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PRACTICE GUIDELINE

Evidence-based guidelines for the use of tyrosine kinase inhibitors in adults with Philadelphia chromosome–positive or *BCR-ABL*–positive acute lymphoblastic leukemia: a Canadian consensus

S. Couban MD, L. Savoie MD,† Y. Abou Mourad MD,‡*
B. Leber MD,§ M. Minden MD,|| R. Turner MD,#
*V. Palada MD,** N. Shehata MD,***
A. Christofides MSc RD,†† and S. Lachance MD‡‡

ABSTRACT

Adult Philadelphia chromosome–positive (Ph+) or *BCR-ABL*–positive (*BCR-ABL*+) acute lymphoblastic leukemia (ALL) is an acute leukemia previously associated with a high relapse rate, short disease-free survival, and poor overall survival. In adults, allogeneic hematopoietic cell transplant in first remission remains the only proven curative strategy for transplant-eligible patients. The introduction of tyrosine kinase inhibitors (TKIs) in the treatment of patients with Ph+ or *BCR-ABL*+ ALL has significantly improved the depth and duration of complete remission, allowing more patients to proceed to transplantation. Although TKIs are now considered a standard of care in this setting, few randomized trials have examined the optimal use of TKIs in patients with Ph+ ALL. Questions of major importance remain, including the best way to administer these medications, the choice of TKI to administer, and the schedule and the duration to use. We present the results of a systematic review of the literature with consensus recommendations based on the available evidence.

KEY WORDS

Acute lymphoblastic leukemia, ALL, hematology, Philadelphia chromosome–positive, Ph+, tyrosine kinase inhibitors

1. INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common cancer in children. Approximately one third of cases occur in adults[1,2]. Treatment has produced remarkable improvements in outcome for children with ALL, but the outlook for adults remains poor[3]. Treatment with chemotherapy alone or with chemotherapy and allogeneic transplantation in adults with ALL results in 5-year overall survival (OS) between 45% and 53% for those less than 60 years of age[4] and less than 10% for those 60 years of age and older[3]. Until recently, the outcome of adults with Philadelphia chromosome–positive (Ph+) ALL has been even worse, particularly if treatment includes only chemotherapy and not allogeneic transplantation.

The Philadelphia chromosome is the most common chromosomal abnormality in adults with ALL, and the prevalence of Ph+ or *BCR-ABL*–positive (*BCR-ABL*+) ALL increases with age, from 12.7% in adolescents to 44% in patients 35–44 years of age[5]. Patients with Ph+ ALL are older and, at presentation, have higher white blood cell counts and higher blast counts than do patients without the translocation[6]. Although these patients often respond to remission-induction therapy, rates of complete remission (CR) are lower than they are for ALL without the Philadelphia chromosome (83% vs. 93%)[3], and 5-year OS is much poorer because of a high relapse rate. Allogeneic transplantation has been the treatment of choice for eligible adult patients with Ph+ ALL who have a matched sibling or unrelated donor.

The Philadelphia chromosome arises from a translocation of the *ABL* gene on chromosome 9 to the *BCR* gene on chromosome 22, yielding a chimeric *BCR-ABL* fusion gene[7]. Depending on the translocation breakpoint, either a p190 Bcr-Abl or a p210 Bcr-Abl protein results, each being a constitutively active tyrosine kinase central to the pathogenesis of ALL. The aberrant tyrosine kinase alters signalling pathways that control cell proliferation, survival, and self-renewal, leading to leukemogenesis (Figure 1).

The development of tyrosine kinase inhibitors (TKIs), which inhibit the constitutively activated aberrant tyrosine kinases, has revolutionized therapy and outcomes for patients with chronic myeloid leukemia (CML), a disease also characterized by the presence of the Ph+ chromosome[8]. Although clinically different, Ph+ ALL shares the constitutive expression of aberrant Bcr-Abl tyrosine kinases central to the pathogenesis of CML. Many reports describing the use of TKIs in the treatment of patients with Ph+ ALL have now been published.

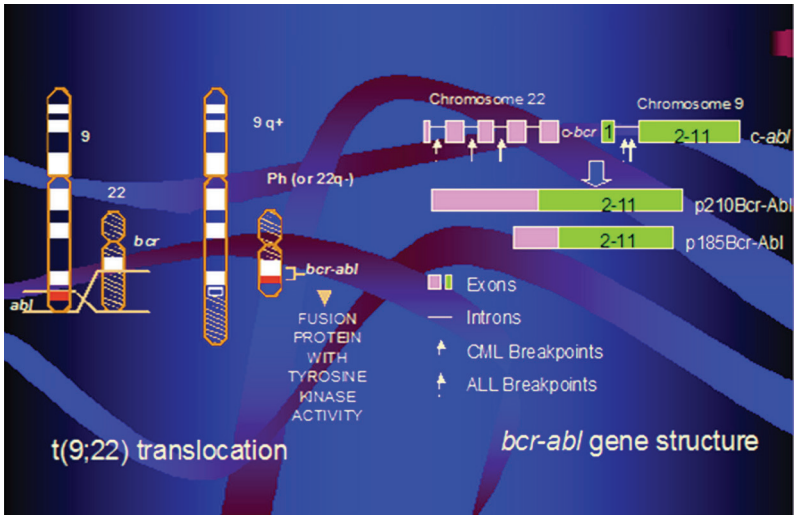

FIGURE 1 *Philadelphia chromosome* BCR-ABL *gene.* CML = *chronic myeloid leukemia;* ALL = *acute lymphoblastic leukemia.*

For the present evidence-based guideline, a panel of physicians with expertise in the treatment of acute leukemia (YAM, SC, SL, BL, MM, LS, RT) and in methodology analysis (NS, VP) systematically reviewed the literature examining the role of TKIs in the treatment of adults with Ph+ ALL. The goal of the guideline is to provide evidence-based recommendations for the use of TKIs in five key areas. We suggest that a guideline is required because of the absence of adequately powered randomized controlled trials addressing the use of TKIs in adults with Ph+ ALL. Furthermore, although reports of observational studies in patients with Ph+ ALL are encouraging, they are not nearly as definitive as the corresponding initial observational studies in patients with CML. For those reasons, physicians can benefit from guidance in this area.

Our purpose in creating the present document was to systematically review and synthesize the evidence and then to formulate recommendations about the use of TKIs in the management of adults with Ph+ ALL.

1.1 Target Population

These guidelines are intended for adults with Ph+ or *BCR-ABL*+ ALL.

1.2 Target Users

These guidelines are for use by physicians responsible for the care of patients with Ph+ or *BCR-ABL*+ ALL.

2. METHODS

2.1 Development of the Guideline

A panel was convened to develop an evidence-based practice guideline for the use of TKIs in patients with Ph+ or *BCR-ABL*+ ALL. The panel members included hematologists responsible for the care of such patients. Also included on the panel were methodology experts. The panel was asked to identify important clinical questions about the use of TKIs in patients with Ph+ or *BCR-ABL*+ ALL. The methodology experts refined key questions, which were used to identify search terms (Table I).

2.2 Formulation of Recommendations

The panel generated recommendations after group discussion of the evidence. The panel considered both the level of evidence and the quality of the studies. Two moderators with guideline expertise (NS, VP) provided initial guidance to the panel to make recommendations based on a formal grading scheme (described next).

2.2.1 Levels of Evidence and Grading of Recommendations

The levels of evidence and grading of recommendations were adapted from the Canadian Task Force on Preventive Health Care[9] and are illustrated in Table II. For each recommendation, the level of evidence is explicitly stated.

2.2.2 Consensus

Areas of disagreement were resolved through consensus with all panel members. The guideline is organized by clinical question. The relevant background, a summary of the evidence, the consensus process, and the recommendation statement (accompanied by level of evidence and grade of recommendation) follow each question. All evidence is summarized in the evidence tables (Tables III–V).

2.3 Identification and Selection of Studies

The MEDLINE, EMBASE, and Cochrane Library databases and abstracts from key conferences were

TABLE I Search strategy

Ovid MEDLINE search

(((exp leukemia, lymphoid/ OR precursor cell lymphoblastic leukemia-lymphoma/ OR precursor b-cell lymphoblastic leukemia-lymphoma/ OR precursor t-cell lymphoblastic leukemia-lymphoma/) AND (exp philadelphia chromosome/ OR philadelphia.mp)) OR (Philadelphia-positive acute lymphocytic leukemia OR Ph+ ALL).mp) AND (dasatinib OR nilotinib OR imatinib OR tyrosine kinase inhibitor OR TKI).mp) limited to English language and publication date ≥1998

Ovid EMBASE search

((Philadelphia-positive acute lymphocytic leukemia.mp OR Ph+ ALL.mp OR (Acute Lymphocytic Leukemia/ AND (exp philadelphia chromosome/ OR philadelphia.mp))) AND (dasatinib OR nilotinib OR imatinib OR tyrosine kinase inhibitor OR TKI).mp) limited to English language and publication date ≥1998

Cochrane Library search

((Philadelphia):ti,ab,kw AND (leukemia):ti,ab,kw) OR (PH ALL):ti,ab,kw) AND ((tyrosine kinase inhibitor):ti,ab,kw OR (tki):ti,ab,kw OR (dasatinib):ti,ab,kw OR (nilotinib):ti,ab,kw OR (imatinib):ti,ab,kw) limited to English language and publication date ≥1998

Grey literature search

Web sites of these international associations were searched for conference and trial abstracts, limited to English language and publication date ≥2004:

- American Society of Clinical Oncology
- American Society of Hematology
- Canadian Blood and Marrow Transplant Group
- European School of Haematology
- European Group for Blood and Marrow Transplantation
- European Hematology Association
- European Leukemia Net

systematically searched to December 2012. The full search strategy is presented in Table I.

The panel selected studies that met these inclusion criteria:

- Randomized controlled trial, cohort or case series, systematic review, or guideline
- Published in English
- Original reports and abstracts
- Studies were excluded if they
  - did not report clinical outcome,
  - were letters or reviews, or
  - included 5 or fewer patients with Ph+ or *BCR-ABL*+ ALL.

We also excluded studies in which outcomes for patients with CML could not be differentiated from outcomes for patients with ALL, unless the patients with CML accounted for fewer than 5% of cohort members.

2.4 Data Extraction

Three reviewers assessed the citations for inclusion (LS, SL, SC). Data were abstracted by the panel members, verified by an author with methodology expertise (NS), and entered into predefined data abstraction forms. The content of the data abstraction forms was used to generate tables describing trial design, quality, and outcomes (Tables III–V). The tables were used as a basis for discussion by the panel and to generate evidence-based conclusions.

3. RESULTS

3.1 Literature Search Results

The search retrieved 277 papers and thirty-six conference abstracts; eighty articles and the thirty-six conference abstracts were examined further for inclusion. Studies were excluded if patients with ALL could not be differentiated from patients with CML[88–92]; if they summarized results from previous studies of TKIs[8,93]; or if treatment did not include TKIs[94]. Several studies reported data from a cohort of patients that were already reported and thus are counted as one report. The evidence tables were therefore generated using sixty-eight studies described in forty-seven papers and twenty-one abstracts (Table III).

3.2 Recommendations

3.2.1 Question 1

For which patients with Ph+ or *BCR-ABL*+ ALL (*de novo* patients, patients in whom prior therapy has

TABLE II Levels of evidence and recommendation grades according to the Canadian Task Force on Preventive Health Care[a]

Levels of evidence	
I	Evidence from one or more randomized controlled trials
II-1	Evidence from controlled trials without randomization
II-2	Evidence from cohort or case–control analytic studies, preferably from more than one centre or research group
II-3	Evidence from comparisons between times or places with or without the intervention (dramatic results in uncontrolled experiments could be included here)
III	Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees
Recommendation grades	
A	There is good evidence to recommend the action.
B	There is fair evidence to recommend the action.
C	The existing evidence is conflicting and does not allow for a recommendation for or against use of the action; however, other factors might influence decision-making.
D	There is fair evidence to recommend against the action.
E	There is good evidence to recommend against action.
I	There is insufficient evidence (in quantity or quality, or both) to make a recommendation; however, other factors might influence decision-making.

[a] Available at http://www.canadiantaskforce.ca.

failed, and patients with relapsed disease) should TKIs be considered?

