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# Evolution of Therapies for Chronic Myelogenous Leukemia

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## Abstract

The clinical outcome for patients with chronic myeloid leukemia (CML) has changed dramatically in the past 15 years. This has been due to the development of tyrosine kinase inhibitors (TKI), compounds which inhibit the activity of the oncogenic BCR-ABL1 protein. Imatinib was the first TKI developed for CML, and it led to high rates of complete cytogenetic responses and improved survival for patients with this disease. However, about 35% of patients in chronic phase treated with imatinib will develop resistance or intolerance to this drug. The recognition of the problem of imatinib failure led to the design of 2$^{nd}$-generation TKI (dasatinib, nilotinib and bosutinib). These drugs are highly active in the scenario of imatinib resistance or intolerance. More recently, both nilotinib and dasatinib were approved for frontline use in patients with chronic phase CML. Ponatinib represents the last generation of TKI, and this drug has been developed with the aim of targeting a specific BCR-ABL1 mutation (T315I) which arises in the setting of prolonged TKI therapy and leads to resistance to all commercially available TKI. Parallel to the development of specific drugs for treating CML, major advances were made in the field of disease monitoring and standardization of response criteria. In this review we summarize how therapy with TKI for CML has evolved over the last decade.

### Keywords

Chronic Myelogenous Leukemia; BCR-ABL1; Tyrosine Kinase Inhibitors; Imatinib; Dasatinib; Nilotinib; Bosutinib; Ponatinib

## Introduction

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder characterized by the presence of translocation t(9;22)(q34;q11) which generates the Philadelphia (Ph) chromosome and the associated fusion gene BCR-ABL1[1]. BCR-ABL1 encodes the chimeric protein BCR-ABL1 which has deregulated tyrosine kinase activity and leads to increased cellular proliferation, resistance to apoptosis and genetic instability[1]. BCR-ABL1 is at the center of CML pathogenesis, as attested by mouse models which replicate the disease[2]. CML classically follows a triphasic course, with most patients being diagnosed in an initial, oligosymptomatic chronic phase (CP) which eventually progress into a more advanced

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accelerated phase (AP) and culminates into a blast phase (BP), which is similar to an acute leukemia.

CML, once considered a fatal disease, is now essentially a chronic disorder, and most patients can enjoy long-term survival[3]. This history of success has been the result of development of tyrosine kinase inhibitors (TKI), compounds which suppress the abnormal tyrosine kinase (TK) activity of the BCR-ABL1 protein (Figure 1). In this article we review the rationale and development of three generations of TKI for therapy of CML.

## Therapy for CML in the pre-imatinib era

Historically, the first treatment for CML was Fowler's solution, a 1% solution of arsenic trioxide, used for therapy of CML back in 1865[4] (Figure 2). Following the discovery of X-rays by Roentgen in 1895, radiation therapy was incorporated into the armamentarium of CML therapy in the first half of the 20$^{th}$ century, used mainly to alleviate symptoms caused by splenomegaly[4]. With the development of chemotherapy in the 1950s, busulphan and hydroxyurea became the main therapeutic options for several decades[5]. While these drugs could effectively control the WBC, they did not eradicate the leukemic clone or altered disease progression[6]. The arise of interferon-α (IFN-α) in the 1980s was a great advance, since the drug could induce hematologic and cytogenetic remissions and improvements in survival, but it was poorly tolerated due to frequent and serious side effects[7]. The use of IFN-α brought for the first time the possibility of eliminating the malignant clone as represented by the elimination of the Ph chromosome. A complete cytogenetic remission (CCyR; 0% Ph+-metaphases) was achieved in a small but significant percentage of patients, and it was recognized that patients who achieved CCyR had longer survival than those who failed to meet this endpoint, thus indicating that cytogenetic response was a surrogate for improved survival and the gold standard for optimal response to therapy[8]. Hematopoietic stem cell transplantation (HSCT) was developed parallel to drug therapy and it has proven curative potential for CML, but it is applicable in only a fraction of patients, mainly younger patients with a matched donor and is associated with considerable morbidity and mortality, although great progress has been made to ameliorate both[9]. Thus, for most patients with CML, therapy was limited to a few available drugs and the possibility of facing the risks of a HSCT.

## First Generation Tyrosine Kinase Inhibitor: Imatinib

### Pre-Clinical Development

Imatinib (formerly known as CGP57148B, or STI-571; Novartis, Basel, Switzerland) was one of the first molecules developed belonging to a class of compounds, named ATP-mimetic kinase inhibitors, which compete with ATP for the ATP-binding pocket of the kinase, thus inhibiting further substrate phosphorylation by the enzyme[10,11] (Figure 3). Imatinib can only bind the TK BCR-ABL1 in its inactive form and this is dependent on crucial interactions with several key amino acid residues[10,11]. Initial studies with purified enzyme based assays showed that imatinib had potent activity against the TK c-Abl (half-maximal inhibitory concentration [IC50]=0.2μM), including oncogenic BCR-ABL1 (IC50=0.25μM)[12]. Imatinib could also inhibit activity of TKs receptors PDGFRα/β(Platelet Derived Growth Factor Receptor-α and −β) and KIT[13,14]. Imatinib inhibited proliferation and induced apoptosis of BCR-ABL1 positive cells.[12,15–17] Animal models of BCR-ABL1-positive leukemias confirmed its *in vivo* activity[12,18].

### Clinical Studies

The phase I clinical trial of imatinib initially recruited patients with chronic phase (CP) CML who had failed therapy with IFN-α[19]. At doses greater than 300 mg, impressive

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clinical activity was observed, with 53 of 54 patients achieving a complete hematological response (CHR; disappearance of all signs and symptoms of the disease) and 31% achieving a major cytogenetic response (MCyR; 0–35% Ph+metaphases), including a CCyR rate of 13%. The dose of 400 mg once daily was chosen for future studies based on pharmacokinetic data showing that it achieved mean plasma through concentration greater than needed to inhibit BCR-ABL1. The phase I study then expanded to include patients with blast phase (BP) CML and patients with refractory/relapsed Ph+-acute lymphoblastic leukemia (Ph+-ALL)[20]. Therapy with imatinib led to a CHR in 11% of patients with myeloid BP (MBP) and 20% of patients with lymphoid phenotype (LBP). Another 10% and 15%, respectively, achieved reduction in blasts to < 5% but without peripheral blood count recovery. Unfortunately, responses were short-lived and most patients rapidly progressed after a few months.

The phase II clinical trials confirmed activity of imatinib in a much larger cohort of patients with CML in all stages[21–23]. Patients with CML in accelerated phase (AP)/BP were treated with imatinib at doses of 400–600 mg once daily, and among 235 patients with AP and 260 patients with myeloid BP, responses were seen in 82% and 52% and a CHR was obtained in 34% and 8%, respectively[21,22]. In patients with AP higher doses of imatinib (i.e. 600 mg vs. 400 mg) led to improved responses, and the Federal Drug and Administration (FDA) approved imatinib at a dose of 600 mg daily for therapy of patients with CML in AP/BP[22]. In the CP trial 454 patients were treated with imatinib 400 mg daily[23]. Response rates were CHR 95%, MCyR 60% and CCyR 41%. Side effects of imatinib were few and usually grade 1–2. Most common were edema (all grades 60%), nausea (all grades 55%), muscle cramps (all grades 49%), rash (all grades 32%) and diarrhea (all grades 29%). Grade 3–4 hematological side effects were anemia (7%), neutropenia (35%) and thrombocytopenia (20%). Only 2% of patients had to discontinue imatinib due to drug related side effects.

