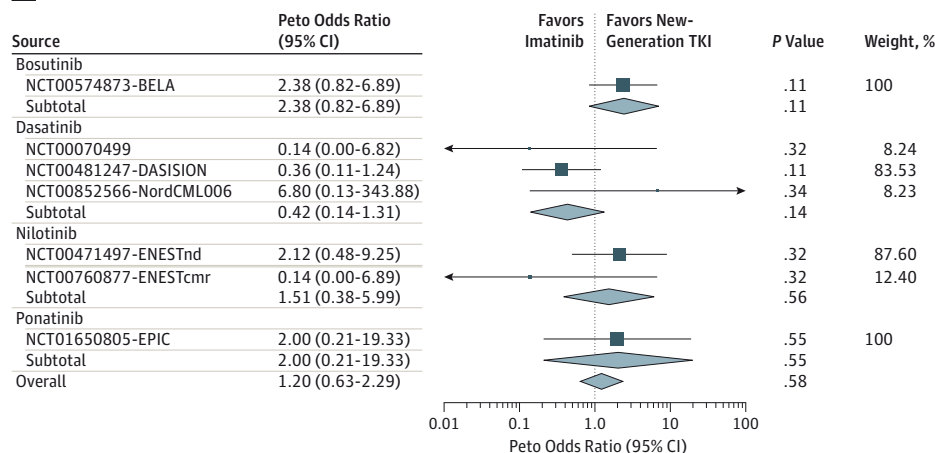
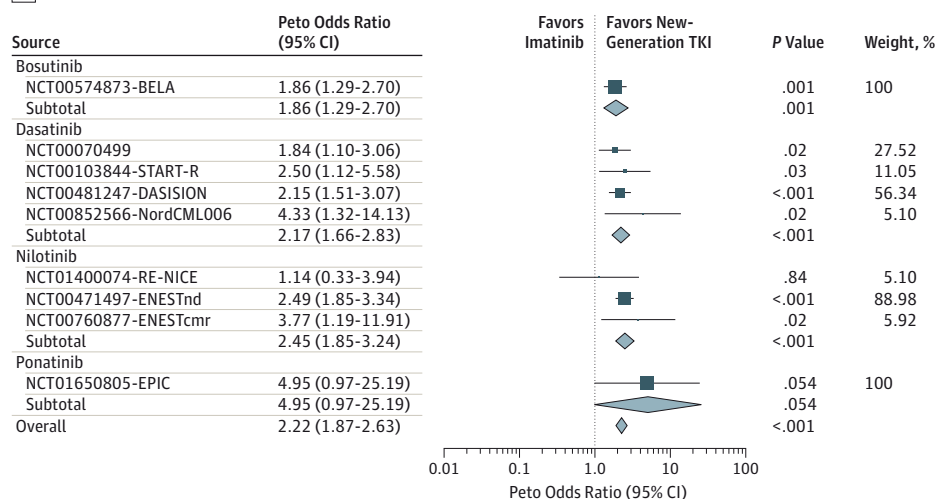
owing to the complexity of the dose tailoring during the trial. Therefore, studies with a Jadad score less than 3 were considered low-quality studies; those with a Jadad score of 3 or higher were considered high-quality studies (eTable 1 in the [Supplement](#)). Among all analyses performed, there was no evidence of publication bias (eFigure 2 in the [Supplement](#)) nor heterogeneity among the studies (Table).

Primary and Secondary Outcomes

The Table summarizes the results for the FEM and random effects model OR_{PETO} for the vascular occlusive events, overall survival, and MMR. A description of the heterogeneity is also provided.

Vascular Occlusive Events

The Figure, A provides the forest plot for vascular occlusive events stratified by treatment group. Vascular occlusive events occurred in 5.88% of patients (93 of 1582) treated with new-generation TKIs vs 1.04% of patients (13 of 1253) treated with imatinib (eTable 2 in the [Supplement](#)). The use of a new-generation TKI was associated with a statistically significant increased risk of vascular occlusive events (FEM OR_{PETO}, 3.45; 95% CI, 2.30-5.18). Subgroup analysis indicates that the risk did not increase with bosutinib (FEM OR_{PETO}, 2.77; 95% CI, 0.39-19.77), but the difference was statistically significant for dasatinib (FEM OR_{PETO}, 3.86; 95% CI, 1.33-11.18), nilotinib (FEM OR_{PETO}, 3.42, 95% CI, 2.07-5.63), and ponatinib (FEM OR_{PETO}, 3.47, 95% CI, 1.23-9.78). The 1-way sensitivity analysis indicated that removing studies 1 by 1 did not change the overall results (eFigure 3A in the [Supplement](#)). However, removing the DASISION trial ([NCT00481247](#)) in the dasatinib subgroup significantly affected the result (eFigure 3B in the [Supplement](#)). Similarly, removing the ENESTnd trial ([NCT00471497](#)) in the nilotinib subgroup made the results nonsignificant.

Figure. Forest Plots of the Outcomes of Interest in Patients With Ph+ Leukemia Treated With New-Generation TKIs vs Imatinib**A** Vascular occlusive events**B** Overall survival**C** Major molecular response

In this illustration of statistical results, squares represent odds ratios (the size of the squares reflecting the weight assigned to the study) and the whiskers, 95% CIs, both calculated using the Peto method.¹² Diamonds reflect the summary effect for each treatment when the different studies were pooled together. No forest plot contains all 10 trials because for each analysis (overall survival, major molecular response, and vascular occlusive events), at least 1 study did not report the event of interest. PH+ indicates Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor.

Overall Survival

The Figure, B presents the forest plot for survival stratified by treatments. Death during the first year occurred in 22 (1.49%) of 1473 patients treated with a novel TKI compared with 24 (2.01%) of 1194 patients treated with imatinib (eTable 2 in the [Supplement](#)). The analysis revealed a similar mortality rate at 1 year between new-generation TKIs and imatinib (FEM OR_{PETO}, 1.20; 95% CI, 0.63-2.29). Stratification by treatment did not change the results (bosutinib, FEM OR_{PETO}, 2.38; 95% CI, 0.82-6.89; dasatinib, FEM OR_{PETO}, 0.42; 95% CI, 0.14-1.31; nilotinib, FEM OR_{PETO}, 1.51; 95% CI, 0.38-5.99; and ponatinib, FEM OR_{PETO}, 2.00; 95% CI, 0.21-19.33). One-way sensitivity analysis indicated the robustness of the results (eFigure 4 in the [Supplement](#)).

Efficacy

The Figure, C presents the forest plot for MMR rate at 1 year: 607 (44.18%) of 1374 patients treated with a new-generation TKI achieved an MMR compared with 288 (27.35%) of 1053 patients treated with imatinib (eTable 2 in the [Supplement](#)). This led to a significant result favoring new-generation TKIs rather than imatinib (FEM OR_{PETO}, 2.22; 95% CI, 1.87-2.63). Stratification by treatment indicated similar results for each TKI except for ponatinib (FEM OR_{PETO}, 4.95; 95% CI, 0.97-25.19). One-way sensitivity analysis supported the robustness of the results (eFigure 4 in the [Supplement](#)).