Evidence: Of the sixty-eight included studies examining the efficacy of TKIs in patients with Ph+ or *BCR-ABL*+ ALL (Tables III–V), four examined the addition of TKIs after transplantation and were not included in the discussion related to Question 1. Three studies included *de novo* and relapsed patients in their analysis and did not stratify results accordingly. Those studies were also not included in the discussion related to Question 1, leaving sixty-one studies for consideration.

De Novo *Population*: One randomized study of 56 newly diagnosed older patients with Ph+ ALL compared imatinib with chemotherapy during remission induction[10,11]. It demonstrated a clear benefit for patients randomized to imatinib during induction compared with patients randomized to chemotherapy alone. Patients who received imatinib during induction had a higher rate of hematologic response, which was the primary outcome of the study. The overall CR rate was statistically higher in the imatinib induction group (96.3% vs. 50%, $p < 0.0001$). Patients in both arms subsequently received imatinib with consolidation chemotherapy, and the 18-month disease-free survival (DFS) and OS were similar in both groups [29.5% and 57.2% for the imatinib group vs. 34.6% and 41% for the chemotherapy group, p = nonsignificant (NS)].

Thirty-five observational studies had examined the efficacy of induction with TKIs, with or without chemotherapy, in patients with Ph+ ALL. Three studies included a mix of *de novo* and relapsed patients and did not stratify the results by exposure to prior therapies[29,43,65]; those studies were therefore excluded during the discussion of this question. Of the remaining thirty-five studies, twenty-nine administered imatinib, five administered dasatinib, and one administered nilotinib. In thirty prospective studies examining 1677 patients, CR rates ranged from 56% to 100%, with CR rates exceeding 80% in twenty-eight of thirty-one studies. Median DFS ranged from 10 months to 20 months, and median OS ranged from 20 months to 40 months. In addition, 5-year OS ranged from 40% to 60%.

A prospective study comparing imatinib plus chemotherapy with chemotherapy alone showed improvement for both the CR rate (92% vs. 80%) and the median OS (3.1 years vs. 1.1 years, $p = 0.009$) in the imatinib-plus-chemotherapy group[46]. In addition, one abstract reported a comparison of imatinib after induction, imatinib with the second phase of induction, and chemotherapy alone[70]. The abstract reported comparable rates of CR and OS at 3 years in patients treated with or without imatinib (OS: 23% vs. 26%). Among the reviewed studies that addressed this question, the latter study was important, but a notable outlier. Finally, four studies described improved relapse-free survival (RFS) or OS for treated patients compared with historical controls[21,25,26,30,35,59].

Five retrospective studies in 186 patients examined the efficacy of TKI induction, showing similar results. One study comparing imatinib plus chemotherapy with imatinib alone showed statistically comparable CR rates (85% vs. 75%, p = NS), but improved OS with the addition of imatinib to chemotherapy (43% vs. 0% for chemotherapy alone at 1 year, $p = 0.032$)[60]. In addition, a second retrospective study comparing imatinib plus chemotherapy with chemotherapy alone observed improved median OS in the imatinib-plus-chemotherapy group (21.5 months vs. 11.5 months)[48].

Relapsed Population: In the relapsed population, no studies comparing TKIs with chemotherapy were located. One randomized study examined the efficacy of a TKI in relapsed patients with Ph+ ALL. That study randomized 85 patients who had relapsed on imatinib or who were resistant to imatinib to receive dasatinib 140 mg once daily or dasatinib 70 mg twice daily[12]. Compared with patients randomized to 70 mg dasatinib twice daily, those randomized to 140 mg dasatinib once daily had a higher CR rate (50% vs. 38%), but a similar median OS (6.5 months vs. 9.1 months, $p = 0.34$).

TABLE III Study characteristics

Reference	*Country*	*Centre type*	*Patient population*	*Tyrosine kinase inhibitor (TKI)*
Randomized studies				
Ottmann *et al.,* 2007[10]; Wassmann *et al.,* 2003[11]	Germany	Multicentre	*De novo,* not eligible for transplantation; >55 years of age	Imatinib induction 600 mg daily for 4 weeks vs. chemotherapy induction, then imatinib 600 mg for all patients
Lilly *et al.,* 2010[12]	International	Multicentre	Resistant/intolerant to imatinib; median age: 51.0 years (range: 15–80 years)	Dasatinib 140 mg daily vs. 70 mg twice daily until disease progression
Observational studies				
Ottmann *et al.,* 2002[13]	Multinational	Multicentre	Relapsed or refractory	Imatinib 400 mg or 600 mg daily; duration: 24 weeks to indefinite
Wassmann *et al.,* 2002[14]	Germany	Single centre	Relapsed or refractory	Imatinib 600 mg daily before hemopoietic SCT until adverse event or progression
Pfeifer *et al.,* 2003[15] (patients from Ottmann *et al.,* 2002[13])	Germany	Multicentre	Relapsed or refractory	Imatinib 300–600 mg daily; duration not stated
Scheuring *et al.,* 2003[16] (patients from Ottmann *et al.,* 2002[13])	Germany	Single centre	Relapsed or refractory	Imatinib 400 mg or 600 mg daily until toxicity or lack of benefit
Shimoni *et al.,* 2003[17]	Israel, Germany	Multicentre	Pre SCT or donor lymphocyte infusion; 23–61 years of age	Imatinib 400–600 mg daily before SCT or donor lymphocyte infusion
Wassmann *et al.,* 2003[18]	Germany	Single centre	Relapsed or refractory	Imatinib 400 mg or 600 mg daily, plus interferon alfa; median duration: 16 months
Houot *et al.,* 2004[19]	France	Single centre	*De novo*; >55 years of age	Imatinib dose and duration not stated
Piccaluga *et al.,* 2004[20]	Italy	Multicentre	*De novo* or relapsed after complete remission	Imatinib 400–800 mg daily until relapse
Thomas *et al.,* 2004[21]	U.S.A.	Single centre	*De novo,* minimally-treated, or refractory; ≥15 years of age	Induction and consolidation: imatinib 400 mg daily for 2 weeks of each course Maintenance: imatinib 600 mg daily for 13 months

TABLE III Continued

Reference	*Country*	*Centre type*	*Patient population*	*Tyrosine kinase inhibitor (TKI)*
Observational studies continued				
Towatari *et al.,* 2004[22]	Japan	Multicentre	*De novo*; 15–65 years of age	Imatinib 600 mg daily during induction for 8 weeks; consolidation, maintenance for 2 years
Wassmann *et al.,* 2004[23] (patients from Ottmann *et al.,* 2002[13])	Germany	Multicentre	Relapsed, refractory, or minimal residual disease; median age: 48 years	Imatinib 300–600 mg daily; duration: 24 weeks
Brandwein *et al.,* 2005[24]	Canada	Single centre	*De novo*; ≥60 years of age	Imatinib 400–600 mg daily for induction, with or without consolidation, with or without maintenance
Lee *et al.,* 2005[25]	Korea	Single centre	*De novo*; >15 years of age	Imatinib 600 mg daily for induction for 14 days, 400 mg daily for consolidation, 400 mg daily for maintenance for 2 years
Lee *et al.,* 2005[26], 2003[27]	Korea	Single centre	*De novo*; <60 years of age	After induction, in complete remission: imatinib 400 or 600 mg daily for 4 weeks No complete remission: imatinib 600 mg daily
Potenza *et al.,* 2005[28]	Italy	Single centre	Complete remission	Imatinib 800 mg daily for maintenance indefinitely or to toxicity or relapse
Deininger *et al.,* 2006[29]	Europe, U.S.A.	Multicentre	Received imatinib before hematopoietic SCT	Imatinib dose not stated; median 45 days before transplantation
Delannoy *et al.,* 2006[30]	Belgium, France	Multicentre	*De novo*; ≥55 years of age	Imatinib 600 mg daily for 8 weeks, consolidation and maintenance
Kantarjian *et al.,* 2006[31]	U.S.A.	Multicentre	Imatinib resistant; hematologic relapse	Nilotinib 50–1200 mg daily or 400–600 mg twice daily for 12 months
Rea *et al.,* 2006[32]	France	Multicentre	Relapsed, refractory, or resistant disease	Imatinib 400 mg twice daily for 56 days maximum during induction, plus dexamethasone, plus vincristine

TABLE III Continued

Reference	*Country*	*Centre type*	*Patient population*	*Tyrosine kinase inhibitor (TKI)*
Observational studies continued				
Wassmann *et al.,* 2006[33]	Germany	Multicentre	*De novo*; >18 years of age	Group I: imatinib 400–600 mg daily after complete remission for 28 days, with or without imatinib for 8 weeks after consolidation 1 Group II: imatinib 600 mg with induction and up to 8 weeks after consolidation 1
Yanada *et al.,* 2006[34], 2008[35]; Zembutsu *et al.,* 2007[36]	Japan	Multicentre	*De novo*; 15–64 years of age	Imatinib 600 mg daily induction for 7 weeks; consolidation, maintenance for 4 weeks
Carpenter *et al.,* 2007[37]	U.S.A.	Multicentre	Adults and children after hematopoietic SCT	Imatinib 400 mg daily after myeloablative hematopoietic SCT from engraftment to day +365
de Labarthe *et al.,* 2007[38]	France	Multicentre	*De novo*	If complete remission after induction: imatinib 600 mg daily for 90 days for consolidation until SCT If poor response: imatinib 800 mg induction plus chemotherapy, then 800 mg daily for 90 days for consolidation until SCT
Ottmann *et al.,* 2007[39]	Multinational	Multicentre	Imatinib resistant or intolerant	Dasatinib 70 mg twice daily until progression or toxicity
Pfeifer *et al.,* 2007[40]	Germany	Multicentre	*De novo*; >55 years of age	Imatinib induction 600 mg daily vs. imatinib 600 mg daily plus chemotherapy induction for 4 weeks
Vignetti *et al.,* 2007[41]	Italy	Multicentre	*De novo*; >60 years of age	Imatinib 800 mg daily for 45 days during induction, then until progression, plus steroids
Burke *et al.,* 2009[42]	U.S.A.	Single centre	Adults and children undergoing SCT; median age: 21.9 years (range: 2.8–55.2 years)	Imatinib 400–800 mg before or after SCT in adults as tolerated

TABLE III Continued

Reference	*Country*	*Centre type*	*Patient population*	*Tyrosine kinase inhibitor (TKI)*
Observational studies continued				
Nicolini *et al.,* 2009[43]	International	Multicentre	Patients possessing the T315I mutation; >18 years of age between the years 1999 and 2008	Imatinib, dasatinib, nilotinib
Sakamaki *et al.,* 2009[44]	Japan	Not stated	Adults 20–75 years of age resistant or intolerant to imatinib	Phase I: Dasatinib 50, 70, or 90 mg twice daily Phase II: Dasatinib 70 mg twice daily for 12 weeks
Tojo *et al.,* 2009[45]	Japan	Multicentre	Relapsed; ≥20 years of age	Nilotinib 400 mg twice daily as tolerated
Bassan *et al.,* 2010[46] Bassan *et al.,* 2009[47] (abstract)	Italy	Multicentre	*De novo*; median age: 47.1 years (range: 19.5–66 years)	Imatinib 600 mg daily for 7 days
Li *et al.,* 2010[48]	China	Single centre	*De novo*; ≥15 years of age	Imatinib 600 mg daily after induction until next chemotherapy and consolidation
Nishiwaki *et al.,* 2010[49]	Japan	Multicentre	After SCT; median age: 40 years (range: 7–62 years)	Imatinib 400–600 mg after SCT
Olsson–Stromberg *et al.,* 2010[50]	Sweden	Multicentre	After SCT relapse; 13–65 years of age	Dasatinib (dose not stated)
Ravandi *et al.,* 2010[51]; Ravandi *et al.,* 2008[52] (abstract)	U.S.A.	Single centre	*De novo*; ≥21 years of age	Dasatinib 50 mg twice daily for the first 14 days of each chemotherapy cycle; then indefinitely if complete remission
Ribera *et al.,* 2010[53]; Ribera *et al.,* 2004[54] (abstract)	Spain	Multicentre	*De novo*; ≤65 years of age	Imatinib 400 mg daily induction, consolidation, post-transplantation (given until transplantation and followed by maintenance)
Riva *et al.,* 2010[55]	Italy	Single centre	Post-induction maintenance; 25–84 years of age	Imatinib 600–800 mg daily maintenance

