

Nilotinib for treatment of chronic myeloid leukemia in light of the current evidence and guidelines

Pratap Neelakantan¹ & Jane F Apperley^{*1}



Practice Points

- Nilotinib induces deeper and more rapid responses compared with imatinib in a front-line setting for chronic phase chronic myeloid leukemia (CP-CML) with improved rates of complete cytogenetic response and major molecular response, although survival difference remains to be shown at 4 years follow-up.
- Nilotinib is effective as both second- and third-line therapies in CP-CML patients.
- The side effects are comparable to other tyrosine kinase inhibitors (TKIs). They are manageable and there appears to be minimal cross-intolerance among TKI therapies for nonhematological toxicities.
- Hyperglycemia and pancreatitis appear to be lower than previously thought; few cases of peripheral arterial occlusive disease warrant caution in patients at risk.
- With results from longer follow-up of the Phase III trials, second-generation TKIs could replace imatinib as the standard upfront therapy for CP-CML in the future.

SUMMARY The introduction of the tyrosine kinase inhibitor imatinib, a little over a decade ago, has greatly improved the prognosis for patients with chronic myeloid leukemia. Now with the availability of second-generation tyrosine kinase inhibitors we anticipate further improvements in the outcome of this disease. These agents, namely nilotinib, dasatinib and bosutinib, have not only been effective at treatment of imatinib-resistant and/or -intolerant patients, but are increasingly being advocated for upfront usage. In this review, we focus on nilotinib, its pharmacology, clinical indications and side effects, and suggest guidelines for its usage.

¹Department of Hematology, Hammersmith Hospital, Imperial College, London, UK

^{*}Author for correspondence: Tel.: +44 203 313 4017; Fax: +44 203 313 8223; j.apperley@imperial.ac.uk

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder characterized by the expansion of hematopoietic cells carrying the Philadelphia chromosome (Ph), resulting from a reciprocal translocation of the long arms of chromosomes 9 and 22. A novel fusion gene is formed, BCR-ABL1, which encodes a constitutively active protein tyrosine kinase [1]. First-line tyrosine kinase inhibitor (TKI) therapy with imatinib (STI-571, Gleevec®; Novartis, Basel, Switzerland) has resulted in outstanding responses in patients with chronic phase (CP) [2]. The pivotal Phase III IRIS trial established imatinib, at a preferred daily dose of 400 mg, as the standard of care for patients with CML in CP such that allogeneic stem cell transplantation, the previous standard of care, is now reserved for the minority of patients presenting in accelerated phase (AP) or blast crisis (BC), or with resistant disease [2]. The current estimate for overall survival (OS) from the IRIS trial is in excess of 85% at 8 years [3]. However, despite the excellent results with imatinib, approximately 25–30% of patients switch to a second-generation TKI due to resistance and/or intolerance [4].

Nilotinib (AMN107, Tasigna®; Novartis) is an oral TKI designed to overcome imatinib resistance in CML [5]. In Phase I and II studies, nilotinib achieved good tolerability and durable responses in adult patients with Ph+ CML resistant or intolerant to at least one prior therapy, including imatinib [6–8]. The aim of this article is to examine the role of nilotinib in both front-line and subsequent therapy for CML, to evaluate the adverse event profiles and discuss options for managing them in clinical practice.

Materials & methods

Relevant literature was identified and reviewed using searches of Pubmed (2000 to 1 August 2012), the American Society of Hematology (ASH) and American Society of Clinical Oncology abstracts databases (2002–2012 annual meetings/symposia) and the European Hematology Association abstracts database (2006–2012 annual meetings). Search terms included, but were not limited to: 'nilotinib', 'AMN107', 'chronic myeloid leukemia', 'acute lymphoblastic leukemia', 'BCR-ABL1', 'imatinib resistance', 'adverse events', 'pharmacology' and 'clinical trials'. We used standard definitions for CHR, complete cytogenetic response (CCyR),

major molecular response (MMR), molecular response (MR)⁴ and MR^{4.5} [4].

Pharmacology & mechanism of action

Nilotinib (*N*-[3-[3-(1H-imidazolyl)propoxy]phenyl]-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino] benzamide), an orally bio-available, rationally designed, derivative of imatinib, is a TKI with improved target specificity (Figure 1) [9,10]. Like imatinib, nilotinib appears to have an antiproliferative effect rather than a proapoptotic effect in primitive CML stem cells [11]. Nilotinib inhibits BCR-ABL1 by binding to an inactive, DFG-out (aspartate–phenylalanine–glycine motif exchange positions), conformation of the *ABL1* kinase domain, thus preventing the enzyme from adopting the catalytically active conformation and blocking the tyrosine phosphorylation of proteins involved in BCR-ABL1-mediated signal transduction [12].