Discussion

This meta-analysis of randomized clinical trials in patients with CML treated with new-generation TKIs vs imatinib focused on vascular occlusive events but also on overall survival and efficacy. Dasatinib, nilotinib, and ponatinib were associated with a higher rate of vascular occlusive events than imatinib. Even if the results were not statistically significant with bosutinib, there was a trend toward an increased risk of vascular occlusive events. However, little is known about the exact incidence of vascular occlusive events in long-term TKI-treated patients with CML and about factors predisposing for vascular occlusive events development. Several case reports and retrospective and prospective studies have analyzed correlations between preexisting risk factors and arterial occlusive disease occurrence and demonstrated that arterial occlusive events developed predominantly in patients with 1 or more risk factors (hypertension, diabetes, hyperlipidemia, obesity, smoking, and/or prior vascular disease) prior to TKI treatment (ie, nilotinib and ponatinib).^{5,23-25} The MMR at 1 year was achieved by almost twice as many patients using the novel generation TKI. However, improvement in overall survival was not achieved at this data lock point, ie, 1 year.

A limitation in the present study concerns the lack of access to individual data that might have provided important additional information including, the number of deaths due to vascular occlusive events and the baseline cardiac risk factors in each study arm. Time-to-event results were also not reported, and the fact that evaluation criteria were not similar between studies might have introduced bias into the analysis.²⁶

Moreover, the way of reporting adverse cardiovascular events in trials of cancer therapies is controversial and can compromise detection of cardiotoxic effects and limit the ability to compare safety data between trials.^{26,27} Indeed, detection of vascular adverse events is not optimal in the clinical trials for several reasons. First, vascular events were not expected safety end points, and the clinical trials were not designed to detect them. Oncology clinical trials use the Common Terminology Criteria for Adverse Events (CTCAE) for adverse events reporting. This classification uses vague terms for reporting vascular events (eg, peripheral ischemia), leading to inaccurate reporting of these events.^{28,29} In addition, initial symptoms of vascular adverse events are sometimes misinterpreted.²⁹ This meta-analysis provides information based on terminated clinical trials and does not aim to replace clinical trials designed to evaluate vascular occlusive events. However, no evidence of publication bias was found in the funnel plots (eFigure 2 in the [Supplement](#)). One-way sensitivity analysis confirmed the robustness of the results.

Do New-Generation BCR-ABL TKIs Induce Vascular Occlusive Events?

Due to the difference in the selectivity for additional targets, each TKI has a distinct toxic effect profile.³⁰ Cardiovascular toxic effects are especially difficult to evaluate, since many additional cardiovascular risk factors are encountered in leukemic patients.⁶

For imatinib, clinical trials supporting its approval and several additional clinical studies did not report a safety signal about vascular occlusive events.⁸ Moreover, experimental data suggested that imatinib was able to attenuate diabetes-induced atherosclerosis in association with a reduction in putative mediators of this injury, including cytokines, chemokines, and adhesion molecules via inhibition of platelet-derived growth factor receptor (PDGF-R).³¹ The inhibitory profile of imatinib on PDGF-R suggests that this compound is more potent than new-generation TKIs in this context.³² In addition, imatinib was found to improve the fasting blood glucose level in diabetic patients with CML, explaining a possible protective effect of imatinib on the formation of atherosclerotic plaque and the related cardiovascular diseases.^{32,33}

Regarding dasatinib, the major cardiovascular risk reported concerned the risk of bleeding, and additional clinical trials have reported a low frequency of cerebrovascular accident, transient ischemic attack, and thrombophlebitis.⁹ Our meta-analysis reveals that the risk is also well identified with this TKI. However, the results are mainly driven by the DASISION trial (NCT00481247) (Figure, A; eFigure 3 in the [Supplement](#)). Several studies also reported pulmonary hypertension³⁴⁻³⁶ or pleural effusion^{16,37-39} that appeared to be linked to the dose administered.^{39,40}

Arterial vascular occlusive events were reported in patients receiving nilotinib in both randomized clinical trials and in postmarketing reports.^{3,4} In the ENESTnd trial (NCT00471497), with a median time undergoing therapy of 48 months, ischemic heart disease was reported in 5.0% and 5.8% of the patients in the nilotinib arms (twice-daily doses of 300 and 400 mg, respectively) vs 1.8% in the imatinib arm. Simi-

larly, in the nilotinib arms, peripheral arterial occlusive disease was found to occur more frequently than in imatinib arms (1.8% and 2.2% for twice-daily nilotinib doses of 300 mg and 400 mg, respectively, and 0.0% in the imatinib arm), as were ischemic cerebrovascular events (1.1% and 1.8% for twice-daily nilotinib doses of 300 mg and 400 mg, respectively, and 0.7% in the imatinib arm).³ In this meta-analysis, the signal concerning cardiovascular events related to nilotinib is confirmed. It was reported that nilotinib-treated patients might develop increased fasting glucose levels as well as an elevation of cholesterol level consistent with the increased risk of developing vascular occlusive events.^{5,18,41} As for dasatinib, the risk seems to be correlated with the dose administered.⁴²

Compared with other second- and third-generation TKIs, bosutinib does not show an increase in the risk of cardiovascular events. However, only the BELA trial²² is included in this analysis, and the lack of power in that study possibly masks the harmful effect of bosutinib on cardiovascular outcomes (only 248 and 251 patients in the bosutinib and the imatinib arms, respectively, were included). However, even in this small cohort, 3 patients treated with bosutinib experienced vascular adverse effects compared with 1 patient in the imatinib arm. A retrospective analysis was performed including 2 trials (a phase 1/2 trial and the BELA trial) on the long-term evaluation of vascular toxic effects.⁴³ Most of these vascular adverse events involved arterial hypertension. Nevertheless, pleural effusion and other vascular adverse events have been reported that call into question the vascular safety profile of bosutinib^{43,44} and suggest the need of further investigations.

Vascular occlusive events occurred more frequently with ponatinib than with previously approved TKIs. Indeed, in phase 1 and phase 2 trials, arterial and venous thrombosis have been reported in 27% of patients receiving ponatinib.² These events occurred in clinical trials in patients with or without cardiovascular risk factors at any age.² Importantly, the rate of these events was continually increasing during the follow-up at 1 and 2 years. A recent retrospective study⁴⁵ found that vascular occlusive events were related to the dose of ponatinib administered: each 15-mg decrease in ponatinib dose was associated with a 33% reduction in risk of arterial thrombotic events. However, the significance of the ponatinib role is difficult to interpret owing to the high number of preexisting cardiovascular risk factors, particularly in patients with advanced leukemia who did not respond or could not tolerate previous treatments. Interestingly, in a phase 2 trial, arterial hypertension has been reported as a treatment-related adverse event.⁴⁶

Recommendations About the Use of TKIs in Leukemia and Perspectives for a Safe Use of These Compounds

Overall, new-generation TKIs appear to have a better efficacy in terms of molecular response, inducing an earlier and deeper response than imatinib,^{16,18,22} but without improving the overall survival at 1 year. However, the overall survival reported in this meta-analysis was assessed after 1 year of treatment (or 2 years for the ENESTcmr trial¹⁹), showing a high rate of survival. For nilotinib, the 5-year follow-up of the ENESTnd trial⁴⁷ revealed an improvement in overall survival compared with imatinib. Such long-term follow-up is not yet available for da-

satatinib, and further data are required before any conclusions can be drawn on its overall benefit in CML.

In choosing a therapy, the physician should consider the patient's characteristics, the safety profiles of the different TKIs, and the goals of the treatment. For elderly patients, improving survival is the predominant objective, and imatinib remains an excellent choice.⁴⁸ Patients with a life expectancy greater than 10 years want to achieve a deep molecular response to potentially reach a point of treatment cessation.⁴⁸ In this context, dasatinib and nilotinib seem more appropriate.⁴⁸ The findings of our meta-analysis suggest that the use of dasatinib and nilotinib as first-line treatments requires a screening for potential risk factors (eg, blood glucose level for diabetes assessment before nilotinib use) and an evaluation of the benefit-risk balance, especially for patients with CML in the chronic phase.