A large phase III randomized trial of imatinib versus IFN-α and low dose cytarabine (the standard of care at the time) was then launched for patients with newly diagnosed CP CML. The IRIS (**I**nternational **R**andomized Study of **I**nterferon and **S**TI571) phase III trial randomized 1106 patients with newly-diagnosed CML to imatinib (400 mg daily) and IFN-α plus low dose cytarabine[24]. The initial report demonstrated superiority of imatinib, with a MCyR rate 87% vs. 35% with IFN-α +Ara-C ($p<0.001$), and a CCyR Rate of 76% vs. 15% ($P<0.001$), respectively. At 18 months transformation free survival (TFS) showed benefit of imatinib, 97% vs. 91.5% ($p<0.001$)[24]. Imatinib was much better tolerated than the combination of IFN-α+Ara-C. Only 3% of patients in the imatinib arm discontinued therapy due to side effects or crossed-over to the other arm due to intolerance, versus 30% of patients in the IFN-α+Ara-C arm. Side effects more commonly seen with imatinib included superficial edema, nausea, muscle cramps and rashes. Most were usually grade 1–2 events. Reported grade 3–4 cytopenias were anemia (3.1% [imatinib] vs. 4.3% [IFN-α+Ara-C]), neutropenia (14.3%[imatinib] vs. 25%{IFN-α+Ara-C]) and thrombocytopenia (7.8% [imatinib] vs. 16.5%[IFN-α+Ara-C])[25].

Long term follow up of the IRIS trial have confirmed benefit of imatinib. After 8 years, 304 patients (55% of the original cohort) remain on use of imatinib[26]. The CCyR rate at 8 years is 83%, with 18% having lost CCyR and 3% having progressed to AP/BP. Event-free survival (EFS) is 81% and TFS is 92%. For patients who achieved a major molecular response (MMR, defined in the IRIS trial as a 3-log reduction in *BCR-ABL1* transcripts from a standardized baseline value, assessed by real-time quantitative polymerase chain reaction [RT-PCR]) at 12 months, TFS was 100% at 8 years. The rate of progression to AP/BP decreased over time in the study, being 1.5% (1$^{st}$ year), 2.8% (2$^{nd}$ year), 1.6% (3$^{rd}$ year), 0.9% (4$^{th}$ year), 0.5% (5$^{th}$ year), 0% (6$^{th}$ and 7$^{th}$ year) and 0.4% (8$^{th}$ year). At 8 years, overall survival (OS) is 85% (93% considering only CML-related deaths). Since the design

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of the trial allowed for crossover, no difference in survival between arms was reported. However, several reports comparing cohorts of patients treated with imatinib with historical CML controls showed that imatinib clearly improved survival in patients with CML relative to the former standard, IFN-α and cytarabine[27–29].

## Monitoring Response to TKI Therapy

Achievement of cytogenetic response in patients with CML is associated with improved survival and decreased risk of transformation to AP/BP[8]. Furthermore, data from the imatinib studies showed that the prognostic impact of certain depth of response depended on the timing of their achievement. Patients who achieved a CCyR at 12 months of therapy had a 5-years EFS of 97%, versus 93% for those patients with a partial cytogenetic response (PCyR, 1–35% Ph+-metaphases) and 81% for those patients who had failed to achieve a MCyR altogether ($p<0.001$)[3]. Monitoring of BCR-ABL1 transcript levels by quantitative RT-PCR revealed itself as a method to further quantify residual disease, in patients already in CCyR. Clinical trials began to evaluate the clinical impact of achieving a molecular response. In the IRIS trial, patients who had a CCyR and a MMR, more recently defined as a BCR-ABL/ABL ≤0.1% in the international scale, at 18 months of therapy had a 5-year OS of 100%[3]. The European LeukemiaNet has published guidelines for monitoring patients with CML and criteria for optimal response, suboptimal response and failure to therapy with TKI (Tables 1–3)[30].

The value of achieving a MMR in addition to a CCyR is still a matter of debate. Recently, Hughes et al evaluated the impact of achieving early MMR on outcomes based on data from the IRIS clinical trial[31]. At 18 months, patients who had not achieved a MMR had a significantly inferior 7-years EFS (95% vs. 75%; $p<0.001$) and TFS (99% vs. 90%; $p<0.001$). There was no statistically significant difference in OS (95% vs. 90%)[31]. However, when only the patients who achieved a CCyR are analyzed, achieving a MMR at 18 months is associated with lower rate of loss of CCyR (3% vs. 26%; $p<0.001$) and better 7-years EFS (95% vs. 86%), but no improvement in TFS (99% vs. 96%) or OS (95% vs. 96%). Thus, while achieving MMR is certainly beneficial, achieving CCyR must be considered the minimal acceptable response to be obtained by patients with CML and perhaps the gold standard of CML response as it is the only type of response criteria that is associated with an improvement in survival. It is also important to mention that failure to achieve a MMR or a complete molecular response (CMR; absence of BCR-ABL1 transcripts by quantitative RT-PCR) are not considered criteria for failure[30]. One report analyzed 116 patients who were in continuous CCyR and had increases in BCR-ABL1 transcript level by quantitative PCR on two or more occasions[32]. Only 11 patients (9.5%) had CML progression, and 10 of these were among 44 patients who had an increase >1 log in transcript levels and had either lost or never achieved MMR[32]. Thus, clinicians should refrain from making therapeutic changes based solely on BCR-ABL1 levels if the patient is still maintaining CCyR and the level of BCR-ABL1 increase is < 1 log, as there is no clinical evidence of the benefit of interventions in this setting, and even when improvements in transcript levels are reported (e.g., with increased doses of Imatinib) the long-term impact of such changes has not been demonstrated.

## Mechanisms of Resistance to Imatinib

Despite these important clinical advances obtained with imatinib, it is clear that roughly 30–40% of patients will need additional therapy beyond imatinib. In the 8-year update of the IRIS trial, at least 37% of patients initially treated with imatinib had an unfavorable outcome: 17% failed to achieve CCyR, 15% lost CCyR and 5% had intolerance to imatinib[26]. Resistance to imatinib can be classified into primary (never had a response to frontline therapy with imatinib) or secondary (achieved a response but then lost it) [33].

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Resistance to imatinib has been defined by the European LeukemiaNet as failure to achieve predetermined milestones during therapy (table 3)[30]. While the incidence of resistance to imatinib in untreated CP CML is approximately 4% per year, it is much higher in patients with AP (40%) and BP (90%)[3,34].

There are several distinct mechanisms of resistance to imatinib, conventionally divided into BCR-ABL1 dependent and independent mechanisms[33]. Among BCR-ABL1 dependent mechanisms, overexpression of the *BCR-ABL1* gene and development of *BCR-ABL1* mutations stand as the most relevant ones[35,36]. *BCR-ABL1* mutations are found in 50–80% of patients with CML at time of development of resistance, and are more common in patients with AP/BP (particularly lymphoid BP) than patients remaining in CP[37–40]. Mutations cluster at the kinase domain and either disrupt contact points between imatinib and BCR-ABL1 or induce conformational changes from inactive to active, to which imatinib is unable to bind[25,41]. Some mutations are associated with a high level of resistance to imatinib, including P-Loop mutations (i.e. mutations in amino acid residues 244 to 255; the most common ones include Q252R/H, Y253F/H, E255K/V) and the gatekeeper T315I mutation[36]. The T315I mutation confers resistance to all commercially-available TKI, since it prevents the formation of an important hydrogen bond between the TKI and amino acid residue T315 of the BCR-ABL1 molecule[36]. This blocks binding of the TKI to the BCR-ABL1 protein. The T315I mutation is a common mechanism of resistance in CML patients evolving to AP and BP while on therapy with TKI[37]. Currently, screening for BCR-ABL1 mutations is recommended at the following time points: (1) at diagnosis, solely for patients who present with AP/BP; (2) during therapy with imatinib or other TKI for patients who have criteria for failure or suboptimal response[42].

