Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods 1: Search strategy

A. bosutinib

1. bosutinib [Title] (60)
   ⇒ search details:
Toshinib [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 "randomised controlled trial"[All Fields]
9. (#4) [and] "randomised trial" (0)
   ⇒ search details:
(#4) AND "randomised trial"[All Fields]
10. (#4) AND "randomised clinical trial" (0)
   ⇒ search details:
(#4) AND "randomised 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 clinical trial" )) (11)
6. ( TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomized controlled clinical 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 clinical trial" )) (1)
9. ( TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomised clinical 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 clinical trial") ))) OR ( ( 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 controlled clinical trial") ))) OR ( ( TITLE (ski606) OR TITLE (ski-606) OR TITLE (bosutinib) AND ALL ("randomised clinical trial") )))
ski-606) OR TITLE(bosutinib) AND ALL("randomized trial") ) ) ) OR ( ( TITLE(ski606) 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" [All Fields] (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 "randomised controlled trial"[All Fields]
9. (#4) [and] "randomised trial" (0)
   ⇒ search details:
   (#4) AND "randomised trial"[All Fields]
10. (#4) AND "randomised clinical trial" (1)
    ⇒ search details:
    (#4) AND "randomised 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)
• 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


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 controlled trial" ) ) ) OR ( 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 clinical 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 or « randomized controlled trial » (68)
5. #3 or « randomized trials » (68)
6. #3 or « randomized clinical trial » (68)
7. #3 or « randomised controlled trials » (68)
8. #3 or « randomised trial » (68)
9. #3 or « 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

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 "randomised controlled trial"[All Fields]
8. (#3) [and] "randomised trial" (0)
⇒ search details:
(#3) AND "randomised trial"[All Fields]
9. (#3) [and] "randomised clinical trial" (0)
⇒ search details:
(#3) AND "randomised 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 clinical trial")) OR (TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised controlled trial")) OR ((TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised controlled trial")) OR (TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised trial")) OR ((TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised clinical trial")) OR (TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised clinical trial")) OR (TITLE (ap24534) OR TITLE (ponatinib) AND ALL ("randomised 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
Basilic 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