The improved binding of nilotinib results in greater potency and selectivity over the KIT and PDGF receptor kinases but has no activity against targets such as the SRC family of tyrosine kinases [5]. In preclinical models, nilotinib was 30-times more potent than imatinib in imatinib-sensitive CML cell lines (KBM5 and KBM7), and maintained activity in 32 of 33 imatinib-resistant *BCR-ABL1* mutant cell lines [5,9]. The improved potency was attributed to the better topologic fit of nilotinib to the protein as compared with imatinib. It is inactive against the T315I kinase domain mutation, one of the more frequent mutations seen in imatinib resistance.

Evidence

■ Nilotinib as second-line therapy

Nilotinib was granted an accelerated approval by the US FDA for patients with chronic or AP CML deemed imatinib-resistant and/or -intolerant in 2007. The evidence for approval was based on the results of Phase I and II studies in this setting.

■ Phase I results

Kantarjian *et al.* conducted a Phase I study of the tolerability and efficacy of nilotinib, enrolling 119 patients with imatinib-resistant CML (106 patients; BC: 33, AP: 56, CP: 17) or Ph+ acute lymphoblastic leukemia (ALL; 13 patients) [6]. Nine different doses of nilotinib were used between 50 and 1200 mg once daily or 400 or

600 mg twice daily (b.i.d.). The plasma concentrations at the steady-state level were greater with 400 mg b.i.d. than with a daily dose of 800 mg and also the results were similar for both 400 and 600 mg b.i.d. doses. The median dose of nilotinib was 600 mg/day (range: 400–800 mg/day) and the median duration of administration for CP was 4.9 months (range: 1.4–9.3 months). Complete haematologic response (CHR) was reported in two of 33 patients (6%) in BC, 26 of 56 (46%) in AP and 11 of 17 (65%) in CP. Cytogenetic responses of any degree were observed in 27, 35 and 53% of patients in BC, AP and CP, respectively. Limited clinical efficacy was seen in patients with Ph+ ALL: two of 13 patients (15%) were considered responders (one partial hematologic remission and one complete molecular response). No significant differences in response were noted between groups with and without mutations in the gene coding for Abl kinase (mutations were present in 45% of patients in the study). Patients with imatinib-resistant mutations G250E, M351T, E355G, Y253F, F311L, F317L, F359V, H396P, H396R and E459Q, showed good clinical response to nilotinib. However, two patients carrying the T315I mutation did not respond [5].

■ Phase II

Giles *et al.* have recently reported the 48-month follow up of the international Phase II trial of nilotinib in imatinib-resistant/intolerant patients in CP [13]. MCyR and CCyR were obtained in 59 and 45% of patients while on study. The 59% MCyR rates were obtained at 2 years and there were no further improvements to the response rates over the next 2 years, although there were five additional CCyR from PCyR. The estimated rate of OS and progression-free survival (PFS) at 48 months was 78 and 57%, respectively. Depth of molecular responses at 3 and 6 months positively correlated with long-term outcomes, including PFS and OS at 48 months and patients with CHR at baseline are also likely to have better PFS. Of the 321 patients initially enrolled in the study, 98 (31%) were treated for at least 48 months. By 4 years, 70% of patients had discontinued nilotinib, primarily due to disease progression (30%) or adverse events (21%). Although the rates of discontinuation were high, nilotinib is safe and effective for long-term use in responding patients with CML-CP who are intolerant or resistant to imatinib.

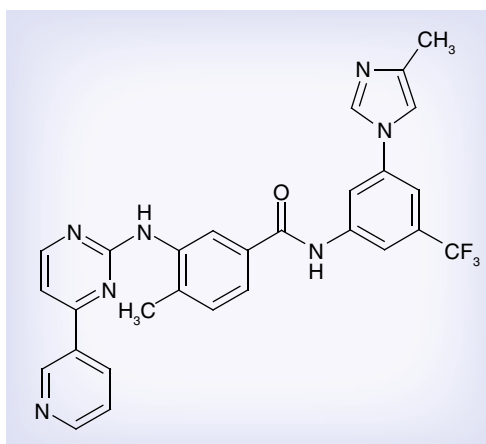


Figure 1. Nilotinib.