Non-BCR-ABL1 dependent resistance mechanisms are diverse and not well understood. Activation of other, BCR-ABL1 independent, signaling pathways is one potential avenue leukemic cells can exploit to escape inhibition by imatinib. Activation of Src family kinase (SFK) enzymes can lead to cell proliferation by a BCR-ABL1 independent pathway[43]. Variable activity of proteins responsible for imatinib transport across the cell membrane can influence intracellular concentrations of imatinib and its efficacy[44]. The human organic cationic transporter-1 (OCT1) is the main protein responsible for imatinib influx, and polymorphisms may influence expression of OCT1[45]. Patients with CML who have low OCT1 activity have inferior rates of MMR (55% vs. 89% at 5 years; p=0.007), CMR (31% vs. 59%; p=0.038), EFS (5 years 48% vs. 74%; p=0.03) and OS (5 years 87% vs. 96%; p=0.031)[46]. Increasing the dose of imatinib might nullify the negative effect of low OCT1 activity, but this strategy needs to be evaluated prospectively[47]. One advantage of 2nd-generation TKI in comparison with imatinib is that neither dasatinib nor nilotinib need OCT1 for cell entry[47,48].

## Strategies for salvage of patients with CML who fail Imatinib: Imatinib Dose Escalation and Second-Generation TKI

### Imatinib Dose Escalation

Currently, the European LeukemiaNet recommends imatinib dose escalation only for those patients who present with suboptimal response criteria[30]. Imatinib dose escalation seems to be more effective in patients who present with cytogenetic relapse (previous cytogenetic response to imatinib) and without signs of hematological relapse. Jabbour et al. reported on 84 patients with CP who had failure on standard dose imatinib and had dose increases to 600 mg or 800 mg[49]. Patients who had dose escalation due to cytogenetic failure had higher rates of CCyR (52%) compared to those who had dose escalation due to hematological failure or resistance (5%). Similarly, patients who had achieved a previous cytogenetic response to

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imatinib had a higher rate of CCyR compared to patients with primary cytogenetic resistance (73% vs. 0%). At 3 years, EFS (58% vs. 19%; p<0.001) and OS (83% vs. 56%; p=0.004) were superior for those patients who had dose escalation while on cytogenetic relapse only[49].

## Second-Generation TKI: Dasatinib

Dasatinib (formerly known as BMS354825; Sprycel; Bristol Myers Squibb, New York, NY) is an orally available TKI which is structurally unrelated to imatinib and is capable of binding BCR-ABL1 both in the active and in the inactive conformation[50,51]. Dasatinib is 325-fold more potent than imatinib against wild type BCR-ABL1 (IC50=0.8nM) and has activity against most imatinib-resistant BCR-ABL1 mutations and against SFK enzymes[35,36]. Dasatinib has no activity against the T315I BCR-ABL1 mutation[36]. Dasatinib is currently approved by the FDA for the frontline therapy of CML and for salvage of CML patients in all phases who are resistant or intolerant to imatinib.

In the phase I dose escalation study, 84 patients with imatinib-resistant/-intolerant CML or Ph+-ALL (CP=40, AP=11, MBP=23, LBP/Ph+-ALL=10) received therapy with dasatinib at doses ranging from 15–240 mg daily, administered in a once or twice daily schedule[52]. Most patients (86%) were resistant to imatinib. No maximum tolerated dose was determined, and pharmacokinetic and pharmacodynamic data supported a dose schedule of 70 mg twice daily in order to achieve constant TK inhibition. Most common toxicities included grade 3–4 neutropenia (CP: 45%; advanced CML: 89%), grade 3–4 thrombocytopenia (CP: 35%; advanced CML: 80%), grade 1–4 pleural effusion (18%), grade 1–2 diarrhea (23%), grade 1–2 edema (19%) and grade 1–2 headache (10%). Response data are summarized in Table 4. Briefly, patients with CP and AP had high rates of CHR (92% [CP] and 82% [AP]), MCyR (45% and 27%) and CCyR (35% and 18%). After a median follow-up of 12 and 5 months for patients with CP and AP, respectively, 95% and 82% were maintaining their response. Dasatinib was effective against all types of imatinib-resistant *BCR-ABL1* mutations, with the exception of the T315I mutation.

Following the results of the Phase I trial, several Phase II studies (START trials; **S**rc-ABL1 **T**yrosine Kinase Inhibition **A**ctivity **R**esearch **T**rials) were launched to evaluate the efficacy of dasatinib against all spectra of Ph-positive leukemias post intolerance or failure of imatinib: CP CML (START-C), AP CML (START-A), MBP (START-B) and LBP (START-L)[53–55]. Patients were treated with dasatinib at a dose of 70 mg twice daily. Results are summarized in Table 4. Overall, these phase II studies confirmed that dasatinib is a highly active TKI in the setting of imatinib failure or intolerance. Among patients treated with dasatinib in CP CML, the rate of MCyR and CCyR was 59% and 49%[53]. Cytogenetic responses were seen independently of duration of prior imatinib therapy, prior imatinib dose, presence of *BCR-ABL1* mutations and prior CHR. Responses were durable, and after 15 months of follow up progression free survival (PFS) was 90% and OS was 96%[53].

Two other studies with dasatinib deserve mention. In the START-R trial, patients with imatinib failure at doses of 400–600 mg daily were randomized in a 2:1 fashion to dasatinib (70 mg twice daily) or imatinib (800 mg daily)[56,57]. One hundred and fifty patients were enrolled. CHR rates were higher with dasatinib (93% vs. 82%; p=0.034), as well as MCyR (53% vs. 33%; p=0.017) and CCyR (44% vs. 18%; p=0.0025). Dasatinib also resulted in superior PFS (2 years 86% vs. 65%; p=0.0012) but was more toxic than high dose imatinib, with pleural effusion occurring in 17% of patients (versus 0%) and higher rates of grade 3–4 myelosuppression (neutropenia 61% vs. 39%; thrombocytopenia 56% vs. 14%)[56,57].

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A randomized phase III study evaluated the optimal dose and schedule of dasatinib in patients with CML in CP[58]. Six hundred and seventy patients were randomized among four different schedules of dasatinib: 100 mg once daily, 50 mg twice daily, 140 mg once daily and 70 mg twice daily. The rationale for this trial was that in the START-C study the median daily administered dose was 101 mg, lower than the approved 140 mg daily dose, but still with a significant response rate. After median treatment duration of 8 months, no difference was seen among the four treatment arms regarding CHR, MCyR, CCyR and PFS. However, the 100 mg once daily arm, compared to the approved schedule of 70 mg twice daily, was significantly less toxic, with lower rates of pleural effusion (all grades 7% vs. 16%; p=0.024), grade 3–4 thrombocytopenia (22% vs. 37%; p=0.004), grade 3–4 anemia (10% vs. 16%; p=0.07), treatment interruption, dose reductions and treatment discontinuation due to toxicity[58]. Dasatinib was then approved at 100 mg once daily for the treatment of imatinib-resistant/intolerant CML. A similar phase III study randomized patients with AP/BP or Ph+-ALL to dasatinib at two different schedules: 140 mg once daily or 70 mg twice daily. The 140 mg once daily arm led to similar response and survival outcomes but with improved toxicity[59].