TABLE III Continued

Reference	*Country*	*Centre type*	*Patient population*	*Tyrosine kinase inhibitor (TKI)*
Observational studies continued				
Chen *et al.,* 2011[56]	China	Single centre	After SCT; 26 adults, 3 children	Imatinib 400 mg daily after SCT for at least 1 month
Foà *et al.,* 2011[57]; Foà *et al.,* 2007[58] (abstract)	Italy	Multicentre	*De novo*; median age: 53.6 years (range: 23.8–76.5 years)	Dasatinib 70 mg twice daily for 84 days during induction
Mizuta *et al.,* 2011[59]; Yanada *et al.,* 2006[34], 2008[35]; Zembutsu *et al.,* 2007[36]	Japan	Multicentre	*De novo*; median age: 38 years (range: 15–64 years)	Imatinib 600 mg daily induction, consolidation, maintenance
Wang *et al.,* 2011[60]	China	Single centre	*De novo*; median age: 30 years (range: 15–50 years)	Imatinib plus chemotherapy vs. chemotherapy alone (dose not stated)
Bose *et al.,* 2012[61]	U.S.A.	Multicentre	Hematologic relapse (CML, AML); ≥18 years of age	Flavopiridol 30 mg/m^2 each week and imatinib 400 mg daily escalating to 60 mg/m^2 and 1000 mg respectively for 3 weeks every 4 weeks
Caocci *et al.,* 2012[62]	Italy	Single centre	Post SCT; median age: 41 years (range: 18–56 years)	Dasatinib 50–100 mg daily for post-SCT maintenance
Chen *et al.,* 2012[63]	China	Single centre	After SCT; median age: 28.5 years (range: 3–51 years)	Imatinib 400 mg daily for 3–12 months after SCT until complete molecular remission was sustained for at least 3 months (260 mg twice daily, >17 years of age)
Lee *et al.,* 2012[64]	Korea	Single centre	*De novo*; median age: 34 years (range: 15–59 years)	Imatinib 100 mg daily for 4 weeks' induction, consolidation
Pfeifer *et al.,* 2012[65] (patients from Ottmann *et al.,* 2007[39]; Ottmann *et al.,* 2002[13]; Wassmann *et al.,* 2004[23])	Germany	Multicentre	Hematologic relapse and *de novo*; 17–79 years of age	Imatinib 400 mg or 600 mg daily for 4 weeks

TABLE III Continued

Reference	*Country*	*Centre type*	*Patient population*	*Tyrosine kinase inhibitor (TKI)*
Observational studies continued				
Thyagu *et al.,* 2012[66]	Canada	Single centre	*De novo*; median age: 46 years (range: 18–60 years)	Imatinib 400 mg daily for 4 weeks, 400 mg daily maintenance, 600 mg daily indefinitely after maintenance
Abstracts				
Dombret *et al.,* 2004[67]	France	Not stated	Complete remission after HAM chemotherapy	Imatinib 400, 600, or 800 mg daily from day 1 of HAM chemotherapy
Thomas *et al.,* 2004[68]	Not stated	Not stated	*De novo,* minimally treated	Imatinib 400 mg daily, days 1–14 of each chemotherapy cycle
Wetzler *et al.,* 2006[69]	U.S.A.	Multicentre	<60 Years	Imatinib 400 mg twice daily for 4 weeks after induction and after CNS prophylaxis and after treatment until molecularly negative for 12 months
Fielding *et al.,* 2007[70]	U.K., U.S.A.	Multicentre	Not stated	Imatinib 600 mg daily after induction and after hematopoietic SCT or 600 mg daily phase II induction
Pasquini *et al.,* 2007[71]	Multinational	Multicentre	Imatinib resistant or intolerant	Dasatinib 70 mg twice daily or 140 mg daily
Gambacorti–Passerini *et al.,* 2008[72]	Italy	Single centre	Resistant or intolerant to imatinib	Bosutinib 500 mg daily
Arellano *et al.,* 2009[73]	U.S.A.	Single centre	*De novo*; median age: 51 years (range: 22–72 years)	Imatinib plus hyperCVAD; imatinib maintenance
Carella *et al.,* 2009[74]	Italy	Single centre	*De novo*; >18 years of age	Imatinib 600 mg daily plus chemotherapy induction; nilotinib or dasatinib consolidation
Pfeifer *et al.,* 2009[75] (patients from Ottmann *et al.,* 2007[39])	Germany	Single centre	Maintenance therapy after imatinib; median age: 66 years	Imatinib 400 mg daily plus low-dose interferon alfa maintenance

TABLE III Continued

Reference	*Country*	*Centre type*	*Patient population*	*Tyrosine kinase inhibitor (TKI)*
Abstracts continued				
Ribera *et al.,* 2004[54]	Spain	Multicentre	*De novo,* pre- and post-SCT	Imatinib 400 mg daily; imatinib maintenance
Pfeifer *et al.,* 2010[76]	Germany	Multicentre	*De novo*; median age: 43 years	Imatinib 600 mg daily induction, after induction, consolidation
Rousselot *et al.,* 2010[77]	France	Multicentre	*De novo*; median age: 69.1 years	Dasatinib 140 mg daily plus chemotherapy induction for 4 weeks; sequential consolidation, alternating maintenance up to 2 years
Thomas *et al.,* 2010[78]	U.S.A.	Single centre	*De novo* or minimally treated; median age: 51 years	Imatinib 600 mg plus hyperCVAD
Kim *et al.,* 2011[79]	Korea	Multicentre	*De novo*; >18 years of age	Nilotinib 400 mg twice daily plus chemotherapy induction from day 8 of induction to transplantation
Lee *et al.,* 2011[80]	Korea	Single centre	*De novo*; median age: 47 years	Dasatinib100 mg daily for 4 weeks plus chemotherapy; dasatinib maintenance up to 2 years
Lee *et al.,* 2011[81]; Ravandi *et al.,* 2008[52]; Ravandi *et al.,* 2009[82]	U.S.A.	Single centre	*De novo*; median age: 56 years	Dasatinib 50 mg twice daily for first 14 days of 8 cycles or 100 mg daily plus hyperCVAD; maintenance dasatinib for 2 years
Liu–Dumlao *et al.,* 2011[83]; Ravandi *et al.,* 2009[82]	U.S.A.	Single centre	Relapsed; median age: 50 years	Dasatinib 100 mg daily plus alternating hyperCVAD, and high-dose cytarabine with methotrexate for 2 weeks in each of 8 cycles, followed by maintenance dasatinib monthly for 2 years
Pfeifer *et al.,* 2011[84]	Germany	Single centre	Post-transplantation	Imatinib 400–600 mg daily prophylactically or pre-emptively (after detection of Bcr-Abl transcripts)

TABLE III Continued

Reference	*Country*	*Centre type*	*Patient population*	*Tyrosine kinase inhibitor (TKI)*
Abstracts continued				
Brummendorf *et al.*, 2012[85]	Multinational	Multicentre	Relapsed after TKI	Bosutinib 500 mg daily
Cortes *et al.*, 2012[86]	U.S.A.	Multicentre	Resistant	Ponatinib 45 mg daily

SCT = stem-cell transplantation; CML = chronic myelogenous leukemia; AML = acute myeloid leukemia; HAM = cytarabine, mitoxantrone; CNS = central nervous system; hyperCVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone.

TABLE IV Quality of the studies

Reference	*Study design*	*Outcomes*		*Follow-up duration*	*Not included in final analysis*	
		Primary	*Secondary*		(n)	(%)
Randomized studies						
Ottmann *et al.*, 2007[10] Wassmann *et al.*, 2003[11]	Randomized controlled trial	Hematologic response after induction	Complete molecular response Recurrence Death Discontinuation of imatinib Toxicity	Median: 11 months	2/55	3
Lilly *et al.*, 2010[12]	Randomized open-label phase III	Major hematologic response	Overall response Cytogenetic response Progression-free survival Overall survival Safety Time to response	2 Years	1	
Observational studies						
Ottmann *et al.*, 2002[13]	Prospective case series	Complete hematologic response Marrow complete response Partial response	Cytogenic response Time to progression Overall survival	Approximately 12 months	Not stated	
Wassmann *et al.*, 2002[14]	Case series	Efficacy Tolerability	Response to hematopoietic stem-cell transplantation	Median: 13 months	8/30 (not transplanted)	

TABLE IV Continued

Reference	*Study design*	*Outcomes*		*Follow-up duration*	*Not included in final analysis*	
		Primary	*Secondary*		(n)	*(%)*
Observational studies continued						
Pfeifer *et al.*, 2003[15]	Retrospective case series	Incidence and risk factors for CNS relapse	Complete remission	Not stated	0	
Scheuring *et al.*, 2003[16]	Retrospective case series	Predictors Prognosis of *BCR-ABL* to duration of response	Complete remission Molecular response Time to progression Overall survival	4 Weeks	Variable	
Shimoni *et al.*, 2003[17]	Case series	Stem-cell transplantation and donor lymphocyte infusion outcomes	Complete remission Cytogenic response Toxicity Graft-vs-host disease Engraftment	Median: 10 months	0	
Wassmann *et al.*, 2003[18]	Prospective case series	Efficacy Tolerability Safety	Time to progression Relapse Refractoriness Overall survival	Median: 16 months	0	
Houot *et al.*, 2004[19]	Retrospective case series	Characteristics Response	Not stated	Median: 8 months	0	
Piccaluga *et al.*, 2004[20]	Case series	Significance of molecular remission	Not stated	Up to 40 months	0	
Thomas *et al.*, 2004[21]	Prospective cohort	Not stated	Not stated	Median: 20 months	0	
Towatari *et al.*, 2004[22]	Prospective case series	Complete remission	Toxicity Response duration Survival	Median: 12 months	0	
Wassmann *et al.*, 2004[23]	Retrospective case series	Factors predicting response and response duration	Time to progression Overall survival	Not stated	0	

TABLE IV Continued

Reference	*Study design*	*Outcomes*		*Follow-up duration*	*Not included in final analysis*	
		Primary	*Secondary*		(n)	(%)
Observational studies continued						
Brandwein *et al.*, 2005[24]	Retrospective case series	Predictors of response	Complete remission Progression-free survival Overall survival	Not stated	0	
Lee *et al.*, 2005[25]	Prospective cohort	Complete remission Remission duration Overall survival	Not stated	Median: 26 months	0	
Lee *et al.*, 2005[26] Lee *et al.*, 2003[27]	Prospective cohort	Time to stem-cell transplantation Transplantation outcome	Response rate Overall survival Disease-free survival	Median: 25 months	0	
Potenza *et al.*, 2005[28]	Case series	Efficacy	Minimal residual disease	24 Months	0	
Deininger *et al.*, 2006[29]	Retrospective cohort	Overall survival Progression-free survival Relapse rate Time to engraftment	Not stated	21.6 Months	0	
Delannoy *et al.*, 2006[30]	Prospective cohort	Overall survival	Complete remission Relapse-free survival Toxicity Minimum residual disease	Median: 24 months survivors 14	1/30 (complete response)	3
Kantarjian *et al.*, 2006[31]	Prospective case series	Safety Hematologic response Cytogenic response Tolerability	Not stated	12 Months	Not stated; 45% did not complete the study	
Rea *et al.*, 2006[32]	Case series	Complete hematologic response	Overall survival Disease-free survival	Median: approximately 8 months	0	

TABLE IV Continued

Reference	*Study design*	*Outcomes*		*Follow-up duration*	*Not included in final analysis*	
		Primary	*Secondary*		(n)	(%)
Observational studies continued						
Wassmann *et al.*, 2006[33]	Prospective cohort	Feasibility Toxicity	Complete remission Response rate Transplantation rate Minimal residual disease	Not stated, to stem-cell transplantation	0	
Yanada *et al.*, 2006[34], 2008[35]; Zembutsu *et al.*, 2007[36]	Prospective cohort	Complete remission	Response duration Overall survival Toxicity	38 Months	0	
Carpenter *et al.*, 2007[37]	Prospective case series	Safety and tolerability 90 days after stem-cell transplantation	Survival Molecular relapse	Median: 11 months	0	
de Labarthe *et al.*, 2007[38]	Prospective case series	Not stated	Not stated	Median: 18 months	0	
Ottmann *et al.*, 2007[39]	Prospective case series	Major hematologic response plus overall hematologic response	Cytogenic response Duration of hematologic response Safety Tolerability	Minimum: 8 months	0	
Pfeifer *et al.*, 2007[40]	Retrospective	Kinase domain mutation	Kinase domain mutation and hematologic response Relapse	NA	7/55	12
Vignetti *et al.*, 2007[41]	Prospective case series	Complete hematologic response Complete molecular response Complete remission Toxicities	Not stated	Maximum: 32 months	1/30	3