Choice of second- and third-line treatment is based on mutational analysis, adverse events, and the medical condition of the patient. In cases of intolerance or resistance, it is recommended to switch to one of the other TKIs approved for first-line therapy.⁴⁹ If treatment failure occurs, a more potent TKI is preferred. In this setting, ponatinib, and to a lesser extent bosutinib, should be considered as potential treatment.⁴⁹ If the patient has the T315I mutation, ponatinib is clearly the rational choice because it is reserved for patients with serious conditions and must be avoided in patients with good prognosis, such as patients with CML in chronic phase without the T315I mutation.⁴⁹

Regarding nilotinib, the risk of vascular occlusive events is likely to be dose related.⁴² However, the currently available data on the dose-efficacy and dose-toxicity relationship are not sufficient to make a formal recommendation on dose reduction, and there is a risk that lower doses might have reduced efficacy. Safety and efficacy data concerning dose reduction following major cytogenetic response have been included in the European Union's Summary of Product Characteristics for ponatinib (Iclusig; Ariad Pharmaceuticals Inc).⁵⁰ This provides information to the prescriber to facilitate an individual assessment of the benefit-risk balance of ponatinib with regard to dose reduction. If a reduced dose of ponatinib is used, physicians should monitor patients for maintenance of therapeutic response. Furthermore, at the time of this writing, a dose-ranging study in patients with chronic phase CML is recruiting to determine the optimal starting dose of ponatinib and characterize the safety and efficacy of ponatinib following dose reduction after achieving major cytogenetic response (OPTIC trial: [NCT02467270](https://clinicaltrials.gov/ct2/show/study/NCT02467270)).

Such risk-minimization measures have not yet been implemented with the other TKIs of interest (ie, dasatinib and nilotinib) for which the risk of vascular occlusive events is clearly identified. Thus, the marketing authorization holders of all other BCR-ABL TKIs should perform a dose-ranging study to find the dose regimen that will confer the best benefit-risk profile. The monitoring of such treatment is of utmost importance to ensure a sufficient response with the lowest dose possible. Furthermore, the prospective collection of data on the risk of vascular occlusive events, the adequate collection of data in randomized clinical trials, and the implementation of specific registries are mandatory.

The implementation of a prophylactic antithrombotic therapy (eg, antiplatelet and/or anticoagulant therapy) for high-risk patients requires further investigation to clearly determine their benefits in patients with CML treated with dasatinib, nilotinib, or ponatinib.²⁶ Use of additional comedications aiming to treat comorbidities (eg, diabetes, dyslipidemia) should also be investigated.²⁹ Otherwise, reduction of new-generation TKI exposure time may also be an acceptable risk-minimization strategy. For this purpose, discontinuation of TKI therapy after induction of a deep and stable molecular response (at least 2 years) could be an alternative and is currently being analyzed for second-generation TKIs in clinical trials (eg, [NCT01744665](#), [NCT01698905](#), and [NCT01784068](#)).^{51,52} Another strategy proposes the use of second-generation TKIs to induce a stable complete molecular response followed by a switch to a less toxic TKI (ie, imatinib).²⁹ Finally, the upcoming marketing of imatinib as a generic drug will renew the discussion of cost as a factor in treatment choice.

Conclusions

This meta-analysis demonstrates a significant increase in the rate of vascular occlusive events associated with the use of dasatinib, nilotinib, and ponatinib compared with imatinib. However, even if no statistical significance was found for bosutinib, a trend was also found. Treatment with dasatinib, nilotinib, and ponatinib should be associated with frequent cardiovascular monitoring and an intensive support of comorbidities. Ponatinib should be reserved for patients with advanced disease, with the T315I mutation, or for whom other treatments cannot be used. Further dose-ranging studies are required to define the dose regimen of each BCR-ABL TKI that will provide the best benefit-risk profile. Finally, monitoring the response at the individual level is of utmost importance to reduce the risk of vascular occlusive events while maintaining the MMR benefit.

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Study concept and design: Douxfils, Haguet, Mullier, Chatelain, Dogné.

Acquisition, analysis, or interpretation of data: Douxfils, Haguet, Graux, Dogné.

Drafting of the manuscript: Douxfils, Haguet.
Critical revision of the manuscript for important intellectual content: Douxfils, Mullier, Chatelain, Graux, Dogné.

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Supplementary Online Content

Douxflis J, Haguet H, Mullier F, Chatelain C, Graux C, Dogné J-M. Use of BCR-ABL tyrosine kinase inhibitors in chronic myeloid leukemia: a systematic review and meta-analysis of the risk of cardiovascular events, major molecular response, and overall survival. *JAMA Oncology*. Published online February 4, 2016.
doi:10.1001/jamaoncol.2015.5932.

eMethods 1: Search strategy

eMethods 2: List of vascular occlusive adverse events

eFigure 1: Flow diagram of study selection according to PRISMA (preferred reporting items for systematic reviews and meta-analysis) statement

eTable 1: Characteristics of included clinical trials and quality assessment

eFigure 2: Evaluation of publications bias

eTable 2: Rates of outcomes of interest across the included studies stratified by treatment

eFigure 3: One-way sensitivity analysis of the risk of vascular occlusive events in the leukemic population and stratified by treatment

eFigure 4: One-way sensitivity analysis for the overall survival at 1 year and for the major molecular response rate.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1: Search strategy

A. bosutinib

• Database: PubMed: 1946 to September 12th 2014 (5) update October 21th 2014

1. bosutinib [Title] (60)
⇒ search details :
Bosutinib [Title]
2. SKI-606 [Title] (17)
⇒ search details :
SKI-606 [Title]
3. SKI606 [Title] (1)
4. ((# 1) OR # 2) OR # 3 (70)
⇒ search details :
((bosutinib[Title]) OR SKI-606[Title]) OR SKI606[Title]
5. (# 4) [and] "randomized controlled trial" (5)
⇒ search details :
(# 4) AND "randomized controlled trial"[All Fields]
6. (# 4) [and] "randomized trial" (0)
⇒ search details :
(# 4) AND "randomized trial"[All Fields]
7. (# 4) AND "randomized clinical trial" (0)
⇒ search details :
(# 4) AND "randomized clinical trial"[All Fields]
8. (# 4) [and] "randomised controlled trial" (0)
⇒ search details :
(# 4) AND "randomized controlled trial"[All Fields]
9. (# 4) [and] "randomised trial" (0)
⇒ search details :
(# 4) AND "randomized trial"[All Fields]
10. (# 4) AND "randomised clinical trial" (0)
⇒ search details :
(# 4) AND "randomized clinical trial"[All Fields]
11. (((((# 5) OR # 6) OR # 7) OR # 8) OR # 9) OR # 10 (5)
⇒ search details :
((((# 5) OR # 6) OR # 7) OR # 8) OR # 9) OR # 10

• Database: Scopus: 1946 to September 12th 2014 (14) update October 21th 2014

1. TITLE (bosutinib) (73)
2. TITLE (SKI-606) (18)
3. TITLE (SKI606) (1)
4. (TITLE (bosutinib)) OR (TITLE (ski-606)) OR (TITLE (ski606)) (83)
5. (TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomized controlled trial")) (11)
6. (TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomized trial")) (3)
7. (TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomized clinical trial")) (1)
8. (TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomised controlled trial")) (11)
9. (TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomised trial")) (3)
10. (TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomised clinical trial")) (1)
11. # 10 OR # 9 OR # 8 OR # 7 OR # 6 OR # 5
((TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomised clinical trial"))) OR ((TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomised trial"))) OR ((TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomised controlled trial"))) OR ((TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomized clinical trial"))) OR ((TITLE (ski606) OR TITLE (

ski-606) OR TITLE (bosutinib) AND ALL ("randomized trial"))) OR ((TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomized controlled trial"))) (14)