Major side effects of dasatinib include pleural effusions, myelosuppression and bleeding diathesis. Pleural effusions occur in 5–15% of patients receiving therapy with dasatinib, with a higher incidence among patients receiving high doses (140 mg daily), a twice daily schedule, in advanced stages of CML or with a previous history or cardiac disease[60]. Pleural effusions are usually managed with diuretics, dose reduction/interruption, corticosteroids and thoracocentesis[60]. Dasatinib can induce bleeding episodes in patients without coagulation abnormalities[61]. This might be secondary to dasatinib-induced platelet aggregation abnormalities, inhibiting aggregation in response to epinephrine and arachidonic acid[62]. Thus, concomitant use of dasatinib and platelet inhibitors should be avoided if possible. Myelosuppression is a relatively common side effect of dasatinib. In patients with CP CML receiving 100 mg once daily, incidence of grade 3–4 cytopenias are 10% (anemia), 33% (neutropenia) and 22% (thrombocytopenia)[53]. In patients with more advanced CML, who frequently start therapy with baseline cytopenias, grade 3–4 cytopenias are in the range of 80% (neutropenia), 82–88% (thrombocytopenia) and 50–69% (anemia)[12]. Cytopenias are usually managed with growth factor support and treatment interruption/dose reduction as needed[63]. Another peculiar hematological effect of dasatinib is the induction, in 30–46% of patients, of large granular cell (LGL) lymphocytosis[64–66]. These lymphocytes have been shown to be either T-cell or NK-cell, and represent expansion of pre-existing oligoclonal populations of T/NK lymphocytes[67]. Development of T/NK-LGL lymphocytosis has been associated with development of colitis, pleuritis, with a higher incidence of CCyR and MMR and with improved survival[64,65]. This suggests that dasatinib might not only act through inhibition of BCR-ABL1 but also through modulation of the immune system in some patients.

### Second- Generation TKI: Nilotinib

Modification of the methylpiperazinyl group of imatinib in order to improve its binding characteristics led to the development of nilotinib (formerly known as AMN107; Tasigna; Novartis, Basel, Switzerland), an orally available TKI which has 10–30 fold greater potency than imatinib against BCR-ABL1 (IC50 25 nM)[68]. Nilotinib also has activity against most imatinib-resistant mutations, but it fails to inhibit the T315I mutation[36,68,69]. Compared to imatinib, nilotinib has a relative increase in specificity against BCR-ABL1, showing reduced activity against TK PDGFRβ (IC50 57 nM) and KIT (IC50 160 nM)[68]. Similar to imatinib, nilotinib does not inhibit SFK. Nilotinib is currently approved as first line therapy of CML and for patients with CML in CP or AP who are intolerant or resistant to imatinib.

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The phase I dose escalation study recruited 119 patients with CML (CP=17, AP=56, BP=33) or Ph+-ALL (N=13) who were treated with nilotinib at doses ranging from 50–1,200 mg once daily and 400–600 mg twice daily[70]. Maximum tolerated dose was 600 mg twice daily. Dose limiting toxicities (DLT) at that dose level included grade 3–4 bilirubin elevation (11%) and grade 3–4 lipase elevation (11%). Other non-hematological toxicities were (percentage of all patients): rash (all grades: 22%; grade 3–4: 2%), pruritus (all grades: 17%; grade 3–4: 2%), dry skin (all grades: 12%), constipation (all grades:8%), nausea/vomiting (all grades:8%), fatigue (all grades:6%)[68]. Grade 3–4 hematological side effects were thrombocytopenia (20%), neutropenia (13%) and anemia (6%). The half-life of nilotinib was 15 hours, and there was saturation of plasma levels when nilotinib was given at doses ≥400 mg once daily. Thus, a twice daily schedule was explored, and the mean through level at steady state with 400 mg twice daily was 1.700 nM, which far exceeds the IC50 value for inhibiting both wild-type BCR-ABL1 and most imatinib resistant mutations (IC50 19–709 nM)[70].

Clinical efficacy of nilotinib was first shown in the Phase I trial (table 5)[70]. The hematologic response (HR; includes CHR, marrow response and return to CP) was 92% in CP, 74% in AP and 39% in BP. MCyR were seen in 18% of BP patients, 31% of AP patients and 53% of CP patients. Among 91 patients who had a mutation analysis at baseline, 37 patients were found to harbor 51 different mutations. Nilotinib had similar efficacy in patients with and without *BCR-ABL1* mutations, except in the case of the T315I mutation.

Four different phase II studies were launched to evaluate the clinical efficacy of nilotinib (400 mg twice daily) in patients with CML in CP, AP, BP and patients with Ph+ ALL[71–74]. Results are summarized in Table 5. The study in CP recruited 321 patients with resistance (71%) or intolerance (29%) to imatinib. The MCyR, CCyR and MMR rates were 59%, 44% and 28%, respectively. The 2-years PFS was 64% and 2-years OS was 87%. In the AP trial, 138 patients were enrolled and the majority (80%) had imatinib resistance. The HR was 56% (CHR 30%), MCyR was 32% and CCyR was 19%. Median time to progression was 16 months, and OS at 1 year was 82%.

Overall, nilotinib is a very well tolerated drug. Myelosuppression is observed in 30–40% and usually comprises grade 3–4 neutropenia and thrombocytopenia, but these are easily managed with treatment interruption and or dose reductions[72,73]. The dose of 400 mg twice daily seems to be higher than the minimal required dose, as dose reductions of 2$^{nd}$-generation TKI do not seem to impact the clinical outcomes of CML patients receiving these drugs as salvage or frontline therapy[75]. Grade 3–4 laboratorial abnormalities are relatively frequent in patients receiving nilotinib. Most common ones are lipase increase (17%), bilirubin increase (8%), hypophosphatemia (12–15%) and hyperglycemia (12%)[72,73]. Despite the high frequency of increase in lipase levels, clinically significant pancreatitis is uncommon (<1% of patients). Non-hematological clinical side effects are usually mild; most common ones (> 20%) include rash (all grades: 28%; grade 3–4: 3%), nausea (all grades: 24%; grade 3–4: 1%) and pruritus (all grades: 24%; grade 3–4: 1%). Prolongation of QTc interval has been reported, but is very uncommon, happening in 2.5% of patients[72,73]. However, there have been reports of sudden deaths in patients receiving therapy with nilotinib, and physician prescribing this drug should be aware of potential drug interactions that might increase the QTc interval[70].

### Second-Generation TKI: Bosutinib

Bosutinib (formerly known as SKI-606, Pfizer, New York, NY) is an orally available, 2$^{nd}$-generation TKI with dual activity against Src and Abl kinases. Bosutinib is more potent than imatinib, with an IC50 for BCR-ABL1 of 13 nM, but has very limited activity against PDGFRβ (IC50 370 nM) and KIT (IC50 6,000 nM)[76]. In a recently published phase I/II

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trial, bosutinib was administered to 288 patients with CP CML who were intolerant (N=88) or resistant (N=200) to imatinib[77]. The MTD was determined to be 500 mg daily. After a median follow-up of 24 months, a CHR was achieved in 86% of patients, a MCyR in 53% and a CCyR in 41%. Two-year PFS and OS were 79% and 92%, respectively. Bosutinib had activity against all subtypes of patients with imatinib-resistance or intolerance, except for those harboring the T315I mutation. Bosutinib was very well tolerated. The most common grade 3–4 non-hematological toxicities were diarrhea (9%), rash (9%) and vomiting (3%). Grade 3–4 cytopenias were also uncommon and included anemia (13%), neutropenia (18%) and thrombocytopenia (23%). Another phase II trial evaluated bosutinib (500 mg/day) in 114 CP CML patients who had failed two TKIs, either imatinib/nilotinib or imatinib/dasatinib[78]. Rates of CHR, MCyR and CCyR were 73%, 32% and 22%, respectively, demonstrating that bosutinib has activity in this scenario.

## Issues with 2nd-generation TKI in patients post-imatinib failure

Two points regarding therapy with 2nd-generation TKI post imatinib failure merit further discussion: (1) time to intervene post-imatinib failure; (2) prognostic factors for response and survival with 2nd-generation TKI.

One study sought to determine the answer to the first question[79]. Among 293 patients with resistance to imatinib and treated with dasatinib, 151 had only lost MCyR (but maintained CHR), 33 had lost both MCyR and CHR, and 109 had lost CHR and had never achieved MCyR. The rates of CCyR and MMR with dasatinib were higher in the first group (72% and 60%, respectively) versus the second group (42% and 29%) and the third group (26% and 26%). The EFS was also better for those patients who had only lost MCyR. Thus, the appropriate time to intervene and change therapy is when the patient loses a MCyR (or a CCyR) but remains in CHR, as intervening at later time points will lead to an inferior outcome.