Patients with less sensitive mutations (cellular IC_{50} : 201–800 nM) show poorer rates of response to nilotinib as compared with mutations that were more sensitive (IC_{50} <200) [14–16].

Nilotinib as front-line therapy

■ Phase II results

Phase II studies of nilotinib in newly diagnosed patients have been reported from both the Italian GIMEMA group and MD Anderson Cancer Center (TX, USA). The most recent update from the GIMEMA study presented at ASH 2012 reported 73 early CP, untreated, Ph+ CML patients, who received nilotinib at a dose of 400 mg b.i.d. [17,18]. The primary end point was attainment of CCyR at 1 year. With a median follow-up of 51 months, the cumulative incidence of CCyR at 1 year was 100%. Responses were rapidly attained, with 78% attaining CCyR and 52% MMR at 3 months. A total of 68 patients continued to remain in MMR at the most recent follow-up with one progression due to T315i mutation and 11 of 73 patients (15%) had discontinued nilotinib due to various side effects.

In the MD Anderson Cancer Center study, upfront nilotinib (400 mg b.i.d.) was evaluated in 100 CP patients. The primary end point was MMR rate at the end of 1 year. The median follow-up was 24 months with a MMR rate of 89% at 18 months (in the 51 patients evaluated) and CCyR rate of 95% at the end of 1 year. Responses occurred rapidly, with 96% of patients achieving CCyR by 3 months and 98% achieving CCyR by 6 months. A total of 19 patients (19%) discontinued due to toxicity, and the OS at 48 months was 96%. Although

the primary end point was different, in both studies, upfront nilotinib led to deeper and quicker responses as compared with historical cohorts treated with imatinib. These two trials resulted in US FDA approval and the subsequent ENESTnd Phase III trial.

■ Phase III

The 3-year results from ENESTnd, a Phase III trial comparing upfront usage of nilotinib 300 mg b.i.d., nilotinib 400 mg b.i.d. and imatinib 400 mg once daily in newly diagnosed CP CML patients, was presented at American Society of Clinical Oncology and EHA and ASH recently [19,20]. The patients were stratified according to Sokal risk score [21] at the time of diagnosis [22]. A total of 846 patients with Ph+ CML-CP were randomized to nilotinib 300 mg b.i.d. (n = 282), nilotinib 400 mg b.i.d. (n = 281), or imatinib 400 mg once daily (n = 283). Both nilotinib doses demonstrated significantly higher rates of MMR, MR⁴, and MR^{4.5} versus imatinib at 3 years. Cumulative response rates according to risk stratification by Sokal score are shown in Table 1. Nilotinib was associated with a significantly lower probability of progression to AP/BC versus imatinib (two [0.7%] progressions on nilotinib 300 mg b.i.d., three [1.1%] on nilotinib 400 mg b.i.d. and 12 [4.2%] on imatinib). In keeping with previously published data, the 3-year follow-up did not show any difference in the discontinuation rates between nilotinib and imatinib. The side-effect profile was different between nilotinib and imatinib in that the incidence of rash, headache, pruritus and deranged liver function tests were higher in the nilotinib arms as compared with nausea, vomiting, diarrhea, muscle cramps and edema, which were lower.

In a landmark analysis, patients with BCR-ABL transcript levels ≤10% at 3 months had a higher probability of achieving MMR by 1 and 2 years than patients with transcript levels >10% [23]. At 3 years, OS considering only CML-related deaths was significantly higher for nilotinib.

Nilotinib for third-line & beyond

We have, along with other groups, demonstrated that nilotinib is effective as a third-line therapy when two previous TKIs have failed either due to resistance or intolerance [24,25]. Achievement of CyR on imatinib or second-line therapy along with low Sokal score were found to be the most important factors determining response to a third-line TKI. Also, patients with hematological intolerance on previous line of therapy fared poorly compared with nonhematological toxicities that led to change. Kinase domain mutation at the time of initiation of a third-line therapy was not found to influence outcome.

Side effects & tolerability

The Phase I and II trials in second-line usage and clinical trials looking at first-line therapy have shown nilotinib to be fairly well tolerated.

