The Use of Imatinib Mesylate (Gleevec™) in Patients with Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia


Report Date: September 29, 2008

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The 2008 guideline recommendations were put in the Education and Information section

This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes.

SUMMARY

QUESTIONS
Does treatment with imatinib mesylate (imatinib) in patients with newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) or relapsed/refractory imatinib/dasatinib naïve Ph+ ALL affect overall survival, progression free survival, response, quality of life, and adverse events?

TARGET POPULATION
Adult patients with newly diagnosed or relapsed or refractory imatinib/dasatinib-naive Ph+ ALL.

RECOMMENDATIONS
- The opinion of the authors is that imatinib is recommended for all patients with imatinib/dasatinib-naive Ph+ ALL, to be administered as part of remission induction therapy.

Key Evidence
⇒ A single randomized trial that reported much higher complete remission rates for patients receiving induction with imatinib alone compared to induction with chemotherapy (96.3% versus [vs.] 50.0%, respectively; p=0.0001) (1).
• A number of comparative phase II studies reported improvements in complete remission rate, disease-free survival, relapse-free survival or overall survival when imatinib was combined with chemotherapy compared with chemotherapy alone (8,10, 11, 13, 14).

• The opinion of the authors is that patients who are unsuitable to receive intensive chemotherapy may achieve remission when imatinib is combined with prednisone alone or with non-intensive chemotherapy.

**Key Evidence**

⇒ One non-comparative phase II trial reported a complete remission rate of 96.7% for 29 elderly patients that received imatinib and prednisone alone (2).

⇒ Another non-comparative phase II trial reported a complete remission rate of 100% for 10 elderly patients that received imatinib, prednisone and vincristine (3).

**Qualifying Statements**

• There is insufficient evidence to recommend a specific dose and schedule of imatinib. Published studies have used imatinib 400-800 mg/d until the end of the treatment program (1-3).

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REFERENCES—SUMMARY


I. QUESTIONS

- Does treatment with imatinib mesylate (imatinib) in patients with newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) affect overall survival, progression free survival, response, quality of life, and adverse events? In the context of acute leukemia, the best measure of response is the rate of complete remission.

- Does treatment with imatinib in patients with relapsed or refractory Ph+ ALL affect overall survival, progression free survival, response, quality of life, and adverse events? In the context of acute leukemia, the best measure of response is the rate of complete remission.

II. CHOICE OF TOPIC AND RATIONALE

Acute lymphoblastic leukemia (ALL) is a rare cancer that, in the United States, had an age-adjusted incidence rate of 1.6 per 100,000 men and women per year from 2001-2005 (1). While the survival rate is high for children, most of whom are likely cured, the corresponding results for adults are poor. One of the reasons for the poorer outcome in adults is the higher prevalence of Philadelphia chromosome, a well-established indicator of adverse prognosis.

In a large recently completed United Kingdom/United States (UK/US) trial on adults with newly diagnosed ALL, aged 15-64, the percentage of Philadelphia chromosome-positive cases was 19% (267/1373), and the prevalence increased with age, from 4% in the 15-19 years age group to 26% in those over 50 years of age (2). The trial did not include patients over 64 years of age in whom the prevalence of Philadelphia chromosome is likely to be even higher. In this trial the overall survival at five years in patients having Philadelphia chromosome was significantly worse than that of patients without Philadelphia chromosome (43% vs. 22%, statistics not given) (3).

Imatinib is an inhibitor of the BCR-ABL tyrosine kinase (4,5). It has shown efficacy in patients with Ph+ chronic myeloid leukemia (CML). An early trial of imatinib for CML included a small number of patients with Ph+ ALL in the subgroups with blast crisis CML (6). That trial indicated that imatinib is an active agent in Ph+ ALL. Given the rarity of ALL, the even greater rarity of Ph+ ALL, and the fact that tyrosine kinase inhibitor therapy is now included as standard therapy, it is doubtful that a randomized trial of sufficient size will be conducted to determine the effect of imatinib on survival in this patient population.

III. METHODS

This advice report, produced by the Program in Evidence-based Care (PEBC), is a convenient and up-to-date source of the best available evidence on the role of imatinib in the treatment of adult patients with Ph+ ALL, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

A systematic search of the published literature identified all reports relating to the use of imatinib for the treatment of patients with Ph+ ALL. The MEDLINE (1996 to July Week 2, 2008 [July 16]), EMBASE (1996 to 2008, Week 29 [July 16]), and the Cochrane Database of
Systematic Reviews and Cochrane Central Register of Controlled Trials (2008, Issue 3) databases were searched according to the strategies in Appendix A. Abstracts from the American Society of Clinical Oncology (ASCO) (2000-2008) and the American Society of Hematology (ASH) (2000-2007) annual conference proceedings were searched. The National Cancer Institute (NCI) Clinical Trials Register and the United States National Institutes of Health (NIH) Clinical Trials databases were searched to identify ongoing clinical trials, and the National Guidelines Clearinghouse and the CMA Infobase were searched for clinical practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers (IW and AH), and the reference lists from those sources were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review if they met the following criteria:
1. Studies were systematic reviews, meta-analyses, or evidence-based practice guidelines that assessed the use of imatinib in patients with Ph+ ALL.
2. Studies were prospective, randomized phase II or III clinical trials assessing the use of imatinib in patients with Ph+ ALL.
3. Studies were non-randomized, prospective phase II clinical trials.
4. Results were reported for any of the following outcomes of interest: overall survival, progression-free survival, response, quality of life, and adverse events.
5. In studies where patients with a disease other than Ph+ ALL were included (e.g., chronic myelogenous leukemia), results must have been reported separately for the group of patients with Ph+ ALL.

Exclusion Criteria

1. Reports published in a language other than English.
2. Letters, editorials, notes, comments, and books.

Synthesizing the Evidence

The authors will conduct a meta-analysis of the results of the identified trials if the design and quality of these trials are appropriate.

IV. RESULTS

Literature Search Results

A total of 139 citations were retrieved from the MEDLINE, EMBASE, and the Cochrane Library databases. Sixteen citations met the inclusion criteria. In addition, 40 abstracts from the annual conference proceedings of ASCO and ASH were identified that met the inclusion criteria. Many of the identified abstracts were of trials that have since been fully published or for which more up-to-date abstracts were available. Only the full publication or most up-to-date abstract has been referenced for each trial. One randomized controlled trial comparing induction therapy with imatinib to age-adapted chemotherapy in patients with newly diagnosed Ph+ ALL was identified (7). In addition, 19 non-randomized clinical trials of imatinib in patients with Ph+ ALL were identified (8-28). No systematic reviews or evidence-based practice guidelines of imatinib in Ph+ ALL were identified.

Trial Quality

One RCT was identified that randomized 55 patients aged >55 years with newly diagnosed Ph+ ALL to remission induction therapy with imatinib (600 mg/day) or to age-adjusted multi-agent chemotherapy (Appendix B) after a short five-day pre-phase period during which all patients received chemotherapy (7). Patients who completed remission
induction therapy, regardless of patient remission status, received up to five cycles of consolidation therapy with imatinib (600 mg/day) and chemotherapy (Appendix B). The primary endpoint of the study was hematologic response rate after remission induction. The authors did not report a sample size requirement; therefore, it is unknown whether that requirement was met. The randomization method, blinding, allocation concealment, and losses to follow-up were not reported. The analysis was intention-to-treat and final. The study received ethics approval.

Nineteen studies were prospective single-arm phase II clinical trials (8-28), of which seven compared the results of enrolled patients to a control group (8-14). Six trials treated patients with Ph+ ALL with imatinib (in induction and/or consolidation/salvage and/or maintenance) and compared the results to a historical control group that did not receive imatinib (8-11,13,14). One trial compared sequential cohorts of patients that received different schedules of imatinib (12). The reported method of analysis in each study was variable. None of the trials reported whether the patients in the treatment group were matched to similar patients in the control group. Three studies reported on similarities and differences for summary statistics of pre-treatment patient characteristics between the treatment and control group (9,11,13). Those included, but are not limited to, factors such as age, gender, hemoglobin, platelets, and central nervous system (CNS) involvement (9,11,13).

The 11 remaining phase II trials were single-arm non-comparative studies (15-28).

Trial Characteristics

Randomized Trials

The randomized trial (7) compared induction imatinib (n=28) to induction chemotherapy without imatinib (n=27) in patients with newly diagnosed Ph+ ALL (Table 1). Both arms received consolidation that included imatinib. The median age was similar in both arms (66 years vs. 68 years, respectively). The full details of the treatment regimen can be found in Appendix B.