It is important to determine which patients with imatinib resistant CML have a low probability of response to 2nd-generation TKI, since these patients could be considered for other therapeutic strategies such as allogeneic HSCT[80]. In one study, two variables were found to be associated with low EFS: lack of prior cytogenetic response to imatinib and performance status ≥1[81]. Patients with both variables had an EFS of only 20%. In a subsequent study by the same group, the achievement of a CCyR after 3 months of therapy in CML-CP patients receiving 2nd-generation TKI post imatinib failure was the only variable associated with EFS (3-years: 74% vs. 43%) and OS (98% vs. 79%)[82]. Another prognostic model recently published identified the following 3 variables as prognostic: (1) best cytogenetic response achieved with imatinib; (2) Sokal risk score; (3) presence or absence of grade 3–4 neutropenia during treatment with imatinib necessitating dose reduction and/or growth factors[83]. With these 3 variables the authors built a prognostic score which could predict the rate of CCyR achieved with a 2nd-generation TKI. For those patients who present with mutations, the presence of intermediate-sensitivity *BCR-ABL*1 mutations (IC50 ≥3 nM for dasatinib and ≥150 nM for nilotinib) is associated with inferior response rates[84,85]. Mutations with a low response rate to dasatinib include F317L, Q252H and V299L. Mutations with a low response rate to nilotinib include Y253H, E255V/K and F359V/C. Clinicians should tailor therapy for patients with imatinib-resistant CML who present with BCR-ABL1 mutations in order to choose the most adequate TKI to eradicate mutant clones.

## Second-Generation TKI as Frontline Therapy for CML

The higher potency of 2nd-generation TKI as compared to imatinib led to the investigation of their use in untreated patients with CML CP. Three phase 2 studies (2 with nilotinib and 1

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with dasatinib) were published and demonstrated very high response rates of these drugs when used as frontline therapy (Table 6)[86–88]. For nilotinib, at 3 months the rate of CCyR was 78–90% and of MMR was 42–52%. At 12 months of therapy, rates of CCyR and MMR were 96% and 81–85%. Dasatinib led to a CCyR rate at 3 months of 82% and at 12 months of 98%; comparative rates of MMR were 24% and 71%. Thus, it appears that these drugs do not only lead to higher rates of response but also to faster responses compared to imatinib. While patients who achieve a late response appear to have a similar survival as patients who achieve an early response[89], a drug that is able to lead to a higher response rate earlier in the treatment course might decrease the rate of evolution to AP/BP[90].

Two phase III studies were published in 2010 comparing nilotinib and dasatinib against standard dose imatinib, and a phase III trial comparing bosutinib against imatinib has been recently presented (Table 6). In the nilotinib trial, ENESTnd (Evaluating Nilotinib Efficacy and Safety in clinical trials-newly diagnosed patients), 846 patients were randomized in a 1:1:1 fashion to three treatment arms (nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, imatinib 400 mg daily)[91]. The primary endpoint was the MMR at 12 months. Patients were equally distributed between three groups with no imbalance in pretreatment characteristics. Nilotinib was superior to imatinib regarding the primary endpoint, rendering a MMR rate of 44% (300 mg), 43% (400 mg) and 22% (imatinib) ($P<0.0001$ for both comparisons). The cumulative rate of CCyR was also higher with nilotinib: 80% (300 mg), 78% (400 mg) and 65% (imatinib). Response was achieved faster with nilotinib, as MMR rate at 6 months was 33% (nilotinib 300 mg), 30% (nilotinib 400 mg) and 12% (imatinib 400 mg). Longer follow-up continues to demonstrate improved response rate for patients treated with nilotinib, with a MMR at 24 months of 71% (300 mg), 67% (400 mg) and 44% (imatinib)[92]. There was also a higher rate of CMR (26% [300 mg], 21% [400 mg], 10% [imatinib]; $p<0.0001$). Importantly, nilotinib at both dose schedules decreased time to progression to AP or BP. At the time of first report, 11 patients (4%) on the imatinib had progressed to AP or BP, while only 2 patients (<1%) and 1 patient (<1%) had progressed on the nilotinib 300 mg and 400 mg arms, respectively. The majority of grade 3–4 nonhematological adverse events occurred in <1% of patients in all 3 arms. Grade 3–4 hematological side effects included thrombocytopenia (10%–12% [nilotinib] vs. 9% [imatinib]), neutropenia (10–12%[nilotinib] vs. 20% [imatinib]) and anemia (3% [nilotinib] vs. 5% [imatinib]). Grade 3–4 biochemical abnormalities which were more common with nilotinib than with imatinib included hyperbilirrubinemia (4–8% vs. <1%), hyperglycemia (4–6% vs. 0%), hyperlipasemia (6% vs. 3%) and increased ALT (4–9% vs. 2%).

The DASISION trial randomized 519 patients (1:1) to dasatinib (100 mg once daily) or imatinib standard dose[93]. The primary endpoint was confirmed CCyR at 12 months. Dose escalation to imatinib 400 mg twice daily or dasatinib 140 mg once daily was allowed for patients with suboptimal responses. At 12 months, dasatinib led to superior rates of CCyR (83% vs. 72%; $p<0.001$) and MMR (46% vs. 28%; $p<0.0001$). After 18 months of follow-up, there was improvement in CCyR (85% vs. 80%) and MMR (57% vs. 41%; $p=0.0002$)[94]. CMR was attained in 13% of dasatinib patients versus 7% of imatinib patients. There were fewer events of transformation to AP or BP in the dasatinib arm (2.3% vs. 3.5%, p=non-significant). There was no difference in OS (12 months: 97% [dasatinib] vs. 99% [imatinib]). Drug related side effects were primarily grade 1–2. Dasatinib led to higher rates of grade 3–4 thrombocytopenia (19% vs. 10%), but similar rates of grade 3–4 neutropenia (21% vs. 20%). Dasatinib, led to more episodes of pleural effusion (10% vs. 0%); all were grade 1–2, while imatinib caused more superficial edema (36% vs. 9%). Incidence of other common non-hematological side effects, including diarrhea, nausea, vomiting, myalgia, rash and fatigue were more common with imatinib than with dasatinib.

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The BELA trial randomized 502 CP CML patients to either bosutinib 500 mg/day (N=250) or imatinib 400 mg/day (N=252)[95]. The primary endpoint was rate of CCyR at 12 months. In the 18-month follow-up report, the 12 month CCyR rate was 70% (bosutinib) and 68% (imatinib). The cumulative 12-months CCyR rate was 79% for bosutinib and 75% for imatinib. The MMR rate at 1 year was higher for bosutinib, 39% vs. 26% (p=0.002). Time to CCyR and MMR were shorter with bosutinib compared to imatinib (p<0.001 for both comparisons). Transformation to AP or BP occurred in 2% of patients in bosutinib arm versus 4% of patients on imatinib arm (p=0.053). Grade 3–4 side effects with bosutinib included diarrhea (10%), vomiting (3%), pneumonia (3%) and dyspnea (2%). Grade 3–4 cytopenias included thrombocytopenia (14% [bosutinib], 14% [imatinib]) and neutropenia (9% [bosutinib], 21% [imatinib]). Despite the perceived better toxicity profile for bosutinib because of its narrower inhibition spectrum, discontinuation due to adverse events occurred in 22% of patients treated with bosutinib and 6% of those receiving imatinib. This probably reflects the lesser familiarity with the management of side effects induced by bosutinib among investigators and the early switch to alternative available treatment options.