• **Database: The Cochrane Library (all Cochrane product) : From 1972 to September 12th 2014 (8) update October 21th 2014**

1. bosutinib (17)
2. SKI-606 (8)
3. SKI606 (0)
4. # 1 or # 2 or # 3 (17)
5. # 4 and « randomized controlled trial » (8)
6. # 4 and « randomized trials » (0)
7. # 4 and « randomized clinical trial » (0)
8. # 4 and « randomised controlled trials » (8)
9. # 4 and « randomised trial » (0)
10. # 4 and « randomised clinical trials » (0)
11. # 5 or # 6 or # 7 or # 8 or # 9 or # 10 (8)

Then only « Trials » results were included in the meta-analysis (8)

B. dasatinib

• **Database: PubMed : 1946 to September, 15th 2014 (23) update October 21th 2014**

1. Dasatinib [title] (680)
⇒ search details :
Dasatinib[title]
2. BMS-354825 [title] (26)
⇒ search details :
BMS-354825[title]
3. BMS354825 [title] (1)
⇒ Search details :
BMS354825[title]
4. ((# 1) OR # 2) OR # 3 (686)
⇒ search details :
((# 1) OR # 2) OR # 3)
5. (# 4) [and] "randomized controlled trial" (19)
⇒ search details :
(# 4) AND "randomized controlled trial"[All Fields]
6. (# 4) [and] "randomized trial" (4)
⇒ search details :
(# 4) AND "randomized trial"[All Fields]
7. (# 4) AND "randomized clinical trial" (0)
⇒ search details :
(# 4) AND "randomized clinical trial"[All Fields]
8. (# 4) [and] "randomised controlled trial" (1)
⇒ search details :
(# 4) AND "randomized controlled trial"[All Fields]
9. (# 4) [and] "randomised trial" (0)
⇒ search details :
(# 4) AND "randomized trial"[All Fields]
10. (# 4) AND "randomised clinical trial" (1)
⇒ search details :
(# 4) AND "randomized clinical trial"[All Fields]
11. (((((# 5) OR # 6) OR # 7) OR # 8) OR # 9) OR # 10 (23)
⇒ search details :
((((# 5) OR # 6) OR # 7) OR # 8) OR # 9) OR # 10

• **Database: Scopus : 1946 to September 15th 2014 (71) update October 21th 2014**

1. TITLE(dasatinib) (762)

2. TITLE(BMS-354825) (28)
3. TITLE(BMS354825) (2)
4. (TITLE(dasatinib)) OR (TITLE(BMS-354825) OR (TITLE(BMS354825))) (770)
5. (TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomized clinical trial")) (4)
6. (TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomized trial")) (32)
7. (TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomized controlled trial")) (49)
8. (TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomised clinical trial")) (4)
9. (TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomised trial")) (32)
10. (TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomised controlled trial")) (49)
11. ((TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomized clinical trial"))) OR ((TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomized controlled trial"))) OR ((TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomized trial"))) OR ((TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomised trial"))) OR ((TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomised controlled trial"))) OR ((TITLE (bms354825) OR TITLE (bms-354825) OR TITLE (dasatinib) AND ALL ("randomised clinical trial"))) (71)

• **Database : The Cochrane Library (all Cochrane product) : From 1972 to 2014 (34) update October 21th 2014**

1. dasatinib (108)
2. BMS-354825 (1)
3. BMS354825 (0)
4. # 1 or # 2 or # 3 (108)
5. # 4 and « randomized controlled trial » (33)
6. # 4 and « randomised controlled trials » (1)
7. # 4 and « randomized clinical trial » (1)
8. # 4 and « randomised clinical trials » (0)
9. # 4 and « randomized trial » (3)
10. # 4 and « randomised trials » (0)
11. # 5 or # 6 or # 7 or # 8 or # 9 or # 10 (35)

Then only « Trials » results were included in the meta-analysis (34)

C. nilotinib

• **Database: PubMed : 1946 to September 12th 2014 (17) update October 21th 2014**

1. nilotinib [Title] (408)
⇒ search details :
Nilotinib [Title]
2. AMN107 [Title] (33)
⇒ search details :
AMN107 [Title]
3. ((# 1) OR # 2) (425)
⇒ search details :
(Nilotinib[Title]) OR AMN107[Title]
4. (# 3) [and] "randomized controlled trial" (15)
⇒ search details :
(# 3) AND "randomized controlled trial"[All Fields]
5. (# 3) [and] "randomized trial" (1)
⇒ search details :
(# 3) AND "randomized trial"[All Fields]
6. (# 3) AND "randomized clinical trial" (0)
⇒ search details :

(# 3) AND "randomized clinical trial"[All Fields]
 7. (# 3) [and] "randomised controlled trial" (1)
 ⇒ search details :
 (# 3) AND "randomized controlled trial"[All Fields]
 8. (# 3) [and] "randomised trial" (0)
 ⇒ search details :
 (# 3) AND "randomized trial"[All Fields]
 9. (# 3) AND "randomised clinical trial" (1)
 ⇒ search details :
 (# 3) AND "randomized clinical trial"[All Fields]
 10. (((((# 4) OR # 5) OR # 6) OR # 7) OR # 8) OR # 9 (17)
 ⇒ search details :
 (((((# 4) OR # 5) OR # 6) OR # 7) OR # 8) OR # 9

• **Database: Scopus : 1946 to September 12th 2014 (60) update October 21th 2014**

1. TITLE (nilotinib) (472)
 2. TITLE(AMN107) (37)
 3. (TITLE (nilotinib)) OR (TITLE (amn107)) (492)
 4. (TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomized controlled trial")) (50)
 5. (TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomized trial")) (22)
 6. (TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomized clinical trial")) (1)
 7. (TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomised controlled trial")) (50)
 8. (TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomised trial")) (22)
 9. (TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomised clinical trial")) (1)
 10. # 9 OR # 8 OR # 7 OR # 6 OR # 5 OR # 4
 ((TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomised clinical trial"))) OR ((TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomised trial"))) OR ((TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomised controlled trial"))) OR ((TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomized clinical trial"))) OR ((TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomized trial"))) OR ((TITLE (amn107) OR TITLE (nilotinib) AND ALL ("randomized controlled trial"))) (60)

• **Database: The Cochrane Library (all Cochrane product) : From 1972 to September 12th 2014 (50) update October 21th 2014**

1. nilotinib (68)
 2. AMN107 (2)
 3. # 1 or # 2 (70)
 4. # 3 and « randomized controlled trial » (68)
 5. # 3 and « randomized trials » (68)
 6. # 3 and « randomized clinical trial » (68)
 7. # 3 and « randomised controlled trials » (68)
 8. # 3 and « randomised trial » (68)
 9. # 3 and « randomised clinical trials » (68)
 10. # 4 or # 5 or # 6 or # 7 or # 8 or # 9 (68)

Then only « Trials » results were included in the meta-analysis (50)

D. ponatinib

• **Database: PubMed : 1946 to September 12th 2014 (1) – update October 21th 2014**

1. ponatinib [Title] (69)
 ⇒ search details :
 Ponatinib [Title]
 2. AP24534 [Title] (8)
 ⇒ search details :
 AP24534[Title]