Non-randomized comparative phase II trials

Five trials enrolled patients with only newly diagnosed Ph+ ALL (10-14), one trial enrolled newly diagnosed patients as well as those with minimally-treated Ph+ ALL (8), and one trial included patients with newly diagnosed or previously treated Ph+ ALL (9). The treatment regimens used were varied between the trials (Appendix B). Imatinib was added to induction and/or consolidation/salvage and/or maintenance. Most trials either treated patients with stem cell transplantation (SCT) after consolidation or did not report on the use of SCT (Table 1). The largest trial enrolled 153 patients and compared the results with 267 historical patients (9). The remaining trials enrolled 20 to 54 patients. The treatment details for the historical control group in the trial reported by de Labarthe et al (10) were reported by Dombret et al (29).

Non-comparative phase II trials

Twelve non-comparative phase II trials were identified (15-28). The trials enrolled patients with either newly diagnosed or relapsed/refractory Ph+ ALL, or both (Appendix C1). The full regimen details for these trials can be found in Appendix B. The majority of trials treated patients with imatinib added to induction therapy (16-28). Imatinib was also administered either prior to or following SCT (15,18,19,23,25,27,28). The trials ranged in size from 10 patients to 68 patients, with the median age ranging from 41.5 years to 69 years in seven trials (Appendix C1).
Table 1. Patient and trial characteristics of comparative trials examining imatinib in Ph+ ALL.

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Patient characteristics</th>
<th>Interventiona</th>
<th>N</th>
<th>Age, mdn (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ottmann, 2007 (7)</td>
<td>Newly diagnosed Ph+ ALL or Ph+ CML in first lymphoid or bilineage BP, age &gt; 55 years, not a candidate for allogeneic SCT, WHO PS ≤2, no prior tx except prephase chemo</td>
<td>induction: imatinib → consolidation: imatinib + chemo</td>
<td>28</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>induction: chemo → consolidation: imatinib + chemo</td>
<td>27</td>
<td>68</td>
</tr>
<tr>
<td><strong>Non-randomized comparative phase II trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomas, 2008 (8) abs</td>
<td>Newly diagnosed or minimally-treated Ph+ ALL</td>
<td>Imatinib + hyper-CVAD</td>
<td>54</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyper-CVAD</td>
<td>48</td>
<td>NR</td>
</tr>
<tr>
<td>Fielding, 2007 (9) abs</td>
<td>Ph+ ALL</td>
<td>Induction chemo → imatinib consolidation imatinib → allogeneic SCT → imatinib</td>
<td>153b</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction → allogeneic SCT</td>
<td>267</td>
<td>40</td>
</tr>
<tr>
<td>de Labarthe, 2007 (10)</td>
<td>Newly diagnosed Ph+ ALL, age 15-59 years</td>
<td>Prephase chemo → variable induction + imatinib → consolidation + imatinib</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No imatinib - details NR</td>
<td>198</td>
<td>NR</td>
</tr>
<tr>
<td>Delannoy, 2006 (11)</td>
<td>Newly diagnosed Ph+ ALL, age ≥55 years</td>
<td>Induction chemo → consolidation/salvage → maintenance for patients with CR—2 with imatinib</td>
<td>30</td>
<td>65.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction → consolidation/salvage → maintenance</td>
<td>21</td>
<td>61.3</td>
</tr>
<tr>
<td>Wassmann, 2006 (12)</td>
<td>Newly diagnosed Ph+ ALL or CML lymphoid blast crisis, age &gt;18 years, ECOG PS 0-2. Patients enrolled in the alternating imatinib schedule had achieved CR for 25d.</td>
<td>Alternating imatinib: prephase chemo → induction → imatinib consolidation chemo → imatinib → SCT</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent imatinib: prephase chemo → induction chemo + imatinib → consolidation + imatinib → SCT</td>
<td>45</td>
<td>41</td>
</tr>
<tr>
<td>Lee, 2005 (13)</td>
<td>Newly diagnosed Ph+ ALL, age &lt;60 years, ECOG PS 0-2,</td>
<td>Induction Hyper-CVAD → imatinib → consolidation/salvage chemo → imatinib → SCT (patients in CR) or salvage chemo (patients not in CR)</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction (ida/vinc/pred/asparginase) → consolidation/salvage chemo → SCT</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Lee, 2005 (14)</td>
<td>Newly diagnosed Ph+ ALL, age ≥15 years, Karnofsky PS ≥70</td>
<td>Induction chemo + imatinib → consolidation + imatinib → maintenance imatinib</td>
<td>20</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction chemo → consolidation</td>
<td>18</td>
<td>44</td>
</tr>
</tbody>
</table>

Notes: abs=abstract; ALL=acute lymphoblastic leukemia; BP=blast phase; chemo=chemotherapy; CML=chronic myeloid leukemia; CR=complete remission; CVAD=cyclophosphamide, vincristine, doxorubicin, dexamethasone; d=day(s); ECOG=Eastern Cooperative Oncology Group; ida=idarubicin; N=number of patients; Ph+=Philadelphia chromosome-positive; pred=prednisone; PS=performance status; ref=reference; SCT=stem cell transplantation; tx=treatment; vinc=vincristine; WHO=World Health Organization; yr=year(s).

aFull regimen details including dose and schedule information can be found in Appendix B.
bEighty-nine patients received imatinib following induction; after an amendment in 2005, 64 patients received imatinib with the second phase of induction in addition.
Results

Survival and response

Randomized trials

The randomized trial (7) reported no significant differences in overall survival (OS) or disease-free survival (DFS) for patients that received imatinib induction compared to chemotherapy induction after a median follow-up of 11.2 months (Table 2). The complete remission (CR) rate after induction therapy was significantly higher for imatinib induction compared to chemotherapy induction (96.3% vs. 50.0%; p=0.0001). The CR rate after consolidation therapy was 100% vs. 85.2%, respectively (p=not reported).

Non-randomized comparative phase II trials

The results of the non-randomized comparative phase II trials can be found in Table 2. Three trials reported comparisons between summary statistics for certain pre-treatment patient characteristics but did not report whether treatment patients were matched to a control (9,11,13). Fielding et al reported no significant differences in OS or CR after induction (9). Lee et al (13) reported a significant difference in OS for imatinib compared to no imatinib (median 29.4 months vs. 12.8 months; p=0.019). Delannoy et al (11) reported significant differences in relapse-free survival (RFS) for imatinib vs. no imatinib (median 20.1 months vs. 4.2 months; p=0.0003). Complete remission rate was significantly higher for imatinib after induction (70% vs. 28.5%, respectively; p=0.003) and after consolidation/salvage (90% vs. 48%; p=0.001).

The remaining trials did not report whether pre-treatment differences existed between the treatment and historical control groups, nor did they report on how the groups were compared (8,10,14). Two trials (8,10) reported significantly higher OS and DFS for imatinib compared to no imatinib (Table 2). One of those trials also reported a significant difference in CR after induction for patients that received imatinib (10).

Another trial compared an alternating schedule of imatinib to a concurrent schedule (12). No significant differences in OS or RFS were identified (Table 2).

Non-comparative phase II trials

The results for the non-comparative phase II trials of imatinib can be found in Appendix C2. Complete remission after induction was reported in eight trials and ranged from 30% to 100% of patients (Appendix C2). Overall survival was reported in five trials (16-23) and ranged from 13.3 months (follow-up not reported) to 29.9 months (follow-up median 18 months). Median disease-free survival was reported in two trials and was eight months (follow-up median five months) and 9.9 months (follow-up not reported) (17,28). One trial reported a complete remission rate of 96.7% in 29 patients that received imatinib in combination with prednisone, without chemotherapy or with palliative chemotherapy (16).

Adverse events

The incidence of adverse events for each of the comparative trials can be found in Table 3. In the randomized trial (7), the rates of grade 3/4 non-hematological adverse events were significantly higher among patients that received induction chemotherapy compared to induction with imatinib (86% vs. 39%; p=0.005). Grade 3/4 nausea/vomiting (7.1% vs. 3.7%) and grade 3/4 diarrhea (3.6% vs. 0) were more common in the imatinib arm; however, the authors did not report whether those differences were significant (7).

None of the non-randomized comparative phase II trials reported the rates of adverse events for the control groups, and four trials did not report any adverse event data, for either arm (8,9,12,14). Delannoy et al (11) reported that 30% of 30 patients experienced a grade 3/4 non-hematological adverse event. Two studies reported that 10% of patients experienced grade 3/4 nausea/vomiting (10,13); however, in one study no patients experienced grade 3/4
nausea/vomiting (11). Lee et al (13) also reported that 50% of 20 patients experienced febrile neutropenia and that all patients experienced grade 3/4 neutropenia.