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Experimental Dosage Admin frequency</th>
<th>Control Dosage Admin frequency</th>
<th>No. of pts</th>
<th>Populati on</th>
<th>Age (mean ± SD)</th>
<th>% male</th>
<th>Primary endpoint</th>
<th>Secondary endpoint(s)</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>BELA NCT005748 73</td>
<td>Randomized Open-label</td>
<td>bosutinib 500mg once daily</td>
<td>imatinib 400mg once daily</td>
<td>50 2 CP CML newly diagnose d</td>
<td>46.53 ± 14.62</td>
<td>56</td>
<td>CCyR at 12 months</td>
<td>MMR, MCR, CHR at 12 months</td>
<td>Safety Duration of response Pharmacokinetics Time to transformatio n to AP/BP</td>
<td>2</td>
</tr>
<tr>
<td>NCT000704 99</td>
<td>Randomized Open-label</td>
<td>dasatinib 100mg once daily</td>
<td>imatinib 400 or 800mg</td>
<td>39 1 CP CML untreated</td>
<td>50</td>
<td>61.40</td>
<td>MMR rate at 12 months</td>
<td>HR 2-year OS 2-year relapse-free survival Toxicity</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>START-R NCT001038 44</td>
<td>Randomized Open-label</td>
<td>dasatinib 70mg twice daily</td>
<td>imatinib 400mg twice daily</td>
<td>15 0 CP CML previousl y treated with imatinib</td>
<td>51 ± 13.6</td>
<td>50</td>
<td>MCR at 12 weeks</td>
<td>MCR at any time Duration of MCR CHR, CyR, MMR Duration of CHR AEs, SAEs, deaths QoL, PK</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>NCT003201 90</td>
<td>Randomized Open-label</td>
<td>dasatinib 100mg</td>
<td>imatinib 800mg</td>
<td>32 CP CML previously treated with imatinib</td>
<td>48.6 ± 14.8</td>
<td>71.90</td>
<td>MMR rate at 12 months</td>
<td>Deaths, AEs, SAEs Median time to treatment failure, to PFS Time to MMR CyR Safety</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>DASHION NCT004812 47</td>
<td>Randomized Open-label</td>
<td>dasatinib 100mg once daily</td>
<td>imatinib 800mg</td>
<td>51 9 CP CML newly diagnose d</td>
<td>46.7 ± 14.2</td>
<td>59.40</td>
<td>CyR rate by 12 months</td>
<td>Time to CCyR and MMR OS PFS MMR</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>NordCML00 6 NCT008525 66</td>
<td>Randomized Open-label</td>
<td>dasatinib 100mg once daily</td>
<td>imatinib 400mg once daily</td>
<td>46 CP CML newly diagnose d</td>
<td>dasatinib: 54</td>
<td>48</td>
<td>Proportion of Ph+ CD34+/CD 38- bone marrow cells at 6 months</td>
<td>Fraction of Ph+ cells at 1 and 3 months Molecular and cytogenetic responses at 3, 6, 12 and 18 months</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>ENESTnd NCT004714 97</td>
<td>Randomized Open-label</td>
<td>nilotinib 300mg twice daily nilotinib 400mg twice daily</td>
<td>imatinib 400mg once daily</td>
<td>84 6 CP CML newly diagnose d</td>
<td>nilotinib 300mg: 47</td>
<td>58</td>
<td>Rate of MMR at 12 months</td>
<td>Rate of durable MMR by 24 months Progression to AP/BP CyR Rate reduction in BCR-ABL transcript levels</td>
<td>3</td>
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<tr>
<td>ENESTcmr NCT007608 77</td>
<td>Randomized Open-label</td>
<td>nilotinib 400mg twice daily</td>
<td>imatinib 400 or 600mg once daily</td>
<td>20 7 CP CML previouls y treated with imatinib</td>
<td>nilotinib: 46</td>
<td>58</td>
<td>Rate of confirmed best cumulative CMR within the 1st year</td>
<td>Kinetics of CMR PFS, EFS and OS</td>
<td>2</td>
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</tr>
<tr>
<td>Study</td>
<td>Phase</td>
<td>Assignments</td>
<td>Results</td>
<td></td>
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<tr>
<td>RE-NICE NCT01400074</td>
<td>Randomized Open-label</td>
<td>Nilotinib 400mg twice daily, Imatinib 400mg twice daily</td>
<td>CML, early CP previously treated, 74.40% MMR rate at 12 months, Time and duration of MMR and CMR, Cumulative rate of MMR, CMR and MR4.0, PFS, Safety</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EPIC NCT01650805</td>
<td>Randomized Open-label</td>
<td>Ponatinib 45mg once daily, Imatinib 400mg once daily</td>
<td>CP, CML, newly diagnosed, 51.5 ± 15.4 1, 61.50% MMR rate at 12 months, Time to MR CCyR rate, Safety OS, PFS</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>
eFigure 2: Evaluation of publications bias

A. Vascular occlusive events
B. Overall survival
C. **Major molecular response**

![Funnel Plot of Standard Error by Log Peto odds ratio](image-url)
**eTable 2:** Rates of outcomes of interest across the included studies stratified by treatment