3. ((# 1) OR # 2) (71)
⇒ search details :
Ponatinib[Title] OR AP24534[Title]
4. (# 3) [and] "randomized controlled trial" (1)
⇒ search details :
(# 3) AND "randomized controlled trial"[All Fields]
5. (# 3) [and] "randomized trial" (0)
⇒ search details :
(# 3) AND "randomized trial"[All Fields]
6. (# 3) AND "randomized clinical trial" (0)
⇒ search details :
(# 3) AND "randomized clinical trial"[All Fields]
7. (# 3) [and] "randomised controlled trial" (0)
⇒ search details :
(# 3) AND "randomized controlled trial"[All Fields]
8. (# 3) [and] "randomised trial" (0)
⇒ search details :
(# 3) AND "randomized trial"[All Fields]
9. (# 3) AND "randomised clinical trial" (0)
⇒ search details :
(# 3) AND "randomized clinical trial"[All Fields]
10. (((((# 4) OR # 5) OR # 6) OR # 7) OR # 8) OR # 9 (1)
⇒ search details :
((((# 4) OR # 5) OR # 6) OR # 7) OR # 8) OR # 9

• **Database: Scopus : 1946 to September 12th 2014 (3) update October 21th 2014**

1. TITLE (ponatinib) (87)
2. TITLE(AP24534) (9)
3. (TITLE (AP24534) OR TITLE (ponatinib)) (90)
4. (TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomized clinical trial")) (0)
5. (TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomized trial")) (1)
6. (TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomized clinical trial")) (0)
7. (TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised controlled trial")) (2)
8. (TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised trial")) (1)
9. (TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised clinical trial")) (0)
10. # 9 OR # 8 OR # 7 OR # 6 OR # 5 OR # 4
((TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised clinical trial"))) OR ((TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised trial"))) OR ((TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised controlled trial"))) OR ((TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomized clinical trial"))) OR ((TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomized trial"))) OR ((TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomized clinical trial"))) (3)

• **Database: The Cochrane Library (all Cochrane product) : From 1972 to September 12th 2014 (3) update October 21th 2014**

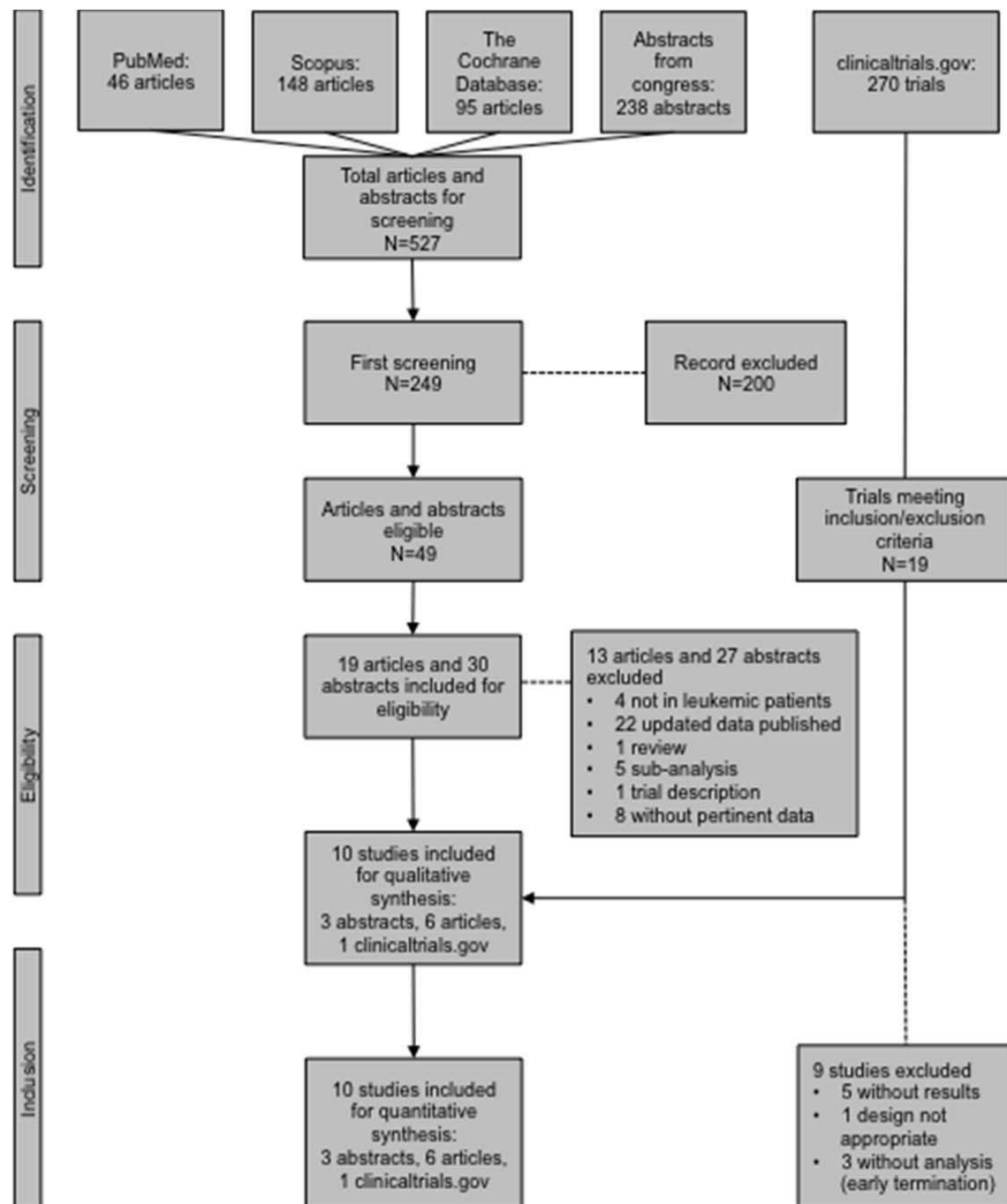
1. ponatinib (6)
2. AP24534 (1)
3. # 1 or # 2 (6)
4. # 3 and « randomized controlled trial » (6)
5. # 3 and « randomized trials » (6)
6. # 3 and « randomized clinical trial » (6)
7. # 3 and « randomised controlled trials » (6)
8. # 3 and « randomised trial » (6)
9. # 3 and « randomised clinical trials » (6)
10. # 4 or # 5 or # 6 or # 7 or # 8 or # 9 (6)

Then only « Trials » results were included in the meta-analysis (3)

eMethods 2: list of vascular occlusive adverse events

Acute myocardial infarction
Angina pectoris
Angina unstable
Aortic stenosis
Arterial occlusive disease
Arterial stenosis limb
Arteriosclerosis
Arteriosclerosis coronary artery
Atrial thrombosis
Basilar artery stenosis
Cardiac arrest
Cardiac discomfort
Cardiac infarction
Cardiac ischaemia
Cardiogenic shock
Cardio-respiratory arrest
Central nervous system lesion
Cerebral infarction
Cerebrovascular accident
Cerebrovascular disorder
Chest pain
Coronary artery disease
Coronary artery restenosis
Coronary artery stenosis
Deep vein thrombosis
Dysarthria
Electrocardiogram ST-segment depression
Femoral arterial stenosis
Hypoxic-ischemic encephalopathy
Iliac artery stenosis
Intermittent claudication
Ischaemic heart disease
Ischaemic stroke
Mesenteric artery embolism
Myocardial infarction
Myocardial ischaemia
Peripheral arterial occlusive disease
Peripheral artery disease
Peripheral artery thrombosis
Peripheral vascular disorder
Phlebitis
Pulmonary embolism
Retinal vein thrombosis
Thrombophlebitis
Thrombosis in device
Transient ischaemic attack
Varicose vein
Vascular graft occlusion
Vena cava thrombosis

eFigure 1: Flow diagram of study selection according to PRISMA (preferred reporting items for systematic reviews and meta-analysis) statement.