Overall these phase III trials confirmed the superior efficacy of 2$^{nd}$-generation TKI versus imatinib for the frontline therapy of CML, leading to faster and deeper responses, and with a similar or improved toxicity profile. The FDA has approved both nilotinib and dasatinib for the frontline therapy of patients with CML. Since the follow-up of these trials is still relatively short, the potential impact of these agents on PFS, EFS, and OS remain to be determined. One initial report from the ENESTnd trial has suggested that nilotinib may lower the incidence of *BCR-ABL1* mutations, which occurred in only 2.3% of patients receiving nilotinib, versus 6% of patients receiving imatinib[96]. However, it must be emphasized that an important number of patients fail TKI therapy for reasons different from *BCR-ABL1* mutations. Another potential concern is the outcome of patients after they progress while on 2$^{nd}$-generation TKI. An analysis of 23 patients treated on two frontline phase 2 trials with nilotinib and dasatinib at M.D. Anderson Cancer Center has revealed that, in the majority of cases, failure to 2$^{nd}$-generation TKI is related to toxicity or patient preference, and patients not infrequently respond to the alternative 2$^{nd}$-generation TKI[97].

### Third-Generation TKI: Ponatinib

The T315I mutation of BCR-ABL1 is associated with a high level of resistance to all available TKI. The isoleucine side chain does not form a hydrogen bond with the TKI and prevents binding of the drug due to steric hindrance. Ponatinib (formerly known as AP24534, Ariad Pharmaceuticals, Cambridge, MA) is the first TKI to have potent and consistent activity against BCR-ABL1 with the T315I mutation[98]. Ponatinib was developed based on a scaffold that, unlike current available TKI, does not make a hydrogen bond with T315, and has a long and flexible ethynil tri-carbon linker which permits its accommodation in the catalytic domain even in the presence of the bulky side chain of isoleucine at residue 315[98]. Ponatinib inhibits both wild-type (IC50=0.37 nM) and T315I mutated (IC50=2.0 nM) BCR-ABL1, while having activity against several common BCR-ABL1 mutations such as E255K, Y253H and G250E. Ponatinib also inhibits other TK, including SFK, PDGFRα and KIT[98]. In vivo, ponatinib prolonged survival of mice injected with both wild-type and T315I BCR-ABL1 cells. In a cell based mutagenesis screen, 40nM of ponatinib, a concentration achieved in humans at doses above 30mg daily, completely abolished growth of resistant *BCR-ABL1* mutations, suggesting that this drug may prevent the emergence of resistance mediated by *BCR-ABL1* mutations[98].

Results from a recently completed phase I study of ponatinib in patients with advanced hematological malignancies were recently presented[99]. Seventy-four patients (64 with refractory CML or Ph+-ALL) were recruited. Patients received ponatinib at doses ranging from 2–60 mg once daily. The most common side effects were thrombocytopenia (23%),

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rash (22%) and arthralgia (15%). The DLT was pancreatitis, and the MTD was set at 45 mg once daily[99]. Among 38 patients with CML in CP recruited into the trial, a CHR was obtained in 95%, a MCyR in 66% and a CCyR in 53%. Among 9 patients with the T315I mutation evaluable for response, 100% achieved a CHR and MCyR, and 89% achieved a CCyR. The phase II PACE study is currently evaluating further the efficacy of ponatinib in Ph+ leukemias.

## Conclusions

Looking back, it is mesmerizing the impressive amount of progress made in the treatment of CML with TK inhibition strategies overall the last decade, first establishing the activity of imatinib, then recognizing and delineating several mechanisms of resistance to TKIs, and finally, developing 2$^{nd}$ and 3$^{rd}$ generation TKI for the management of imatinib resistance. Such fast pace of developments in the field of CML therapy is the direct result of the close collaboration between basic scientists, biochemists and physicians, which has produced a greater understanding of the pathophysiology of CML and the mechanisms of resistance to TKI. However, there is still room for improvement, particularly for the patient who progress to more advanced stages of the disease, where outcomes are still poor despite the use of potent TKI. Important advancements are still needed regarding our understanding of BCR-ABL1 independent mechanisms of resistance, the biology of primitive CML progenitors, which are resistant to TKI therapy, the possibility of stopping TKI therapy in patients with no evidence of residual disease, and the development of definite curative strategies. We can only hope that strengthening the collaboration between basic and translational investigators and with the invaluable collaboration of patients and their families we will be able to overcome all remaining obstacles in our quest to curing CML in the near future.

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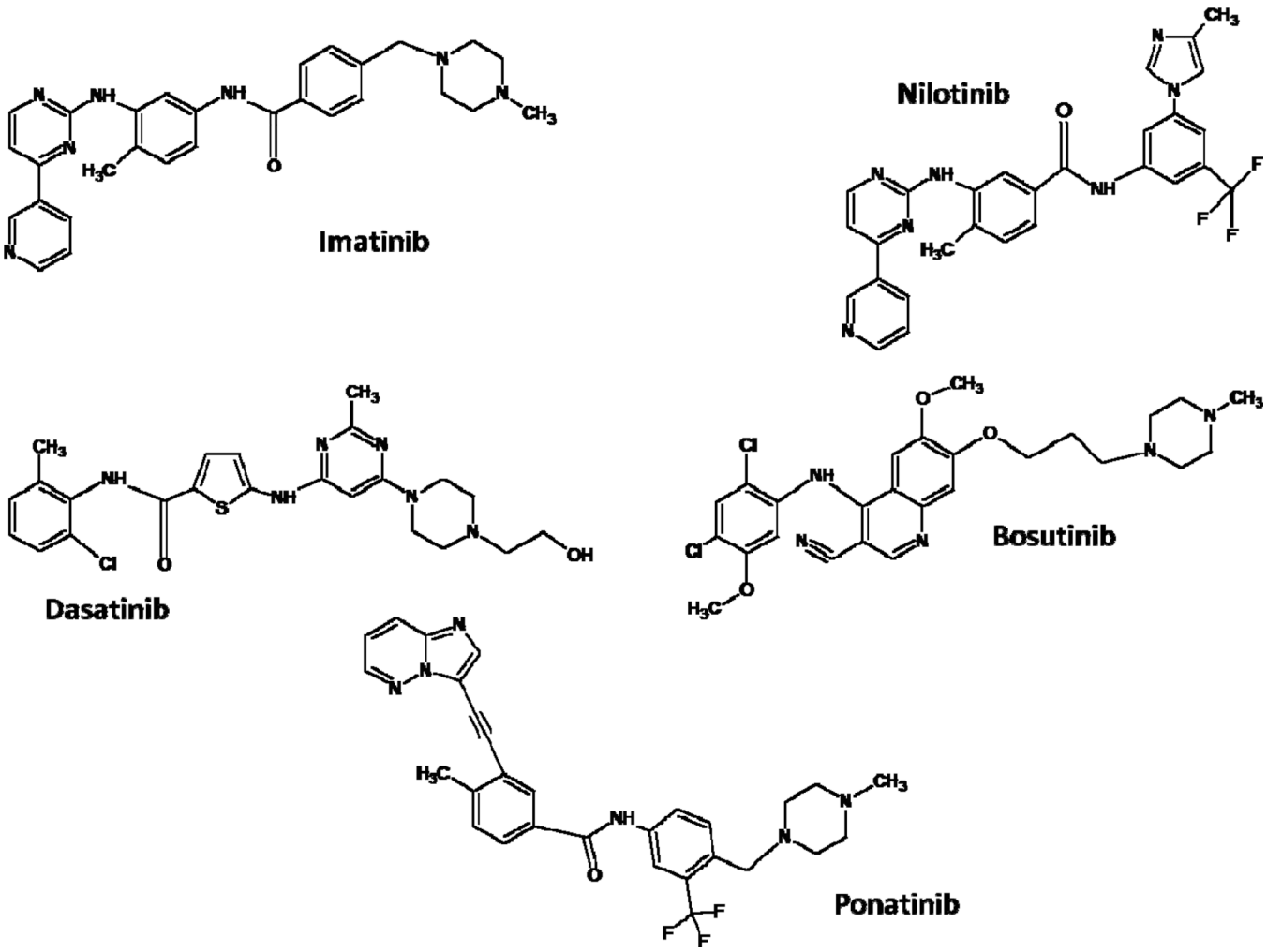


