Dasatinib Efficacy in Patients with CML in Chronic Phase (CML-CP) and Pre-existing BCR-ABL Mutations

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Dasatinib efficacy by baseline BCR-ABL mutation

Background

● Dasatinib (SPRYCEL®) is a potent Bcr-Abl inhibitor
  – 325-fold more potent than imatinib and 16-fold more potent than nilotinib in vitro against unmutated Bcr-Abl

● In a series of phase II and III trials in >2,000 patients, dasatinib has demonstrated durable efficacy in CML patients following resistance, suboptimal response, or intolerance to prior imatinib

● BCR-ABL mutations are associated with imatinib resistance and suboptimal response

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3 Kantarjian et al. ASH 2008 (abstract 3224)
4 Shah et al. ASH 2008 (abstract 3225)
5 Saglio et al. ASH 2008 (abstract 3226)
Objective of the present analysis

- To determine the efficacy of dasatinib in CML-CP patients with or without \textit{BCR-ABL} mutations following prior imatinib treatment
Dasatinib efficacy by baseline BCR-ABL mutation

Methods

- Pooled analysis of >1,000 patients treated with dasatinib during phase II/III trials in CML-CP

- BCR-ABL kinase domain point mutations were detected in baseline peripheral blood cell mRNA using RT-PCR and direct sequencing
  - known single nucleotide polymorphisms (T240T, K247R, F311V, E499E) were not considered as mutations

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Dasatinib efficacy by baseline *BCR-ABL* mutation

## Patients and treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease phase</th>
<th>Eligibility following imatinib treatment</th>
<th>Dasatinib treatment</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA180-013 (START-C)(^1)</td>
<td>CML-CP</td>
<td>Resistance or intolerance</td>
<td>70 mg BID</td>
<td>387</td>
</tr>
<tr>
<td>CA180-017 (START-R)(^2)</td>
<td>CML-CP</td>
<td>Resistance</td>
<td>70 mg BID</td>
<td>101</td>
</tr>
<tr>
<td>CA180-034(^3)</td>
<td>CML-CP</td>
<td>Resistance, suboptimal response, or intolerance</td>
<td>100 mg once daily</td>
<td>165</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70 mg BID</td>
<td>167</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>140 mg once daily</td>
<td>163</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 mg BID</td>
<td>167</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>1,150</td>
</tr>
</tbody>
</table>

Minimum follow-up 24 months in all 3 studies (last patient first visit to database lock)

\(^1\)Hochhaus et al. Leukemia 2008;22:1200–6


\(^3\)Shah et al. J Clin Oncol 2008;26:3204–12
## Baseline characteristics and dasatinib dose

<table>
<thead>
<tr>
<th></th>
<th>Total (N=1,043)</th>
<th>Resistant/ Suboptimal response (n=805)</th>
<th>Intolerant (n=238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of CML (months)</td>
<td>58</td>
<td>68</td>
<td>24</td>
</tr>
<tr>
<td>Prior imatinib therapy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;600 mg/day</td>
<td>38</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>Duration &gt;3 years</td>
<td>45</td>
<td>55</td>
<td>13</td>
</tr>
<tr>
<td>MCyR on prior imatinib (%)</td>
<td>37</td>
<td>36</td>
<td>41</td>
</tr>
<tr>
<td>Other prior therapy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-α</td>
<td>59</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>Stem cell transplantation</td>
<td>7</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Dasatinib dose (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg once daily</td>
<td>14</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>70 mg BID</td>
<td>58</td>
<td>59</td>
<td>56</td>
</tr>
<tr>
<td>140 mg once daily</td>
<td>13</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>50 mg BID</td>
<td>14</td>
<td>14</td>
<td>15</td>
</tr>
</tbody>
</table>
Dasatinib efficacy by baseline *BCR-ABL* mutation

**Baseline *BCR-ABL* mutational status**

- Of 1,150 patients with CML-CP who received dasatinib, 1,043 had a mutational assessment prior to treatment.