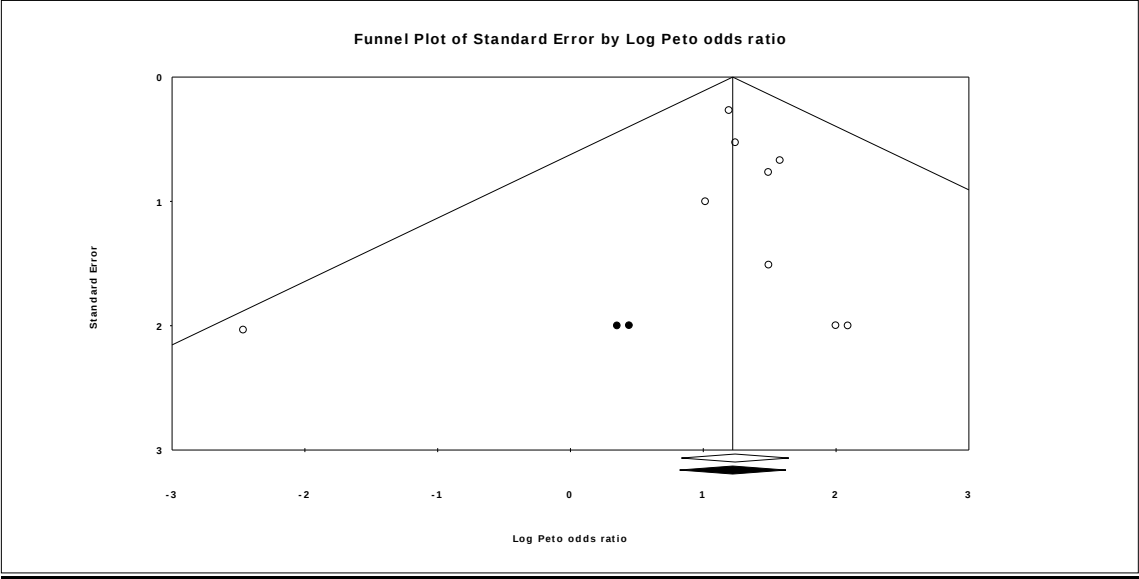
eTable 1: Characteristics of included clinical trials and quality assessment

Study ID	Study design	Experimental Dosage Admin frequency	Control Dosage Admin frequency	No. of pts	Population	Age (mean $\pm$ SD)	% male	Primary endpoint	Secondary endpoint(s)	Jadad score
BELA NCT00574873	Randomized Open-label	bosutinib 500mg once daily	imatinib 400mg once daily	502	CP CML newly diagnosed	46.53 $\pm$ 14.62	56	CCyR at 12 months	MMR, MCyR, CHR at 12 months Safety Duration of response Pharmacokinetics Time to transformation to AP/BP	2
NCT00070499	Randomized Open-label	dasatinib 100mg once daily	imatinib 400 or 800mg	391	CP CML untreated	50	61.40	MMR rate at 12 months	HR 2-year OS 2-year relapse-free survival Toxicity	2
START-R NCT00103844	Randomized Open-label	dasatinib 70mg twice daily	imatinib 400mg twice daily	150	CP CML previously treated with imatinib	51 $\pm$ 13.6	50	MCyR at 12 weeks	MCyR at any time Duration of MCyR CHR, CCyR, MMR Duration of CHR AEs, SAEs, deaths QoL, PK	2
NCT00320190	Randomized Open-label	dasatinib 100mg	imatinib 800mg	32	CML previously treated with imatinib	48.6 $\pm$ 14.85	71.90	MMR rate at 12 months	Deaths, AEs, SAEs Median time to treatment failure, to PFS Time to MMR CCyR Safety	2
DASISION NCT00481247	Randomized Open-label	dasatinib 100mg once daily	imatinib 400mg once daily	519	CP CML newly diagnosed	46.7 $\pm$ 14.2	59.40	CCyR rate by 12 months	Time to CCyR and MMR OS PFS MMR	3
NordCML006 NCT00852566	Randomized Open-label	dasatinib 100mg once daily	imatinib 400mg once daily	46	CP CML newly diagnosed	dasatinib: 54 imatinib: 60	48	Proportion of Ph+ CD34+/CD38- bone marrow cells at 6 months	Fraction of Ph+ cells at 1 and 3 months Molecular and cytogenetic responses at 3, 6, 12 and 18 months	3
ENESTnd NCT00471497	Randomized Open-label	nilotinib 300mg twice daily nilotinib 400mg twice daily	imatinib 400mg once daily	846	CP CML newly diagnosed	nilotinib 300mg: 47 nilotinib 400mg: 47 Imatinib : 46	58	Rate of MMR at 12 months	Rate of durable MMR by 24 months Progression to AP/BP CCyR Rate reduction in BCR-ABL transcript levels	3
ENESTcmr NCT00760877	Randomized Open-label	nilotinib 400mg twice daily	imatinib 400 or 600mg once daily	207	CP CML previously treated with imatinib	nilotinib: 46 imatinib: 52	nilotinib: 68 imatinib: 63	Rate of confirmed best cumulative CMR within the 1st year	Kinetics of CMR PFS, EFS and OS	2

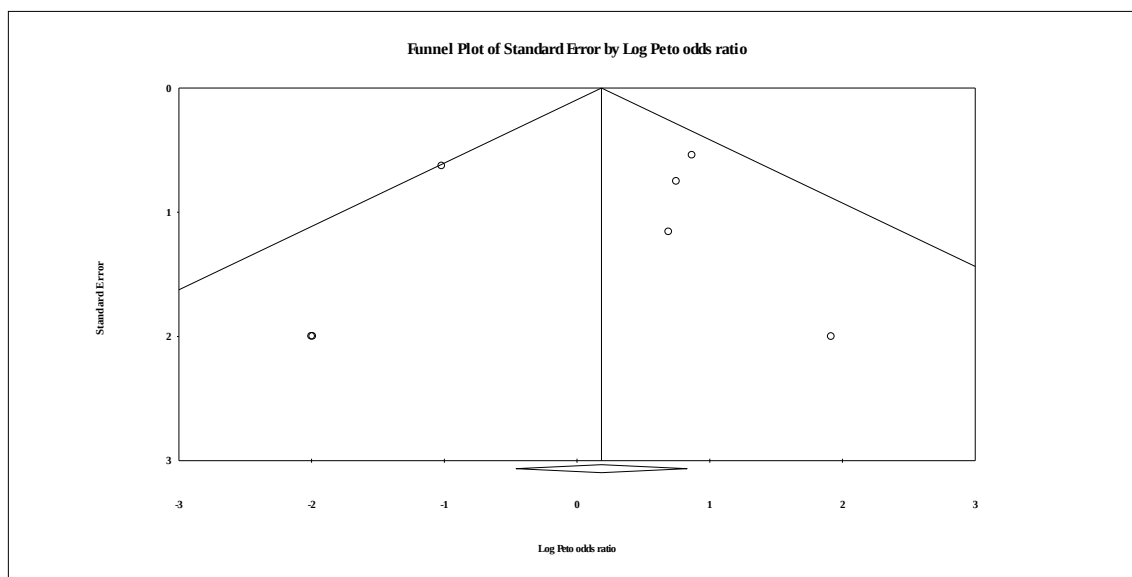
RE-NICE NCT01400074	Randomized Open-label	nilotinib 400mg twice daily	imatinib 400mg twice daily	43	CML early CP previously treated	nilotinib: 45 imatinib: 35	74.40	Cumulative rate of MMR at 12 months	Time and duration of MMR and CMR Cumulative rate of CMR, MMR and MR4.0 PFS Safety	1
EPIC NCT01650805	Randomized Open-label	ponatinib 45mg once daily	imatinib 400mg once daily	307	CP CML newly diagnosed	51.5 ± 15.4 1	61.50	MMR at 12 months	MR rate at 3,6,9 and 12 months Time to MR CCyR rate Safety OS, PFS	2