### A. Vascular occlusive events

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of events/total No. (%)</th>
<th>Fixed-effect model</th>
<th>Random-effect model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New generation TKI</td>
<td>imatinib</td>
<td>OR (_{PETO}) (95%CI)</td>
</tr>
<tr>
<td>NCT00574873 (BELA)</td>
<td>1/248 (1.21)</td>
<td>1/251 (0.40)</td>
<td>2.77 (0.39 – 19.77)</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>3/248 (1.21)</td>
<td>1/251 (0.40)</td>
<td>2.77 (0.39 – 19.77)</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>244/248 (96.39)</td>
<td>241/251 (96.02)</td>
<td>2.38 (0.82 – 6.89)</td>
</tr>
<tr>
<td>NCT0070499</td>
<td>123/123 (99.19)</td>
<td>123/123 (100.00)</td>
<td>0.14 (0.00 – 6.82)</td>
</tr>
<tr>
<td>NCT00481247 (DASISION)</td>
<td>250/258 (97.00)</td>
<td>255/258 (99.00)</td>
<td>0.36 (0.11 – 1.24)</td>
</tr>
<tr>
<td>NCT00852566 (NordML006)</td>
<td>22/22 (100.00)</td>
<td>23/24 (95.83)</td>
<td>0.80 (0.13 – 43.08)</td>
</tr>
<tr>
<td>NCT00471497 (ENESTnd)</td>
<td>103/104 (99.04)</td>
<td>103/104 (99.00)</td>
<td>2.12 (0.48 – 9.25)</td>
</tr>
<tr>
<td>NCT00760877 (ENESTcmr)†</td>
<td>602/607 (99.25)</td>
<td>382/380 (98.96)</td>
<td>1.51 (0.38 – 5.99)</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>154/155 (99.35)</td>
<td>150/152 (98.60)</td>
<td>2.00 (0.21 – 19.33)</td>
</tr>
<tr>
<td>Overall</td>
<td>1,454/1,473 (98.71)</td>
<td>1,170/1,194 (97.99)</td>
<td>1.23 (0.67 – 2.23)</td>
</tr>
</tbody>
</table>

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

### B. Overall survival

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of events*/total No. (%)</th>
<th>Fixed-effect model</th>
<th>Random-effect model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New generation TKI</td>
<td>imatinib</td>
<td>OR (_{PETO}) (95%CI)</td>
</tr>
<tr>
<td>NCT00574873 (BELA)</td>
<td>103/250 (41.00)</td>
<td>68/252 (27.00)</td>
<td>1.86 (1.29 – 2.70)</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>103/250 (41.00)</td>
<td>68/252 (27.00)</td>
<td>1.86 (1.29 – 2.70)</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>525/305 (44.30)</td>
<td>130/146 (28.51)</td>
<td>2.17 (1.66 – 2.83)</td>
</tr>
<tr>
<td>NCT00103844 (START-R)</td>
<td>29/101 (28.71)</td>
<td>6/49 (12.25)</td>
<td>2.50 (1.12 – 5.58)</td>
</tr>
<tr>
<td>NCT00481247 (DASISION)</td>
<td>119/259 (45.95)</td>
<td>73/260 (28.08)</td>
<td>2.15 (1.51 – 3.07)</td>
</tr>
<tr>
<td>NCT00852566 (NordML006)</td>
<td>16/22 (81.80)</td>
<td>11/14 (85.71)</td>
<td>4.33 (1.32 – 14.13)</td>
</tr>
<tr>
<td>NCT01650805 (EPIC)</td>
<td>8/10 (80.00)</td>
<td>5/13 (50.7)</td>
<td>4.95 (0.97 – 25.19)</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>8/10 (80.00)</td>
<td>5/13 (50.7)</td>
<td>4.95 (0.97 – 25.19)</td>
</tr>
<tr>
<td>Overall</td>
<td>607/1,374 (44.18)</td>
<td>288/1,053 (27.35)</td>
<td>2.22 (1.87 – 2.63)</td>
</tr>
</tbody>
</table>

### C. Major molecular response
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

Vascular occlusive events

<table>
<thead>
<tr>
<th>Study name</th>
<th>Treatment</th>
<th>Comparison</th>
<th>Statistics with study removed</th>
<th>Peto odds ratio (95%) CI with study removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00574873 - BIELA</td>
<td>bosutinib</td>
<td>imatinib</td>
<td>3.49 2.31 5.28 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT00570999</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>3.43 2.26 5.15 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT004320180</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>3.44 2.28 5.17 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT00481247 - DASSISON</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>3.59 2.39 5.40 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT00582566 - NordCML006</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>3.33 2.18 5.10 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT00547107 - ENESTnd</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>3.42 2.28 5.14 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT007060877 - ENESTerr</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>3.68 1.96 6.91 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT01650805 - EPIC</td>
<td>ponatinib</td>
<td>imatinib</td>
<td>3.39 2.22 5.16 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT01609085 - EPIC</td>
<td>ponatinib</td>
<td>imatinib</td>
<td>3.45 2.22 5.36 0.000</td>
<td></td>
</tr>
</tbody>
</table>