■ Common side effects & their management

Hematological toxicities

An overview of the side effects reported in the various Phase II and III trials has been provided in Table 2. Myelosuppression is one of the most common reasons for treatment interruption or dose reductions and therefore successful therapy depends on managing these side effects effectively [6,7,13,18,22]. Grade 3/4 myelosuppression, as expected, was less frequent in the front-line setting when compared with

Table 1. Cumulative response rates according to Sokal risk by 3 years.									
Sokal risk	Low			Intermediate			High		
	Nilotinib 300 mg b.i.d. (n = 103)	Nilotinib 400 mg b.i.d. (n = 103)	Imatinib 400 mg q.d. (n = 104)	Nilotinib 300 mg b.i.d. (n = 101)	Nilotinib 400 mg b.i.d. (n = 100)	Imatinib 400 mg q.d. (n = 101)	Nilotinib 300 mg b.i.d. (n = 78)	Nilotinib 400 mg b.i.d. (n = 78)	Imatinib 400 mg q.d. (n = 78)
MMR (%)	76.7	76.7	62.5	75.2	69	54.5	66.7	64.1	38.5
MR ⁴ (%)	50.5	51.5	33.7	55.4	40	24.8	42.3	38.5	17.9
MR ^{4.5} (%)	30.1	34	18.3	39.6	22	16.8	24.4	26.9	9.0
b.i.d.: Twice daily; MMR: Major molecular response; MR: Molecular response; q.d.: Once daily. Adapted with permission from [22].									

Table 2. Hematological side effects as reported by all Phase I and II trials as first- and second-line treatment.

Phase	Study	Grade	Patients (%)			Ref.
			Neutropenia	Thrombocytopenia	Anemia	
Second-line trials						
Phase II	2101 (n = 321)	All grades	53	53	58	[15]
		Grade 3/4	31	30	11	
Phase III	ENACT (n = 1422)	All grades	52	49	43	[35]
		Grade 3/4	14	22	11	
First-line trials						
Phase II	MDACC (n = 61)	All grades	52	49	43	[44]
		Grade 3/4	12	5	3	
	GIMEMA (n = 76)	All grades	16	14	3	[17,18]
		Grade 3/4	0	4	2	
Phase III	ENESTnd 300 mg b.i.d. (n = 279)	All grades	43	48	38	[22,23]
		Grade 3/4	12	10	3	
	ENESTnd 400 mg b.i.d. (n = 277)	All grades	38	49	38	[22,23]
		Grade 3/4	20	12	3	
b.i.d.: Twice daily. Adapted with permission from [26].						

b.i.d.: Twice daily.
Adapted with permission from [26].

the heavily pretreated population second-line setting. Thrombocytopenia, neutropenia and anemia occurred in 30, 31 and 11%, respectively, of patients in the Phase I and II studies compared with 10, 12 and 4% in the ENESTnd study [6,13,18]. We recommend weekly monitoring of blood counts for the first 4 weeks after start of treatment, every 2 weeks for the following month and then every 4–6 weeks until 6 months to ensure that pancytopenia does not occur. Grade 1 or 2 cytopenias should simply be monitored without intervention [101] until normalization or worsening [7]. For grade 3 or 4 cytopenias, nilotinib can either be withheld temporarily or dose reduced. The doses can be recommenced or re-escalated following stabilization of the counts [26]. Growth factors may be administered to maintain continuity of treatment as reported in imatinib usage [27,28].

Nonhematological toxicities

Skin rashes

The development of a rash is a frequent class–effect toxicity associated with all TKIs and appears to be more common with higher doses of imatinib and in females [29]. In the ENESTnd trial all grades of dermatologic side effects did not differ significantly between imatinib and nilotinib (Table 3) [22]. The rashes usually vary from minor itching and redness to rare cases of intense pruritus and severe eruptions. Minor manifestations such as itching and redness are usually controlled with antihistaminics

and topical steroids. Rarely short courses of oral prednisolone are required. It is unusual to have to discontinue nilotinib because of skin toxicity but occasionally this is necessary in very severe widespread macular–papular eruptions.

Gastrointestinal & other side effects

Gastrointestinal side effects appear to be less frequent and less severe than with treatment with imatinib or dasatinib. Musculoskeletal side effects such as spasms, cramps and joint pains are usually of grade 1 or 2 in severity and settle with adequate analgesia and correction of electrolyte imbalance. Ongoing problems should be investigated with creatine kinase levels. In our practice we occasionally find creatine kinase levels to be elevated under these circumstances. If serum creatine kinase levels do not respond to temporary interruptions of therapy, they may need further investigation.

Cardiovascular side effects

Preclinical experiments showed that nilotinib could potentially affect cardiac repolarization and prolong the QT interval [30]. However, subsequent clinical trials have shown the cardiac toxicities to be <1% [6,13,18,22]. ECG is routinely performed prior to nilotinib initiation. In practice, with adequate history to rule out significant cardiovascular disorders and baseline ECGs, the incidences of cardiac toxicities have been minimal. We repeat the ECG at 6 months after initiation and annually thereafter. Ischemic

Table 3. Common nonhematological side effects across all trials with nilotinib.