TABLE IV Continued

Reference	*Study design*	*Outcomes*		*Follow-up duration*	*Not included in final analysis*	
		Primary	*Secondary*		(n)	*(%)*
Observational studies continued						
Burke *et al.*, 2009[42]	Prospective case series	Overall survival Relapse-free survival Risk of relapse Cardiac toxicity	Not stated	Median: 0.93 years	0	
Nicolini *et al.*, 2009[43]	Cross-sectional survey	Mutation testing Overall survival Progression-free survival	Not stated	Not stated	0	
Sakamaki *et al.*, 2009[44]	Prospective case series	Hematologic response Major cytogenic response Safety	Not stated	Not stated	1	
Tojo *et al.*, 2009[45]	Prospective case series	Hematologic response Complete remission Pharmacokinetics Safety	Not stated	Minimum: 12 months	0	
Bassan *et al.*, 2010[46] Bassan *et al.*, 2009[47] (abstract)	Prospective case series	Overall survival	Disease-free survival Treatment-related mortality Cumulative incidence relapse Minimal residual disease	Median: 5 years	6	
Li *et al.*, 2010[48]	Retrospective case series	Overall survival Disease-free survival Complete remission Molecular complete response Relapse	Not stated	Median: 12.5 months	0	
Nishiwaki *et al.*, 2010[49]	Retrospective case series	Hematologic response Overall survival Minimal residual disease	Not stated	Maximum: 2 years	0	
Olsson–Stromberg *et al.*, 2010[50]	Not stated	Mutation analysis	Not stated	Not stated	0	

TABLE IV Continued

Reference	*Study design*	*Outcomes*		*Follow-up duration*	*Not included in final analysis*	
		Primary	*Secondary*		(n)	*(%)*
Observational studies continued						
Ravandi *et al.,* 2010[51] Ravandi *et al.,* 2008[52] (abstract)	Prospective case series	Minimal residual disease Complete remission Disease-free survival Event-free survival Overall survival	Adverse events	Median: 14 months	2/35 (complete response)	6
Ribera *et al.,* 2010[53] Ribera *et al.,* 2004[54] (abstract)	Prospective case series	Complete hematologic response Percentage of patients reaching transplantation Feasibility of imatinib treatment	Toxicity Safety Disease-free survival Overall survival	Median: 4.1 years	0	
Riva *et al.,* 2010[55]	Prospective cohort	Minimal residual disease Hematologic response	Not stated	Minimum: 4 months	0	
Chen *et al.,* 2011[56]	Prospective case series	Minimal residual disease Overall survival Disease-free survival Response rate Safety	Not stated	Median: 24 months	0	
Foà *et al.,* 2011[57] Foà *et al.,* 2007[58] (abstract)	Prospective case series	Complete hematologic response	Toxicity Immunophenotypic response rate Molecular response Disease-free survival Response rate Overall survival	Median: 24.8 months	2/55	4
Mizuta *et al.,* 2011[59] Yanada *et al.,* 2006[34], 2008[35]; Zembutsu *et al.,* 2007[36]	Prospective cohort	Transplantation outcome Overall survival	Disease-free survival Response duration	Not stated	0	

TABLE IV Continued

Reference	*Study design*	*Outcomes*		*Follow-up duration*	*Not included in final analysis*	
		Primary	*Secondary*		(n)	*(%)*
Observational studies continued						
Wang *et al.*, 2011[60]	Retrospective case series	Complete remission Overall survival Relapse-free survival	Not stated	Approximately 40 months	0	
Bose *et al.*, 2012[61]	Prospective case series	Safety Complete hematologic response Pharmacodynamics	Not stated	Not stated	1/22 (CML)	
Caocci *et al.*, 2012[62]	Prospective case series	Minimal residual disease	Not stated	17 Months after stem-cell transplantation	0	
Chen *et al.*, 2012[63]	Prospective case series	Safety	Response rate Disease-free survival Overall survival	31 Months	2/82 (imatinib group)	2
Lee *et al.*, 2012[64]	Prospective case series	Complete hematologic response Major molecular response Complete molecular response Overall survival Disease-free survival	Not stated	61 Months	18	
Pfeifer *et al.*, 2012[65] Patients from Ottmann *et al.*, 2007[39]; Ottmann *et al.*, 2002[13]; Wassmann *et al.*, 2004[23]	Prospective case series	Mutation status	Not stated	Multiple	Not available	
Thyagu *et al.*, 2012[66]	Prospective case series	Complete remission Major cytogenic response Overall survival Event-free survival	Not stated	85 Months	0	

TABLE IV Continued

Reference	*Study design*	*Outcomes*		*Follow-up duration*	*Not included in final analysis*	
		Primary	*Secondary*		(n)	*(%)*
Abstracts						
Dombret *et al.,* 2004[67]	Prospective case series	Increased molecular response Feasibility of autologous stem-cell collection	Safety	Not stated	Not stated	
Thomas *et al.,* 2004[68]	Prospective case series	Not stated	Not stated	Median: 24 months	4/22	18
Wetzler *et al.,* 2006[69]	Case series	Not stated	Not stated	Not stated	11/18	65
Fielding *et al.,* 2007[70]	Prospective cohort	Role of etoposide or total body irradiation in SCT	Not stated	More than 6 months	Not stated	
Pasquini *et al.,* 2007[71]	Randomized controlled trial	Major hematologic response	Not stated	Median: 6.5 months	Not stated	
Gambacorti–Passerini *et al.,* 2008[72]	Prospective case series	Complete hematologic response Major cytogenic response Adverse events	Not stated	Median: 6.1 weeks	0	
Thomas *et al.,* 2008[87]	Prospective case series	Complete hematologic response Complete molecular response	Not stated	Not stated	Not stated	
Arellano *et al.,* 2009[73]	Prospective case series	Complete hematologic response Complete molecular response Disease-free survival Overall survival	Not stated	Median: 18.3 months	1 (after complete cytogenic response)	

TABLE IV Continued

Reference	*Study design*	*Outcomes*		*Follow-up duration*	*Not included in final analysis*	
		Primary	*Secondary*		(n)	(%)
Abstracts continued						
Carella *et al.*, 2009[74]	Prospective case series	Complete remission Molecular response	Not stated	Not stated	Not stated	
Pfeifer *et al.*, 2009[75] (patients from Ottmann *et al.*, 2007[39])	Prospective case series	Complete remission Minimal residual disease Mutational analysis	Disease-free survival Overall survival Response rate	Not stated	0	
Ribera *et al.*, 2004[54]	Prospective case series	Complete remission Complete molecular response Major molecular response Disease-free survival Overall survival	Not stated	Median: 4.1 years	0	
Pfeifer *et al.*, 2010[76]	Prospective case series	Complete remission Minimal residual disease Mutation analysis	Not stated	Median: 26 months	0	
Rousselot *et al.*, 2010[77]	Prospective case series	Complete remission Relapse-free survival Cytogenetics	Not stated	Maximum: 4 years	0	
Thomas *et al.*, 2010[78]	Prospective case series	Complete remission Major cytogenic response Overall survival	Not stated	Median: 16.3 months	0	
Kim *et al.*, 2011[79]	Prospective case series	Hematologic complete response Major cytogenic response Overall survival Event-free survival Relapse-free survival	Not stated	Median: 77 months	0	

TABLE IV Continued

Reference	*Study design*	*Outcomes*		*Follow-up duration*	*Not included in final analysis*	
		Primary	*Secondary*		(n)	(%)
Abstracts continued						
Lee *et al.*, 2011[80]	Prospective case series	Complete remission Minimal residual disease Major molecular response	Not stated	Median: 1.4 months	0	
Lee *et al.*, 2011[81] Ravandi *et al.*, 2008[52]; Ravandi *et al.*, 2009[82]	Prospective case series	Complete remission Disease-free survival Overall survival	Not stated	Median: 10 months	6/36	
Liu–Dumlao *et al.*, 2011[83] Ravandi *et al.*, 2009[82]	Prospective case series	Complete remission Cytogenic response Molecular response	Not stated	Median: 26.1 months	Not stated	
Pfeifer *et al.*, 2011[84]	Prospective case series	Minimal residual disease Remission duration Tolerability	Not stated	Median: 139 weeks	0	
Brummendorf *et al.*, 2012[85]	Prospective case series	Major hematologic response Complete hematologic response	Not stated	Median: 30 months	Not stated	
		Major cytogenic response Complete cytogenic response	Not stated	Median: 31 months	0	
Cortes *et al.*, 2012[86]	Prospective case series	Adverse events Major hematologic response Molecular response Cytogenic response Dose-limiting toxicities	Not stated	Median: 56 weeks	0	

TABLE V Outcomes

Reference	*Patients* (n)	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation* [n *(%)*]	*Time to relapse*	*Overall survival*
			Hematologic [n *(%)*]	*Molecular or cytogenic* [n *(%)*]				
Randomized studies								
Ottmann *et al.*, 2007[10]; Wassmann *et al.*, 2003[11]	Total: 55 28 27 (2 CML)	Induction with: Imatinib Chemotherapy	CR: 26/27 (96%) 13/26 (50%) (p<0.0001)	CR: 11/27 (41%) 11/22 (50%) (p=NS)	Relapse: 15/28 (54%) 10/27 (37%)	Not available	Remission duration: 17 months 20 months	 79% 70% (p=NS)
Lilly *et al.*, 2010[12]	Total: 84 40 44	Dasatinib: 140 mg daily 70 mg twice daily	 20/40 (50%) 15/44 (38%)	 28/40 (70%) 23/44 (52%)	Median PFS: 4.1 months 3.1 months (p=0.73)	Not stated	Median HR: 4.6 months 11.5 months	Median: 6.5 months 9.1 months (p=0.34)
Observational studies								
Ottmann *et al.*, 2002[13]	48	Imatinib	Complete HR: 9/48 (19%) Marrow CR: 5/48 (10%) Marrow PR: 15 (31%)	CYR: 8/48 (17%)	At 6 months: PFS, 12%	Not available	Median TTP: 2.2 months	At 6 months: 40% Median OS: 5 months
Wassmann *et al.*, 2002[14]	46	Imatinib before transplantation	5/46 (11%)	5/46 (11%)	12/46 (25.5%)	22/46 (48%)	Not available	Not available
Pfeifer *et al.*, 2003[15]	65	Single-agent imatinib	2/8 (25%) with CNS relapse	Not stated	8/65 (12%)	Not available	CNS relapse: 11–274 days	2/8 (25%) with CNS relapse
Scheuring *et al.*, 2003[16]	56	Single-agent imatinib	Complete HR or marrow CR: 40/56 (71%) HR: 60%–70%	14/56 (25%) had one PCR	Relapse: 24/40 (60%) with complete HR; Bcr-Abl level not predictive of TTP	Not available	Median: 1.5–3.5 months	Bcr-Abl level not predictive of OS
Shimoni *et al.*, 2003[17]	6	Imatinib before transplantation	CR: 5/6 after transplantation	2/6 (33%)	4/6 (67%)			3/6 (50%)