eFigure 2: Evaluation of publications bias

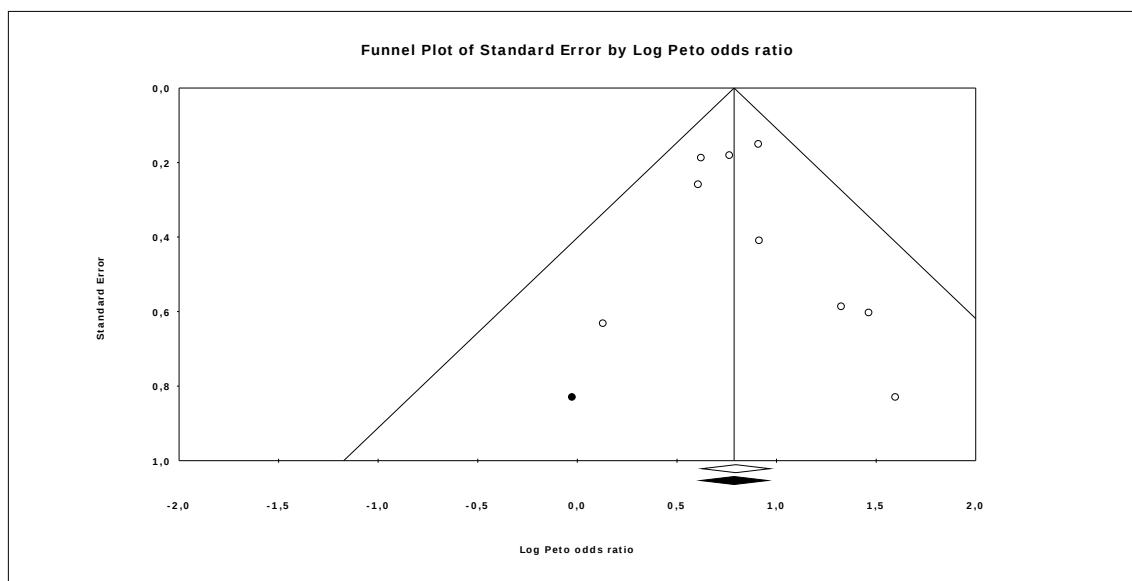
A. Vascular occlusive events



B. Overall survival



C. Major molecular response



eTable 2: Rates of outcomes of interest across the included studies stratified by treatment

A. Vascular occlusive events

Study	No. of events/total No. (%)		Fixed-effect model	Random-effect model
	New generation TKI	imatinib	OR _{PETO} (95%CI)	OR _{PETO} (95%CI)
NCT00574873 (BELA)	3/248 (1.21)	1/251 (0.40)	2.77 (0.39 – 19.77)	2.77 (0.39 – 19.77)
Bosutinib	3/248 (1.21)	1/251 (0.40)	2.77 (0.39 – 19.77)	2.77 (0.39 – 19.77)
NCT0070499	1/123 (0.81)	0/123 (0.00)	7.39 (0.15 – 372.38)	7.39 (0.15 – 372.38)
NCT00103844 (START-R)	2/101 (1.98)	0/49 (0.00)	4.46 (0.23 – 86.51)	4.46 (0.23 – 86.51)
NCT00320190	0/19 (0.00)	1/13 (7.69)	0.09 (0.00 – 4.61)	0.09 (0.00 – 4.61)
NCT00481247 (DASISION)	8/258 (3.10)	1/258 (0.39)	4.86 (1.30 – 18.12)	4.86 (1.30 – 18.12)
NCT00852566 (NordCML006)	1/22 (4.55)	0/24 (0.00)	8.09 (0.16 – 409.34)	8.09 (0.16 – 409.34)
Dasatinib	12/523 (2.30)	2/467 (0.43)	3.86 (1.33 – 11.18)	3.86 (1.33 – 11.18)
NCT00471497 (ENESTnd)	61/556 (10.97)	6/280 (2.14)	3.31 (1.95 – 5.61)	3.31 (1.95 – 5.61)
NCT00760877 (ENESTcmr)	6/101 (5.94)	1/103 (0.97)	4.45 (0.99 – 20.02)	4.45 (0.99 – 20.02)
Nilotinib	67/657 (10.20)	7/383 (1.83)	3.42 (2.07 – 5.63)	3.42 (2.07 – 5.63)
NCT01650805 (EPIC)	12/154 (7.79)	3/152 (1.97)	3.47 (1.23 – 9.78)	3.47 (1.23 – 9.78)
Ponatinib	12/154 (7.79)	3/152 (1.97)	3.47 (1.23 – 9.78)	3.47 (1.23 – 9.78)
Overall	94/1,582 (5.94)	13/1,253 (1.04)	3.45 (2.30 – 5.18)	3.45 (2.30 – 5.18)

B. Overall survival

Study	No. of events*/total No. (%)		Fixed-effect model	Random-effect model
	New generation TKI	imatinib	OR _{PETO} (95%CI)	OR _{PETO} (95%CI)
NCT00574873 (BELA)	244/248 (98.39)	241/251 (96.02)	2.38 (0.82 – 6.89)	2.38 (0.82 – 6.89)
bosutinib	244/248 (98.39)	241/251 (96.02)	2.38 (0.82 – 6.89)	2.38 (0.82 – 6.89)
NCT0070499	122/123 (99.19)	123/123 (100.00)	0.14 (0.00 – 6.82)	0.14 (0.00 – 6.82)
NCT00481247 (DASISION)	250/258 (97.00)	255/258 (99.00)	0.36 (0.11 – 1.24)	0.36 (0.11 – 1.24)
NCT00852566 (NordCML006)	22/22 (100.00)	23/24 (95.83)	6.80 (0.13 – 343.88)	6.80 (0.13 – 343.88)
dasatinib	394/403 (97.77)	397/405 (98.03)	0.42 (0.14 – 1.31)	0.46 (0.11 – 2.01)
NCT00471497 (ENESTnd)	559/563 (99.29)	279/283 (98.59)	2.12 (0.48 – 9.25)	2.12 (0.48 – 9.25)
NCT00760877 (ENESTcmr)†	103/104 (99.04)	103/103 (100.00)	0.14 (0.00 – 6.89)	0.14 (0.00 – 6.89)
nilotinib	662/667 (99.25)	382/386 (98.96)	1.51 (0.38 – 5.99)	1.01 (0.09–10.96)
NCT01650805 (EPIC)	154/155 (99.35)	150/152 (98.68)	2.00 (0.21 – 19.33)	2.00 (0.21 – 19.33)
ponatinib	154/155 (99.35)	150/152 (98.68)	2.00 (0.21 – 19.33)	2.00 (0.21 – 19.33)
Overall	1,454/1,473 (98.71)	1,170/1,194 (97.99)	1.23 (0.67 – 2.23)	1.14 (0.46 – 2.81)