The non-comparative phase II trials of imatinib in patients with Ph+ ALL can be found in Appendix C3. Most trials reported very little data for adverse events. Grade 3/4 nausea/vomiting was the most commonly reported adverse event, occurring in 3.3% of 30 patients to 17% of 24 patients in three trials (16-19). One of those trials also reported that grade 3/4 diarrhea occurred in 4% of 24 patients (18,19). Grade 3/4 non-hematological adverse events were reported in two trials and occurred in 43.3% of 30 patients and in 5.6% of 54 patients (16,23). One trial reported that 50% of 22 patients experienced a grade 3/4 adverse event (15). Grade 3/4 neutropenia occurred in 50% of 68 patients in one trial (20-22). In a different trial, 26% of 24 patients experienced neutropenic fever (18,19).
### Table 2. Efficacy outcomes of comparative trials examining imatinib in Ph+ ALL.

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Intervention</th>
<th>N</th>
<th>OS</th>
<th>DFS/PFS/RFS</th>
<th>CR after induction (%)</th>
<th>CR after induction with PB recovery (%)</th>
<th>CR after consolidation/salvage (%)</th>
<th>Follow-up mdn (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ottmann, 2007 (7)</td>
<td>Induction: imatinib → consolidation: imatinib + chemo</td>
<td>28</td>
<td></td>
<td>Mdn (mos)</td>
<td>Mdn DFS (mos)</td>
<td>96.3(^a)</td>
<td>85.2(^a)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Induction: chemo → consolidation: imatinib + chemo</td>
<td>27</td>
<td></td>
<td>12.3</td>
<td>14.5</td>
<td>50.0(^c)</td>
<td>23.1(^a)</td>
<td>85.2</td>
</tr>
<tr>
<td>Fielding, 2007 (9)</td>
<td>Induction chemo + imatinib → consolidation imatinib → allogeneic SCT → imatinib</td>
<td>153(^b)</td>
<td></td>
<td>Mdn (mos)</td>
<td>Mdn RFS (mos)</td>
<td>77.8</td>
<td>1.9</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Induction → allogeneic SCT</td>
<td>267</td>
<td></td>
<td>26</td>
<td>NR</td>
<td>83</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>de Labarthe, 2007 (10)</td>
<td>Prephase chemo → variable induction + imatinib → consolidation + imatinib</td>
<td>45</td>
<td></td>
<td>Mdn (mos)</td>
<td>Mdn RFS (mos)</td>
<td>96</td>
<td>NR</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>No imatinib - details NR</td>
<td>198</td>
<td></td>
<td>39</td>
<td>31</td>
<td>71</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Delannoy, 2006 (11)</td>
<td>Induction chemo → consolidation/salvage + imatinib → 10 blocks of maintenance (for patients with CR) → 2 with imatinib</td>
<td>30</td>
<td></td>
<td>Mdn (mos)</td>
<td>Mdn RFS (mos)</td>
<td>70</td>
<td>NR</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Induction → consolidation/salvage → maintenance</td>
<td>21</td>
<td></td>
<td>11.2</td>
<td>4.2</td>
<td>28.5</td>
<td>NR</td>
<td>48</td>
</tr>
<tr>
<td>Wassmann, 2006 (12)</td>
<td>Alternating imatinib: prephase chemo → induction → imatinib → consolidation chemo → imatinib → SCT</td>
<td>47</td>
<td></td>
<td>Mdn (mos)</td>
<td>RFS 2-yr (%)</td>
<td>94</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Concurrent imatinib: prephase chemo → induction chemo + imatinib→ consolidation + imatinib → SCT</td>
<td>45</td>
<td></td>
<td>Mdn (mos)</td>
<td>RFS 2-yr (%)</td>
<td>96</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lee, 2005 (13)</td>
<td>Induction Hyper-CVAD → imatinib → consolidation/salvage chemo → imatinib → SCT (patients in CR) or salvage chemo (patients not in CR)</td>
<td>29</td>
<td></td>
<td>Mdn (mos)</td>
<td>Mdn RFS (mos)</td>
<td>79.3</td>
<td>NR</td>
<td>Salvage 50 (3/6)</td>
</tr>
<tr>
<td></td>
<td>Induction (ida/vinc/pred/asparaginase) → consolidation/salvage chemo → SCT</td>
<td>33</td>
<td></td>
<td>11.6</td>
<td>11.6</td>
<td>81.8</td>
<td>NR</td>
<td>16.7 (1/6)</td>
</tr>
<tr>
<td>Lee, 2005 (14)</td>
<td>Induction chemo + imatinib → consolidation + imatinib → maintenance imatinib</td>
<td>20</td>
<td></td>
<td>Mdn (mos)</td>
<td>Mdn RFS (mos)</td>
<td>95</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Induction chemo → consolidation</td>
<td>18</td>
<td></td>
<td>12.8</td>
<td>9.3</td>
<td>83</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Notes:** abs=abstract; chemo=chemotherapy; CR=complete remission rate; CVAD=cyclophosphamide, vincristine, doxorubicin, dexamethasone; DFS=disease-free survival; ida=idarubicin; mdn=median; mos=months; N=number of patients; NR=not reported; ns=not significant; OS=overall survival; PB=peripheral blood; PFS=progression-free survival; pred=prednisone; ref=reference; RFS=relapse-free survival; SCT=stem cell transplantation; vinc=vincristine; yr=year(s).

\(^a\)For CR after induction, only 27 patients were evaluable in the induction imatinib arm and 26 in the induction chemotherapy arm.

\(^b\)Of 153 patients that received imatinib, 89 patients received imatinib during consolidation only, while 64 patients also received imatinib during induction therapy due to a protocol amendment if 2005 that added imatinib to induction therapy.

\(^c\)Complete response after induction for: induction imatinib patients (n=64)/chemotherapy induction only patients (n=89).
### Table 3. Grade 3 or 4 adverse events related to treatment with imatinib in trials of patients with Ph+ ALL.

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Intervention</th>
<th>N</th>
<th>All G3/4 AE’s (%)</th>
<th>Non-heme G3/4 AE’s (%)</th>
<th>G3/4 nausea/vomiting (%)</th>
<th>G3/4 diarrhea (%)</th>
<th>Neutropenic fever (%)</th>
<th>G3/4 Neutropenia</th>
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<td><strong>Randomized Trials</strong></td>
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<tr>
<td>Ottmann, 2007 (7)</td>
<td>induction: imatinib → consolidation: imatinib + chemo</td>
<td>28</td>
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<td>39</td>
<td>7.1</td>
<td>3.6</td>
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<tr>
<td></td>
<td>induction: chemo → consolidation: imatinib + chemo</td>
<td>27</td>
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<td>86</td>
<td>3.7</td>
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<td><strong>Non-randomized phase II trials</strong></td>
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<td><strong>Comparative trials</strong></td>
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<tr>
<td>Thomas, 2008 (8) abs</td>
<td>Iatinib + hyper-CVAD</td>
<td>54</td>
<td></td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td>Hyper-CVAD</td>
<td>48</td>
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<td>NR</td>
<td>NR</td>
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<tr>
<td>Fielding, 2007 (9) abs</td>
<td>Induction chemo + imatinib → consolidation imatinib → allogeneic SCT → imatinib</td>
<td>153b</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td></td>
<td>Induction → allogeneic SCT</td>
<td>267</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>de Labarthe, 2007 (10)</td>
<td>Prephase chemo → variable induction + imatinib → consolidation + imatinib</td>
<td>45</td>
<td></td>
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<td>NR</td>
<td>10/36a</td>
<td>NR/14a</td>
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<td></td>
<td>No imatinib - details NR</td>
<td>198</td>
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<td>Delannoy, 2006 (11)</td>
<td>Induction chemo → consolidation/salvage + imatinib → 10 blocks of maintenance (for patients with CR)--2 with imatinib</td>
<td>30</td>
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<td>30</td>
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<td>0</td>
<td>NR</td>
<td>NR</td>
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<td></td>
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<td>21</td>
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<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Wassmann, 2006 (12)</td>
<td>Alternating imatinib: prephase chemo → induction → imatinib → consolidation chemo → imatinib → SCT</td>
<td>47</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td>Concurrent imatinib: prephase chemo → induction chemo + imatinib → consolidation + imatinib → SCT</td>
<td>45</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lee, 2005 (13)</td>
<td>Induction Hyper-CVAD → imatinib → consolidation/salvage chemo → imatinib → SCT (patients in CR) or salvage chemo (patients not in CR)</td>
<td>29</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Induction (ida/vinc/pred/asparaginase) → consolidation/salvage chemo → SCT</td>
<td>33</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lee, 2005 (14)</td>
<td>Induction chemo + imatinib → consolidation + imatinib → maintenance imatinib</td>
<td>20</td>
<td></td>
<td>10</td>
<td>0</td>
<td>50</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Induction chemo → consolidation</td>
<td>18</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Notes: abs=abstract; AE=adverse event(s); chemo=chemotherapy; CR=complete remission; CVAD=cyclophosphamide, vincristine, doxorubicin, dexamethasone; G3/4=grade 3 or 4; ida=idarubicin; N=number of patients; non-heme=non-hematological; NR=not reported; PFS=progression-free survival; pred=prednisone; ref=reference; RFS=relapse-free survival; SCT=stem cell transplantation; vinc=vincristine.