TABLE V Continued

Reference	*Patients* (n)	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation* [n *(%)*]	*Time to relapse*	*Overall survival*
			Hematologic [n *(%)*]	*Molecular or cytogenic* [n *(%)*]				
Observational studies continued								
Wassmann *et al.,* 2003[18]	6	Imatinib plus interferon	3/6 (50%)	3/6 (50%) MRD-negative	At 17 months: 2/6 (33%)	Not available	Not stated	4/6 (67%)
Houot *et al.,* 2004[19]	8	Imatinib plus chemotherapy	4/4 Imatinib plus chemotherapy induction; 0/4 imatinib after induction	Not stated	DFS: 2–7 months for imatinib plus chemotherapy induction	Not available	Not stated	4/4 for imatinib at consolidation; 2–8 months for imatinib after induction
Piccaluga *et al.,* 2004[20]	12	Imatinib	10/12 (84%) after 4 weeks	Complete MR: 6/12 (50)	Complete MR: 7/12 (58%); yes, 8 months no, 4 months ($p<0.01$)	Not available	Not stated	5/12 (42%)
Thomas *et al.,* 2004[21]	Total: 81	Group:		PCR-negative:	DFS:	Not available	Not stated	At 20 months:
	20	Imatinib plus hyperCVAD	15/15 (100%)	12/20 (60%)	18/20 (90%)			15/20 (75%)
	31	VAD	19/31 (61%)	Not stated	5/19 (26%)			1/31 (3%)
	50	HyperCVAD	47/50 (94%) ($p<0.01$)	Not stated	14/47 (9%) ($p<0.01$)			8/50 (16%) ($p<0.01$)
Towatari *et al.,* 2004[22]	24	Chemotherapy plus imatinib with or without hematopoietic SCT	23/24 (96%) after induction	18/24 (78%)	4/24 (17%) 1-year EFS: 68%	Not available	4–10	1 Year OS: 89%
Wassmann *et al.,* 2004[23]	68	Single-agent imatinib	HR: 70% Complete HR: 30%	Complete MR: 10/36 (28%)	PFS: 23% at 6 months	Not available	Median: 4 months	1 Year: 33% 18 Months: 23%

TABLE V Continued

Reference	*Patients* (n)	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation* [n *(%)*]	*Time to relapse*	*Overall survival*
			Hematologic [n *(%)*]	*Molecular or cytogenic* [n *(%)*]				
Observational studies continued								
Brandwein *et al.*, 2005[24]	9	Imatinib 400–600 mg daily, plus chemotherapy	Not stated	Not stated	Not stated	Not stated	Not stated	44% >24 months
Lee *et al.*, 2005[25]	20	Chemotherapy plus imatinib	CR: 19/20 (95%) Median: 28 days	12/17 (70%) Negative after cycle 1	13/19 (68%) Median duration of CR: 26 months	Not stated	Median CR: 27 months	Median survival: 29 months
	18	Historical controls receiving chemotherapy only	15/18 (83%)	Not stated	1/15 (7%)		9.5 months ($p<0.05$)	13 months ($p<0.02$)
Lee *et al.*, 2005[26]		Group:	CR:	19/27 (70%)	3-Year EFS:	Not available	Not stated	24/29 (83%);
Lee *et al.*, 2003[27]	29	HyperCVAD plus imatinib	23/29 (79%)		78%			median: 25 months
	33	Historical controls receiving hyperCVAD	27/33 (82%) after induction	Not stated	5-Year estimated DFS: 39% ($p<0.01$)			12/31 (39%); median: 51 months
Potenza *et al.*, 2005[28]	7	Imatinib	6/7 (86%) at median follow-up	4/7 (57%) at follow-up	6/7 (84%) PFS: 64% at 24 months	Not available	15	At 24 months: 75%
Deininger *et al.*, 2006[29]	21	Imatinib before transplantation in relapsed, and *de novo*	13/21 (62%) before transplantation	Not stated	Not stated	Not stated	Not stated	Not available

TABLE V Continued

Reference	*Patients* (n)	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation* [n *(%)*]	*Time to relapse*	*Overall survival*
			Hematologic [n *(%)*]	*Molecular or cytogenic* [n *(%)*]				
Observational studies continued								
Delannoy *et al.*, 2006[30]	30	Group: Imatinib for 60 days after consolidation	CR: 70%; 27/30 (90%) after consolidation	Not stated	Median: 20 months; at 1 year: 58%	Not available	Median: 11 months	At 1 year: 66%
	21	Historical controls receiving chemotherapy plus interferon	CR: 29% ($p<0.01$); 10/21 (48%) after consolidation		Median: 4 months ($p<0.01$); at 1 year: 11%		Not stated	43% ($p<0.01$)
Kantarjian *et al.*, 2006[31]	13	Nilotinib	PR: 1/10 (10%)	1/3 (33%)	Not stated	Not stated	Not stated	Not stated
Rea *et al.*, 2006[32]	18	Imatinib plus DIV	17/18 (94%)	Major CYR: 10/11 (90%) MR: 1/15 (7%)	Not stated	Not available	Not stated	Median: 14 months
Wassmann *et al.*, 2006[33]	47 (4 CML)	Group I: Imatinib 400–600 mg daily after induction	CR: 78%	19%	Not stated	Not stated	Not stated	Median survival: 19 months
	45	Group II: Imatinib 600 mg with induction	56% after induction	52% Negative MRD ($p=0.01$)				44% >24 months
Yanada *et al.*, 2006[34], 2008[35]; Zembutsu *et al.*, 2007[36] (gene analysis)	2006: 80 2008: 100	Imatinib with multiagent induction, consolidation, maintenance, with or without SCT	97.6% After induction	At day 63: 33/66 (50%)	EFS at 1 year: 60%; RFS at 3 years: 46% of the 97 achieving CR	Not stated	Not stated	At 1 year: 76% At 3 years: 55%
	51	Historical controls receiving chemotherapy	51% ($p<0.01$)		20% ($p<0.01$)			At 3 years: 60% ($p<0.01$)

TABLE V Continued

Reference	*Patients* (n)	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation* [n *(%)*]	*Time to relapse*	*Overall survival*
			Hematologic [n *(%)*]	*Molecular or cytogenic* [n *(%)*]				
Observational studies continued								
Carpenter *et al.*, 2007[37]	15	Imatinib after SCT	13/15 (80%)	PCR before SCT: 6/13 (46%) PCR after SCT: 12/15 (80%)	2/15 (13%)	Not available	After SCT: 0.3–2 years	12/15 (80%); median: 15 months
de Labarthe *et al.*, 2007[38]	45	Imatinib plus chemotherapy induction, consolidation with or without SCT OR Imatinib plus chemotherapy induction, and imatinib consolidation with or without SCT	96%	13/45 (29%); PCR: 25/45 (56%) and $<10^{-4}$	8/43 (19%) of patients achieving CR	Not available	Not stated	35/45 (77%)
Ottmann *et al.*, 2007[39]	36	Dasatinib alone	Overall HR: 18/36 (50%)	Major CYR: 21/36 (58%)	Median PFS: 3.3 months	Not available	Not stated	89%
Pfeifer *et al.*, 2007[40]	Not stated	Group: Imatinib induction Chemotherapy induction	Kinase domain mutation: Yes, 9/9 (100%) No, 9/10 (90%) Yes, 5/8 (63%) No, 6/11 (55%)	Kinase domain mutation: Yes, 5/17 (29%) No, 7/21 (33.3%)	Kinase domain mutation: Relapsed— Yes, 11/17 (64%) No, 11/25 (24%)	Not available	Not stated	Yes, 12/17 (70%); no, 21/25 (84%)
Vignetti *et al.*, 2007[41]	30	Imatinib plus prednisone	29/29 (100%)	4/27 (15%)	15/29 (52%) DFS at 12 months: 48%	Not available	14/29 (48%) Median relapse rate: 4 months	Median: 20 months; OS: 74% at 12 months; 13/29 (45%) at 10 months

TABLE V Continued

Reference	*Patients (n)*	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation [n (%)]*	*Time to relapse*	*Overall survival*
			Hematologic [n (%)]	*Molecular or cytogenic [n (%)]*				
Observational studies continued								
Burke *et al.*, 2009[42]	Total: 32	Group:	Not stated	Not stated	RFS at 2 years:	Not stated	Not stated	At 2 years:
	15	Imatinib (before stem-cell transplantation)			10/15 (67%)			9/15 (61%)
	13				8/13 (62%)			7/13 (54%)
	2	(after stem-cell transplantation)			2/2 (100%)			2/2 (100%)
	17	Non-imatinib			6/17 (35%) (p=0.12)			7/17 (41%) (p=0.19)
Nicolini *et al.*, 2009[43]	222 (46 ALL)	Imatinib: 96%	Not stated	Not stated	Median PFS: 2.5 months	Not stated	Not stated	Median: 4.9 months
Sakamaki *et al.*, 2009[44]	55 (13 ALL)	Dasatinib	Major HR: 5/13 (38%) Complete HR: 1/13 (8%)	CYR: major, 7/13 (54%) complete, 6/13 (46%)	Not stated	Not stated	Not stated	Not stated
Tojo *et al.*, 2009[45]	34 (7 ALL)	Nilotinib	HR: 3/7 (43%) CR	MRD: 2/7 (29%) Major MR: 1/7 (14%)	Not stated	Not stated	Median duration of major CYR not reached	Not stated
Bassan *et al.*, 2010[46]; Bassan *et al.*, 2009[47] (abstract)	Total: 100	Group:	CR:	PCR-negative:	Median DFS:		Not stated	Median:
	59	Imatinib plus chemotherapy	49/53 (92%)	29%–40%	1.5 years	39/54 (72%)		3.1 years
	35	Chemotherapy only	33/41 (80%)	25%–14%	0.8 years (p=0.044) DFS probability at 5 years: 0.39 vs. 0.25 (p=0.044)	15/28 (54%)		1.1 years (p=0.009) Probability at 5 years: 0.38 vs. 0.23 (p=0.009)

TABLE V Continued

Reference	*Patients (n)*	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation [n (%)]*	*Time to relapse*	*Overall survival*
			Hematologic [n (%)]	*Molecular or cytogenic [n (%)]*				
Observational studies continued								
Li *et al.*, 2010[48]	Total: 110	Group:	Not stated		Median DFS:	22/110 (20%)	9 Months	
	41	Imatinib plus chemotherapy		Complete MR: 16/41 (49%) CYR: 37/41 (90.2%)	10 months			22/41 (54%); median: 21.5 months
	47	Chemotherapy only		Complete MR: 6/47 (12.8%) CYR: 37/47 (78.7%)	7 months			9/47 (19%); median: 11.5 months
	22	SCT		Complete MR: 8/22 (36.4%) CYR: 22/22 (100%)	23 months			13/22 (59%); median: 25 months
Nishiwaki *et al.*, 2010[49]	34	Imatinib	Not stated	After 1 year: MRD-positive in all patients	At 2 years: relapse rate, 45.8% DFS, 35.2%	All had SCT	At 1 year: relapse rate, 45.3%	At 1 year: 45.35%; at 2 years: 37.8%
Olsson–Stromberg *et al.*, 2010[50]	Total: 11 (3 relapsed ALL; 8 CML)	Dasatinib	CR: 1/3 (33%)	Complete MR: 2/3 (67%) CYR: 1/3 (33%)	Not stated	Not stated	Not stated	1/3 (33%)
Ravandi *et al.*, 2010[51]; Ravandi *et al.*, 2008[52] (abstract)	35	Dasatinib with hyperCVAD	CR: 33/35 (94%) after 1 cycle	Complete MR: 7/35 (20%) CYR: 27/35 (77%)	Relapse: 5; in CR: 24 (69%)	In first CR: 4/35 (11%)	Median: 57 weeks	Estimated 2-year: 64%
Ribera *et al.*, 2010[53]; Ribera *et al.*, 2004[54] (abstract)	30	Imatinib plus chemotherapy	CR: 27/30 (90%)	PCR-negative: 11/26 (42%) before cycle 2; 15/26 (58%) negative for MRD	Median DFS: 1.5 years; at 4.1 years: 30%	Stem-cell transplantation: 21/27 (78%)	Not stated	Median: 1.7 years; at 4.1 years: 30%
Riva *et al.*, 2010[55]	10	Imatinib	6/10 (60%)	Complete MR: 1/10 (10%)	Not stated	Not stated	Not stated	7/10 (70%)