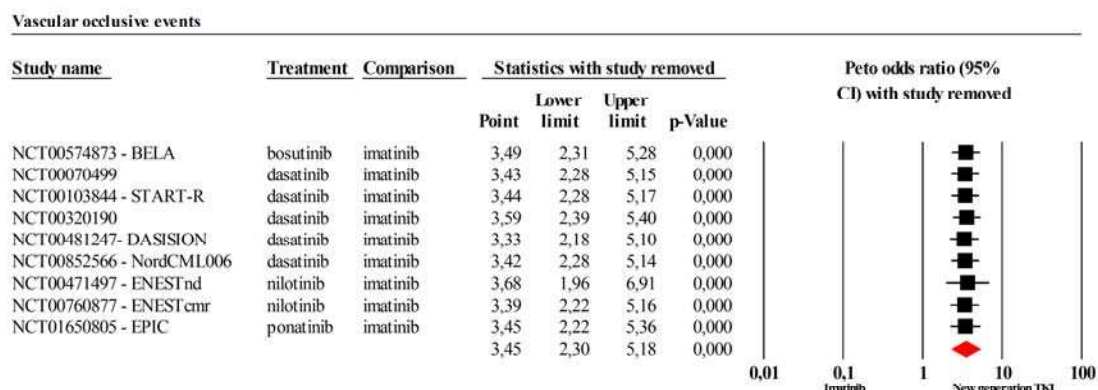
* Number of events represents the number of patients alive after one or two years† of treatment

C. Major molecular response

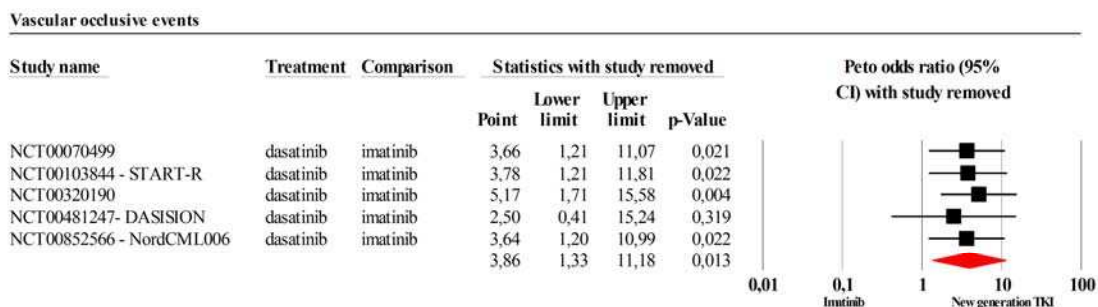
Study	No. of events/total No. (%)		Fixed-effect model	Random-effect model
	New generation TKI	imatinib	OR _{PETO} (95%CI)	OR _{PETO} (95%CI)
NCT00574873 (BELA)	103/250 (41.00)	68/252 (27.00)	1.86 (1.29 – 2.70)	1.86 (1.29 – 2.70)
bosutinib	103/250 (41.00)	68/252 (27.00)	1.86 (1.29 – 2.70)	1.86 (1.29 – 2.70)
NCT0070499	58/123 (47.15)	40/123 (32.52)	1.84 (1.10 – 3.06)	1.84 (1.10 – 3.06)
NCT00103844 (START-R)	29/101 (28.71)	6/49 (12.25)	2.50 (1.12 – 5.58)	2.50 (1.12 – 5.58)
NCT00481247 (DASISION)	119/259 (45.95)	73/260 (28.08)	2.15 (1.51 – 3.07)	2.15 (1.51 – 3.07)
NCT00852566 (NordCML006)	18/22 (81.00)	11/24 (46.00)	4.33 (1.32 – 14.13)	4.33 (1.32 – 14.13)
dasatinib	224/505 (44.36)	130/456 (28.51)	2.17 (1.66 – 2.83)	2.17 (1.66 – 2.83)
NCT01400074 (RE-NICE)	8/22 (36.36)	7/21 (33.33)	1.14 (0.33 – 3.94)	1.14 (0.33 – 3.94)
NCT00471497 (ENESTnd)	244/563 (43.34)	63/283 (22.26)	2.49 (1.85 – 3.34)	2.49 (1.85 – 3.34)
NCT00760877 (ENESTcmr)	20/24 (83.33)	15/28 (53.57)	3.77 (1.19 – 11.91)	3.77 (1.19 – 11.91)
nilotinib	272/609 (44.66)	85/332 (25.60)	2.45 (1.85 – 3.24)	2.45 (1.84 – 3.26)
NCT01650805 (EPIC)	8/10 (80.00)	5/13 (5.07)	4.95 (0.97 – 25.19)	4.95 (0.97 – 25.19)
ponatinib	8/10 (80.00)	5/13 (5.07)	4.95 (0.97 – 25.19)	4.95 (0.97 – 25.19)
Overall	607/1,374 (44.18)	288/1,053 (27.35)	2.22 (1.87 – 2.63)	2.22 (1.87 – 2.63)

eFigure 3: One-way sensitivity analysis of the risk of vascular occlusive events in the leukemic population and stratified by treatment

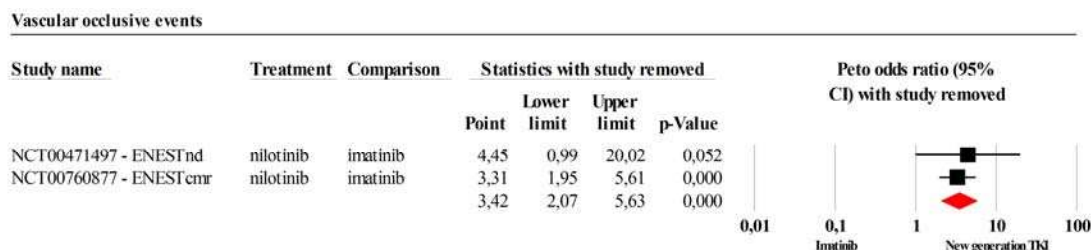
A. One-way sensitivity analysis of the risk of vascular occlusive events in the leukemic population



B. One-way sensitivity analysis of the risk of vascular occlusive events in the leukemic population stratified with only dasatinib trials



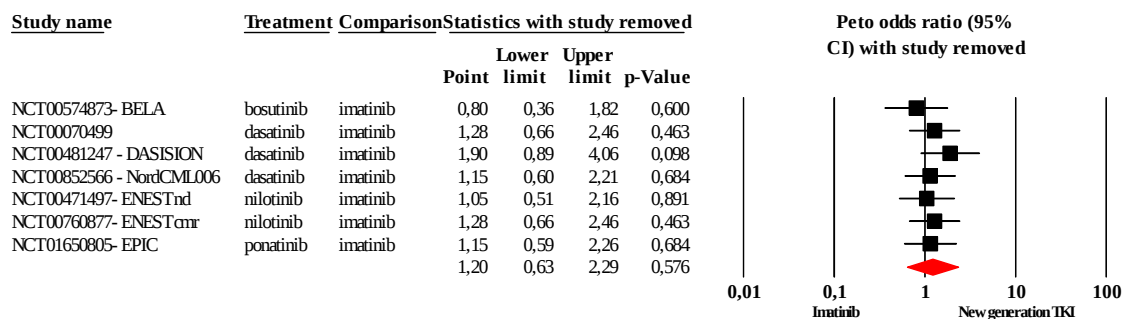
C. One-way sensitivity analysis of the risk of vascular occlusive events in the leukemic population stratified with only nilotinib trials



eFigure 4: One-way sensitivity analysis for the overall survival at 1 year and for the major molecular response rate.

A. Overall survival

Overall survival



B. Major molecular response

Major molecular response