- 480 baseline *BCR-ABL* mutations were identified.

- 402 patients (39%) had a baseline *BCR-ABL* mutation:
  - 48% of patients with resistance or suboptimal response to imatinib (n=805)
  - 8% of patients with intolerance to imatinib (n=238)

- Excluding known polymorphisms, 64 different *BCR-ABL* mutations were detected, affecting 49 amino acids.
  - 64 patients had ≥2 different *BCR-ABL* mutations detected simultaneously at baseline.

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Dasatinib efficacy by baseline BCR-ABL mutation

Patients with resistance or suboptimal response to imatinib: Dasatinib response rates after ≥24 months

Overall MMR rate in patients with samples available
MMR = BCR-ABL ratio ≤0.1% on the international scale by RQ-PCR
Dasatinib efficacy by baseline *BCR-ABL* mutation

Patients with resistance or suboptimal response to imatinib: Time to MCyR

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**No mutation (all doses)**

**Any mutation (all doses)**

**No mutation (100 mg once daily)**

**Any mutation (100 mg once daily)**

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Dasatinib efficacy by baseline *BCR-ABL* mutation

Patients with resistance or suboptimal response to imatinib: Duration of CCyR

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Patients without loss of CCyR at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mutation (all doses)</td>
<td>196</td>
<td>95%</td>
</tr>
<tr>
<td>Any mutation (all doses)</td>
<td>164</td>
<td>95%</td>
</tr>
<tr>
<td>No mutation (100 mg once daily)</td>
<td>30</td>
<td>96%</td>
</tr>
<tr>
<td>Any mutation (100 mg once daily)</td>
<td>20</td>
<td>95%</td>
</tr>
</tbody>
</table>
Dasatinib efficacy by baseline BCR-ABL mutation

Patients with resistance or suboptimal response to imatinib: Progression-free survival

<table>
<thead>
<tr>
<th></th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mutation (all doses)</td>
<td>91%</td>
<td>80%</td>
</tr>
<tr>
<td>Any mutation (all doses)</td>
<td>82%</td>
<td>70%</td>
</tr>
<tr>
<td>No mutation (100 mg once daily)</td>
<td>94%</td>
<td>75%</td>
</tr>
<tr>
<td>Any mutation (100 mg once daily)</td>
<td>77%</td>
<td>75%</td>
</tr>
</tbody>
</table>
Dasatinib efficacy by baseline BCR-ABL mutation

Patients with resistance or suboptimal response to imatinib:
Overall survival

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mutation</td>
<td>369</td>
<td>97%</td>
<td>92%</td>
</tr>
<tr>
<td>Any mutation</td>
<td>343</td>
<td>93%</td>
<td>88%</td>
</tr>
<tr>
<td>No mutation (100 mg once daily)</td>
<td>66</td>
<td>96%</td>
<td>88%</td>
</tr>
<tr>
<td>Any mutation (100 mg once daily)</td>
<td>46</td>
<td>91%</td>
<td>89%</td>
</tr>
</tbody>
</table>

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Dasatinib efficacy by baseline BCR-ABL mutation

Response to dasatinib in patients with common baseline BCR-ABL mutations

P-loop residues 248–256

Includes 375 (78%) of 480 BCR-ABL mutations detected
Dasatinib efficacy by baseline BCR-ABL mutation

Frequency of baseline BCR-ABL mutations by in vitro IC\textsubscript{50} to dasatinib

- No BCR-ABL mutation (n=641) - 61%
- IC\textsubscript{50} ≤ 3 nM (n=254)
- IC\textsubscript{50} > 200 nM (n=21)
- IC\textsubscript{50} > 3 nM (n=44)
  - T315I (n=64)
  - Q252H (n=1)
  - F317L (n=14)
  - E255K/V (n=25)