TABLE V Continued

Reference	*Patients* (n)	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation* [n *(%)*]	*Time to relapse*	*Overall survival*
			Hematologic [n *(%)*]	*Molecular or cytogenic* [n *(%)*]				
Observational studies continued								
Chen *et al.,* 2011[56]	29 (26 adults)	Imatinib	Not stated	7/11 Positive became negative after 1 month (median)	At 3 years: DFS, 75.3% relapse rate, 11.3%	Not stated	Not stated	At 24 months: 22/29 (76%)
Foà *et al.,* 2011[57] Foà *et al.,* 2007[58] (abstract)	55	Dasatinib and prednisone	Complete HR: 53/53 (100%)	Day 85: 8/53 (15%) maintained PCR negativity	At 20 months: no relapse, 42.9% DFS, 51%	Not available	Median: 23 days to complete HR; 5.9 months to relapse from complete HR	At 20 months: 69.2%
Mizuta *et al.,* 2011[59]	Total: 173	Group:	Not stated	36/48 MRD-negative at SCT	DFS at 3 years:	All had SCT		At 3 years:
Yanada *et al.,* 2006[34], 2008[35];	51	Imatinib			58%		Median: 137 days;	65%
Zembutsu *et al.,* 2007[36]	122	Pre-imatinib historical controls			37% (p=0.039)		range: 68–728 days Median: 240 days; range: 42–2302 days	44% (p=0.0148)
Wang *et al.,* 2011[60]	Total: 21	Group:	CR:	Not stated	RFS at 1 year:	4/21 (19%)	Not stated	At 1 year:
	13	Imatinib plus chemotherapy	11/13 (84.6%)		27%			43%
	8	Chemotherapy only	6/8 (75.0%) (p=0.59)		0/8 (0) (p=0.079)			0/8 (0%) (p=0.032)
Bose *et al.,* 2012[61]	Total: 21 (17 CML) (4 AML)	Imatinib plus flavopiridol (relapsed setting)	Complete HR: 0/4 (bone marrow and peripheral blood)	CyR: 1/4 (25%)	Not stated	Not stated	Not stated	Not stated
Caocci *et al.,* 2012[62]	10	Dasatinib after SCT	Not stated	MRD-negative: 8/8 (100%)	Not stated	All (10/10)	Not stated	Median OS: 22 months

TABLE V Continued

Reference	*Patients* (n)	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation* [n *(%)*]	*Time to relapse*	*Overall survival*
			Hematologic [n *(%)*]	*Molecular or cytogenic* [n *(%)*]				
Observational studies continued								
Chen *et al.,* 2012[63]	82	Imatinib after SCT	100% after engraftment	8/14 *BCR-ABL*+ became negative; 4/48 *BCR-ABL*− became positive	At 5 years: median DFS, 68.9%	Not available	9 Months	At 31 months: 52/62 (84%); at 5 years: 71%
Lee *et al.,* 2012[64]	95	Imatinib plus chemotherapy, induction and consolidation	CR: 90/95 (95%) at induction end	MR: major, 33/95 (35%) complete, 12/95 (12.6%)	Median DFS: 61.5% at 5 years	Not available	11 Months after SCT	At 61 months: 61/95 (64%); at 5 years: 63.7%
Pfeifer *et al.,* 2012[65] patients from Ottmann *et al.,* 2007[39]; Ottmann *et al.,* 2002[13]; Wassmann *et al.,* 2004[23]	91	Imatinib induction or relapsed setting	CR by kinase domain mutation: Yes, 13/24 (54%) No, 20/35 (57%)	Not stated	Not stated	SCT: 10/65	Median TTP: *de novo,* 452 days; salvage, 67 days	Not stated
Thyagu *et al.,* 2012[66]	32	Imatinib induction, intensification, maintenance	CR: 30/32 (94%)	Complete MR: 2/19 (11%)	Median EFS: 30.1 months; at 3 years: 50%	SCT: 16/32	Not stated	Median OS: 40.7 months; at 3 years: 53%
Abstracts								
Dombret *et al.,* 2004[67]	22	Imatinib plus chemotherapy (HAM)	Not available	At 45 days: 5/15 (33%)	18-Month DFS: 58%	Not available	Not stated	18-Month OS: 78%
Thomas *et al.,* 2004[68]	32	Imatinib plus hyperCVAD	25/26 (96%)	19 (50%)	2-Year DFS: 87%	Not stated	Not stated	Not stated
Wetzler *et al.,* 2006[69]	18	Chemotherapy plus imatinib	Not stated	3/3	3/7 (43%)	Need for transplantation	Not stated	5/7 (71%)

TABLE V Continued

Reference	*Patients (n)*	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation [n (%)]*	*Time to relapse*	*Overall survival*
			Hematologic [n (%)]	*Molecular or cytogenic [n (%)]*				
Abstracts continued								
Fielding *et al.,* 2007[70]		Imatinib:			Not stated	Not available	Not stated	At 3 years: 23% with imatinib; 26% without
	89	After induction	81%					
	64	With phase II induction	91%					
	267	Chemotherapy	83%					
Pasquini *et al.,* 2007[71]		Dasatinib:		Major CyR:	Not stated	Not stated	Not stated	Not stated
	Not stated	Daily	38%	68%				
	Not stated	Twice daily	32%	55%				
Gambacorti–Passerini *et al.,* 2008[72]	72 (17 ALL)	Bosutinib	HR: complete, 2/13 (15%); major, 2/13 (15%)	CyR: complete, 1/11 (9%); major, 2/11 (18%); Major MR: 5/14 (36%)	Not stated	Not stated	Not stated	Not stated
Thomas *et al.,* 2008[87]	54	Imatinib plus hyperCVAD	CR: 48/51 (94%)	52%	3-Year DFS: 66%	Not available	At 15 months: 22%	3-Year: 55%
Arellano *et al.,* 2009[73]	33	Imatinib plus hyperCVAD, imatinib	Complete HR: 32/33 (97%)	Complete MR: 24/32 (75%) Complete CyR: 32/33 (97%)	DFS: 15 months in SCT and maintenance patients	13/33 (39%)	Relapse: 10/32 (32%) after 18.3 months	SCT patients: 18 months; maintenance patients: 20 months
Carella *et al.,* 2009[74]	3	Imatinib induction, dasatinib or nilotinib	Complete HR: 3/3 (100%)	Complete CyR: 3/3 (100%)	Not stated	2/3 (67%)	Not stated	3/3 (100%)

TABLE V Continued

Reference	*Patients* (n)	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation* [n *(%)*]	*Time to relapse*	*Overall survival*
			Hematologic [n *(%)*]	*Molecular or cytogenic* [n *(%)*]				
Abstracts continued								
Pfeifer *et al.*, 2009[75] patients from Ottmann *et al.*, 2007[39]	19	Imatinib maintenance plus low-dose interferon alfa	CR: 7/19 (37%)	Not stated	DFS: 76.7 months	Not stated	Not stated	61 Months
Ribera *et al.*, 2004[54]	30	Imatinib plus chemotherapy induction, maintenance	CR: 27/30 (90%)	MR: major, 86%; complete, 21%	After median 4.1 years: DFS, 30%	21	Relapsed: 9	After median 4.1 years: OS, 30%
Pfeifer *et al.*, 2010[76]		Group:		MR after consolidation:	Not stated		Relapse after SCT:	
	51	Imatinib after induction and after consolidation	Not available	2/47 (4.2%)		39	30.8%	Not available
	105	Imatinib second half induction and through consolidation	Induction CR: 89.4%	5/40 (12.5%)		74	24.3%	Induction death: 5.8%
	179	Imatinib start induction and through consolidation	Induction CR: 85.7%	26/79 (33%) (p=0.01)		106	11.3%	Induction death: 11.3%
Rousselot *et al.*, 2010[77]	71	Dasatinib plus chemotherapy induction, consolidation, alternating maintenance	CR: 64/71 (90%)	Bcr-Abl/Abl ratio ≤0.1% in 40/71 (55.7%)	Median: response duration, 19.2 weeks; RFS, 22.1 months	4		Died: 12/71 (16.9%) after median response of 19.2 weeks; median OS: 27.1 months

TABLE V Continued

Reference	*Patients* (n)	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation* [n *(%)*]	*Time to relapse*	*Overall survival*
			Hematologic [n *(%)*]	*Molecular or cytogenic* [n *(%)*]				
Abstracts continued								
Thomas *et al.,* 2010[78]	54	Imatinib plus hyperCVAD, induction	CR: 50/54 (93%)	Complete MR: 52%	Not stated	16	Not stated	At 3 years: OS with STC, 77%; OS without STC, 57%
Kim *et al.,* 2011[79]	50	Nilotinib plus chemotherapy induction,	Hematologic CR: 45 (90%)	Complete MR: 27/50 (54%)	At 1 year: EFS, 49.4%	33	At 2 years: RFS, 71.1%	At 2 years: OS, 66.2%
Lee *et al.,* 2011[80]	30	Dasatinib plus chemotherapy induction, maintenance	CR: 30/30 (100%)	MR: Major, 13/30 (43%) Complete, 5/30 (17%)	At 1 year: DFS, 76%	24/30 (80%)	Not stated	After median 10 months: 25/30 (83%) At 1 year: OS, 83%
Lee *et al.,* 2011[81]; Ravandi *et al.,* 2008[52]; Ravandi *et al.,* 2009[82]	61	Dasatinib plus hyperCVAD, maintenance	CR1: 57/61 (94%)	Not stated	At 3 years: DFS, 49%	15	Relapsed: 12/61 (19%)	At 3 years: OS, 62%
Liu–Dumlao *et al.,* 2011[83]; Ravandi *et al.,* 2009[82]	32 (18 ALL)	Dasatinib induction, maintenance	CR: 23/32 (72%)	CyR: 25/32 (83%) Complete MR: 13/32 (43%) Major MR: 10/32 (33%)	Not stated	9 (2 ALL)	Not stated	At 3 years: OS, 33%; median: 42 weeks
Pfeifer *et al.,* 2011[84]	26 29	Imatinib: Prophylactic Preemptive	At 30 months: 82%	MRD: 10/26 (40%) 20/29 (69%) (p=0.046)	Not stated	Not stated	Not stated	After 5 years: 80% 74.5% (p=NS)

TABLE V Continued

Reference	*Patients (n)*	*Treatment*	*Response type*		*Relapse-free survival*	*Need for transplantation [n (%)]*	*Time to relapse*	*Overall survival*
			Hematologic [n (%)]	*Molecular or cytogenic [n (%)]*				
Abstracts continued								
Brummendorf *et al.,* 2012[85]	570 (164 CML or ALL)	Bosutinib	HR: complete, 14%; major, 28% (≥65 years); complete, 25%; major, 30% (≤65 years)	CyR: complete, 19%; major, 23% (≥65 years); complete, 22%; major, 32% (≤65 years)	Not stated	Not stated	Not stated	Not stated
Cortes *et al.,* 2012[86]	81 (60 CML; 5 ALL)	Ponatinib	Major HR: 17/46 (37%)	CyR: major, 14/41 (34%) complete, 11/41 (27%)	Not stated	Not stated	Not stated	Not stated

PFS = progression-free survival; HR = hematologic response; CR = complete remission; CML = chronic myeloid leukemia; NS = nonsignificant; hyperCVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; CyR = cytogenic response; PCR = polymerase chain reaction; DFS = disease-free survival; MRD = minimal residual disease; MR = molecular response; SCT = stem-cell transplantation; ALL = acute lymphoblastic leukemia; OS = overall survival; TTP = time to progression; RFS = relapse-free survival; EFS = event-free survival; PR = partial response; DIV = dexamethasone, imatinib, vincristine; CNS = central nervous system; HAM = cytarabine, mitoxantrone.

Twenty-four observational studies (twenty prospective, four retrospective) have examined the efficacy of a TKI for the treatment of relapsed patients with Ph+ ALL. Of those studies, fourteen gave imatinib[13–16,23,29,32,37,42,49,55,56,61,63,75], five gave dasatinib[44,50,71,83,88], two gave nilotinib[50,75], two gave bosutinib[72,85], and one gave ponatinib[86]. The TKIs were given with or without chemotherapy. In twenty prospective studies examining 1164 patients, CR rates varied widely (from 0% to 90%), and OS rates ranged from 30% to 70% at 1 year (median OS: 5–60 months). In the four retrospective studies examining 223 patients, the CR rate ranged from 20% to 70%, and the OS rate ranged from 20% to 45% at 1 year.