aAdverse events reported for induction/consolidation.
V. DISCUSSION

Only one randomized trial evaluating the use of imatinib in patients with Ph+ ALL has been conducted and reported to date. In this trial, there was a markedly improved remission rate in those receiving imatinib, 96.3% compared with 50.0% in those not receiving imatinib. Overall survival was not different between both arms. Given the small number of patients enrolled in the trial and the inclusion of imatinib in the administration of consolidation to patients in both arms following the remission induction phase, a survival difference would not be expected. Three of the seven non-randomized trials report improved complete response rates and three report improved survival. In patients with acute leukemia, achievement of a complete remission is felt to be a very important outcome.

It is important to note that Ph+ ALL is rare; therefore accruing enough patients to attain sufficient statistical power to evaluate an endpoint such as OS could take up to a decade. A search of the U.S National Institutes of Health (NIH) clinical trials database revealed two ongoing randomized trials of imatinib in Ph+ ALL. The first is enrolling young adults with ALL (age 18-59 years) and separating patients into one of three subgroups based on disease: group A: T-ALL or B-ALL that is Ph-; group B: B-ALL that is Ph- and CD20+; group C Ph+ ALL. Ph+ ALL patients are to be randomized to receive either an imatinib-based induction or a chemotherapy + imatinib induction. Although the target enrolment is 1080 patients, the record does not indicate how many patients with Ph+ ALL are to be enrolled. The primary endpoint for the patients with Ph+ ALL is minimal residual disease after induction and/or consolidation. The second trial is randomizing elderly patients (age > 55 years) to an imatinib-based induction or to a standard chemotherapy induction. The target enrolment was not reported; however, the primary outcome is the complete remission rate after induction therapy. Neither trial has overall survival as a primary endpoint, and neither trial is likely to have sufficient statistical power to compare OS between the treatment and control arms. It is unlikely that definitive trials examining OS will be conducted because of the rarity of the disease and because the high early responses already observed have resulted in widespread use of imatinib or other tyrosine kinase inhibitors in all patients. Given these two facts, the trial reported by Ottmann et al (7) constitutes the highest quality evidence that currently exists for Ph+ ALL.

The randomized trial by Ottmann demonstrated that induction with imatinib significantly improves the CR rate compared to induction with chemotherapy. Complete remission following induction was the trial’s primary outcome. The authors reported that no significant differences existed for OS and DFS for imatinib compared to chemotherapy; however, the median follow-up was only 11.2 months, patients in both arms received consolidation that included imatinib, and the trial was, most likely underpowered to detect differences in survival endpoints. The phase II trials had similar CR rates with imatinib in patients with newly diagnosed or relapsed/refractory Ph+ ALL.

The toxicity of imatinib was significantly better with respect to the rate of grade 3/4 non-hematological adverse events for induction with imatinib compared to induction chemotherapy. The rates of grade 3/4 nausea/vomiting appeared to be raised with the use of imatinib; however, no significant differences were reported.

The opinion of the authors is that imatinib is recommended for all patients with Ph+ ALL, and imatinib should be initiated at the onset of ALL therapy. It can be used in combination with chemotherapy, either intensive or non-intensive; alternatively, in patients who are unsuitable for chemotherapy, it may be combined with prednisone alone.

VI. ONGOING TRIALS

The National Cancer Institute’s clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical
Trials database (http://clinicaltrials.gov/) were searched for reports of new or ongoing randomized trials investigating the use of imatinib in patients with Ph+ ALL that met our eligibility criteria. Appendix D provides details of the identified ongoing trials.

VII. RECOMMENDATIONS AND EVIDENCE

Target Population

Adult patients with newly diagnosed or relapsed or refractory imatinib/dasatinib-naive Ph+ ALL.

Recommendations

- The opinion of the authors is that imatinib is recommended for all patients with imatinib/dasatinib-naive Ph+ ALL, to be administered as part of remission induction therapy.

  Key Evidence
  
  ⇒ A single randomized trial that reported much higher complete remission rates for patients receiving induction with imatinib alone compared to induction with chemotherapy (96.3% versus [vs.] 50.0%, respectively; \( p=0.0001 \)) (1).
  
  ⇒ A number of comparative phase II studies reported improvements in complete remission rate, disease-free survival, relapse-free survival or overall survival when imatinib was combined with chemotherapy compared with chemotherapy alone (8, 10, 11, 13, 14).

- The opinion of the authors is that patients who are unsuitable to receive intensive chemotherapy may achieve remission when imatinib is combined with prednisone alone or with non-intensive chemotherapy.

  Key Evidence
  
  ⇒ One non-comparative phase II trial reported a complete remission rate of 96.7% for 29 elderly patients that received imatinib and prednisone alone (2).
  
  ⇒ Another non-comparative phase II trial reported a complete remission rate of 100% for 10 elderly patients that received imatinib, prednisone and vincristine (3).

Qualifying Statements

- There is insufficient evidence to recommend a specific dose and schedule of imatinib. Published studies have used imatinib 400-800 mg/d until the end of the treatment program (1-3).

VIII. CONFLICTS OF INTEREST

The authors of this report were asked to disclose conflicts of interest. No potential conflicts were declared.

IX. ACKNOWLEDGEMENTS

The PEBC would like to thank Dr. Irwin Walker, Dr. Kevin Imrie, Dr. Tom Kouroukis, and Mr. Adam Haynes for taking the lead in drafting and revising this CED-CCO advice report.
REFERENCES


25. Wetzler M, Stock W, Donohue KA, Owzar K, Sher DA, Hoke EE, et al. Autologous stem cell transplantation (SCT) following sequential chemotherapy and imatinib for adults with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+)


Appendix A. Literature search strategies.

MEDLINE (OVID)
1. acute lymphoblastic leukemia:.mp.
2. exp leukemia, lymphoid/
3. 1 or 2
4. (philadelphia adj2 positive).mp.
5. (Ph adj2 positive).mp.
6. Ph+.mp.
7. Philadelphia chromosome/
8. or/4-7
9. 3 and 8
10. imatinib.mp.
11. gleevec.mp.
12. glivec.mp.
13. STI571.mp.
14. or/10-13
15. 9 and 14
16. meta-analysis as topic/
17. meta analysis.pt.
18. meta analy$.tw.
19. metaanaly$.tw.
20. (systematic adj (review$1 or overview$1)).tw.
21. or/16-20
22. cochrane.ab.
23. embase.ab.
24. (cinahl or cinhal).ab.
25. science citation index.ab.
26. bids.ab.
27. cancerlit.ab.
28. or/22-27
29. reference list$.ab.
30. bibliograph$.ab.
31. hand-search$.ab.
32. relevant journals.ab.
33. manual search$.ab.
34. or/29-33
35. selection criteria.ab.
36. data extraction.ab.
37. 35 or 36
38. review.pt.
39. review literature as topic/
40. 38 or 39
41. 37 and 40
42. comment .pt.
43. letter.pt.
44. editorial.pt.
45. or/42-44
46. 21 or 28 or 34 or 41
47. 46 not 45
48. randomized controlled trials as topic/
49. randomized controlled trial.pt.
50. random allocation/
51. double blind method/
52. single blind method/
53. exp Clinical Trials as Topic/
54. exp clinical trial/
55. (clinic$ adj trial$1).tw.
56. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
57. placebos/
58. placebo$.tw.
59. (allocated adj2 random$).tw.
60. random allocation.tw.
61. randomly allocated.tw.
62. or/48-61
63. case report.tw.
64. letter.pt.
65. historical article.pt.
66. or/63-65
67. 62 not 66
68. 47 or 67
69. practice guideline/
70. practice guideline$.mp.
71. 69 or 70
72. 68 or 71
73. 15 and 72
74. limit 73 to (English language and humans)