Unknown IC\textsubscript{50} to dasatinib (n=83)
- 43 different BCR-ABL mutations
- 24%
- 8%
- 1%
- <1%
- 2%

64 patients had ≥2 BCR-ABL mutations at baseline

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Dasatinib efficacy by baseline BCR-ABL mutation

**Frequency of baseline BCR-ABL mutations by in vitro IC\(_{50}\) to dasatinib**

**Patients with resistance or suboptimal response to imatinib**

- **No BCR-ABL mutation** (n=421) - 52%
  - Unknown IC\(_{50}\) to dasatinib (n=74)
  - 38 different BCR-ABL mutations
  - IC\(_{50}\) ≤3 nM (n=248)
  - IC\(_{50}\) >3 nM (n=42)
    - 5%
    - T315I (n=20)
      - IC\(_{50}\) >200 nM
    - E255K/V (n=25)
    - F317L (n=13)
    - Q252H (n=6)
    - <1% V299L (n=1)

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Dasatinib efficacy by baseline BCR-ABL mutation

Response rates by individual mutation in vitro IC$_{50}$ to dasatinib (excluding T315I)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>CHR</th>
<th>MCyR</th>
<th>CCyR</th>
<th>MMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>96</td>
<td>73</td>
<td>54</td>
<td>43</td>
</tr>
<tr>
<td>≤3 nM</td>
<td>94</td>
<td>58</td>
<td>47</td>
<td>34</td>
</tr>
<tr>
<td>&gt;3 nM</td>
<td>82</td>
<td>34</td>
<td>25</td>
<td>18</td>
</tr>
</tbody>
</table>

IC$_{50}$ to dasatinib
- Unknown (n=83)
- ≤3 nM (n=254)
- >3 nM (n=44)

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Dasatinib efficacy by baseline *BCR-ABL* mutation

**New *BCR-ABL* mutations arising during dasatinib therapy**

- Among 1,043 patients analyzed, 174 had a mutational assessment at the time of dasatinib discontinuation.

- In these 174 patients, 54 new mutations occurred in 47 patients:
  - 7 patients developed more than 1 new mutation
  - 42 patients had new mutations with an IC$_{50}$ to dasatinib >3 nM

<table>
<thead>
<tr>
<th>Mutation</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>M244V</td>
<td>1</td>
</tr>
<tr>
<td>Q252H</td>
<td>1</td>
</tr>
<tr>
<td>E255K</td>
<td>3</td>
</tr>
<tr>
<td>V299L</td>
<td>7</td>
</tr>
<tr>
<td>F311L</td>
<td>1</td>
</tr>
<tr>
<td>T315I</td>
<td>25</td>
</tr>
<tr>
<td>F317I</td>
<td>1</td>
</tr>
<tr>
<td>F317L</td>
<td>10</td>
</tr>
<tr>
<td>M351T</td>
<td>3</td>
</tr>
<tr>
<td>F359V</td>
<td>1</td>
</tr>
<tr>
<td>V379I</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>54</strong></td>
</tr>
</tbody>
</table>
Dasatinib efficacy by baseline *BCR-ABL* mutation

### Participating centers

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- P Erben, Germany
- B Hanfstein, Germany
- T Schenck, Germany

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Conclusions

- In 1,043 CML-CP patients, dasatinib had high rates of durable responses in patients with or without BCR-ABL mutations.

- Even in patients who had rarely occurring baseline mutations with a dasatinib IC$_{50}$ of >3 nM, CCyRs and MMRs were observed after dasatinib treatment.

- Efficacy of dasatinib 100 mg once daily in patients with baseline mutations was similar to other doses, including 70 mg BID.

- In a phase III dose-optimization study, dasatinib 100 mg once daily (dose in CML-CP) had similar efficacy and significantly minimized key side effects compared with other dosing schedules following resistance, suboptimal response, or intolerance to prior imatinib$^{1,2}$

$^2$Shah et al. ASH 2008 (abstract 3225)