Consensus: The panel agreed that the reported duration of follow-up was insufficient to make a definitive statement about the effect of TKIs on long-term OS. Some panel members felt that the observation that TKIs improve early outcome in Ph+ and *BCR-ABL*+ ALL, allowing more patients to undergo allogeneic transplantation (which remains the definitive curative therapy for this condition), was sufficient to imply that an OS benefit is likely. Other panel members reserved judgement until a longer-term OS benefit is actually reported.

Recommendation 1(A): Use a TKI in all newly diagnosed patients with Ph+ or *BCR-ABL*+ ALL to increase complete response (hematologic, cytogenetic, and molecular), prolong time to relapse, improve transplant eligibility, and improve leukemia-free survival. (Level of evidence: I to II-2; Grade of recommendation: A)

Clinical Considerations: This recommendation applies to both transplant-eligible and non-transplant-eligible patients, including elderly patients.

The evidence about the effects of TKIs on OS is conflicting. The panel agreed that there was definitive evidence that, compared with standard therapy without a TKI or with no therapy respectively, the addition of a TKI to standard therapy or the use of a TKI alone for Ph+ and *BCR-ABL*+ ALL improves hematologic, cytogenetic, and molecular response; lengthens time to progression (TTP); and improves progression-free survival (PFS).

The panel also agreed that improved PFS was a particularly relevant clinical outcome because clinical progression in this disease is rapid without a TKI and a late survival benefit can be realized only if patients survive beyond the first 12–24 months after diagnosis. Again, delaying the TTP would allow for an increased number of patients to proceed to allogeneic transplantation, particularly those in search of an unrelated donor.

Recommendation 1(B): Use a TKI in patients with relapsed or refractory Ph+ and *BCR-ABL*+ ALL. (Level of evidence: II-2; Grade of recommendation: A)

Clinical Considerations: Most of the evidence supports the use of imatinib at a dose of 400 mg orally twice daily for patients with *de novo*, relapsed, or refractory Ph+ or *BCR-ABL*+ ALL.

For patients with Ph+ or *BCR-ABL*+ ALL who progress or relapse while receiving imatinib, it is reasonable to administer a second- or subsequent-generation TKI with or without further additional chemotherapy. The comparative clinical data from the published clinical literature are insufficient to make a recommendation about the best second- or subsequent-generation TKI to use in this setting. However, the observation of clinically significant dasatinib levels in the central nervous system[90] is noted by the panel as a significant potential advantage of dasatinib and suggests that dasatinib would be an appropriate agent to use in this circumstance. The panel also noted the reported efficacy of ponatinib in patients with CML who have the T315I mutation and would recommend consideration of the use of this agent if there is evidence of the T315I mutation in Ph+ or *BCR-ABL*+ ALL.

Although there are no data suggesting that the use of a TKI alone or in addition to chemotherapy is curative in either the first-line or the relapsed and refractory settings, the use of a TKI alone or in combination with chemotherapy might prolong clinical response enough to allow the patient to proceed to an allogeneic transplant, which can be curative.

Even in non-transplant-eligible patients, the hematologic response to TKI, although often short-lived, might improve quality of life.

3.2.2 Question 2

When in the clinical course of a patient with Ph+ or *BCR-ABL*+ ALL should a TKI be administered?

Question 2(A): Should a TKI be administered during induction, consolidation, and pre-transplantation?

Evidence: De Novo *Population:* In the only randomized controlled trial in *de novo* patients[10,11], 55 individuals not eligible for transplantation were given imatinib during induction and were compared with patients given only chemotherapy during induction. Patients in both arms subsequently received imatinib. This study demonstrated a clear benefit for patients randomized to imatinib during induction compared with those randomized to chemotherapy alone during induction. Patients who received imatinib during induction had a higher rate of hematologic response, which was the primary outcome of the study. The overall CR rate was statistically higher in the imatinib induction group (96.3% vs. 50%, $p < 0.0001$). Patients in both arms subsequently received imatinib with consolidation chemotherapy, and the 18-month DFS and OS were similar in both groups (29.5% and 57.2% respectively for the imatinib group vs. 34.6% and 41% for the chemotherapy group, p = NS).

Thirty-eight observational studies in 1863 *de novo* patients and 334 patients who were a mixture of *de novo* and relapsed (from three studies) gave a TKI during induction. In twelve of the thirty-eight studies, a TKI was given only during induction. Twenty studies gave a TKI during consolidation or for maintenance (or both) in addition to during induction. Three studies gave imatinib before allogeneic transplantation[17,29,42].

In some studies, imatinib was started during induction, as soon as Ph+ or *BCR-ABL*+ status was determined[26,34–36]. In other studies, imatinib was started after remission was achieved, and the drug administered either continuously[25.27,30] or intermittently[21]. In one study, imatinib was administered in two different ways in the same study (either after CR or during induction and after CR)[33]. The rate of hematologic response was higher in the group receiving imatinib after induction (78%) compared with the group receiving imatinib during induction (56%), although no difference in RFS or OS was observed. In a second study, imatinib was given as consolidation after induction with chemotherapy, or with a second phase of induction[70]. The CR rate was higher in patients given imatinib in the second induction phase than in those given imatinib as consolidation (91% vs. 81%). A third study compared patients given imatinib after induction and consolidation with patients given imatinib in the second half of induction and through consolidation or at the beginning of induction and through consolidation[76]. Molecular response was greatest in the group given imatinib from the beginning of induction (33% vs. 12.5% vs. 4.2% respectively, $p = 0.01$).

In most studies, better outcomes were observed when imatinib was started earlier and administered for a longer period, although that was not the case in one study[33].

Relapsed Population: The only randomized trial in relapsed patients examined the efficacy of two different doses of dasatinib after failure of imatinib or imatinib intolerance[12]. Dasatinib was administered orally at either 140 mg once daily or 70 mg twice daily. Treatment continued until disease progression, unacceptable toxicity, or withdrawal at the request of the patient or investigator. Compared with patients given 70 mg dasatinib twice daily, those given 140 mg dasatinib once daily experienced a higher CR rate (50% vs. 38%), but a statistically similar median OS (6.5 months vs. 9.1 months, $p = 0.34$).

Eighteen observational studies examined the efficacy of a TKI given during induction, maintenance, consolidation, or pre-transplantation for the treatment of relapsed patients with Ph+ or *BCR-ABL*+ ALL. As discussed earlier, three of the studies included both *de novo* and relapsed patients who had been given a TKI. In five of the eighteen, a TKI was given during induction for only a limited duration[23,31,32,44,71]; ten studies gave a TKI indefinitely until progression or toxicity[11,14–16,45,61,72,85,86,88]; and one study gave imatinib from 24 weeks onwards (that is, indefinitely)[13]. In addition, one study gave imatinib only as maintenance[55]. Finally, one study gave imatinib during induction and maintenance[83].

Consensus: The panel suggests introducing a TKI as soon as the diagnosis of Ph+ or *BCR-ABL*+ ALL is confirmed.

Recommendation 2(A): Use a TKI during induction, consolidation, and pre-transplantation. The panel found most evidence supports the use of imatinib at an oral dose of 400 mg twice daily. The data about the use of other TKIS (dasatinib, nilotinib, bosutinib, ponatinib) in these settings was felt to be less substantive. (Level of evidence: II; Grade of recommendation: B)

Clinical Considerations: In the clinical reports, TKIS have been administered during various phases of treatment and in both an intermittent and a continuous manner. The panel recommends that a TKI be started as soon as the Ph+ or *BCR-ABL*+ status is established and that it be continued without a break and indefinitely until progression, intolerance, or allogeneic transplantation.

Question 2(B): Should a TKI be administered in the post-transplantation period?

Evidence: Ten studies in 376 patients gave a TKI in the post-transplantation period: eight studies administered imatinib, and two studies administered dasatinib[37,42,49,50,53,56,62,63,70,84]. Seven studies gave a TKI only in the post-transplantation period. In those studies, the CR rate ranged from 33% to 100%, and the DFS rate ranged from 35% to 100%. One study gave imatinib plus chemotherapy as induction, consolidation, and post-transplantation[53]. Imatinib was started after transplantation in 13 of 21 patients (62%). After a median follow-up of 4.1 years, the median DFS and OS were 1.5 years and 1.7 years respectively. In addition, a second study gave imatinib pre-transplantation ($n = 13$) or post-transplantation ($n = 2$)[42]. The RFS rate was 62% in patients given imatinib pre-transplantation and 100% in patients given imatinib post-transplantation; however, the number of patients in this report—and especially in the post-transplantation group—was particularly small.

Consensus: There are compelling theoretical reasons to consider the use of TKIS after transplantation as either consolidation or maintenance therapy. The frequency of relapse, the rapidity of relapse, the favourable toxicity profile of the TKIS, and the simplicity of therapy (an oral medication administered once or twice daily) all favour consideration of a consolidation or maintenance strategy after transplantation. Of

course, for the subset of patients with Ph+ or *BCR-ABL*+ ALL who are cured with allogeneic transplantation, administration of a TKI after transplantation exposes them to the risk of adverse effects with no discernible benefit. Poor hematologic tolerance was also noted in one study when the TKI was introduced early after transplantation[53]. However, clinicians can neither accurately predict who will relapse after allogeneic transplantation nor reliably distinguish the group of patients at higher risk of relapse from those who are cured. Although the presence of minimal residual disease (MRD) before transplantation is perceived as a risk for relapse and the persistence of MRD after transplantation is more predictive of disease progression, neither observation allows clinicians to reliably predict who will relapse.

Given the limited number of reports about the use of TKIs after transplantation, the panel could not make an evidence-based recommendation. The panel acknowledges that some centres use a post-transplantation TKI-based consolidation or maintenance strategy. No evidence-based recommendation can be made about the dose or duration of TKI administration in the post-transplant setting.

Recommendation 2(B): The evidence is insufficient to recommend for or against the routine use of a TKI as consolidation or maintenance therapy after allogeneic transplantation. (Level of evidence: III; Grade of recommendation: C)

Clinical Considerations: Although the panel could not make any evidence-based recommendations about the routine use of a TKI after allogeneic transplantation, the panel was unanimous in recommending that a TKI be started as soon as there is any evidence (molecular or cytogenetic) of Ph+ or *BCR-ABL*+ disease.

3.2.3 Question 3

Is there a difference in efficacy between the various TKIs in patients with Ph+ or *BCR-ABL*+ ALL?

Evidence: No randomized controlled trials have compared the efficacy of the various TKIs in patients with Ph+ or *BCR-ABL*+ ALL. The panel therefore examined the response rates for the various TKIs, recognizing that this approach involves comparison of different reports, with accompanying limitations. The panel also studied reports in which patients with Ph+ or *BCR-ABL*+ ALL had progressed while taking one TKI and were evaluated for subsequent response to a second TKI.

Imatinib: As discussed earlier, one randomized study of 56 newly diagnosed older patients with Ph+ ALL compared imatinib with chemotherapy during remission induction[10,11]. That study demonstrated a clear benefit for patients randomized to imatinib compared with patients randomized to chemotherapy alone during induction, with CR rates of 96% in the imatinib group and 50% in the chemotherapy group.

Forty-three observational studies used imatinib: twenty-nine in *de novo* patients, fourteen in relapsed patients, and three in mixed *de novo* and relapsed patients. In the *de novo* setting, CR rates ranged from 56% to 100%, with rates exceeding 80% in most studies. Median DFS ranged from 10 months to 20 months, and OS ranged from a median of 20 to 40 months. In addition, the 5-year OS rate ranged from 40% to 60%. In the relapsed setting, CR rates varied widely (0%–90%), and OS rates ranged from 30% to 70% at 1 year, with median OS ranging from 5 months to 60 months.

Dasatinib: Eleven studies examined the efficacy of dasatinib: five in *de novo* patients[51,58,77,80,81] and six in relapsed patients[12,44,50,71,83,88]. In the *de novo* population, CR rates ranged from 90% to 100%, and the OS rate was approximately 65% at 2 years (median OS: 27 months). In the relapsed setting, one randomized study compared two different oral doses of dasatinib (140 mg once daily vs. 70 mg twice daily)[12]. Compared with patients given 70 mg dasatinib twice daily, those given 140 mg dasatinib once daily experienced a higher CR rate (50% vs. 38%), but a statistically similar median OS (6.5 months vs. 9.1 months, $p = 0.34$). In the remaining observational studies, CR rates ranged from 8% to 72%, and OS rates ranged from 33% to 80% at 1 year (median OS: approximately 10 months).