**EMBASE (OVID)**
1. acute lymphoblastic leukemia/
2. acute lymphoblastic leuk?emia$.mp.
3. 1 or 2
4. Philadelphia 1 Chromosome/
5. (philadelphia adj2 positive).mp.
6. (Ph adj2 positive).mp.
7. Ph+.mp.
8. or/4-7
9. 3 and 8
10. imatinib.mp.
11. gleevec.mp.
12. glivec.mp.
13. STI571.mp.
14. imatinib/
15. or/10-14
16. 9 and 15
17. exp meta-analysis/
18. ((meta adj analy$) or metaanaly$).tw.
19. (systematic ad (review$1 or overview$1)).tw.
20. or/17-19
21. cancerlit.ab.
22. cochrane.ab.
23. embase.ab.
24. (cinahl or cinhal).ab.
25. science citation index.ab.
26. bids.ab.
27. or/21-26
28. reference list$.ab.
29. bibliograph$.ab.
30. hand-search$.ab.
31. manual search$.ab.
32. relevant journals.ab.
33. or/28-32
34. data extraction.ab.
35. selection criteria.ab.
36. 34 or 35
37. review.pt.
38. 36 and 37
40. editorial.pt.
41. 39 or 40
42. 20 or 27 or 33 or 38
43. 42 not 41
44. clinical trial/
45. randomized controlled trial/
46. randomization/
47. single blind procedure/
48. double blind procedure/
49. crossover procedure/
50. placebo/
51. randomized control$ trial$.tw.
52. RCT.tw.
53. random allocation.tw.
54. randomly allocated.tw.
55. allocated randomly.tw.
56. (allocated adj2 random$).tw.
57. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
58. placebo.tw.
59. prospective study/
60. or/44-59
61. case study/
62. case report.tw.
63. abstract report/
64. letter/
65. or/61-64
66. 60 not 65
67. 43 or 66
68. exp practice guidline/
69. practice guideline/
70. practice guideline$.tw.
71. 68 or 69
72. 67 or 70
73. 16 and 71
74. limit 73 to (human and English language)

Cochrane Central Register of Controlled Trials (CCTR) and Cochrane Database of Systematic Reviews (CDSR)
1. acute lymphoblastic leukemia$.mp.
2. (Philadelphia adj2 positive).mp.
3. (Ph adj2 positive).mp.
4. Ph+.mp.
5. or/2-4
6. 1 and 5
7. imatinib.mp.
8. gleevec.mp.
9. glivec.mp.
10. STI571.mp.
11. or/7-10
12. 6 and 11

Annual Conference Proceedings of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH)
Search terms used: imatinib, Gleevec, Glivec, Philadelphia-chromosome, Ph+, acute lymphoblastic leukemia.
**APPENDIX B. Dose and schedule information for trials of imatinib in Ph+ ALL.**

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<tr>
<th>Author, year (ref)</th>
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<td><strong>Randomized trials</strong></td>
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<tr>
<td>de Labarthe, 2007 (10)</td>
<td>Prephase: <strong>imatinib</strong> → consolidation + <strong>imatinib</strong></td>
<td></td>
</tr>
<tr>
<td>Ottmann, 2007 (7)</td>
<td>Induction + <strong>imatinib</strong> → consolidation + <strong>imatinib</strong></td>
<td></td>
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<tr>
<td>Thomas, 2008 abs (8)</td>
<td>Induction → consolidation + <strong>imatinib</strong></td>
<td></td>
</tr>
<tr>
<td>Fielding, 2007 abs (9)</td>
<td>Prephase: <strong>imatinib</strong> + Hyper-CVAD</td>
<td></td>
</tr>
<tr>
<td>de Labarthe, 2007 (10)</td>
<td>Induction → <strong>allogeneic SCT</strong>  → <strong>imatinib</strong></td>
<td></td>
</tr>
<tr>
<td>Delannoy, 2006 (11)</td>
<td>Prephase → induction with <strong>imatinib</strong> → maintenance with alt <strong>imatinib</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Non-randomized phase II trials</strong></td>
<td></td>
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<td><strong>Comparative trials</strong></td>
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<td>Induction + <strong>imatinib</strong> → consolidation + <strong>imatinib</strong></td>
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<tr>
<td>Fielding, 2007 abs (9)</td>
<td>Induction → <strong>allogeneic SCT</strong> → <strong>imatinib</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Hyper-CVAD**

NR

**Induction:** 2 phases of chemotherapy (details NR) + **imatinib** 600 mg/d phase 2 (added in 2005) → consolidation: **imatinib** 600 mg/d → intensification: high-dose MTX + **allogeneic SCT** → **imatinib** 600 mg/d for 2yr or until relapse.

**Induction:** 2 phases of chemotherapy (details NR) → intensification: high-dose MTX + **allogeneic SCT**.

**Prephase:**

- Pred 60 mg/m²/d orally d7-to-1 + MTX 15 mg l.th. d7-to-4 → induction 1: daun 50 mg/m²/d i.v. d1-3 + cyclo 750 mg/m²/d i.v. d1 + vinc 2 mg i.v. d1,8 + pred 60 mg/m²/d orally d1-14 + asparaginase 6000 IU/m² d.i.v. d8,10,12 + MTX 15 mg l.th. d1,8 + Ara-C 40 mg i.th. d1,8 + dex 40 mg l.th. d1,8 → For good early responders: induction 2: daun 30 mg/m²/d i.v. d15,16 + cyclo 750 mg/m²/d d15 + vinc 2 mg i.v. d15 + asparaginase 6000 IU/m² i.v. d20,22,24,26,28 + G-CSF 150 μg/m²/d s.c. or i.v. from d17 → consolidation: mitox 10 mg/m²/d i.v. d1,3 + Ara-C 2000 mg/m²/12hr i.v. d1-4 + imatinib 600 mg/d orally d1-SCT + MTX 15 mg l.th. d8,15 + Ara-C 40 mg i.th. d8,15 + dex 40 mg l.th. d8,15 + G-CSF 5 μg/kg/d s.c. or i.v. from d9 → SCT for patients in CR.

For poor early responders, following induction 1: vinc 2 mg i.v. d1,8,15,22 + dex 40 mg l.th. i.v. or i.v. d1,8,15,22 + imatinib 800 mg/d orally d1-SCT + MTX 15 mg l.th. d1,8,15,22 + Ara-C 40 mg i.th. d1,8,15,22 + dex 40 mg l.th. d1,8,15,22 → SCT for patients in CR.

**Induction:**

- Pred 60 mg/m² orally or i.v. d7-15-21 + vinc 2 mg i.v. d1,8,15,22 + cyclo 750 mg/m² i.v. d1,8 + anthra³ + MTX 15 mg i.th. d1,8,15,22 + Ara-C 40 mg i.th. d1,8,15,22 → imatinib 600 mg/d + methylpred 40 mg i.th. d1,8,15,22 → consolidation + **imatinib** (good early responders) → chemotherapy.