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

Vascular occlusive events

<table>
<thead>
<tr>
<th>Study name</th>
<th>Treatment</th>
<th>Comparison</th>
<th>Statistics with study removed</th>
<th>Peto odds ratio (95%) CI with study removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT004320180</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>3.66 1.21 11.07 0.021</td>
<td></td>
</tr>
<tr>
<td>NCT030305344 - START-R</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>3.78 1.21 11.81 0.022</td>
<td></td>
</tr>
<tr>
<td>NCT00481247 - DASSISON</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>3.17 1.71 15.8 0.004</td>
<td></td>
</tr>
<tr>
<td>NCT00582566 - NordCML006</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>2.50 0.41 15.24 0.319</td>
<td></td>
</tr>
<tr>
<td>NCT00547107 - ENESTnd</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>3.64 1.20 10.99 0.022</td>
<td></td>
</tr>
<tr>
<td>NCT007060877 - ENESTerr</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>3.86 1.33 11.18 0.013</td>
<td></td>
</tr>
</tbody>
</table>

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

Vascular occlusive events

<table>
<thead>
<tr>
<th>Study name</th>
<th>Treatment</th>
<th>Comparison</th>
<th>Statistics with study removed</th>
<th>Peto odds ratio (95%) CI with study removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00471497 - ENESTnd</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>4.45 0.99 20.02 0.052</td>
<td></td>
</tr>
<tr>
<td>NCT007060877 - ENESTerr</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>3.31 1.95 5.61 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT007060877</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>3.42 2.07 5.63 0.000</td>
<td></td>
</tr>
</tbody>
</table>
**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

<table>
<thead>
<tr>
<th>Study name</th>
<th>Treatment</th>
<th>Comparison</th>
<th>Statistics with study removed</th>
<th>Peto odds ratio (95% CI) with study removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00574873 - BELA</td>
<td>bosutinib</td>
<td>imatinib</td>
<td>0.80 0.36 1.82 0.600</td>
<td></td>
</tr>
<tr>
<td>NCT00070499</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>1.28 0.66 2.46 0.463</td>
<td></td>
</tr>
<tr>
<td>NCT00481247 - DASISION</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>1.90 0.89 4.06 0.098</td>
<td></td>
</tr>
<tr>
<td>NCT00802566 - NonCML006</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>1.15 0.60 2.21 0.684</td>
<td></td>
</tr>
<tr>
<td>NCT00471497 - ENESTnd</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>1.05 0.51 2.16 0.891</td>
<td></td>
</tr>
<tr>
<td>NCT00760877 - ENESTcmr</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>1.28 0.66 2.46 0.463</td>
<td></td>
</tr>
<tr>
<td>NCT01650805 - EPIC</td>
<td>ponatinib</td>
<td>imatinib</td>
<td>1.15 0.59 2.26 0.684</td>
<td></td>
</tr>
</tbody>
</table>

#### B. Major molecular response

<table>
<thead>
<tr>
<th>Study name</th>
<th>Treatment</th>
<th>Comparison</th>
<th>Statistics with study removed</th>
<th>Peto odds ratio (95% CI) with study removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00574873 - BELA</td>
<td>bosutinib</td>
<td>imatinib</td>
<td>2.32 1.92 2.81 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT00070499</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>2.27 1.89 2.72 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT00103844 - START-R</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>2.20 1.85 2.62 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT00481247 - DASISION</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>2.24 1.84 2.72 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT00802566 - NonCML006</td>
<td>dasatinib</td>
<td>imatinib</td>
<td>2.19 1.84 2.60 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT01400074 - RE-NICE</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>2.24 1.89 2.67 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT00471497 - ENESTnd</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>2.09 1.70 2.58 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT00760877 - ENESTcmr</td>
<td>nilotinib</td>
<td>imatinib</td>
<td>2.19 1.84 2.60 0.000</td>
<td></td>
</tr>
<tr>
<td>NCT01650805 - EPIC</td>
<td>ponatinib</td>
<td>imatinib</td>
<td>2.20 1.85 2.61 0.000</td>
<td></td>
</tr>
</tbody>
</table>