Nilotinib: Three studies in a total of 70 patients examined the efficacy of nilotinib: one in *de novo* patients and two in relapsed patients[31,45,79]. In the *de novo* study, induction with nilotinib plus chemotherapy was given to 50 patients with Ph+ ALL. Results demonstrated a CR rate of 90%, with an OS rate of 66% at 2 years[79]. In one study in the relapsed setting, a partial response of 10% was found[31]. In the second study in the relapsed setting, a CR rate of 43% was achieved[45].

Bosutinib: Two studies in 1019 relapsed patients, including some patients with Ph+ ALL, examined the efficacy of bosutinib[72,85]. In both studies, bosutinib was given at an oral dose of 500 mg once daily. Results showed CR rates ranging from 14% to 25% and cytogenetic response rates ranging from 9% to 22%.

Ponatinib: One study in 81 relapsed patients with Ph+ ALL examined the efficacy of ponatinib[86]. Oral ponatinib was escalated from 45 mg once daily. A major hematologic response was reported in 17 of 46 patients (37%) and a cytogenetic response was reported in 11 of 41 patients (27%).

Consensus: Although there are no comparative studies of the various TKIs for patients with Ph+ or

BCR-ABL+ ALL, imatinib has been extensively studied. A TKI should be initiated as soon as the diagnosis of Ph+ or *BCR-ABL*+ ALL is established by standard cytogenetic, fluorescence *in situ* hybridization, or molecular studies. A TKI can be used with any chemotherapeutic regimen, or it can be used with steroids alone or as a single agent. Imatinib in combination with prednisone is a reasonable option for induction and consolidation in elderly patients in whom allogeneic transplantation or aggressive chemotherapy is not an option.

Recommendation 3(A): Use imatinib either alone or in combination with steroids or chemotherapy as soon as Ph+ or *BCR-ABL*+ is determined in patients with acute lymphoblastic leukemia. (Level of evidence: II; Grade of recommendation: B)

Clinical Considerations: Imatinib is typically administered orally at a dose of either 600 mg once daily or 400 mg twice daily when used with steroids or chemotherapy. It can be used orally at a dose of 400 mg twice daily when used alone.

Dasatinib[12,44,50,51,58,71,77,80,81,83,88], nilotinib[31,45,79], bosutinib[31,45,79], and ponatinib[86] have been studied in patients who are resistant or intolerant to imatinib. Those agents have produced hematologic and cytogenetic responses in that group of patients. In patients who are resistant to imatinib, the duration of response to subsequent TKIs has been short.

Dasatinib at an oral dose of 50 mg or 70 mg twice daily can be used for patients who are intolerant to imatinib. Most of the published data describe the use of an oral dose of 70 mg twice daily, but the panel would also consider 50 mg twice daily because the latter dose might be associated with a lower incidence of pleural effusion.

Nilotinib at an oral dose of 400 mg twice daily, bosutinib at an oral dose of 500 mg daily, and ponatinib at an oral dose of up to 60 mg daily can also be used for patients who are either intolerant to imatinib or another TKI, or who progress while receiving imatinib or another TKI.

There are theoretical advantages to the initial use of a second- or subsequent-generation TKI, including higher potency (dasatinib, nilotinib, bosutinib, ponatinib), broader spectrum of activity (dasatinib, ponatinib), and central nervous system penetration (dasatinib); however, the panel felt that the data were currently insufficient to recommend the up-front use of a second- or subsequent-generation TKI outside the setting of a clinical trial.

Because most patients with Ph+ or *BCR-ABL*+ ALL will have been treated with imatinib alone or in combination with steroids or chemotherapy at presentation, it is reasonable to consider a second- or subsequent-generation TKI either alone or in combination with steroids or chemotherapy for patients with refractory or relapsed disease. Most of the published clinical experience has used dasatinib at an oral dose of 70 mg twice daily. However, the panel is aware of studies in patients with CML which suggest that a lower oral dose of 100 mg once daily is better tolerated and equally effective in that disease. No definitive recommendation about the dose of dasatinib to be used in patients with refractory or relapsed Ph+ or *BCR-ABL*+ ALL can be made at this time. However, the panel felt that most published data favoured 70 mg orally twice daily.

Although the panel is aware of three studies using nilotinib[31,45,79], three studies using bosutinib[50,58,75], and one study using ponatinib[86] in patients with Ph+ or *BCR-ABL*+ ALL, very few data are available, and the duration of follow-up with the use of those agents is less than that with imatinib and dasatinib in the relapsed and refractory setting.

3.2.4 Question 4

How long should therapy with a TKI continue in a patient with Ph+ or *BCR-ABL*+ ALL?

Evidence: No randomized studies have examined the optimal duration of treatment with TKIs during induction, consolidation, or maintenance.

Induction: Thirty-nine studies examined induction treatment with TKIs in *de novo* patients. In nine of those studies, a TKI was given only at induction for a range of 1–12 weeks and for a limited number of courses; however, a number of studies gave a TKI indefinitely or until progression. Two studies gave a TKI indefinitely after induction[28,51,66], three studies gave a TKI until progression or until molecular negativity was attained[20,41,69], and one study gave a TKI until transplantation[38].

In twenty studies, a TKI was given for consolidation or maintenance (or both) as well as for induction. In those studies, the duration of induction was typically 4 weeks, but ranged from 2 weeks to 8 weeks. In one study, a TKI was given after induction until the next chemotherapy course[48]. Three studies gave imatinib before transplantation[17,29,42]. In one study giving a TKI before transplantation, imatinib was given for a median of 45 days[29].

Relapsed Setting: In the relapsed setting, a TKI was typically given indefinitely as tolerated[12–14,16,39,45]. However, several studies used other schedules: dasatinib for 12 weeks[44]; imatinib for 3 weeks every 4 weeks[61]; nilotinib for 12 months[31]; imatinib for a maximum of 56 days[32]; and imatinib for 24 months[23]. Finally, one study gave dasatinib for 2 weeks of every 8-week cycle, followed by monthly maintenance with dasatinib for 2 years[83].

Maintenance Setting: Nineteen studies gave a TKI during maintenance treatment. Duration of maintenance ranged from 4 weeks to 2 years, with one

study giving maintenance indefinitely[66]. Several studies gave a TKI as maintenance after transplantation[37,42,49,50,53,56,62,63,70,84]. Individual studies also gave imatinib for at least 1 month after transplantation[56], until a complete molecular remission was sustained for 3 months[63], starting at engraftment and continuing for at least 1 year[37], and indefinitely as tolerated[42].

Consensus: No study has examined the impact on disease control of TKIs used upon achievement of CR, but the panel recommended continuing therapy until disease progression or transplantation, provided that the TKI is well tolerated.

Recommendation 4(A): Continue a TKI beyond completion of chemotherapy until transplantation or disease progression. (Level of evidence: III; Grade of recommendation: B)

Clinical Considerations: The panel found no clinical evidence to support intermittent drug administration or drug holidays. Similarly, there was neither clinical evidence to support the use of more than one TKI at the same time, nor evidence to support the use of a strategy of alternating TKIs in an individual patient. Such strategies could be the subject of future investigation.

3.2.5 Question 5

Which measure of disease response should be used to follow patients with Ph+ or *BCR-ABL*+ ALL?

Evidence: Studies examining the efficacy of TKIs used a variety of outcome measures, including hematologic response (HR) such as CR, complete HR, and overall response rate; molecular response (MR) such as MRD, cytogenetic response (CyR), complete CyR, major CyR, complete MR, and major MR; and measures of duration of response such as PFS, DFS, RFS, event-free survival, and OS.

Data on HR were reported in fifty-eight of sixty-eight studies; MR data were available for fifty-six studies; duration of response was available in forty-six studies; and OS results were available in fifty-seven studies.

Consensus: Hematologic CR is a poor predictor of OS in patients with Ph+ or *BCR-ABL*+ ALL in almost all contexts except after allogeneic transplantation. However, failure to achieve a hematologic response is highly predictive of poor OS. In contrast, molecular monitoring by quantification of the Bcr-Abl transcript level in bone marrow or peripheral blood in assays capable of detecting disease reduction to molecular transcript levels as low as 10^{-5} is much more predictive of RFS (and sometimes OS).

Although widely practiced, the value of monitoring is not well established. The best frequency for molecular assessment and whether the source of cells for testing should be blood or marrow is not known. Although marrow assessment is thought to be more sensitive, the panel felt that use of a quantitative assay to measure the reverse transcriptase–polymerase chain reaction level of Bcr-Abl transcripts in peripheral blood once per month would be a reasonable strategy. The panel felt that the initial 2 years of therapy represent the period during which the risk of relapse is greatest, but acknowledged that no data are available to inform a recommendation about the duration of monitoring. In the absence of clinical data, the panel recommended long-term monitoring for patients in whom the resulting information would lead to a medical intervention and a change in treatment strategy.

Recommendation 5(A): To aid in prognostic evaluation, use quantitative assessment of the Bcr-Abl transcript level to follow molecular status after the patient achieves a hematologic remission. (Level of evidence: III; Grade of recommendation: B)

Clinical Considerations: The panel felt that using a quantitative assay to measure the reverse transcriptase–polymerase chain reaction level of Bcr-Abl transcripts in peripheral blood once per month would be a reasonable and practical monitoring strategy.

Achievement of a complete HR is a poor predictor of OS in patients with Ph+ or *BCR-ABL*+ ALL after conventional chemotherapy without a TKI because almost all patients relapse after first responding. However, failure to achieve a HR is highly predictive of poor OS. In contrast, molecular monitoring by quantification of the Bcr-Abl transcript level in bone marrow or peripheral blood in assays capable of detecting disease reduction to 10^{-5} is predictive of RFS and sometimes OS in most series where that outcome was examined. Conversely, reappearance of Bcr-Abl transcripts when they were previously absent usually predicts relapse.

Thus, although widely practiced, the value of monitoring has not been critically or explicitly evaluated in large trials. The value of such testing in predicting relapse cannot therefore be calculated with confidence. This issue is further complicated by the variety of combination chemotherapy regimens and schedules that have used with TKIs, making widely applicable recommendations about the frequency and timing of molecular monitoring difficult. Nevertheless, common practice from larger series includes molecular monitoring at the end of various treatment blocks (induction, consolidation, intensification, and so on) and frequently after definitive treatment is completed (that is, after transplantation or maintenance, as appropriate). The best frequency for molecular assessment and the best source of cells for testing (blood or marrow) is therefore not entirely known. Furthermore, relapses in Ph+ ALL can occur

rapidly, and the true value of molecular monitoring is to allow for earlier interventions that would make a difference in the ultimate outcome. Thus, the utility and impact of molecular monitoring has not been formally demonstrated.

Information about the importance of monitoring for *BCR-ABL* mutations in patients with Ph+ or *BCR-ABL*+ ALL is insufficient.

4. AUTHORSHIP

In these evidence-based guidelines, YA, SC, SL, BL, MM, LS, and RT systematically reviewed the data and created recommendations. SC wrote the article, and all authors reviewed the manuscript. NS and VP were responsible for the methodology analyses. After the initial version of the manuscript was written, SC asked Anna Christofides, a medical writer, to update the literature search; based on the updated search, SC and AC revised relevant aspects of the descriptive text. The conclusions and recommendations were not changed.

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6. CONFLICT OF INTEREST DISCLOSURES

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Correspondence to: Stephen Couban, Department of Medicine, Dalhousie University, Room 430, Bethune Building, 1278 Tower Road, Halifax, Nova Scotia B3H 2Y9.
E-mail: stephen.couban@cdha.nshealth.ca

* Department of Medicine, Dalhousie University, Halifax, NS.
† University of Calgary, Calgary, AB.
‡ Leukemia and Bone Marrow Transplant Program of British Columbia, University of British Columbia, Vancouver, BC.
§ McMaster University, Hamilton, ON.
‖ Department of Medical Oncology, University Health Network, University of Toronto, Toronto, ON.
Cross Cancer Institute, Edmonton, AB.
** University of Toronto, St Michael's Hospital, Toronto, ON.
†† Senior Medical Writer, Toronto, ON.
‡‡ Hospital Maisonneuve–Rosemont, University of Montreal, Montreal, QC.