**Prephase → induction with **imatinib** → maintenance with alt **imatinib****
<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Treatment Arms</th>
<th>Treatment details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee, 2005 (14)</td>
<td>Induction + imatinib → consolidation + imatinib → SCT</td>
<td>Induction: daun 50 mg/m² i.v. d1-3 + vinc 2 mg i.v. d1,8,15,22 + pred 60 mg/m² d1-28 + asparaginase i.m. 4000 U/m² d17-28 → consolidation A (courses 1,3,5,7): daun 50 mg/m² i.v. d1,2 + vinc 2 mg i.v. d1,8 + pred 60 mg/m² orally d1-14 + asparaginase 12000 U/m² i.m. d2,4,7,9,11; consolidation B (courses 2,4,6,8): Ara-C 300 mg/m² i.v. d1,4,8,11 + etop 75 mg/m² d1,4,8,11 → SCT First 12 patients: induction: imatinib mg/d x14d → consolidation: imatinib 400 mg/m² d1,8,15,22 or vinc (details NR) + cyclo 400 mg/m² d1,8,15,22 + daun 40 mg/m² d1,8,15,22 + methylpred 60 mg/m² alt d1-22 + MTX 10 mg i.th. 2 times → consolidation: Ara-C 1 g/m² 2-hr i.v. twice daily x5d + mitox 10 mg/m² i.v. x2d then IFN-α for 3 mos then vinc 0.4 mg/d c.i.v. x4d + dox 9 mg/m² c.i.v. x4d + dex 40 mg/d x4d → maintenance: 6-MP + MTX for 18 mos (details NR).</td>
</tr>
<tr>
<td>Wassmann, 2006 (12)</td>
<td>Prephase → induction + imatinib and consolidation → SCT</td>
<td>Prephase: dex 10 mg/m² orally d1-5 + cyclo 200 mg/m² i.v. d3-5 + MTX 15 mg i.th. → induction 1: dex 10 mg/m² orally d6-7,13-16 + vinc 2 mg i.v. d6,13,20 + daun 45 mg/m² i.v. d6,7,13,14 + asparaginase 1000 U/m² 2-hr i.v. d20 + G-CSF 5 μg/kg s.c. d6+ → induction 2: cyclo 1000 mg/m² i.v. d26-46 + Ara-C 75 mg/m² i.v. d28-31,35,38-42-45 + 6-MP 60 mg/m² orally d26-46 + MTX 15 mg i.th. d28,35,42 + G-CSF 5 μg/kg s.c. until ANC &gt; 1x10⁹/L + CNS irradiation 24 Gy over 12d → imatinib 400-600 mg/d → consolidation: dex 10 mg/m² orally d1-5 + vind 3 mg/m² i.v. d1 + MTX 1.0-1.5 mg/m² 24-hr i.v. d1 + etop 250 mg/m² 1-hr i.v. d4,5 + Ara-C 1-2 g/m² 3-hr i.v. d5 + G-CSF 5 μg/kg s.c. d7+ + MTX 15 mg i.th. d12 + Ara-C 40 mg i.th. + dex 4 mg i.th. → imatinib 400-600 mg/d → SCT</td>
</tr>
<tr>
<td>Lee, 2005 (13)</td>
<td>Induction → imatinib → consolidation/salvage → imatinib → SCT</td>
<td>Induction: hyper cyclo 300 mg/m²/12h d1-3 + vinc 1.4 mg/m² d4,11 + ida 12 mg/m² d4,11 + dex 40 mg i.d. 1-14; after recovery of WBC and platelets: For patients in CR → imatinib 400 or 600 mg/d x4wk → consolidation: Ara-C 2 g/m²/12h d1-5 + mitox 12 mg/m² d1,2 → imatinib 400 or 600 mg/d until SCT. For patients not in CR → imatinib 600 mg/d x4wk → salvage: Ara-C 2 g/m²/12h d1-4 + mitox 12 mg/m² d1-4 + etop 100 mg/m² d5-7. MTX + Ara-C + methylpred administered i.th. during induction and consolidation (6x total).</td>
</tr>
<tr>
<td></td>
<td>Induction → consolidation/salvage → SCT</td>
<td>Induction: ida + vinc + pred + asparaginase → consolidation/salvage: except imatinib, patients received same regimens as imatinib group → SCT. MTX + Ara-C + methylpred administered i.th. during induction and consolidation (6x total).</td>
</tr>
<tr>
<td></td>
<td>Induction → imatinib → consolidation/salvage → imatinib → SCT</td>
<td>Induction: daun 30 mg/m² i.v. d1-3 + vinc 2 mg i.v. d1,8,15,22 + pred 60 mg/m² d1-28 + asparaginase i.m. 4000 U/m² d17-28 → consolidation A (courses 1,3,5,7): daun 50 mg/m² i.v. d1,2 + vinc 2 mg i.v. d1,8 + pred 60 mg/m² orally d1-14 + asparaginase 12000 U/m² i.m. d2,4,7,9,11; consolidation B (courses 2,4,6,8): Ara-C 300 mg/m² i.v. d1,4,8,11 + etop 75 mg/m² d1,4,8,11 → SCT</td>
</tr>
<tr>
<td>Author, year (ref)</td>
<td>Treatment Arms</td>
<td>Treatment details</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>400 mg/d d1-14 x8 courses</td>
<td>Induction → consolidation → SCT</td>
<td>Subsequent patients: induction: imatinib 600 mg/d → consolidation: imatinib 400 mg/d</td>
</tr>
<tr>
<td>400 mg/d d1-365</td>
<td>Induction → consolidation → SCT</td>
<td>Induction: daun 50 mg/m(^2) i.v. d1-3 + vinc 2 mg i.v. d1,8,15,22 + pred 60 mg/m(^2) d1-28 + asparaginase i.m. 4000 U/m(^2) d17-28 → consolidation A (courses 1,3,5,7): daun 50 mg/m(^2) i.v. d1,2 + vinc 2 mg i.v. d1,8 + pred 60 mg/m(^2) orally d1-14 + asparaginase 12000 U/m(^2) i.m. d2,4,7,9,11; consolidation B (courses 2,4,6,8): Ara-C 300 mg/m(^2) i.v. d1,4,8,11 + etoposide 75 mg/m(^2) d1,4,8,11 → SCT</td>
</tr>
</tbody>
</table>