Phase	Study	Grade	Patients (%)								Ref.
			Rash	Headache	Nausea	Myalgia	Fatigue	Vomiting	Diarrhea	Alopecia	
Second-line trials											
Phase II	2101 (n = 321)	All grades	28	19	24	8	19	11	11	NR	[15]
		Grade 3/4	3	2	1	1	1	<1	2	NR	
Phase III	ENACT (n = 1422)	All grades	25	16	38	11	14	7	NR	NR	[35]
		Grade 3/4	3	2	0	1	2	<1	NR	NR	
First-line trials											
Phase II	MDACC (n = 61)	All grades	49	30	38	NR	67	11	21	NR	[44]
		Grade 3/4	2	0	0	NR	3	0	0	NR	
	GIMEMA (n = 76)	All grades	42	30	11	NR	22	11	7	NR	[17,18]
		Grade 3/4	5	2	1	NR	1	1	2	NR	
Phase III	ENESTnd 300 mg b.i.d. (n = 279)	All grades	31	14	12	10	11	5	8	8	[22,23]
		Grade 3/4	<1	1	<1	<1	0	0	<1	0	
	ENESTnd 400 mg b.i.d. (n = 277)	All grades	36	21	20	10	9	9	7	13	[22,23]
		Grade 3/4	3	1	1	0	<1	1	0	0	
b.i.d.: Twice daily; NR: Not reported. Adapted with permission from [26].											

b.i.d.: Twice daily; NR: Not reported.
Adapted with permission from [26].

heart disease (IHD) was found to be increased in the nilotinib arms of the ENESTnd trial as compared with imatinib [22]. There were nine patients (3.2%) in the nilotinib 300 mg b.i.d. and 11 patients (4%) in 400 mg b.i.d. arms with IHD as compared with three (1.1%) in the imatinib arm. Three patients in the nilotinib 400 mg arm had to discontinue treatment due to IHD and none of the patients had an ejection fraction <45%. In our practice, we perform ECHO cardiograms only in patients with clinical symptoms or signs suggestive of IHD or cardiac failure.

Peripheral arterial occlusive disease

Nilotinib has been shown to be implicated in peripheral arterial occlusive disease (PAOD) [31,32]. Some early reports put the incidence of severe PAOD at as much as 17% [32]. The MD Anderson group looked at 233 patients treated with nilotinib retrospectively and showed an incidence of 5% for severe PAOD [33]. Le Coutre *et al.* showed an increased incidence of PAOD by an elevated ankle-brachial index (ABPI) and abnormal duplex ultrasound in nilotinib-treated patients as compared with imatinib (9.6%, $p = 0.1057$ for second-line nilotinib; 15.6%, $p = 0.0166$ for nilotinib first-line or patients previously exposed to nilotinib; 17.4%, $p = 0.0123$ as compared with patients on first-line imatinib: 1.9%) [31]. It is important to screen for risk factors prior to commencing nilotinib, especially diabetes, previous history

of claudication and anginal symptoms. There is no clear consensus on the management of PAOD symptoms. In our institution we investigate them with Doppler ultrasound, ABPI and angiography as appropriate, and consider referral to a vascular surgeon. It may not always be possible to switch to an alternative TKI, but wherever possible, dasatinib, bosutinib and, in some cases, even imatinib may be a better alternative as it is thought to provide some degree of protection against diabetes-induced atherosclerosis [34]. In instances where alternatives are not feasible, we manage the patient according to symptoms closely with the vascular surgeons.

Hepatotoxicity & other biochemical abnormalities

Hyperbilirubinemia is a common adverse event from all TKIs including nilotinib and usually requires dose interruptions [35]. In the ENACT trial of second-line nilotinib usage 4% of patients experienced hyperbilirubinemia, with 2% requiring dose interruptions and less than 1% requiring permanent discontinuation. Nilotinib has also been associated with elevations in lipase and amylase levels [7,15,30,36], although the incidence of acute pancreatitis is very low (27 of 1793 [1.5%] patients in the ENACT trial transiently interrupted nilotinib due to pancreatitis and only four patients permanently interrupted treatment) [35]. In the GIMEMA nilotinib front-line study, no case of pancreatitis was described [18]. In the

ENESTnd trial, 11 events of pancreatitis have been reported (five in the 300 mg b.i.d. arm and six in the 400 mg b.i.d. arm) and only one grade 3 or 4 event was reported [22]. The pathophysiology of elevations in pancreatic enzymes is currently unknown.