**Figure 1.**
Three Generations of Tyrosine Kinase Inhibitors. First-generation: Imatinib; Second-generation: Nilotinib, Dasatinib and Bosutinib; Third-generation: Ponatinib

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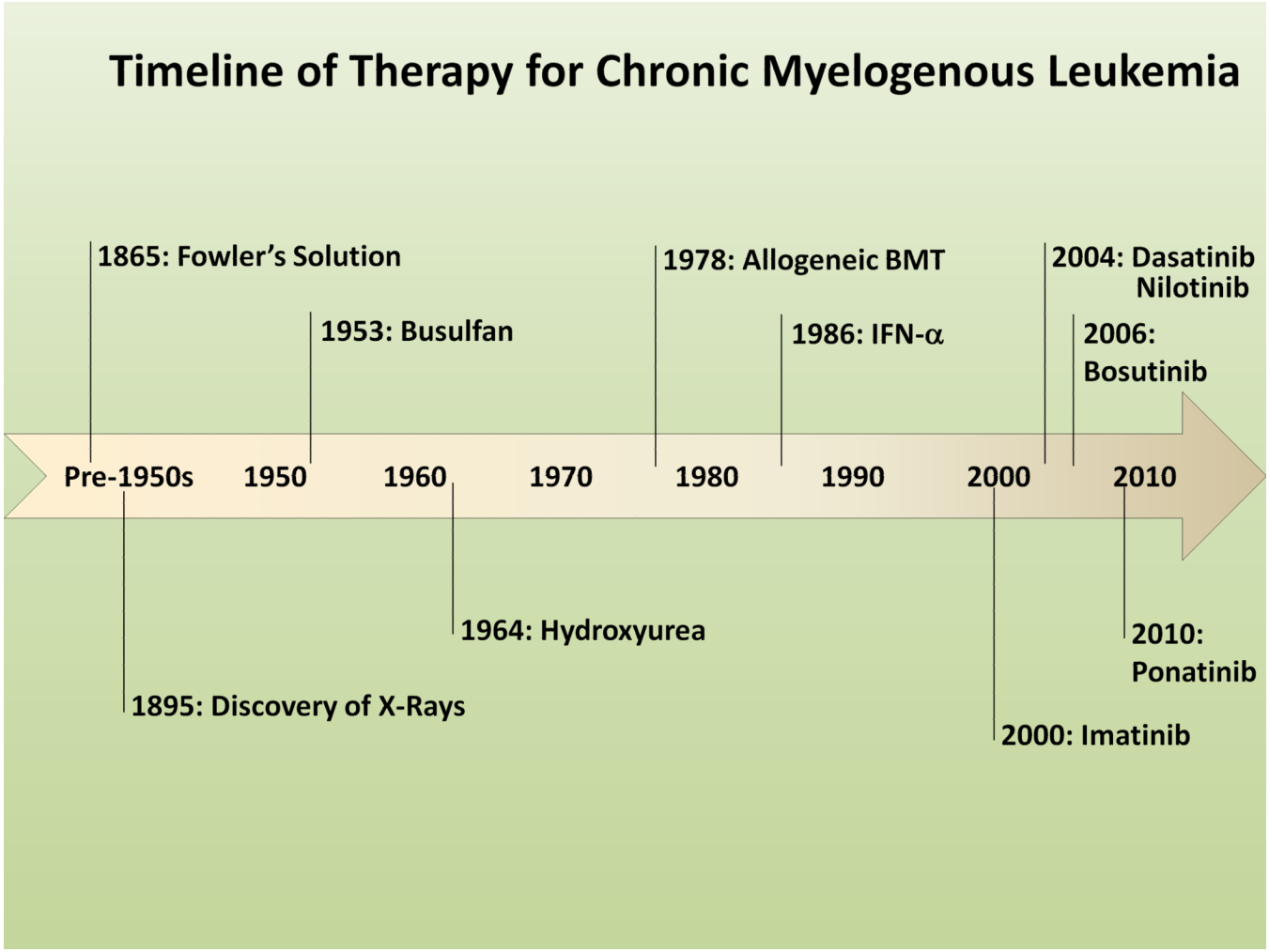


**Figure 2.**
Timeline of Development of Therapy for Chronic Myelogenous Leukemia

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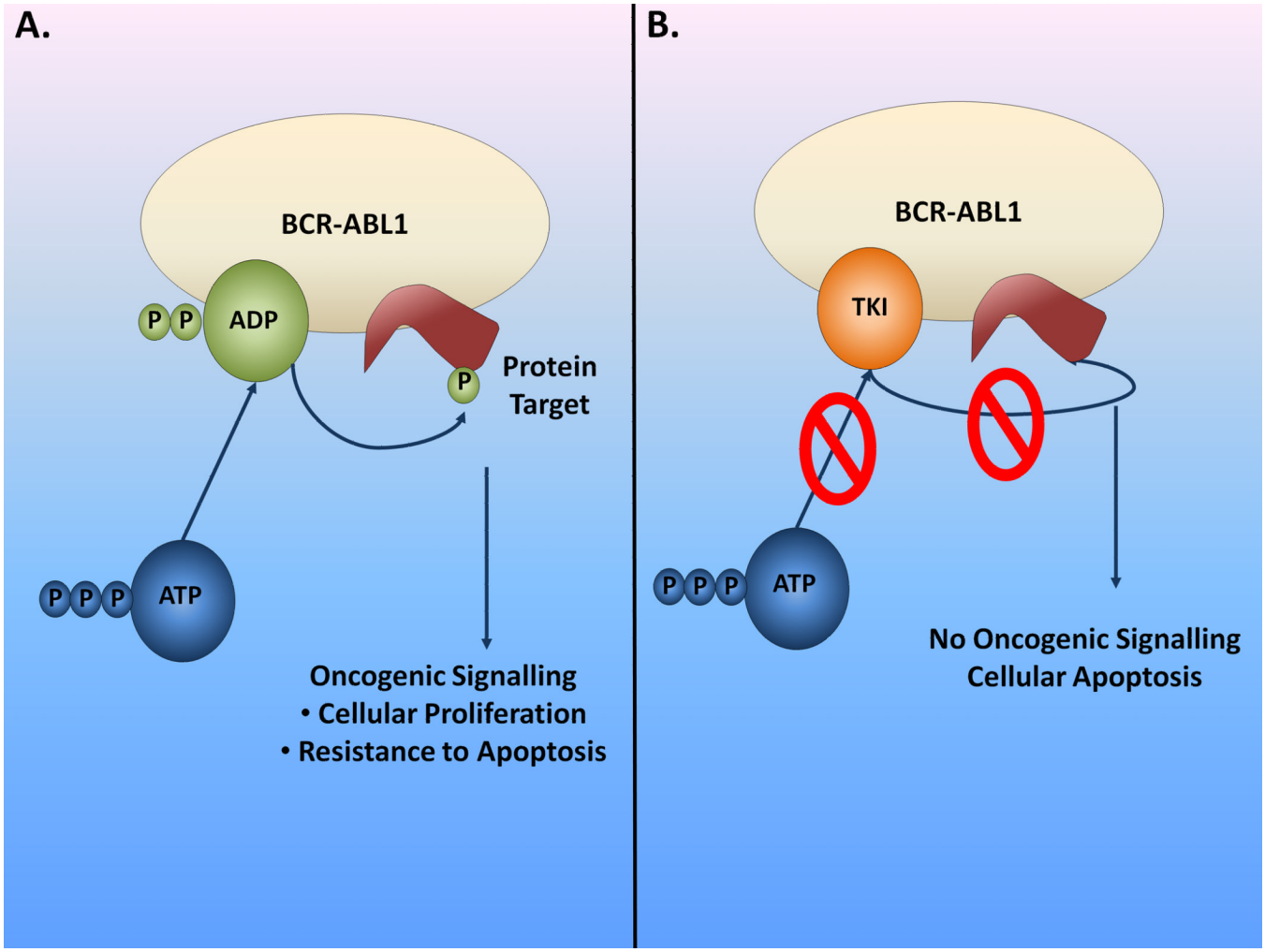


**Figure 3.**

Mechanism of action of Imatinib and other TKI. A. The BCR-ABL1 oncogenic TK phosphorylates protein targets leading to activation of intracellular pathways associated with increased cellular proliferation and apoptosis resistance. ATP binds to BCR-ABL1 and supplies phosphate groups for the phosphorylation reaction. B. Current available TKI are ATP-mimetic compounds, competing with ATP for the ATP-binding site at BCR-ABL1. Binding of the TKI to BCR-ABL1 prevents phosphorylation of protein substrates, since no phosphate group is available for the reaction to occur. As a consequence, oncogenic signaling pathways are no longer activated and the cell undergoes apoptosis.