**Non-comparative trials**

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Treatment Arms</th>
<th>Treatment details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carpenter, 2007 (15)</td>
<td>SCT → imatinib</td>
<td>Prephase: pred 10-40 mg/m(^2)/d d1-7 → induction: imatinib 800 mg/d + pred 40 mg/m(^2)/d d1-45</td>
</tr>
<tr>
<td>Vignetti, 2007 (16)</td>
<td>Prephase → induction imatinib</td>
<td>Imatinib 80 mg/d d1-56 + vinc 2 mg i.v. d1,8,15,22 + dex 40 mg/d orally or i.v. d1-2,8-9,15-16 + MTX 15 mg i.th. d1,8,15,22 + Ara-C 40 mg i.th. d1,8,15,22 + dex 40 mg i.th. d1,8,15,22</td>
</tr>
<tr>
<td>Rea, 2006 (17)</td>
<td>Induction + imatinib</td>
<td>Induction: cyclo 1200 mg/m(^2) 3-hr i.v. d1 + daun 60 mg/m(^2) 1-hr i.v. d1-3 + vinc 1.3 mg/m(^2) i.v. d1,8,15,22 + pred 60 mg/m(^2) orally d1-21 + imatinib 600 mg/d orally d8-63 + MTX 15 mg i.th. d29 + Ara-C 40 mg i.th. d29 + dex 4 mg i.th. d29 → consolidation, odd courses: MTX 1 g/m(^2) 24-hr i.v. d1 + Ara-C 2 g/m(^2)/12-hr 3-hr i.v. d2-3 + MTX 15 mg i.th. d1 + Ara-C 40 mg i.th. d1 + dex 4 mg i.th. d1; even courses: imatinib 600 mg/d orally d1-28 + MTX 15 mg i.th. d1 + Ara-C 40 mg i.th. d1 + dex 4 mg i.th. d1 → maintenance: vinc 1.3 mg/m(^2) i.v. d1 + pred 60 mg/m(^2) orally d1-5 + imatinib 600 mg/d orally d1-28</td>
</tr>
<tr>
<td>Yanada, 2007 (18) abs</td>
<td>Induction + imatinib → consolidation + imatinib → maintenance + imatinib</td>
<td>Induction: vinc 2 mg/d i.v. x2d + dex 40 mg/d orally x2d q1wk x4wk + Imatinib 800 mg/d → consolidation: vinc 2 mg/d i.v. x2d + dex 40 mg/d orally x2d q1mo x4mo + imatinib 600 mg/d + 6-MP → Peglys 45 μg s.c. q1wk + imatinib 400 mg/d for 2yr OR SCT</td>
</tr>
<tr>
<td>Towatari, 2004 (19) abs</td>
<td>Induction + imatinib</td>
<td>Imatinib 400 mg/d + pred 40 mg/m(^2)/d for 6wk then tapering dose for 2wk + vinc 2 mg/m(^2)/d x6wk</td>
</tr>
<tr>
<td>Wassmann, 2004 (20)</td>
<td>Imatinib</td>
<td>Imatinib 400 or 600 mg/d (800 mg/d for patients that relapsed)</td>
</tr>
<tr>
<td>Wassmann, 2003 (21)</td>
<td>Imatinib</td>
<td>Imatinib 400 mg/d orally x1wk x4wk → high-dose MTX i.v. and i.th. q1wk x3wk → imatinib 800 mg/d x4wk → allogeneic or autologous SCT → maintenance imatinib</td>
</tr>
<tr>
<td>Ottmann, 2002 (22)</td>
<td>Imatinib</td>
<td>Induction: imatinib 800 mg/d x4wk → relapsed ALL: standard-dose ida + Ara-C + imatinib 600 mg/d → after recovery, imatinib 600 mg/d; newly diagnosed ALL: induction: pred 60 mg/m(^2) orally or i.v. d1-7,15-21 + vinc 2 mg i.v. d1,8,15,22 + cyclo 750 mg/m(^2) i.v. d1,8 + anthra(^3) + MTX 15 mg i.th. d1,8,15,22 + Ara-C 40 mg i.th. d1,8,15,22 + methotrexate 40 mg i.th. d1,8,15,22 → consolidation/salvage: Ara-C 1000 mg/m(^2)/12-hr 3-hr i.v. d1-4 + mitox 10 mg/m(^2) i.v. d3-5 + MTX 15 mg i.th. d1 + Ara-C 40 mg i.th. d1 + methotrexate 40 mg i.th. d1 → autologous SCT</td>
</tr>
<tr>
<td>Rousselet, 2007 (23) abs</td>
<td>Induction + imatinib → consolidation + imatinib → maintenance + imatinib</td>
<td>Induction: imatinib 800 mg/d x4wk → high-dose MTX i.v. and i.th. q1wk x3wk → imatinib 800 mg/d x4wk → allogeneic or autologous SCT → maintenance imatinib</td>
</tr>
<tr>
<td>Mukhopadhyay, 2007 (24) abs</td>
<td>Induction + imatinib</td>
<td>Imatinib 400 mg/d + pred 40 mg/m(^2)/d for 6wk then tapering dose for 2wk + vinc 2 mg/m(^2)/d x6wk</td>
</tr>
<tr>
<td>Wetzler, 2007 (25) abs</td>
<td>Induction + imatinib</td>
<td>Imatinib 400 mg/d orally → allogeneic SCT (after non-myeloablative conditioning) → imatinib 600 mg/d orally x14d</td>
</tr>
<tr>
<td>Lickliter, 2004 (26) abs</td>
<td>Prephase imatinib → induction + imatinib</td>
<td>Prephase: imatinib 600 mg/d x1wk → relapsed ALL: standard-dose ida + Ara-C + imatinib 600 mg/d → after recovery, imatinib 600 mg/d; newly diagnosed ALL: induction: pred 60 mg/m(^2) orally or i.v. d1-7,15-21 + vinc 2 mg i.v. d1,8,15,22 + cyclo 750 mg/m(^2) i.v. d1,8 + anthra(^3) + MTX 15 mg i.th. d1,8,15,22 + Ara-C 40 mg i.th. d1,8,15,22 + methotrexate 40 mg i.th. d1,8,15,22 → consolidation/salvage: Ara-C 1000 mg/m(^2)/12-hr 3-hr i.v. d1-4 + mitox 10 mg/m(^2) i.v. d3-5 + MTX 15 mg i.th. d1 + Ara-C 40 mg i.th. d1 + methotrexate 40 mg i.th. d1 → autologous SCT</td>
</tr>
<tr>
<td>Norasetthada, 2004 (27) abs</td>
<td>Imatinib following non-myeloablative conditioning → imatinib</td>
<td>Imatinib 600 mg/d orally → allogeneic SCT (after non-myeloablative conditioning) → imatinib 600 mg/d orally x14d</td>
</tr>
<tr>
<td>Ribera, 2004 (28) abs</td>
<td>Induction + imatinib → consolidation + imatinib → allogeneic SCT</td>
<td>Induction: imatinib 400 mg/d orally + vinc 1.5 mg/m(^2)/wk + daun 60 mg/m(^2)/wk + pred 60 mg/m(^2)/d x4wk → consolidation 1: imatinib 400 mg/d orally + MTX 1.5 g/m(^2) + teniposide + Ara-C → allogeneic SCT or consolidation 2: imatinib 400 mg/d orally for up to 1-yr + vinc + daun +...</td>
</tr>
</tbody>
</table>
Details of the treatment regimen for the historical control group were obtained from Dombret et al (29).

Patients were randomized to receive either daunorubicin 30 mg/m² i.v. d1-3,15-16 or idarubicin 9 mg/m² d1-3,8.

Second consolidation in patients without an HLA-identical family or marrow unrelated donor.
### Appendix C1. Patient and trial characteristics of non-comparative phase II trials examining imatinib in Ph+ ALL.

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Patient characteristics</th>
<th>Intervention*</th>
<th>N(^{0})</th>
<th>Age, mdn (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carpenter, 2007 (15)</td>
<td>Ph+ ALL or CML beyond first chronic phase who received allogeneic SCT and eligible for myeloablative conditioning.</td>
<td>SCT → imatinib</td>
<td>15</td>
<td>NR</td>
</tr>
<tr>
<td>Vignetti, 2007 (16)</td>
<td>Ph+ ALL age &gt; 60 years.</td>
<td>Prephase → induction imatinib</td>
<td>30</td>
<td>69</td>
</tr>
<tr>
<td>Rea, 2006 (17)</td>
<td>Ph+ ALL or LBC CML, ECOG PS 0-2, no CNS involvement</td>
<td>Induction + imatinib</td>
<td>18</td>
<td>NR</td>
</tr>
<tr>
<td>Yanada, 2007 (18) abs Towatari, 2004 (19)</td>
<td>Newly diagnosed Ph+ ALL age 15-64 years, ECOG PS 0-3.</td>
<td>Induction + imatinib → consolidation + imatinib → maintenance + imatinib</td>
<td>24</td>
<td>41.5</td>
</tr>
<tr>
<td>Wassmann, 2004 (20) Wassmann, 2003 (21) Ottmann, 2002 (22)</td>
<td>Relapsed/refractory Ph+ ALL age ≥ 18 years, ECOG PS 0-2.</td>
<td>Imatinib</td>
<td>68</td>
<td>48</td>
</tr>
<tr>
<td>Rousselot, 2007 (23) abs</td>
<td>Resistant/refractory Ph+ ALL or lymphoid blast crisis CML or newly diagnosed Ph+ ALL age &gt;55 years.</td>
<td>Induction + imatinib → consolidation + imatinib → maintenance Pegasy/s or SCT</td>
<td>54(^{c})</td>
<td>62</td>
</tr>
<tr>
<td>Mukhopadhyay, 2007 (24) abs</td>
<td>Ph+ ALL, age &gt; 50 years</td>
<td>Induction + imatinib</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>Wetzler, 2007 (25) abs</td>
<td>Ph+ ALL age 15-59 years with CR/PR after one cycle of a 4-5 drug induction regimen</td>
<td>Induction imatinib → SCT → maintenance imatinib</td>
<td>35</td>
<td>NR</td>
</tr>
<tr>
<td>Lickliter, 2004 (26) abs</td>
<td>Ph+ ALL</td>
<td>Prephase imatinib → induction + imatinib</td>
<td>17</td>
<td>NR</td>
</tr>
<tr>
<td>Norasetthada, 2004 (27) abs</td>
<td>Ph+ ALL</td>
<td>Imatinib → SCT following non-myeloablative conditioning → imatinib</td>
<td>11(^{d})</td>
<td>51</td>
</tr>
<tr>
<td>Ribera, 2004 (28) abs</td>
<td>Newly diagnosed Ph+ ALL</td>
<td>Induction + imatinib → consolidation + imatinib → allogeneic SCT</td>
<td>19</td>
<td>43(^{e})</td>
</tr>
</tbody>
</table>

Notes: abs=abstract; ALL=acute lymphoblastic leukemia; CML=chronic myeloid leukemia; CNS=central nervous system; CR=complete response; ECOG=Eastern Cooperative Oncology Group; LBC=lymphoid blast crisis; mdn=median; N=number of patients; Ph+=Philadelphia chromosome-positive; PR=partial response; PS=performance status; ref=reference; SCT=stem cell transplantation; yr=year(s).

*Full regimen details including dose and schedule information can be found in Appendix B.

\(^{a}\)Number of patients with Ph+ ALL.

\(^{b}\)Twenty-two patients had resistant or refractory Ph+ ALL; three patients had relapsed Ph+ ALL, 25 patients were elderly and had newly diagnosed Ph+ ALL, and four patients had lymphoid blast crisis CML.

\(^{c}\)The 11 patients were split into two cohorts: six patients received imatinib\(^{2}\) while five patients did not.

\(^{d}\)Mean age.
Appendix C2. Efficacy outcomes reported in non-comparative phase II trials examining imatinib in Ph+ ALL.