Hyperglycemia

Hyperglycemia was problematic in less than 0.1% patients in the ENACT trial and only one patient had to discontinue treatment due to it [35]. In the ENESTnd trial, glucose levels were found to be elevated in both the nilotinib arms of the trial as compared with none of the patients in the imatinib arm (6.1 and 5.4 vs 0%). Two patients had grade 3 or 4 hyperglycemia in the nilotinib 400 mg arm [22]. In our practice, we regularly see hyperglycemia and recommend that blood sugars are monitored closely in diabetic patients. We would consider either dasatinib or imatinib as an alternative to nilotinib wherever possible. Imatinib has been shown to be protective in reducing glucose levels and atherosclerotic changes in diabetic patients.

Cross intolerance

Cortes *et al.* showed in their retrospective analysis of two large Phase II studies [7,15] that there was minimal cross intolerance due to non-hematological toxicities between imatinib and nilotinib [37]. In our practice, if patients are good responders but intolerant to the TKI for non-hematologic toxicities we can usually change the drug without impacting on efficacy and without recurrence of the original adverse event. Using a TKI with a lower incidence of any particular side effect seems logical; for example, nilotinib would be useful in patients with severe fluid retention or pleural effusion and would need to be used with caution in patients with peripheral arterial disease or diabetics.

Compliance

Nilotinib is taken b.i.d. with food restriction, in that patients should fast for up to 2 h prior to the dose and for up to an hour afterwards. Compliance has been shown to be one of the most significant parameters determining the outcome of CML patients on imatinib therapy [38]. There have been no prospective studies to evaluate compliance in patients taking nilotinib. Hence, monitoring patient adherence and education on compliance are important considerations.

Discussion

Imatinib has greatly improved the outcome of patients with CP CML, with event-free survival greater than 80% at 8 years [3]. However, intolerance, resistance and disease progression all limit the success of imatinib therapy. In the front-line setting, nilotinib induces deeper responses more rapidly and in more patients than imatinib. In addition, progression appears to be less frequent than on imatinib [22,35]. Like imatinib, nilotinib does not kill quiescent BCR-ABL1-positive CD34-positive stem cells, which might represent a reservoir of cells susceptible to additional genetic events, leading to disease progression in some patients, but is thought to reduce them [39,11]. It is speculated that effective prevention of progression requires a profound reduction in the numbers of these cells (response depth) that occurs quickly (response speed), and is sustained (response duration). Although these attributes are not evidence-based, they do favor the use of nilotinib upfront to achieve results earlier, but it remains to be seen if this translates into tangible results on longer follow-ups. Nilotinib reduced but did not entirely prevent progression.

Nilotinib has been shown to be effective in CP and APs of the disease, and there is little evidence that it improves survival in BC CML patients [40]. In the BC patients, there were hematologic and cytogenetic improvements in most, however the median OS (10.1 months in myeloid BC and 7.9 months in lymphoid BC) was not significantly different from the results obtained from the landmark IRIS trial. Similar results were obtained from the ENACT trial looking at nilotinib treatment in advanced phase CML [41]. Imatinib or dasatinib, together with conventional chemotherapy is currently the preferred treatment of BC with a view to proceed towards an allogeneic transplant at remission [42,43].

The randomized trials show that nilotinib is safe and fairly well tolerated when compared with imatinib. Economic considerations may play a significant part in the choice of TKI therapy. In the UK, nilotinib has been approved by NICE for both first- and second-line usage for CP CML patients. The NICE guidelines after first-line imatinib therapy are to use nilotinib without resorting to an increased dose of imatinib in the event of intolerance or resistance. Nilotinib has approval for both first and second-line setting in the USA, EU and other countries.

Which second-generation TKI is best for both first- and second-line treatment of CP CML remains an unanswered question. No direct comparisons between second-generation TKIs have been reported both upfront and in a second-line setting. Although results of randomized studies suggest that dasatinib is also superior to imatinib, a head-to-head comparison of nilotinib and dasatinib will be required to establish which second-generation TKI is superior. Differences in OS are still to be shown in any of the trials compared with imatinib. As the patients with CML live longer with fewer CML related deaths, event-free survival may become the new surrogate for OS. With nilotinib and dasatinib appearing to be more effective, they may become the new standard of

care. Appropriate management of side effects and ensuring patients' compliance should be the cornerstone of effective management.

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