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## Table 1

CML Response Criteria Definition (from[30])

| Hematologic | Cytogenetic | Molecular |
|---|---|---|
| Complete: Normal complete blood cell count, non-palpable spleen and disappearance of all disease signs and symptoms | Complete: 0% Ph+-metaphases | Complete: Undetectable BCR-ABL1 transcripts on two consecutive quantitative RT-PCR or nested PCR assays (sensitivity at least $10^{-4}$) |
| | Partial: 1–35% Ph+-metaphases | Major: Ratio BCR-ABL1:ABL1 transcripts ≤ 0.1% in the international scale by quantitative RT-PCR |
| | Major: 0–35% Ph+-metaphases | |
| | Minor: 36–65% Ph+-metaphases | |
| | Minimal: 66–95% Ph+-Metaphases | |
| | No Response: ≥ 96% Ph+-metaphases | |

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## Table 2

Recommendations for disease monitoring (from[30])

| Exam | Frequency |
|---|---|
| Complete Blood Cell Count | Every 2 weeks until CHR, them every 3 months or as needed |
| Cytogenetic | At diagnosis, 3 months, 6 months and every 6 months until CCyR, then every 12 months if no molecular test available |
| | At failure or unexpected myelosuppression |
| Molecular | Every 3 months until MMR, then every 6 months |
| Mutation analysis | In case of failure, suboptimal response and before changing 2nd-generation TKI |

**Abbreviations:** CCyR, complete cytogenetic response; CHR, complete hematological response; MMR, major molecular response; TKI, tyrosine kinase inhibitor

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## Table 3

Criteria for Failure, Suboptimal Response and Optimal Response (from[30])

| Time (mo) | Failure | Suboptimal | Optimal |
|---|---|---|---|
| 3 | No CHR | ≥ 96% Ph+ metaphases | CHR and Ph+ ≤ 65% |
| 6 | No CHR | > 35% Ph+ metaphases | < 35% Ph+ metaphases |
| | ≥ 96% Ph+ metaphases | | |
| 12 | > 35% Ph+ metaphases | 1–35% Ph+ metaphases | 0% Ph+ metaphases |
| 18 | ≥ 1% Ph+ metaphases | No MMR | MMR |
| Any | Loss of CHR | Loss of MMR | Stable or improving MMR |
| | Loss of CCyR | Mutation (intermediate sensitivity imatinib) | |
| | Mutation (poor sensitivity imatinib) | | |
| | Clonal Evolution | | |

**Abbreviations:** CCyR, Complete Cytogenetic Response; CHR, complete hematological Response; MMR, Major Molecular Response

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**Table 4**

Studies with Dasatinib as Salvage Therapy for Imatinib Resistance or Intolerance

| Study | Disease Stage | Dose | N | % Response | | |
|---|---|---|---|---|---|---|
| | | | | CHR | Cytogenetic Response | |
| | | | | | MCyR | CCyR |
| Phase I[52] | CP | 15–240 mg daily | 40 | 92 | 45 | 35 |
| | AP | | 11 | 45 | 27 | 18 |
| | MBP | | 23 | 35 | 35 | 26 |
| | LBP/Ph+ ALL | | 10 | 70 | 80 | 30 |
| START-C[53] | CP | 70 mg twice daily | 387 | 90 | 59 | 49 |
| START-A[54] | AP | 70 mg twice daily | 174 | 45 | 39 | 32 |
| START-B[55] | MBP | 70 mg twice daily | 109 | 27 | 33 | 27 |
| START-L[55] | LBP | 70 mg twice daily | 48 | 29 | 52 | 46 |
| START-R[57] | CP | 70 mg twice daily | 101 | 93 | 53 | 44 |
| Dose Optimization[58] | CP | 100 mg daily | 167 | 92 | 63 | 50 |

**Abbreviations:** AP, advanced phase; BP, blast phase (myeloid [M] or lymphoid [L]); CCyR, Complete Cytogenetic Response; CHR, Complete Hematological Response; CP, Chronic Phase; MCyR, Major Cytogenetic Response Ph+-ALL, Philadelphia-Positive Acute Lymphoblastic Leukemia;

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**Table 5**

Studies with Nilotinib as Salvage Therapy for Imatinib Resistance or Intolerance

| Study | Disease Stage | N | % Response | | | |
|---|---|---|---|---|---|---|
| | | | Hematologic Response | | Cytogenetic Response | |
| | | | HR | CHR | MCyR | CCyR |
| Phase I[70] | CP | 17 | 92 | 92 | 35 | 35 |
| | AP | 56 | 74 | 51 | 27 | 14 |
| | BP | 33 | 39 | 6 | 18 | 6 |
| | Ph+-ALL | 10 | 10 | - | - | - |
| Phase II | CP[72] | 321 | NR | 76 | 59 | 44 |
| | AP[73] | 134 | 56 | 30 | 32 | 19 |
| | BP[71] | 135 | 38 | 25 | - | - |
| | Ph+-ALL[74] | 41 | 27 | 24 | - | - |

**Abbreviations:** AP, advanced phase; BP, blast phase; CCyR, Complete Cytogenetic Response; CHR, Complete Hematological Response; CP, Chronic Phase; HR, Hematological Response; MCyR, Major Cytogenetic Response Ph+-ALL, Philadelphia-Positive Acute Lymphoblastic Leukemia;

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## Table 6

Studies with 2nd-generation TKI as Frontline Therapy in CML

| Study | Drug | N | % Response at 12 months | |
|---|---|---|---|---|
| | | | CCyR | MMR |
| Phase II-MDACC[86] | Nilotinib 400 mg twice daily | 67 | 97 | 81 |
| Phase II-MDACC[12] | Dasatinib 100 mg once daily | 62 | 98 | 71 |
| Phase II-GIMEMA[88] | Nilotinib 400 mg twice daily | 73 | 96 | 85 |
| Phase III-ENESTnd[91] | Nilotinib 300 mg twice daily | 282 | 80 | 55 |
| | Nilotinib 400 mg twice daily | 281 | 78 | 51 |
| | Imatinib 400 mg once daily | 283 | 65 | 27 |
| Phase III-DASISION[93] | Dasatinib 100 mg once daily | 259 | 83 | 46 |
| | Imatinib 400 mg once daily | 260 | 72 | 28 |
| Phase III-BELA[95] | Bosutinib 500 mg once daily | 250 | 70 | 39 |
| | Imatinib 400 mg once daily | 252 | 68 | 26 |

**Abbreviations:** CCyR, Complete Cytogenetic Response; ENESTnd, Evaluation of Nilotinib Efficacy and Safety in clinical Trials-newly diagnosed patients; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; MDACC, M.D. Anderson Cancer Center; MMR, Major Molecular Response.