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Intervention</th>
<th>N</th>
<th>OS</th>
<th>DFS/PFS/ RFS</th>
<th>CR after induction (%)</th>
<th>CR after induction with PB recovery (%)</th>
<th>CR after consolidation/salvage (%)</th>
<th>Follow-up mdn (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carpenter, 2007 (15)</td>
<td>SCT → imatinib</td>
<td>15</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>17</td>
</tr>
<tr>
<td>Vignetti, 2007 (16)</td>
<td>Prephase → induction imatinib</td>
<td>29</td>
<td>Mdn 20 mos</td>
<td>DFS 1-yr: 48%</td>
<td>96.7</td>
<td>NR</td>
<td>NR</td>
<td>14</td>
</tr>
<tr>
<td>Rea, 2006 (17)</td>
<td>Induction + imatinib</td>
<td>18</td>
<td>Mdn 13.3 mos</td>
<td>Mdn DFS 9.9 mos</td>
<td>94.4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yanada, 2007 (18)</td>
<td>Induction + imatinib → consolidation + imatinib</td>
<td>24</td>
<td>1-yr 89%</td>
<td>1-yr EFS 68%</td>
<td>95.8</td>
<td>NR</td>
<td>NR</td>
<td>12</td>
</tr>
<tr>
<td>Towatari, 2004 (19)</td>
<td>Induction + imatinib → maintenance + imatinib</td>
<td>68</td>
<td>18-mos 22.6%</td>
<td>6-mos PFS 22.8%</td>
<td>30</td>
<td>NR</td>
<td>NA</td>
<td>NR</td>
</tr>
<tr>
<td>Wassmann, 2003 (21)</td>
<td>Imatinib</td>
<td>54</td>
<td>Mdn 29.9 mos</td>
<td>Mdn DFS 22.6%</td>
<td>85</td>
<td>NR</td>
<td>NR</td>
<td>18</td>
</tr>
<tr>
<td>Ottmann, 2002 (22)</td>
<td>Induction + imatinib → consolidation + imatinib → maintenance Pegasys/imatinib or SCT</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>8</td>
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<tr>
<td>Rousselot, 2007 (23)</td>
<td>Induction imatinib → SCT → maintenance imatinib</td>
<td>35</td>
<td>NR</td>
<td>NR</td>
<td>88.6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mukhopadhyay, 2007 (24)</td>
<td>Induction + imatinib</td>
<td>35</td>
<td>NR</td>
<td>NR</td>
<td>88.6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lickliter, 2004 (26)</td>
<td>Prephase imatinib → induction + imatinib</td>
<td>14</td>
<td>NR</td>
<td>NR</td>
<td>64.3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Norasetthada, 2004 (27)</td>
<td>Imatinib → SCT following non-myeloablative conditioning → imatinib</td>
<td>24</td>
<td>NR</td>
<td>NR</td>
<td>64.3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ribera, 2004 (28)</td>
<td>Induction + imatinib → consolidation + imatinib → allogeneic SCT</td>
<td>19</td>
<td>NR</td>
<td>Mdn DFS 8 mos</td>
<td>NR</td>
<td>NR</td>
<td>84.2</td>
<td>5</td>
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</tbody>
</table>

Notes: abs=abstract; CR=complete remission rate; DFS=disease-free survival; EFS=event-free survival; maint=maintenance; mdn=median; mos=months; N=number of evaluable patients; NA=not applicable; NR=not reported; OS=overall survival; PB=peripheral blood; PFS=progression-free survival; ref=reference; RFS=relapse-free survival; SCT=stem cell transplantation; yr=year(s).

*All six patients had previously received induction therapy. Patients received imatinib upon enrolment and all six relapsed prior to SCT.*
### Appendix C3. Grade 3 or 4 adverse events related to treatment with imatinib in non-comparative phase II trials.

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Intervention</th>
<th>N</th>
<th>All G3/4 AE’s (%)</th>
<th>Non-heme G3/4 AE’s (%)</th>
<th>G3/4 nausea/vomiting (%)</th>
<th>G3/4 diarrhea (%)</th>
<th>Neutropenic fever (%)</th>
<th>G3/4 Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carpenter, 2007 (15)</td>
<td>SCT → imatinib</td>
<td>22&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Vignetti, 2007 (16)</td>
<td>Prephase → induction imatinib</td>
<td>30</td>
<td>NR</td>
<td>43.3</td>
<td>3.3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rea, 2006 (17)</td>
<td>Induction + imatinib</td>
<td>31&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>9.7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Yanada, 2007 (18) abs</td>
<td>Induction + imatinib → consolidation + imatinib → maintenance + imatinib</td>
<td>24</td>
<td>NR</td>
<td>NR</td>
<td>17</td>
<td>4</td>
<td>26</td>
<td>NR</td>
</tr>
<tr>
<td>Towatari, 2004 (19)</td>
<td>Induction + imatinib → consolidation + imatinib → maintenance + imatinib</td>
<td>24</td>
<td>NR</td>
<td>NR</td>
<td>17</td>
<td>4</td>
<td>26</td>
<td>NR</td>
</tr>
<tr>
<td>Wassmann, 2003 (21)</td>
<td>Imatinib</td>
<td>68</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>50</td>
</tr>
<tr>
<td>Wassmann, 2004 (20)</td>
<td>Imatinib</td>
<td>68</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>50</td>
</tr>
<tr>
<td>Rousselot, 2007 (23) abs</td>
<td>Induction + imatinib → consolidation + imatinib → maintenance Pegasys/ imatinib or SCT</td>
<td>54</td>
<td>NR</td>
<td>5.6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Mukhopadhyay, 2007 (24) abs</td>
<td>Induction + imatinib</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Wetzler, 2007 (25) abs</td>
<td>Induction imatinib → SCT → maintenance imatinib</td>
<td>35</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lickliter, 2004 (26) abs</td>
<td>Prephase imatinib → induction + imatinib</td>
<td>14</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Norasetthada, 2004 (27) abs</td>
<td>Imatinib → SCT following non-myeloablative conditioning → imatinib</td>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Ribera, 2004 (28) abs</td>
<td>Induction + imatinib → consolidation + imatinib → allogeneic SCT</td>
<td>19</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Notes: abs=abstract; AE=adverse event(s); G3/4=grade 3 or 4; N=number of patients; non-heme=non-hematological; NR=not reported; PFS=progression-free survival; ref=reference; RFS=relapse-free survival; SCT=stem cell transplantation.

<sup>a</sup>Toxicity data were reported for all patients: data for Ph+ ALL patients were not reported separately.

<sup>b</sup>Grade 2-5 adverse events.

<sup>c</sup>All six patients had previously received induction therapy. Patients received imatinib upon enrolment and all six relapsed prior to SCT.

<sup>d</sup>Adverse events reported for induction/consolidation.
### APPENDIX D. ONGOING TRIALS.

Study comparing imatinib with chemotherapy as induction in elderly patients (age > 55 years) with Philadelphia positive acute lymphoblastic leukemia (ALL)

<table>
<thead>
<tr>
<th>Protocol ID:</th>
<th>NCT00199186, CSTI571ADE10, GMALL-STI571-ELDERLY-01/02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last date modified:</td>
<td>October 18, 2007</td>
</tr>
<tr>
<td>Trial type:</td>
<td>Randomized, open-label, active control</td>
</tr>
<tr>
<td>Accrual:</td>
<td>NR</td>
</tr>
<tr>
<td>Primary outcome:</td>
<td>Complete remission rate after induction therapy</td>
</tr>
<tr>
<td>Sponsorship:</td>
<td>Johann Wolfgang Goethe University Hospitals</td>
</tr>
<tr>
<td>Status:</td>
<td>Accruing</td>
</tr>
</tbody>
</table>

Young adult (age 18-59 years) with acute lymphoblastic leukemia (ALL): randomized trial between an imatinib-based induction and a chemotherapy + imatinib induction. Trial is split into three subgroups based on disease: GRALL 2005 (T ALL or B ALL Ph-); GRAALL 2005 R (ALL Ph- CD20+); GRAAPH 2005 (ALL Ph+).

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<tr>
<th>Protocol ID:</th>
<th>NCT00327678, GRAAPH 2005: ALL Ph</th>
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<td>Last date modified:</td>
<td>May 6, 2008</td>
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<td>Accrual:</td>
<td>1080 (Ph+ ALL group: NR)</td>
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<td>Trial type:</td>
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<tr>
<td>Primary outcome:</td>
<td>Event-free survival, percentage of patients with minimal residual disease &lt; 10^-4 after induction and/or consolidation</td>
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<td>Sponsorship:</td>
<td>Group for Research in Adult Acute Lymphoblastic Leukemia, Projet Hospitalier de Recherche Clinique no. AO-O444-P040429 Assistance Publique - Hôpitaux de Paris</td>
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<td>Status:</td>
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Notes: NR = not reported.